ASPECTS OF THE CHEMISTRY OF THE MANNICH REACTION

by

George Papageorgiou B.Sc., M.Sc., G.R.S.C.

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Supervisor: Professor H. Heaney B.A., Ph.D., D.Sc.

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To my wife Alexandra and baby daughter Xanthy, with love.
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ABSTRACT

The work described in the thesis is concerned with the development of new methodologies for the aminoalkylation of a wide range of aromatic substrates using non-aqueous conditions. The Mannich reagents derived from secondary amines, bis(N,N-dialkylamino)methanes (aminals), and alkoxy(N,N-dialkylamino)methanes (aminol ethers), were used in "in situ" reactions activated by various Lewis acids. The objective was to devise new methods whereby a high concentration of hydrogen chloride did not accumulate in the reaction mixture.

It was established that aminals activated by acetyl chloride or sulphur dioxide can be used for the aminoalkylation of \( \tau \)-excessive heterocycles. Good regioselective control was achieved for ortho-aminoalkylation of phenols, especially 2,5-dimethylphenol, by both aminals and aminol ethers in the presence of sulphur dioxide. The use of chlorosilane derivatives in "in situ" reactions of aromatic heterocycles was investigated. Good yields of monosubstitution products were obtained using trichloromethyl-, dichlorodimethyl- and chlorotrimethyl-silane with aminol ethers in reactions with \( N \)-methylpyrrole. Aminals, however, activated by chlorotrimethylsilane afforded the 2,5-diaminoalkylated pyrroles. The catalytic effect of chlorotrimethylsilane in this system was established. The ipso addition-with-elimination reactions of aryltrialkylstannanes with aminals and aminol ethers in the presence of chlorosilane derivatives were examined.

The Mannich reagents derived from primary amines bis(N-alkoxymethyl)-alkyl and -aralkyl amines (bis(aminol ethers)) have been used in reactions with electron rich aromatic compounds. The aim was to activate an alkoxymethyl group and to protect the product by the same functional group. A versatile method for the preparation of secondary amine Mannich bases was developed. The possibility of carrying out tandem reactions with two different nucleophiles was investigated briefly. Bis(aminol ethers) derived from \( \beta \)-phenylethylamines, possessing a methoxy substituent at the 3-position of the ring, afforded a convenient method for the preparation of \( N \)-arylmethyltetrahydroysoquinoline derivatives.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AIBN</td>
<td>Azobi-iso-butynitriile</td>
</tr>
<tr>
<td>Ac</td>
<td>Acyl</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>b.p.</td>
<td>Boiling point</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-Butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5,4,0]undec-7-ene</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Di-iso-butyllanium hydride</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramid</td>
</tr>
<tr>
<td>i.r.</td>
<td>Infra-Red</td>
</tr>
<tr>
<td>L.D.A</td>
<td>Lithium di-iso-propylamide</td>
</tr>
<tr>
<td>L.U.T.</td>
<td>Loughborough University of Technology</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>M.S.</td>
<td>Mass spectrum</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
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<tr>
<td>n.m.r.</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>i-Pr</td>
<td>iso-Propyl</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-Butyltrimethylsily</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>Tetramethylsilane</td>
</tr>
<tr>
<td>p-TSA</td>
<td>para-Toluenesulphonic acid</td>
</tr>
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CHAPTER ONE

1. Introduction

The Mannich reaction has enjoyed widespread investigations since the beginning of this century. Although the reaction has been known since the end of the last century, Mannich was the first to recognise the generality of the reaction and hence this versatile synthetic process bears his name.

Several studies\(^1\) conducted before 1960, together with two books\(^2,3\), provide an excellent coverage of the early investigations of the subject. The continuing interest in this reaction is demonstrated by the more recent comprehensive reviews of the field by Tramontini\(^4a,b\). An overview of the latest more interesting work in this area will appear shortly in forthcoming reviews, concentrating on bimolecular aromatic\(^5a\) and aliphatic\(^5b\) Mannich reactions.

The importance of the Mannich reaction relates to the fact that the products of this reaction, known as Mannich bases, have provided an enormous number of applications. The basic functionality of the molecules renders them soluble in aqueous solvents upon protonation or alkylation. This property facilitates the pharmacological usage of the biologically active analogues. The amino function also provides a good synthetic tool for the transformation to numerous other compounds due to its reactivity.

The reaction provides a good method for C–C bond formation. It essentially consists of the condensation of an aldehyde (mostly formaldehyde) and an amine with a substrate possessing acidic hydrogens. The most general reaction is represented in Equation 1.
The classical reaction was carried out under aqueous acidic conditions. This, however, limits the number of substrates suitable for this chemical transformation. The prolonged reaction times, high temperatures and the high concentration of acid reduce the yields and promote side reactions and even polymerisation.

In more recent years, however, these problems have largely been overcome by the use of non-aqueous acidic media under milder conditions. The prediction that preformed iminium salts can be employed for the aminoalkylation of aromatic compounds has been verified for a number of systems. This enabled the use of weak nucleophiles in this field. Thus, although thiophene is reported not to undergo the Mannich reaction under classical conditions, a good yield of aminoalkylation product was obtained using preformed iminium salt in acetonitrile under reflux. Other systems that have been investigated within the past few years include phenols and indoles. Furan does not undergo the Mannich reaction under classical conditions but more recent work carried out in these laboratories showed that furan also undergoes the reaction using preformed iminium salts at room temperature.

In view of the extensive coverage given to this reaction over the years this chapter will concentrate on some important pharmaceutical, technological and unusual applications. The versatility of Mannich bases for chemical transformations will briefly be surveyed. The ever increasing number of
substrates investigated broadens the views of the accessible mechanistic pathways. A general survey of proposed mechanisms will be given.

1.1 Some Pharmaceutical and Technological Applications

The most important applications of Mannich bases are in pharmaceutical chemistry. The reaction has been employed for the preparation of numerous biologically active compounds. A series of acetylenes containing bis(2-chloroethyl)amine functionalities synthesised by the Mannich reaction in good yields showed antitumour properties. The highest antitumour activity was observed by the representative example (1) shown in Scheme 1.

\[
\begin{align*}
\text{Et} & \quad \text{HO-C-C=CH} & \quad \text{Et} \\
\text{Et} & \quad \text{Et} & \quad \text{(CICH}_2\text{CH}_2\text{)}_2\text{NH.HCl} & \quad \text{Et} \\
\text{Et} & \quad \text{Et} & \quad \text{Et} & \quad \text{Et} \\
\text{Et} & \quad \text{Et} & \quad \text{Cl} & \quad \text{Cl} \quad \text{Cl}
\end{align*}
\]

\[\text{SCHEME 1}\]

Reagents (i) HCHOaq.; (ii) CuCl$_2$

In a separate study\textsuperscript{12} 2-methyl-3-butyn-2-ol was also used as an acetylene precursor in the Mannich reaction for the synthesis of enzyme inactivators of monoamine oxidase (MAO), (2a) and (2b). The more general MAO inhibitor (2c) has been used therapeutically as an antihypertensive agent. The protected acetylene was used in order to avoid
the potential hazards associated with acetylene as well as the formation of disubstituted by-products. The acetylenic carbinols afforded the acetylene Mannich bases and acetone upon catalytic decomposition with potassium hydroxide (Scheme 2).

\[
\begin{align*}
\text{Me}_2\text{C}=-\text{C}=-\text{C}-\text{H} + \text{HCHO} + \text{RNHCH}_3 & \xrightarrow{\text{i}} \text{Me}_2\text{C}=-\text{C}=-\text{C}-\text{CH}_2\text{N}-\text{R} \xrightarrow{\text{ii}} \\
\text{OH} & \xrightarrow{\text{OH}} \text{H}-\text{C}=-\text{C}-\text{CH}_2\text{N}-\text{R} + \text{Me}_2\text{CO}
\end{align*}
\]

(2a) \( R = \text{OCH}_2\text{CH}_2\text{CH}_2- \)  
(2b) \( R = \text{PhCH}_2-\text{CH}- \)  
(2c) \( R = \text{Bn} \)

SCHEME 2

Reagents (i) CuCl; (ii) KOH, heat

The Mannich reaction of vinyl keto ester (3) with benzylamine and isotopically labelled formaldehyde followed by conjugated addition and decarboxylation afforded the piperidone (4). Grignard reaction of (4) with 3-bromobenzotrifluoride gave the hydroxy piperidine (5) which was converted to the radio-labelled neuroleptic butyrophenone (6) in five steps, (Scheme 3).
Isotopically labelled compounds provide an efficient approach for the elucidation of the metabolic fate and quantitative behaviour of a drug in the organism, especially for the drug substances belonging to the class of peptide ergot alkaloids which are administered in milligram doses. Thus, [3-\textsuperscript{14}C]-tryptophan was prepared by the Mannich reaction of indole, followed by alkylation of gramine in the presence of sodium hydroxide and hydrolytic cleavage of the formamido and ester groups of the skatyl derivative (7), as shown in Scheme 4\textsuperscript{14}.
Biosynthetic incorporation of radiolabelled tryptophan into paspalic (8) and lysergic (9) acids afforded the synthesis of radiolabelled peptide ergot alkaloids.

In the last two decades the technological applications of Mannich bases in polymer chemistry have assumed comparable importance. A recent comprehensive review\textsuperscript{16} surveys the enormous number of applications of the Mannich reaction in this field. The nature of the reaction enables the connection of two molecular entities via a methylene bridge, thus affording products with properties which can be exploited in a variety of applications.
The polymeric products of the Mannich reaction are most frequently obtained using a substrate containing at least two active hydrogens and a bis-secondary amine, or a primary amine in polycondensation with formaldehyde. The secondary bis-amines usually employed in this process are piperazine and 1,3-bis(4-piperidyl)propane which, in the presence of formaldehyde and cyclohexanone, forms for example (10), the polymeric aminoketone (10) shown in Equation 2.

Another class of substrates used in this context is the monomeric compounds containing the amino group. Most of the examples described in the literature deal with arylamino derivatives which behave simultaneously as amines and as substrates capable of C-aminomethylation. N-Aminomethylation, however, can also occur as in the case of the arylamine nitrogen leading to the synthesis of aniline resins. p-Aminobenzoic acid (17) is an example combining the two possibilities leading to polymeric material (11) shown in Equation 3.
The applications of the polymeric materials, formed in these reactions, arise from their ionic character complexing power and their ability to include into the polymer mass magnetizable metallic particles. They are used as deodorants and as supports for immobilised enzymes.

1.2 Reactions of Mannich Bases

The versatility of Mannich bases is demonstrated by the large number of reactions these compounds can be subjected to. They are useful intermediates in synthetic chemistry for the preparation of a variety of new compounds. Some of their reactions are now discussed.

1.2.1 Cleavage

Cleavage of Mannich bases can be achieved either by deaminomethylation, that is a retro-Mannich reaction (a possible side reaction in Mannich synthesis) or by deamination producing the amine and an unsaturated derivative of the substrate. The pH of the medium is an important factor affecting cleavage. Thus, the heterocyclic Mannich base (12) is deaminomethylated (13) by hydrogen chloride and the hydroxymethyl derivative (14) is produced by deamination in acetic acid\textsuperscript{18}, Scheme 5.
Deaminomethylation is important in that it determines the stability of Mannich bases. It has also been linked to trans-aminomethylation which has pharmacological interest in some amidic Mannich bases which may yield useful pro-drugs of NH-acidic compounds, such as amides and ureas\textsuperscript{19}. C-Mannich bases are in general more stable to cleavage than O- or N-Mannich bases which can be regarded as Mannich reagents due to their ease of cleavage and the formation of electrophilic species. Acidic conditions are most commonly used because deaminomethylation is more efficient in acidic than neutral or alkaline media.

Deamination is more strongly associated with the stability of the compounds, particularly in the free base form, as far as storage and handling are concerned. From the synthetic point of view, it constitutes the first step of substitution reactions discussed later. In addition, it is important in pharmacological and technological applications.

β-Aminoketones and similar carbonyl derivatives undergo deamination in suitably modified conditions, so that the α,β-unsaturated carbonyl derivative is formed directly. Thus, by using such methods the syntheses of the tumour inhibitors (±)-vernolepin (15) and (±)-vernomenin (16) have
been accomplished by Danishefsky's group\textsuperscript{20,21}. It was established by these workers that dimethylaminomethylation of ketones and lactones can be achieved from the silyl enol ether and lithium enolates respectively using Eshenmoser's salt (17)\textsuperscript{22}. Treatment of lactones (18) and (18a) with LDA, in the presence of HMPA, followed by addition of an excess of (17) afforded the Mannich bases (19) and (19a). Conversion to methiodides (20) and (20a), followed by deamination using (DBU), resulted in the isolation of the natural products in reasonable yields without the need for protection of the hydroxyl moieties, as shown in Scheme 6.

\begin{center}
\includegraphics[width=\textwidth]{scheme6.png}
\end{center}

\textbf{SCHEME 6}

Reagents (i) 3 equiv. LDA, 78°C, THF; (ii) 2.5 equiv. HMPA; (iii) 6.5 equiv. (17) Me\textsubscript{2}N=CH\textsubscript{2} I\textsuperscript{−}, 78°C to -42°C; (iv) MeI; (v) DBU, THF, Acidic Workup.
Hydroxymethyl derivatives can be formed instead of unsaturated carbonyl compounds by deamination reactions. In a kinetic study\textsuperscript{23} of the hydrolysis of labile quaternary ammonium salts of \textit{para}-aminomethylphenols (21), it was found that the intermediate methylenequinones (22) react with water forming the hydroxymethyl phenols (23) as shown in Equation 4.

\begin{equation}
(21) \rightarrow (22) \overset{H_2O}{\rightarrow} (23)
\end{equation}

Equation 4

In a concurrent study\textsuperscript{24a}, in these laboratories, deamination of the crude Mannich bases to yield \(\alpha,\beta\)-unsaturated ketones was observed during distillation. Thus, formation of the Mannich base (24), Scheme 7, from the silyl enol ether of \(\alpha\)-tetralone was easily achieved, but upon distillation the deaminated product (25) was isolated.

\begin{equation}
(24) \overset{i}{\rightarrow} (24) \overset{\text{ii}}{\rightarrow} (25)
\end{equation}

SCHEME 7

Reagents (i) \(\text{Et}_2\text{NCH}_2\text{OEt, TMSCl, MeCN} \); (ii) heat, \(-\text{Et}_2\text{NH}\)
1.2.2 Substitution

Substitution of the amino group of Mannich bases can be achieved by various nucleophilic reagents, generally represented by Equation 5.

\[
R-\text{CH}_2-\text{NR}_2^+ \xrightarrow{\text{Nu-H}} (-\text{R}_2^2\text{NH}) \xrightarrow{} R-\text{CH}_2-\text{Nu}
\]

**Equation 5**

Besides the usual reagents for hydrogen substitution (hydrogen and catalyst, zinc and acid) the more effective reducing agents can also be used. The methiodides formed from acetylenic Mannich bases\(^{25}\) (26), for example, can be reduced conveniently to \(\alpha\)-allenic alcohols (27) with lithium aluminium hydride in THF at room temperature, as shown in Equation 6.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{CH}_2 \quad + \quad \text{NR}_3^+ \quad \text{I}^- \\
\text{OH} & \quad \text{LIAIH}_4/\text{THF/r.t.} \\
\text{R}^1 & \quad \text{R}^2 \quad \text{CH} \quad \text{C} \quad \text{C} \quad \text{CH}_2 \\
\text{OH} & \quad (27)
\end{align*}
\]

**Equation 6**

Carbon nucleophiles (as well as heteroatom analogues) are also used in this context, forming a wide range of compounds of important synthetic utility.
An interesting substitution reaction of ketonic Mannich bases (28) (Scheme 8) occurs with aldehydes, catalysed by alkali cyanide in DMF, by a mechanism not following the usual addition–with–elimination pathway. A variety of 1,4-diketones (29) can be obtained from this reaction.

\[
\begin{align*}
R^1\text{O} & \quad \text{NR}_2^3
\end{align*}
\]

(28) + \[
\begin{align*}
\text{H} & \quad \text{R}^4
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & \quad \text{O} \\
\text{R}^2 & \quad \text{NR}_2^3 \\
\text{H} & \quad \text{R}^4
\end{align*}
\]

(29)

\[\text{Reagents (i) NaCN, DMF; (ii) -R}_2^3\text{NH}\]

SCHEME 8

1.2.3 Organometallic Addition Reactions

Organometallic addition to chiral ketonic Mannich bases (Equation 7) results in the formation of diastereoisomeric amino alcohols. Grignard and organolithium reagents are used more frequently.

\[\text{Equation 7}\]
Treatment of achiral aminopropiophenones with α-bromo esters in the presence of zinc (the Reformatsky reaction) gives diastereoisomeric hydroxy-amino esters, Equation 8. The mechanism of these reactions has been investigated\textsuperscript{27} and the predominance of \textit{erythro}-diastereoisomer has been interpreted on the basis of competing cyclic and open chain transition states.

\[
\begin{align*}
\text{Zn} & \quad \xrightarrow{\text{\textup{Ph}+\text{CH}_2\text{CH}_2\text{NR}_3\text{OH}}} \\
\text{CO}_2\text{R}^2 & \quad \text{R'} \quad \text{Ph} \quad \text{H} \\
\text{Br} & \quad \text{OH} \quad \text{erythro} \\
\text{Ph} & \quad \text{OH} \quad \text{threo}
\end{align*}
\]

\textbf{Equation 8}

Acetylenic Mannich bases also give interesting reactions with organometallic reagents involving regioselective and stereoselective features. Thus, the allylamine (30) is predominantly formed by the \textit{anti}-addition of methylmagnesium chloride at the unsaturated carbon furthest away from the aminomethyl group of the Mannich base. Acetylation of (30) with acetic anhydride gives the allylamine (31), which upon reaction with ethylchloroformate affords the allyl chloride (32)\textsuperscript{28}, shown in Scheme 9.
 Allyl magnesium chloride\textsuperscript{20a}, however, in reactions with allylic or acetylenic Mannich bases, or even primary allylamines, attacks exclusively the unsaturated carbon nearest to the amino function, Scheme 10.

SCHEME 10
Reagents (i) $\text{CH}_2=\text{CHCH}_2\text{MgCl}$, THF/reflux; (ii) hydrolysis.
Organolithium reagents\textsuperscript{29b}, on the other hand, give similar products with allylic Mannich bases but with primary allylamines ketone formation is observed after hydrolysis, Scheme 11.

\[
\begin{align*}
\text{PhCH}=\text{CHCH}_2\text{NMe}_2 & \xrightarrow{\text{i, ii}} \text{PhCH}_2\text{CHCH}_2\text{NMe}_2 \\
\text{CH}_2=\text{CHCH}_2\text{NH}_2 & \xrightarrow{\text{i, ii}} \text{R-CH}_2\text{CH}_2-\text{C-R}
\end{align*}
\]

**SCHEME 11**

Reagents (i) \( n \)-BuLi, hexane; (ii) hydrolysis

1.2.4 Cyclization

Mannich bases are useful synthetic intermediates for several types of cyclization reactions. The process can take place either with elimination of the amino moiety, involving ring closure at the methylene carbon, or without elimination of the amino group.

Most of the cyclization reactions incorporating the amino moiety are based on classical methods for the preparation of heterocyclic compounds. Homocyclic compounds can also be prepared from acetylenic Mannich bases. The reaction of the triple bond of propargylamines (33), **Equation 9**, with rhodacyclopentadien-c-complexes (34) results in the formation of the aromatic ring of the anthraquinone derivatives (35)\textsuperscript{30}. 

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The phthalimidic Mannich bases (36) formed from phthalimide, formaldehyde and a secondary amine give the N-substituted 3-hydroxy-isoindolin-1-ones (37) upon reduction with aluminium. Treatment of (37) with hot concentrated sulphuric acid results in cyclization to the 2,4-benzodiazepine derivatives (38) shown in Scheme 12\textsuperscript{31}.

**SCHEME 12**

Reagents (i) HCHOaq., R(Bn)NH; (ii) Al/Hg; (iii) hot conc. H\textsubscript{2}SO\textsubscript{4}
More recently it has been shown that the Mannich base (39), prepared from the primary nitroalkane, by the classical procedures, can undergo radical cyclization\(^{32}\) to give the pyrrolidine derivative (40), Scheme 13.

![Scheme 13](image)

**SCHEME 13**

Reagents (i) Na\(^+\) -OMe, MeOH, Et\(_2\)O; (ii) K\(_3\)Fe(CN)\(_6\), H\(_2\)O

Numerous examples of the cyclization of Mannich bases with amine elimination are reported in the literature. Ketonic Mannich bases are most frequently studied and a detailed review\(^{33}\) on the synthesis of pyridines reports the reaction with keto-pyridinium salts in the presence of ammonia. A series of pyridine derivatives (41) was prepared as shown in Scheme 14.

![Scheme 14](image)

**SCHEME 14**

Reagents (i) -R\(_2\)NH; (ii) NH\(_3\); (iii) -Py.HX
1.3 Some New Developments of the Mannich Reaction

The importance of the Mannich reaction is reflected in the ever increasing number of suitable substrates and reaction conditions developed over the past seventy five years. The most common co-reactants used are aromatic heterocycles and phenols. In recent years many new substrates have been used in this reaction for the preparation of a variety of new compounds with specific properties. In view of the large number of reactions reported in the literature only a few selected examples will be given in this section.

An improved method for the preparation of aminomethylbenzotriazoles has recently been reported\textsuperscript{34}. Instead of the condensation of benzotriazole with formaldehyde and an amine, 1-hydroxymethylbenzotriazole can react with primary aromatic amines producing the corresponding aminomethylbenzotriazoles (42) in quantitative yields. A number of these compounds was prepared by this method, as shown Scheme 15.

![Scheme 15](image)

**SCHEME 15**

Reagents (i) ArNH\textsubscript{2}, H\textsubscript{2}O, EtOH, AcOH, Reflux

Primary aliphatic amines, however, afford the tertiary amines (43) as the predominant products in reactions using equimolar amounts of reagents, as shown in Scheme 16. These compounds, in addition to their biological activity, are also used as corrosion inhibitors, additives to lubricating oils, and adhesion agents for photopolymerisable paints.
Aldehydes, other than formaldehyde, were successfully used for the condensation of benzotriazole and primary aromatic amines, Scheme 17. Although the formation of the equivalent tertiary amines (43) with aliphatic aldehydes did not succeed it was possible to obtain the corresponding products using phthalaldehyde.

Methanesulphonanilides have been reported recently\textsuperscript{35} to give exclusively parar-aminalkylation products using classical Mannich conditions, Scheme 18. Phenols, on the other hand, give predominantly ortho-substitution products under similar conditions. The NH group is essential for the reactivity of these substrates as N-methylmethanesulphonanilide
does not react with amines and formaldehyde. Similarly, trifluoromethanesulphonanilide does not produce the Mannich base indicating that the strong electron-withdrawing effect of the trifluoromethanesulphonyl group deactivates the ring.

\[
\text{CH}_3\text{SO}_2\text{NH} + \text{R}_2\text{NH} \rightarrow \text{CH}_3\text{SO}_2\text{NH} \text{NR}_2
\]

**SCHEME 18**

Reagents (i) HCHO, EtOH, H\textsubscript{2}O, heat

In an effort to develop labile aminomethyl analogues of drugs containing exocyclic amino groups, aminomethylated derivatives of adenine, cytosine and guanine have been prepared\textsuperscript{38} by the Mannich reaction. Aminomethyl derivatives of drugs containing amide and imide groups, for example 5-fluorouracil and theophylline, enhance the delivery of their parent drugs through the skin.

The reactions were carried out at room temperature in THF using a variety of secondary amines and formaldehyde. Mono-aminomethylated products were obtained from the reaction of adenine (44) with the less basic amines, (such as morpholine and N-methylpiperazine), using equimolar amounts of reagents, and bis-aminomethylated products were obtained from more basic amines irrespective of stoichiometry, Scheme 19. On the other hand, cytosine (45) and guanine (46) afforded only the bis-aminomethylated products regardless of the secondary amine or the molar ratios used in the reaction.
Aminomethanephosphonic acids are obtained by aminomethylation of orthophosphorous acid. Thus, the suitably modified substrate (47) has been used in recent years for the preparation of \( N-(phosphonomethyl)-glycine \) (48), which is used as herbicide and plant growth regulator. This is obtained by aminomethylation of (47) followed by acid hydrolysis of the ester groups, Scheme 20.

\[
\begin{align*}
(\text{MeO})_2\text{P} &- \text{H} &\overset{i}{\longrightarrow} & (\text{MeO})_2\text{P}-\text{N} &\text{CO}_2\text{Me} &\longrightarrow \\
\text{(47)} & & & \text{(48)} & &
\end{align*}
\]

**Scheme 20**

Reagents (i) HCHO, \( \text{H}_2\text{NCH}_2\text{CO}_2\text{Me} \); (ii) conc. HCl
Secondary amides can either be used as substrates or as amine reactants. Phthalimide affords the amidomethylated product (49) by its reaction with 2,3-dimethyl-5-methoxyindole and formaldehyde. This allows the introduction of the primary aminomethyl group on the 6-position of the indole derivative (50) after treatment with hydrazine\(^{38}\) in methanol.

**Scheme 21**

Reagents (i) HCHO; (ii) \(\text{H}_2\text{N}-\text{NH}_2\), MeOH

Formaldehyde is the aldehyde that is normally used in the Mannich reaction. However, it has recently been successfully replaced by other aldehydes (mainly arylaldehydes) or by other derivatives. Thus, \(\alpha\)-haloethers (51) react with sodium bis(trimethylsilyl)amide in hexamethyldisilazane to form the aminol ethers (52). On treatment with Grignard reagents the aminol ethers (52) are converted to \(N,N\)-bis(trimethylsilyl)amines (53) with elimination of magnesium alkoxides (54). The silylamines (53) are easily transformed to the primary amine hydrochlorides (55) on contact with acid as shown in Scheme 22\(^{39}\).
Glyoxylic acid and its derivatives are particularly interesting aldehyde reagents in the Mannich reaction for the synthesis of $\alpha$-amino acids. R.F. Wilkins, working in these laboratories, has recently developed a new method of amino acid synthesis based on the use of methyl glyoxylate. It was found that the best method for the preparation of this reagent involved the reaction of methyl dimethoxyacetate (57) and glyoxylic acid monohydrate (58) in the presence of para-toluenesulphonic acid, Scheme 23, followed by dehydration with phosphorous pentoxide.

\[
\begin{align*}
\text{MeO} & \quad \text{CHCO}_2\text{Me} \\
\text{MeO} & \quad \text{CHCO}_2\text{Me} \\
\text{H}_2\text{O} & \quad \text{H} \quad \text{H}_2\text{O} \\
i \quad ii & \quad \text{2 OHC-CO}_2\text{Me}
\end{align*}
\]

SCHEME 23
Reagents (i) $p$-TSA, $80^\circ$C, 18hrs.; (ii) $\text{P}_2\text{O}_5$, 4hrs.
Condensation of methyl glyoxylate (56) with N-methylethanolamine (59), Equation 10, afforded 2-methoxycarbonyl-3-methyl-1,3-oxazolidine (60) in good yield.

\[ \text{OHC-CO}_2\text{Me} + \text{MeNHCH}_2\text{CH}_2\text{OH} \]
\[ \text{Benzene/Reflux} \]
\[ \text{Dean-Stark trap} \]

\[ \text{Me-N} \]
\[ \text{O} \]
\[ \text{CO}_2\text{Me} \]

\( \text{Equation 10} \)

Although initial attempts to activate this Mannich reagent (60) with various Lewis acids in reactions with 2-methylfuran failed, the use of thionyl chloride (a reagent known for the conversion of alcohols to alkyl chlorides) yielded the N-chloroethyl Mannich base (61), Equation 11.

\[ \text{Me} \]
\[ \text{O} \]
\[ \text{CO}_2\text{Me} \]

\( \text{Equation 11} \)
These preliminary findings are currently under active investigation in these laboratories. The introduction of a chiral centre is a desirable objective for the development of new methods whereby stereoselective Mannich reactions could afford the synthesis of arylglycine derivatives.

In the last few years a considerable interest has grown in the Mannich reaction as a means of amidoalkylation of a wide range of suitable substrates. The use of N-acyliminium species in intramolecular amidoalkylation reactions has been reviewed by Speckamp and Hiemstra. More recently the utilisation of N-acyl imines and related hetero dienes as well as N-acyliminium species in [4+2]-cycloaddition reactions has been surveyed. These compounds can act as dienophiles to produce a variety of tetrahydropyridines (62), Equation 12, or as electron deficient hetero dienes to yield 5,6-dihydro-4H-1,3-oxazines (63), regio- and stereospecifically, in a Diels–Alder fashion.

![Equation 12](image)

In another investigation in these laboratories being carried out by R.A. Fairhurst, acyliminium and alkoxycarbonylmethyleneiminium species are being used as co-reactants with silyl enol ethers, silyl ketene...
acetals, and allyl silanes. The precursors to these strong electrophilic intermediates, α-methoxycarbamates, are conveniently prepared in good yields from a variety of imines and alkyl or aryl chloroformates.

Reactions of these species with prochiral silyl enol ethers, for example, in the presence of catalytic amounts of trimethylsilyl triflate, afforded good diastereoselectivity, Equation 13. The predominant diastereoisomer (64) has two chiral centres of opposite relative stereochemistry and is thermodynamically the least favoured product$^{24b}$.

![Equation 13](image)

The origins of the observed diastereoselectivity has been investigated and it has been shown that the integrity of the chiral centre α- to the ketone carbonyl group is retained under the reaction conditions used. The diastereoselectivity is attributed to a kinetic differentiation between the energies of the two diastereomeric transition states.
The products of these reactions, being tertiary carbamates, are in fact protected secondary amines. Treatment of t-butylaminocarbamate derivatives with 1 mol.% of triflic acid results in cleavage of the t-butyl group forming secondary carbamates (65) in high yields with the elimination of isobutene, Equation 14
c

\[
\begin{array}{c}
R_3N\biggarrow{\text{1 mol.}\%\ \text{TfOH}}\biggarrow{\text{MeCN}}\biggarrow{\text{R}_2N}
\end{array}
\]

\text{(65)}

Equation 14

Hydrogenolysis of the benzyloxy carbonyl protecting group will afford the formation of primary amines. Alternatively, if a t-butoxycarbonyl group is present, removal of both protecting groups by triflic acid may occur in one step so that the formation of a wide range of primary amines might be accomplished.

The search for new reagent systems in the Mannich reaction is enjoying continuous coverage. The preparation of \(N\)-aryl-\(\alpha\)-aminoketones (66) has recently been reported\(^{46}\). Activation of the Schiff’s bases (67) by catalytic amount of trimethylsilyl triflate and the subsequent addition of silyl enol ethers (68) affords good yields of the secondary amines, as shown in Scheme 24.

\[
\begin{array}{c}
\text{Ar}^1\text{CH}=\text{NAr}^2 \\
(67)
\end{array}
\rightarrow
\begin{array}{c}
\left[\text{Ar}^1\text{CH}=\overset{+}{\text{NAr}^2}\left(\text{SiMe}_3\right)\overset{-}{\text{OSO}_2\text{CF}_3}\right]
\end{array}
\]

\[
\begin{array}{c}
\left[\text{Ar}^1\text{CH}=\overset{+}{\text{NAr}^2}\left(\text{SiMe}_3\right)\overset{-}{\text{OSO}_2\text{CF}_3}\right]
\end{array}
\rightarrow
\begin{array}{c}
\text{R}^\biggarrow{\text{Ar}^1\text{NAr}^2}
\end{array}
\]

\text{(66)}

SCHEME 24

Reagents (i) 15 mol% TMSOTf; (ii) \(\text{CH}_2\text{=C(R)OSiMe}_3\) (68)
Recent work of Grieco and his collaborators has concentrated on the reactions of allylsilanes and allylstannanes with "in situ" generated iminium salts in protic media. It was shown that iminium trifluoroacetates derived from primary amines in contact with allylsilanes undergo an aminomethylation-desilylation-cyclization process leading to N-substituted piperidines\(^{46,47}\), (69), Scheme 25.

\[
\begin{align*}
\text{Reagents (i) } & \text{RNH}_3^+\text{OCOCF}_3, \text{HCHO, H}_2\text{O; (ii) CF}_3\text{CO}_2\text{H, H}_2\text{O, HCHO.}
\end{align*}
\]

In contrast, the trifluoroacetate salt of the secondary amine (70) under the same conditions undergoes aminomethylation-desilylation forming the terminal alkene Mannich base (71), Equation 15, without ring formation.

\[
\begin{align*}
\text{PhCH}_2\text{NHMe}^-\text{OCOCF}_3 & \quad \text{PhCH}_2\text{NMe} \\
(70) & \quad (71)
\end{align*}
\]
The more reactive allyltributylstannane (72) and methallyltributylstannane (73), in reactions with iminium species generated from primary amines, yield the bis-homoallylamines (74) and (75) respectively without any evidence of piperidine ring formation\textsuperscript{48}, Equation 16.

\[ \text{Bu}_3\text{Sn} \begin{array}{c} \text{R}^1 \end{array} \xrightarrow{R^2\text{NH}_3^-\text{COOCF}_3} R^2\text{N}(\text{CH}_2\text{CH}_2\text{CH}==\text{CH}_2)_2 \]

(72) $R^1 = \text{H}$
(73) $R^1 = \text{Me}$

(74) $R^1 = \text{H}$
(75) $R^1 = \text{Me}$

Equation 16

It is noteworthy that the iminium trifluoroacetate salt derived from homoveratrylamine (76) together with allyltributylstannane (72) gave the tertiary amine (77a) in 82% yield and only 10% of the Pictet-Spengler cyclization product (78), Scheme 26. Methallyltributylstannane (73), however, afforded only the tertiary amine (77b) in 94% yield without any trace of intramolecular cyclization.

\[ \text{MeO} \begin{array}{c} \text{H} \end{array} \xrightarrow{\text{i}} \text{MeO} \begin{array}{c} \text{N} \end{array} \xrightarrow{\text{ii}} \begin{array}{c} \text{MeO} \end{array} \begin{array}{c} \text{R}^1 \end{array} \]

(76)

(77a) $R^1 = \text{H}$
(77b) $R^1 = \text{Me}$

(78)

\textbf{SCHEME 26}

Reagents (i) HCHO, EtOH-CHCl\textsubscript{3}; (ii) Bu\textsubscript{3}SnCH\textsubscript{2}C(R')=CH\textsubscript{2}, R'=H (72), R'=Me (73)
The potential of the aminomethylation—destannylation process has been applied in the synthesis of alkaloids\textsuperscript{48}. Thus, treatment of the trifluoroacetate salt of tryptamine (79) with glyoxylic acid over a 24 hour period, followed by formaldehyde and allyltributylstannane (72), afforded the acid (80) in good yield, Scheme 27.

![Scheme 27](image)

**SCHEME 27**

Reagents (i) HOC–CO$_2$H, MeOH, CHCl$_3$, 24hrs;

(ii) HCHOaq., Bu$_3$SnCH$_2$CH=CH$_2$

The process was also applied using preformed iminium trifluoroacetate salts\textsuperscript{48}. The trifluoroacetate salt of dihydro-α-carboline (81) in reaction with methallyltributylstannane afforded the tetrahydro-α-carboline (82) in excellent yield, Equation 17.

![Equation 17](image)
1.4 The Mechanism of the Mannich Reaction

The mechanism of this reaction has been the subject of a considerable amount of discussion over the years since Mannich reported the classical reaction of antipyrine (83), formaldehyde and ammonium chloride, Equation 18.

\[
\begin{align*}
3 \text{Ph}-\text{N} & \quad \text{Me} \\
3 \text{HCHO} & \quad + \quad \text{NH}_4\text{Cl} \\
\text{(83)} \\
\downarrow \\
\left[ \begin{array}{c}
\text{Ph}-\text{N} \\
\text{Me} \\
\text{Me} \\
\text{CH}_2 \\
\text{N}\text{HCl} \\
3 \text{H}_2\text{O}
\end{array} \right]
\end{align*}
\]

Equation 18

Despite the extensive investigations and applications of this reaction, no single mechanism has been proposed which accounts for all the experimental evidence. Most of the mechanistic studies conducted so far are concerned with reactions carried out in aqueous or other protic solvents. A general mechanistic pattern has been proposed which fits most observations. The nature of the reactive intermediates involved depends on the pH of the operating medium.
The early mechanistic investigations have been summarised\textsuperscript{4,50}. The possibility that the reaction proceeds through an initial condensation of the substrate with formaldehyde followed by reaction with amine has been discounted on the basis of strong experimental evidence\textsuperscript{51,57}. The initial step of the reaction, therefore, must involve the interaction of formaldehyde with amine forming the carbinolamine (\textsuperscript{84}) which is in equilibrium with the reactants. The shift of the equilibrium depends on the pH of the system. At low pH the formation of iminium salt (\textsuperscript{85}) is favoured which then reacts with a suitable substrate via an $S_{N}1$-type mechanism. At high pH, in the presence of excess secondary amine, the carbinolamine (\textsuperscript{84}) is converted into bis($N,N$-dialkylamino)methane (aminal) (\textsuperscript{86}). If the reaction is carried out in alcoholic medium conversion to alkoxy-$N,N$-dialkylaminomethane (\textsuperscript{87}), (aminol ether) is feasible. The intermediates (\textsuperscript{86}) and (\textsuperscript{87}) may then give substitution products through an $S_{N}2$-type mechanism. Alternatively, in the presence of acid they may be converted to the iminium species (\textsuperscript{85}).

The equilibria are summarised in Scheme 28. The first suggestion that iminium ions are involved in the Mannich reaction, either using classical reagents or aminals under acidic conditions, appeared in a paper in 1949\textsuperscript{52}. An intermediate iminium ion was also postulated in the kinetic studies of the Mannich reaction of ethylmalonic acid\textsuperscript{53}. Different mechanisms were proposed at a later stage\textsuperscript{54}, contradicting the earlier suggestions, for reactions carried out in acidic or basic media.

Although the formation of iminium salts has been suggested at pH's well above pH 7 it is likely that the carbinolamine (\textsuperscript{84}) would be the predominant species present if an iminium ion were produced in the presence of hydroxyl ions. The possibility that the protonated carbinolamine (\textsuperscript{84A}) could function as a Mannich reagent has very
recently been suggested\textsuperscript{5a}. An $S_{N}2$ displacement of water from such a cation at intermediate pHs would be as favourable as the displacement of the poorer leaving group (OH\textsuperscript{-}) by a carbanion from the carbinolamine (84) in reactions carried out at high pH.

\[
\begin{align*}
\text{R}_2\text{NH} + \text{HCHO} & \rightleftharpoons \text{R}_2\text{NCH}_2\text{OH} \quad (84) \\
\text{R}_2\text{NCH}_2\text{OH} & \xrightarrow{\text{i}} \text{R}_2\text{NCH}_2\text{OH}_2 \quad (84a) \\
\text{R}_2\text{NCH}_2\text{NR}_2 & \quad (86) \\
\text{R}_2\text{NCH}_2\text{OR}' & \quad (87)
\end{align*}
\]

\textbf{SCHEME 28}

Reagents (i) H\textsuperscript{+}; (ii) $-\text{H}_2\text{O}$; (iii) $\text{R}_2\text{NH}$; (iv) $\text{R'}\text{OH}$

The preponderance of ortho--versus para--substitution in the Mannich reactions of unhindered phenols\textsuperscript{55} was attributed to the formation of a quasi 6-membered transition state (88), as shown in Scheme 29. Hydrogen
bonding between the phenolic hydrogen and the basic nitrogen of the Mannich reagent brings the reactive methylene carbon into a favourable position for ortho–substitution. New developments in the Mannich reaction of phenols accomplished in this study will be presented in Chapter Two.

A similar hydrogen–bonded complex has been suggested from a series of kinetic studies\(^{56}\) of the reactions of aliphatic nitro–alkanes with aminals in aprotic solvents of low dielectric constants. 2–Nitropropane, for example, in the aci form (89) interacts with an aminal forming the hydrogen–bonded complex (90) which rearranges to form the Mannich base (91) and a molecule of secondary amine, Scheme 30.
The incorporation of the more basic amine in the Mannich product (92) in the reaction of 2-naphthol with the unsymmetrical aminal, 5-bromo-1-piperidylmethylisatin (93)\textsuperscript{50b}, suggests that the stronger base should form more effective hydrogen bonding. The lower steric demand of the piperidyl moiety, as compared to 5-bromoisatin, may also favour the observed pathway, Equation 19.

\textbf{Equation 19}

The co-enzyme tetrahydrofolate (94) functions as a biological one-carbon transfer agent. The mechanism of its conversion into the imidazolidine
derivative \( N(5)-N(10)\)-methylene tetrahydrofolate (95) has been investigated. The reaction was found to be favoured under acidic conditions with rate enhancement observed in the presence of secondary amines such as morpholine and imidazole. The reaction pathway is thought to involve the iminium ion. The Mannich reaction of tetrahydroquinoxaline derivative (96) has also been studied over a broad pH range and an amine, an iminium ion and a protonated amine have been detected in equilibrium, as shown in Scheme 31.

\[
\begin{align*}
\text{(94)} & \quad \text{(95)} & \quad \text{(96)} \\
\end{align*}
\]

SCHEME 31
Reagents (i) HCHO; (ii) H\(^+\); (iii) \(-\text{H}_2\text{O}\); (iv) \(-\text{H}^+\)
The work reported in this thesis concentrates on some new aspects of the Mannich reaction. New reagent systems have been investigated and the possibility of additional mechanistic pathways were uncovered. The results obtained suggest that a range of mechanisms may operate in the Mannich reaction. The choice of reaction conditions depends on the nucleophilicity of the substrate under investigation and also on the electrophilicity of the reactive intermediate involved in the reaction.

Although a considerable amount of work has been carried out in this domain, a great deal of further investigation is required as new developments open the door to a better understanding of the chemistry of this versatile reaction.
2. RESULTS AND DISCUSSION

2.1 Introduction

The objective of this study was to develop new methodologies for the aminoalkylation of a wide range of aromatic substrates using non-aqueous conditions. In the initial stages of an earlier study\textsuperscript{40} it was established that preformed iminium salts can be successfully used for the aminoalkylation of pyrroles in non-aqueous aprotic solvents. It was envisaged that such reactions could be carried out by using "one-pot" procedures without the isolation of the reactive intermediates.

The generation of iminium salts by the reaction of acetyl chloride and aminals\textsuperscript{60}, or trifluoroacetic anhydride with trimethylamine-N-oxide\textsuperscript{61,62} suggested the use of acid chlorides, anhydrides, or Lewis acids for the activation of aminals or aminol ethers.

2.2 Mannich Reagents Derived From Secondary Amines

It was anticipated that aminals and aminol ethers, activated by weak acids, could participate in the Mannich reaction of aromatic compounds without the accumulation of a high concentration of hydrogen chloride.
A variety of methods have been reported in the literature where these reagents are used for the preparation of iminium salts. Iminium fluoroborate is formed by the treatment of an aminal with boron trifluoride in the presence of butyryl fluoride\textsuperscript{63}. \textit{N,N-}Dimethyl-(methylene)iminium iodide (Eschenmoser’s salt)\textsuperscript{22} was prepared by thermal decomposition of the ammonium salt derived from the reaction of trimethylamine with di-iodomethane. A more convenient method involves the reaction of an aminal and iodotrimethylsilane\textsuperscript{64}. On treatment with trichloromethylsilane, aminol ethers also afford the formation of a range of iminium chlorides\textsuperscript{65}. These are more conveniently handled than iodides and can be stored at room temperature for prolonged times under nitrogen if moisture is excluded.

### 2.2.1 Preparation of Aminals

A convenient method described in the literature\textsuperscript{68} resulted in the formation of aminals in good yields. Thus, secondary amines and aqueous formaldehyde were stirred at room temperature, \textit{Equation 20}, to give the aminals (97) shown in Table 1.

\[
2 \text{R}_2\text{NH} + \text{HCHO}_{aq.} \quad \rightarrow \quad \text{R}_2\text{NCH}_2\text{NR}_2 + \text{H}_2\text{O}
\]

\begin{equation}
(97)
\end{equation}

\textit{Equation 20}
### TABLE 1
Preparation of Aminals

<table>
<thead>
<tr>
<th>Amine</th>
<th>Aminal</th>
<th>Structure</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₂NH</td>
<td>97a</td>
<td></td>
<td>89-92</td>
</tr>
<tr>
<td>Et₂NH</td>
<td>97b</td>
<td></td>
<td>82-90</td>
</tr>
<tr>
<td>(CH₂₄)₄NH</td>
<td>97c</td>
<td></td>
<td>72-85</td>
</tr>
<tr>
<td>(CH₂₆)₆NH</td>
<td>97d</td>
<td></td>
<td>76-93</td>
</tr>
<tr>
<td>O(CH₂·CH₂)₂NH</td>
<td>97e</td>
<td></td>
<td>76</td>
</tr>
</tbody>
</table>

2.2.2 Preparation of Aminol Ethers

Aminol ethers were prepared in reasonable yields by following a procedure described in the literature. Anhydrous secondary amines and an excess of dried alcohol were stirred with paraformaldehyde in the presence of potassium carbonate, Equation 21. The products were isolated and purified by distillation and are listed in Table 2. It was observed, however, that in these reactions a higher boiling material was also formed. This resulted in the reduction of the yield of the desired products. In two cases the by-products formed were isolated and characterised by ¹H and ¹³C n.m.r. spectroscopy. It was shown that these were alkoxymethoxy-\(N,N\)-dialkylaminomethanes (98).

\[
\begin{align*}
R₂NCH₂OCH₂OR' & \\
(98) & \\
\end{align*}
\]

\[
\begin{align*}
R₂NH + (CH₂O)_n + R'OH & \xrightarrow{K₂CO₃} R₂NCH₂OR' + H₂O \\
(99) & \\
\end{align*}
\]

Equation 21
TABLE 2
Preparation of Aminol Ethers

<table>
<thead>
<tr>
<th>Aminol ether (99)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₂NCH₂OEt</td>
<td>15</td>
</tr>
<tr>
<td>Me₂NCH₂O¹Pr</td>
<td>15</td>
</tr>
<tr>
<td>Et₂NCH₂OEt</td>
<td>54</td>
</tr>
<tr>
<td>Et₂NCH₂O¹Pr</td>
<td>55</td>
</tr>
<tr>
<td>(CH₂)₄NCH₂OEt</td>
<td>66</td>
</tr>
<tr>
<td>(CH₂)₅NCH₂OEt</td>
<td>57</td>
</tr>
<tr>
<td>O(CH₂·CH₂)₂NCH₂OEt</td>
<td>61</td>
</tr>
<tr>
<td>'PrNCH₂OEt</td>
<td>67</td>
</tr>
</tbody>
</table>

(a) Hexane was added to the reaction mixture to remove excess alcohol as a negative azeotrope.
(b) 19% of Et₂NCH₂OCH₂OEt (98a) was also isolated.
(c) 23% of Et₂NCH₂OCH₂O'Pr (98b) was also isolated.

The formation of such compounds has been reported earlier by the reaction of aminol ethers and paraformaldehyde. The apparent incorporation of a second molecule of formaldehyde into the product may have resulted from the reaction of the carbinol formed, with formaldehyde, before the nucleophilic addition of the alcohol, as shown in Scheme 32. Alternatively they may have been formed from the aminol ethers as stated earlier. These by-products, however, give the same products as the aminol ethers in reactions with aromatic heterocycles.

The competitive formation of aminals as well as aminol ethers in these reactions has previously been reported. It was suggested that increasing the molecular weight and the molar ratio of the primary alcohol promotes an increase in the proportion of the aminol ether formed. The formation of aminals in these reactions was not a major problem due to the large excess of alcohol used.
2.3 Mannich Reactions of Aromatic Heterocycles

The five-membered heterocycles pyrrole, furan, and thiophene, and their benzoderivatives, such as indole, can be regarded as aromatic on the basis of their physical properties and resonance energies. They have an excess of \( \pi \)-electrons as compared to benzene since six electrons are distributed over five atoms and are thus said to be "\( \pi \)-excessive". They are electron-rich and can be attacked by relatively weak electrophiles.
Substitution generally takes place at the 2-position rather than at the 3-position in the unsubstituted five-membered ring systems. This is due to the greater degree of delocalisation of the positive charge in the intermediate cationic species, as shown below.

\[
\begin{align*}
\text{2-Substitution} & \\
\text{3-Substitution}
\end{align*}
\]

\[X = \text{NH, NR, S, O}\]

The introduction of a bulky substituent on the nitrogen of the pyrrole ring, however, promotes the electrophilic attack at the 3-position. Recent developments in this area have been summarised in a comprehensive review. The greatest 3-directing effect of bulky substituents at the 1-position is exerted by the t-butyl group followed by iso-propyl and benzyl groups. A recent study relating to the reactions of N-substituted pyrroles with nitrilium salts has also shown the same trend towards 3-substitution in the presence of bulky 1-substituents.

The benzo fused analogue, indole, undergoes electrophilic substitution at the 3-position because the lowest energy cationic intermediate is stabilised by resonance without involving the adjacent benzene ring. The Mannich reactions of unsubstituted indoles therefore proceed to give aminoalkylation at the 3-position when this is free. The highly substituted indoles, for example N-methyltetrahydrocarbazole, undergoes aminoalkylation on the carbon α-to the 2-position. This reaction
presumably proceeds by a mechanism similar to electrophilic substitution by other electrophiles of highly alkylated indoles, as shown in Scheme 33.

![Scheme 33](image)

**SCHEME 33**

Reagents (i) \((\text{CH}_2)_6\text{NH}, \text{HCHO}, \text{H}^+\); (ii) \(-\text{H}^+\); (iii) \(-\text{(CH}_2)_6\text{N}=\text{CH}_2\)

Only the more nucleophilic \(\pi\)-excessive aromatic heterocycles undergo the Mannich reaction under the classical aqueous acidic conditions. The different experimental conditions needed reflect the changing distribution of \(\pi\)-electron densities. It is reported in the literature that \(N\)-methyl- and \(N\)-ethyl-pyrrole do not react with formaldehyde and amines at room temperature\(^7\). In a different report\(^7\) the use of amine hydrochlorides afforded reasonable yields of aminoalkylated products of \(N\)-methyl- and \(N\)-phenyl-pyrrole at ambient temperatures. Similarly, 2-methylfuran gives a Mannich base using the classical procedures but furan does not\(^7\).
2.3.1 "In Situ" Reactions of N-Methylpyrrole Activated with Acetyl Chloride

Aminals react readily with acetyl chloride in anhydrous ether forming the corresponding iminium chlorides in quantitative yields\textsuperscript{60}, Equation 22.

\[
R_2NCH_2NR_2 + CH_3COCl \xrightarrow{Et_2O, 0}^\circ C R_2N=CH_2 Cl^-
\]

Equation 22

It was envisaged that the reaction of pyrroles with aminals in the presence of acetyl chloride could succeed in one step without the isolation of the iminium salts. This investigation was initially concentrated on N-methylpyrrole because the classical reaction only succeeds using strongly acidic conditions\textsuperscript{73} or preformed iminium salts\textsuperscript{40}. It was found that N-methylpyrrole does not give a Mannich base with bis(N,N-dimethylamino)methane in acetonitrile at room temperature in the absence of an acidic reagent.

A mixture of N-methylpyrrole and an aminal or aminol ether, was treated with acetyl chloride in acetonitrile under nitrogen at 5°C and allowed to warm to room temperature. After a suitable interval the Mannich bases were isolated by an aqueous work-up. An equimolar mixture of reagents afforded some reasonable yields of 2-dialkylaminomethyl-N-methylpyrroles (100), whereas two equivalents of the aminal and acetyl chloride gave the 2,5-disubstituted products (101). The results obtained are summarised in Table 3.
TABLE 3
Reactions of N-Methylpyrrole with Aminals and Aminol Ethers
Activated with Acetyl Chloride

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Time</th>
<th>Product(s) (R₂)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Me₂N)₂CH₂/1 mol</td>
<td>2h</td>
<td>(100); Me₂</td>
<td>18</td>
</tr>
<tr>
<td>[(CH₂)₆N]₂CH₂/1 mol</td>
<td>2h</td>
<td>(100); (CH₂)₆</td>
<td>41</td>
</tr>
<tr>
<td>[O(CH₂·CH₂)₂N]₂CH₂/1 mol</td>
<td>2h</td>
<td>(100); O(CH₂)₄</td>
<td>54</td>
</tr>
<tr>
<td>(CH₂)₆NCH₂OEt/1 mol</td>
<td>6h</td>
<td>(100); (CH₂)₆</td>
<td>9</td>
</tr>
<tr>
<td>O(CH₂·CH₂)₂NCH₂OEt/1 mol</td>
<td>6h</td>
<td>(100); O(CH₂)₄</td>
<td>18</td>
</tr>
<tr>
<td>(Me₂N)₂CH₂/2 mol</td>
<td>5 days</td>
<td>(101); Me₂</td>
<td>0</td>
</tr>
<tr>
<td>(Me₂N)₂CH₂/2 mol</td>
<td>6 days</td>
<td>(101); Me₂</td>
<td>20</td>
</tr>
<tr>
<td>[(CH₂)₆N]₂CH₂/2 mol</td>
<td>6 days</td>
<td>(101); (CH₂)₆</td>
<td>82</td>
</tr>
<tr>
<td>[O(CH₂·CH₂)₂N]₂CH₂/2 mol</td>
<td>6 days</td>
<td>(101); O(CH₂)₄</td>
<td>87</td>
</tr>
</tbody>
</table>

(a) Reagents were mixed at −30°C and kept at −20°C for 6 days.
(b) Yields not optimised.

Although reasonable yields of monosubstitution products (100) were obtained using di(N-piperidyl)methane and di(N-morpholinyldimethane, surprisingly, bis(N,N-dimethylamino)methane gave a poor yield (18%). A similar variation was observed in the 2,5-disubstitution products (101) using two mole equivalents of reagents. In fact bis(N,N-dimethylamino)methane and acetyl chloride (2 equivalents of each) failed to produce the Mannich base at room temperature. The reaction only succeeded in a poor yield (20%) when it was conducted at a lower temperature.
It is believed that the failure of the di-substitution reaction is due to the subsequent reaction of the monosubstitution product with acetyl chloride. The acylammonium salt (102) generated can fragment to \(N,N\)-dimethylacetamide and a benzylic-type cation which can then capture a second molecule of \(N\)-methylpyrrole. This then leads to the formation of \(N,N'\)-dimethyl-2,2'-dipyrrylmethane (103), as shown in Scheme 34.

\[
\begin{align*}
\text{Me} & \quad \text{NMe}_2 \quad \overset{i}{\rightarrow} \quad \text{Me} \quad \overset{\text{Cl}^-}{\rightarrow} \\
\text{Me} & \quad \overset{\text{Me}}{\rightarrow} \quad \text{Me} \quad \overset{\text{Cl}^-}{\rightarrow}
\end{align*}
\]

\(102\)

\[
\begin{align*}
\text{Me} & \quad \overset{i}{\rightarrow} \quad \text{Cl}^- \\
\text{Me} & \quad \overset{\text{Me}}{\rightarrow} \quad \text{Me} \\
\end{align*}
\]

\(103\)

**SCHEME 34**

**Reagents**

(i) \(\text{CH}_3\text{COCl}\); (ii) \(-\text{CH}_3\text{CONMe}_2\); (iii) \(N\)-methylpyrrole; (iv) \(-\text{HCl}\)

Although no attempt was made to isolate this compound from the reaction mixtures, it was prepared separately from the monosubstitution product. Acetyl chloride was added to a mixture of 2-(\(N,N\)-dimethylaminomethyl)-1-methylpyrrole and an excess of \(N\)-methylpyrrole affording, after work-up, the dipyrrylmethane (103) in 75% yield. An attempt to prepare the same compound from the more sterically demanding 2-(\(N\)-piperidylmethyl)-1-methylpyrrole, using the above-mentioned procedure, failed and led to some polymerisation. The only product isolated from the reaction was the starting Mannich base which was recovered in 49% yield.
It became obvious from the results obtained that only the least sterically hindered monosubstitution product can react further with acetyl chloride. Molecular models of the monosubstitution products prepared by these reactions support this theory. The piperidyl and morpholinyl rings present in the products restrict the approach of the incoming acetyl chloride only from the lower face of the molecule. When the N,N-dimethyl group is present the attack can take place from either side of the molecule.

It is noteworthy that in these reactions no precipitate was observed on mixing the reagents. Although the mechanism or mechanisms operating in this system are not clearly established it is possible that free iminium species are not entirely involved. In certain cases where iminium salts are known to participate they appear as precipitates in the reaction mixture. It is, however, possible that the reactive intermediate in the cases using aminol ethers is the acyloxonium salt, (103a). The low yields of Mannich bases obtained in both cases may support this theory. An attempt to form N,N-diethyl(methylene)iminium chloride from ethoxy-N,N-diethylaminomethane and acetyl chloride failed to produce the expected salt within the time required, as in the case of aminals. A crystalline solid was, however, isolated after a long period of time but this appeared different from the desired iminium species. On treatment with 2-methylfuran the uncharacterised solid gave the Mannich base 2-(N,N-diethylamino-methyl)-5-methylfuran in only 15% yield as shown in Scheme 35.

The relatively poor yields of Mannich bases obtained in these reactions also suggested that acetyl chloride may be too strong an acid and the hydrogen chloride generated in the reaction mixture may cause some polymerisation of N-methylpyrrole or the monosubstitution product. It is well known that pyrroles polymerise in the presence of mineral acids.
2.3.2 "In Situ" Reactions of Aromatic Heterocycles Activated by Sulphur Dioxide

The limited success achieved using acetyl chloride as an activating agent in the Mannich reactions of N-methylpyrrole prompted the use of the anhydride, sulphur dioxide, as a non-protic acidic reagent. The reason for the choice of this reagent was its relative mildness and also that the expected by-products would be relatively weak acids, avoiding the generation of hydrogen chloride in the reaction mixture.

In preliminary investigations of the effect of sulphur dioxide on bis(N,N-dimethylamino)methane, no change was observed on the $^{13}$C n.m.r. spectrum in CD$_3$CN over a period of 24 hours. On addition of 1 mole equivalent of N-methylpyrrole, however, the spectrum showed after 1 hour signals that could be assigned to 2-(N,N-dimethylamino-methyl)-1-methylpyrrole and N,N-dimethylaminosulphinate. Preparative scale reactions were carried out by adding an excess of sulphur dioxide (22.4 molar excess) to a mixture of the heterocycle and an...
aminal. Useful yields of monoaminoalkylated derivatives of \( N \)-methylpyrrole and other heterocycles were obtained from a variety of aminals.

Initially the reactions were carried out at low temperature in acetonitrile. It was, however, later realised that sulphur dioxide is quite soluble in the solvent at higher temperatures and that the reactions could also be performed at room temperature. The results obtained are summarised in Table 4 and have been reported in a preliminary communication together with the findings using acetyl chloride\(^7\). The results obtained from these reactions indicate that almost exclusive monoaminoalkylation of the pyrrole ring can be achieved using sulphur dioxide. It is noteworthy that in a concurrent study\(^40,7\) 2-methylfuran reacted with both di(\( N \)-pyrrolidinyl)methane and ethoxy-\( N \)-pyrrolidinylmethane in the presence of sulphur dioxide affording the 5-aminoalkylated products in 34 and 68\% yield respectively. Furan, however, failed to produce the Mannich base in a reaction with ethoxy-\( N \)-pyrrolidinylmethane and sulphur dioxide. The aminal, di(\( N \)-pyrrolidinyl)methane, was isolated in the latter reaction following hydrolytic work-up. This indicates that the intermediate formed between the aminol ether and sulphur dioxide is not electrophilic enough to react with the weakly nucleophilic furan.

As in the reactions using acetyl chloride, the presence of iminium salts was not observed, but clear yellow solutions persisted during the course of the reactions. It is therefore conceivable that the likely reactive intermediates in these reactions may be the dipolar species (104) and (105) rather than the iminium ions.
Reactions of Heterocycles with Aminals in the Presence of Sulphur Dioxide

<table>
<thead>
<tr>
<th>Heterocycle</th>
<th>Aminal</th>
<th>Time (h)</th>
<th>Product(s) (R₂)</th>
<th>Yield(s) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Me-pyrrole</td>
<td>(Me₂N)₂CH₂</td>
<td>2</td>
<td>(100); Me₂</td>
<td>40</td>
</tr>
<tr>
<td>1-Me-pyrrole</td>
<td>(Me₂N)₂CH₂</td>
<td>39</td>
<td>(100); Me₂</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+(101); Me₂</td>
<td>3</td>
</tr>
<tr>
<td>1-Me-pyrrole</td>
<td>(Me₂N)₂CH₂</td>
<td>90</td>
<td>(100); Me₂</td>
<td>56</td>
</tr>
<tr>
<td>1-Me-pyrrole</td>
<td>(Me₂N)₂CH₂</td>
<td>88</td>
<td>(100); Me₂</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+(101); Me₂</td>
<td>4</td>
</tr>
<tr>
<td>1-Me-pyrrole</td>
<td>[(CH₂)₆N]₂CH₂</td>
<td>89</td>
<td>(100); (CH₂)₆</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+(101); (CH₂)₆</td>
<td>7</td>
</tr>
<tr>
<td>1-Me-pyrrole</td>
<td>[O(CH₂·CH₂)₂N]₂CH₂</td>
<td>67</td>
<td>(100); O(CH₂·CH₂)₂</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+(101); O(CH₂·CH₂)₂</td>
<td>10</td>
</tr>
<tr>
<td>1-Me-pyrrole</td>
<td>[(CH₂)₄N]₂CH₂</td>
<td>102</td>
<td>(100); (CH₂)₄</td>
<td>83</td>
</tr>
<tr>
<td>1-Me-indole</td>
<td>(Me₂N)₂CH₂</td>
<td>41</td>
<td>(109); Me₂</td>
<td>81</td>
</tr>
<tr>
<td>Indole</td>
<td>(Me₂N)₂CH₂</td>
<td>72</td>
<td>(108); Me₂</td>
<td>96</td>
</tr>
</tbody>
</table>

(a) The reaction was carried out at -50°C to -10°C allowing the mixture to warm to room temperature before work-up.
(b) The reagents were mixed at -40°C, kept at -22°C and allowed to warm to room temperature before work-up.
(c) The reagents were mixed at -22°C left at that temperature and worked-up without reaching room temperature.
(d) All other reactions were carried out at room temperature.
The results described so far suggest that a number of mechanisms are plausible in the Mannich reactions of aromatic heterocycles. The reactive intermediate in the system depends on the Mannich reagent used, the activating agent and the operating conditions of the reaction. More evidence about this statement will be produced later.

2.3.3 Chlorosilane Derivatives as Activating Agents in "In Situ" Mannich Reactions

In order to improve the applicability of aminoalkylation of aromatic heterocycles in "one-pot" systems, it was decided to use halosilane derivatives as mild acid chlorides. The electrophilicity of halosilanes is known to follow the sequences:

\[
\text{Me}_3\text{SiI} > \text{Me}_3\text{SiBr} > \text{Me}_3\text{SiCl} > \text{Me}_3\text{SiF} \quad \text{and} \\
\text{SiCl}_4 > \text{MeSiCl}_2 > \text{Me}_2\text{SiCl}_2 > \text{Me}_3\text{SiCl}.
\]

As mentioned earlier, iodotrimethylsilane has been used for the generation of Eschenmoser's salt\(^{22}\). More recently, the preparation of iminium chlorides from aminol ethers has been reported using trichloromethylsilane\(^{65}\). These results suggested that an investigation of "in situ" reactions using chlorosilane derivatives would be valuable.

\(^{13}\)C N.m.r. spectroscopy indicated that iminium salts are formed when solutions of aminol ethers in deuterioacetonitrile-sulphur dioxide were treated with trichloromethyl-, dichlorodimethyl-, and chlorotrimethylsilanes. The methylene carbon signal is typically observed as a triplet in the broad band \(^1\)H-decoupled spectrum. For example, it was found that when a solution of ethoxy-\(N,N\)-diethylaminomethane in deuterioacetonitrile-sulphur dioxide was treated with 1 mol. equivalent
of dichlorodimethylsilane, the broad band decoupled $^{13}$C n.m.r. spectrum was immediately changed and showed three resonances at $\delta_c = 12.5$ (s), 55.0 (t, $J=3.5$Hz) and 165.4 (t, $J=13.5$Hz) ppm. On the other hand, although both trichloromethyl- and dichloromethyl-silanes indicated the formation of iminium salts when treated with aminals, chlorotrimethylsilane did not. The addition of 1 mol. equivalent of $N$-methylpyrrole to the solution, however, quickly resulted in the appearance of absorptions due to the formation of the Mannich base $2-(N,N$-dialkylaminomethyl)$-1-$ methylpyrrole, even in the case of aminals and chlorotrimethylsilane.

It is well known that secondary amines can be protected as their trialkylsilyl derivatives and, like the trialkylsilyl derivatives of hydroxy-compounds, can be regenerated by reaction with a nucleophile in the presence of a proton source. The important difference between silylated amines and the analogous hydroxy-compounds relates to the strength of Si-O and Si-N bonds. An indication of the bond strengths reported in the literature$^{77}$ is shown below.

- Si-N bond $320$ kJmol$^{-1}$ in $\text{Me}_3\text{Si-NHSiMe}_3$
- Si-Cl bond $530$ kJmol$^{-1}$ in $\text{Me}_3\text{Si-Cl}$
- Si-O bond $530$ kJmol$^{-1}$ in $\text{Me}_3\text{Si-OMe}$

The lack of iminium salt formation in the reactions of aminals with chlorotrimethylsilane suggests that a low equilibrium concentration of quaternary silylammonium salts (106) is formed which do not break down to the iminium salts, as shown in Equation 23.
In the presence of a nucleophile, however, the unstable quaternary silylammonium salts (106) react rapidly forming the Mannich bases and the trialkylsilylamines. The hydrogen chloride generated in the reaction mixture reacts with these amines forming quaternary silylammonium chlorides which collapse to the free amines and chlorotrimethylsilane. This process is exemplified in Equations (24) and (25). It is known that the majority of quaternary silylammonium salts are unstable except those possessing non-nucleophilic counter ions such as [Co(CO)₄]⁻.

\[
\text{Equation 24}
\]

\[
\text{Equation 25}
\]

It is reasonable to assume that if the above proposed mechanism operates in the reactions using aminals and chlorotrimethylsilane in the presence
of a reasonably strong nucleophile, the reaction should be catalytic with respect to the silane derivative. Initial experiments indicated that this might be the case and a subsequent detailed investigation confirmed this hypothesis.

2.3.3.1 Reactions Using Aminals and Chlorosilane Derivatives

This investigation was initiated by carrying out reactions of \(N\)-methylpyrrole and bis\(N,N\)-dimethylamino)methane in the presence of chlorotrimethylsilane. To an equimolar mixture of the pyrrole and the aminal, chlorotrimethylsilane was added at ca 5°C under nitrogen in acetonitrile. The reaction mixture was then stirred at room temperature for a specified period of time. After work-up it was found that the predominant product was the disubstitution material, \(2,5(\text{bis-}N,N\text{-dimethylaminomethyl})\text{-1-methylpyrrole}\), as shown in Equation 26. It is important to recall that the same system in the presence of acetyl chloride failed to give the product and led to polymerisation.

This reaction system was investigated using a number of aminals under various lengths of time. In all cases the 2,5-disubstitution product was isolated exclusively or predominantly. The use of other heterocycles in such systems was also investigated, affording good yields of the products shown below.

It became apparent from the results obtained that the amount of chlorotrimethylsilane in the reaction mixtures was not important. According to the mechanism proposed earlier, chlorotrimethylsilane can act as a catalyst in the reaction. This possibility was studied in some depth and the results obtained substantiated this argument.
Initially catalytic amounts of chlorotrimethylsilane were added to a mixture of N-methylpyrrole and an aminal in acetonitrile. The mixture was allowed to react at room temperature. Although low yields of both the mono and disubstitution products were isolated these were dramatically improved when the catalytic reactions were performed under reflux in acetonitrile.

![Chemical structures](image)

Equation 26

The use of trichloromethylsilane for the activation of aminals in the reactions of pyrroles was also investigated in some depth. In these cases the monosubstitution product was isolated exclusively. This observation suggested that in this case the Mannich product is formed as the amine hydrochloride, whereas in the case using chlorotrimethylsilane the initial product is formed as the free base. The monosubstitution product, being the free amine is more nucleophilic than the starting material and therefore reacts further affording the 2,5-disubstitution material in higher yields. It is reported\(^7\) that alkylated pyrroles are more reactive towards electrophiles than pyrrole itself. A summary of the results obtained in this investigation are shown in Table 5.
### TABLE 5
Reactions of Aminals with Heterocycles in the Presence of Chlorosilanes

<table>
<thead>
<tr>
<th>Heterocycle</th>
<th>Aminal</th>
<th>Silane*</th>
<th>Time (h)</th>
<th>Product(s)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Me-Pyrrole</td>
<td>(Me₂N)₂CH₂</td>
<td>Me₃SiCl 100</td>
<td>2</td>
<td>(100); Me₂</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ (101); Me₂</td>
<td>40</td>
</tr>
<tr>
<td>1-Me-Pyrrole</td>
<td>(Me₂N)₂CH₂</td>
<td>Me₃SiCl 100</td>
<td>24</td>
<td>(101); Me₂</td>
<td>66</td>
</tr>
<tr>
<td>1-Me-Pyrrole</td>
<td>(Me₂N)₂CH₂</td>
<td>Me₃SiCl 12.5</td>
<td>24</td>
<td>(100); Me₂</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ (101); Me₂</td>
<td>13</td>
</tr>
<tr>
<td>1-Me-Pyrrole</td>
<td>(Me₂N)₂CH₂</td>
<td>Me₃SiCl 5</td>
<td>24</td>
<td>(101); Me₂</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>1-Me-Pyrrole</td>
<td>(Et₂N)₂CH₂</td>
<td>Me₃SiCl 12.5</td>
<td>24</td>
<td>(101); Et₂</td>
<td>78</td>
</tr>
<tr>
<td>1-Me-Pyrrole</td>
<td>[(CH₂)₅N]₂CH₂</td>
<td>Me₃SiCl 12.5</td>
<td>24</td>
<td>(100); (CH₂)₅</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ (101); (CH₂)₅</td>
<td>46</td>
</tr>
<tr>
<td>1-Me-Pyrrole</td>
<td>[(CH₂)₄N]₂CH₂</td>
<td>Me₃SiCl 100</td>
<td>118</td>
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<td>70</td>
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<tr>
<td>1-Me-Pyrrole</td>
<td>[(CH₂)₅N]₂CH₂</td>
<td>Me₃SiCl 12.5</td>
<td>24</td>
<td>(100); (CH₂)₅</td>
<td>61</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>+ (101); (CH₂)₅</td>
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<tr>
<td>1-Me-Pyrrole</td>
<td>[(CH₂)₆N]₂CH₂</td>
<td>Me₃SiCl 100</td>
<td>120</td>
<td>(101); (CH₂)₆</td>
<td>90</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Pyrrole</td>
<td>(Me₂N)₂CH₂</td>
<td>Me₃SiCl 100</td>
<td>24</td>
<td>(107); Me₂</td>
<td>54</td>
</tr>
<tr>
<td>Indole</td>
<td>(Me₂N)₂CH₂</td>
<td>Me₃SiCl 100</td>
<td>65</td>
<td>(108); Me₂</td>
<td>73</td>
</tr>
<tr>
<td>Indole</td>
<td>(Me₂N)₂CH₂</td>
<td>Me₃SiCl 100</td>
<td>91</td>
<td>(108); Me₂</td>
<td>29</td>
</tr>
<tr>
<td>1-Me-Indole</td>
<td>(Me₂N)₂CH₂</td>
<td>Me₃SiCl 100</td>
<td>48</td>
<td>(109); Me₂</td>
<td>59</td>
</tr>
</tbody>
</table>

(a) 100 mol% at room temperature and using catalytic amounts under reflux except (b).  
(b) The reaction were carried out at room temperature.  
(c) Yields based on Mannich reagent-heterocycle ratio = 1:1
The results presented in Table 5 support the theory that chlorotrimethylsilane is regenerated in the reaction mixture in cases where aminals are used. Further evidence that different reactive intermediates may be involved in these reactions was obtained by R.F. Wilkins in a concurrent study. He showed that the less nucleophilic substrate furan affords only 15% of the Mannich base from the reaction of di(N-piperidyl)methane activated by trichloromethylsilane, Equation 27. The reaction proceeds via an iminium salt.

\[
\begin{align*}
\text{(NCH}_2\text{N)} + \text{MeSiCl}_3 & \xrightarrow{\text{CH}_3\text{CN}} \left[ \text{N}^+\text{CH}_2\text{Cl}^- \right] \\
\text{15%} & \quad \text{CH}_3\text{CN} \\
\text{RT} / \text{N}_2 & \rightarrow \text{MeCN} \\
\text{MeCN} & \xrightarrow{} \text{Fur} \\
\end{align*}
\]

Equation 27

2-Methylfuran, on the other hand, although a stronger nucleophile did not give the Mannich base in a reaction with di(N-pyrrolidinyl)methane and chlorotrimethylsilane, but 58% of Mannich base was isolated using dichlorodimethylsilane, as shown in Equation 28.

\[
\begin{align*}
\text{MeF} + \text{MeSiCl}_3 & \xrightarrow{\text{MeCN}} \text{No Reaction} \\
\text{MeSiCl}_2, \text{MeCN} & \rightarrow \text{58%} \\
\end{align*}
\]

Equation 28
This shows that the weaker nucleophiles furan and 2-methylfuran afford the corresponding Mannich bases in systems that can proceed via the iminium salt. The stronger nucleophiles, pyrroles and indoles can, however, react with the least electrophilic intermediates involved affording good yields of Mannich bases.

These observations strengthen the argument that different mechanisms may operate in the reactions involving aminals and chlorosilanes. They also broaden the view that the Mannich reaction may proceed through a variety of different reactive intermediates in addition to iminium species.

2.3.3.2 Reactions Using Aminol Ethers and Chlorosilane Derivatives

As indicated in the earlier preliminary investigations, aminol ethers react with all the chlorosilane derivatives mentioned forming iminium salts. The use of such systems in "in situ" reactions was also investigated with a variety of aromatic heterocycles. Again this investigation began using N-methylpyrrole as the nucleophilic substrate. The reactions were carried out by adding the chlorosilane derivative dropwise to a mixture of the aminol ether and N-methylpyrrole in acetonitrile. After stirring the mixture for a reasonable length of time the products were isolated.

It was noted that in the case of N-methylpyrrole, for example, the predominant product was the monosubstitution Mannich base. This was contrary to earlier results using aminals and further reinforces the argument that in these cases the reaction proceeds through the iminium salt, affording the product as the amine hydrochloride. It is presumed that the hydrochlorides of the monosubstitution products are less nucleophilic than the starting materials, but that the free bases are significantly more reactive than the starting materials.
It is believed that the "in situ" reactions of aromatic heterocycles with aminol ethers in the presence of chlorosilanes follows the pathway shown in Scheme 36. Some representative examples of the reactions carried out are summarised in Table 6. These findings have been reported in a preliminary communication.

\[
\text{R}_2\text{NCH}_2\text{OR}' + \text{Me}_n\text{SiCl}_{4-n} \rightarrow \text{R}_2\text{N}^+\text{CH}_2\text{OR'} \quad \text{Cl}^- \\
\text{Me}_n\text{SiCl}_{4-(n+1)}
\]

\[
\begin{align*}
\text{(i)} & \quad \rightarrow \quad \text{R}_2\text{N}^+\text{CH}_2 \quad \text{Cl}^- \\
\text{(ii)} & \quad \rightarrow \quad \text{Ar}^+\text{CH}_2\text{NR}_2 \quad \text{Cl}^- \\
\text{(iii)} & \quad \rightarrow \quad \text{Ar}^-\text{CH}_2\text{NR}_2 \\
\text{(iv)} & \quad \rightarrow \quad \text{Ar}^-\text{CH}_2\text{NR}_2 \quad \text{Cl}^- \\
\end{align*}
\]

**SCHEME 36**

Reagent (i) -\text{Me}_n\text{SiCl}_{4-(n+1)}-\text{OR}' (ii) \text{ArH} (iii) -\text{HCl} (iv) \text{HCl}

It was considered possible that the hydrogen chloride generated was responsible for the propagation of the reactions, especially when using aminals as reagents. Thus, in order to elucidate the mechanism bis(trimethylsilyl)acetamide, a hydrogen chloride scavenger, was used in a set of duplicate reactions, as shown in Scheme 37. Parallel reactions of \text{N}-methylpyrrole and ethoxy-\text{N}-pyrrolidinylmethane with half an equivalent of bis(trimethylsilyl)acetamide were carried out. In one reaction 10 mol.% of chlorotrimethylsilane was also added. After stirring the mixtures in acetonitrile at room temperature, under nitrogen, for 68 hours the products were isolated. In the case where chlorotrimethylsilane was not added no Mannich base was formed and...
only the aminal was isolated, after hydrolytic workup, in 30% yield. In the other experiment, however, the disubstitution product 2,5-di(N-pyrrolidinylmethyl)-1-methylpyrrole was isolated in 52% yield.

**TABLE 6**

Reactions of Aminol Ethers with Heterocycles in the Presence of Chlorosilanes

<table>
<thead>
<tr>
<th>Heterocycle</th>
<th>Aminol ether</th>
<th>Silane</th>
<th>Time (h)</th>
<th>Product(s) ((R_2))</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Me-Pyrrole</td>
<td>Me₂NCH₂OEt</td>
<td>Me₃SiCl</td>
<td>24</td>
<td>(100); Me₂ + (101); Me₂</td>
<td>21.5</td>
</tr>
<tr>
<td>1-Me-Pyrrole</td>
<td>Et₂NCH₂OEt</td>
<td>Me₃SiCl</td>
<td>24</td>
<td>(100); Et₂ + (101); Et₂</td>
<td>23</td>
</tr>
<tr>
<td>1-Me-Pyrrole</td>
<td>'PrNCH₂OEt</td>
<td>Me₃SiCl</td>
<td>24</td>
<td>(100); 'Pr₂ + (101); 'Pr₂</td>
<td>21</td>
</tr>
<tr>
<td>1-Me-Pyrrole</td>
<td>'PrNCH₂OEt</td>
<td>MeSiCl₃</td>
<td>68</td>
<td>(100); 'Pr₂ + (101); 'Pr₂</td>
<td>42</td>
</tr>
<tr>
<td>1-Me-Pyrrole</td>
<td>(CH₂)₆NCH₂OEt</td>
<td>Me₃SiCl</td>
<td>24</td>
<td>(100); (CH₂)₆ + (101); (CH₂)₆</td>
<td>43</td>
</tr>
<tr>
<td>1-Me-Pyrrole</td>
<td>Et₂NCH₂O'Pr</td>
<td>MeSiCl₃</td>
<td>17</td>
<td>(100); Et₂ + (101); Et₂</td>
<td>67</td>
</tr>
<tr>
<td>1-Me-Pyrrole</td>
<td>Et₂NCH₂OCH₂O'Pr</td>
<td>MeSiCl₃</td>
<td>24</td>
<td>(100); Et₂ + (101); Et₂</td>
<td>55</td>
</tr>
<tr>
<td>1-Me-Indole</td>
<td>Et₂NCH₂O'Pr</td>
<td>MeSiCl₃</td>
<td>20</td>
<td>(109); Et₂</td>
<td>89</td>
</tr>
<tr>
<td>1-Me-Indole</td>
<td>OCH₂-CH₂NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>20</td>
<td>(109); OCH₂-CH₂</td>
<td>93</td>
</tr>
</tbody>
</table>
These results indicate that the powerful silylating agent bis(trimethylsilyl)acetamide failed to activate the aminol ether and therefore the aminoalkylation did not take place. The presence of 10 mol.% of chlorotrimethylsilane, however, was enough to initiate the reaction. The hydrogen chloride produced reacted with the scavenger forming more chlorotrimethylsilane, Equation 29, which assisted in the completion of the reaction.

\[
\text{Me}_3\text{Si}-\text{N}=\text{C}_{\text{Me}}^{\text{O} \text{SiMe}_3} + 2\text{HCl} \rightarrow 2\text{Me}_3\text{SiCl} + \text{Me}-\text{C}^{-}\text{NH}_2
\]

Equation 29

The fact that more than 10% of Mannich product was isolated proves that chlorotrimethylsilane is the activating agent and its regeneration in the reactions of aminals is essential for the reactions to proceed. The monosubstitution product was not isolated because in the absence of hydrogen chloride it was found as the free base, and being more nucleophilic than \(N\)-methylpyrrole reacted faster affording the disubstitution product.
2.3.4 Preliminary Investigation of the Relative Rates of Reactions of 1-Methylpyrrole and 2-Aminoalkylated-1-methylpyrrole Towards Iminium Salts

The results described so far suggest that 2-aminoalkylated-N-methylpyrrole is more nucleophilic than N-methylpyrrole itself. This prompted a quantitative investigation in order to obtain a measurable calculation of the relative rates of the reactions.

Competition experiments were carried out in which a 50 molar excess of both N-methylpyrrole and a monosubstituted Mannich base competed for preformed iminium salt. The ratio of products isolated was determined by Gas Chromatography.

The first experiment, Equation 30, indicated that the Mannich base is about 2.2 times more reactive towards the iminium salt than N-methylpyrrole.

![Equation 30](image)

The second experiment, Equation 31, suggested that the Mannich base is about 9 times more reactive than N-methylpyrrole. These findings support the results obtained from the preparative scale reactions of
N-methylpyrrole with preformed iminium salts\textsuperscript{40} or in "in situ" reactions proceeding via the iminium species. However, these results should be accepted with caution as any mixing effect of the reagents could not be taken into account.

\[
\begin{align*}
\text{NMe} & \quad \text{Me}_2\text{N}=\text{CH}_2 \quad \text{Cl}^- \\
\begin{array}{c}
\text{NMe} \\
\text{Me}
\end{array} & \quad \begin{array}{c}
\text{NMe}_2 \\
\text{Me}
\end{array}
\end{align*}
\]

Equation 31

In order to use the mixed aminoalkylated N-methylpyrrole (110) for calibration purposes it was made in a preparative scale from the monosubstituted Mannich base and preformed iminium salt in 85\% yield, as shown in Equation 32.

\[
\begin{align*}
\text{Me}_2\text{N} & \quad \text{NMe}_2 \\
\text{MeCN}/\text{RT}/\text{N}_2
\end{align*}
\]

Equation 32
2.3.5 Competition Experiments of Heterocycles with Electrophilic Intermediates Generated "In Situ"

In order to establish that different electrophiles are involved in the reactions of aminals and aminol ethers activated by chlorosilanes a series of competition experiments were carried out. It was anticipated that such experiments would avoid any mixing problems of the reagents as the reactive intermediates would be in a very low concentration. Efforts were concentrated on two sets of reagents which showed in the preparative scale reactions that different mechanisms may be operating.

Duplicate experiments were performed where a 50 molar excess of two different heterocycles were allowed to compete for a small amount of the reagents. In the first experiment an aminol ether activated by trichloromethylsilane was used, a system which is known to generate the iminium chloride. In the other experiment an aminal in the presence of chlorotrimethylsilane was used, and thus no formation of iminium species was anticipated.

The different nucleophilicities of aromatic heterocycles have been established for a number of electrophilic systems. Thus, competition data for trifluoroacetylation using trifluoroacetic anhydride at 75°C gave the following relative rates: thiophene (1.0), furan (1.4 x 10^2), 2-methylfuran (1.2 x 10^6), 2-methoxythiophene (9.1 x 10^6), pyrrole (5.3 x 10^7), and N-methylpyrrole (1.0 x 10^9). Similar values were also obtained for reactions using [C_6H_7Fe(CO)_3]^+: thiophene (1.0), furan (3.0 x 10^3), and pyrrole (5.0 x 10^5).

The reactions were carried out by adding the reagent to the mixture of heterocycles which were then allowed to react for two hours in
acetonitrile. The ratio of products isolated was determined by Gas Chromatography and the results obtained are summarised in Table 7.

**TABLE 7**

**Ratio of Products in Competition Experiments**

<table>
<thead>
<tr>
<th>Heterocycle pair</th>
<th>Reagents*</th>
<th>Product ratio(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Me-indole : 2-Me-furan</td>
<td>I</td>
<td>99.9 : 0.1</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>99.2 : 0.8</td>
</tr>
<tr>
<td>2-Me-furan : furan</td>
<td>I</td>
<td>98.8 : 1.2</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>98.8 : 1.2</td>
</tr>
<tr>
<td>1-Me-pyrrole : 1-Me-indole</td>
<td>I</td>
<td>58.5 : 41.5</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>63.5 : 36.5</td>
</tr>
<tr>
<td>1-Me-pyrrole : 1-Me-indole^a</td>
<td>I</td>
<td>57.5 : 42.5</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>55.0 : 45.0</td>
</tr>
<tr>
<td>1-Me-pyrrole : 1-Me-indole^b</td>
<td>I</td>
<td>46.4 : 53.6</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>52.2 : 47.8</td>
</tr>
<tr>
<td>1-Me-pyrrole : 1-Me-indole</td>
<td>MeN=CH2Cl^-</td>
<td>48.9 : 51.1</td>
</tr>
<tr>
<td>1-Me-pyrrole : 2-Me-furan</td>
<td>I</td>
<td>99.0 : 0.1</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>98.75 : 1.25</td>
</tr>
<tr>
<td>2-MeO-thiophene : 2-Me-furan</td>
<td>I</td>
<td>99.1 : 0.9</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>95.9 : 4.1</td>
</tr>
<tr>
<td>2-MeO-thiophene : 2-Me-furan</td>
<td>MeN=CH2Cl^-</td>
<td>97.2 : 2.8</td>
</tr>
</tbody>
</table>

* Reagents (I) MeNCH2OPr/MeSiCl3  
  (II) MeNCH2NMMe2/Me3SiCl

(a) The reactions were performed at -40°C.

(b) The reagents were allowed to react for 1/2 hr before the addition of the mixture of heterocycles.

(c) Preformed iminium salt was used.
The ratio of products obtained in these competition experiments suggested that different intermediates may be involved. A positive conclusion cannot be drawn, however, since either the pair of heterocycles exhibit similar nucleophilicity or the reactivity is far apart. In the latter case this is due to the mildness of electrophilic species involved. It is known that iminium species are relatively weak electrophiles in comparison with trifluoroacetylium ion for example. The most interesting pair of heterocycles used is 2-methoxythiophene and 2-methylfuran. The values quoted for trifluoroacetylation showed that 2-methoxythiophene is about 7.5 times more reactive than 2-methylfuran. In the experiments reported now, using much weaker electrophiles, the reactivity difference increases to about 110 when the iminium species is thought to be involved and to about 23 times in the other system. In contrast to the preparative scale reactions this suggests that the intermediate involved using an aminal and chlorotrimethylsilane is more reactive than the iminium salt. At present the reason for this observation remains obscure. Further investigations in this area are required before a firm conclusion can be drawn.

All the Mannich bases apart from one detected in these experiments were prepared in other investigations. The Mannich base derived from 2-methoxythiophene (110a) was prepared especially for calibration purposes in this study. Treatment of 2-methoxythiophene with preformed iminium salt in acetonitrile at room temperature afforded the product in 93% yield as shown in Equation 33.

\[
\begin{align*}
\text{MeO} & \quad + \quad \text{Me}_2\text{N} = \text{CH}_2 \quad \text{Cl}^- \quad \xrightarrow{\text{MeCN} \quad \text{RT/N}_2} \quad \text{MeO} \\
\text{S} & \quad \quad \quad \quad \quad \quad \quad \text{NMe}_2 \\
\text{93\%} & \quad \quad \quad \quad \quad \quad \quad \text{(110a)}
\end{align*}
\]

Equation 33
2.4 Mannich Reactions of Aryltrialkylstannanes

Aryltrialkylstannanes can be transformed into a variety of compounds with predetermined regiochemistry by means of *ipso* electrophilic addition–with–elimination reactions\(^8^3\). The high polarisability of the carbon–tin bond increases the reactivity of these compounds towards electrophiles as compared with related arenes.

In a previous study\(^8^4\) it was shown that these activated benzenoid systems can participate in the Mannich reaction using preformed \(N,N\)-dimethyl(methylene)iminium chloride, as shown in Equation 34.

\[
\text{ArSnR}_3 + \text{Me}_2\text{N}^+\text{CH}_2\text{Cl}^- \xrightarrow{\text{Reflux, } N_2} \text{ArCH}_2\text{NMMe}_2
\]

Equation 34

Although aryltrialkylsilanes exhibit substantial reactivity towards strong electrophiles, as for example in Friedel–Crafts acylation\(^8^5\), they showed very little or no reactivity towards iminium species.

As an extension of the previous study\(^8^4\) a decision was made to demonstrate the generality of the Mannich reaction using a variety of preformed iminium salts. It was also decided to find out whether the method could be simplified by carrying out "in situ" reactions. This section of work was undertaken in close collaboration with R.F. Wilkins\(^4^0, ^8^6\) and the results presented here are the writer's contribution.
2.4.1 Preparation of Aryltrialkylstannanes

Some of the aryltrialkylstannanes used in this investigation were prepared from Grignard or organolithium reagents by reaction with a trialkyltin chloride, as exemplified in Scheme 38.

![Scheme 38](image_url)

**Scheme 38**

Reagents (i) Mg, THF, Reflux; (ii) n-Bu₃SnCl, THF, Reflux; (iii) n-BuLi, Et₂O, -78°C; (iv) Me₃SnCl, -78°C to r.t.
2.4.2 "In Situ" Reactions of Aryltrialkylstannanes

The main contribution by the writer to this work concentrated on "in situ" reactions using aminol ethers activated by silicon reagents which were thought to proceed via the iminium species. The reactions were carried out in acetonitrile under reflux in view of the fact that better yields were previously obtained at elevated temperatures, as shown in Equation 35 and Table 8.

\[
\begin{align*}
\text{ArSnR}^1_3 + R^2_2 NCH_2 OR^3 + \text{Me}_n \text{SiCl}_{4-n} \\
\text{MeCN, N}_2, \text{Reflux} \\
\text{Ar-CH}_2-\text{NR}^2_2 \\
(111)
\end{align*}
\]

Equation 35
TABLE 8

"In Situ" Reactions of Aryltrialkylstannanes

<table>
<thead>
<tr>
<th>ArSnR₃</th>
<th>Aminol Ether</th>
<th>Silane</th>
<th>Time (h)</th>
<th>Mannich Structure</th>
<th>Base Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-MeO(C₆H₄)SnBu₃</td>
<td>Me₂NCH₂O¹Pr</td>
<td>MeSiCl₃</td>
<td>18</td>
<td>(111a)</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Me₂NCH₂O¹Pr</td>
<td>Me₂SiCl</td>
<td>44</td>
<td>(111a)</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>(CH₂)₄NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>68</td>
<td>(111b)</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>O(CH₂·CH₂)₂NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>44</td>
<td>(111c)</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>¹Pr₂NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>24</td>
<td>(111d)</td>
<td>0</td>
</tr>
<tr>
<td>2,4-di-</td>
<td>O(CH₂·CH₂)₂NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>21</td>
<td>(111e)</td>
<td>60</td>
</tr>
<tr>
<td>MeO(C₆H₄)SnBu₃</td>
<td>Me₂NCH₂O¹Pr</td>
<td>MeSiCl₃</td>
<td>21</td>
<td>(111f)</td>
<td>56</td>
</tr>
<tr>
<td>4-MeO(C₆H₄)SnMe₃</td>
<td>Me₂NCH₂O¹Pr</td>
<td>MeSiCl₃</td>
<td>22</td>
<td>(111a)</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>O(CH₂·CH₂)₂NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>22</td>
<td>(111c)</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>(CH₂)₄NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>22</td>
<td>(111b)</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Et₂NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>22</td>
<td>(111h)</td>
<td>18</td>
</tr>
<tr>
<td>3-thienyl-SnMe₃</td>
<td>Me₂NCH₂O¹Pr</td>
<td>MeSiCl₃</td>
<td>23</td>
<td>(111i)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Me₂NCH₂O¹Pr</td>
<td>MeSiCl₃</td>
<td>91</td>
<td>(111i)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>O(CH₂·CH₂)₂NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>19</td>
<td>(111k)</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>O(CH₂·CH₂)₂NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>89</td>
<td>(111k)</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>(CH₂)₄NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>90</td>
<td>(111l)</td>
<td>38</td>
</tr>
<tr>
<td>PhCH₂SnBu₃</td>
<td>O(CH₂·CH₂)₂NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>21</td>
<td>(111g)</td>
<td>31</td>
</tr>
<tr>
<td>3-MeO(C₆H₄)SnBu₃</td>
<td>O(CH₂·CH₂)₂NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>23</td>
<td>(111j)</td>
<td>28</td>
</tr>
</tbody>
</table>

(a) Yields not optimised
(b) Reactions were carried out at room temperature.

The results presented in Table 8 indicate that there is no difference in the yields observed in reactions involving aryltrimethyl—or the bulkier
aryltributyl-stannanes. This is in accordance with the previous observations\textsuperscript{84} and the effect was attributed to a greater relief of steric strain using the bulkier substituents. It was postulated that the transition states leading to Wheland intermediates (112) and (113) occur at a later stage than in some other electrophilic destannylation reactions. The failure of the reaction using the bulkier ethoxy–N,N-di-iso-propylamino-methane indicates that the reactions may be subject to complex steric features.

Better yields of aminoalkylation products were obtained using substrates possessing electron-donating groups. The more electron-rich compound 2,4-dimethoxyphenyltributylstannane, for example, afforded the highest yields as compared with phenyltributylstannane\textsuperscript{40}, or 3-methoxyphenyltributylstannane.

The moderate yield of the α-phenylethylamine derivative (111g), obtained from benzyltributylstannane, suggested that an alternative route to these useful compounds may be available. It was also observed by M.S. Cooper in a previous study\textsuperscript{84} that benzyltributylstannane reacts with preformed iminium salt in dichloromethane under reflux, affording a reasonable yield of \(N,N\)-dimethyl-α-phenylethylamine (114), as shown in Equation 36.
The mechanism involved in the reactions of benzyltributylstannanes is not obvious. Electrophilic cleavage of benzyl–tin bonds is less common than aryl–tin cleavage and requires strong electrophiles such as acids or mercury (II) salts. Attempts to elucidate the mechanism of this reaction failed to produce firm evidence. The addition of fluoride ion did not have a catalytic effect excluding therefore the involvement of an intermediate with anionic character. Similarly, no evidence for a benzyl radical was obtained when the reaction was irradiated with ultra violet light, or conducted in the presence of AIBN in degassed solvent, or by passing a stream of oxygen through the reaction mixture. It is known that allyl- and benzyl-silanes react with pyrrolidinium salts by a photochemical process that is thought to involve electron transfer from the silane to the iminium salt.

The most important results are the regiospecific aminoalkylation–destannylation reactions of 3-thienyltrimethylstannane. It was reported earlier that 3-((N,N-dimethylaminomethyl)thiophene (115) can be obtained from the reaction of preformed iminium salt and the thienyl derivative in dichloromethane at room temperature. The 2-substituted analogue (116), however, is obtained on treatment of thiophene with the iminium salt in dichloromethane or acetonitrile under reflux, as shown in Equations 37 and 37a.
This regiospecificity was extended by the formation of 3-(N-morpholinylmethyl)- and 3-(N-pyrrolidinylmethyl)-thiophenes. The procedure was also simplified by generating the iminium species "in situ". The reaction could be performed at room temperature over a few days or accelerated under reflux. The most interesting feature of these reactions is the controlled regioselectivity observed since reactions with very strong electrophiles might have resulted in a mixture of products. It is reported in the literature\textsuperscript{90} that 3-thienyl- and 2-thienyl-trimethylsilanes undergo Friedel-Crafts acylation at the 5-position.
2.4.3 Reactions of Aryltrialkylstannanes with Preformed Iminium Salts

A number of reactions were also carried out using preformed iminium chlorides in order to compare the results from "in situ" reactions. The results obtained are disclosed in Table 9.

\[
\text{ArSnR}_3^1 + R_2^+ N=CH_2 \text{Cl}^- \xrightarrow{\text{CH}_3\text{CN}} \text{ArCH}_2\text{NR}_2^2
\]

(Equation 38)

<table>
<thead>
<tr>
<th>ArSnR₃¹</th>
<th>Iminium Salt</th>
<th>Time (h)</th>
<th>Temp.</th>
<th>Mannich Base Structure</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-di-MeO(C₆H₅)SnBu₃</td>
<td>O(CH₂₂CH₂)₂ (CH₂₄)</td>
<td>23</td>
<td>Reflux</td>
<td>(111e)</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23</td>
<td>Reflux</td>
<td>(111m)</td>
<td>18</td>
</tr>
<tr>
<td>3-thienyl-SnMe₃</td>
<td>O(CH₂₂CH₂)₂ (CH₂₄)</td>
<td>19</td>
<td>Reflux</td>
<td>(111k)</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>94</td>
<td>r.t.</td>
<td>(111k)</td>
<td>59</td>
</tr>
<tr>
<td>4-MeO(C₆H₄)SnMe₃</td>
<td>¹Pr₂</td>
<td>24</td>
<td>Reflux</td>
<td>(111d)</td>
<td>0</td>
</tr>
<tr>
<td>3-MeO(C₆H₄)SnMe₃</td>
<td>O(CH₂₂CH₂)₂ (CH₂₄)</td>
<td>19</td>
<td>Reflux</td>
<td>(111j)</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19</td>
<td>Reflux</td>
<td>(111n)</td>
<td>13</td>
</tr>
</tbody>
</table>
A reasonable correspondence of yields of products were obtained in these reactions as compared to "one-pot" procedures. This was in slight contrast to the observations made by R.F. Wilkins in reactions using less nucleophilic substrates such as phenytributylstannane. Higher yields were obtained using preformed iminium salts as opposed to "in situ" conditions. It was assumed that the Mannich bases formed might be partly destroyed by the chlorosilane present, or any exchange of trialkyltin with trialkylsilyl residue could reduce the reactivity of the substrates. Alternatively, an interaction between the Mannich reagent and aryltrialkylstannane may inhibit the formation of the electrophile.

The use of aryltrialkylstannanes in the Mannich reaction increases the number of nucleophilic substrates capable of undergoing the reaction. It is reported that benzenoid compounds less reactive than $m$-dimethoxybenzene do not undergo the Mannich reaction. The regioselectivity obtained demonstrates that the introduction of an aminomethyl residue in a position that is normally unfavourable is possible. This is particularly demonstrated in the reactions of $3$-methoxyphenyltributylstannane, where substitution occurs at the position meta to the methoxy group, and also for $3$-thienyl derivatives.

2.5 Mannich Reactions of Phenols

The Mannich reaction of phenols has been extensively studied over the years. The precise reaction conditions needed depend on the nucleophilicity of the phenol under investigation and also on the amine used. The introduction of the aminomethyl group usually occurs at the ortho-position. The resulting increase of electron density on the ring may lead to polysubstitution which is reminiscent of Friedel–Crafts alkylation. Phenol, for example, when heated at ca $60^\circ$C for 2 hours with
dimethylamine and aqueous formaldehyde produces the 2,4,6-triaminoalkylated product\textsuperscript{92} in 86\% yield.

A recent investigation\textsuperscript{93} of the reactions of 3-pentadecylphenol with formaldehyde and a number of secondary amines revealed the stepwise introduction of dialkylaminomethyl-groups. It was shown that substitution occurs first at the 6-position then at the 4-position and then more slowly at the 2-position. An enhancement in the rates of reactions of various phenols was observed by increasing the amount of water in the medium. Phase transfer catalysis was suggested in the cases where two phase systems were present, because the rate increase was considerably greater than the expected effect due to the greater polarity of the medium. The involvement of an aminal as the reactive intermediate and the effect of water for the possible formation of an expanded cyclic transition state (117)\textsuperscript{93} was suggested, as shown in Equation 39.

![Equation 39](image)

The mechanism of the reaction has been the subject of many investigations\textsuperscript{50}. The condensation of 2,4-dimethylphenol with morpholine and formaldehyde at pH 9–10.45 supports the view that di(N-morpholinyI)methane is the intermediate in the reaction\textsuperscript{65b}. 
Similarly, di(N-piperidyl)methane\textsuperscript{94} has been shown to react with 4-methyltropolone in ethanolic solution affording the 7-substitution product (118), as shown in Equation 40.

\[\begin{align*}
\text{4-methyltropolone} + \text{N-piperidylmethane} & \xrightarrow{\text{EtOH reflux}} \text{(118)} \\
\end{align*}\]

Equation 40

The reaction of 2-naphthol with ethoxy-N-piperidylmethane in dioxan is the only previously reported case of an aminol ether being used in a non-protic solvent\textsuperscript{96}.

It has been suggested\textsuperscript{50b} that the ortho-aminalkylation of phenols may be compared with the Claisen rearrangement of allyl ethers rather than a normal electrophilic addition–with–elimination process. If that is the case, the reaction then proceeds a concerted intermolecular rearrangement, as shown in Scheme 39.

\[\begin{align*}
\text{SCHEME 39} \\
\text{Reagents (i) } R_2\text{NCH}_2\text{OR}^1; \text{ (ii) } -R^1\text{OH} \\
\end{align*}\]
An attempt to investigate this possibility was undertaken in this study. Treatment of mesitol with ethoxy-\(N\)-piperidylmethane in acetonitrile failed to produce mesitoxy-\(N\)-piperidylmethane (119), as expected from that proposal, Equation 41.

![Chemical structure (119)](image)

Equation 41

The method has been used to effect nuclear methylation of phenols and naphthols\(^{96}\) by hydrogenolysis of the Mannich products. For example 4-methoxy-2,6-dimethylphenol\(^{97}\) was obtained from the 2,6-diaminoalkylated Mannich base derived from hydroquinone monomethyl ether via hydrogenolysis catalysed by copper chromite. More recently deamination of phenolic Mannich bases has been carried out using tri-\(n\)-butyltin hydride at elevated temperatures\(^{98}\).

The preparation of a wide range of aminoalkylated phenols as potential antimalarial agents has been reported\(^{99}\).

The use of phenolic Mannich bases derived from common amino acids has been investigated in connection with the preparation of certain heterocyclic compounds\(^{100}\). Thus, condensation of sarcosine (\(N\)-methylglycine) with 2,4-dimethylphenol and formaldehyde in ethanol affords the Mannich base (120) which can be lactonised to the benzoazepinone derivative (121), by thionyl chloride, Equation 42. 2,6-Dimethoxyphenol, however, under the same conditions forms the Mannich base (122) which, in the presence
of sulphuric acid undergoes cyclization with demethylation producing the dihydroisoquinolone derivative (123), Equation 42a.

\[
\begin{align*}
\text{MeOH} & \quad \xrightarrow{\text{MeNHCH}_2\text{CO}_2\text{H}, \text{PhCH}_2, \text{EtOH}, \text{Reflex.}} \quad \text{MeO} \\
& \quad \xrightarrow{\text{SOCl}_2} \quad \text{MeO} \\
& \quad \xrightarrow{\text{H}_2\text{SO}_4\text{aq., heat}} \quad \text{MeO}
\end{align*}
\]

Equation 42

The reactions of phenols reported in this thesis are mainly concerned with an investigation of the effect of sulphur dioxide in Mannich reactions carried out under non-aqueous conditions. The results obtained are now discussed.
2.5.1 The Effect of Sulphur Dioxide in the Mannich Reactions of Phenols

Following the successful use of sulphur dioxide in the aminoalkylation of aromatic heterocycles, it was anticipated that this methodology could be extended to phenols. The initial reactions were also carried out by adding a large excess (22 mol. excess) of sulphur dioxide to a mixture of the phenol and an aminal or aminol ether in acetonitrile at room temperature. Parallel reactions were also carried out in the absence of sulphur dioxide in order to examine the relative acidity of the phenols and to monitor the effect of sulphur dioxide in the reaction.

In the initial experiments dichloromethane was used as the organic solvent for the extractions during aqueous work-up. It was found, however, that in some cases it could extract the amine hydrochloride of the Mannich base from the acidic aqueous layer. Ether was a better solvent for extraction and afforded better isolated yields of the Mannich bases.

Phenol, in reactions with aminals in the absence of sulphur dioxide, produced only the 2-aminoalkylated product (124) in low yields, whereas in the presence of sulphur dioxide the 2,4-diaminoalkylated phenol (125) was also formed as a minor product, as shown in Equation 43 and Table 10.

\[
\begin{align*}
\text{Ph} & \quad \text{+} \quad R_2\text{NCH}_2\text{NR}_2 \quad \text{or} \quad R_2\text{NCH}_2\text{OR} \quad \xrightarrow{\text{MeCN, SO}_2} \quad \text{Ph} \quad \text{+} \quad R_2\text{NCH}_2\text{NR}_2 \\
\text{(124)} & \quad \text{(125)}
\end{align*}
\]

Equation 43
TABLE 10
Reactions of Phenol

<table>
<thead>
<tr>
<th>Reagent</th>
<th>SO₂ (mol. ratio)</th>
<th>Time/h</th>
<th>Yields (%) (124)</th>
<th>Yields (%) (125)</th>
<th>%S.M. Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Me₂N)₂CH₂</td>
<td>22</td>
<td>42</td>
<td>47</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>41</td>
<td>14</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>[(CH₂)₆N]₂CH₂</td>
<td>22</td>
<td>42</td>
<td>48</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>41</td>
<td>18</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>(CH₂)₅NCH₂OEt</td>
<td>22</td>
<td>43</td>
<td>51</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>43</td>
<td>62</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Et₂NCH₂OEt</td>
<td>0</td>
<td>69</td>
<td>46</td>
<td>0</td>
<td>53</td>
</tr>
</tbody>
</table>

A number of Mannich bases (126) were also prepared from 2,4-dimethylphenol as shown in Equation 44 and summarised in Table 11.

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

\[ + \quad \text{R}_2\text{NCH}_2\text{NR}_2 \quad \text{Me}_2\text{NCH}_2\text{OR'} \quad \text{Me}_2\text{NCH}_2\text{OEt} \quad \text{Me}_2\text{NCH}_2\text{OR'} \quad \text{SO}_2 \quad \rightarrow \]

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

\[
\text{NR}_2
\]

\[
(126)
\]

Equation 44

The reactions of phenol and 2,4-dimethylphenol indicated that although aminals gave low yields of Mannich bases, the yields were significantly improved when sulphur dioxide was added to the reaction mixture. Sulphur dioxide did not, however, produce a dramatic effect in the reactions using aminol ethers.
### TABLE 11
Reactions of 2,4-Dimethylphenol

<table>
<thead>
<tr>
<th>Reagent</th>
<th>( \text{SO}_2 ) \text{(mol. ratio)}</th>
<th>Time/h</th>
<th>Yields (%) ( \text{(126)} )</th>
<th>%S.M. Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>((\text{Me}_2\text{N})_2\text{CH}_2)</td>
<td>22, 22, 0, 1.1 (^a)</td>
<td>114, 41, 42, 42</td>
<td>44, 59, 19, 40</td>
<td>40, 24, 78, 55</td>
</tr>
<tr>
<td>(\text{Me}_2\text{NCH}_2\text{NMe}_2) ((1.5\text{mol})^b)</td>
<td>22</td>
<td>42</td>
<td>62</td>
<td>34</td>
</tr>
<tr>
<td>(\text{[(CH}_2)_5\text{N}]_2\text{CH}_2)</td>
<td>22, 0</td>
<td>42, 42</td>
<td>68, 27</td>
<td>25, 67</td>
</tr>
<tr>
<td>((\text{Et}_2\text{N})_2\text{CH}_2)</td>
<td>22, 0</td>
<td>42, 42</td>
<td>72, 40</td>
<td>20, 54</td>
</tr>
<tr>
<td>(\text{Et}_2\text{NCH}_2\text{OEt})</td>
<td>22, 0</td>
<td>42, 42</td>
<td>52, 51</td>
<td>46, 46</td>
</tr>
</tbody>
</table>

\(^a\) Reduced amount of \(\text{SO}_2\) was used.  
\(^b\) 1.5 Molar excess of aminal used.

It can be concluded that phenol and 2,4-dimethylphenol are not acidic enough to activate an aminal. In the presence of sulphur dioxide, however, the generation of a dipolar species such as \(104\) is implicated and this accounts for the increased electrophilicity of the reagent, which affords moderate yields of Mannich bases.

Although initial n.m.r. experiments indicated that both aminals and aminol ethers, are relatively stable in the presence of sulphur dioxide at low temperatures, this is not the case at higher temperatures. Indeed later n.m.r. experiments have confirmed that aminals and aminol ethers react with
sulphur dioxide at and especially above room temperature. It is possible that some of the Mannich reagent may have been destroyed by sulphur dioxide.

As mentioned earlier a Mannich reaction of 2-naphthol in a non-protic solvent has been reported. The effect of sulphur dioxide in this reaction, Equation 45, has been investigated briefly. The results obtained are given in Table 12.

![Equation 45](image)

**Equation 45**

<table>
<thead>
<tr>
<th>TABLE 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactions of 2- Naphthol</td>
</tr>
<tr>
<td>Reagent</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>[(CH₂)₅N]₂CH₂</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>(CH₂)₅NCH₂OEt</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
As expected, substitution took place exclusively at the 1-position due to the lower activation energy of the transition state involved. The yields of the product obtained indicated that sulphur dioxide does not enhance the reactivity of 2-naphthol in these systems. 2-Naphthol is sufficiently nucleophilic to initiate the reaction even with aminals in a non-protic solvent. The stability of the phenoxide anion, due to extended delocalisation of the negative charge, may contribute to this observation.

2.5.2 The Mannich Reaction of 2,5-Dimethylphenol

2,5-Dimethylphenol is undoubtedly the best phenol for investigation of regioselectivity in the Mannich reaction. It has two activated positions for aromatic electrophilic substitution, since an ortho- and the para-position are vacant.

It is reported in the literature\textsuperscript{101} that under classical aqueous conditions aminoalkylation takes place exclusively at the para-position, although this result is questioned in Hellman and Opitz's book\textsuperscript{3}. Two reactions of 2,5-dimethylphenol under such conditions were repeated and were shown to give predominantly the para-substitution product (128) together with small amounts of the 2,4-disubstitution product (129), as shown in Equation 46 and Table 13.

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \quad \text{HCHOaq} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{Me} & \quad \text{NR}_2
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{Me} & \quad \text{NR}_2
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{Me} & \quad \text{NR}_2
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{Me} & \quad \text{NR}_2
\end{align*}
\]

Equation 46
The effect of sulphur dioxide in the Mannich reaction of 2,5-dimethylphenol in non-aqueous aprotic conditions has been investigated in some depth. As in the reactions of other phenols mentioned earlier, the reactions were initially carried out by adding a 22 molar excess of sulphur dioxide to a mixture of the reagent and 2,5-xylenol in acetonitrile at room temperature. Again duplicate reactions were also carried out in the absence of sulphur dioxide. In each reaction three products were isolated, indicating that aminoalkylation took place at both the ortho- and para- positions, Equation 47 and Table 14.

![Chemical structures and equations](image)
TABLE 14
Reactions of 2,5-Dimethylphenol in the Absence or Excess of SO₂

<table>
<thead>
<tr>
<th>Reagent</th>
<th>SO₂ (mol. ratio)</th>
<th>Time/h</th>
<th>Aminoalkylation Yields (%)</th>
<th>%S.M. Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>[(CH₂)₅N₂CH₂</td>
<td>22</td>
<td>42</td>
<td>40 7 21</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>43</td>
<td>24 24 10</td>
<td>40</td>
</tr>
<tr>
<td>(Et₂N)₂CH₂</td>
<td>22</td>
<td>43</td>
<td>42 2 4</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>44</td>
<td>22 38 20</td>
<td>19</td>
</tr>
<tr>
<td>(CH₂)₅NCH₂OEt</td>
<td>22</td>
<td>42</td>
<td>18 25 31</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>43</td>
<td>17 51 16</td>
<td>11</td>
</tr>
<tr>
<td>Et₂NCH₂OEt</td>
<td>22</td>
<td>45</td>
<td>25 9 17</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>45</td>
<td>12 31 10</td>
<td>42</td>
</tr>
</tbody>
</table>

It was noticed, however, that the presence of sulphur dioxide in the reaction mixture promoted ortho-aminoalkylation (130) at the expense of the para-position. This suggested that sulphur dioxide exerts a regioselective effect towards reaction at the 2-position. The regioisomers may easily be identified by ¹H n.m.r. spectroscopy and it was shown that they were not formed reversibly. Each product was allowed to stand at room temperature in acetonitrile in the presence or absence of sulphur dioxide for a few days. After removing the solvent in vacuo the product was isolated unchanged and no isomerisation was detected by ¹H n.m.r. spectroscopy.

An indication that the amount of sulphur dioxide could be reduced without affecting the outcome of the reaction was obtained using 2,4-dimethylphenol (Table 11). It was decided, therefore, that the reaction conditions should be altered. The amount of sulphur dioxide was reduced and was
added to 2,5-xylenol 24 hours prior to the addition of the Mannich reagent. It was envisaged that the phenol would interact with sulphur dioxide forming a half-sulphite ester (131). Reaction of (131) with the Mannich reagent would form an aminol ester (132) which could collapse, with the loss of sulphur dioxide, as shown in Scheme 40, to afford exclusively the ortho-aminoalkylation product (130).

\[
\begin{align*}
\begin{array}{c}
\text{(130)} \\
\text{SCHEME 40}
\end{array}
\end{align*}
\]

Reagents (i) \( \text{SO}_2 \); (ii) \( \text{R}_2 \text{NCH}_2 \text{OR} \), \( \text{ROH} \) or \( \text{(R}_2 \text{N})_2 \text{CH}_2 \), \( \text{R}_2 \text{NH} \); (iii) \( \text{SO}_2 \)

A number of reactions were carried out with various molar ratios of sulphur dioxide and Mannich reagents. The reactions were performed at room temperature in dry acetonitrile or under reflux. These findings are summarised in Table 15.
<table>
<thead>
<tr>
<th>Reagent</th>
<th>(Mol.)</th>
<th>SO₂ (mol. ratio)</th>
<th>Time (h)</th>
<th>Temp.</th>
<th>Aminoalkylation Yields (%)</th>
<th>%S.M. Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Et₂N)₂CH₂</td>
<td>(1)</td>
<td>1.1 42 r.t.</td>
<td>18 18%</td>
<td></td>
<td>6 trace 74</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.1 44 -22°C</td>
<td>25 0</td>
<td></td>
<td>7 trace 72</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 42 reflux</td>
<td>40 0</td>
<td></td>
<td>6 trace 53</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.1 42 r.t.</td>
<td>25 5</td>
<td></td>
<td>7 trace 65</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.1 42 reflux</td>
<td>8 0</td>
<td></td>
<td>0 trace 87</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.1 2 reflux</td>
<td>17 0</td>
<td></td>
<td>0 trace 78</td>
<td></td>
</tr>
<tr>
<td>(Et₂N)₂CH₂</td>
<td>(2)</td>
<td>2.2 42 r.t.</td>
<td>12 4</td>
<td></td>
<td>4 trace 75</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 2 reflux</td>
<td>10 0</td>
<td></td>
<td>2 trace 87</td>
<td></td>
</tr>
<tr>
<td>Et₂NCH₂OEt</td>
<td>(1)</td>
<td>1.1 42 r.t.</td>
<td>31 0</td>
<td></td>
<td>15 trace 54</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.1 2 reflux</td>
<td>21 0</td>
<td></td>
<td>0 trace 71</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.1 4 reflux</td>
<td>25 0</td>
<td></td>
<td>0 trace 68</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.4 42 reflux</td>
<td>40 0</td>
<td></td>
<td>15 trace 44</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 2 reflux</td>
<td>19 28</td>
<td></td>
<td>4 trace 33</td>
<td></td>
</tr>
<tr>
<td>Et₂NCH₂OEt</td>
<td>(2)</td>
<td>2.2 42 reflux</td>
<td>31 0</td>
<td></td>
<td>21 trace 40</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 2 reflux</td>
<td>66 d</td>
<td></td>
<td>0 trace 30</td>
<td></td>
</tr>
<tr>
<td>[(CH₂)₆N]₂CH₂</td>
<td>(1)</td>
<td>1.1 20 days -22°C</td>
<td>6 9</td>
<td></td>
<td>4 trace 62</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.1 42 r.t.</td>
<td>26 7</td>
<td></td>
<td>8 trace 56</td>
<td></td>
</tr>
<tr>
<td>[(CH₂)₆N]₂CH₂</td>
<td>(2)</td>
<td>2.2 2 reflux</td>
<td>20 0</td>
<td></td>
<td>36 trace 43</td>
<td></td>
</tr>
<tr>
<td>(CH₂)₆NCH₂OEt</td>
<td>(1)</td>
<td>0.5 2 reflux</td>
<td>31 33</td>
<td></td>
<td>15 trace 16</td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td></td>
<td>2.2 2 reflux</td>
<td>48 0</td>
<td></td>
<td>37 trace 5</td>
<td></td>
</tr>
<tr>
<td>(1.5)</td>
<td></td>
<td>2.2 1 reflux</td>
<td>57 0</td>
<td></td>
<td>26 trace 3</td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td></td>
<td>2.2 2 reflux</td>
<td>44 0</td>
<td></td>
<td>38 trace 13</td>
<td></td>
</tr>
<tr>
<td>(1.5)</td>
<td></td>
<td>2.2 0.5 reflux</td>
<td>58 0</td>
<td></td>
<td>26 trace 5</td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td></td>
<td>2.2 0.5 reflux</td>
<td>67 0</td>
<td></td>
<td>19 trace 15</td>
<td></td>
</tr>
<tr>
<td>(1.5)</td>
<td></td>
<td>1.6 0.5 reflux</td>
<td>56 0</td>
<td></td>
<td>25 trace 15</td>
<td></td>
</tr>
<tr>
<td>[(OCH₂·CH₂)₆N]₂CH₂</td>
<td>(2)</td>
<td>2.2 2 reflux</td>
<td>27 10</td>
<td></td>
<td>0 trace 62</td>
<td></td>
</tr>
<tr>
<td>Reagent</td>
<td>(Mol)</td>
<td>SO₂ (mol. ratio)</td>
<td>Time (h)</td>
<td>Temp.</td>
<td>Aminoalkylation Yields (%)</td>
<td>%S.M.</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------</td>
<td>------------------</td>
<td>----------</td>
<td>-------</td>
<td>---------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>O(CH₂CH₂)₂NCH₂OEt</td>
<td>(1)</td>
<td>4.4</td>
<td>68</td>
<td>r.t.</td>
<td>44</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>(2)</td>
<td>2.2</td>
<td>2</td>
<td>reflux</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>(1.5)</td>
<td>1.6</td>
<td>0.5</td>
<td>reflux</td>
<td>49</td>
<td>3</td>
</tr>
<tr>
<td>[(CH₂)₄N]₂CH₂</td>
<td>(2)</td>
<td>2.2</td>
<td>2</td>
<td>reflux</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>(CH₂)₄NCH₂OEt</td>
<td>(2)</td>
<td>2.2</td>
<td>2</td>
<td>reflux</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(1.5)</td>
<td>1.6</td>
<td>0.5</td>
<td>reflux</td>
<td>31</td>
<td>0</td>
</tr>
</tbody>
</table>

(a) Addition of sulphur dioxide last, i.e. to a mixture of the phenol and the aminal.
(b) Addition of sulphur to the aminal 24 hours prior to addition of 2,5-dimethylphenol.
(c) Control experiment-- to test the effect of refluxing without SO₂
(d) Complete regioselectivity achieved.

Although some attempt was made to optimise certain of the reactions further improvements may still be possible. The best conditions attained involved initial reaction of the phenol with 2.2 mol. equivalents of sulphur dioxide at room temperature, followed by the addition of a 2 molar excess of an aminal ether, and then heating the mixture briefly under reflux in acetonitrile. Aminals gave inferior yields to aminol ethers. It is possible that as the temperature is raised both aminals and aminol ethers are converted by sulphur dioxide into products that cannot function as Mannich reagents. This effect may relate, for example, to the rearrangement of the dipolar species (104) and (105) to products in which the carbon–sulphur bond is formed, as shown below:

\[
\begin{align*}
R₂NCH₂ NR₂ & \rightarrow R₂NCH₂ NR₂ \\
\text{(104)} \\
R₂NCH₂ OR' & \rightarrow R₂NCH₂ OR' \\
\text{(105)}
\end{align*}
\]
Such a rearrangement would resemble the formation of bisulphite adducts from aldehydes and ketones and aminomethanesulphonic acids\textsuperscript{164}.

The results obtained show that regioselectivity may be achieved in the presence of sulphur dioxide. These findings also support the theory that a number of mechanisms may be involved in the Mannich reactions of phenols. These developments have been reported in a preliminary communication\textsuperscript{102}.

In order to substantiate the proposed mechanism (Scheme 40) attempts were made to isolate and characterise the intermediates involved. An attempt to isolate the half-sulphite ester (131) from the reaction of 2,5-dimethylphenol and sulphur dioxide failed. A liquid initially isolated proved very unstable collapsing into a solid within a few minutes. In another experiment, Equation 48, treatment of the intermediate with diazomethane resulted in the methyl ester (133) being detected in the crude reaction mixture after removal of the solvent \textit{in vacuo}. The methyl group of the half-sulphinate ester appeared as a singlet at $\delta=3.63$ ppm in the $^1$H n.m.r. spectrum.

\begin{equation}
\begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array} \quad \text{CH}_3\text{CH}_2\text{SO}_2 \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array} \quad \text{CH}_2\text{N} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array}
\end{equation}

\textbf{Equation 48}
A recent report\(^8\) claims that preformed iminium salts can be used in the presence of potassium carbonate in aprotic solvents for regioselective ortho-aminooalkylation of mono-substituted electron-rich phenols such as ortho-cresol and 2-t-butylphenol. It was suggested by the authors\(^8\) that solid-liquid phase transfer conditions exist in such systems, and that the reactions proceed via a reactive "ion-pair", as shown in Scheme 41, which collapses to give ortho-aminooalkylation products.

The reactions of 2,5-dimethylphenol with preformed \(N\)-piperidylmethyleneiminium chloride in different solvents under the conditions suggested\(^8\) gave a mixture of products, as shown in Equation 49 and Table 16.
\[
\begin{array}{c}
\text{Me} \quad \text{OH} \\
\text{Me} \quad \text{Me}
\end{array}
\quad + \quad
\begin{array}{c}
\text{N}^{+}\text{CH}_{2}\text{Cl}^{-}
\end{array}
\]

\[
\text{Solvent, } \text{K}_2\text{CO}_3, \text{ r.t.}
\]

\[
\begin{array}{c}
\text{Me} \quad \text{OH} \quad \text{N} \\
\text{Me} \quad \text{Me} \\
(130a)
\end{array}
\quad + \quad
\begin{array}{c}
\text{Me} \quad \text{OH} \quad \text{N} \\
\text{Me} \\
(128a)
\end{array}
\quad + \quad
\begin{array}{c}
\text{Me} \quad \text{OH} \quad \text{N} \\
\text{Me} \\
(129a)
\end{array}
\]

Equation 49

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Time/h</th>
<th>Yield(%)</th>
<th>% S.M. Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>6</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>10</td>
<td>2</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>6</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23</td>
</tr>
</tbody>
</table>

There is no previous report of the use of 2,5-dimethylphenol under such conditions. If the mechanism proposed recently\textsuperscript{a} operates in such systems then clearly it is not favoured in the case of 2,5-dimethylphenol, according to the results shown in Table 16. It is reasonable to assume that
the 2,4-diaminoalkylated product (129a) may have arisen from the *ortho*-substituted Mannich base (130a), which reacted with the iminium salt present, rather than from (128a). Some evidence which supports this view was secured from the attempted reaction of 2,5-dimethyl-4-(N-morpholinylmethyl)phenol with preformed iminium salt. No further aminoalkylation at the 6-position took place. The use of sulphur dioxide, however, Equation 50, led to the successful formation of 2,4-diaminoalkylated phenol (129c), which reinforces our previous mechanistic proposal.

\[ \begin{array}{c}
\text{Me} & \text{OH} \\
\text{Me} & \text{OH} \\
\text{N} & \text{Me}
\end{array} \quad \xrightarrow{1. \text{SO}_2, \text{CH}_3\text{CN, r.t.}} \quad \begin{array}{c}
\text{Me} & \text{OH} \\
\text{Me} & \text{OH} \\
\text{N} & \text{Me} & \text{O} & \text{N}
\end{array} \quad \xrightarrow{2. \text{O} \text{N} = \text{CH}_2 \text{OEt}} \quad \begin{array}{c}
\text{Me} & \text{OH} \\
\text{Me} & \text{OH} \\
\text{N} & \text{Me} & \text{O} & \text{N}
\end{array}
\]

42%

(129c)

Equation 50

2.5.4 Reactions of Phenols with 3-Methyl-1,3-oxazolidine

Although 3-substituted-1,3-oxazolidines\textsuperscript{403} have been known for many years their use has been restricted, until recently, to reactions with Grignard reagents\textsuperscript{404}. In concurrent studies in these laboratories these interesting reagents have been employed in the Mannich reactions of aromatic heterocycles\textsuperscript{40} and silyl enol ethers\textsuperscript{24}. A reaction of N-methyl-oxazolidine with t-butylchlorodimethylsilane (TBDMSCl) and 2-methyl-
furan in the presence of 1,2,4-triazole afforded, the Mannich base (134) in good yield with simultaneous protection of the resulting alcoholic function, as shown in Equation 51.

\[
\text{Furan} + \text{Me-N} \rightarrow \text{Mannich base (134)}
\]

Equation 51

Phenols are reported to react with \(N\)-methylethanolamine and formaldehyde under classical conditions. The intermediacy of 3-methyl-1,3-oxazolidine in such systems might be a possibility. An improved method for the preparation of 3-methyl-1,3-oxazolidine involves heating \(N\)-methylethanolamine, paraformaldehyde and potassium carbonate in the absence of a solvent, as shown in Equation 52.

\[
\text{MeNHCH}_2\text{CH}_2\text{OH} + (\text{CH}_2\text{O})_n \xrightarrow{\text{K}_2\text{CO}_3, \text{heat}} \text{Me-N} \quad 65\%
\]

Equation 52

A brief investigation of the reactions of phenols with 3-methyl-1,3-oxazolidine in acetonitrile was undertaken. The presence of sulphur dioxide did not have an effect on the yield of the reaction and attempts to activate the reagent with chlorosilane derivatives resulted in complete deactivation of the phenol. Highly nucleophilic phenols,
however, afforded good yields of the Mannich bases (135) without any acidic reagent being required. The results obtained are summarised in Equation 53 and Table 17, and indicate that this versatile reagent could be used for the preparation of highly functionalised Mannich bases.

\[
\begin{align*}
\text{Phenol} & \quad \text{SO}_2 & \text{Time/h} & \text{Yield(\%) (135)} & \% \text{S.M. Recovered} \\
R^1=R^3=\text{Me}, & 0 & 50 & 26 & 56 \\
R^2=\text{H} & 1.5 & 48 & 28 & 65 \\
& 2.2 & 72 & 21 & 69 \\
R^1=R^2=\text{H}, & 0 & 52 & 22 & 63 \\
R^3=\text{OMe} & 2.2 & 52 & 18 & 75 \\
R^1=\text{OMe}, & 0 & 48 & 28 & 65 \\
R^2=\text{H}, & 0 & 46 & 69 & 22 \\
R^3=\text{Me} & 0 & 50 & 95^{b} & 4 \\
\end{align*}
\]

(a) SO₂ was allowed to react with the phenol for 24 hours at r.t. before the addition of 3-methyl-1,3-oxazolidine.
(b) The product was characterised as the hydrochloride salt.
2.5.5 The Effect of Chlorosilane Derivatives in the Mannich Reactions of Phenols

Following the successful use of silicon reagents in the Mannich reactions of aromatic heterocycles an attempt was made to extend the use of these reagents in the reactions of phenols. The investigation concentrated on 2,4-dimethylphenol. It was found, however, that very little or no product was formed in "in situ" reactions activated by chlorosilanes, as shown in Table 18.

**TABLE 18**
Reactions of 2,4-Dimethylphenol in the Presence of Chlorosilanes

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Silane</th>
<th>Yield(%)</th>
<th>% S.M. Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Me₂N)₂CH₂</td>
<td>Me₃SiCl</td>
<td>24</td>
<td>69</td>
</tr>
<tr>
<td>[(CH₂)₅N]₂CH₂</td>
<td>Me₃SiCl</td>
<td>4ᵃ</td>
<td>85</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>Me₃SiCl</td>
<td>0</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>Me₂SiCl₂</td>
<td>0</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>MeSiCl₃</td>
<td>0</td>
<td>95</td>
</tr>
</tbody>
</table>

(a) 78% unreacted aminal was also recovered.

These results suggest that the chlorosilane derivative may react with the phenol forming an arylsilyl ether. The protection of the phenol by the alkylsilyl group results in the reduction of the nucleophilicity of the phenol. Benzenoid compounds less nucleophilic than *meta*-dimethoxybenzene do not react with the relatively weak electrophiles involved in Mannich reactions, as mentioned earlier.¹
Some evidence for this proposal was obtained from the total inertness of 2,5-(dimethylphenoxy)trimethylsilane (136) towards aminol ethers. The silyl ether (136) was prepared in high yield by treatment of 2,5-dimethylphenol with sodium hydride and quenching the 2,5-dimethylphenoxide anion with chlorotrimethylsilane, as shown in Equation 54.

\[
\text{NaH, THF} \quad \overset{\text{N}_2}{\text{Me}_3\text{SiCl}} \quad \text{Product (136))}
\]

Equation 54

Treatment of the silyl ether (136) with aminol ethers in the presence of chlorosilane derivatives failed to produce Mannich bases. Even the presence of fluoride ion did not succeed in reactivating the ring by removing the silyl residue. The only product isolated after hydrolytic work-up was 2,5-dimethylphenol, as shown in Table 19.

These results indicate that the presence of the free phenolic moiety is essential for the reactions to take place. The acidity of the phenols derives from their ability to form the related anions in neutral or slightly alkaline media. Under acidic conditions phenoxide anion formation is not favoured and the nucleophilicity of the ring is reduced. 4-Hydroxyacetophenone\textsuperscript{407}, for example, reacts at the enolised ketone function under acidic conditions and ring substitution only occurs in a mildly basic medium, as shown in Equation 55.
TABLE 19
Attempted Reactions of 2,5-(dimethylphenoxy)trimethylsilylamine with Aminol Ethers

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Silane</th>
<th>Time/h</th>
<th>2,5-DiMe-phenol Recovered (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et₂NCH₂OEt</td>
<td>Me₃SiCl</td>
<td>22</td>
<td>92</td>
</tr>
<tr>
<td>Et₂NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>22</td>
<td>93</td>
</tr>
<tr>
<td>Et₂NCH₂OEt</td>
<td>MeSiCl₃</td>
<td>22</td>
<td>90</td>
</tr>
<tr>
<td>Et₂NCH₂OPr</td>
<td>MeSiCl₃⁺</td>
<td>24</td>
<td>91</td>
</tr>
<tr>
<td>Et₂NCH₂OPr</td>
<td>MeSiCl₃⁻</td>
<td>48</td>
<td>95</td>
</tr>
</tbody>
</table>

(a) The silane was allowed to react with the aminol ether for 1/2 hour before the addition of the silyl ether (136).
(b) As in (a), n-tetrabutylammonium fluoride (TBAF) was added in the reaction mixture after 24 hours.

\[
\text{HO} \quad + \quad \text{p} \quad \text{CH₂O, EtOH} \quad \rightarrow \quad \text{HO} \quad \text{COCH₃}
\]

Equation 55

In summary the results presented in this chapter demonstrate that a variety of aromatic compounds can be aminoalkylated under mild non-aqueous conditions. They support the view that a number of mechanisms may be involved in the Mannich reactions of aromatic heterocycles and phenols. The reactive intermediates generated depend on the reagent systems and the operating reaction conditions used. Useful aminoalkylation procedures have been developed especially for the regioselective reactions of pyrroles and phenols. The aminoalkylation–destannylation reactions of aryltrialkylstannanes have been further exemplified.
CHAPTER THREE

MANNICH REACTIONS USING PRIMARY AMINES

3.1 Introduction

Although the use of secondary amines in the Mannich reaction is extensively documented the utilisation of primary amines is, in fact, limited. One reason for the infrequent use of primary amines is that the products of the reactions are in fact secondary amines which can participate further in the reaction, leading to the formation of undesired by-products.

The classical Mannich reactions of pyrroles afford much lower yields of aminoalkylation products using primary amines than those obtained using secondary amines\textsuperscript{73,108}. Some useful improvements were made\textsuperscript{109} in the condensation of pyrroles, aqueous formaldehyde and primary amine hydrochlorides. It was found that the yield of the secondary amine is increased by using a 3 molar excess of amine hydrochloride or by increasing the steric bulk of the alkyl group on the nitrogen.

The condensation of selected pyrroles with formaldehyde and primary amines led to the formation of dihydroimidazo-pyrrole derivatives. Thus, the reaction of 2,4-dimethyl-3-carbethoxypyrrrole (137)\textsuperscript{110} with formaldehyde and cyclohexylamine in a molar ratio of 2:2:1 respectively, resulted in the formation of 6-carbethoxy-2-cyclohexyl-2,3-dihydro-5,7-dimethyl-1-H-imidazo[1.5-a]pyrrrole (138) in 66\% yield, as shown in Scheme 42.
Preparation of the secondary amine Mannich bases (139a) and (139b) in this study, by the literature procedure, and subsequent treatment with paraformaldehyde in 1,4-dioxane under reflux, resulted in the formation of the hydroimidazo-pyrrole derivatives (140a) and (140b). Attempts to react (140a) and (140b) with pyrrole in the presence of trichloromethylsilane in acetonitrile failed and the imidazopyrrole derivatives were recovered unchanged, as shown in Scheme 43. The apparent stability of these compounds in both acidic and alkaline conditions has been reported previously.

SCHEME 42
Reagents (i) HCHO; (ii) C₆H₅NH₂; (iii) -H₂O.

SCHEME 43
Reagents (i) HCHO aq.; (ii) MeNH₂.HCl (3mol) or 'PrNH₂.HCl (1mol); (iii) (CH₂O)n, 1,4-dioxane, reflux; (iv) pyrrole, MeSiCl₃,
CH₃CN.
The main substrates that have been employed in cyclization reactions using primary amines are phenols. As in the case of secondary amines aminoalkylation occurs principally at the ortho-position of the hydroxyl group. The first formed secondary amines react with a second molecule of formaldehyde leading to the formation of benzoxazines. A wide range of phenols for the preparation of a variety of benzoxazines have been used by Burke's group\textsuperscript{111}. The two possible bis-benzoxazines derived from hydroquinone have been isolated\textsuperscript{112}. The use of bis(alkoxymethyl)amines, [bis(amino ethers)], as bis-aminoalkylating agents proved particularly useful for the determination of the structure of bis-benzoxazine (141), derived from 2-methylhydroquinone\textsuperscript{113}, as shown in Equation 56.

\begin{center}
\begin{equation}
\text{Equation 56}
\end{equation}
\end{center}

The cleavage of the heterocyclic ring in benzoxazines in hot ethanol has been reported\textsuperscript{114}. Hydrolysis with dilute hydrochloric acid produced high yields of ortho-secondary aminomethylphenol hydrochlorides\textsuperscript{111b}. The ring-chain tautomerism of 2-aryl-1,3-benzoxazines has also been investigated indicating that an equilibrium exists between the benzoxazine and the ring opened Schiff's base\textsuperscript{115}. Until very recently, the only use of these compounds as potential Mannich reagents had been restricted to reactions with nucleophilic phenols. 2,4-Dimethylphenol\textsuperscript{116}, for example, reacts with the dichlorobenzoxazine (142) very effectively due to the
enhanced electrophilicity of this compound caused by the presence of chlorine atoms, Equation 57.

![Chemical Structure](image)

Equation 57

It has recently been shown in these laboratories\(^\text{40}\), that these reagents when activated by trichloromethylsilane, can participate in the Mannich reactions of aromatic heterocycles such as 2-methylfuran and \(N\)-methylindole, producing the corresponding phenolic Mannich bases (143) in high yields, as shown in Equation 58.

![Chemical Structure](image)

Equation 58

Another interesting class of reagents derived from the condensation of primary amines and formaldehyde in aqueous sodium hydroxide is 1,3,5-trialkylhexahydrotriazines (144), Equation 59.

104
In a series of investigations\textsuperscript{117} these reagents, when treated with hydrogen chloride in aprotic solvents, formed useful intermediates for the introduction of an aminomethyl group into some compounds capable of undergoing the Mannich reaction.

A wide variety of secondary aminomethyl sulphide hydrochlorides (145) were obtained in high yields from the reactions of various mercaptans\textsuperscript{117a} and hexazydrotriazine derivatives, Equation 60. The high-yielding reactions were attributed to the reactive nature of the aminomethylating agent and also to the protonation of the amino-nitrogen reducing the nucleophilicity of the products (145).
Hydrogen sulphide\(^{17a}\), however, afforded the bis(secondary-aminomethyl)sulphide hydrochlorides (146) in excellent yields due to self-reaction of the mercaptomethylamine salt (147) rather than from further reaction with the intermediate aminomethylating reagent, as shown in Equation 61.

\[
\begin{align*}
2 \quad & + \quad 6 \quad H_2S \quad + \quad 6 \quad HCl \\
\longrightarrow & \quad 6 \left[ R\text{NHO}_2-CH_2SH \right] Cl^- \\
\longrightarrow & \quad 3 \quad \text{RNH}_2-CH_2-S-CH_2-\text{NH}_2R \quad 2\text{Cl}^-
\end{align*}
\]  

(147)  

Equation 61

The same procedure was applied to the reactions of phenols\(^{19b}\), resulting rather surprisingly, in the introduction of the aminomethyl residue exclusively at the para-position, as shown in Equation 62.

\[
\begin{align*}
\text{Phenol: } R^1-R^2=R^3=H; R^1=R^2=Me, R^3=H;  \\
R^1=H, R^2=R^3=Me, R^1=R^2=R^3=Me
\end{align*}
\]  

Equation 62
Treatment of hydroquinones\textsuperscript{17c} under the same conditions resulted in the formation of monobenzoxazine hydrochlorides (148) in good yields. However, purification proved difficult due to the formation of equimolar amounts of amine hydrochlorides. This was overcome by the use of bis(aminol ethers) in the presence of hydrogen chloride. In contrast with previous observations\textsuperscript{113,114} bis-benzoxazines were not formed, as shown in Equation 63. The effect of hydrogen chloride on bis(aminol ethers) was investigated during the course of the work reported in this thesis and will be discussed in subsequent sections.

\[
\text{Equation 63}
\]

The formation of secondary Mannich bases using 1,3,5-trialkyl-hexahydrotriazines is an interesting observation. This chapter concentrates partly on the formation of secondary amines derived from aromatic heterocycles using bis(aminol ethers). The employment of hexahydrotriazines in such systems will be worthy of investigations in future work. The introduction of a secondary aminomethyl unit to a ketone function is a desirable objective in various synthetic programs\textsuperscript{118}. 

\[\text{107}\]
3.2 RESULTS AND DISCUSSION

3.2.1 Preparation of Bis(Aminol Ethers)

Although bis(aminol ethers) have been known for a long time\(^\text{119}\) they have enjoyed restricted usage, as indicated earlier\(^\text{112, 113}\). A limited amount of success was achieved in the employment of bis(n-butoxymethyl)-t-butylamine in reactions with α-bromo esters and zinc (Reformatsky reaction)\(^\text{120}\).

The further exploration of the use of these reagents was therefore appealing. A number of bis(aminol ethers) \((149)\) were prepared by the condensation of anhydrous primary alkyl- or aralkyl-amines with paraformaldehyde in an excess of methanol or ethanol in the presence of potassium carbonate. The reagents prepared are summarised in Table 20, and Equation 64.

\[
\text{RNH}_2 + (\text{CH}_2\text{O})_n + \text{R'OH} \xrightarrow{\text{K}_2\text{CO}_3} R-N\underbrace{\text{OR'} - \text{OR'}}_{\text{OR'}}
\]

\text{Equation 64 (149)}

As in the preparations of aminol ethers derived from secondary amines a higher boiling material was also formed in these preparations. This may have caused some decrease in the yields of the isolated products. In one case the by-product was isolated and characterised spectroscopically and was shown to be analogous to \((98)\). The insertion of a molecule of formaldehyde resulted in the formation of \((150)\) shown below. This by-product gives a similar reactive intermediate and Mannich products in reaction with nucleophiles.
TABLE 20
Preparation of Bis(Aminol Ethers)

<table>
<thead>
<tr>
<th>Aminol Ether</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-PrN(CH₂OEt)₂</td>
<td>45</td>
</tr>
<tr>
<td>n-BuN(CH₂OEt)₂</td>
<td>55</td>
</tr>
<tr>
<td>t-BuN(CH₂OMe)₂</td>
<td>33</td>
</tr>
<tr>
<td>EtN(CH₂OEt)₂</td>
<td>40</td>
</tr>
<tr>
<td>PhCH₂N(CH₂OEt)₂</td>
<td>56</td>
</tr>
<tr>
<td>PhCH₂CH₂N(CH₂OEt)₂</td>
<td>50</td>
</tr>
<tr>
<td>3,4-di-MeO-(C₆H₄)CH₂CH₂N(CH₂OMe)₂</td>
<td>60</td>
</tr>
<tr>
<td>3-MeO-(C₆H₄)CH₂CH₂N(CH₂OEt)₂</td>
<td>80</td>
</tr>
</tbody>
</table>

(a) 17% of (150) was also isolated.
(b) The reaction was carried out in benzene using a Dean–Stark trap.¹¹²

3.2.2 Iminium Species Derived from Bis(Aminol Ethers)

Treatment of bis(aminol ethers) with acidic reagents such as acetyl chloride, chlorosilane derivatives or ethereal hydrogen chloride, in petroleum ether, resulted in the precipitation of white crystalline solids in quantitative yields. These iminium chlorides, however, are more hygroscopic than N,N-dialkyl(methylene)iminium chlorides and filtration proved difficult, even under an atmosphere of dry nitrogen. They can, however, be purified by successive washing with solvent and
evaporation of the solvent, under high vacuum. They cannot be stored for a long time and should be freshly prepared each time they are required.

The \(^1\text{H}\) and \(^{13}\text{C}\) n.m.r. spectra obtained for two of these iminium salts exhibited some interesting features. The iminium methylene group was observed at a higher field than the \(N,N\)-dialkyl analogues. The iminium methylene carbon of \(N,N\)-diethyl(methylene)iminium chloride, for example, appears at \(\delta=165.4\) ppm. The significant high field shift brings the group into the lower range of expectancy\(^{121}\), (\(^{13}\text{C}\) n.m.r., \(\delta=152.2-215\) ppm), as shown below in Equations 65 and 66.
The most interesting observation is the downfield shift of the methylene group adjacent to the nitrogen. This indicates that a fast equilibration of the iminium methylene group between the two indistinguishable groups may occur. Thus, it is suggested that the positive charge may be distributed over a longer range, enabling the oxygen to accommodate some positive charge. The lower field shift of the methoxy group ($\delta = 4.7$ ppm in $^{13}$C n.m.r., Equation 65) and the methylene group adjacent to oxygen ($\delta = 5.1$ ppm, in $^{13}$C n.m.r., Equation 66) suggests that this may be possible. It is therefore plausible that the structure of these $N$-alkyl-$N$-alkoxy(methylene)-iminium species may be better represented by the canonical forms shown below:

\[
\begin{align*}
R^+ CH_2 \quad \leftrightarrow \quad & R^+ OR' \\
& R^+ N \quad \leftrightarrow \quad R^+ OR'
\end{align*}
\]

A small contribution of the oxonium species explains the deshielding of the adjacent groups. A much greater downfield shift of adjacent methoxy and methylene groups is observed in the $^{13}$C n.m.r. spectra of trialkyl-oxonium fluoroborates, as shown below:\textsuperscript{122}:

\[
\begin{align*}
\text{Me-O-Me} & \quad \uparrow \quad \text{Me}_3O^+ BF_4^- \quad \text{and} \quad \text{Et-OCH}_2-\text{Me} \\
\delta_c & \quad 60.0 & \quad 78.8 & \quad 66.10 & \quad 15.4 \\
\text{Et}_2O-\text{CH}_2-\text{Me} & \quad \uparrow \quad \text{BF}_4^- \\
\delta_c & \quad 84.6 & \quad 12.5
\end{align*}
\]
The transient existence of $N$-alkyl-$N$-alkoxymethyl(methylene)iminium salts has been suggested in a proposed mechanism of the reaction of phenols with bis(aminol ethers)$^{123}$ for the preparation of benzoxazines. The participation of such electrophilic species in the Grignard-Reformatsky reaction of bis($n$-butoxymethy)-$t$-butylamine is another example where $N$-alkyl-$N$-alkoxy(methylene)iminium salt has been suggested as an intermediate$^{124}$. In this case it was postulated that magnesium bromide generated in the reaction functions as the Lewis acid that is involved in the formation of the reactive intermediate. The use of these species in the Mannich reactions of aromatic compounds is now discussed.

3.3 An Investigation of the Reactions of Bis(Aminol Ethers) with 2-Methylfuran in the Presence of Acidic Reagents

It was anticipated that by using bis(aminol ethers) it would be possible to generate a methylene(iminium) group and to protect the product by using the same functional group. The objective was to design conditions such that a protected secondary amine could be intercepted giving rise to the possibility of having sequential reactions with two different nucleophiles. Alternatively, bis(aminol ethers) could be used as bis-aminoalkylating agents for the formation of tertiary amines.

A mixture of secondary (151) and tertiary (152) Mannich bases was isolated during initial investigations of "in situ" reactions of bis(aminol ethers) with 2-methylfuran in acetonitrile activated by various acidic reagents. Bis(ethoxymethyl)-iso-propylamine was used in most cases in order to evaluate the effect of the acidic reagents. The results obtained are given in Table 21, and Equation 67.
The results indicate that the best yields of secondary Mannich bases (151) are obtained when hydrogen chloride is the only acid present in the reaction mixtures. The chlorosilane derivatives promote the formation of tertiary amines (152). An explanation of this observation will be given in the following section. Some attempt was made to increase the amounts of secondary amines formed by varying the order of addition of the reagents. The elevation of temperature resulted in the lowering of the yields of the reaction. Sulphur dioxide and trifluoroacetic anhydride gave low yields of both products. It is noteworthy that the reaction of \( N\text{-bis(ethoxymethyl)}-\alpha\text{-phenylethylamine} \) gave the secondary amine in reasonable yield without any evidence of intramolecular cyclization.

The reaction pathway is thought to proceed via the formation of an iminium species which reacts with 2-methylfuran generating an aminol ether. The formation of such species was detected by \( ^\text{1}H \) n.m.r. spectroscopy in reactions worked-up under non-aqueous conditions. This may survive the reaction conditions and after hydrolytic work-up give the secondary amine. Alternatively, it may form a second iminium species which reacts further with 2-methylfuran present, resulting in the formation of the tertiary amine. A more detailed interpretation will be given later.

\[
\begin{align*}
\text{Me} & \quad + \quad \text{R-N(CH}_2\text{OR'}_2)\quad \xrightarrow{\text{Acid, MeCN}} \quad \text{Me} \\
\text{Me} & \quad \text{R-N(CH}_2\text{OR')}_2 \quad \xrightarrow{\text{Acid, MeCN}} \quad \text{Me} \\
\quad & \quad \text{Me} \\
\end{align*}
\]

\( \text{Equation 67} \)
**TABLE 21**

"In Situ" Reactions of 2-Methylfuran with Bis(Aminol Ether)

<table>
<thead>
<tr>
<th>Bis(Aminol Ether)</th>
<th>Acid</th>
<th>Time (h)</th>
<th>Temp.</th>
<th>Mannich Bases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2° (151) 3° (152)</td>
</tr>
<tr>
<td>i-PrN(CH₂OE₄)₂</td>
<td>Me₃SiCl</td>
<td>16</td>
<td>r.t</td>
<td>38  56</td>
</tr>
<tr>
<td></td>
<td>Me₃SiCl a</td>
<td>42</td>
<td>r.t</td>
<td>7   71</td>
</tr>
<tr>
<td>i-PrN(CH₂OE₄)₂</td>
<td>Me₃SiCl b</td>
<td>42</td>
<td>r.t</td>
<td>17  67</td>
</tr>
<tr>
<td>i-PrN(CH₂OE₄)₂</td>
<td>Me₃SiCl c</td>
<td>1.5</td>
<td>reflux</td>
<td>22  17</td>
</tr>
<tr>
<td>i-PrN(CH₂OE₄)₂</td>
<td>Me₃SiCl (5mol%)</td>
<td>18</td>
<td>r.t</td>
<td>39  28</td>
</tr>
<tr>
<td>i-PrN(CH₂OE₄)₂</td>
<td>CH₃COCl</td>
<td>19</td>
<td>r.t</td>
<td>44  37</td>
</tr>
<tr>
<td>i-PrN(CH₂OE₄)₂</td>
<td>CH₃COCl</td>
<td>1.5</td>
<td>reflux</td>
<td>19  39</td>
</tr>
<tr>
<td>i-PrN(CH₂OE₄)₂</td>
<td>CH₃COCl d</td>
<td>20</td>
<td>r.t</td>
<td>38  43</td>
</tr>
<tr>
<td>Me₃SiCl</td>
<td>TiCl₄ (25mol%)</td>
<td>18</td>
<td>-55°C to r.t</td>
<td>31  49</td>
</tr>
<tr>
<td>Me₃SiCl</td>
<td>TiCl₄ (5mol%)</td>
<td>22</td>
<td>-55°C to r.t</td>
<td>26  50</td>
</tr>
<tr>
<td>Me₃SiCl</td>
<td>TiCl₄ (25mol%)</td>
<td>4*</td>
<td>r.t</td>
<td>58  15</td>
</tr>
<tr>
<td>Me₃SiCl</td>
<td>TiCl₄ (25mol%)</td>
<td>2*</td>
<td>-60°C to -20°C</td>
<td>42  16</td>
</tr>
<tr>
<td>Me₃SiCl</td>
<td>TiCl₄ (25mol%)</td>
<td>16</td>
<td>r.t</td>
<td>34  59</td>
</tr>
<tr>
<td>Me₃SiCl</td>
<td>TiCl₄ (25mol%)</td>
<td>18</td>
<td>r.t</td>
<td>14  37</td>
</tr>
<tr>
<td>Me₃SiCl</td>
<td>(CF₃CO)₂O</td>
<td>3</td>
<td>r.t</td>
<td>24  17</td>
</tr>
<tr>
<td>Me₃SiCl</td>
<td>SO₂</td>
<td>3</td>
<td>r.t</td>
<td>22  21</td>
</tr>
<tr>
<td>PhCH₂N(CH₂OE₄)₂</td>
<td>MeSiCl₃</td>
<td>21</td>
<td>r.t</td>
<td>33  -</td>
</tr>
<tr>
<td>PhCH₂CH₂N(CH₂OE₄)₂</td>
<td>Me₂SiCl₂</td>
<td>22</td>
<td>r.t</td>
<td>43  -</td>
</tr>
<tr>
<td>n-BuN(CH₂OE₄)₂ /2mol</td>
<td>MeSiCl₃ /2mol</td>
<td>18</td>
<td>r.t</td>
<td>87  87</td>
</tr>
<tr>
<td>i-PrN(CH₂OE₄)₂</td>
<td>MeSiCl₃</td>
<td>72</td>
<td>r.t</td>
<td>20  43</td>
</tr>
<tr>
<td>i-PrN(CH₂OE₄)₂</td>
<td>Et₂O.HCl g</td>
<td>16</td>
<td>r.t</td>
<td>63  19</td>
</tr>
<tr>
<td>i-PrN(CH₂OE₄)₂</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>r.t</td>
<td>63  18</td>
</tr>
<tr>
<td>EtN(CH₂OE₄)₂</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>r.t</td>
<td>41  23</td>
</tr>
<tr>
<td>t-BuN(CH₂OMe)₂</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>r.t</td>
<td>72  22</td>
</tr>
<tr>
<td>PhCH₂N(CH₂OE₄)₂</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>r.t</td>
<td>45  -</td>
</tr>
</tbody>
</table>
TABLE 21 continued.

(a) Me₂SiCl was allowed to react with the bisaminol ether for 3h. before adding 2-Me-furan.
(b) 3 Mol. equiv. of bisaminol ether used.
(c) A mixture of 2-Me-furan and bisaminol ether added to the acidic reagent very slowly dropwise.
(d) As in (c) 1.5 mol. of bisaminol ether and 2 mol. equiv. of acetyl chloride used.
(e) The reaction was carried out in dichloromethane.
(f) TiCl₄ added in MeCN at -10 C followed by the reagent and then 2-Me-furan.
(g) Et₂O.HCl added to bisaminol ether solution for 2h. before adding 2-Me-furan.

3.4 Reactions of 2-Methylfuran with Preformed $N$-Alkoxyethyl-$N$-Alkyl(methylene)iminium chlorides.

As mentioned earlier the iminium salts derived from bisaminol ethers can be isolated. In order to optimise the yields of secondary amines a series of reactions of 2-methylfuran was carried out with preformed iminium salts generated by using various acidic reagents. Once again two products were isolated, as shown in Table 22, and Equation 68.

\[
\text{MeO} \quad + \quad R' \text{N}^+\text{CH}_2\text{Cl}^- \xrightarrow{\text{MeCN}} \quad \text{MeO}_2\text{N}^+\text{R} \quad (151)
\]

\[
R' = \text{Me or Et}
\]

Equation 68
# TABLE 22
Reactions of 2-Methylfuran with Preformed Iminium Salts

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Iminium Salt</th>
<th>Acid</th>
<th>Time (h)</th>
<th>Temp.</th>
<th>Mannich Bases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-Pr</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>26</td>
<td>r.t.</td>
<td>59</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>41</td>
<td>r.t.</td>
<td>9</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>24</td>
<td>r.t.</td>
<td>65</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;SiCl</td>
<td>18</td>
<td>r.t.</td>
<td>16</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr&lt;sup&gt;b&lt;/sup&gt;</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4</td>
<td>r.t.</td>
<td>34</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>i-Pr&lt;sup&gt;b&lt;/sup&gt;</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4</td>
<td>-22°C</td>
<td>45</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>i-Pr&lt;sup&gt;c&lt;/sup&gt;</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2</td>
<td>r.t.</td>
<td>48</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>n-Bu</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>22</td>
<td>r.t.</td>
<td>54</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>n-Bu</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>24</td>
<td>r.t.</td>
<td>57</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>n-Bu</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>24</td>
<td>r.t.</td>
<td>23</td>
<td>41</td>
</tr>
<tr>
<td>11</td>
<td>t-Bu</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>24</td>
<td>r.t.</td>
<td>68</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>t-Bu&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3days</td>
<td>r.t.</td>
<td>35</td>
<td>51</td>
</tr>
<tr>
<td>13</td>
<td>t-Bu&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3days</td>
<td>-40 to -20°C</td>
<td>46</td>
<td>16</td>
</tr>
<tr>
<td>14</td>
<td>t-Bu</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;SiCl</td>
<td>42</td>
<td>r.t.</td>
<td>62</td>
<td>33</td>
</tr>
<tr>
<td>15</td>
<td>n-Bu&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;SiCl</td>
<td>18</td>
<td>r.t.</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>16</td>
<td>i-Pr</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;COCl</td>
<td>24</td>
<td>r.t.</td>
<td>14</td>
<td>55</td>
</tr>
<tr>
<td>17</td>
<td>i-Pr</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;COCl</td>
<td>3</td>
<td>r.t.</td>
<td>23</td>
<td>45</td>
</tr>
<tr>
<td>18</td>
<td>i-Pr</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;COCl</td>
<td>10days</td>
<td>-40 to -20°C</td>
<td>55</td>
<td>31</td>
</tr>
<tr>
<td>19</td>
<td>n-Bu</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;COCl</td>
<td>24</td>
<td>r.t.</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>20</td>
<td>Et</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>18</td>
<td>r.t.</td>
<td>13</td>
<td>42</td>
</tr>
<tr>
<td>21</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>21</td>
<td>r.t.</td>
<td>41</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>MeSiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>18</td>
<td>r.t.</td>
<td>55</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>i-Pr</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O.HCl</td>
<td>64</td>
<td>r.t.</td>
<td>75</td>
<td>13</td>
</tr>
<tr>
<td>24</td>
<td>i-Pr</td>
<td>HCl(gas)</td>
<td>2</td>
<td>r.t.</td>
<td>77</td>
<td>15</td>
</tr>
<tr>
<td>25</td>
<td>t-Bu</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O.HCl</td>
<td>3</td>
<td>r.t.</td>
<td>80</td>
<td>13</td>
</tr>
<tr>
<td>26</td>
<td>t-Bu&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;SiCl</td>
<td>3</td>
<td>r.t.</td>
<td>74</td>
<td>19</td>
</tr>
<tr>
<td>27</td>
<td>n-Bu</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;SiCl</td>
<td>2</td>
<td>-40°C</td>
<td>59</td>
<td>6</td>
</tr>
<tr>
<td>28</td>
<td>4MeO-PhCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O.HCl</td>
<td>18</td>
<td>r.t.</td>
<td>59</td>
<td>-</td>
</tr>
<tr>
<td>29</td>
<td>t-Bu&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O.HCl</td>
<td>2</td>
<td>r.t.</td>
<td>51</td>
<td>22</td>
</tr>
</tbody>
</table>

(a) 2-Methylfuran added dropwise to a solution of the iminium salt at 0°C allowing the reaction to reach room temperature.
(b) The reaction was carried out in dichloromethane.
(c) 2 Mol. equiv. of iminium salt was used.
(d) The iminium salt was prepared in dichloromethane.
(e) The reaction was carried out in the presence of NaHCO<sub>3</sub>.
Some interesting conclusions can be drawn from these results. As in the case of "in situ" reactions, the best yields of secondary amines (151) can be obtained from iminium salts prepared using hydrogen chloride. Attempts to duplicate the results from the reactions where the iminium species were generated by chlorosilane derivatives were unsuccessful. It is assumed that in some cases the silanes were occluded in the precipitated salt, promoting the formation of a second iminium species and hence the tertiary amine (152). Some indication that the reactions could be carried out at lower temperatures were also obtained. The use of dichloromethane as a solvent did not have a pronounced advantage. Again no evidence of intramolecular cyclization was obtained in the reactions of the salts derived from α-phenylethylamine (entry 22) or 4-methoxy-α-phenylethylamine (entry 28). It also became more obvious that the yields of secondary amines depend on the structure of the N-alkyl residue. The more sterically demanding alkyl group inhibits the formation of tertiary amine. This may be due to inhibition of formation of the second iminium salt.

The presence of sodium bicarbonate in the reaction for neutralising the acid produced did not have a great effect, and a small decrease in the yields was observed (entry 29). This was possibly due to the generation of water in the reaction mixture from the reaction of hydrogen chloride with sodium bicarbonate. A series of experiments where a non-nucleophilic base was added to the reaction mixtures resulted in complete or partial inhibition of the reactions. The bases used were di-iso-propylethylamine, dicyclohexylmethylamine, 2,6-lutidine, propylene oxide, and potassium carbonate in a large excess.

Two key experiments provided strong evidence concerning the reaction pathway and the effect of chlorosilane derivatives in the mixture.
Duplicate reactions of \( N-t\)-butyl-\( N\)-methoxymethyleneiminium chloride, prepared using hydrogen chloride, with 2-methylfuran were carried out. In one a half-mole equivalent of bis(trimethylsilyl)acetamide was also added. In the control experiment (entry 25) the yields of secondary and tertiary amines were 80% and 13% respectively. In the presence of hydrogen chloride scavenger complete reversal occurred yielding the secondary amine in 12% and the tertiary amine in 80%. This evidence supports the view that the strongly azophilic hydrogen chloride protonates the nitrogen in the intermediate aminol ether, Scheme 44, which therefore survives until the end of the reaction. On the other hand the hydrogen chloride scavenger generates 2 mole equivalents of chlorotrimethylsilane in the reaction mixture. The silicon reagent, being oxophilic, silylates the intermediate aminol ether at the oxygen and leads to the generation of the second iminium salt (153) and ultimately to the tertiary amine. The intermediacy of the aminol ether (154) was further substantiated by its isolation in 47% yield, from a reaction whose work-up required the addition of Hunig's base to the reaction mixture after 24 hours. The proposed sequence of reactions is shown in Scheme 44.

Further evidence for the involvement of aminol ether (154) was provided by the preparation of the equivalent intermediate aminol ether (155) from the secondary amine (151a), by the usual procedure\(^6\), in 74% yield. Subsequent reaction of (155) with \( N\)-methylindole, in the presence of trichloromethylsilane, afforded the mixed tertiary amine (156) in 71% yield, as shown in Scheme 45.

This reaction also supports the view that it is possible to carry out sequential reactions with two different nucleophiles. As was shown earlier, the isolation of the intermediate aminol ether is possible and this reaction can therefore be performed in two steps. It should also be possible to carry out such a sequence in "one pot" by generating the protonated
aminol ether (155) or (154), followed by the addition of bis(trimethylsilyl)-acetamide and a different nucleophile.

\[
\begin{align*}
\text{Scheme 44} & \\
\text{Reagents} & (i) \text{ 2-Me-furan; (ii) Hunig's base; (iii) } H_2O; \\
 & (iv) \text{ bis(trimethylsilyl)acetamide.}
\end{align*}
\]
3.5 Reactions of \(N\)-Alkoxy methyl-\(N\)-Alkyl(methylene)iminium Chlorides with Other Aromatic Compounds

The reactions of 2-methylfuran with these iminium species assisted in the development of the methodology for the preparation of secondary Mannich bases. An exploration of this technology was therefore undertaken using other aromatic compounds in order to extend the investigation.

A variety of aromatic heterocycles and also \(meta\)-dimethoxybenzene were used. The results obtained are summarised in Table 23, and Equation 69. The reactions performed above \(-40^\circ C\) were carried out in acetonitrile, whereas those at \(-7.8^\circ C\) used dichloromethane as the solvent. The importance of preparing the iminium salts from hydrogen chloride became more evident and the acidic reagent used is given in the Table for the reasons indicated earlier.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Co-reactant</th>
<th>Iminium Salt</th>
<th>Acid</th>
<th>Time (h)</th>
<th>Temp.</th>
<th>Products (yield%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td>2° (157)</td>
</tr>
<tr>
<td>1</td>
<td>Furan (1 mol)</td>
<td>i-Pr</td>
<td>MeSiCl₃</td>
<td>22</td>
<td>r.t.</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>(1 mol)</td>
<td>i-Pr</td>
<td>MeSiCl₃</td>
<td>50</td>
<td>r.t.</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>(1 mol)</td>
<td>i-Pr</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>r.t.</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>(1 mol)</td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>r.t.</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>(10 mol)</td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>18</td>
<td>r.t.</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>(10 mol)</td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>1.5</td>
<td>r.t.</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>(10 mol)</td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>23</td>
<td>-22°C</td>
<td>51</td>
</tr>
<tr>
<td>8</td>
<td>(1 mol)</td>
<td>t-Bu</td>
<td>Et₂O.HCI</td>
<td>90</td>
<td>-22°C</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>(1 mol)</td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>22</td>
<td>r.t.</td>
<td>63</td>
</tr>
<tr>
<td>10</td>
<td>1-Me-indole</td>
<td>i-Pr</td>
<td>MeSiCl₃</td>
<td>2</td>
<td>r.t.</td>
<td>26</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>i-Pr</td>
<td>MeSiCl₃</td>
<td>22</td>
<td>r.t.</td>
<td>32</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>i-Pr</td>
<td>MeSiCl₃</td>
<td>2</td>
<td>r.t.</td>
<td>14</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>i-Pr</td>
<td>MeSiCl₃</td>
<td>2</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>i-Pr</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>r.t.</td>
<td>64</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>-78°C</td>
<td>80</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>i-Pr</td>
<td>Et₂O.HCI</td>
<td>2</td>
<td>-78°C</td>
<td>49</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>i-Pr</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>-78°C</td>
<td>51</td>
</tr>
<tr>
<td>18</td>
<td>1-Me-pyrrole</td>
<td>i-Pr</td>
<td>MeSiCl₃</td>
<td>2</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>i-Pr</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>-40°C</td>
<td>22</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>-78°C</td>
<td>46</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>4</td>
<td>-78°C</td>
<td>56</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>8</td>
<td>-78°C</td>
<td>59</td>
</tr>
<tr>
<td>24</td>
<td>1,3-diMeO-benzene</td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>24</td>
<td>r.t.</td>
<td>32</td>
</tr>
<tr>
<td>25</td>
<td>(1 mol)</td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>5 days</td>
<td>r.t.</td>
<td>44</td>
</tr>
<tr>
<td>26</td>
<td>(1 mol)</td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>2</td>
<td>-50°C</td>
<td>38</td>
</tr>
<tr>
<td>27</td>
<td>(5 mol)</td>
<td>t-Bu</td>
<td>Et₂O.HCl</td>
<td>5 days</td>
<td>reflux</td>
<td>66</td>
</tr>
</tbody>
</table>

(a) 2.5-Disubstituted secondary amine (159) was also isolated in 21% yield.
(b) 2 Mol. equiv. of iminium salt used.
(c) 17% of (159) was also isolated.
(d) An "in situ" reaction.
(e) Polymeric material isolated.
(f) Starting material isolated entry 24, 52%; entry 25, 53%; entry 27, 79%.
(g) Prepared by literature procedure in 90% yield.
A qualitative indication that this class of iminium salts is more reactive than \( N,N \)-dialkyl(methyleneliminium) salts is given by the results obtained. It is of interest to note that \( N,N \)-dimethyl(methyleneliminium) chloride, in a reaction with \textit{meta}-dimethoxybenzene at room temperature gave only 4\% of the expected Mannich base.

\[
\begin{align*}
\text{Ar}-\text{H} & \quad + \quad \text{R} \quad + \quad \text{Cl}^- \\
\text{R}' \text{=} \text{Me or Et}
\end{align*}
\]

Equation 69

The results obtained substantiate further the greater reactivity of these iminium salts as compared to \( N,N \)-dialkyl-analogues. The least nucleophilic substrate, \textit{meta}-dimethoxybenzene affords reasonable yields of secondary amines at room temperature which are improved with heating under reflux. The duplication of results was not possible when the iminium salts were prepared using trichloromethylsilane. \( N \)-methylindole (entry 13) and \( N \)-methylpyrrole (entry 18), for example, afforded only the tertiary amines indicating that some silane was present in the precipitated salt.

Furan also afforded the 2,5-di\( N-t \)butylaminomethylfuran (159) when the reaction was performed at room temperature. Increasing the amount of furan resulted, as expected, in the predominance of tertiary amine after a prolonged reaction, though this could be avoided by reducing the reaction time or by lowering the temperature.
N-methylpyrrole gave reasonable yields of secondary amines only when the reaction was conducted at low temperature. Attempts to perform the reaction at room temperature resulted in the formation of a polymeric material. N.m.r. spectroscopy indicated that both the α-positions were substituted. The high field \(^1H\) and \(^{13}C\) n.m.r. spectra suggested that the polymer (160) was formed. The molecular weight distribution of the polymer was not investigated.

\[
\text{(159)}
\]

\[
\text{(160)}
\]

N-methylindole, having only one position activated towards aminomethylation, gave reasonable yields of secondary amines at room temperature in the absence of chlorosilane derivatives. Exclusive secondary amine formation was obtained when the reaction was performed at low temperature using a sterically demanding alkyl substituent on nitrogen (entry 15).

In a concurrent study\(^{42}\) a preliminary investigation of the reactions of enol trimethylsilyl ethers with these iminium salts was carried out. The corresponding secondary Mannich bases were isolated in good yields when the reactions were performed at \(-10^\circ C\) in dichloromethane. Silyl ketene acetals, however, rather surprisingly afforded only tertiary amines under the same conditions. These findings, together with some of the results already presented in this chapter, have been reported in a preliminary communication\(^{126}\).
This investigation furnished useful information about the mechanistic aspects of the reactions of bis(aminol ethers) with electron-rich aromatic compounds. The interception of the reaction could be achieved when hydrogen chloride was the only acid present in the reaction mixture. This provides a new method for the preparation of secondary amines. The use of chlorosilane derivatives is important if the preparation of tertiary amines is desired. The possibility of carrying out sequential reactions with two different nucleophiles has been briefly demonstrated.

3.6 Preparation of 2-Arylmethyltetrahydroisoquinolines

The frequent occurrence of the isoquinoline nucleus in naturally occurring alkaloids has led to a considerable interest in the synthesis of isoquinoline derivatives.

The synthesis of tetrahydroisoquinolines by the Pictet–Spengler reaction is well documented. α-Arylethylamines possessing electron releasing substituents at the 3-position react with aldehydes to form imines. These reagents, which are sometimes isolated, undergo intramolecular Mannich type reaction upon protonation with hydrochloric acid when heated to 100°C. These drastic conditions, however, are not favoured when labile functional groups are present.

Recent modifications employing milder reaction conditions have been developed. Thus, condensation of phenylethylamine derivatives with paraformaldehyde in formic acid at 40°C afforded good yields of N-formyltetrahydroisoquinoline derivatives. The use of 3 mol equivalents of paraformaldehyde in this system enabled the preparation of N-methyltetrahydroisoquinolines in one step. In the latter case formic acid can function as the solvent and acidic catalyst in the Pictet–
Spengler reaction as well as the reducing agent in the Eschweiler–Clarke \(N\)-methylation process.

A variety of \(N\)-substituted-tetrahydroisoquinolines have been reported recently. 2-Formyl-1,2,3,4-tetrahydroisoquinolines have been prepared from \(N\)-formylphenylethylamines\(^{129}\) (possessing electron-donating groups as well as without substituents in the benzene ring) on reaction with a variety of aldehydes as shown in Equation 70.

\[
\begin{array}{c}
\text{R}^1\text{CHO} + \text{H}^+ \\
\text{Reflux} \\
\end{array}
\]

\(\text{Equation 70}\)

2-Arylsulphonyl-1,2,3,4-tetrahydroisoquinolines have been prepared from the imines derived from \(\alpha\)-phenylethylamines in reaction with sulphonyl chlorides\(^{130}\). Similarly, 2-acyl-1,2,3,4-tetrahydroisoquinolines have been reported in reactions with acyl chlorides\(^{131}\).

Following the investigation of the reactions of bis(aminol ethers) for the preparation of secondary amines, a decision was taken to explore the use of bis(aminol ethers) derived from \(\alpha\)-phenylethylamines. Treatment of a solution of \(N,N\)-bis(methoxymethyl)-3,4-dimethoxy-\(\alpha\)-phenylethylamine in acetonitrile with 2-methylfuran, at room temperature, in the presence of trichloromethylsilane, resulted in the isolation of tetrahydroisoquinoline derivative (162) in 65% yield, as shown in Scheme...
It is anticipated that the product was formed in a tandem reaction in which the first iminium salt generated cyclized intramolecularly to give 2-methoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (163). The second iminium species (164) reacted with 2-methylfuran yielding the product (162).

SCHEME 46
Reagents (i) MeSiCl₃, MeCN; (ii) MeSiCl₃; (iii) 2-methylfuran

An attempt to identify the second intermediate iminium salt was undertaken. Upon treatment of the aminol ether with 2 mole equivalents of trichloromethylsilane, a relatively stable pale yellow crystalline solid (165) was isolated in quantitative yield. The $^{13}$C n.m.r. spectra of the solid determined in CDCl₃ and CD$_3$CN, even in the presence of sulphur dioxide, did not reveal the expected iminium resonances. A methylene resonance was observed at $\delta_c=78.4$ ppm which can be assigned to a chloromethyl-amino group.
It is noteworthy that the $^1$H decoupled $^{13}$C n.m.r. spectrum of $N,N$-dimethyl(methylene)iminium chloride$^{84}$b in (CD$_2$Cl$_2$/SO$_2$) showed the presence of four different carbons at $\delta_c = 38.7(s)$, 49.4(t), 79.0(s), and 168.1(t) ppm. This indicates that an equilibrium exists between the ionic and covalent species in that solvent system. Similarly the $^{13}$C n.m.r. spectrum of $N$-piperidyl(methylene)iminium chloride also showed similar features when recorded in (CD$_2$Cl$_2$/SO$_2$). $N$-piperidyl(methylene)iminium iodide$^{84}$, prepared by the interaction of di($N$-piperidyl)methane with iodotrimethylsilane, showed in its $^1$H decoupled $^{13}$C n.m.r. spectrum no evidence for the iminium carbon. Singlets were observed at $\delta_c$(DMSO–d$_6$) = 21.3, 22.0, 48.3, and 78.0 ppm. It is reasonable to conclude, therefore, that the pale yellow crystalline solid (165) is an equilibrium mixture in which the covalent species predominates, as shown in Equation 71.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{MeO} \\
\text{N} & \quad \text{N} & \quad \text{N} & \quad \text{N} & \quad \text{N} \\
\text{MeSiCl$_3$} & \quad \text{Et}_{2}O & \quad \text{MeSiCl$_3$} & \quad \text{Et}_{2}O & \quad \text{MeSiCl$_3$} \\
\rightarrow & \quad \rightarrow & \quad \rightarrow & \quad \rightarrow & \quad \rightarrow \\
\text{MeO} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{MeO} \\
\text{N} & \quad \text{N} & \quad \text{N} & \quad \text{N} & \quad \text{N} \\
\text{MeCl} & \quad \text{MeCl} & \quad \text{MeCl} & \quad \text{MeCl} & \quad \text{MeCl} \\
\end{align*}
\]

Equation 71

An attempt to hydrolyse the yellow crystalline solid (165) to 6,7-dimethoxytetrahydroisoquinoline on treating with water and adjusting the pH to 14, resulted in the formation of the aminal (166) in 95% yield, Equation 72. The preparation of an aminal from an iminium salt is not unprecedented$^{132}$. This observation reinforces the proposed structure of the yellow crystalline solid.
It is interesting to note that the iminium salts derived from $N,N'$-bis(ethoxymethyl)-$\alpha$-phenylethylamine and $N,N'$-bis(ethoxymethyl)-$\alpha$-(4-methoxyphenyl)ethylamine under the same conditions did not give the corresponding aminals. The $N,N''$-tris[$\alpha$-arylethyl]hexahydro-$s$-triazine derivatives (167) and (168) were formed in 70% and 74% respectively.

This is not unexpected as these iminium salts failed to undergo intramolecular cyclization and the secondary amines were isolated on treatment with 2-methylfuran (Table 22, entries 22 and 28). An electron-donating substituent at the 3-position on the benzene ring is essential in order to activate the para-position for intramolecular Mannich reaction.

The aminal (166) was fully characterised by elemental analysis and by spectroscopic methods. It was also identified by reaction with acetyl chloride which gave 2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline in 54% yield together with the solid (165), in 93% yield. Upon reaction with 2-methylfuran the isolated solid (165) gave the tetrahydroisoquinoline (162) in 95% yield, Equation 73.
Although subsequent "in situ" reactions of other aromatic heterocycles gave reasonable yields of the corresponding 2-arylmethyltetrahydroisoquinolines, isolation and purification proved somewhat difficult. N-methylindole, for example, afforded the corresponding crude product in 85% yield. Thus a decision was taken to carry out the reactions in two steps. It was argued that reactions of the solid (165) should allow the formation of cleaner products in higher yields as was the case of the reaction of 2-methylfuran with the solid isolated from the aminal (166).

A number of novel 2-arylmethyl- and 2-benzyl-tetrahydroisoquinolines were prepared in high yields on treatment of the solid (165)
with various heterocycles and electron rich aromatic compounds, as shown below in Equation 74. The results obtained are disclosed in Table 24, and have recently been reported in a preliminary communication$^{33}$.

\[ \text{Equation 74} \]
### TABLE 24
Preparation of N-Arylmethyl-1,2,3,4-tetrahydroisoquinolines

<table>
<thead>
<tr>
<th>Aromatic Substrate</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furan</td>
<td>72</td>
<td>(169)</td>
<td>83</td>
</tr>
<tr>
<td>2-Me-furan</td>
<td>24</td>
<td>(162)</td>
<td>90</td>
</tr>
<tr>
<td>Pyrrole</td>
<td>20</td>
<td>(170)</td>
<td>83</td>
</tr>
<tr>
<td>1-Me-pyrrole</td>
<td>20</td>
<td>(171)</td>
<td>87</td>
</tr>
<tr>
<td>Indole</td>
<td>22</td>
<td>(172)</td>
<td>93</td>
</tr>
<tr>
<td>1-Me-indole</td>
<td>20</td>
<td>(173)</td>
<td>89</td>
</tr>
<tr>
<td>1,3-di-MeO-benzene&lt;sup&gt;b&lt;/sup&gt;</td>
<td>72</td>
<td>(174)</td>
<td>77</td>
</tr>
<tr>
<td>2,4-di-MeO-phenyltributylstannane</td>
<td>48</td>
<td>(174)</td>
<td>87</td>
</tr>
<tr>
<td>2-MeO-phenyltributylstannane</td>
<td>72</td>
<td>(175)</td>
<td>73</td>
</tr>
<tr>
<td>Resorcinol</td>
<td>16</td>
<td>(176)</td>
<td>80</td>
</tr>
<tr>
<td>2-Naphthol</td>
<td>16</td>
<td>(177)</td>
<td>91</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields not optimised.

The yields of products obtained from these reactions indicate the high reactivity of the solid (165). It is of interest to note that the product (175) is the methyl ether of the alkaloid sendaverine<sup>134</sup> which was isolated from *Corydalis aurea* Willd. (Fumariaceae) by Manske in 1938<sup>135</sup>.
The methodology developed in this study demonstrates the potential applicability of the Mannich reaction for the preparation of naturally occurring alkaloids.
CHAPTER FOUR

EXPERIMENTAL

All solvents were dried and distilled before use. Liquid starting materials were freshly distilled before use and solids recrystallised from appropriate solvents.

**Acetonitrile:** Distilled from phosphorous pentoxide, then anhydrous potassium carbonate, and stored over 3A molecular sieves.

**Dichloromethane:** Distilled from phosphorous pentoxide and stored over 3A molecular sieves.

**Diethyl Ether:** Allowed to stand over calcium chloride overnight and distilled. In some cases redistilled from lithium aluminium hydride.

**Dimethyl Sulphoxide:** Stirred over barium oxide overnight and distilled under reduced pressure.

**1,4-Dioxane:** Distilled from sodium.

**Methanol:** Distilled from magnesium methoxide and stored over 4A molecular sieves.

**Ethanol:** Distilled from magnesium ethoxide and stored over 4A molecular sieves.

**Tetrahydrofuran:** Distilled from lithium aluminium hydride–triphenylmethane and used immediately.
Petroleum Ether (40–60°C): Fractionally distilled.

Benzene: Fractionally distilled and stored over 3A molecular sieves.

Toluene: Fractionally distilled and stored over 3A molecular sieves.

Nitrogen: Oxygen–free nitrogen was dried by passing successively through concentrated sulphuric acid, sodium hydroxide pellets and silica gel.

All the solutions of products in organic solvents were dried over magnesium sulphate.

Infra–Red Spectra were recorded on a Perkin–Elmer 257 spectrophotometer; only selected absorbances are reported. Spectra were taken as thin films (film), potassium bromide discs (KBr) or nujol mulls (nujol).

N.M.R. Spectra: All spectra were recorded in CDCl₃ unless otherwise stated using TMS as reference. ¹H n.m.r. spectra were recorded on Varian EM 360 A (60 MHz), Perkin–Elmer R32 (90 MHz), Jeol GSX–400/54 (400 MHz), or Bruker AC–250 (250 MHz) spectrometers. ¹³C N.m.r. spectra were recorded on Bruker WP 80 (20.1 MHz), Jeol GSX/54 (100.4 MHz), Bruker AMX 360 (90.6 MHz), or Bruker AC–250 (62.9 MHz) spectrometers.

Multiplicities are reported as broad singlet (br.s), singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), septet (sept), and double doublet (dd).

High field ¹³C n.m.r. – Distortionless Enhancement by Polarisation Transfer (DEPT) spectra; methyl and methine carbon signals upwards, methylene carbon signals downwards, and quaternary carbon signals absent.
Mass Spectra were recorded by electron impact using a Kratos (M.S.80) spectrometer or by fast atom bombardment (FAB) using a V.G.70–250 S spectrometer.

Melting Points were recorded using a Kofler hot stage apparatus and are uncorrected.

Analyses: Microanalyses were carried out by Fisons P.L.C., Pharmaceutical Division (Loughborough).
2.2.1 Preparation of Aminals (97) (General Procedure)

Dialkylamine (2 mol, 40% aqueous solution) was added dropwise to stirred, ice-cooled formaldehyde (1 mol; 36% aqueous solution). The mixture was allowed to stand overnight and then saturated with solid potassium hydroxide. The upper layer was separated and dried over potassium hydroxide pellets. The residual liquid was then fractionally distilled. The following aminals were prepared:

Bis(N,N-dimethylamino)methane (97a)

Yields (89–92%), b.p. 82–83°C, (lit. 81.5–83°C).

$^1$H n.m.r. (60 MHz), $\delta = 2.19$ (12H, s, CH$_3$) and 2.66 (2H, s, CH$_2$) ppm.

Bis(N,N-diethylamino)methane (97b)

Yields (82–90%), b.p. 47–48°C / 7.5 mmHg, (lit. 166–67°C).

$^1$H n.m.r. (60 MHz), $\delta = 1.00$ (12H, t, J = 7.5 Hz, CH$_2$CH$_3$), 2.62 (8H, q, J = 7.5 Hz, CH$_2$CH$_3$), and 3.05 (2H, s, NCH$_2$N) ppm.

M.S. (m/z); 158 (0.39%), 86 (100%), $^{+}$M 158.1765; C$_9$H$_{22}$N$_2$ requires 158.1783.

Di(N-pyrrolidinyl)methane (97c)

Yields (72–85%), b.p. 70°C / 7 mmHg, (lit. 60°C / 3.5 mmHg).

$^1$H n.m.r. (60 MHz), $\delta = 1.57–1.98$ (8H, m, C[3 and 4] H), 2.38–2.81, (8H, m, C[2 and 5] H), and 3.23 (2H, s, CH$_2$) ppm.
M.S. \((m/z)\): 154 (59\%), 84 (100\%), \((\text{M}^+)\) 154.1447; \(\text{C}_9\text{H}_{19}\text{N}_2\) requires 154.1470.

Di\((N\text{-piperidyl})\text{methane (97d)}\)

Yields (76–93\%), b.p. 100°C / 10 mmHg, (lit.\(^{137}\), 103–4°C / 14 mmHg).
\(^1\text{H n.m.r. (60 MHz), } \delta = 1.39–1.73 \) (12H, m, C\([3, 4 \text{ and } 5] \) H), 2.23–2.53 (8H, m, C\([2 \text{ and } 6] \) H), and 2.77 (2H, s, CH\(_2\) ppm.

Di\((N\text{-morpholinyll})\text{methane (97e)}\)

Yield 76\%, b.p. 110°C / 10 mmHg (lit.\(^{138}\), 99–107°C / 2mmHg).
\(^1\text{H n.m.r. (60 MHz), } \delta = 2.40–2.60 \) (8H, m, C\([2 \text{ and } 6] \) H), 2.87 (2H, s, CH\(_2\)), and 3.58–3.80 (8H, m, C\([3 \text{ and } 5] \) H) ppm.

2.2.2 Preparation of Aminol Ethers (98) (General Procedure)

Anhydrous dialkylamine (1 mol), dry alcohol (4 mol), and anhydrous potassium carbonate (1.0 mol) were stirred at 0°C for 15 minutes. Paraformaldehyde (1.0 mol equiv.) was added in one portion and the mixture was stirred for two days. The solid was filtered and washed with dry ether. The combined filtrates were concentrated \textit{in vacuo} and fractionally distilled through an 18" Vigreux column. The following aminol ethers were prepared:

Ethoxy-\(N, N\text{-dimethylaminomethane}\)

Dimethylamine (20.0g, 0.44 mol), ethanol (92.16g, 2 mol), potassium carbonate (89.93g, 0.60 mol), and paraformaldehyde (12.01g, 0.4 mol equiv.) were treated as described in the general procedure. The excess
ethanol was removed as a negative azeotrope with hexane (b.p. 59°C). The residue, after distillation afforded ethoxy-\(N,N\)-dimethylaminomethane (6.87g, 15%), b.p. 95°C, (lit.\(^{139}\), 123°C / 760 mmHg).

\(^1\)H n.m.r. (60 MHz), \(\delta = 1.23\) (3H, t, \(J = 7.5\) Hz, OCH\(_2\)CH\(_3\)), 2.30 (6H, s, NCH\(_3\)), 3.43 (2H, q, \(J = 7.5\) Hz, OCH\(_2\)CH\(_3\)), and 4.13 (2H, s, NCH\(_2\)O) ppm.

**Iso-propoxy-\(N,N\)-dimethylaminomethane**

Dimethylamine (65.0g, 1.44 mol), iso-propanol (180.03g, 3 mol), potassium carbonate (276.42g, 2 mol), and paraformaldehyde (42.04g, 1.40 mol equiv.), were treated as described in the general procedure. The excess iso-propanol was removed as negative azeotrope with hexane (b.p. 63°C). The residue was fractionally distilled, affording iso-propoxy-\(N,N\)-dimethylaminomethane (25.61g, 15%), b.p. 98–101°C.

\(^1\)H n.m.r. (60 MHz), \(\delta = 1.17\) (6H, d, \(J = 6\) Hz, CH(CH\(_3\))\(_2\)), 2.33 (6H, s, NCH\(_3\)), 3.37–3.93 (1H, sept., \(J = 6\) Hz, CHMe\(_2\)), and 4.03 (2H, s, NCH\(_2\)O) ppm.

\(^13\)C n.m.r. (20.1 MHz), \(\delta = 22.5\) (q, CH[CH\(_3\)]\(_2\)), 41.6 (q, NCH\(_3\)), 69.6 (d, CHMe\(_2\)), and 87.4 (d, OCH\(_2\)N) ppm.

M.S. (m/z): 117 (4.1%), 45 (100%), (M\(^+\)) 117.1144; C\(_6\)H\(_{15}\)NO requires 117.1153.

**Ethoxy-\(N,N\)-diethylaminomethane**

Diethylamine (146.28g, 2 mol), ethanol (180.28g, 4 mol), potassium carbonate (276.42g, 2 mol), and paraformaldehyde (60.06g, 2 mol equiv.) were treated as described in the general procedure. The residue was fractionally distilled affording two fractions. First fraction ethoxy-\(N,N\)-diethylaminomethane (140.2g, 54%), b.p. 76–78°C / 80 mmHg,
(lit. 87, 132–134°C / 756 mmHg).

1H n.m.r. (60 MHz), δ = 1.10 (6H, t, J = 7.5 Hz, NCH$_2$CH$_3$), 1.27 (3H, t, J = 7.5 Hz, OCH$_2$CH$_3$), 2.73 (4H, q, J = 7.5 Hz, NCH$_2$CH$_3$), 3.43 (2H, q, J = 7.5 Hz, OCH$_2$CH$_3$), and 4.23 (2H, s, NCH$_2$O) ppm.

13C n.m.r. (20.1 MHz), δ = 13.4 (q, NCH$_2$CH$_3$), 15.5 (q, OCH$_2$CH$_3$), 46.6 (t, NCH$_2$CH$_3$), 63.3 (t, OCH$_2$CH$_3$), and 84.4 (t, NCH$_2$O) ppm.

M.S. (m/z); 131 (18.55%), 86 (100%), (M$^+$) 131.1298; C$_7$H$_{17}$NO requires 131.1310.

Second fraction ethoxymethoxy-$N,N$-diethylaminomethane (67.5g, 19%), b.p. 67–69°C / 20 mmHg.

1H n.m.r. (60 MHz), δ = 1.10 (6H, t, J = 7.5 Hz, NCH$_2$CH$_3$), 1.23 (3H, t, J = 7.5 Hz, OCH$_2$CH$_3$), 2.77 (4H, q, J = 7.5 Hz, NCH$_2$CH$_3$), 3.63 (2H, q, J = 7.5 Hz, OCH$_2$CH$_3$), 4.43 (2H, s, NCH$_2$O), and 4.73 (2H, s, OCH$_2$O) ppm.

13C n.m.r. (20.1 MHz), δ = 13.5 (q, NCH$_2$CH$_3$), 15.3 (q, OCH$_2$CH$_3$), 45.6 (t, NCH$_2$CH$_3$), 63.2 (t, OCH$_2$CH$_3$), 82.3 (t, NCH$_2$O), and 93.3 (t, OCH$_2$O) ppm.

Iso-propoxy-$N,N$-diethylaminomethane

Diethylamine (36.57g, 0.5 mol), iso-propanol (60.11g, 1 mol), potassium carbonate (69.10g, 0.5 mol), and paraformaldehyde (15.01g, 0.5 mol equiv.) were treated as described in the general procedure. The residue was fractionally distilled affording two fractions.

First fraction, iso-propoxy-$N,N$-diethylaminomethane (39.89g, 55%), b.p. 62–64°C / 43 mmHg.

1H n.m.r. (60 MHz), δ = 1.07 (6H, t, J = 7.5 Hz, NCH$_2$CH$_3$), 1.13 (6H, d, J = 6 Hz, CHICH$_2$J$_2$), 2.70 (4H, q, J = 7.5 Hz, NCH$_2$CH$_3$), 3.60
(1H, sept., J = 6 Hz, CHMe₂), and 4.20 (2H, s, NCH₂O) ppm.
¹³C n.m.r. (20.1 MHz), δ = 13.3 (q, NCH₂CH₃), 22.5 (q, CH[CH₃]₂), 45.5 (t, NCH₂CH₃), 68.8 (d, CHMe₂), and 82.2 (t, NCH₂O) ppm.
M.S. (m/z): 145 (4.2%), 86 (100%), (M⁺) 145.1460; C₆H₁₅NO requires 145.1462.

Second fraction, iso-propoxymethoxy-N,N-diethylaminomethane (20.56g, 23%), b.p. 78°C / 20 mmHg.
¹H n.m.r. (60 MHz), δ = 1.08 (6H, t, J = 7.5 Hz, NCH₂CH₃), 1.13 (6H, d, J = 6Hz, CH[CH₃]₂), 2.67 (4H, q, J = 7.5 Hz, NCH₂CH₃), 3.87 (1H, sept., CHMe₂), 4.37 (2H, s, NCH₂O), and 4.70 (2H, s, OCH₂O) ppm.
¹³C n.m.r. (20.1 MHz), δ = (13.3, q, NCH₂CH₃), 22.6 (q, CH[CH₃]₂), 45.4 (t, NCH₂CH₃), 68.7 (d, CHMe₂), 82.1 (t, NCH₂O), and 91.3 (t, OCH₂O) ppm.
M.S. (m/z); 175 (0.11%), 86 (100%), (M⁺) 175.1555; C₉H₂₁NO requires 175.1567.

Ethoxy-N-pyrrolidinylmethane

Pyrrolidine (142.24g, 2 mol), ethanol (180.28g, 4 mol), potassium carbonate (331.70g, 2.4 mol), and paraformaldehyde (60.03g, 2 mol equiv.) were treated as described in the general procedure. The residue was fractionally distilled to yield ethoxy-N-pyrrolidinylmethane (168.9g, 66%), b.p. 42-44°C / 16 mmHg.
¹H n.m.r. (60 MHz), δ = 1.23 (3H, J = 7.5 Hz, CH₃), 1.55-1.92 (4H, m, C[3 and 4] H), 2.56-2.94 (4H, m, C[2 and 5] H), 3.53 (2H, q, J = 7.5 Hz, CH₂CH₃), and 4.24 (2H, s, OCH₂) ppm.
M.S. (m/z); 129 (10.9%), 84 (100%) (M⁺) 129.1125; C₇H₁₅NO requires 129.1154.
Ethoxy-N-piperidylmethane

Piperidine (42.58g, 0.5 mol), ethanol (92.16g, 2 mol), potassium carbonate (69.08g, 0.5 mol), and paraformaldehyde (12.01g, 0.4 mol equiv.) were treated as described in the general procedure. The residue was then distilled, affording ethoxy-N-piperidylmethane (81.66g, 57%), b.p. 62-64°C / 10 mmHg, (lit. 139°C , b.p. 101°C / 25 mmHg).

\[ ^1H \text{n.m.r. (} 60 \text{ MHz)} , \delta = 1.17 (3H, t, J = 7.5 \text{ Hz, CH}_3), 1.37-1.63 (6H, m, C\{3, 4 and 5\} H), 2.27-2.80 (4H, m, C\{2 and 6\} H), 3.37 (2H, q, J = 7.5 Hz, OCH}_2), \text{and } 3.95 (2H, s, NCH}_2O) \text{ ppm.}

M.S. (m/z): 143 (9.9%), 98 (100%), (M*) , 143.1279; C\text{_{8}H_{17}NO} \text{ requires } 143.1310.

Ethoxy-N-morpholinylmethane

Morpholine (108.9g, 1.25 mol), ethanol (225.3g, 5 mol), potassium carbonate (207.3g, 1.5 mol), and paraformaldehyde (30.03g, 1 mol equiv.) were treated as described in the general procedure. The residue was distilled affording the title compound (181.54g, 61%), b.p. 72-74°C / 9 mmHg, (lit. 58-63°C / 6 mmHg).

\[ ^1H \text{n.m.r. (} 250 \text{ MHz)} , \delta = 1.20 (3H, t, J = 6.97 \text{ Hz, CH}_3), 2.48-2.52 (4H, m, C\{2 and 6\} H), 3.52 (2H, q, J = 6.97 Hz, OCH}_2CH}_3), 3.68-3.77 (4H, m, C\{3 and 5\} H), \text{and } 4.04 (2H, s, NCH}_2O) \text{ ppm.}

Ethoxy-N,N-di-iso-propylaminomethane

Di-iso-propylamine (50.59g, 0.5 mol), ethanol (92.16g, 2 mol), potassium carbonate (82.93g, 0.6 mol), and paraformaldehyde (12.01g, 0.4 mol equiv.) were treated as described in the general procedure. The residue was then fractionally distilled to afford the title compound
\[ (42.69 \text{g, 67\%}) \text{ b.p. \(42^\circ\text{C} / 5 \text{mmHg, (lit.}^{139} \text{, b.p. \(81^\circ\text{C} / 25 \text{mmHg).} \]

\(^1\text{H n.m.r. (60 MHz), } \delta = 1.11 (12\text{H, d, } J = 6 \text{ Hz, CH(CH}_3)_2), \ 1.17 (3\text{H, t, } J = 7.5 \text{ Hz, CH}_2\text{CH}_3), \ 3.15 (2\text{H, sept., } J = 6 \text{ Hz, CHMe}_2), \ 3.37 (q, J = 7.5 \text{ Hz, CH}_2\text{CH}_3), \text{ and } 4.23 (2\text{H, s, NCH}_2\text{O}) \text{ ppm.} \]

\(^{13}\text{C n.m.r. (20.1 MHz), } \delta = 15.5 (q, \text{ CH}_2\text{CH}_3), \ 22.3 (q, \text{ CH(CH}_3)_2), \ 48.7 (d, \text{ CHMe}_2), \ 61.4 (t, \text{ CH}_2\text{CH}_3), \text{ and } 79.6 (t, \text{ NCH}_2\text{O}) \text{ ppm.} \]

M.S. (m/z); (M\textsuperscript{+}) 159.1612; C\textsubscript{9}H\textsubscript{21}NO \text{ requires 159.1623.} \]

2.3.1 "In Situ" Reactions of \(N\text{--Methylpyrrole Activated with Acetyl Chloride} \]

(A) Preparation of 2-(\(N,N\text{--dialkylaminomethyl}\)--1--methylpyrroles (100) 

General Method (A)

A mixture of freshly distilled 1--methylpyrrole (1.1 equiv.) and an aminal or aminol ether (1 equiv.) was stirred in acetonitrile at 0°C under a still head of dry nitrogen. Acetyl chloride (1.1 equiv.) was added dropwise and the reaction mixture was allowed to warm to room temperature. Stirring was continued for the required time before water (20 ml) was added. The solvent was removed in vacuo and the residue was acidified to pH1 with 2N hydrochloric acid. The aqueous solution was washed with dichloromethane (3 x 30 ml) and then basified to pH14 with 4N sodium hydroxide. The cloudy suspension was extracted with dichloromethane (3 x 40 ml) and the combined organic extracts from the basic solution were dried and concentrated \textit{in vacuo}. The residue was then distilled under reduced pressure using a Kugelröhr apparatus.

(1) Acetyl chloride (2.16g, 27.5 mmol) was added to the mixture of 1--methylpyrrole (2.23g, 27.5 mmol) and bis(\(N,N\text{--dimethylamino}\)--
methane (2.56g, 25 mmol) in acetonitrile (90 ml). The mixture was stirred for 2 hours at room temperature to yield 2-(\(N,N\)-dimethylaminomethyl)-1-methylpyrrole (0.63g, 18%), b.p. 56-58°C/5 mmHg, (lit.\(^{73}\), 53-54°C/6 mmHg).

i.r. (film) \(\nu_{\text{max}}\) 1635 (aromatic ring) cm\(^{-1}\).

\(^1\)H n.m.r. (60 MHz), \(\delta = 2.16\) (6H, s, N(CH\(_3\))\(_2\)), 3.29 (2H, s, CH\(_2\)), 3.57 (3H, s, NCH\(_3\)), 5.96-6.07 (2H, m, C[3 and 4] H), and 6.45-6.56 (1H, m, C[5] H) ppm.

\(^{13}\)C n.m.r. (20.1 MHz), \(\delta = 33.5\) (q, NCH\(_3\)), 44.7 (q, N(CH\(_3\))\(_2\)), 55.7 (t, CH\(_2\)), 106.4 (d, C[3]), 109.3 (d, C[4]), 122.4 (d, C[5]), and 129.8 (s, C[2]) ppm.

M.S. (m/z): (M\(^+\)) 138.1149; \(\text{C}_8\text{H}_{14}\text{N}_2\) requires 138.1157.

(2) Acetyl chloride (1.73g, 22 mmol) was added to a mixture of \(N\)-methylpyrrole (1.78g, 22 mmol) and di(N-piperidyl)methane (3.65g, 20 mmol) in acetonitrile (120 ml). The mixture was stirred at room temperature for 2 hours, yielding 2-(\(N\)-piperidylmethyl)-1-methylpyrrole (1.46g, 41%), b.p. 115-120°C/5.5 mmHg, (lit.\(^{73}\), 97°C/5 mmHg).

\(^1\)H n.m.r. (60 MHz), \(\delta = 1.29-1.70\) (6H, m, C[3', 4' and 5']) H), 2.22-2.42 (4H, m, C[2' and 6']) H), 3.32 (2H, s, CH\(_2\)), 3.58 (3H, s, NCH\(_3\)), 5.86-6.01 (2H, m, C[3 and 4] H), and 6.42-6.52 (1H, m, C[5] H) ppm.

\(^{13}\)C n.m.r. (20.1 MHz), \(\delta = 24.7\) (t, C[4']), 26.2 (t, C[3' and 5'])), 33.6 (q, NCH\(_3\)), 54.3 (t, C[2' and 6']), 55.3 (t, CH\(_2\)), 106.2 (d, C[3]), 109.3 (d, C[4]), 122.2 (d, C[5]), and 129.4 (s, C[2]) ppm.

M.S. (m/z): (M\(^+\)) 178.1473; \(\text{C}_{11}\text{H}_{18}\text{N}_2\) requires 178.1470.

(3) Acetyl chloride (1.29g, 16.5 mmol) was added to a mixture of \(N\)-methylpyrrole (1.34g, 16.5 mmol) and di(N-morpholiny)methane (2.79g, 15mmol) in acetonitrile (90 ml). The mixture was stirred at room temperature for 2 hours, yielding 2-(\(N\)-morpholinylmethyl)-1-methyl-
pyrrole (1.45g, 54%), b.p. 110°C/3.5 mmHg, (lit.73, 113–114°C/5 mmHg).
i.r. (film) \( \nu_{\text{max}} \) 1630 (aromatic ring) cm\(^{-1}\).
'\( H \) n.m.r. (60 MHz, \( \delta = 2.17-2.46 \) (4H, m, C [3’ and 5’] H), 3.37 (2H, s, CH\(_2\)), 3.60 (3H, s, NCH\(_3\)), 3.44–3.73 (4H, m, C [2’ and 6’] H), 5.87–6.02 (2H, m, C [3 and 4] H), and 6.40–6.55 (1H, m, C [5] H) ppm.
'\( C \) n.m.r. (20.1 MHz, \( \delta = 33.0 \) (q, NCH\(_3\)), 52.7 (t, C [3’ and 5’]), 54.1 (t, C [2’ and 6’]), 66.3 (t, NCH\(_2\)O), 105.7 (d, C [3]), 109.1 (d, C [4]), 121.9 (d, C [5]), and 127.5 (s, C [2]) ppm.
M.S. (m/z); (M\(^+\)) 180.1258; C\(_{10}\)H\(_{16}\)N\(_2\)O requires 180.1263.

(4) Acetyl chloride (1.57g, 22 mmol) was added to a mixture of N–methylpyrrole (1.78g, 22 mmol) and ethoxy–N–piperidylmethane (2.86g, 20 mmol) in acetonitrile (120 ml). The mixture was stirred at room temperature for 6 hours to yield 2–(N–piperidylmethyl)–1–methylpyrrole (0.32g, 9%), b.p. 115°C / 5.5 mmHg.

(5) Acetyl chloride (1.57g, 22 mmol) was added to a mixture of N–methylpyrrole (1.78g, 22 mmol) and ethoxy–N–morpholinylmethane (2.91g, 20 mmol) in acetonitrile (120 ml). The mixture was stirred at room temperature for 6 hours to yield 2–(N–morpholinylmethyl)–1–methylpyrrole (0.65g, 18%), b.p. 110°C / 3.5 mmHg.

(B) Preparation of 2,5-Bis(N,N–dialkylaminomethyl)–1–methylpyrroles (101)

General Method (B)

A mixture of N–methylpyrrole (1.0 equiv.) and an aminal (2.1 equiv.) was stirred in acetonitrile at 0°C under an atmosphere of dry nitrogen. Acetyl chloride (2.1 equiv.) was added dropwise and the mixture was allowed to
reach room temperature with continuous stirring for the required time. The work-up procedure described in General Method (A) was then followed. The crude product was then distilled using a Kugelröhr apparatus or recrystallised from a suitable solvent.

(6) 2,5-Bis(N,N-dimethylaminomethyl)-1-methylpyrrole (101a)

Acetyl chloride (2.75g, 35 mmol) was added to a mixture of N-methylpyrrole (1.30g, 16 mmol) and bis(N,N-dimethylamino)methane in acetonitrile (150 ml). The reaction mixture was stirred at room temperature for 5 days. No Mannich base was isolated after work-up. The reaction was repeated at -22°C for 6 days. After work-up and distillation the title compound was isolated (0.65g, 20%), b.p. 87°C / 3.5 mmHg, (lit.73 87-88°C / 3.5 mmHg).

\[ \begin{align*} \text{1H n.m.r. (90 MHz),} & \quad \delta = 2.21 (12H, s, NCH}_3\text{)2, 3.39 (4H, s, NCH}_2\text{),} \\
& \quad 3.67 (3H, s, NCH}_3\text{), and 5.87 (2H, s, C[3 and 4] H) ppm.} \end{align*} \]

\[ \begin{align*} \text{13C n.m.r. (20.1 MHz),} & \quad \delta = 30.2 (q, NCH}_3\text{), 44.8 (q, NCH}_3\text{), 56.1 (t, CH}_2\text{),} \\
& \quad 107.7 (d, C[3 and 4]), and 130.3 (s, C[2 and 5]) ppm.} \end{align*} \]

M.S. (m/z); (M+) 195.1731, \( \text{C}_{11}\text{H}_{21}\text{N}_3 \); requires 195.1735.

(7) 2,5-Di(N-piperidylmethyl)-1-methylpyrrole (101b)

Acetyl chloride (3.30g, 42 mmol) was added to a mixture of N-methylpyrrole (1.22g, 15 mmol) and di(N-piperidyl)methane (6.93g, 38 mmol) in acetonitrile (110 ml). The mixture was stirred at room temperature for 6 days yielding the title compound (3.40g, 82%), b.p. 120°C / 0.5 mmHg, (lit.73, 165-167°C / 3 mmHg).

\[ \begin{align*} \text{1H n.m.r. (250 MHz),} & \quad \delta = 1.40-1.56 (12H, m, C[3', 4' and 5']) \text{H}, \\
& \quad 2.30-2.32 (8H, m, C[2' and 6']) \text{H}, 3.36 (4H, s, CH}_2\text{), 3.60 (3H, s, NCH}_3\text{),} \\
& \quad \text{and 5.87 (2H, s, C[3 and 4] H) ppm.} \end{align*} \]
$^{13}$C n.m.r. (62.9 MHz), δ = 24.6 (C[4']), 26.1 (C[3' and 5']), 30.6 (NCH$_3$), 54.2 (C[2' and 6']), 55.5 (NCH$_2$), 107.4 (C[3 and 4]), and 129.9 (C[2 and 5]) ppm.

M.S. (m/z); 275 (22.8%), 191 (100%), (M$^+$) 275.2363; C$_{17}$H$_{29}$Na requires 275.2361.

(8) 2,5-Di(N-morpholinylmethyl)-1-methylpyrrole (101c)

Acetyl chloride (2.16 g, 27.5 mmol) was added to a mixture of N-methylpyrrole (0.81 g, 10 mmol) and di(N-morpholinyldimethyl) methane (4.66 g, 22 mmol) in acetonitrile (110 ml). The mixture was stirred at room temperature for 6 days and the title compound was isolated as a white solid (2.42 g, 87%), and recrystallised from ethyl acetate, m.p. 70–72°C.

$^1$H n.m.r. (60 MHz), δ = 2.24–2.60 (8H, m, C[3' and 5']) H), 3.41 (4H, s, CH$_2$), 3.52–3.86 (8H, m, [2' and 6'] H), 3.64 (3H, s, NCH$_3$), and 5.90 (2H, s, C[3 and 4]) ppm.

$^{13}$C n.m.r. (20.1 MHz), δ = 30.7 (q, NCH$_3$), 53.4 (t, C[3' and 5']), 55.2 (t, NCH$_2$), 67.2 (t, C[2' and 6']), 108.2 (d, C[3 and 4]), and 129.3 (s, C[2 and 5]) ppm.

M.S. (m/z); (M$^+$) 279.1951; C$_{15}$H$_{26}$N$_3$O$_2$ requires 279.1947.

(9) Preparation of 1,1'-Dimethyl-2,2'-dipyrrolylmethane (103)

Acetyl chloride (3.14 g, 40 mmol) was added dropwise to a mixture of 2-(N-dimethylaminomethyl)-1-methylpyrrole (5.53 g, 40 mmol) and N-methylpyrrole (12.98 g, 160 mmol) in acetonitrile (200 ml) at 0°C under an atmosphere of dry nitrogen. The mixture was allowed to warm to room temperature with continuous stirring for 18 hours. The solvent was then removed in vacuo and the residue was dissolved in water (50 ml). The aqueous acidic solution was then extracted with dichloromethane.
(3 x 40 ml). The combined organic washings were dried and concentrated in vacuo to a dark brown solid (6.29 g). Recrystallisation from ethyl acetate afforded the title compound as a white solid (5.23 g, 75%), m.p. 74–76°C, (lit.75 m.p. 75–76°C).

'H n.m.r. (250 MHz), δ = 3.49 (6H, s, NCH₃), 3.88 (2H, s, CH₂), 5.80 (2H, m, C[4 and 4'] H), 6.02 (2H, m, C[3 and 3'] H), and 6.87 (2H, m, C[5 and 5'] H) ppm.

'13C n.m.r. (62.9 MHz), δ = 25.0 (CH₂), 33.8 (NCH₃), 106.2 (C[3 and 3']), 107.4 (C[4 and 4']), 121.6 (C[5 and 5']), and 129.6 (C[2 and 2']) ppm.

M.S. (m/z); 174 (100%) (M⁺) 174.1139; C₁₁H₁₄N₂ requires 174.1157.

(10) Preparation of 2-(N,N-DiethylaminomethyO-5-methylfuran

Acetyl chloride (1.73 g, 22 mmol) was added dropwise to ethoxy-N,N-diethylaminomethane (2.62 g, 20 mmol) in petrol (40–60°C) (60 ml) at 0°C under an atmosphere of nitrogen. The mixture was allowed to stand at room temperature for 20 hours when a white solid precipitated out. The solvent was decanted and the solid was washed with more petrol (3 x 60 ml) and then concentrated in vacuo. The solid was then dissolved in acetonitrile (60 ml) and 2–methylfuran (1.64 g, 20 mmol) was added and the mixture stirred at room temperature for 24 hours under nitrogen. The solvent was removed in vacuo and the residue dissolved in water (20 ml), acidified with 2N hydrochloric acid and washed with ether (3 x 30 ml). The aqueous layer was basified with 4N sodium hydroxide and extracted with ether (3 x 40 ml). The combined organic washings from the basic solution were dried and concentrated in vacuo to a yellow liquid (0.60 g). Kugelröhr distillation afforded the title compound (0.49 g, 15%), b.p. 70°C / 4 mmHg, (lit.140, 75–8 °C / 25 mmHg).

'H n.m.r. (60 MHz), δ = 1.08 (6H, t, J = 7.5 Hz NCH₂CH₃), 2.30 (3H, s, C[5]-CH₃), 3.50 (4H, q, J = 7.5 Hz, NCH₂CH₃), 3.63 (2H, s, NCH₂),
5.80–6.00 (1H, m, C[4] H), and 6.07 (1H, d, J_{AB} = 3 Hz, C[3] H) ppm.
M.S. (m/z); 167 (8.1%), 58 (100%), (M') 167.1311; C_{10}H_{17}NO requires 167.1310.

2.3.2 "In Situ" Reactions of Aromatic Heterocycles Activated by Sulphur Dioxide

General Method (C)

Sulphur dioxide (1 ml per mmol of reagent, [1 ml = 22.4 mmol], was added to a mixture of heterocycle (1.1 equiv.) and an aminal (1 equiv.) in acetonitrile under nitrogen at 0°C. The mixture was allowed to stand at room temperature for a specified length of time and the work-up procedure described in General Method (A) was then followed.

(1) Reactions of N–Methylpyrrole with Bis(N,N-dimethylamino)methane and Sulphur Dioxide

(a) Sulphur dioxide (25 ml) was added to a mixture of N–methylpyrrole (3.24g, 40 mmol) and bis(N,N–dimethylamino)methane (4.09g, 40 mmol) in acetonitrile (125 ml) at −50°C. The mixture was allowed to warm to −10°C for 2 hours before reaching room temperature. After work-up 2–(N,N–dimethylaminomethyl)–1–methylpyrrole (2.24g, 40%) was isolated, b.p. 58°C / 5 mmHg.

(b) The reaction was repeated by mixing the reagents at −40°C and keeping the reaction flask in the freezer at −22°C for 39 hours. The reaction was then allowed to reach room temperature before work-up. Kugelröhr distillation of the crude product afforded 2–(N,N–dimethylaminomethyl)–1–methylpyrrole (3.00g, 54%), b.p. 58°C / 5 mmHg, and
2,5-bis(N,N-dimethylaminomethyl)-1-methylpyrrole (0.12g, 3%), b.p. 87°C / 3 mmHg.

(c) Sulphur dioxide (2.5 ml) was added to a mixture of N-methylpyrrole (2.23g, 27.5 mmol) and bis(N,N-dimethylamino)methane (2.56g, 25 mmol) in acetonitrile (75 ml) at -22°C. The reaction flask was sealed under nitrogen and kept in the freezer at -22°C for 90 hours and worked-up before reaching room temperature. Kugelrohr distillation afforded 2-(N,N-dimethylaminomethyl)-1-methylpyrrole (1.94g, 56%), b.p. 58°C / 5 mmHg.

(d) The reaction (c) was repeated by mixing the reagents at 0°C and then allowing the mixture to reach room temperature, affording 2-(N,N-dimethylaminomethyl)-1-methylpyrrole (1.99g, 58%), b.p. 58°C / 5 mmHg and 2,5-bis(N,N-dimethylaminomethyl)-1-methylpyrrole (0.09g, 4%), b.p. 87°C / 3 mmHg.

(2) Reaction of N-methylpyrrole with Di(N-piperidyl)methane and Sulphur Dioxide

Sulphur dioxide (25 ml) was added to a mixture of N-methylpyrrole (2.23g, 27.5 mmol) and Di(N-piperidyl)methane (4.56g, 25 mmol) in acetonitrile (75 ml) at 0°C. The reaction mixture was then stirred at room temperature for 89 hours. After work-up and Kugelröhr distillation of the crude product, 2-(N-piperidylmethyl)-1-methylpyrrole (3.30g, 74%), b.p. 115°C / 2 mmHg, and 2,5-bis(N-piperidylmethyl)-1-methylpyrrole (0.23g, 7%), b.p. 150°C / 0.5 mmHg were isolated.
(3) Reaction of N-Methylpyrrole with Di(N-morpholiny) methane and Sulphur Dioxide

Sulphur dioxide (15 ml) was added to a mixture of N-methylpyrrole (1.22g, 15 mmol) and di(N-morpholiny)methane (2.25g, 12.5 mmol) in acetonitrile (75 ml) at 0°C. The mixture was then allowed to stand at room temperature for 67 hours. After work-up and Kugelröhr distillation of the crude product, 2-(N-morpholiny)methyl)-1-methylpyrrole (1.11g, 49%), b.p. 100°C / 0.5 mmHg was isolated. The residue, a crystalline solid, was recrystallised from ethyl acetate to give 2,5-bis(N-morpholiny)methyl)-1-methylpyrrole (0.17g, 10%), m.p. 74-76°C.

(4) Reaction of N-Methylpyrrole with Di(N-pyrrolidiny) methane and Sulphur Dioxide

Sulphur dioxide (25 ml) was added to a mixture of N-methylpyrrole (2.23g, 27.5 mmol) and di(N-pyrrolidiny)methane (3.86g, 25 mmol) in acetonitrile (75 ml) at 0°C. The mixture was then allowed to stand at room temperature for 102 hours. After work-up and Kugelröhr distillation of the crude product, 2-(N-pyrrolidiny)methyl)-1-methylpyrrole (3.40g, 83%) was isolated, b.p. 100°C / 4 mmHg.

$^1$H n.m.r. (60 MHz), δ = 1.50-1.87 (4H, m, C [3' and 4'] H), 2.30-2.70 (4H, m, C [2' and 5'] H), 2.55 (2H, s, NCH$_2$), 2.63 (3H, s, NCH$_3$), 5.93-6.06 (2H, m, C [3 and 4] H), and 6.47-6.60 (1H, m, C [5] H) ppm.

$^{13}$C n.m.r. (20.1 MHz), δ = 23.6 (t, C [3' and 4']), 33.5 (q, NCH$_2$), 51.8 (t, NCH$_2$), 53.8 (t, C [2' and 5']), 106.3 (d, C [3]), 108.4 (d, C [4]), 121.9 (d, C [5]), and 130.4 (s, C [2]) ppm.

M.S. (m/z); 164 (11.6%), 94 (100%), (M$^+$) 164.1300; C$_{10}$H$_{18}$N$_2$ requires 164.1313.
(5) Reaction of $N$-Methylindole with Bis($N,N$-dimethylamino)methane and Sulphur Dioxide

Sulphur dioxide (20 ml) was added to a mixture of $N$-methylindole (2.62 g, 20 mmol) and bis($N,N$-dimethylamino)methane (2.04 g, 20 mmol) in acetonitrile (120 ml) at 0°C. The mixture was then stirred at room temperature for 41 hours. After work-up the crude product (3.18 g) was isolated and purified by Kugelröhr distillation, affording 3-($N,N$-dimethylaminomethyl)-1-methylindole (109) (3.03 g, 81%), b.p. 98°C / 0.2 mmHg, (lit.¹⁴¹ b.p. 94–96°C / 0.2 mmHg)

$^1$H n.m.r. (60 MHz), δ = 2.27 (6H, s, N[CH$_3$]$_2$), 3.60 (2H, s, CH$_2$), 3.63 (3H, s, NCH$_3$), 6.90 (1H, s, C[2] H), 7.00–7.33 (3H, m, C[4, 5 and 6] H), and 7.60–7.83 (1H, m, C[7] H) ppm.

$^{13}$C n.m.r. (20.1 MHz), δ = 31.5 (q, NCH$_3$), 44.7 (q, N[CH$_3$]$_2$), 54.0 (t, NCH$_2$), 108.5 (d, C[7]), 111.3 (s, C[3]), 118.4 (d, C[4]), 118.9 (d, C[6]), 120.9 (d, C[5]), 127.5 (d, C[2]), 128.8 (s, C[3a]), and 136.5 (s, C[7a]) ppm.

M.S. (m/z); 188 (19%), 144 (100%) (M$^+$) 188.1316; C$_{12}$H$_{18}$N$_2$ requires 188.1313.

(6) Reaction of Indole with Bis($N,N$-dimethylamino)methane and Sulphur Dioxide

Sulphur dioxide (50 ml) was added to a mixture of indole (5.86 g, 50 mmol) and bis($N,N$-dimethylamino)methane (5.11 g, 50 mmol) in acetonitrile (150 ml) at 0°C. The mixture was then allowed to stand at room temperature for 72 hours. After work-up the crude product was isolated as a yellow solid (8.69 g) and recrystallised from acetone to give 3-($N,N$-dimethylaminomethyl)indole (gramine) (108) (8.36 g, 96%), m.p. 134–135°C (lit.¹⁴² m.p. 134°C).
2.3.3.1 Reactions of Aminals with Heterocycles in the Presence of Chlorosilanes

General Method (D)

A chlorosilane derivative (1 equiv. or a catalytic amount) was added to a mixture of a heterocycle (1 equiv.) and an aminal (1 equiv.) in acetonitrile at 0°C under a still head of dry nitrogen. The reaction mixture was stirred at room temperature (1 equiv. of chlorosilane) or heated under reflux (catalytic amount of chlorosilane) for a specified length of time. The reaction was quenched by adding water and the solvent was removed in vacuo. The residue was then acidified to pH1 with 2N hydrochloric acid when necessary and washed with dichloromethane (3 x 30 ml). The aqueous layer was then basified to pH14 with 4N sodium hydroxide and washed with dichloromethane (4 x 40 ml). The combined organic extracts from the basic solution were dried and concentrated in vacuo. The residue was distilled using a Kugelröhr apparatus or recrystallised from a suitable solvent.

(1) Reactions of N-Methylpyrrole with Bis(N,N-dimethylamino)methane and Chlorosilane Derivatives

(a) Chlorotrimethylsilane (2.99g, 27.5 mmol) was added dropwise to a mixture of N-methylpyrrole (2.23g, 27.5 mmol) and bis(N,N-dimethyl-
aminomethane (2.56g, 25 mmol) in acetonitrile (150 ml) at 0°C. The mixture was then stirred at room temperature for 2 hours. After work-up and Kugelröhr distillation of the crude product two products were isolated. 2-(N,N-Dimethylaminomethyl)-1-methylpyrrole (0.69g, 20%) b.p. 58°C / 5 mmHg and 2,5-bis(N,N-dimethylaminomethyl)-1-methylpyrrole (0.98g, 40%), b.p. 87°C / 3.5 mmHg.

(b) The reaction (a) was repeated for 24 hours affording only 2,5-bis(N,N-dimethylaminomethyl)-1-methylpyrrole (1.62g, 66%), b.p. 87°C / 3.5 mmHg.

(c) Chlorotrimethylsilane (0.54g, 5 mmol) (12.5 mol%) was added to a mixture of N-methylpyrrole (3.24g, 40 mmol) and bis(N,N-dimethylamino)methane (4.09g, 40 mmol) in acetonitrile (150 ml) at 0°C. The mixture was stirred at room temperature for 24 hours and after work-up gave 2-(N,N-dimethylaminomethyl)-1-methylpyrrole (0.18g, 7%), b.p. 58°C / 5 mmHg, and 2,5-bis(N,N-dimethylaminomethyl)-1-methylpyrrole (0.49, 13%), b.p. 87°C / 3.5 mmHg.

(d) Chlorotrimethylsilane (0.22g, 2 mmol), (5 mol%) was added to a mixture of N-methylpyrrole (3.24g, 40 mmol) and bis(N,N-dimethylamino)methane (4.09g, 40 mmol) in acetonitrile (150 ml) and the mixture was heated under reflux for 24 hours. After work-up and Kugelröhr distillation of the crude product, 2,5-bis(N,N-dimethylaminomethyl)-1-methylpyrrole (2.45g, 63%) was isolated, b.p. 87°C / 3.5 mmHg.

(e) The reaction (d) was repeated using 12.5 mol% chlorotrimethylsilane (0.54g, 5 mmol), affording 2,5-bis(N,N-dimethylaminomethyl)-1-methylpyrrole (2.45g, 63%).
(f) The reaction (d) was repeated using 25 mol% chlorotrimethyl silane (1.08g, 10 mmol), affording 2,5-bis(N,N-dimethylaminomethyl)-1-methylpyrrole (2.41g, 62%).

(g) Trichloromethylsilane (4.11g, 27 mmol) was added dropwise to a mixture of N-methylpyrrole (2.23g, 27.5 mmol) and bis(N,N-dimethylamino)methane (2.56g, 25 mmol) in acetonitrile (150 ml). The mixture was then stirred at room temperature for 20 hours affording after work-up and distillation, 2-(N,N-dimethylaminomethyl)-1-methylpyrrole (1.81g, 52%).

(2) Reaction of N-Methylpyrrole with Bis(N, N-diethylamino)methane and Chlorotrimethylsilane

Chlorotrimethylsilane (0.54g, 5 mmol), (12.5 mol%) was added to a mixture of N-methylpyrrole (3.24g, 40 mmol) and bis(N,N-diethylamino)methane (6.33g, 40 mmol) in acetonitrile (150 ml). The mixture was heated under reflux for 24 hours and after work-up and Kugelröhr distillation 2,5-bis(N,N-diethylaminomethyl)-1-methylpyrrole (3.94g, 78%) was isolated, b. p. 120°C / 0.4 mmHg.

$^1$H n.m.r. (60 MHz), δ = 0.99 (12H, t, J = 7.5 Hz, NCH$_2$CH$_3$)$_2$, 2.49 (8H, q, J = 7.5 Hz, N(CH$_2$CH$_3$)$_2$), 3.50 (4H, s, NCH$_2$), 3.63 (3H, s, NCH$_3$), and 5.83 (2H, s, CH$_2$N) ppm.

$^{13}$C n.m.r. (20.1 MHz), δ = 11.8 (q, NCH$_2$CH$_3$), 30.7 (q, NCH$_3$), 46.6 (t, NCH$_2$CH$_3$), 50.4 (t, CH$_2$N), 107.6 (d, C[3 and 4]), and 130.6 (s, C[2 and 5]) ppm.

M.S. (m/z); (M$^+$) 251.2355; C$_{15}$H$_{29}$N$_3$ requires 251.2361.
(3) Reactions of N-methylpyrrole with Di(N-piperidyl)methane and Chlorotrimethylsilane

(a) Chlorotrimethylsilane (0.54g, 5 mmol), (12.5 mol%) was added to a mixture of N-methylpyrrole (3.24g, 40 mmol) and di(N-piperidyl)methane (7.29g, 40 mmol) in acetonitrile (150 ml). The mixture was heated under reflux for 24 hours and after work-up and Kugelrohr distillation two fractions were isolated. First fraction 2-(N-piperidylmethyl)-1-methylpyrrole (1.32g, 19%), b.p. 120°C / 15 mmHg. Second fraction 2,5-di(N-piperidylmethyl)-1-methylpyrrole (2.54g, 46%), b.p. 150°C / 0.4 mmHg.

(b) Chlorotrimethylsilane (1.63g, 15 mmol), (100 mol%), was added to a mixture of N-methylpyrrole (1.22g, 15 mmol) and di(N-piperidyl)methane (2.74g, 15 mmol) in acetonitrile (110 ml) at 0°C. The mixture was then stirred at room temperature for 120 hours. After work-up and Kugelrohr distillation, 2,5-di(N-piperidylmethyl)-1-methylpyrrole (3.72g, 90%) was isolated, b.p. 125°C / 0.2 mmHg.

(4) Reactions of N-Methylpyrrole with Di(N-pyrrolidinyl)methane and Chlorosilane Derivatives

(a) Chlorotrimethylsilane (2.99g, 27.5 mmol) was added dropwise to a mixture of N-methylpyrrole (2.23g, 27.5 mmol) and di(N-pyrrolidinyl)methane (3.86g, 25 mmol) in acetonitrile (100 ml) at 0°C. The mixture was then stirred at room temperature for 118 hours. After work-up and Kugelrohr distillation 2,5-di(N-pyrrolidinylmethyl)-1-methylpyrrole (2.17g, 70%) was isolated, b.p. 125°C / 0.5 mmHg.

1H n.m.r. (60 MHz), δ = 1.57–2.03 (8H, m, C[3' and 4']H), 2.23–2.70 (8H, m, C[2' and 5']H), 3.55 (4H, s, NCH₂), 3.65 (3H, s, NCH₃), and 5.92
(2H, s, C[3 and 4] H) ppm.

$^{13}$C n.m.r. (20.1 MHz), $\delta = 23.5$ (t, C[3' and 4']), 30.3 (q, NCH$_3$), 52.2 (t, NCH$_2$), 53.8 (t, C[2' and 5']), 106.7 (d, C[3 and 4]), and 130.5 (s, C[2 and 5]) ppm.

M.S. (m/z); 247 (21.8%), 177 (100%), (M$^+$) 247.2039; C$_{15}$H$_{25}$Na requires 247.2048.

(b) Trichloromethylsilane (4.11g, 27.5 mmol) was added dropwise to a mixture of N-methylpyrrole (2.23g, 27.5 mmol) and di(N-pyrrolidinyl)methane (3.86g, 25 mmol) in acetonitrile (125 ml) at 0°C. The mixture was then stirred at room temperature for 116 hours. After work-up and Kugelröhr distillation the monosubstituted Mannich base 2-(N-pyrrolidinylmethyl)-1-methylpyrrole was isolated (3.09g, 75%), b.p. 100°C / 4 mmHg.

(c) Chlorotrimethylsilane (0.22g, 2 mmol), (5 mol%) was added to a mixture of N-methylpyrrole (3.24g, 40 mmol) and di(N-pyrrolidinyl)methane (6.17g, 40 mmol) in acetonitrile (150 ml). The mixture was then heated under reflux for 24 hours. After work-up and Kugelröhr distillation two fractions were isolated. First fraction 2-(N-pyrrolidinylmethyl)-1-methylpyrrole (1.12g, 17%), b.p. 120°C / 5 mmHg.

Second fraction 2,5-di(N-pyrrolidinylmethyl)-1-methylpyrrole (3.01g, 61%), b.p. 120°C / 0.3 mmHg.

(5) Reaction of N-Methylpyrrole with Di(N-morpholinyl)methane and Chlorotrimethylsilane

Chlorotrimethylsilane (0.54g, 5 mmol), (12.5 mol%), was added to a mixture of N-methylpyrrole (3.24g, 40 mmol) and di(N-morpholinyl)methane (7.45g, 40 mmol) in acetonitrile (150 ml). The mixture was
then heated under reflux for 24 hours. After work-up the crude product was Kugelröhr distilled, affording 2-(N-morpholinylmethyl)-1-methylpyrrole (1.71g, 24%). The residue was recrystallised from ethyl acetate, giving 2,5-di(N-morpholinylmethyl)-1-methylpyrrole (2.23g, 40%), m.p. 70-72°C.

(6) Reaction of Pyrrole with Bis(N,N-dimethylamino)methane and Chlorotrimethylsilane

Chlorotrimethylsilane (4.89g, 45 mmol) was added dropwise to a mixture of pyrrole (3.02g, 45 mmol) and bis(N,N-dimethylamino)methane (4.60g, 45 mmol) in acetonitrile (150 ml) at 0°C. The mixture was then stirred at room temperature for 24 hours. After work-up and Kugelröhr distillation 2,5-bis(N,N-dimethylaminomethyl)pyrrole (107) was isolated (4.39g, 54%), b.p. 95°C / 0.7 mmHg, (lit.72, 56–8 / 2 mmHg).

i.r. (film) $\nu_{\text{max}}$ 3140 (NH), 1606 (aromatic ring) cm$^{-1}$.

$^1$H n.m.r. (60 MHz), $\delta = 2.18$ (12H, s, N[CH$_3$]$_2$), 3.38 (4H, s, NCH$_2$), 5.88 (2H, d, J = 3 Hz, C[3 and 4]H), and 9.80 (1H, br.s, D$_2$O ex. NH) ppm.

$^{13}$C n.m.r. (20.1 MHz), $\delta = 44.2$ (q, N[CH$_3$]$_2$), 52.3 (t, NCH$_2$), 107.0 (d, C[3 and 4]), and 128.4 (s, C[2 and 5]) ppm.

M.S. (m/z); 181 (13.9%), 58 (100%) (M$^+$) 181.1569; C$_{10}$H$_{15}$N$_3$ requires 181.1579.

(7) Reactions of Indole with Bis(N,N-dimethylamino)methane and Chlorotrimethylsilane

(a) Chlorotrimethylsilane (2.72g, 25 mmol) was added dropwise to a mixture of indole (3.22g, 27.5 mmol) and bis(N,N-dimethylamino)methane (2.56g, 25 mmol) in acetonitrile (125 ml) at 0°C. The mixture was then stirred at room temperature for 65 hours. After work-up the
crude product was isolated and recrystallised from acetone to give 3-((N,N-dimethylaminomethyl)indole (108) (3.18g, 73%), m.p. 134–135°C.

(b) Chlorotrimethylsilane (0.54g, 5 mmol) (10 mol%) was added to a mixture of indole (5.86g, 50 mmol) and bis(N,N-dimethylamino)methane (5.11g, 50 mmol) in acetonitrile (200 ml) and the mixture was stirred at room temperature for 91 hours. After work-up and recrystallisation 3-((N,N-dimethylaminomethyl)indole (108), (0.87g, 29%) was isolated, m.p. 134–135°C.

(8) Reaction of N-Methylindole with Bis(N,N-dimethylamino)methane and Chlorotrimethylsilane

Chlorotrimethylsilane (2.39g, 22 mmol) was added dropwise to a mixture of N-methylindole and bis(N,N-dimethylamino)methane (2.04g, 20 mmol) in acetonitrile (120 ml) at 0°C. The mixture was then stirred at room temperature for 48 hours and after work-up 3-((N,N-dimethylaminomethyl)-1-methylindole was isolated (2.23g, 59%) b.p. 100°C / 0.2 mmHg.

2.3.3.2 Reactions of Aminol Ethers with Heterocycles in the Presence of Chlorosilanes

General Method (E)

Chlorosilane derivative (1.1 equiv.) was added dropwise to a mixture of the heterocycle (1.1 equiv.) and an aminol ether (1 equiv.) in acetonitrile at 0°C under nitrogen, and the mixture was stirred at room temperature for a specified length of time. Work-up procedure as General Method (D).
(1) Reactions of N-Methylpyrrole with Aminol Ethers and Chlorosilanes

(a) Chlorotrimethylsilane (2.99g, 27.5 mmol) was added dropwise to a mixture of N-methylpyrrole (2.23g, 27.5 mmol) and ethoxy-N,N-dimethylaminomethane (2.58g, 25 mmol) in acetonitrile (125 ml) at 0°C. After stirring at room temperature for 24 hours followed by work-up and Kugelrohr distillation two fractions were isolated. First fraction 2-(N,N-dimethylaminomethyl)-1-methylpyrrole (0.74g, 21.5%), b.p. 58°C / 5 mmHg. Second fraction 2,5-bis(N,N-dimethylaminomethyl)-1-methylpyrrole (0.45g, 18.5%), b.p. 87°C / 3.5 mmHg.

(b) Chlorotrimethylsilane (2.99g, 27.5 mmol) was added dropwise to a mixture of N-methylpyrrole (2.23g, 27.5 mmol) and ethoxy-N,N-diethylaminomethane (0.28g, 25 mmol) in acetonitrile (125 ml) at 0°C. The mixture was then stirred at room temperature for 24 hours. After work-up and Kugelrohr distillation two fractions were isolated. First fraction 2-(N,N-diethylaminomethyl)-1-methylpyrrole (0.94g, 23%), b.p. 70°C / 3.5 mmHg, (lit.73 75–77°C / 6 mmHg).

1H n.m.r. (60 MHz), δ = 0.99 (6H, t, J = 7.5 Hz, N(CH₂CH₃)₂), 2.51 (4H, q, J = 7.5 Hz, N(CH₂CH₃)₂), 3.49 (2H, s, NCH₂), 3.63 (3H, s, NCH₃), 5.98–6.09 (2H, m, C[3 and 4] H), and 6.50–6.67 (1H, m, C[5] H) ppm.

13C n.m.r. (20.1 MHz), δ = 11.8 (q, NCH₂CH₃), 33.7 (q NCH₃), 46.5 (t, NCH₂CH₃), 50.0 (t, CH₂N), 106.3 (d, C[3]), 109.3 (d, C[4]), 122.2 (d, C[5]), and 130.1 (s, C[2]) ppm.

M.S. (m/z); (M⁺) 166.1462; C₁₃H₁₉N₂ requires 166.1470.

Second fraction 2,5-bis(N,N-diethylaminomethyl)-1-methylpyrrole (1.55g, 49%), b.p. 120°C / 0.3 mmHg.
(c) Chlorotrimethylsilane (2.99g, 27.5 mmol) was added dropwise to a mixture of \( N \)-methylpyrrole (2.23g, 27.5 mmol) and ethoxy-\( N,N \)-di-iso-propylaminomethane (3.98g, 25 mmol) in acetonitrile (125 ml) at \( 0^\circ \text{C} \). The mixture was then stirred at room temperature for 24 hours. After work-up and Kugelrohr distillation two products were isolated. First product 2-(\( N,N \)-di-iso-propylaminomethyl)-1-methylpyrrole (1.03g, 21%), b.p. (90°C / 0.5 mmHg).

\[ ^1\text{H n.m.r. (250 MHz), } \delta = 1.00 (12H, d, J = 6.8 \text{ Hz, CH}\text{[CH}_3\text{]_2}), 3.01 (2H, sept., J = 6.8 \text{ Hz, CHMe}_2), 3.62 (2H, s, CH\text{[H]}\text{N}), 3.65 (3H, s, NCH}_3\text{), 5.96-6.02 (2H, m, C[3 and 4] H), \text{and 6.54-6.55 (1H, m, C[5] H)} \text{ ppm.} \]

\[ ^{13}\text{C n.m.r. (62.9 MHz)} \delta = 20.3 (\text{CH}\text{[CH}_3\text{]_2}), 33.9 (\text{NCH}_3\text{), 41.3 (CH}_2\text{N), 46.9 (CHMe}_2\text{, 106.0 (C[3]), 109.1 (C[4]), 122.1 (C[5]) and 130.9 (C[2]) ppm.} \]

M.S. (m/z); 194 (6.8%), 94 (100%), \((M^+194.1778; \text{C}_{12}\text{H}_{22}\text{N}_2 \text{ requires 194.1783.} \)

Second product 2,5-bis(\( N,N \)-di-iso-propylaminomethyl)-1-methylpyrrole (1.17g, 31%), b.p. 140°C / 0.03 mmHg which crystallised in the Kugelrohr bulb, m.p. 61°C.

\[ ^1\text{H n.m.r. (250 MHz), } \delta = 0.99 (24H, d, J = 6.7 \text{ Hz, CH}\text{[CH}_3\text{]_2}), 3.00 (4H, sept. J = 6.7 \text{ Hz, CHMe}_2\text{, 3.61 (4H, s, CH}_2\text{N), 3.65 (3H, s, NCH}_3\text{, and 5.86 (2H, s, C[3 and 4] H)} \text{ ppm.} \]

\[ ^{13}\text{C n.m.r. (62.9 MHz)} \delta = 20.3 (\text{CH}\text{[CH}_3\text{]_2}), 30.8 (\text{NCH}_3\text{), 41.7 (CH}_2\text{N), 46.9 (CHMe}_2\text{, 107.3 (C[3 and 4]), and 131.2 (C[2 and 5]) ppm.} \]

M.S. (m/z); 307 (15.6%), 207 (100%), \((M^+307.2984; \text{C}_{19}\text{H}_{37}\text{N}_3 \text{ requires 307.2987.} \)

(d) Reaction (c) was repeated using trichloromethylsilane (4.11g, 27.5 mmol), for 68 hours, affording 2-(\( N,N \)-di-iso-propylaminomethyl)-1-methylpyrrole (2.05g, 42%), b.p. 90°C / 0.5 mmHg.
and 2,5-bis(N,N-di-iso-propylaminomethyl)-1-methylpyrrole (1.17g, 28%) b.p. 150°C / 0.5 mmHg.

(e) Chlorotrimethylsilane (2.99g, 27.5 mmol) was added dropwise to a mixture of N-methylpyrrole (2.23g, 27.5 mmol) and ethoxy-N-piperidylmethane (3.58g, 25 mmol) in acetonitrile (125 ml) at 0°C. Stirring at room temperature for 24 hours, followed by work-up and Kugelröhr distillation, gave 2-(N-piperidylmethyl)-1-methylpyrrole (1.62g, 47%), b.p. 140°C / 0.3 mmHg.

(f) Trichloromethylsilane (4.11g, 27.5 mmol) was added dropwise to a mixture of N-methylpyrrole (2.23g, 27.5 mmol) and iso-propanol-N,N-diethylaminomethane (3.63g, 25 mmol) in acetonitrile 125 ml at 0°C. Stirring the mixture at room temperature for 17 hours, followed by work-up and Kugelröhr distillation, gave 2-(N,N-diethylaminomethyl)-1-methylpyrrole (2.79g, 67%), b.p. 70°C / 3.5 mmHg, and 2,5-bis(N,N-diethylaminomethyl)-1-methylpyrrole (0.63g, 20%), b.p. 100°C / 0.2 mmHg.

(g) Reaction (f) was repeated using (98b) iso-propoxymethoxy-N,N-diethylaminomethane (4.38g, 25 mmol) for 24 hours yielding 2-(N,N-diethylaminomethyl)-1-methylpyrrole (2.29g, 55%) and 2,5-bis(N,N-diethylaminomethyl)-1-methylpyrrole (0.79g, 25%).

(2) Reactions of N-Methylindole with Aminol Ethers and Trichloromethylsilane

(a) Trichloromethylsilane (4.93g, 33 mmol) was added dropwise to a mixture of N-methylindole (3.94g, 30 mmol) and iso-propanol-N,N-diethylaminomethane (4.79g, 33 mmol) in acetonitrile (150 ml) at
0°C. The mixture was then stirred at room temperature for 20 hours. Work-up and Kugelröhr distillation gave 3-(N,N-diethylamino- methyl)-1-methylindole (5.71g, 89%), b.p. 126°C / 0.07 mmHg, (lit.143, hydrochloride salt, m.p. 174°C).

\[ \text{\text{\textsuperscript{1}H n.m.r. (60 MHz), } \delta = 1.07 (6H, t, J = 7.5 Hz, N[CH\text{\textsubscript{2}}CH\text{\textsubscript{3}}]_2), 2.53 (4H, q, J = 7.5 Hz, N[CH\text{\textsubscript{2}}CH\text{\textsubscript{3}}]_2), 3.56 (3H, s, NCH\text{\textsubscript{3}}), 3.73 (2H, s, CH\text{\textsubscript{2}}N), 6.83 (1H, s, C[2] H), 6.92–7.30 (3H, m, C [4, 5 and 6] H), and 7.50–7.80 (1H, m, C [7] H) ppm.} \]

\[ \text{\text{\textsuperscript{13}C n.m.r. (20.1 MHz), } \delta = 12.1 (q, N[CH\text{\textsubscript{2}}CH\text{\textsubscript{3}}]_2), 32.4 (q, NCH\text{\textsubscript{3}}), 46.7 (t, N[CH\text{\textsubscript{2}}CH\text{\textsubscript{3}}]_2), 48.0 (t, CH\text{\textsubscript{2}}N), 109.0 (d, C [7]), 112.3 (s, C [3]), 118.9 (d, C [4]), 119.7 (d, C [6]), 121.5 (d, C [5]), 128.1 (d, C [2]), 128.6 (s, C [3a]), and 137.1 (s, C [7a]) ppm.} \]

M.S. (m/z); 216 (17.0%), 144 (100%), (M+) 216.1626; C\text{\textsubscript{14}}H\text{\textsubscript{20}}N\text{\textsubscript{2}} requires 216.1625.

(b) Trichloromethylsilane (4.11g, 27.5 mmol) was added dropwise to a mixture of N-methylindole (3.28g, 25 mmol) and ethoxy-N-morpholiny1methane (3.99g, 27.5 mmol) in acetonitrile (150 ml) at 0°C. The mixture was stirred at room temperature for 20 hours and after work-up and distillation gave 3-(N,N-morpholiny1methy1)-1-methylindole (5.36g, 93%), b.p. 140°C / 0.02 mmHg.

\[ \text{\text{\textsuperscript{1}H n.m.r. (60 MHz), } \delta = 2.33–2.57 (4H, m, C [2' and 6'] H), 3.53–3.83 ((4H, m, C [3' and 5'] H), 3H, s, NCH\text{\textsubscript{3}}) and (2H, s, CH\text{\textsubscript{2}}N)), 6.90 (1H, s, C [2] H), 6.93–7.30 (3H, m, C [4, 5 and 6] H), and 7.53–7.67 (1H, m, C [7] H) ppm.} \]

\[ \text{\text{\textsuperscript{13}C n.m.r. (20.1 MHz), } \delta = 32.3 (q, NCH\text{\textsubscript{3}}), 53.5 (t, C [3' and 5']), 53.9 (t, CH\text{\textsubscript{2}}N), 67.0 (t, C [2' and 6']), 109.0 (d, C [8]), 110.7 (s, C [3]), 119.0 (d, C [4]), 119.6 (d, C [6]), 121.5 (d, C [5]), 128.3 (d, C [2]), and s, C [3a]), and 137.1 (s, C [7a]) ppm.} \]
M.S. (m/z): 230 (11.6%), 144 (100%), (M+) 230.1416; C_{14}H_{18}N_2O requires 230.1419.

(3) Reactions of *N*-Methylpyrrole with Ethoxy-*N*-pyrrolidinyl-methane in the Presence of Bis(trimethylsilyl)acetamide

(a) Bis(trimethylsilyl)acetamide (1.24 ml, 1.02 g, 5 mmol) was added with a syringe into a mixture of *N*-methylpyrrole (0.81 g, 10 mmol) and ethoxy-*N*-pyrrolidinylmethane (1.09 g, 10 mmol) in acetonitrile (30 ml). Chlorotrimethylsilane (0.10 g, 1 mmol, (10 mmol%) was also added and the mixture was stirred at room temperature for 68 hours. After work-up, (using ether as the solvent of extraction), Kugelröhr distillation yielded 2,5-di(*N*-pyrrolidinylmethyl)-1-methylpyrrole (0.64 g, 52%) b.p. 110°C / 0.02 mmHg.

(b) Reaction (a) was repeated without the addition of chlorotrimethylsilane. After work-up no Mannich product was formed and the aminol ether was converted to di(*N*-pyrrolidinyl)methane (97c) (0.23 g, 30%).

2.3.4. Preparation of 2-(*N*,*N*-Dimethylaminomethyl)-5-(*N*-piperidylmethyl)-1-methylpyrrole

Preformed *N*-piperidyl(methylene)iminium chloride (2.20 g, 16.5 mmol) was added to a solution of 2-(*N*,*N*-dimethylaminomethyl)-1-methylpyrrole (2.10 g, 15 mmol) in acetonitrile (100 ml) and the mixture was stirred at room temperature under nitrogen for 24 hours. After work-up (General Method B) and Kugelrörhr distillation the title compound was isolated (3.00 g, 85%), b.p. 110°C / 5 mmHg.

^1^H n.m.r. (90 MHz), δ = 1.30-1.67 (6H, m, C [3', 4' and 5'] H), 2.15 (6H, s, N(CH₃)₂), 2.22-2.31 (4H, m, C [2' and 6'] H), 3.27 (2H, s, CH₂N), 3.31 (2H, s, CH₂N), 3.55 (3H, s, NCH₃), and 5.79 (2H, s, C [3 and 4] H) ppm.
13C n.m.r. (20.1 MHz) δ = 24.7 (t, C[4']), 26.2 (t, C[3' and 5']), 30.5 (q, NCH₃), 45.0 (q, N[CH₃]₂), 54.3 (t, C[2' and 6']), 55.7 (t, CH₃NMe₂), 56.1 (t, CH₂N), 107.6 and 107.7 (d, C[3 and 4]), 130.2 and 130.3 (s, C[2 and 5]) ppm.

M.S. (m/z); 235 (8.6%), 151 (100%), M+ 235.2033; C₁₄H₂₈N₃ requires 235.2048.

C, H, N analysis; Found: C (71.20%), H (10.71%), N (18.15%); Requires: C (71.42%), H (10.73%), N (17.85%).

2.3.5 Preparation of 2-(N,N-dimethylaminomethyl)-5-methoxythiophene

Preformed N,N-dimethyl(methylene)iminium chloride (1.03g, 11 mmol) was added to a solution of 2-methoxythiophene (0.14g, 10 mmol) in acetonitrile (50 ml). The mixture was stirred at room temperature for 20 hours and after work-up, (using ether as the solvent of extraction), and Kugelröhr distillation, the title compound was isolated (1.60g, 93%), b.p. 105°C / 18 mmHg, (lit.14, 106°C / 15 mmHg).

1H n.m.r. (250 MHz), δ = 2.25 (6H, s, N[CH₃]₂), 3.47 (2H, s, CH₂N), 3.65 (3H, s, OCH₃), 6.00 (1H, d, J = 3.7 Hz, C[3] H), and 6.50 (1H, d, J = 3.7 Hz, C[4] H) ppm.

13C n.m.r. (62.9 MHz), δ = 44.9 (N[CH₃]₂), 59.2 (CH₂N), 60.0 (OCH₃), 102.6 (C[4]), 123.0 (C[3]), 128.6 (C[2]), and 165.9 (C[5]) ppm.

M.S. (m/z); 171 (18.7%), 127 (100%), (M⁺) 171.0703; C₈H₁₅NOS requires 171.0718.

2.4.1. Preparation of Aryltrialkylstannanes

(a) 1-Bromo-2,4-dimethoxybenzene (1.519g, 70 mmol) was added to dry magnesium turnings (1.58g) in dry THF (65 ml) under a still head of
nitrogen with the addition of an iodine crystal to initiate the reaction. The reaction was completed by gentle reflux for 2 hours. Tri-n-butyltin chloride (17.90g, 55 mmol) in THF (65 ml) was added slowly to maintaining a gentle reflux and the reaction was then heated under reflux for a further 16 hours. The mixture was cooled, poured into ice-ammonium chloride and acidified with 2M sulphuric acid. The aqueous solution was extracted with ether (3 x 100 ml) and the combined organic extracts were washed with saturated sodium bicarbonate (100 ml) and then with water (2 x 100 ml). The ether solution was stirred with saturated ethanolic potassium fluoride (100 ml) for 2 hours, filtered, dried and concentrated in vacuo. The residue was fractionally distilled to yield 2,4-dimethoxyphenyltri-n-butylstannane (14.21g, 61%), b.p. 138-142°C / 0.1 mmHg.

1H n.m.r. (60 MHz), δ = 0.47-2.10 (27H, m, Bu₃Sn), 3.73 (3H, s, OCH₃), 3.78 (3H, s, OCH₃), 6.37-6.67 (2H, m, C[5 and 6] H), and 7.30 (1H, d, J = 8 Hz, C[3] H) ppm.
M.S. (m/z); (M⁺) 428.1780, 426.1476, and 424.1357; C₂₀H₃₆O₂Sn requires 428.1737, 426.1736, and 424.1737.

(b) Benzylbromide (22.13g, 130 mmol) was added to dry magnesium turnings (2.92g) in dry THF (125 ml) under nitrogen with the addition of an iodine crystal. The mixture was heated under reflux for 2 hours followed by the dropwise addition of tri-n-butyltin chloride (32.55g, 100 mmol) in THF (75 ml) and the mixture was heated under reflux for a further 16 hours. Following the work-up procedure described for (a) above the crude product was isolated and fractionally distilled to give benzyltri-n-butylstannane, (19.45g, 51%), b.p. 128-134°C/15 mmHg, (lit.¹⁴ 192-194°C/24 mmHg).

1H n.m.r. (60 MHz), δ = 0.53-2.13 (27H, m, Bu₃Sn), 2.30 (2H, s, CH₂), and 6.73-7.37 (5H, m, PhH) ppm.
M.S. (m/z); (M⁺) 382.1355, 380.1228, and 378.9340; C₉H₉₄Sn requires 382.1682, 380.1681, and 378.1682.

(c) A 9% solution of n-butyllithium (2.43g, 38 mmol) was added dropwise with a syringe to a stirred solution of 3-bromothiophene (6.86g, 40 mmol) in dried ether (40 ml) at -78°C under nitrogen. The mixture was then stirred for 30 min. and trimethyltin chloride (7.00g, 35 mmol) in ether (20 ml) was added dropwise at that temperature. Stirring was continued for a further 10 hours at -78°C and the reaction was allowed to warm to room temperature overnight. Water (100 ml) was added and the separated organic layer was washed with water (3 x 50 ml), dried and concentrated in vacuo. The residue (8.64g) was fractionally distilled to give 3-thienyltrimethylstannane ¹⁴₈ (7.53g, 87%) b.p. 85-90°C / 6 mmHg. (lit. ¹⁴₉ 90-92°C / 6 mmHg).

1H n.m.r. (60 MHz), δ = 0.31 (9H, s, (CH₃)₃ and 7.07-7.53 (3H, m, C[2, 4 and 5]H) ppm.

M.S. (m/z); 247 (10.1%), 233 (100%), (M⁺) 247.9678; C₇H₁₂SSn requires 247.8112.

2.4.2. "In Situ" Reactions of Aryltrialkylstannanes

General Method (F)

 Aryltrialkylstannanes (1 equiv.) and an aminol ether (1.1 equiv.) were stirred together in acetonitrile at 0°C under nitrogen. Chlorosilane derivative (1.1 equiv.) was added dropwise and then the mixture was heated under reflux or stirred at room temperature for a specified length of time. Water (20 ml) was added and the reaction mixture was concentrated in vacuo. The residue was acidified to pH1 with 2N hydrochloric acid and washed with ether (3 x 30 ml). The aqueous
layer was basified to pH14 with 4M sodium hydroxide and washed with ether (3 x 40 ml). The combined organic extracts from the basic solution were then dried and concentrated in vacuo. The residue was purified by Kugelröhr distillation.

4-Methoxy-N,N-dimethylbenzylamine (111a)

(a) 4-Methoxyphenyltributylstannane (1.99g, 5 mmol), iso-propoxy-N,N-dimethylaminomethane (0.64g, 5.5 mmol) and trichloromethylsilane (0.82g, 5.5 mmol) were heated under reflux in acetonitrile for 18 hours to yield (111a) (0.34g, 41%) b.p. 100°C / 12 mmHg, (lit.147 104–106°C / 12 mmHg).

i.r. (film) $v_{\text{max}}$ 1610 (aromatic ring) cm$^{-1}$.

$^1$H n.m.r. (60 MHz), $\delta$ = 2.22 (6H, s, N[CH$_3$]$_2$), 3.33 (2H, s, CH$_2$N), 3.75 (3H, s, OCH$_3$), and 6.73–7.40 (4H, AA' BB', $J_{AB} =$, 8 Hz, PhH) ppm.

$^{13}$C n.m.r. (20.1 MHz), $\delta$ = 45.2 (q, NCH$_3$), 55.0 (q, OCH$_3$), 63.8 (t, CH$_2$N), 113.7 (d, C[3 and 5]), 130.2 (d, C[2 and 6]), 131.1 (s, C[1]), and 158.9 (s, C[4]) ppm.

M.S. (m/z); 165 (29.0%), 121 (100%), (M$^+$) 165.1146; C$_{15}$H$_{15}$NO requires 165.1154.

(b) 4-Methoxyphenyltributylstannane (3.97g, 10 mmol), iso-propoxy-N,N-dimethylaminomethane (1.29g, 11 mmol) and chlorotrimethylsilane (1.20g, 11 mmol) were heated under reflux in acetonitrile (100 ml) for 44 hours to yield (111a) (0.79g, 48%), b.p. 100°C / 12 mmHg.

(c) 4-Methoxyphenyltributylstannane (1.35g, 5 mmol), iso-propoxy-N,N-dimethylaminomethane (0.65g, 5.5 mmol) and trichloromethyl-
silane (0.82 g, 5.5 mmol) were heated under reflux in acetonitrile (50 ml) for 22 hours yielding (111a) (0.28 g, 33%), b.p. 100°C / 12 mmHg.

**N-(4-Methoxybenzyl)pyrrolidine (111b)**

(a) 4-Methoxyphenyltributylstannane (1.99 g, 5 mmol), ethoxy-\(\text{N-}\)pyrrolidinylmethane (0.71 g, 5.5 mmol) and trichloromethylsilane (0.82 g, 5.5 mmol) were heated under reflux in acetonitrile for 68 hours, yielding (111b) (0.28 g, 29%) b.p. 120°C / 3 mmHg.

\(\text{i.r. (film) } \nu_{\text{max}} 1610 \text{ (aromatic ring) cm}^{-1}\)

\(\text{\(^1\)H n.m.r. (60 MHz), } \delta = 1.61-1.95 (4\text{H, m, C}[3\text{ and } 4]\text{ H}), 2.30-2.70 (4\text{H, m, C}[2\text{ and } 5]\text{ H}), 3.52 (2\text{H, s, CH}_2\text{), 3.76 (3\text{H, s, OCH}_3\text{), and 6.64-7.46 (4\text{H, AA' BB'}, J_{AB} = 8 Hz, PhH ppm.}}\)

\(\text{\(^{13}\)C n.m.r. (20.1 MHz), } \delta = 23.5 (t, \text{ C}[3\text{ and } 4]), 54.1 (t, \text{ C}[2\text{ and } 5]), 55.2 (q, \text{ OCH}_3\text{), 60.1 (t, CH}_2\text{N), 113.7 (d, \text{ C}[3'\text{ and } 5']), 130.1 (d, \text{ C}[2'\text{ and } 6']), 131.7 (s, \text{ C}[1']), \text{ and 158.8 (s, \text{ C}[4']) ppm.}}\)

\(\text{M.S. (m/z): 191 (22.6%), 121 (100%) M^+ 191.1310; C_{12}H_{17}NO \text{ requires 191.1310.}}\)

(b) 4-Methoxyphenyltrimethylstannane (1.36 g, 5 mmol), ethoxy-\(\text{N-}\)pyrrolidinylmethane (0.71 g, 5.5 mmol) and trichloromethylsilane (0.82 g, 5.5 mmol) were heated under reflux in acetonitrile (50 ml) for 22 hours, yielding (111b) (0.25 g, 26%), b.p. 100°C / 2 mmHg.

**N-(4-Methoxybenzyl)morpholine (111c)**

(a) 4-Methoxyphenyltributylstannane (3.97 g, 10 mmol), ethoxy-\(\text{N-}\)morpholinylmethane (1.62 g, 11 mmol) and trichloromethylsilane (1.64 g, 11 mmol) were heated under reflux in acetonitrile for 44 hours yielding (111c) (1.30 g, 63%), b.p. 120°C / 0.75 mmHg, (lit.\(^{148}\) 136–139°C / 1 mmHg).
i.r. (film) $v_{max}$ 1610 (aromatic ring) cm$^{-1}$

$^1$H n.m.r. (60 MHz), $\delta = 2.27$–2.60 (4H, m, C[3 and 5] H), 3.43 (2H, s, CH$_2$N), 3.53–3.90 (4H, m, C[2 and 6] H), 3.77 (3H, s, OCH$_3$), and 6.70–7.47 (4H, AA’ BB’, $J_{AB} = 10$ Hz, PhH) ppm.

$^{13}$C n.m.r. (20.1 MHz), $\delta = 53.6$ (t, C[3 and 5]), 55.0 (q, OCH$_3$), 62.8 (t, CH$_2$N), 66.9 (t, C[2 and 6]), 113.7 (d, C[3’ and 5’]), 129.9 (s, C[1’]), 130.3 (d, C[2’ and 6’]), and 158.9 (s, C[4’]) ppm.

M.S. (m/z); 207 (24%), 121 (100%), (M$^+$) 207.1256; C$_{12}$H$_{17}$NO$_2$ requires 207.1259.

(b) 4-Methoxyphenyltrimethylstannane (1.36g, 5 mmol), ethoxy-N-morpholinylmethane (0.81g, 5.5 mmol) and trichloromethylsilane (0.82g, 5.5 mmol) were heated under reflux in acetonitrile (50 ml) yielding (111c) (0.33g, 32%), b.p. 120°C / 0.7 mmHg.

$N$-(2,4-Dimethoxybenzyl)morpholine (111e)

2,4-Dimethoxyphenyltributylstannane (2.14g, 5 mmol), ethoxy-N-morpholinylmethane (0.81g, 5.5 mmol) and trichloromethylsilane (0.82g, 5.5 mmol) were heated under reflux in acetonitrile (50 ml) for 21 hours yielding (111e) (0.71g, 60%), b.p. 120°C / 0.07 mmHg, (lit.$^{91}$, hydrobromide salt m.p. 181 °C, from ethanol).

i.r. (film) $v_{max}$ 1612 (aromatic ring) cm$^{-1}$

$^1$H n.m.r. (250 MHz), $\delta = 2.46$–2.50 (4H, m, C[3 and 5] H), 3.50 (2H, s, CH$_2$N), 3.65–3.73 (4H, m, C[2 and 6] H), 3.79 (6H, s, OCH$_3$), 6.44–6.48 (2H, m, C[5’ and 6’] H), and 7.22 (1H, d, $J_{AB} = 8.8$ Hz, C[3’] H) ppm.

$^{13}$C n.m.r. (62.9 MHz), $\delta = 53.4$ (C[3 and 5]), 55.3 (OCH$_3$), 55.4 (OCH$_3$), 56.1 (CH$_2$N), 70.0 (C[2 and 6]), 98.4 (C[3’]), 104.1 (C[5’]), 117.9 (C[1’]), 131.09 (C[6’]), 158.9 (C[4’]), and 160.1 (C[2’]) ppm.
M.S. (m/z); 237 (20.3%), 151 (100%) (M+) 237.1359; C\textsubscript{13}H\textsubscript{19}NO\textsubscript{3} requires 237.1365.

2,4-Dimethoxy-\(N,N\)-dimethylbenzylamine (111f)

2,4-Dimethoxyphenyltributylstannane (2.14g, 5 mmol), iso-propoxy-\(N,N\)-dimethylaminomethane (0.64g, 5.5 mmol) and trichloromethylsilane (0.82g, 5.5 mmol) were heated under reflux in acetonitrile (50 ml) for 21 hours to give (111f)\textsuperscript{149} (0.54g, 56%) b.p. 90°C/0.07 mmHg.

\(^1\)H n.m.r. (60 MHz) \(\delta = 2.23\) (6H, s, NCH\textsubscript{3}), 3.38 (2H, s, CH\textsubscript{2}N), 3.80 (6H, s, OCH\textsubscript{3}), 6.30–6.70 (2H, m, C[5 and 6] H), and 7.12 (1H, d, J\textsubscript{AB} = 8 Hz, C[3] H) ppm.

M.S. (m/z); 195 (27.7%), 151 (100%), (M+) 195.1243; C\textsubscript{12}H\textsubscript{17}NO\textsubscript{2} requires 195.1259

\(N\)-(\(\alpha\)-Phenylethyl)morpholine (111g)

Benzyltributylstannane (1.91g, 5 mmol), ethoxy-\(N\)-morpholinylmethane (0.81g, 5.5 mmol) and trichloromethylsilane (0.82g, 5.5 mmol) were heated under reflux in acetonitrile (50 ml) for 21 hours to give (111g) (0.30g, 31%) b.p. 90°C/0.07 mmHg (lit.\textsuperscript{150}, b.p. 76–78°C/0.05 mmHg).

i.r. (film) \(v\)\textsubscript{max} 1602 (aromatic ring) cm\textsuperscript{-1}.

\(^1\)H n.m.r. (250 MHz) \(\delta = 2.48–2.63\) (6H, m, C[3 and 5] H and NCH\textsubscript{3}), 2.78–2.90 (2H, m, PhCH\textsubscript{2}), 3.67–3.77 (4H, m, C[2 and 6] H), and 7.19–7.29 (5H, m, PhH) ppm.

\(^{13}\)C n.m.r. (62.9 MHz), \(\delta = 33.3\) (CH\textsubscript{2}N), 53.7 (C[3 and 5]), 60.9 (PhCH\textsubscript{2}), 70.0 (C[2 and 6]), 126.1 (C[4\textsuperscript{'})], 128.4 (C[3\textsuperscript{'} and 5\textsuperscript{'}]), 128.7 (C[2\textsuperscript{'} and 6\textsuperscript{'})], and 140.1 (C[1\textsuperscript{'})] ppm.

M.S. (m/z); 191 (0.92%), 100 (100%), (M+) 191.1275; C\textsubscript{12}H\textsubscript{17}NO requires 191.1310.
4-Methoxy-\(N,N\)-diethylbenzylamine (111h)

4-Methoxypheny1trimethylstannane (1.36g, 5 mmol), ethoxy-\(N,N\)-diethylaminomethane (0.72g, 5.5 mmol) and trichloromethylsilane (0.82g, 5.5 mmol) were heated under reflux in acetonitrile (50 ml) for 22 hours to give (111h) (0.17g, 18%), b.p. 90 / 1 mmHg, (lit.\(^{151}\), b.p. 126°C / 15 mmHg).

\(^1H\) n.m.r. (250 MHz), \(\delta = 1.07 (6H, t, J = 7.1 \text{ Hz NCH}_2\text{CH}_3), 2.54 (4H, q, J = 7.1 \text{ Hz NCH}_2\text{CH}_3), 3.55 (2H, s, \text{CH}_2\text{N}), 3.80 (3H, s, \text{OCH}_3), \text{and 6.84-7.28 (4H, AA' BB', J = 8.8 Hz, C}[2, 3, 5 \text{ and 6}]\) ppm.

\(^13C\) n.m.r. (62.9 MHz), \(\delta = 11.6 (\text{CH}_2\text{CH}_3), 46.5 (\text{NCH}_2\text{CH}_3), 55.3 (\text{OCH}_3), 56.8 (\text{PhCH}_2\text{N}), 113.6 (\text{C}[3 \text{ and 5}]), 130.1 (\text{C}[2 \text{ and 6}]), 131.5 (\text{C}[1]), \text{and 158.6 (C}[4]\) ppm.

M.S. (m/z); 193 (9.3%), 121 (100%), (M\(^+\)) 193.1464; \(\text{C}_{12}\text{H}_{19}\text{NO}\) requires 193.1467.

3-\(N,N\)-Dimethylaminomethyl)thiophene (111i)

(a) 3-Thienyltrimethylstannane (1.48g, 6 mmol), iso-propoxy-\(N,N\)-dimethylaminomethane (0.77g, 6.6 mmol) and trichloromethylsilane (0.98g, 6.6 mmol) were heated under reflux in acetonitrile (60 ml) for 23 hours to give (111i) (0.28g, 25%), b.p. 80°C / 9 mmHg, (lit.\(^{152}\) b.p. 28–32°C / 0.12 mmHg).

i.r. (film) \(\nu_{\text{max}}\) 1454, 1356 (thiophene ring) cm\(^{-1}\)

\(^1H\) n.m.r. (60 MHz), \(\delta = 2.21 (6H, s, N[\text{CH}_3])_2, 3.42 (2H, s, \text{CH}_2\text{N}), \text{and 6.90-7.25 (3H, m, C}[2, 4 \text{ and 5}]\) ppm.

\(^13C\) n.m.r. (90.6 MHz), \(\delta = 45.2 (\text{NCH}_3), 58.8 (\text{NCH}_2), 122.7 (\text{C}[4]), 125.4 (\text{C}[2]), 128.4 (\text{C}[5]), \text{and 139.7 (C}[3]\) ppm.

M.S. (m/z); 141 (34.1%), 97 (100%), (M\(^+\)) 141.0591; \(\text{C}_7\text{H}_{11}\text{NS}\) requires 141.0612.
(b) Reaction (a) was repeated at room temperature for 91 hours, yielding (111i) (0.15g, 18%), b.p. 80°C / 9 mmHg.

3-(N-Morpholinylmethyl)thiophene (111k)

(a) 3-Thienyltrimethyl stannane (1.23g, 5 mmol), ethoxy-N-morpholinylmethane (0.81g, 5.5 mmol) and trichloromethylsilane (0.82g, 5.5 mmol) were heated under reflux in acetonitrile (50 ml) for 19 hours, yielding (111k) (0.42g, 45%), b.p. 100°C / 1 mmHg.

i.r. (film) \( \nu_{\text{max}} \) 1640, 1432, 1356, (thiophene ring) cm\(^{-1}\)

\(^1H\) n.m.r. (60 MHz), \( \delta = 2.26-2.54 \) (4H, m, C[3' and 5']H), 3.53 (2H, s, CH\(_2\)N), 3.55-3.83 (4H, m, C[2' and 6']H), and 6.98-7.37 (3H, m, C[2, 4 and 5]H) ppm.

\(^13C\) n.m.r. (90.6 MHz), \( \delta = 53.3 \) (C[3' and 5']), 57.7 (CH\(_2\)N), 66.7 (C[2' and 6']), 122.7 (C[4]), 125.3 (C[2]), 128.2 (C[5]), and 138.4 (C[3]) ppm.

M.S. (m/z); 183 (24.2%), 97 (100%), (M\(^+\) 183.0713; C\(_9\)H\(_{13}\)NOS requires 183.0718.

(b) Reaction (a) was repeated at room temperature for 89 hours yielding (111k) (0.47g, 51%), b.p. 100°C / 1 mmHg.

3-(N-Pyrrolidinylmethyl)thiophene (111l)

3-Thienyltrimethylstannane (1.23g, 5mmol), ethoxy-N-pyrrolidinylmethane (0.71g, 5.5 mmol) and trichloromethylsilane (0.82g, 5.5 mmol) were stirred at room temperature in acetonitrile (50 ml) for 90 hours to give (111l) (0.52g, 38%), b.p. 90°C / 1 mmHg, (lit.\(^{153}\), no physical data given).

i.r. (film) \( \nu_{\text{max}} \) 1664, 1444, 1368 (thiophene ring) cm\(^{-1}\)
\[
^1\text{H n.m.r. (60 MHz), } \delta = 1.62-1.97 (4\text{H, m, C[3' and 4']} \text{H}), 2.30-2.67 (4\text{H, m, C[2' and 5']} \text{H}), 3.63 (2\text{H, s, CH}_2\text{N}), \text{ and } 6.96-7.35 (3\text{H, m, C[2, 4 and 5]} \text{H}) \text{ ppm.}
\]

\[
^{13}\text{C n.m.r. (90.6 MHz), } \delta = 23.4 (\text{C[3' and 4']}), 53.9 (\text{C[2' and 5']}), 55.1 (\text{CH}_2\text{N}), 122.3 (\text{C[4]}), 125.2 (\text{C[2]}), 128.4 (\text{C[5]}) \text{ and } 140.3 (\text{C[3]}) \text{ ppm.}
\]

M.S. (m/z): 167 (16.8%), 97 (100%), (M\textsuperscript{+}) 167.0753; \text{C}_9\text{H}_{13}\text{NS requires 167.0769.}

\[
\text{N-(3-Methoxybenzyl)morpholine (111j)}
\]

3-Methoxyphenyltributylstannane (1.99g, 5 mmol) ethoxy-N-morpholinylmethane (0.81g, 5.5 mmol) and trichloromethylsilane (0.82g, 5.5 mmol) were heated under reflux in acetonitrile for 23 hours, yielding (111j) (0.29g, 28%) b.p. 120°C / 0.2 mmHg.

\[
i.r. \text{ (film) } v_{\text{max}} 1602 (\text{benzene ring}) \text{ cm}^{-1}
\]

\[
^1\text{H n.m.r. (250 MHz), } \delta = 2.43-2.47 (4\text{H, m, C[3 and 5]} \text{H}), 3.48 (2\text{H, s, PhCH}_2), 3.69-3.73 (4\text{H, m, C[2 and 6]} \text{H}), 3.81 (3\text{H, s, OCH}_3), 6.79-6.92 (3\text{H, m, C[4', 5' and 6']} \text{H}), \text{ and } 7.21 (1\text{H, d, J}_{AB} = 8.0 \text{ Hz, C[2']} \text{H}) \text{ ppm.}
\]

\[
^{13}\text{C n.m.r. (62.9 MHz), } \delta = 53.6 (\text{C[3 and 5]}), 55.2 (\text{OCH}_3), 63.4 (\text{PhCH}_2\text{N}), 67.0 (\text{C[2 and 6]}), 112.5 (\text{C[2']}), 114.7 (\text{C[4']}), 121.5 (\text{C[6']}), 129.2 (\text{C[5']}), 139.5 (\text{C[1']}), \text{ and } 159.7 (\text{C[3']} \text{ ppm.}
\]

M.S. (m/z): 207 (30.9%), 121 (100%) (M\textsuperscript{+}) 207.1256; \text{C}_{12}\text{H}_{17}\text{NO}_2 \text{ requires 207.1259.}
2.4.3. Reactions of Aryltrialkylstannanes with Preformed Iminium Salts

General Method (G)

Preformed iminium salt (1.1 equiv.) was added to a solution of aryltrialkylstannane (1.0 equiv.) in acetonitrile and the mixture was heated under reflux or stirred at room temperature for a specified length of time. Work-up procedure as for General Method (F).

\[ \text{N-(2,4-Dimethoxybenzyl)morpholine (111e)} \]

\[ \text{N-MorpholinyHmethylene>iminium chloride (0.75g, 5.5 mmol) and 2,4-dimethoxyphenyltributylstannane (2.14g, 5 mmol) were heated under reflux in acetonitrile (50 ml) for 23 hours to give (111e) (0.53g, 45%), b.p. 120°C / 0.07 mmHg.} \]

\[ \text{N-(2,4-Dimethoxybenzyl)pyrrolidine (111m)} \]

\[ \text{N-PyrrolidinyHmethylene>iminium chloride (0.66g, 5.5 mmol) and 2,4-dimethoxyphenyltributylstannane (2.14g, 5 mmol) were heated under reflux in acetonitrile (50 ml) for 23 hours, affording (111m) (0.20g, 18%), b.p. 110°C / 0.07 mmHg (lit.117°C / 0.1 mmHg).} \]

\[ \text{^1H n.m.r. (60 MHz), } \delta = 1.60-1.93 (4H, m, C[3 and 4] H), 2.36-2.73 (4H, m, C[2 and 5] H), 3.60 (2H, s, PhCH}_2, 3.78 (6H, s, OCH}_3, 6.30-6.53 (2H, m, C[5' and 6'] H), and 7.21 (1H, d, J_{AB} = 8.5 Hz, C[3'] H) ppm.} \]

M.S. (m/z); 221 (20.9%), 151 (100%), (M^+ 221.1419; C_{13}H_{19}NO requires 221.1416.} \]
3-(N-MorpholinyImethyl)thiophene (111k)

(a) N-MorpholinyImethyleneiminium chloride (0.75g, 5.5 mmol) and 3-thienyltrimethylstannane (1.23g, 5 mmol) were heated under reflux in acetonitrile (50 ml) for 19 hours to give (111k) (0.60g, 66%), b.p. 100°C / 1 mmHg.

(b) Reaction (a) was repeated at room temperature for 94 hours affording (111k) (0.54g, 59%), b.p. 100°C / 1 mmHg.

3-(N-MorpholinyImethyl)thiophene (111l)

(a) N-PyrrolidinyImethyleneiminium chloride (0.79g, 6.6 mmol) and 3-thienyltrimethylstannane (1.48g, 6 mmol) were heated under reflux in acetonitrile (60 ml) for 19 hours to give (111l) (0.36g, 36%), b.p. 90°C / 1 mmHg.

(b) Reaction (a) repeated at room temperature for 90 hours affording (111l) (0.30g, 30%), b.p. 90°C / 1 mmHg.

N-(3-Methoxybenzyl)morpholine (111j)

N-MorpholinyImethyleneiminium chloride (0.75g, 5.5 mmol) and 3-methoxyphenyltributylstannane (1.99g, 5 mmol) were heated under reflux in acetonitrile (50 ml) for 19 hours to give (111j) (0.18g, 17%), b.p. 120°C / 0.2 mmHg.

N-(3-Methoxybenzyl)pyrrolidine (111n)

N-PyrrolidinyImethyleneiminium chloride (0.66g, 5.5 mmol) and 3-methoxyphenyltributylstannane (1.99g, 5 mmol) were heated under
reflux in acetonitrile for 19 hours, affording (111n) (0.13g, 13%), b.p. 110°C / 0.2 mmHg.

\[ \text{i.r. (film) } \nu_{\text{max}} \text{ 1602 (benzene ring) cm}^{-1} \]

\[ \text{\textsuperscript{1}H n.m.r. (60 MHz), } \delta = 1.57-1.97 (4\text{H, m, C[3 and 4]} \text{H}), 2.37-2.77 (4\text{H, m, C[2 and 5]} \text{H}), 3.61 (2\text{H, s, PhCH}_2), 3.79 (3\text{H, s, OCH}_3), 6.58-7.00 (3\text{H, m, C[4', S', and 6']} \text{H}), \text{and 7.13 (1H, d, J = 8 Hz, C[2']} \text{H} \text{ppm.} \]

\[ \text{M.S. (m/z); 191 (23%), 122 (100%), (M^+)} \text{191.1301; } \text{C}_{12}\text{H}_{17}\text{NO requires 191.1310.} \]

2.5.1 The Effect of Sulphur Dioxide in the Mannich Reactions of Phenols

**General Method (H)**

Sulphur dioxide (22 molar excess), (1 ml per mmol of reagents) was added to a mixture of the phenol (1.1 equiv.) and the Mannich reagent (1.0 equiv.) in acetonitrile at 0°C under a still head of dry nitrogen. The mixture was then allowed to stand at room temperature for a specified length of time. Water (20 ml) was added and the solvent was removed \textit{in vacuo}. The residue was acidified to pH1 with 2M hydrochloric acid and was extracted with ether (3 x 30 ml). The combined organic washings were dried and concentrated \textit{in vacuo} to give the unreacted phenol. The aqueous layer was then carefully basified to pH9 with 2M sodium hydroxide and extracted with ether (3 x 40 ml). The combined organic washings were dried and concentrated \textit{in vacuo} to give the Mannich products which were distilled using a Kugelröhr apparatus or recrystallised from a suitable solvent.

**Mannich Reactions of Phenol**

(a) Phenol (2.59g, 27.5 mmol), bis(N,N-dimethylamino)methane (2.56g, 25 mmol) and sulphur dioxide (25 ml) in acetonitrile (75 ml) at room
temperature for 42 hours gave two fractions after Kugelröhr distillation.

First fraction 2- \((N,N\text{-dimethylaminomethyl})\text{phenol (124a)}\) (1.77g, 47%),
b.p. 60°C / 5 mmHg, (lit.\(^8\) b.p. 100–101°C / 12 mmHg).

\(^1\)H n.m.r. (60 MHz), \(\delta = 2.27\) (6H, s, NCH\(_3\)), 3.55 (2H, s, CH\(_2\)N), 6.67–7.30
(4H, m, PhH) and 10.47 (1H, s, D\(_2\)O ex. OH) ppm.

\(^13\)C n.m.r. (20.1 MHz), \(\delta = 42.2\) (q, NCH\(_3\)), 62.7 (t, CH\(_2\)N), 116.1 (d, C [6]),
119.1 (d, C [4]), 128.4 (s, C [2]), 128.8 (d, C [5]), 129.6 (d, C [3]), and 158.2
(s, C [1]) ppm.

M.S. (m/z); 151 (100%), (M\(^+\)) 151.0989; C\(_9\)H\(_{13}\)NO requires 151.0997.

Second fraction 2,4- \((N,N\text{-dimethylaminomethyl})\text{phenol (125a)}\)
(0.15g, 6%), b.p. 110°C / 0.3 mmHg, (lit.\(^5\), no physical data given).

\(^1\)H n.m.r. (60 MHz), \(\delta = 2.27\) (12H, s, NCH\(_3\)), 3.43 (2H, s, CH\(_2\)N), 3.57
(2H, s, CH\(_2\)N), 6.60–7.27 (3H, m, PhH), and 9.17 (1H, br.s. D\(_2\)O ex. OH) ppm.

M.S. (m/z); 208 (34.1%) 164 (100%) (M\(^+\)) 208.1581; C\(_{12}\)H\(_{20}\)N\(_2\)O requires
208.1575.

The reaction was also carried out without sulphur dioxide for 41 hours
giving (124a) (0.53g, 14%).

(b) Phenol (2.59g, 27.5 mmol), di(N-piperidyl)methane (4.56g, 25 mmol)
and sulphur dioxide (25 ml) in acetonitrile (75 ml) at room temperature
for 42 hours gave two fractions after Kugelröhr distillation. First fraction
2- \((N\text{-piperidylmethyl})\text{phenol (124b)}\) (2.28g, 48%), b.p. 100°C / 2 mmHg,
(lit.\(^6\), no physical data given).

i.r. (film) \(\nu_{\max} \text{ (OH)} \), 3340 (OH), 1590 (aromatic ring) cm\(^{-1}\)

\(^1\)H n.m.r. (60 MHz), \(\delta = 1.07–1.83\) (6H, m, C [3‘, 4’ and 5’] H), 2.10–2.63
(4H, m, C [2’ and 6’] H), 3.55 (2H, s, CH\(_2\)N), 6.47–7.30 (4H, m, PhH), and
11.0 (1H, s, D\(_2\)O ex. OH) ppm.
$^{13}$C n.m.r. (20.1 MHz), $\delta = 24.0$ (t, C [4']), 25.8 (t, C [3' and 5']), 53.7 (t, C [2' and 6']), 62.1 (t, CH$_2$N), 116.0 (d, C [6]), 118.8 (d, C [4]), 121.6 s, C [2]), 128.5 (d, C [5]), 129.4 (d, C [3], and 158.3 (s, C [1]) ppm.

M.S. (m/z): 191 (100%), (M$^+$) 191.1313; C$_{12}$H$_{17}$NO requires 191.1310.

Second fraction 2,4-di(N-piperidylmethyl)phenol (125b) (0.32g, 9%), b.p. 150°C / 0.2 mmHg.

$^1$H n.m.r. (60 MHz), $\delta = 1.27$–1.80 (12H, m, C [3', 4' and 5']H), 2.20–2.63 (8H, m, C [2' and 6']H), 3.38 (2H, s, C [4]–CH$_2$N), 3.60 (2H, s, C [2]–CH$_2$N), 6.50–7.20 (3H, m, PhH), and 10.27 (1H, br.s. D$_2$O ex. OH) ppm.

M.S. (m/z): 288 (1.0%), 84 (100%), (M$^+$) 288.2189; C$_{16}$H$_{28}$N$_2$O requires 288.2201.

The reaction was also carried out without sulphur dioxide for 41 hours giving (124b) (0.88g, 18%), b.p. 100°C / 2.5 mmHg.

(c) Phenol (2.35g, 25 mmol), ethoxy–N–piperidylmethane (3.58g, 25 mmol) and sulphur dioxide (25 ml) in acetonitrile (75 ml) at room temperature for 43 hours gave (124b) (2.44g, 51%) b.p. 100°C / 2 mmHg and (125b) (0.35g, 10%), b.p. 150°C / 0.2 mmHg.

The reaction was also carried out without sulphur dioxide giving (124b) (2.98g, 62%), and (125b) (0.57g, 16%).

(d) Phenol (2.59g, 27.5 mmol) and ethoxy–N,N–diethylaminomethane (3.28g, 25 mmol) in acetonitrile at room temperature for 69 hours gave 2–(N,N–diethylaminomethyl)phenol (124c) (2.06g, 46%), b.p. 90°C / 2 mmHg, (lit.$^{185}$, no physical data given).

$^1$H n.m.r. (60 MHz), $\delta = 1.10$ (6H, t, J = 7.5 Hz, NCH$_2$CH$_3$), 2.63 (4H, q, J = 7.5 Hz, NCH$_2$CH$_3$), 3.77 (2H, s, CH$_2$N), 6.90–7.30 (4H, m, PhH),
and 10.93 (1H, s, D$_2$O ex., OH) ppm.

$^{13}$C n.m.r. (20.1 MHz), $\delta$ = 11.2 (q, CH$_2$CH$_3$), 46.4 (t, NCH$_2$CH$_3$), 56.9 (t, PhCH$_2$N), 116.1 (d, C[6]), 118.9 (d, C[4]), 122.2 (s, C[2]), 128.5 (d, C[5]), 129.5 (d, C[3]), and 158.5 (s, C[1]) ppm.

M.S. (m/z); 179 (43.1%), 58 (100%), $M^+$ 179.1306; $C_{11}H_{17}NO$ requires 179.1310.

Mannich Reactions of 2,4-Dimethylphenol

(a) 2,4-Dimethylphenol (2.69 g, 22 mmol), bis(N,N-dimethylamino)methane (2.04 g, 20 mmol) and sulphur dioxide (22 ml) in acetonitrile (75 ml) at room temperature for 114 hours gave 2-(N,N-dimethylaminomethyl)-4,6-dimethylphenol (126a) (0.73 g, 44%), b.p. 70°C / 0.5 mmHg, (lit.$^{158}$, 90°C / 0.9 mmHg).

i.r. (film) $\nu_{\text{max}}$ 3304 (OH), 1610 (aromatic ring) cm$^{-1}$

$^1$H n.m.r. (60 MHz), $\delta$ = 2.23 (6H, s, C[4 and 6] -CH$_3$), 2.30 (6H, s, NCH$_3$), 3.53 (2H, s, PhCH$_2$N), 6.50–6.67 (1H, br.s, C[3] H), 6.77–6.94 (1H, br.s, C[5] H), and 10.63 (1H, br.s, D$_2$O ex. OH) ppm.

$^{13}$C n.m.r. (20.1 MHz), $\delta$ = 15.6 (q, C[4]–CH$_3$), 20.4 (q, C[6]–CH$_3$), 44.2 (q, NCH$_3$), 63.0 (t, PhCH$_2$N), 121.0 (s, C[6]), 124.3 (s, C[2]), 126.5 (d, C[3]), 127.1 (s, C[4]), 130.7 (d, C[5]), and 154.0 (s, C[1]) ppm.

M.S. (m/z); 179 (100%) $M^+$ 179.1304; $C_{11}H_{17}NO$ requires 179.1310.

The reaction was repeated for 41 hours affording (126a) (2.13 g, 59%).

The reaction was carried out without sulphur dioxide for 42 hours yielding (126a) (0.68 g, 19%).

The reaction was carried out using 1.1 equiv. of sulphur dioxide for 42 hours affording (126a) (1.43 g, 40%).
2,4-Dimethylphenol (2.44g, 20 mmol), bis(N,N-dimethylamino)methane (3.07g, 30 mmol) and sulphur dioxide (20 mmol) in acetonitrile (90 ml) at room temperature for 42 hours gave (126a) (2.20g, 62%).

(b) 2,4-Dimethylphenol (2.44g, 20 mmol), di(N-piperidyl)methane (4.01g, 22 mmol) and sulphur dioxide (20 ml) in acetonitrile (75 ml) at room temperature for 42 hours afforded 2-(N-piperidylmethyl)-4,6-dimethylphenol (126b) (3.01g, 68%), b.p. 110°C / 0.2 mmHg (lit.\(^{157}\), m.p. 90°C, maleate salt).

i.r. (film) \(\nu_{\text{max}}\) 3310 (OH), 1608 (aromatic ring) cm\(^{-1}\)

\(^1\)H n.m.r. (60 MHz), \(\delta = 1.26-1.87\) (6H, m, C [3', 4' and 5'] H), 2.22 (6H, s, C [4 and 6'-CH\(_3\)]), 2.28-2.33 (4H, m, C [2' and 6'] H), 3.58 (2H, s, PhCH\(_2\)N), 6.50-6.63 (1H, br.s, C [3] H), 6.77-6.93 (1H, br.s, C [5] H), and 10.87 (1H, br.s, D\(_2\)O ex OH) ppm.

\(^{13}\)C n.m.r. (20.1 MHz), \(\delta = 15.7\) (q, C [4]-CH\(_3\)), 20.4 (q, C [6]-CH\(_3\)), 24.1 (t, C [4']), 26.0 (t, C [3' and 5']'), 53.8 (t, C [2' and 6']'), 62.3 (t, PhCH\(_2\)N), 120.6 (s, C [6]), 124.3 (s, C [2]), 126.6 (d, C [3]), 127.1 (s, C [4]), 130.5 (d, C [5]), and 154.0 (s, C [1]) ppm.

M.S. (m/z); 219 (48%), 84 (100%), (M\(^+\)) 219.1613; C\(_{14}\)H\(_{21}\)NO requires 219.1623.

The reaction was carried out without sulphur dioxide for 42 hours affording (126b) (1.18g, 27%), b.p. 100°C / 0.2 mmHg.

(c) 2,4-Dimethylphenol (2.44g, 20 mmol), 2,5-bis(N,N-diethylamino)methane (3.48g, 22 mmol) and sulphur dioxide (20 ml) in acetonitrile (60 ml) at room temperature for 42 hours afforded 2-(N,N-diethylaminomethyl)-4,6-dimethylphenol (126c) (2.99g, 72%), b.p. 90°C / 0.1 mmHg (lit.\(^{158}\), no physical data given).

i.r. (film) \(\nu_{\text{max}}\) 3308 (OH), 1610 (aromatic ring) cm\(^{-1}\)
$^1$H n.m.r. (60 MHz), $d = 1.10$ (6H, t, $J = 7.5$ Hz NCH$_2$CH$_3$), 2.23 (6H, s, C[4 and 6]-CH$_3$), 2.63 (4H, q, $J = 7.5$ Hz, NCH$_2$CH$_3$), 3.70 (2H, s, PhCH$_2$N), 6.57–6.73 (1H, br.s, C[3] H), 5.80–5.97 (1H, br.s, C[5] H), and 10.93 (1H, br.s, D$_2$O ex., OH) ppm.

$^{13}$C n.m.r. (20.1 MHz), $\delta = 11.3$ (q, NCH$_2$CH$_3$), 15.6 (q, C[4]-CH$_3$), 20.4 (q, C[6]-CH$_3$), 46.4 (t, NCH$_2$CH$_3$), 57.0 (t, PhCH$_2$N), 121.2 (s, C[6]), 124.3 (s, C[2]), 126.6 (d, C[3]), 127.1 (s, C[4]), 130.4 (d, C[5]), and 154.2 (s, C[1]) ppm.

M.S. (m/z); 207 (49.9%), 58 (100%), (M$^+$) 207.1615; C$_{18}$H$_{21}$NO requires 207.1623.

The reaction was also carried out without sulphur dioxide for 42 hours giving (126c) (1.68g, 40%), b.p. 90°C / 0.1 mmHg.

(d) 2,4-Dimethylphenol (2.44g, 20 mmol), ethoxy-N,N-diethylamino-methane (2.89g, 22 mmol) and sulphur dioxide (20 ml) in acetonitrile at room temperature for 42 hours gave (126c) (2.16g, 52%), b.p. 90°C / 0.01 mmHg.

The reaction was carried out in the absence of sulphur dioxide affording (126c) (2.12g, 51%).

Mannich Reactions of 2-Naphthol

(a) 2-Naphthol (2.88g, 20 mmol), di(N-piperidyl)methane (4.01g, 22 mmol) and sulphur dioxide (20 ml) in acetonitrile (75 ml) at room temperature for 26 hours afforded 1-(N-piperidylmethyl)-2-naphthol (127)$^{26}$ (2.59g, 54%) m.p. 101–102°C (recrystallised from ethanol), (lit.$^{19}$, m.p. 96 °C, from aqueous ethanol).

i.r. (KBr) $\nu_{\max}$ 2924, 2848, 2820, 2664, 1910, 1620, 1596, 1584, 1518,
1478, 1454, 1416, cm⁻¹

¹H n.m.r. (60 MHz), δ = 1.33–1.87 (6H, m, C [3', 4' and 5'] H), 2.33–2.80 (4H, m, C [2' and 6'] H), 4.00 (2H, s, CH₂N), 6.90–7.83 (6H, m, ArH), and 12.33 (1H, s, D₂O ex. OH) ppm.

¹³C n.m.r. (62.9 MHz), δ = 23.8 (C [4']), 25.7 (C [3' and 5']), 53.9 (C [2' and 6']), 57.1 (t, CH₂N), 110.9 (C [1]), 119.2 (C [3]), 120.9 (C [6]), 122.2 (C [8]), 126.2 (C [7]), 128.4 (C [4a]), 128.8 (d, C [5]), 128.9 (C [4]), 132.8 (C [8a]), and 156.8 (C [2]) ppm.

M.S. (m/z): 241 (17.5%), 84 (100%), M⁺ 241.1465; C₁₉H₁₉NO requires 241.1466.

The reaction was repeated for 43 hours, affording (127) (3.33 g, 69%).

The reaction was also carried out without sulphur dioxide at room temperature, affording (127) after 27 hours (2.06 g, 43%), and after 43 hours (3.24 g, 67%).

(b) 2-Naphthol (2.88 g, 20 mmol), ethoxy-N-piperidylmethane (3.15 g, 22 mmol) and sulphur dioxide (22 ml) in acetonitrile for 42 hours afforded (127) (3.24 g, 67%).

The reaction was also carried out in the absence of sulphur dioxide affording the product (127) (3.38 g, 70%).

2.5.2 Mannich Reactions of 2,5-Dimethylphenol

General Method (I)

2,5-Dimethylphenol (1 equiv.) and an aminal or aminol ether (1.1 equiv.) in acetonitrile in the presence of sulphur dioxide (1 ml per mmol of reagents) were allowed to stand at room temperature for a specified
length of time. Following the work-up procedure described above (General Method H) the crude product was isolated as an oily solid. Recrystallisation from petroleum ether (40–60°C) afforded the para-substituted Mannich base (128). The mother liquor was then concentrated in vacuo and the residue was Kugelröhr distilled to give the ortho-isomer (130), and the 2,4-disubstituted material (129) was isolated by distillation or recrystallisation from a suitable solvent.

(a) 2,5-Dimethylphenol (2.44g, 20 mmol), di(N-piperidyl)methane (4.01g, 22 mmol) and sulphur dioxide (20 ml) in acetonitrile (75 ml) at room temperature for 42 hours afforded three products.

First product 4-(N-piperidylmethyl)-2,5-dimethylphenol (128a) (0.29g, 7%), m.p. 132–134°C from petroleum ether (40–60°C), (lit.101, m.p. 131.5–132°C).

i.r. (Nujol) \( \nu_{\text{max}} \) 3064 (OH), 1616 (aromatic ring) cm\(^{-1}\)

\(^1\)H n.m.r. (60 MHz), \( \delta = 1.30–1.53 \) (6H, m, C[3', 4' and 5'] \text{H}), 2.13 (6H, s, CH\(_3\)), 2.27–2.63 (4H, m, C[2' and 6'] \text{H}), 3.30 (2H, s, PhCH\(_2\text{N}\)), 5.57 (1H, br.s, D\(_2\text{O}\) ex., OH), 6.12 (1H, s, C[6] \text{H}), and 6.88 (1H, s, C[3] \text{H}) ppm.

\(^{13}\)C n.m.r. (20.1 MHz), \( \delta = 15.4 \) (q, C[5]-CH\(_3\)), 18.8 (q, C[2]-CH\(_3\)), 24.1 (t, C[4']), 25.0 (t, C[3' and 5']), 54.6 (t, C[2' and 6']), 60.5 (t, C[4]-CH\(_2\text{N}\)), 117.6 (d, C[6]), 121.5 (s, C[2]), 126.4 (s, C[4]), 133.0 (d, C[3]), 135.7 (s, C[5]), and 153.4 (s, C[1]) ppm.

M.S. (m/z); 219 (40.2%), 134 (100%), (M\(^+\)) 219.1612; C\(_{14}\)H\(_{21}\)NO requires 219.1623.

Second product 6-(N-piperidylmethyl)-2,5-dimethylphenol (130a) (1.75g, 40%), b.p. 110°C / 0.2 mmHg, (lit.160 no physical data given).

i.r. (film) \( \nu_{\text{max}} \) 3040 (OH), 1616 (aromatic ring) cm\(^{-1}\)

\(^1\)H n.m.r. (60 MHz), \( \delta = 1.37–1.63 \) (6H, m, C[3', 4' and 5'] \text{H}), 2.20
(6H, s, CH₃), 2.18-2.57 (4H, m, C[2’ and 6’] H), 3.67 (2H, s, PhCH₂N), 6.52 (1H, d, J_AB = 8 Hz, C[4] H), 6.93 (1H, d, J_AB = 8 Hz, C[3] H) and 10.93 (1H, br.s, D₂O ex. OH) ppm.

¹³C n.m.r. (20.1 MHz), δ = 15.7 (q, C[5]-CH₃), 19.5 (q, C[2]-CH₃), 24.0 (t, C[4’]), 25.8 (t, C[3’ and 5’]), 53.8 (t, C[2’ and 6’]), 64.2 (t, PhCH₂N), 118.8 (s, C[6]), 120.3 (d, C[4]), 123.0 (s, C[2]), 129.1 (d, C[3]), 133.6 (s, C[5]), and 156.8 (s, C[1]) ppm.

M.S. (m/z); 219 (0.4%), 98 (100%) (M⁺) 219.1612; C₁₄H₂₆N₂O requires 219.1623.

Third product 4,6-bis(N-piperidylmethyl)-2,5-dimethylphenol (129a), (0.67g, 21%), b.p. 160°C / 0.1 mmHg.

¹H n.m.r. (60 MHz), δ = 1.00-1.87 (12H, m, C[3’, 3”, 4’, 4” and 5’, 5”] H), 2.20 (s, 6H, CH₃), 2.27-2.73 (8H, m, C[2’, 2” and 6’, 6”] H), 3.30 (2H, s, C[4]-CH₂N), 3.33 (2H, s, C[2]-CH₂N), 6.88 (1H, s, C[3] H) and 11.17 (1H, br.s, D₂O ex. OH) ppm.

¹³C n.m.r. (20.1 MHz), δ = 14.7 (q, C[5]-CH₃), 15.6 (q, C[2]-CH₃), 24.0 (t, C[4’]), 24.6 (t, C[4’]), 25.8 (t, C[3’ and 5’]), 26.1 (t, C[3’ and 5’]), 53.8 (t, C[2’ and 6’]), 54.4 (t, C[2’ and 6’]), 58.3 (t, C[6]-CH₂N), 62.4 (t, C[4]-CH₂N), 119.3 (s, C[6]), 121.1 (s, C[2]), 126.7 (s, C[4]), 131.9 (d, C[3]), 133.5 (s, C[5]), and 155.8 (s, C[1]) ppm.

M.S. (m/z); 316 (20.6%), 232 (100%), (M⁺) 316.2517; C₂₀H₃₂N₂O requires 316.2515.

The reaction was also carried out without sulphur dioxide, at room temperature, affording the products (128a) (1.05g, 24%), (130a) (1.03g, 24%), and (129a) (0.30g, 10%).

(b) 2,5-Dimethylphenol (3.05g, 25 mmol), bis(N,N-diethylamino)methane (4.35g, 27.5 mmol) and sulphur dioxide (25 ml) in acetonitrile.
(75 mL) at room temperature for 43 hours afforded three products. First product 4-(N,N-diethylaminomethyl)-2,5-dimethylphenol (128b) (0.09 g, 2%), m.p. 104–105°C (from pet. ether 40–60°C), (lit., no physical data given).

i.r. (Nujol) νmax 3040 (OH), 1610 (aromatic ring) cm⁻¹

¹H n.m.r. (60 MHz), δ = 1.10 (6H, t, J = 7.5 Hz, NCH₂CH₃), 2.13 (6H, s, C[2 and 5]-CH₃), 2.62 (4H, q, J = 7.5 Hz, NCH₂CH₃), 3.38 (2H, s, CH₂N), 6.07 (1H, s, C[6] H), 6.82 (1H, s, C[3] H), and 6.93 (1H, s, D₂O ex. OH) ppm.

¹³C n.m.r. (20.1 MHz), δ = 11.0 (q, NCH₂CH₃), 16.0 (q, C[5]-CH₃), 19.4 (q, C[2]-CH₃), 46.6 (t, NCH₂CH₃), 54.9 (t, C[4] CH₂N), 118.4 (d, C[6]), 122.4 (s, C[2]), 127.7 (s, C[4]), 133.5 (d, C[3]), 136.1 (s, C[5]), and 154.2 (s, C[1]) ppm.

M.S. (m/z): 207 (20.6%), 135 (100%), (M⁺) 207.1629; C₁₃H₂₁NO requires 207.1623.

Second product 6-(N,N-diethylaminomethyl)-2,5-dimethylphenol (130b) (1.6 g, 42%), b.p. 110°C / 0.2 mmHg.

i.r. (film) νmax 3040 (OH), 1610 (aromatic ring) cm⁻¹

¹H n.m.r. (60 MHz), δ = 1.12 (6H, t, J = 7.5 Hz, NCH₂CH₃), 2.23 (6H, s, C[2 and 5]-CH₃), 2.63 (4H, q, J = 7.5 Hz, NCH₂CH₃), 3.77 (2H, s, C[6]-CH₂N), 6.53 (1H, d, JAB = 8 Hz, C[4] H), 6.93 (1H, d, JAB = 8 Hz, C[3] H), and 11.90 (1H, s, D₂O ex. OH) ppm.

¹³C n.m.r. (20.1 MHz), δ = 11.3 (q, NCH₂CH₃), 15.6 (q, C[5]-CH₃), 19.5 (q, C[2]-CH₃), 46.5 (q, NCH₂CH₃), 52.8 (t, C[6]-CH₂N), 119.4 (s, C[6]), 120.3 (d, C[4]), 122.8 (s, C[2]), 129.1 (d, C[3]), 133.7 (s, C[5]), and 157.1 (s, C[1]) ppm.

M.S. (m/z): 207 (23.5%), 58 (100%), (M⁺) 207.1629; C₁₃H₂₁NO requires 207.1623.
Third product 4,6-bis(N,N-diethylaminomethyl)-2,5-dimethylphenol (129b) (0.16g, 4%), b.p. 150°C / 0.1 mmHg.

i.r. (film) $v_{max}$ 3420 (OH), 1614 (aromatic ring) cm$^{-1}$

$^1$H n.m.r. (60 MHz), $\delta$ = (12H, q, $J = 7.5$ Hz, NCH$_2$CH$_3$), 2.10 and 2.20 (6H, s, C[2 and 5]-CH$_3$), 2.53 (8H, q, $J = 7.5$ Hz, NCH$_2$CH$_3$), 3.43 (2H, s, C[4]-CH$_2$N), 3.80 (2H, s, C[6]-CH$_2$N), 6.93 (1H, s, C[3] H), and 7.73 (1H, br.s, D$_2$O ex., OH) ppm.

$^{13}$C n.m.r. (20.1 MHz), $\delta$ = 11.4 (q, NCH$_2$CH$_3$), 14.7 (q, C[5]-CH$_3$), 15.6 (q, C[2]-CH$_3$), 46.5 (q, NCH$_2$CH$_3$), 53.1 (t, C[6]-CH$_2$N), 56.5 (t, C[4]-CH$_2$N), 119.7 (s, C[6]), 121.2 (s, C[2]), 127.3 (s, C[4]), 132.0 (d, s, C[3]), 133.3 (s, C[5]), and 155.9 (s, C[1]) ppm.

M.S. (m/z); 292 (6.2%), 84 (100%), (M$^+$) 292.2514; C$_{18}$H$_{32}$N$_2$O requires 292.2515.

(c) 2,5-Dimethylphenol (3.05g, 25 mmol), ethoxy-N-piperidylmethane (3.94g, 27.5 mmol) and sulphur dioxide (25 ml) in acetonitrile (75 ml) at room temperature for 42 hours gave (128a) (1.39g, 25%), (130a) (0.99g, 18%), and (129a) (1.25g, 31%).

The reaction was also carried out without sulphur dioxide affording (128a) (2.80g, 51%), (130a) (0.94g, 17%) and (129a) (0.63g, 16%).

(d) 2,5-Dimethylphenol (3.05g, 25 mmol), ethoxy-N,N-diethylaminomethane (3.61g, 27.5 mmol) and sulphur dioxide (25 ml) in acetonitrile (75 ml) at room temperature for 45 hours gave (128b) (0.49g, 9%), (130b) (2.12g, 25%) and (129b) (0.63g, 17%).

The reaction was also carried out in the absence of sulphur dioxide, affording (128b) (1.59g, 31%), (130b) (0.63g, 12%) and (129b) (0.36g, 10%).
2.5.2.1 Reactions of 2,5-Dimethylphenol in the Presence of a Reduced Amount of Sulphur Dioxide

General Method (J)

2,5-Dimethylphenol (1 equiv.) was allowed to react with sulphur dioxide (1.1 to 4.4 equiv.) in acetonitrile at room temperature for 24 hours. The amount of sulphur dioxide was measured from a standard solution of sulphur dioxide in acetonitrile. An aminal or aminol ether, in various molar ratios, were added and the mixture was allowed to react at different temperatures. The crude products were isolated following the work-up procedure given in (General Method H) and were separated as described in (General Method I).

(a) (i) 2,5-Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (1 ml), and bis(N,N-diethylamino)methane (3.17g, 20 mmol) in acetonitrile at room temperature for 42 hours gave (130b) (0.75g, 18%) and (129b) (0.17g, 6%).

(ii) Repeating the reaction (i) for 44 hours at -22°C followed by 2 hours under reflux gave (130b) (1.00g, 25%) and a trace of (129b)

(iii) Repeating the reaction (i) using (2 ml) sulphur dioxide at room temperature for 42 hours gave (130b) (1.67g, 40%) and (129b) (0.20g, 7%).

(iv) The reaction was also repeated by adding sulphur dioxide (1 ml) to a mixture of 2,5-xylenol (2.44g, 20 mmol) and bis(N,N-diethylamino)methane (3.17g, 20 mmol) affording (128b) (0.19g, 5%), (130b) (1.04g, 25%) and (129b) as a trace.
(v) Bis(N,N-diethylamino)methane (3.17g, 20 mmol) was allowed to react with sulphur dioxide in acetonitrile (60 ml) for 24 hours at room temperature followed by the addition of 2,5-dimethylphenol (2.44g, 20 mmol). The mixture was then allowed to stand at room temperature for a further 4 hours affording (130b) (0.35g, 8%).

(vi) Repeating the reaction (i) using (1 ml) of sulphur dioxide under reflux for 2 hours gave (130b) (0.70g, 17%) and a trace of (129b).

(vii) 2,5-dimethylphenol (2.44g, 20 mmol), bis(N,N-diethylamino)methane (6.33g, 40 mmol) and sulphur dioxide (2 ml) in acetonitrile (80 ml) at room temperature for 42 hours gave (128b) (0.16g, 4%), (130b) (0.53g, 12%) and (129b) (0.25g, 4%).

(viii) Repeating the reaction (vii) for 2 hours under reflux gave (130b) (0.41g, 10%) and (129b) (0.09g, 2%).

(b) (i) 2,5-Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (1 ml) and ethoxy-N,N-diethylaminomethane (2.63g, 20 mmol) in acetonitrile (60 ml) at room temperature for 42 hours afforded (130b) (1.27g, 31%) and (129b) (0.43g, 15%).

(ii) Repeating the reaction (i) for 2 hours under reflux gave (130b) (0.88g, 21%).

(iii) Repeating the reaction (i) for 4 hours under reflux gave (130b) (1.06g, 25%).

(iv) Repeating the reaction (i) using (2 ml) of sulphur dioxide at room temperature for 42 hours gave (130b) (1.43g, 35%) and (129b) (0.62g, 21%).
(v) Repeating the reaction (iv) using (4 ml) of sulphur dioxide gave (130b) (1.67g, 40%) and (129b) (0.88g, 15%).

(vi) The reaction (ii) was also repeated without any sulphur dioxide under reflux for 2 hours as a control experiment affording (128b) (1.17g, 28%), (130b) (0.80g, 19%) and (129b) (0.12g, 4%).

(vii) 2,5-Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (2 ml) and ethoxy-N,N-diethylaminomethane (5.25g, 40 mmol) in acetonitrile (80 ml) at room temperature for 42 hours gave (130b) (1.30g, 31%) and (129b) (1.19g, 21%).

(viii) Repeating the reaction (vii) for 2 hours in acetonitrile heated under reflux gave (130b) (2.73g, 66%) exclusively.

(c) (i) 2,5 Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (1 ml) and di(N-piperidyn)methane (3.65g, 20 mmol) in acetonitrile (60 ml) were kept in the freezer at -22°C for 20 days. After work-up gave (128a) (0.39g, 9%), (130a) (0.27g, 6%) and (129a) (0.13g, 4%).

(ii) The reaction (i) was repeated at room temperature for 42 hours affording (128a) (0.33g, 7%), (1230a) (1.13g, 26%) and (129a) (0.25g, 8%).

(iii) 2,5-Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (2 ml) and, di(N-piperidyn)methane (7.29g, 40 mmol) were heated under reflux in acetonitrile (80 ml) for 2 hours, affording (130a) (0.88g, 20%) and (129a) (2.27g, 36%).

(d) (i) 2,5-Dimethylphenol (2.44g, 20 mmol) and ethoxy-N-piperidyn-methane (2.86g, 20 mmol) in acetonitrile (60 ml) were heated under reflux for 2 hours in the absence of sulphur dioxide as a control.
experiment, affording (128a) (1.46g, 33%), (130a) (1.38g, 31%) and (129a) (0.48g, 15%).

(ii) 2,5-Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (2 ml) and ethoxy-N-piperidylmethane (5.73g, 40 mmol) in acetonitrile (80 ml) were heated under reflux for 2 hours to give (130a) (2.09g, 48%) and (129a) (2.34g, 37%).

(iii) The reaction (ii) was repeated for 1 hour under reflux, affording (130a) (2.50g, 57%) and (128a) (1.68g, 26%).

(iv) 2,5-Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (2 ml) and ethoxy(N-piperidyl)methane (4.30g, 30 mmol) were heated under reflux in acetonitrile (80 ml) for 2 hours to give (130a) (1.92g, 44%) and (129a) (2.44g, 38%).

(v) The reaction (ii) was repeated for ½ hour under reflux affording (130a) (2.55g, 58%) and (129a) (1.63g, 26%).

(vi) The reaction (iv) was repeated for ½ hour under reflux affording (130a) (2.97g, 67%) and (129a) (1.21g, 19%).

(vii) The reaction (iv) was repeated using sulphur dioxide (1.5 ml) under reflux for ½ hour affording (130a) (2.47g, 56%) and (129a) (1.58g, 25%).

(e) 2,5-Dimethylphenol (2.43g, 20 mmol), sulphur dioxide (2 ml) and di(N-morpholinyl)methane (7.45g, 40 mmol) in acetonitrile (80 ml) under reflux for 2 hours gave a white solid (1.65g) from which two products were isolated. Recrystallisation from cyclohexane / ethyl acetate (90:10) afforded 4-(N-morpholinylmethyl)-2,5-dimethylphenol (128c) (0.44g, 10%), m.p. 151-152°C, (lit.\(^\text{162}\), 148-149 °C, from aqueous
methanol).

i.r. (film) \( \nu_{\text{max}} \) 3040 (OH), 1610 (aromatic ring).

\(^1\)H n.m.r. (60 MHz), \( \delta = 2.17 \) (3H, s, C [2] - CH\(_3\)), 2.24 (3H, s, C [5] - CH\(_3\)), 2.30 - 2.57 (4H, m, C [3' and 5'] H), 3.35 (2H, s, PhCH\(_2\)N), 3.57 - 3.80 (4H, m, C [2' and 6'] H), 6.43 (1H, s, C [6] H), and 6.92 (1H, s, C [3] H) ppm, (OH not detected).

\(^13\)C n.m.r. (20.1 MHz), \( \delta = 15.5 \) (q, C [5] - CH\(_3\)), 18.7 (q, C [2] - CH\(_3\)), 53.4 (t, C [3' and 5']), 60.7 (t, C [4] - CH\(_2\)N), 66.8 (t, C [2' and 6']), 116.9 (d, C [6]), 120.8 (s, C [2]), 126.2 (s, C [4]), 132.8 (d, C [3]), 135.7 (s, C [5]), and 154.2 (s, C [1]) ppm.

The mother liquor was concentrated \textit{in vacuo} giving a solid which, upon recrystallisation from aqueous ethanol, gave 6-(N-morpholinylmethyl)-2,5-dimethylphenol (13Oc) (1.21g, 27%), m.p. 98 - 99°C, (lit.\(^{82}\), hydrochloride salt m.p. 188 - 90°C, from 2-propanol).

i.r. (nujol) \( \nu_{\text{max}} \) 3040 (OH), 1610 (aromatic ring).

\(^1\)H n.m.r. (60 MHz), \( \delta = 2.20 \) (6H, s, C [2 and 5] - CH\(_3\)), 2.33 - 2.73 (4H, m, C [3' and 5'] H), 3.50 - 3.90 (2H, s, CH\(_2\)N and 4H, m, C [2' and 6'] H), 6.53 (1H, d, \( J_{\text{AB}} = 8 \) Hz, C [4] H), 6.93 (1H, d, \( J_{\text{AB}} = 8 \) Hz, C [3] H), and 10.07 (1H, br.s, D\(_2\)O ex. OH) ppm.

\(^13\)C n.m.r. (20.1 MHz), \( \delta = 15.6 \) (q, C [5] - CH\(_3\)), 19.5 (q, C [2] - CH\(_3\)), 52.8 (t, C [3' and 5']), 57.5 (t, C [6] - CH\(_2\)N), 66.7 (t, C [2' and 6']), 118.0 (s, C [6]), 120.8 (d, C [4]), 122.7 (s, C [4]), 129.5 (d, C [3]), 133.9 (s, C [5]), and 156.3 (s, C [1]) ppm.

M.S. (m/z); 221 (72.2%), 134 (100%), (M\(^+\)) 221.1416; C\(_{13}\)H\(_{19}\)NO\(_2\) requires 221.1405.

(f) (i) 2,5-Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (4 ml) and ethoxy-N-morpholinylmethane (2.91g, 20 mmol) in acetonitrile (60 ml)
were allowed to stand at room temperature for 68 hours. After work-up the crude product (3.05g) was isolated as a white solid. Recrystallisation from ethyl acetate afforded the ortho-substituted Mannich base (130c) (1.94g, 44%) m.p. 98–99°C. The mother liquor was concentrated in vacuo to yeild a white solid which was recrystallised from water, giving the 4,6-disubstituted Mannich base 4,6-bis(N-morpholinylmethyl)-2,5-dimethylphenol (129c) (0.81g, 13%), m.p. 115–116°C, (lit.,

dihydrochloride salt m.p. 236–7 °C, from aqueous 2-propanol).

\[ \begin{align*}
\text{\textsuperscript{1}H n.m.r. (250 MHz), } & \delta = 2.17 (3H, s, C[2]-CH_3), 2.23 (3H, s, C[5]-CH_3), 2.38–2.56 (8H, s, C[2' and 6'] H), 3.34 (2H, s, C[4]-CH_2N), 3.64–3.77 (8H, m, C[3' and 5'] H), 3.75 (2H, s, C[6]-CH_2N), \text{ and } 6.88 (1H, s, C[3] H) \text{ ppm, (OH not detected).}
\text{\textsuperscript{13}C n.m.r. (62.9 MHz), } & \delta = 14.8 (C[5]-CH_3), 15.5 (C[2]-CH_3), 52.8 (C[3' and 5']), 53.5 (C[3' and 5']), 57.8 (C[6]-CH_2N), 62.0 (C[4]-CH_2N), 66.8 (C[2' and 6'']), 67.1 (C[2' and 6'']), 118.6 (C[6]), 121.4 (C[2]), 126.2 (C[4]), 132.4 (C[3]), 133.8 (C[5]), \text{ and } 155.4 (C[1]) \text{ ppm.}
\end{align*} \]

M.S. (m/z); 320 (25%), 234 (100%), \( M^+ \) 320.2097; \( C_{13}H_{20}N_2O_3 \) requires 320.2100.

(ii) 2,5-Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (2 ml) and ethoxy-N-morpholinylmethane (5.81g, 40 mmol) were heated under reflux in acetonitrile (80 ml) for 2 hours, affording (130c) (2.62g, 59%) and (129c) (1.07g, 17%).

(iii) 2,5-Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (1.5 ml) and ethoxy-N-morpholinylmethane (4.36g, 30 mmol) were heated under reflux in acetonitrile (80 ml) for ¾ hour, giving (130c) (2.15g, 49%) and (129c) (0.21g, 3%).
2,5-Dimethylphenol (2.44 g, 20 mmol), sulphur dioxide (2 ml) and di(N-pyrrolidinyl)methane (6.17 g, 40 mmol) in acetonitrile (80 ml) were heated under reflux for 2 hours. The crude product was isolated as a brown oil (1.24 g) and purified by Kugelröhr distillation, giving two fractions.

First fraction 6-(N-pyrrolidinylmethyl)-2,5-dimethylphenol (130 d) (0.49 g, 12%), b.p. 120°C / 0.2 mmHg.

'H n.m.r. (60 MHz), δ = 1.63–2.00 (4H, m, C [3' and 4'], H), 2.20 (6H, s, C [2 and 5]-CH₃), 2.40–2.78 (4H, m, C [2' and 5'], Η), 3.80 (2H, s, CH₂N'), 6.38 (1H, d, J₉ = 8 Hz, C [4], H), 6.78 (1H, d, J₉ = 8 Hz, C [3], H), and 11.50 (1H, s, D₂O ex. OH) ppm.

'¹C n.m.r. (20.1 MHz), δ = 15.7 (q, C [5]-CH₃), 19.4 (q, C [2]-CH₃), 23.7 (t, C [3' and 4']), 53.5 (t, C [2' and 5']), 54.7 (t, CH₂N), 119.6 (s, C [6]), 120.3 (d, C [4]), 122.5 (s, C [2]), 129.1 (d, C [3]), 133.0 (s, C [5]), and 156.8 (s, C [1]) ppm.

M.S. (m/z): 205 (65.9%), 70 (100%), 134 (78.8%) (M⁺) 205.1456; C₁₃H₁₉NO requires 205.1466.

Second fraction 4,6-bis(N-pyrrolidinylmethyl)-2,5-dimethylphenol (129 d) (0.42 g, 7%) b.p. 140°C / 0.02 mmHg.

'H n.m.r. (60 MHz), δ = 1.67–2.00 (8H, m, C [3' and 4'], H), 2.17 and 2.23 (3H, s, C [2] and C [5]-CH₃), 2.47–2.83 (8H, m, C [2' and 5'], H), 3.53 (2H, s, C [4]-CH₂N), 3.83 (2H, C [6]-CH₂N), 6.93 (1H, s, C [3]H), and 10.00 (1H, br.s. D₂O ex. OH) ppm.

M.S. (m/z): 288 (0.1%), 70 (100%), (M⁺) 288.2082; C₁₈H₂₈N₂O requires 288.2201.
heated under reflux (80 ml) for 2 hours, gave (130d) (1.98g, 48%) and (129d) (1.16g, 20%).

(ii) 2,5-Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (1.5 ml) and ethoxy(N-pyrrolidinyl)methane (3.88g, 30 mmol) in acetonitrile (80 ml), heated under reflux for 1½ hours, gave (130d) (1.29g, 31%) and (129d) (0.83g, 14%).

2.5.3 Reactions of 2,5-Dimethylphenol with Preformed Iminium Salt

(a) N-piperidyl(methylene)iminium chloride (3.65g, 20 mmol) was added to a mixture of 2,5-dimethylphenol (2.44g, 20 mmol) and potassium carbonate (4.15g, 30 mmol) in toluene (100 ml). The reaction mixture was stirred at room temperature for 6 hours and after work-up (General Method H) gave (128a) (1.11g, 25%) (130a) (0.30g, 7%) and (129a) (1.55g, 49%)

(b) N-piperidyl(methylene)iminium chloride (3.65g, 20 mmol) was added to a mixture of 2,5-dimethylphenol (2.44g, 20 mmol) and potassium carbonate (4.15g, 30 mmol) in dichloromethane (100 ml). The mixture was stirred at room temperature for 10 hours, affording, after work-up, (128a) (1.67g, 38%), (130a) (0.11g, 2%) and (129a) (1.27g, 40%).

(c) N-piperidyl(methylene)iminium chloride (3.65g, 20 mmol) was added to a mixture of 2,5-dimethylphenol (2.44g, 20 mmol) and potassium carbonate (4.15g, 30 mmol) in acetonitrile (100 ml). The mixture was stirred at room temperature for 6 hours to give, after work-up, (128a) (0.99g, 21%) (130a) (1.60g, 36%) and (129a) (0.96g, 30%).
Preparation of 4,6-Bis(N-morpholinylmethyl)-2,5-dimethylphenol (129c)

Ethoxy(N-morpholinyl)methane (0.58g, 4 mmol) was added to a solution of 4-(N-morpholinylmethyl)-2,5-dimethylphenol (0.78g, 3.5 mmol) (128c) and sulphur dioxide (1.5 ml) in acetonitrile (50 ml). The mixture was stirred at room temperature for 2 days affording, after work-up, the title compound (0.47g, 42%), recrystallised from water m.p. 115-116°C.

Preparation of 3-Methyl-1,3-oxazolidine

N-Methylethanolamine (112.66g, 1.5 mol), paraformaldehyde (60.06g, 2 mol equiv.) and potassium carbonate (82.93g, 0.6 mol) were heated under gentle reflux for 6 hours. The mixture was allowed to cool down to room temperature, filtered and washed with dried ether (150 ml). The filtrate was dried and fractionally distilled through an 18" Vigreux column to yield the title compound (84.86g, 65%), b.p. 98-100°C, (lit.183 97-99°C) \(^1\)H n.m.r. (60 MHz), \(\delta = 2.43\) (3H, s, NCH\(_3\)), 2.94 (2H, t, \(J = 7\) Hz, NCH\(_2\)CH\(_2\)O), 3.78 (t, \(J = 7\) Hz, NCH\(_2\)CH\(_2\)O), and 4.24 (2H, s, NCH\(_2\)O) ppm.

2.5.4.1 Reactions of Phenols with 3-Methyl-1,3-oxazolidine

(a) (i) 2,4-Dimethylphenol (1.83g, 15 mmol) and 3-methyl-1,3-oxazolidine (1.44g, 16.5 mmol) in acetonitrile (45 ml) were stirred at room temperature for 50 hours. The work-up procedure (General Method HD) yielded 6-(N-2-hydroxyethyl-N-methylaminomethyl)-2,4-dimethylphenol (135a) (0.81g, 26%), b.p. 140°C / 0.2 mmHg.

i.r. (film) \(\nu_{max} \) 3440, 2948, 1664, 1610, 1482 cm\(^{-1}\)

\(^1\)H n.m.r. (60 MHz), \(\delta = 2.20\) (6H, s, C[2 and 4]-CH\(_3\)), 2.27 (3H, s, NCH\(_3\)), 2.60 (2H, t, \(J = 7.5\) Hz, NCH\(_2\)), 3.63 (2H, s, PhCH\(_2\)N),
3.72 (2H, t, J = 7.5 Hz, CH₂OH), 6.03 (2H, br.s. D₂O ex. 2OH's), 6.62 (1H, br.s, C [3] H), and 6.83 (1H, br.s, C [5] H) ppm.

¹³C n.m.r. (20.1 MHz), δ = 15.6 (q, C [4]-CH₃), 20.4 (q, C [2]-CH₃), 41.5 (q, NCH₃), 58.7 (t, NCH₂), 59.5 (t, PhCH₂N), 61.3 (t, NCH₂CH₂OH), 121.1 (s, C [6]), 124.5 (s, C [2]), 126.6 (d, C [5]), 127.6 (s, C [4]), 130.6 (d, C [3]), and 153.5 (s, C [1]) ppm.

M.S. (m/z); 209 (19.2%), 135 (100%), (M⁺) 209.1422; C₁₂H₁₉NO₂ requires 209.1416.

(ii) 2,4-Dimethylphenol (1.22g, 10 mmol), 3-methyl-1,3-oxazolidine (1.31g, 15 mmol) and sulphur dioxide (0.67 ml) in acetonitrile (45 ml) gave (135a) (0.60g, 28%).

(iii) Sulphur dioxide (1 ml) was added to 2,4-dimethylphenol (1.22g, 10 mmol) in acetonitrile (45 ml). After 24 hours 3-methyl-1,3-oxazolidine (1.31g, 15 mmol) was added and the mixture was allowed to stand at room temperature for a further 72 hours. Work-up (General Method H) gave (135a) (0.42g, 21%).

(b) (i) 4-Methoxyphenol (1.86g, 15 mmol) and 3-methyl-1,3-oxazolidine (1.44g, 16.5 mmol) in acetonitrile (45 ml) were stirred at room temperature for 52 hours. Work-up (General Method H) gave 2-(N-2-hydroxyethyl-N-methylaminomethyl)-4-methoxyphenol (135b) (0.71g, 22%), b.p. 150°C / 0.05 mmHg.

i.r. (film) ν max 3400, 3032, 2948, 1652, 1616, 1496, 1418 cm⁻¹

¹H n.m.r. (250 MHz), δ = 2.36 (3H, s, NCH₃), 2.67 (2H, t, J = 5.5 Hz, NCH₂), 3.74 (2H, s, PhCH₂), 3.76 (3H, s, OCH₃), 3.78 (2H, t, J = 5.5 Hz, CH₂OH), 6.55–6.56 (1H, d,d, C [3] H), and 6.70–6.78 (2H, m, C [5 and 6] H) ppm.

(Oh's not shown).

¹H n.m.r. (60 MHz), δ = 6.40 (2H, br.s. D₂O ex. OH's) ppm.
\(^{13}\)C n.m.r. (62.9 MHz), \(\delta = 41.7\) (NCH\(_3\)), 55.7 (PhOCH\(_3\)), 58.8 (NCH\(_2\)), 61.4 (CH\(_2\)OH), 113.5 (C[5]), 114.4 (C[3]), 116.5 (C[6]), 122.7 (C[2]), 151.4 (C[1]) and 152.5 (C[4]) ppm.

M.S. (m/z); 211 (29.5%), 137 (60%), 44 (100%) (M\(^+\)) 211.1212; C\(_{11}\)H\(_{17}\)NO\(_3\) requires 211.1208.

(ii) Repeating the reaction in the presence of sulphur dioxide (1.5 ml) gave the product (135b) (0.57g, 18%).

(c) 2-Methoxy-4-methylphenol (2.76g, 20 mmol) and 3-methyl-1,3-oxazolidine in acetonitrile (60 ml) at room temperature for 48 hours gave, after work-up (General Method H), 6-(N-2-hydroxyethyl-N-methylaminomethyl)-2-methoxy-4-methylphenol (135c) (1.27g, 28%), b.p. 110°C / 0.05 mmHg.

i.r. (film) \(v_{\text{max}}\) 3396, 2944, 2840, 1718, 1600, 1496, 460, 1400. cm\(^{-1}\)

\(^1\)H n.m.r. (250 MHz), \(\delta = 2.25\) (3H, s, C[4]-CH\(_3\)), 2.38 (3H, s, NCH\(_3\)), 2.66 (2H, t, \(J = 5.5\) Hz, NCH\(_2\)), 3.70 (2H, s, PhCH\(_2\)N), 3.77 (2H, t, \(J = 5.5\) Hz, CH\(_2\)OH), 3.84 (3H, s, OCH\(_3\)), 4.20-5.20 (2H, br.s, D\(_2\)O ex.OH's), 6.42 (1H, d, \(J = 1.4\) Hz, C[5] H), and 6.62 (1H, d, \(J = 1.4\) Hz, C[3] H) ppm.

\(^{13}\)C n.m.r. (62.9 MHz), \(\delta = 20.9\) (C[4]-CH\(_3\)), 41.6 (NCH\(_3\)), 55.8 (C[2]-OCH\(_3\)), 58.7 (NCH\(_2\)), 59.4 (PhCH\(_2\)N), 60.8 (CH\(_2\)OH), 112.0 (C[3]), 121.0 (C[5]), 122.0 (C[4]), 128.0 (C[6]), 144.4 (C[1]), and 147.5 (C[2]) ppm.

M.S. (m/z); 225 (12.6%), 151 (100%), (M\(^+\)) 225.1362; C\(_{12}\)H\(_{19}\)NO\(_3\) requires 225.1365.

(d) 3-Methoxyphenol (1.86g, 15 mmol) and 3-methyl-1,3-oxazolidine (1.31g, 15 mmol) in acetonitrile (40 ml) at room temperature for 46 hours gave, after work-up (General Method H), the crude product 2-(N-2-hydroxyethyl-N-methylaminomethyl)-5-methoxyphenol (135d) (2.20g, 69%). Attempts to distil the product led to decomposition.
Spectroscopic data of the crude product assisted in the characterisation of the compound.

i.r. (film) $\nu_{\text{max}}$ 3300, 2940, 1610, 1594, 1508, 1468, 1384 cm$^{-1}$

$^1$H n.m.r. (60 MHz), $\delta$ = 2.23 (3H, s, NCH$_3$), 2.58 (2H, t, $J$ = 7.5 Hz NCH$_2$), 3.63 (2H, s, PhCH$_2$N), 3.68 (3H, s, C[5]–OCH$_3$), 3.70 (2H, t, $J$ = 7.5 Hz, CH$_2$OH), 6.20–6.50 (2H, m, C[3 and 4] H), 6.83 (1H, d, $J$ = 8 Hz, C[6] H), and 7.27 (2H, s, D$_2$O ex. OH) ppm.

M.S. (m/z): 211 (51%), 137 (100%), (M$^+$) 2111.182; requires C$_{11}$H$_{17}$NO$_3$ 211.1208.

(e) 2-Naphthol (2.16g, 15 mmol) and 3-methyl-1,3-oxazolidine (1.44g, 16.5 mmol) in acetonitrile (45 ml) at room temperature for 50 hours afforded, after work-up (General Method H), the crude product 1-(N-2-hydroxyethyl-N-methylaminomethyl)-2-naphthol (135e) (2.97g, 95%). The product was converted to its hydrochloride salt and recrystallised from hexane / ethyl acetate (1:1), m.p. 151–156°C.

i.r. (KBr)$\nu_{\text{max}}$ 3432, 3224, 3040, 1934, 1626, 1604, 1580, 1518, 1462 cm$^{-1}$

$^1$H n.m.r. (250 MHz) (CD$_3$OD), $\delta$ = 2.88 (3H, s, NCH$_3$), 3.38 (2H, t, $J$ = 5.1 Hz, NCH$_2$CH$_2$OH), 3.93 (1H, br.s, D$_2$O ex. OH), 3.99 (2H, t, $J$ = 5.1 Hz, CH$_2$OH), 4.81 (2H, s, ArCH$_2$N), 7.31 (1H, d, $J$ = 8.5 Hz, C[4] H), 7.38–7.86 (4H, m, C[5, 6, 7, and 8] H), and 7.96 (1H, d, $J$ = 8.5 Hz, C[3] H ppm.

$^{13}$C n.m.r. (62.9 MHz) (CD$_3$OD), $\delta$ = 41.3 (NCH$_3$), 52.1 (NCH$_2$), 56.7 (CH$_2$OH), 59.3 (ArCH$_2$N), 108.6 (C[1]), 118.2 (C[3]), 122.7 (C[6]), 124.4 (C[4a and 8]), 128.9 (C[7]), 129.9 (C[5]), 133.4 (C[4]), 134.6 (C[8a]), 156.7 (C[2]) ppm.

M.S. (M$^+$) 231 (hydrochloride salt) not detected, (crude free base) not detected.

F.A.B. (M$^+$+1) 232; C$_{14}$H$_{18}$NO$_2$

C, H, N and Cl analysis; (hydrochloride salt) Found: C (62.77); H (6.75);
N (5.21); and Cl (13.24%); Required C (62.80); H (6.70); N (5.23); and Cl (13.21%).

2.5.5 Reactions of 2,4-Dimethylphenol in the Presence of Chlorotrimethylsilane

(a) Chlorotrimethylsilane (2.39 g, 22 mmol) was added dropwise to a mixture of 2,4-dimethylphenol (2.44 g, 20 mmol) and bis(N,N-dimethylamino)methane (2.25 g, 22 mmol) in acetonitrile (120 ml) at 0°C under nitrogen. The mixture was stirred at room temperature for 48 hours and, after work-up (General Method H), gave (126a) (0.84 g, 24%), b.p. 90°C / 0.1 mmHg.

(b) Chlorotrimethylsilane (2.39 g, 22 mmol) was added dropwise to a mixture of 2,4-dimethylphenol (2.44 g, 20 mmol) and di(N-piperidyl)methane (4.01 g, 22 mmol) in acetonitrile (120 ml) at 0°C under nitrogen. The mixture was stirred at room temperature for 48 hours and, after work-up (General Method H), gave (126b) (0.16 g, 4%) together with unreacted aminal (3.14 g, 78%).

2.5.5.1 Preparation of 2,5-(Dimethylphenoxy)trimethylsilane

A solution of 2,5-dimethylphenol (24.43 g, 0.2 mol) in THF (100 ml) was added dropwise to a suspension of sodium hydride (5.28 g, 0.22 mol) in THF (150 ml) at 0°C under nitrogen. The mixture was stirred at room temperature until no hydrogen gas was given off. Chlorotrimethylsilane (23.90 g, 0.22 mol) in THF (50 ml) was added to the mixture slowly at 0°C under nitrogen and the reaction mixture was then stirred at room temperature overnight. Water (100 ml) was added and the mixture transferred to a separating funnel. The aqueous layer was discarded and the organic layer was washed with water (3 x 50 ml), dried and
concentrated in vacuo to a yellow oil (33.96g). Fractional distillation gave
the title compound (33, 31g, 86%), b.p. 45°C / 5mmHg.

$^1$H n.m.r. (60 MHz), $\delta = 0.23$ (9H, s, OSiCH$_3$)$_3$, 2.08 (3H, s, C[5]-CH$_3$),
2.21 (3H, s, C[2]-CH$_3$), and 6.37-7.00 (3H, m, PhH) ppm.

$^{13}$C n.m.r. (20.1 MHz), $\delta = 4.2$ (q, Si[CH$_3$]$_3$), 11.5 (q, C[5]-CH$_3$), 16.4
(q, C[2]-CH$_3$), 115.2 (d, C[6]), 117.5 (d, C[4]), 121.1 (s, C[5], 126.2
(d, C[3]), 131.6 (s, C[2]), and 149.0 (s, C[1]) ppm.

M.S. (m/z); 194 (84.6%), 179 (100%), (M$^+$) 194.1116; C$_{11}$H$_{15}$OSi requires
194.1127.
CHAPTER THREE - EXPERIMENTAL

3.1 (a) Preparation of 2-(N-Methylaminomethyl)pyrrole (139a)

A solution of methylamine hydrochloride (81.02 g, 1.2 mol) in water (100 ml) and aqueous formaldehyde (30 ml, 0.4 mol, 38% aqueous solution) was added dropwise over 30 minutes to freshly distilled pyrrole (26.84 g, 0.4 mol) at 0°C. The mixture was stirred at room temperature for 24 hours. The aqueous solution was then basified with 2M sodium hydroxide solution and extracted with ether (3x100 ml). The combined organic extracts were dried and concentrated in vacuo to give a brown oil (33.16 g). Fractional distillation afforded the title compound (25.56 g, 58%), b.p. 68°C / 0.6 mmHg, (lit.109 45-65°C / 0.1-1 mmHg).

i.r. (film) \( \nu_{\text{max}} \) 3376 (NH pyrrole), 3300 (NH), 3192, 3120, 2968, 2840, 1574 and 1470 cm\(^{-1}\)

\(^1\)H n.m.r. (60 MHz), \( \delta = 1.36 \) (1H, br.s, D\(_2\)O ex., NH), 2.38 (3H, s, NCH\(_3\)), 3.55 (2H, s, CH\(_2\)N), 5.93-6.23 (2H, m, C[3 and 4]H), 6.47-6.70 (1H, m, C[5]H), and 10.17 (1H, br.s, D\(_2\)O ex., pyrrole NH) ppm.

\(^{13}\)C n.m.r. (20.1 MHz), \( \delta = 35.7 \) (q, NCH\(_3\)), 48.5 (t, CH\(_2\)N), 106.8 (d, C[3]), 107.5 (d, C[4]), 117.8 (d, C[5]), and 129.9 (s, C[2]) ppm.

M.S. (m/z); 110 (35.7%), 80 (100%), (M) 110.0846; C\(_9\)H\(_{10}\)N\(_2\) requires 110.0844.

(b) Preparation of 2-(N-iso-Propylaminomethyl)pyrrole (139b)

A solution of iso-propylamine hydrochloride (9.56 g, 0.1 mol) in water (30 ml) and aqueous formaldehyde (7.5 ml, 0.1 mol, 38% aqueous solution) was added dropwise over 30 minutes to freshly distilled pyrrole (7.38 g, 0.1 mol). The mixture was stirred at room temperature for 67 hours. The aqueous solution was then basified and extracted with ether (3x60 ml). The combined organic washings were dried and concentrated.
in vacuo. The crude product was isolated and distilled to give the title compound (7.41 g, 54%), b.p. 110°C / 1 mmHg (lit.109 b.p. 98°C / 7 mmHg).

i.r. (film) ν_{max} 3380 (NH pyrrole), 3188 (NH), 3120, 2964, 2864, 1574 and 1466 cm^{-1}

{H n.m.r. (60 MHz), δ = 1.10 (6H, d, J = 6 Hz, CH(CH₃)₂), 1.40 (1H, br.s, D₂O ex., NH), 2.86 (1H, sept., J = 6 Hz, CHMe₂), 3.77 (2H, s, CH₂N), 5.93–6.27 (2H, m, C [3 and 4] H), 6.57–6.68 (1H, m, C [5] H), and 9.87 (1H, br.s, D₂O ex., pyrrole NH) ppm.

M.S. (m/z); 138 (14.1%), 80 (100%), (M⁺) 138.1156; C₈H₁₄N₂ requires 138.1157.

(c) Preparation of 2-Methyl-2,3-dihydro-1H-imidazo[1.5-alpyrrole (140a)

A mixture of paraformaldehyde (3.01 g, 0.10 mol equiv.) and 2-(N-methylaminomethyl)pyrrole (5.51 g, 0.05 mol) in 1,4-dioxane (100 ml) was heated under reflux for 2 hours. The solvent was removed in vacuo and the residue was dissolved in water (30 ml), basified to pH14 with 2M sodium hydroxide and extracted with ether (3x30 ml). The combined organic washings were dried and concentrated in vacuo to a brown oil (6.58 g). Kugelröhr distillation afforded the title compound as a colourless liquid which solidified on standing at room temperature (2.05 g, 35%), b.p. 100°C / 0.06 mmHg, m.p. 54°C.

i.r. (film) ν_{max} 2976, 2936, 2872, 2848, 2792, 1482, 1444 and 1418 cm^{-1}

{H n.m.r. (60 MHz), δ = 2.25 (3H, s, NCH₃), 4.00 (2H, s, C [1] H), 4.67 (2H, s, C [3] H), 5.90–6.13 (2H, m, C [6 and 7] H), 6.57–6.73 (1H, m, C [5] H) ppm.

M.S. (m/z); 122 (77.05%), 80 (100%), (M⁺) 122.0832; C₇H₁₀N₂ requires 122.0844.
(d) Preparation of 2-iso-Propyl-2,3-dihydro-1H-imidazo[1.5-a]-pyrrole (140b)

A mixture of paraformaldehyde (1.20g, 40 mmol equiv.) and 2-(N-iso-propylaminomethyl)pyrrole (2.76g, 20 mmol) in 1,4 dioxane (40 ml) was heated under reflux for 2 hours. The solvent was removed \textit{in vacuo} and the residue dissolved in water (30 ml), basified to pH14 with sodium hydroxide and extracted with ether (3x40 ml). The combined organic extracts were dried and concentrated \textit{in vacuo} to give a brown oil (3.10g). Kugelröhr distillation afforded the title compound as a colourless liquid (1.66g, 55%), b.p. 80°C / 1.5 mmHg.

\textit{i.r. (film)} ν\textsubscript{max} 2968, 2928, 2872, 2784, 1660, 1554, 1470, 1426 cm\textsuperscript{-1}

\textit{¹H n.m.r. (60 MHz)}, \delta = 1.13 (6H, d, J = 6 Hz, CH\textsubscript{2}CH\textsubscript{3}), 2.80 (1H, sept., J = 6 Hz, CHMe\textsubscript{2}), 3.83 (2H, s, C [1] H), 4.67 (2H, s, C [3] H), 5.73–5.93 (2H, m, C [6 and 7] H), and 6.53–6.70 (1H, m, C [5] H) ppm.

M.S. (m/z); 150 (72.68%), 80 (100%), M+ 150.1145; \textit{C}_9\textit{H}_{14}\textit{N}_2 \textit{requires} 150.1157.

3.2.1 Preparation of Bis(aminol ethers) (149)

**General Procedure**

Paraformaldehyde (2 equiv.) was added to a stirred mixture of anhydrous primary amine (1 equiv.), ethanol or methanol (4 equiv.) and potassium carbonate (1 equiv.) at 0°C. The mixture was then stirred vigorously for 2 days at room temperature. The solid was filtered and washed with dried ether. The filtrate was fractionally distilled through an 18° Vigreux column to remove the ether and excess alcohol and the residue was fractionally distilled under reduced pressure. The following bis(aminol ethers) were prepared by this method.
(1) *N*,*N*-Bis(ethoxymethyl)-*iso*-propylamine (149a)

* Iso-propylamine (29.55g, 0.5 mol), paraformaldehyde (30.03g, 1 mol equiv.), ethanol (92.16g, 2 mol) and potassium carbonate (138.21g, 1 mol) were treated as described in the general procedure. The residue was fractionally distilled affording two fractions. First fraction bis(ethoxymethyl)-*iso*-propylamine (39.44g, 45%), b.p. 66-72°C / 12 mmHg.

\[ ^1H \text{n.m.r. (60 MHz), } \delta = 1.12 \text{ (6H, d, } J = 6 \text{ Hz, NCH}[^{3}]\text{CH}_3{^2}) , \]
\[ 1.18 \text{ (6H, t, } J = 7.5 \text{ Hz, OCH}_2\text{CH}_3{^3}) , \]
\[ 3.27 \text{ (1H, sept., } J = 6 \text{ Hz, CHMe}_2{^4}) , \]
\[ 3.37 \text{ (4H, q, } J = 7.5 \text{ Hz, CH}_2\text{CH}_3{^5}), \]
\[ \text{and } 4.30 \text{ (4H, s, NCH}_2\text{O) ppm.} \]

\[ ^13\text{C n.m.r. (20.1 MHz), } \delta = 15.3 \text{ (q, CH}_2\text{CH}_3{^6}), \]
\[ 21.8 \text{ (q, CH}[^{3}]\text{CH}_3{^7}), \]
\[ 50.1 \text{ (d, CHMe}_2{^8}), \]
\[ 62.0 \text{ (t, OCH}_2\text{CH}_3{^9}), \]
\[ \text{and } 82.7 \text{ (t, NCH}_2\text{O) ppm.} \]

M.S. (m/z); 175 (13.4%), 59 (100%) (M+) 175.1566; \text{C}_9\text{H}_{21}\text{N}0_2 \text{ requires 175.1572.}

Second fraction \(N\)-ethoxymethyl-\(N\)-ethoxymethoxymethyl-*iso*-propylamine (150) (17.45g, 17%), b.p. 85-95°C / 12 mmHg.

\[ ^1H \text{n.m.r. (60 MHz), } \delta = 1.06-1.40 \text{ (6H, d, CH}[^{3}]\text{CH}_3{^2}), \]
\[ \text{and (6H, t, OCH}_2\text{CH}_3{^3}), \]
\[ 3.10-3.80 \text{ (1H, sept., CHMe}_2{^4}), \]
\[ \text{and (4H, t, OCH}_2\text{CH}_3{^5}), \]
\[ 4.37 \text{ (2H, s, NCH}_2\text{OEt}), \]
\[ 4.53 \text{ (2H, s, NCH}_2\text{OCH}_2{^6}), \]
\[ \text{and } 4.73 \text{ (2H, s, OCH}_2\text{OEt) ppm.} \]

M.S. (m/z); 205 (0.9%), 59 (62.5%), 31 (100%), (M+) 205.1670; \text{C}_{16}\text{H}_{25}\text{NO}_3 \text{ requires 205.1678.}

(2) *N*,*N*-Bis(ethoxymethyl)-*n*-butylamine (149b)

\(n\)-Butylamine (73.14g, 1 mol), paraformaldehyde (60.06g, 2 mol equiv.), ethanol (184.3g, 4 mol) and potassium carbonate (276.4g, 2 mol) were treated as described in the general procedure, yielding the title compound (104.41g, 55%), b.p. 66-68°C / 4 mmHg, (lit.\textsuperscript{165}, no physical data given).
i.r. (film) \( \nu_{\text{max}} \) 2960, 2928, 2856, 1456, 1376 cm\(^{-1}\)

\(^{1}\)H n.m.r. (60 MHz), \( \delta = 1.20 \) (6H, t, J = 7.5 Hz, OCH\(_2\)CH\(_3\)), 0.76–1.67 (7H, m, CH\(_3\)CH\(_2\)CH\(_2\)CH\(_2\)), 2.13 (2H, t, CH\(_2\)N), 3.45 (4H, q, J = 7.5 Hz, OCH\(_2\)CH\(_3\)), and 4.27 (4H, s, NCH\(_2\)O) ppm.

\(^{13}\)C n.m.r. (20.1 MHz), \( \delta = 14.0 \) (q, CH\(_3\)CH\(_2\)CH\(_2\)), 15.2 (q, OCH\(_2\)CH\(_3\)), 20.5 (t, CH\(_3\)CH\(_2\)CH\(_2\)CH\(_2\)), 31.1 (t, CH\(_3\)CH\(_2\)CH\(_2\)CH\(_2\)N), 49.6 (t, CH\(_3\)CH\(_2\)CH\(_2\)CH\(_2\)N), 62.6 (t, OCH\(_2\)CH\(_3\)), and 84.8 (t, NCH\(_2\)O) ppm.

M.S. (m/z); 189 (7.4%), 59 (100%), \( \langle M^+ \rangle \) 189.1725. \( \text{C}_{10}\text{H}_{23}\text{N} \text{O}_2 \) requires 189.1729.

(3) \( N,N\)-Bis(methoxymethyl)–\( t \)-butylamine (149c)

t–Butylamine (73.14g, 1 mol), paraformaldehyde (60.06g, 2 mol equiv.), methanol (256.4g, 8 mol) and potassium carbonate (276.4g, 2 mol) were treated as described in the general procedure affording the title compound (52.57g, 33%), b.p. 72°C / 12 mmHg.

i.r. (film) \( \nu_{\text{max}} \) 3484, 2976, 2804, 2760, 1558, 1538, 1470 cm\(^{-1}\)

\(^{1}\)H n.m.r. (60 MHz), \( \delta = 1.27 \) (9H, s, C\( [\text{CH}_3]_3 \)), 3.27 (6H, s, OCH\(_3\)), and 4.40 (4H, s, NCH\(_2\)O) ppm.

\(^{13}\)C n.m.r. (62.9 MHz), \( \delta = 29.5 \) (C\( [\text{CH}_3]_3 \)), 53.5 (CMe\(_3\)), 53.9 (OCH\(_3\)), and 83.6 (NCH\(_2\)O) ppm.

M.S. (m/z); 161 (4.7%), 70 (100%), \( \langle M^+ \rangle \) 161.1418. \( \text{C}_{8}\text{H}_{13}\text{N} \text{O}_2 \) requires 161.1416.

(4) \( N,N\)-Bis(ethoxymethyl)ethylamine (149d)

Ethylamine (67.65g, 1.5 mol), paraformaldehyde (90.09g, 3 mol equiv.) ethanol (207.3g, 4.5 mol), and potassium carbonate (207.3g, 1.5 mol) were treated as described in the general procedure to yield the title compound (96.76g, 40%), b.p. 90–92°C / 150 mmHg.
\( ^1H \) n.m.r. (60 MHz), \( \delta = 1.10 \) (3H, t, \( J = 7.5 \) Hz, NCH\(_2\)CH\(_3\)), \( 1.18 \) (6H, t, \( J = 7.5 \) Hz, OCH\(_2\)CH\(_3\)), \( 2.90 \) (2H, q, \( J = 7.5 \) Hz, NCH\(_2\)CH\(_3\)), \( 3.46 \) (4H, q, \( J = 7.5 \) Hz, OCH\(_2\)CH\(_3\)), and \( 4.30 \) (4H, s, NCH\(_2\)O) ppm.

\( ^{13}C \) n.m.r. (20.1 MHz), \( \delta = 14.0 \) (q, NCH\(_2\)CH\(_3\)), \( 15.3 \) (q, OCH\(_2\)CH\(_3\)), \( 43.9 \) (t, NCH\(_2\)CH\(_3\)), \( 62.6 \) (t, OCH\(_2\)CH\(_3\)), and \( 84.3 \) (t, NCH\(_2\)O) ppm.

M.S. (m/z); 161 (7.8%), 116 (5.5%), 59 (95.5%), 31 (100%), (M\(^+\)) 161.1410; \( C_{13}H_{19}NO_2 \) requires 161.1416.

(5) \( N,N\)-Bis(ethoxymethyl)benzylamine (149e)

Benzylamine (107.16g, 1 mol), paraformaldehyde (60.06g, 2 mol equiv.), ethanol (230.40g, 5 mol) and potassium carbonate (138.21 g, 1 mol) were treated as described in the general procedure to yield the title compound (124.51g, 56%), b.p. 84-86°C / 0.2 mmHg, (lit.\(^{12}\) b.p. 80°C / 0.1 mmHg). i.r. (film) \( v_{\text{max}} \) 3084, 3060, 3028, 2968, 1948, 1806, 1602, 1584, 1494 cm\(^{-1}\)

\( ^1H \) n.m.r. (60 MHz), \( \delta = 1.17 \) (6H, t, \( J = 7.5 \) Hz, CH\(_2\)CH\(_3\)), \( 3.47 \) (4H, q, \( J = 7.5 \) Hz, CH\(_2\)CH\(_3\)), \( 3.97 \) (2H, s, PhCH\(_2\)N), \( 4.27 \) (4H, s, NCH\(_2\)O), and 7.27 (5H, br.s, PhH) ppm.

\( ^{13}C \) n.m.r. (62.9 MHz), \( \delta = 15.2 \) (CH\(_2\)CH\(_3\)), \( 52.8 \) (PhCH\(_2\)), \( 62.8 \) (OCH\(_2\)CH\(_3\)), \( 83.7 \) (NCH\(_2\)O), \( 126.9 \) (C [4]), \( 128.2 \) (C [3 and 5]), \( 128.8 \) (C [2 and 6]), and \( 139.2 \) (C [1]) ppm.

M.S. (m/z); 223 (2.2%), 91 (100%) (M\(^+\)) 223.1557; \( C_{13}H_{21}NO_2 \) requires 223.1572.

(6) \( N,N\)-Bis(ethoxymethyl)-\( \beta \)-phenylethylamine (149f)

\( \beta \)-Phenylethylamine (24.24g, 0.2 mol), paraformaldehyde (12.01g, 0.4 mol equiv.), ethanol (96.16g, 2 mol) and potassium carbonate (27.16g, 0.2 mol) were treated as described in the general procedure to give the
title compound (23.77g, 50%), b.p. 86°C / 0.25 mmHg.

i.r. (film) $v_{\text{max}}$ 3084, 3060, 3024, 2932, 2860, 1602, 1496, 1454 cm$^{-1}$

$^1$H n.m.r. (60 MHz), $\delta$ = 1.17 (6H, t, J = 7.5 Hz, CH$_2$CH$_3$), 2.67-3.17 (4H, m, PhCH$_2$CH$_2$), 3.40 (4H, q, J = 7.5 Hz, OCH$_2$CH$_3$), 4.30 (4H, s, NCH$_2$O), and 7.23 (5H, s, PhH) ppm.

$^{13}$C n.m.r. (20.1 MHz), $\delta$ = 34.5 (q, CH$_2$CH$_3$), 34.8 (t, PhCH$_2$), 54.4 (t, PhCH$_2$CH$_2$N), 74.4 (t, OCH$_2$CH$_3$), 84.7 (t, NCH$_2$O), 126.0 (d, C [4]), 128.3 (d, C [3 and 5]), 128.7 (d, C [2 and 6]), and 140.4 (s, C [1]) ppm.

M.S. (m/z); 237 (0.2%), 146 (100%), (M$^+$) 237.1704; C$_{14}$H$_{23}$NO$_2$ requires 237.1729.

(7) $N,N$-Bis(methoxymethyl)-3,4-dimethoxy-$\beta$-phenylethylamine
(149g)

(3,4-Dimethoxy)-$\beta$-phenylethylamine (181.24g, 1 mol), paraformaldehyde (60.06g, 2 mol equiv.), methanol (320.5g, 10 mol), and potassium carbonate (276g, 42g, 2 mol) were treated as described in the general procedure, affording the title compound (161.63g, 60%), b.p. 125°C / 0.01 mmHg.

i.r. (film) $v_{\text{max}}$ 2928, 2832, 2064, 1606, 1590, 1514, 1464, 1416 cm$^{-1}$

$^1$H n.m.r. (60 MHz), $\delta$ = 2.63-3.13 (4H, m, PhCH$_2$CH$_2$), 3.23 (6H, s, OCH$_3$), 3.80 and 3.83 (6H, s, C [3 and 4]-OCH$_3$), 4.27 (4H, s, NCH$_2$O), and 6.75 (3H, s, PhH) ppm.

$^{13}$C n.m.r. (20.1 MHz), $\delta$ = 35.3 (q, OCH$_3$), 51.8 (q, C [3 and 4]-OCH$_3$), 54.8 (t, PhCH$_2$), 55.8 (t, PhCH$_2$CH$_2$), 86.7 (t, NCH$_2$O), 111.5 (d, C [5]), 112.3 (d, C [2]), 120.7 (d, C [6]), 133.1 (s, C [1]), 147.5 (s, C [4]), and 149.0 (s, C [3]) ppm.

M.S. (m/z); 269 (4.8%), 206 (22%), 151 (31.5%), 118 (73.5%), 42 (100%), (M$^+$) 269.1604; C$_{14}$H$_{23}$NO$_4$ requires 269.1627.
4-Methoxy-β-phenylethylamine (15.12g, 0.1 mol) was added dropwise to a mixture of paraformaldehyde (6.01g, 0.2 mol equiv.), ethanol (50 ml) and benzene (50 ml). The mixture was stirred at room temperature for 15 minutes before being heated under reflux for 24 hours using a Dean-Stark trap to remove the water as an azeotropic mixture. The solvents were then removed by distillation through an 18" Vigreux column and the residue was fractionally distilled under reduced pressure. The title compound was isolated (21.48g, 80%), b.p. 118-124°C/0.02 mmHg.

i.r. (film) \( \nu_{\text{max}} \) 2972, 1612, 1582, 1512, 1464, 1376 cm\(^{-1}\)

\(^1\)H n.m.r. (250 MHz), \( \delta = 1.19 \) (6H, t, \( J = 3.5 \) Hz, \( \text{CH}_2\text{CH}_3 \)), 2.78 (2H, m, \( \text{PhCH}_2 \)), 3.07 (2H, m, \( \text{PhCH}_2\text{CH}_2\text{N} \)), 3.40 (4H, q, \( J = 3.5 \) Hz, \( \text{OCH}_2\text{CH}_3 \)), 3.78 (3H, s, \( \text{OCH}_3 \)), 4.31 (4H, s, \( \text{NCH}_2\text{O} \)), 6.80-7.14 (4H, AA' BB', \( J_{\text{AB}} = 5.8 \) Hz, \( \text{PhH} \)) ppm.

\(^13\)C n.m.r. (62.9 MHz), \( \delta = 15.2 \) (\( \text{CH}_2\text{CH}_3 \)), 34.7 (\( \text{PhCH}_2 \)), 52.0 (\( \text{PhCH}_2\text{CH}_2 \)), 55.2 (\( \text{OCH}_3 \)), 62.6 (\( \text{OCH}_2\text{CH}_3 \)), 84.8 (\( \text{NCH}_2\text{O} \)), 113.7 (C[3 and 5]), 129.6 (C[2 and 6]), 132.5 (C[1]), and 157.9 (C[4]) ppm.

M.S. (m/z); 267 (1.9%), 222 (100%), (M\(^+\)) 267.1827; \( \text{C}_{15}\text{H}_{25}\text{NO}_3 \) requires 267.1834.

3.2.2 Preparation of \( N-\text{Alkoxymethyl}-N-\text{Alkyl(methylene)iminium} \) Chlorides

A solution of a bis(aminol ether) (1 equiv.) in petroleum ether (40-60°C) was treated with an acidic reagent (1.1 equiv.), such as acetyl chloride, chlorosilane derivative, or ethereal hydrogen chloride, under an atmosphere of dry nitrogen. The solvent was decanted and the precipitated solid was washed with more solvent and then dried under high vacuum.
The hydroscopic solids were obtained in quantitative yields and used immediately after preparation.

3.3 "In Situ" Reactions of Bis(aminol ethers) with 2-Methylfuran in the Presence of Acidic Reagents

General Method (K)

An acidic reagent (1.1 equiv.) was added to a mixture of 2-methylfuran (1.0 equiv.) and a bis(aminol ether) (1.1 equiv.) in acetonitrile under nitrogen. The mixture was then stirred at room temperature or heated under reflux for a specified length of time. Water (20 ml) was added and the solvent removed in vacuo. The residue was washed with ether (3x30 ml) and then basified to pH14 with sodium hydroxide and extracted with ether (3x40 ml). The combined organic extracts from the basic solution were dried and concentrated in vacuo. The crude product was then fractionally distilled using a Kugelrohr apparatus.

(a) Reactions of 2-Methylfuran and \( N,N\)-Bis(ethoxymethyl-iso-propylamine (149a)

(1) 2-Methylfuran (1.23g, 15 mmol), (149a) (2.89g, 16.5 mmol), and chlorotrimethylsilane (1.79g, 16.5 mmol) in acetonitrile (60 ml) were stirred at room temperature for 16 hours. Kugelrohr distillation of the crude product afforded two fractions. First fraction \( N-(5\text{-methylfurfuryl})-iso\text{-propylamine} \) (151a) (0.88g, 38%), b.p. 70°C / 1.5 mmHg, (lit.\(^{168}\), 82–3 °C / 20 mmHg).

i.r. (film) \( \nu_{\text{max}} \) 3324 (NH), 2964, 2924, 1616, 1566, and 1446 cm\(^{-1}\)

\(^1\text{H}\) n.m.r. (60 MHz), \( \delta = 1.10 \) (6H, d, \( J = 6 \text{ Hz}, \text{CH}[\text{CH}_3]_2 \)), 1.73 (1H, br.s, \( \text{D}_2\text{O} \text{ ex., NH} \)), 2.27 (3H, s, \( \text{CH}_3 \)), 2.87 (1H, sept. \( J = 6 \text{ Hz}, \text{CHMe}_2 \)), 3.73 (2H, s, \( \text{CH}_2\text{N} \)), 5.77–5.93 (1H, m, \( \text{C}[4] \text{H} \)), and 6.00 (1H, d,
$J = 3$ Hz, $C[3]$ \text{ppm.}

$^{13}$C n.m.r. (20.1 MHz), $\delta = 13.5$ (q, CH$_3$), 22.8 (q, CH[CH$_3$])$_2$, 44.1 (t, CH$_2$N), 47.7 (d, CHMe$_2$), 106.0 (d, C[4]), 107.3 (d, C[3]), 151.1 (s, C[2]), and 152.6 (s, C[5]) \text{ppm.}

M.S. (m/z): 153 (9.8%), 95 (100%), ($M^+$) 153.1158; C$_9$H$_{15}$NO requires 153.1154.

Second fraction $N,N$-di(5-methylfurfuryl)-iso-propylamine (152a)

(1.04g, 56%), b.p. 120°C / 0.2 mmHg.

i.r. (film) $\nu_{\text{max}}$ 2964, 2924, 1614, 1566, 1450 cm$^{-1}$

$^1$H n.m.r. (60 MHz), $\delta = 1.07$ (6H, d, J = 6 Hz, CH[CH$_3$])$_2$, 2.20 (6H, s, CH$_3$), 3.03 (1H, sept. J = 6 Hz, CHMe$_2$), 3.63 (4H, CH$_2$N), 5.83–5.97 (2H, m, C[4] H), and, 6.08 (2H, d, J = 3 Hz, C[3] H) \text{ppm.}

$^{13}$C n.m.r. (20.1 MHz), $\delta = 13.6$ (q, CH$_3$), 18.6 (q, CH[CH$_3$])$_2$, 46.3 (t, CH$_2$N), 50.5 (d, CHMe$_2$), 106.0 (d, C[4]), 108.9 (d, C[3]), 151.3 (s, C[2]), and 152.7 (s, C[5]) \text{ppm.}

M.S. (m/z): 247 (6.2%), 95 (100%), ($M^+$) 247.1561; C$_{15}$H$_{21}$N$_2$O$_2$ requires 247.1572.

(2) A mixture of chlorotrimethylsilane (1.09g, 10 mmol) and (149a) (1.93g, 11 mmol) in acetonitrile (20 ml) was stirred at room temperature for 3 hours. 2-Methylfuran (0.82g, 10 mmol) in acetonitrile (10 ml) was added and the mixture was stirred for a further 42 hours at room temperature. Work-up and Kugelröhr distillation gave (151a) (0.11g, 7%), b.p. 70°C / 1.5 mmHg, and (152a) (0.88g, 71%), b.p. 110°C / 0.2 mmHg.

(3) 2-Methylfuran (0.82g, 10 mmol), (149a) (5.26g, 30 mmol) and chlorotrimethylsilane (1.09g, 10 mmol) in acetonitrile (40 ml) at room temperature for 42 hours gave (151a) (0.53g, 38%) and (152a) (0.57g, 46%).
(4) 2-Methylfuran (1.23g, 15 mmol), (149a) (2.89g, 16.5 mmol) in acetonitrile (45 ml) under reflux for 1.5 hours gave (151a) (0.50g, 22%), and (152a) (0.31g, 17%).

(5) A mixture of 2-methylfuran (1.64g, 20 mmol) and (149a) (3.86g, 22 mmol) in acetonitrile (80 ml) was added dropwise very slowly to a solution of chlorotrimethylsilane (2.39g, 22 mmol) in acetonitrile (20 ml) at room temperature. The mixture was then stirred at room temperature for 19 hours. Work-up and Kugelröhrr distillation gave (151a) (1.19g, 39%) and, (152a) (0.71g, 28%).

(6) 2-Methylfuran (1.64g, 20 mmol), (149a) (3.86g, 22 mmol) and chlorotrimethylsilane (0.12g, 1.1 mmol) (5 mol.%) in acetonitrile (60 ml) at room temperature for 18 hours gave (151a) (0.54g, 18%), and (152a) (0.14g, 6%).

(7) 2-Methylfuran (1.64g, 20 mmol), (149a) (3.86g, 22 mmol) and acetyl chloride (1.73g, 22 mmol) in acetonitrile (80 ml) at room temperature for 19 hours gave (151a) (1.35g, 44%), and (152a) (0.93g, 33%).

(8) 2-Methylfuran (1.23g, 15 mmol), (149a) (2.89g, 16.5 mmol) and acetyl chloride (1.29g, 16.5 mmol) in acetonitrile (60 ml) under reflux for 1.5 hours gave (151a) (0.44g, 19%), and (152a) (1.85g, 39%).

(9) A mixture of 2-methylfuran (1.15g, 14 mmol) and (149a) (2.60g, 15 mmol) in acetonitrile (60 ml) was added dropwise over 1 hour to a solution of acetyl chloride (1.26g, 16 mmol) in acetonitrile (20 ml). The mixture was then stirred at room temperature for 20 hours, affording after work-up (151a) (0.82g, 38%), and (152a) (0.83g, 48%).
(10) A mixture of 2-methylfuran (1.64g, 20 mmol) and (149a) (5.26g, 30 mmol) in acetonitrile (200 ml) was added dropwise over 2 hours to a solution of acetyl chloride (3.14g, 40 mmol) in acetonitrile (20 mmol). The mixture was then stirred at room temperature for 13 hours, yielding (151a) (1.49g, 49%), and (151b) (0.35g, 14%).

(11) Titanium tetrachloride (1.04g, 0.6 ml, 5.5 mmol) (25 mol.%) was added by syringe into a mixture of 2-methylfuran (1.64g, 20 mmol) and (149a) (3.86g, 22 mmol) in acetonitrile (60 ml) at -55°C. The mixture was then allowed to reach room temperature over 18 hours. Work-up gave (151a) (0.96g, 31%), and (152a) (1.22g, 49%).

(12) Reaction (11) was repeated using 5 mol.% titanium tetrachloride (0.21g, 0.12 ml, 1.1 mmol) giving (151a) (0.79g, 26%) and (152a) (1.23g, 50%).

(13) Titanium tetrachloride (0.79g, 0.44 ml, 4 mmol) (25 mol.%) in dichloromethane (20 ml) was added to a mixture of 2-methylfuran (1.23g, 15 mmol) and (149a) (2.89g, 16.5 mmol) in dichloromethane (40 ml). Stirring at room temperature for 4 hours, followed by work-up, gave (151a) (1.35g, 58%) and (152a) (0.28g, 15%).

(14) Titanium tetrachloride (1.04g, 0.6 ml, 5.5 mmol) (25 mol.%) was added by syringe into a mixture of 2-methylfuran (1.64g, 20 mmol) and (149a) (3.86g, 22 mmol) in dichloromethane (80 ml) at -60°C. The mixture was then allowed to reach -20°C over 2 hours. Work-up gave (151a) (1.29g, 42%) and (152a) (0.40g, 16%).

(15) Titanium tetrachloride (1.04g, 0.6 ml, 5.5 mmol) (25 mol.%) was added to acetonitrile (40 ml) at -10°C. The solution was treated with (149a) (3.55g, 20 mmol) in acetonitrile (20 ml), followed by 2-methyl-
furan (1.64g, 20 mmol) in acetonitrile (20 ml), and the mixture was stirred at room temperature for 16 hours. Work-up and Kugelröhr distillation gave (151a) (1.03g, 34%) and (152a) (1.46g, 59%).

(16) Titanium tetrachloride (1.04g, 0.6 ml, 5.5 mmol) (25 mol.%) was added to acetonitrile (20 ml) at -20°C. A mixture of 2-methylfuran (1.64g, 20 mmol) and (149a) (3.86g, 22 mmol) in acetonitrile (80 ml) was added slowly over 1 hour. The mixture was then stirred at room temperature for 18 hours and, after work-up, it gave (151a) (0.43g, 14%) and (152a) (0.92g, 37%).

(17) A mixture of 2-methylfuran (1.64g, 20 mmol) and (149a) (3.86g, 22 mmol) in acetonitrile (80 ml) was added very slowly to a solution of trichloromethylsilane (3.29g, 22 mmol) in acetonitrile (20 ml) over 1.5 hours. The mixture was then stirred at room temperature for 19 hours, giving, after work-up, (151a) (1.62g, 53%) and (152a) (0.60g, 24%).

(18) Trifluoacetic anhydride (4.62g, 22 mmol) was added dropwise to a mixture of 2-methylfuran (1.64g, 20 mmol) and (149a) (3.86g, 22 mmol) in acetonitrile (80 ml) at 0°C. The mixture was then stirred at room temperature for 3 hours and, after work-up, yielded (151a) (0.74g, 24%) and (152a) (0.43g, 17%).

(19) Sulphur dioxide (1 ml, 22.4 mmol) (10 ml solution in 40 ml acetonitrile) was added to a mixture of 2-methylfuran (1.64g, 20 mmol) and (149a) (3.86g, 22 mmol) in acetonitrile (45 ml). The mixture was allowed to stand at room temperature for 3 hours and, after work-up, it gave (151a) (0.66g, 22%) and (152a) (0.51g, 21%).

(20) Ethereal hydrogen chloride (15.4 ml, 16.5 mmol, 1.07 M) was added to a mixture of 2-methylfuran (1.23g, 15 mmol) and (149a) (2.89g,
16.5 mmol) in acetonitrile (45 ml). The mixture was stirred at room temperature for 16 hours and, after work-up, afforded (151a) (1.44 g, 63%) and (152a) (0.35 g, 19%).

(21) Ethereal hydrogen chloride (15.4 ml, 16.5 mmol, 1.07 M) was added to a solution of (149a) (2.89 g, 16.5 mmol) in acetonitrile (30 ml). The mixture was stirred at room temperature for 2 hours followed by the addition of 2-methylfuran (1.23 g, 15 mmol) in acetonitrile (15 ml). The mixture was then stirred at room temperature for a further 2 hours and, after work-up, gave (151a) (1.45 g, 63%) and (152a) (0.34 g, 18%).

(b) Reaction of 2-Methylfuran with \( N \)-Ethoxymethyl-\( N \)-ethoxy-methoxyethyl-\( isa \)-propylamine (150) and Trichloromethylsilane

Trichloromethylsilane (2.17 g, 20 mmol), 2-methylfuran (1.64 g, 20 mmol) and (150) (4.11 g, 20 mmol) in acetonitrile (60 ml) at room temperature for 72 hours gave (151a) (0.61 g, 20%) and (152a) (1.06 g, 43%).

(c) Reactions of 2-Methylfuran and \( N, N \)-Bis(ethoxymethyl)benzylamine (149e)

(1) 2-Methylfuran (1.64 g, 20 mmol), (149e) (4.91 g, 22 mmol) and trichloromethylsilane (3.29 g, 22 mmol) in acetonitrile (80 ml) at room temperature for 21 hours afforded, after work-up and Kugelröhr distillation, \( N \)-(5-methylfurfuryl)benzylamine (151b) (1.34 g, 33%), b.p. 150°C / 0.02 mmHg, (lit.\(^{66}\), 104–8 °C / 1 mmHg).

i.r. (film) \( \nu_{\text{max}} \) 3228 (NH), 3060, 3024, 2920, 2830, 2828, 2220, 1602, 1564, 1492, 1382 cm\(^{-1}\)

\( ^1H \) n.m.r. (60 MHz), \( \delta = 2.90 \) (1H, br.s. D\(_2\)O ex., NH), 2.27 (3H, s, CH\(_3\)), 3.63 (2H, s, CH\(_2\)N), 3.80 (2H, s, PhCH\(_2\)N), 5.83–6.00 (1H, m, C[4'] H), 6.10 (1H, d, J = 3 Hz, C[3'] H), and 7.33 (5H, br.s, PhH) ppm.
\(^{13}\)C n.m.r. (20.1 MHz), \(\delta = 13.5\) (q, CH\(_3\)), 49.5 (t, CH\(_2\)N), 57.0 (t, PhCH\(_2\)N), 106.0 (d, C [4']), 109.5 (C [3']), 126.9 (d, C [4]), 128.2 (d, C [3 and 5]), 129.0 (d, C [2 and 6]), 139.3 (s, C [1]), 151.0 (s, C [2']), and (s, C [5']) ppm
M.S. (m/z); 201 (15.7%), 91 (100%), (M\(^+\)) 201.1144; C\(_{15}\)H\(_{15}\)NO requires 201.1154.

(2) Ethereal hydrogen chloride (15.4 ml, 16.5 mmol, 1.07 M) was added to a mixture of 2-methylfuran (1.23g, 15 mmol) and (149e) (3.68g, 16.5 mmol) in acetonitrile (45 ml). The mixture was stirred at room temperature for 2 hours affording, after work-up, (151b) (1.35g, 45%).

(d) Reaction of 2-Methylfuran with N,N-Bis(ethoxymethyl)-8-phenylethylamine (149f) and Dichlorodimethylsilane

2-Methylfuran (0.82g, 10 mmol), (149f) (2.61g, 11 mmol) and dichlorodimethylsilane (1.42g, 11 mmol) in acetonitrile (40 ml) at room temperature for 22 hours afforded after work-up N-(5-methylfurfuryl)-8-phenylethylamine (151c) (0.93g, 43%), b.p. 120°C / 0.01 mmHg.
i.r. (film) \(v_{\text{max}}\) 3316 (NH), 3100, 3084, 3060, 3024, 2920, 2820, 1602, 1494, 1452 cm\(^{-1}\)
\(^1\)H n.m.r. (60 MHz), \(\delta = 1.47\) (1H, br.s, D\(_2\)O ex., NH), 2.27 (3H, s, CH\(_3\)), 2.63-3.03 (4H, m, PhCH\(_2\)CH\(_2\)), 3.73 (2H, s, CH\(_2\)N), 5.77-6.00 (1H, m, C [4'] H), 6.03 (1H, d, J = 3 Hz, C [3'] H), and 7.23 (5H, s, PhH) ppm.
M.S. (m/z); 215 (3.5%), 95 (100%), (M\(^+\)) 215.1307; C\(_{14}\)H\(_{17}\)NO requires 215.1310.
(e) Reaction of 2-Methylfuran with N,N-Bis(ethoxymethyl)-n-butylamine (149b) and Trichloromethylsilane

2-Methylfuran (3.28g, 40 mmol), (149b) (3.79g, 20 mmol) and trichloromethylsilane (5.80g, 40 mmol) in acetonitrile (80 ml) at room temperature for 18 hours gave, after work-up, N,N-di(5-methylfurfuryl)-n-butylamine (152d) (4.56g, 87%), b.p. 100°C / 0.2 mmHg.

i.r. (film) \( \nu_{max} \) 2952, 2924, 2816, 1612, 1566, 1452, 1382 cm\(^{-1}\)

\(^1\)H n.m.r. (60 MHz), \( \delta = 0.67-1.80 \) (7H, m, \( \text{CH}_3\text{CH}_2\text{CH}_2 \)), 2.27 (6H, s, CH\(_3\)), 2.43 (2H, t, \( \text{CH}_3\text{(CH}_2\text{)}_2\text{CH}_2\text{N} \)), 3.60 (4H, s, NCH\(_2\)), 5.80-5.97 (2H, m, C\([4]\) H), and 6.07 (2H, d, J = 3 Hz, C\([3]\) H) ppm.

\(^{13}\)C n.m.r. (20.1 MHz), \( \delta = 13.6 \) (q, ArCH\(_3\)), 14.0 (q, CH\(_3\)[CH\(_2\)]\(_3\)), 20.6 (t, \( \text{CH}_3\text{CH}_2[\text{CH}_2]\)), 29.4 (t, \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\)), 49.8 (t, ArCH\(_2\)N), 52.8 (t, NCH\(_2\)[CH\(_2\)]\(_2\)CH\(_3\)), 106.0 (d, C\([4]\)), 109.5 (d, C\([3]\)), 150.7 (s, C\([2]\)), and 151.4 (s, C\([5]\)) ppm.

M.S. (m/z); 261 (67.2%), 218 (100%), (M\(^+\)) 261.1778; \( \text{C}_{16}\text{H}_{23}\text{NO}_2 \) requires 261.1729.

(f) Reaction of 2-Methylfuran and N,N-Bis(ethoxymethyl)ethylamine (149d) with Ethereal Hydrogen Chloride

Ethereal hydrogen chloride (1.07M, 15.4 ml, 16.5 mmol) was added to a mixture of 2-methylfuran (1.23g, 15 mmol) and (149d) (2.66g, 16.5 mmol) in acetonitrile (45 ml) at room temperature. The mixture was stirred for 2 hours giving, after work-up and Kugelröhr distillation, two fractions. First fraction \( \text{N-}(5\text{-methylfurfuryl})\text{ethylamine (151e)} \) (0.85g, 41%), b.p. 85°C / 2.5 mmHg (lit.\(^{16}\), 71–6 °C / mmHg).

i.r. (film) \( \nu_{max} \) 3308 (NH), 2964, 1682, 1568, 1456, 1388 cm\(^{-1}\)

\(^1\)H n.m.r. (60 MHz), \( \delta = 1.10 \) (3H, t, J = 7.5 Hz, \( \text{CH}_2\text{CH}_3\)), 1.43 (1H, s, D\(_2\)O ex., NH), 2.27 (3H, s, ArCH\(_3\)), 2.67 (2H, q, J = 7.5 Hz, CH\(_2\)CH\(_3\)),

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3.70 (2H, s, NCH₂), 5.77–5.93 (1H, m, C[4] H), and 6.00 (1H, d, J = 3 Hz, C[3] H) ppm.

¹³C n.m.r. (20.1 MHz), δ = 13.6 (q, C[5]-CH₃), 15.2 (q, CH₂CH₃), 43.4 (t, CH₂CH₃), 46.3 (t, ArCH₂N), 106.0 (d, C[4]), 107.6 (d, C[3]), 151.3 (s, C[2]), and 152.4 (s, C[5]) ppm.

M.S. (m/z); 139 (27.9%), 95 (100%), (M⁺) 139.0989; C₇H₁₄NO requires 139.0997.

Second fraction N,N-di(5-methylfurfuryl)ethylamine (152e) (0.41g, 23%), b.p. 95°C / 0.02 mmHg, (lit.¹⁸, 127–30 °C / 6 mmHg).

i.r. (film) ν max 2966, 2928, 1612, 1566, 1452, 1380 cm⁻¹

¹'H n.m.r. (60 MHz), δ = 1.10 (3H, t, J = 7.5 Hz, CH₂CH₃), 2.27 (6H, s, ArCH₃), 2.53 (2H, q, J = 7.5 Hz, CH₂CH₃), 3.60 (4H, s, ArCH₂), 5.77–5.93 (2H, m, C[4] H), and 6.06 (2H, d, J = 3 Hz, C[3] H),

¹³C n.m.r. (20.1 MHz), δ = 12.4 (q, CH₂CH₃), 13.6 (q, C[5]-CH₃), 47.0 (t, CH₂CH₃), 49.3 (t, ArCH₂N), 106.0 (d, C[4]), 109.7 (d, C[3]), 150.5 (s, C[2]), and 151.5 (s, C[5]) ppm.

M.S. (m/z); 233 (100%), (M⁺) 233.1397; C₁₄H₁₉N₂O₂ requires 233.1416.

(g) Reaction of 2-Methylfuran and N,N-Bis(methoxymethyl)-t-butyramine (149c) and Ethereal Hydrogen Chloride

Ethereal hydrogen chloride (1.07M, 15.4 ml, 16.5 mmol) was added to a mixture of 2-methylfuran (15 mmol, 1.23g) and (149c) (2.76g, 16.5 mmol) in acetonitrile (45 ml). The mixture was stirred at room temperature for 2 hours giving after work-up and Kugelröhr distillation two fractions. First fraction N-(5-methylfurfuryl)-t-butyramine. (151f) (1.82g, 72%), b.p. 75°C / 1.5 mmHg.

i.r. (film) ν max 3316 (NH), 3104, 2964, 2924, 2836, 1650, 1618, 1568, 1478 cm⁻¹
\[ ^1 \text{H n.m.r. (60 MHz), } \delta = 1.17 (9\text{H, s, C}[CH_3]_3), 1.00-1.30 (1\text{H, br.s, D}_2\text{O ex., NH}), 2.27 (3\text{H, s, ArCH}_3), 3.70 (2\text{H, s, NCH}_2), 5.80-5.93 (1\text{H, m, C}[4] \text{H}), \]
and 6.07 (1\text{H, d, J = 3 Hz, C}[3] \text{H}) ppm.

\[ ^{13} \text{C n.m.r. (100.4 MHz), } \delta = 13.6 (\text{Ar-CH}_3), 28.9 (\text{C}[CH_3]_3), 40.0 (\text{NCH}_2), 50.6 (\text{CMe}_3), 106.0 (\text{C}[4]), 107.1 (\text{C}[3]), 151.3 (\text{C}[2]), \]
and 152.6 (\text{C}[5]) ppm.

M.S. (m/z): 167 (5.9\%), 95 (100\%), \text{(M}^+\text{)} 167.1296; \text{C}_{16}\text{H}_{17}\text{NO requires 167.1310.}

Second fraction \( N,N-\text{di(5-methylfurfuryl)-t-butylamine (152f)} \)
(0.44g, 22\%), b.p. 110°C / 0.01 mmHg.

i.r. (film) \( \nu_{\text{max}} \) 2966, 2920, 2838, 1652, 1616, 1570, 1476 cm\(^{-1}\)

\[ ^1 \text{H n.m.r. (60 MHz), } \delta = 1.17 (9\text{H, s, C}[CH_3]_3), 2.27 (6\text{H, s, ArCH}_3), 3.77 (4\text{H, s, NCH}_2), 5.80-5.93 (2\text{H, m, C}[4] \text{H}), 6.03 (2\text{H, d, J = 3 Hz, C}[3] \text{H}) \]
ppm.

\[ ^{13} \text{C n.m.r. (20.1 MHz), } \delta = 13.6 (q, \text{ArCH}_3), 27.5 (q, \text{C}[CH_3]_3), 44.3 (t, \text{NCH}_2), 54.5 (s, \text{CMe}_3), 106.0 (d, \text{C}[4]), 108.7 (d, \text{C}[3]), 150.7 (s, \text{C}[2]), \]
and 152.7 (s, \text{C}[5]) ppm.

M.S. (m/z): 261 (53.4\%), 152 (100\%), \text{(M}^+\text{)} 261.1721; \text{C}_{16}\text{H}_{23}\text{NO}_2 requires 261.1729.

3.4 Reactions of 2-Methylfuran with Preformed \( N-\text{Alkoxymethyl-} \)
\( N-\text{Alkyl(methylene)iminium Chlorides} \)

**General Method (L)**

Freshly prepared iminium salt (1.1 equiv.) was dissolved in acetonitrile and

\[
\text{treated with 2-methylfuran (1.0 equiv.) in one portion at room temperature under dry nitrogen. After a specified length of time, followed by the work-up procedure described in General Method K, the crude product was isolated and purified by Kugelröhren distillation.}
\]
(1) 2-Methylfuran (0.29g, 3.5 mmol) was added to a solution of the iminium salt (0.59g, 3.5 mmol) (prepared from (149a) and trichloromethylsilane) in acetonitrile (20 ml). The mixture was stirred at room temperature for 26 hours, yielding (151a) (0.32g, 59%) and (152a) (0.18g, 27%).

(2) 2-Methylfuran (1.23g, 15 mmol) was added to the iminium salt prepared from (149a) (3.5lg, 20 mmol) and trichloromethylsilane (2.99g, 20 mmol) in acetonitrile (50 ml). Stirring at room temperature for 41 hours gave (151a) (0.22g, 9%) and (152a) (1.31g, 70%).

(3) 2-Methylfuran (0.49g, 6 mmol) and the iminium salt (1.12g, 6.8 mmol) (prepared from (149a) and trichloromethylsilane) in acetonitrile (40 ml) at room temperature for 24 hours yielded (151a) (0.59g, 65%) and (152a) (0.12g, 17%).

(4) 2-Methylfuran (1.64g, 20 mmol) in acetonitrile (30 ml) was added dropwise over 1 hour to a solution of the iminium salt derived from (149a) (4.38g, 25 mmol) and chlorotrimethylsilane (2.72g, 25 mmol), in acetonitrile (30 ml) at 0°C. The mixture was then stirred at room temperature for 18 hours, affording (151a) (0.48g, 16%) and (152a) (1.05g, 43%).

(5) 2-Methylfuran (1.48g, 18 mmol) was added to a solution of the iminium salt (3.19g, 18 mmol) (prepared from (149a) and trichloromethylsilane) in dichloromethane (50 ml). The mixture was stirred at room temperature for 4 hours, affording (151a) (1.33g, 48%) and (152a) (0.76g, 34%).

(6) Reaction (5) was repeated at -22°C for 4 hours, affording (151a) (1.25g, 45%) and (152a) (0.40g, 18%).

(7) 2-Methylfuran (1.07g, 13 mmol) was added to a solution of the iminium salt (4.26g, 26 mmol), (prepared from (149a) and trichloromethylsilane),
in acetonitrile (80 ml). The mixture was then stirred at room temperature for 2 hours affording (151a) (0.96g, 48%) and (152a) (0.65g, 20%).

(8) 2-Methylfuran (0.66g, 8 mmol) was added to a solution of the iminium salt (1.65g, 9.2 mmol), (prepared from (149b) and trichloromethylsilane), in acetonitrile (40 ml). The mixture was then stirred at room temperature for 22 hours. After work-up and Kugelröhr distillation two products were isolated. First product \(N\)-(5-methylfurfuryl)\(-n\)-butylamine (151d) (0.71g, 54%), b.p. 90°C / 1 mmHg, (lit.\(^{168}\), 110–15°C / 22 mmHg).

i.r. (film) \(v_{\text{max}}\) 3328 (NH), 3104, 2956, 2924, 2872, 1680, 1614, 1566, 1454 cm\(^{-1}\)

\(^1\)H n.m.r. (400 MHz), \(\delta = 0.93\) (3H, t, \(J = 7.5\) Hz, N[CH\(_2\)]\(_3\)CH\(_3\)), 1.27–1.40 (2H, m, N[CH\(_2\)]\(_2\)CH\(_2\)CH\(_3\)), 1.43–1.53 (2H, m, NCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.92 (1H, br.s, D\(_2\)O ex., NH), 2.30 (3H, s, ArCH\(_3\)), 2.63 (2H, t, \(J = 7.5\) Hz, NCH\(_2\)[CH\(_2\)]\(_2\)CH\(_3\)), 3.73 (2H, s, ArCH\(_2\)N), 5.83–5.90 (1H, m, C[4] \(\text{H}\)), and 6.05 (1H, d, \(J = 1.5\) Hz, C[3] \(\text{H}\)) ppm.

\(^{13}\)C n.m.r. (100.4 MHz), \(\delta = 13.6\) (ArCH\(_3\)), 14.0 (CH\(_2\)\(_3\)CH\(_3\)), 20.5 (N[CH\(_2\)]\(_2\)CH\(_2\)CH\(_3\)), 31.9 (NCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 46.3 (ArCH\(_2\)N), 48.8 (NCH\(_2\)[CH\(_2\)]\(_2\)CH\(_3\)), 105.9 (C[4]), and 107.8 (C[3]), 151.4 (C[2]), 151.9 (C[5]) ppm.

\(^1\)H n.m.r.-\(^{13}\)C n.m.r. correlated spectrum of (151d) is shown in FIGURE 1.

M.S. (m/z); 167 (100%), (M\(^+\)) 167.1308; C\(_{10}\)H\(_{17}\)NO requires 167.1310.

Second product (152d) (0.14g, 13%), b.p. 150°C / 0.01 mmHg.

(9) 2-Methylfuran (2.30g, 28 mmol) was added to a solution of the iminium salt (6.12g, 34 mmol) (prepared from (149b) and trichloromethylsilane) in acetonitrile (50 ml). The mixture was stirred at room temperature for 24 hours yielding (151d) (2.37g, 51%) and (152d) (1.36g, 37%).
FIGURE 1: $^1$H n.m.r. -$^{13}$C n.m.r. Correlated Spectrum of $N$-(5-Methylfurfuryl)$-n$-butylamine
(10) 2-Methylfuran (2.46g, 30 mmol) was added to a solution of the iminium salt (6.80g, 38 mmol) (prepared from (149b) and trichloromethylsilane) in acetonitrile (50 ml). The mixture was stirred at room temperature for 24 hours affording (151d) (1.15g, 23%), and (152d) (1.61g, 41%).

(11) 2-Methylfuran (1.23g, 15 mmol) was added to a solution of the iminium salt (2.93g, 17.7 mmol) (prepared from (149c) and trichloromethylsilane) in acetonitrile (40 ml). The mixture was then stirred at room temperature for 24 hours giving (151f) (2.51g, 68%) and (152f) (0.40g, 20%).

(12) 2-Methylfuran (1.64g, 20 mmol) in acetonitrile (40 ml) was added dropwise over 20 minutes to a solution of the iminium salt (3.88g, 23 mmol) (prepared from (149c) and trichloromethylsilane) in acetonitrile (40 ml) at 0°C. The mixture was then stirred at room temperature for 3 days affording (151f) (1.16g, 35%) and (152f) (1.33g, 51%).

(13) 2-Methylfuran (1.23g, 15 mmol) was added dropwise to a solution of the iminium salt (2.83g, 17 mmol) (prepared from (149c) and trichloromethylsilane) in acetonitrile at -40°C. The mixture was then sealed under nitrogen and kept in the freezer at -22°C for 3 days affording, after work-up, (151f) (1.14g, 46%) and (152f) (0.32g, 16%).

(14) 2-Methylfuran (1.23g, 15 mmol) was added to a solution of the iminium salt (2.84g, 17 mmol) (prepared from (149c) and chloromethylsilane) in acetonitrile (60 ml) at room temperature. The mixture was then stirred for 42 hours affording, after work-up, (151f) (1.29g, 62%) and (152f) (0.66g, 33%).

(15) 2-Methylfuran (1.64g, 20 mmol) in acetonitrile (30 ml) was added dropwise to a solution of the iminium salt (derived from (149b) [4.73g,
25 mmol] and chlorotrimethylsilane [2.72g, 25 mmol] in acetonitrile (30 ml) at room temperature. The mixture was stirred for 24 hours affording after work-up (151d) (0.33g, 19%) and (152d) (1.57g, 60%).

(16) 2-Methylfuran (1.31g, 16 mmol) in acetonitrile (30 ml) was added dropwise to a solution of the iminium salt (3.35g, 20 mmol), (prepared from (149a) and acetyl chloride) in acetonitrile (20 ml) at room temperature. The mixture was stirred for 24 hours affording, after work-up, (151a) (0.35g, 14%) and (152a) (1.10g, 55%).

(17) 2-Methylfuran (1.07g, 13 mmol) was added to the iminium salt (2.50g, 15 mmol), [prepared from (149a) and acetyl chloride], in acetonitrile (40 ml) and after 3 hours gave (151a) (0.45g, 23%) and (152a) (0.73g, 45%).

(18) 2-Methylfuran (1.56g, 19 mmol) was added to the iminium salt (3.57g, 21 mmol) [prepared from (149a) and acetyl chloride] in acetonitrile (45 ml) at -40°C. The mixture was then sealed under nitrogen and kept in the freezer at -22°C for 10 days affording after work-up (151d) (1.59g, 55%) and (152d) (0.73g, 31%).

(19) 2-Methylfuran (1.23g, 15 mmol) was added to the iminium salt (2.65g, 15 mmol) (prepared from (149b) and acetyl chloride) in acetonitrile (50 ml) at room temperature. After 24 hours, work-up gave (151d) (0.62g, 18%) and (152d) (0.93g, 24%).

(20) 2-Methylfuran (0.41g, 5 mmol) and the iminium salt (0.83g, 5.5 mmol), (prepared from (149d) and trichloromethylsilane, in acetonitrile (20 ml) at room temperature for 18 hours yielded (151e) (0.09g, 13%) and (152e) (0.25g, 42%).
(21) 2-Methylfuran (1.48g, 18 mmol) was added to the iminium salt [generated from (149e) (4.47g, 20 mmol) and trichloromethylsilane (2.99g, 20 mmol)] in acetonitrile (40 ml). 21 hours at room temperature gave (151b) (1.66g, 41%).

(22) 2-Methylfuran (0.33g, 4 mmol) was added to the iminium salt (0.95g, 4.2 mmol), (prepared from (149f) and trichloromethylsilane), in acetonitrile (30 ml). 18 hours at room temperature followed by work-up gave (151f) (0.47g, 55%).

(23) 2-Methylfuran (1.48g, 18 mmol) and the iminium salt [generated from (149a) (3.51g, 20 mmol) and 1.07M Et₂O.HCl (20.5 ml, 22 mmol)] in acetonitrile (60 ml) at room temperature for 64 hours gave (151a) (2.06g, 75%) and (152a) (0.28g, 13%).

(24) 2-Methylfuran (1.31g, 16 mmol) and the iminium salt [generated from (149a) (3.51g, 20 mmol) and gaseous hydrogen chloride] in acetonitrile (60 ml) at room temperature for 2 hours gave (151a) (1.89g, 77%) and (152a) (0.30g, 15%).

(25) 2-Methylfuran (1.03g, 12.5 mmol) and the iminium salt (2.29g, 13.8 mmol), (prepared from (149c) and 1.07M Et₂O.HCl) in acetonitrile (40 ml) at room temperature gave (151f) (1.68g, 80%) and (152f) (0.22g, 13%).

(26) 2-Methylfuran (1.07g, 13 mmol) was added to the iminium salt (2.42g, 14 mmol), (prepared from (149c) and chlorotrimethylsilane using dichloromethane as solvent) in acetonitrile (40 ml). The mixture was stirred at room temperature for 3 hours affording (151f) (1.60g, 74%) and (152f) (0.33g, 19%).
(27) 2-Methylfuran (1.40g, 17 mmol) was added to a solution of the iminium salt (3.41g, 19 mmol) (generated from (149b) and chlorotrimethylsilane) in acetonitrile (60 ml) at -40°C. The mixture was stirred for 2 hours at that temperature affording, after work-up, (151d) (1.67g, 59%) and (152b) (0.13g, 6%).

(28) 2-Methylfuran (0.74g, 9 mmol) was added to the iminium salt [prepared from N,N-bis(ethoxymethyl)-3-4-methoxyphenylethylamine (149h) (2.67g, 10 mmol) and 3M Et2O.HCl (3.7 ml, 11 mmol)] in acetonitrile (50 ml). The mixture was stirred at room temperature for 18 hours affording, after work-up, N-(5-methylfurfuryl)-4-methoxy-1-phenylethylamine (151g) (1.30g, 59%) b.p. 110-130°C / 0.01 mmHg. i.r. (film) \( \nu_{\text{max}} \) 3320 (NH), 3024, 2996, 2920, 2832, 1610, 1582, 1566, 1510, 1462 cm\(^{-1}\).

\(^1\)H n.m.r. (250 MHz), \( \delta = 1.10 \) (1H, brs D\(_2\)O ex., NH), 2.22 (3H, s, C\([5']\)-CH\(_3\)), 2.67-2.91 (4H, m, ArCH\(_2\)CH\(_2\)N), 3.71 (2H, s, C\([2']\)-CH\(_2\)N), 3.76 (3H, s, OCH\(_3\)), 5.84-5.86 (1H, m, C\([4']\) H), 6.00 (1H, d, J = 3 Hz, C\([3']\) H), 6.80-7.13 (4H, AA' BB', J\(_{AB} = 8 \) Hz, C\([2,3,5\text{ and } 6\])PhH) ppm.

\(^{13}\)C n.m.r. (62.9 MHz), \( \delta = 13.5 \) (CH\(_3\)), 35.4 (PhCH\(_2\)), 46.3 (PhCH\(_2\)CH\(_2\)), 50.5 (C\([2']\)-CH\(_2\)N), 55.0 (OCH\(_3\)), 105.9 (C\([4']\)), 107.6 (C\([3']\)), 113.7 (C\([3\text{ and } 5\])), 129.7 (C\([2\text{ and } 6\])), 132.0 (C\([1]\)), 151.2 (C\([2']\)), 152.1 (C\([5']\)), and 158.1 (C\([4]\)) ppm.

M.S. (m/z); 245 (3.3%), 95 (100%), \( M^+ \) 245.1396; C\(_{15}\)H\(_{16}\)NO\(_2\) requires 245.1416.

(29) 2-Methylfuran (1.23g, 15 mmol) was added to a mixture of the iminium salt (2.66g, 16 mmol) (prepared from (149c) and ethereal hydrogen chloride) and sodium bicarbonate (1.34g, 16 mmol) in acetonitrile (50 ml). The mixture was stirred at room temperature for
2 hours affording after work-up (151f) (1.28g, 51%) and (152f) (0.44g, 22%).

Preparation of \( N-(5\text{-methylfurfuryl})-N\text{-methoxymethyl}-t\text{-butylamine} \) (154)

2-Methylfuran (1.15g, 14 mmol) was added to a solution of \( N\text{-methoxy-methyl-N\text{-t\text{-butyl}(methylene)iminium chloride} (2.48g, 15 mmol) \) (prepared from (149c) and Et\text{2}O.HCl) in acetonitrile (40 ml) under nitrogen. The mixture was stirred at room temperature for 17 hours followed by the addition of di-\text{iso\text{-propylethylamine} (2.07g, 16 mmol). Stirring was continued for 10 minutes and the solvent was removed in vacuo. The residue, a crystalline solid, was washed with light petroleum ether (3x40 ml). The combined organic washings were concentrated in vacuo and the residue, a pale yellow oil (2.20g), was purified by Kugelröhr distillation affording the title compound (154) (1.38g, 47%), b.p. 80°C / 0.1 mmHg.

i.r. \( \nu_{\text{max}} \) 2972, 2804, 1568, 1468, 1394, 1362 cm\(^{-1} \).

\( ^1H \) n.m.r. (250 MHz), \( \delta = 1.21 \) (9H, s, C[CH\(_3\)]\(_3\)), 2.26 (3H, s, ArCH\(_3\)), 3.37 (3H, s, OCH\(_3\)), 3.85 (2H, s, ArCH\(_2\)N), 4.18 (2H, s, NCH\(_2\)OMe), 5.85-5.86 (1H, m, C[4] H), and 6.03 (1H, d = 2.9 Hz, C[3] H) ppm.

\( ^{13}C \) n.m.r. (62.1 MHz), \( \delta = 13.6 \) (C[5]-CH\(_3\)), 28.6 (C[CH\(_3\)]\(_3\)), 42.6 (ArCH\(_2\)N), 54.3 (CMe\(_3\)), 54.4 (OCH\(_3\)), 82.5 (NCH\(_2\)OMe), 105.9 (C[4]), 108.4 (C[3]), 151.1 (C[2]), and 152.7 (C[5]) ppm.

M.S. \( \text{m/z} \); 211 (2.6%), 95 (100%), \( \text{M}^+ \) 211.1579; \( \text{C}_{12}\text{H}_{21}\text{NO}_2 \) requires 211.1572.
Preparation of \(N-(5\text{-methylfurfuryl})-N\text{-ethoxymethyl-iso-propylamine}\) (155)

Paraformaldehyde (1.5g, 50 mmol equiv.) was added to a mixture of \(N-(5\text{-methylfurfuryl}-iso\text{-propylamine}\) (151a) (7.66g, 50 mmol), ethanol (46.08g, 1 mol) and potassium carbonate (6.91g, 50 mmol). The mixture was vigorously stirred for 36 hours at room temperature. The solid was filtered off and washed with dry ethanol (30 ml). The ethanol in the filtrate was removed by distillation through an 18" Vigreux column and the residue was distilled under reduced pressure, using a Kugelröhr apparatus, yielding the title compound (155) (7.85g, 74%), b.p. 65°C / 0.03 mmHg.

\(\text{i.r. (film)} \ \nu_{\text{max}} 2968, 1660, 1566, 1454, 1384 \text{ cm}^{-1}\)

\(\text{\textsuperscript{1}H n.m.r. (60 MHz),} \ \delta = 0.97-1.30 (9H, t, \text{CH}_2\text{CH}_3, \text{and d, CH}[\text{CH}_3]_2),
2.27 (3H, s, C[5]-\text{CH}_3), 3.10 (1H, sept., J = 6 Hz, \text{CHMe}_2), 3.40 (2H, q, J = 7.5 Hz, \text{NCH}_2\text{CH}_3), 3.80 (2H, s, \text{ArCH}_2\text{N}), 4.20 (2H, s, \text{NCH}_2\text{OEt}),
5.77-5.93 (1H, m, C[4] \text{H}), \text{and 6.03 (1H, d, J = 3 Hz, C[3] H)} \ \text{ppm.}\)

\(\text{\textsuperscript{13}C n.m.r. (20.1 MHz),} \ \delta = 13.5 \ (q, \text{C[5]-CH}_3), 15.3 \ (q, \text{CH}_2\text{CH}_3), 20.7
(q, \text{CH}[\text{CH}_3]_2), 44.8 \ (t, \text{ArCH}_2\text{N}), 51.1 \ (d, \text{CHMe}_2), 62.5 \ (t, \text{OCH}_2\text{CH}_3), 82.3
(t, \text{NCH}_2\text{O}), 106.0 \ (d, \text{C[4]}), 108.5 \ (d, \text{C[3]}), 151.2 \ (s, \text{C[2]}), \text{and 152.0}
(s, \text{C[5]}) \ \text{ppm.}\)

\(\text{M.S. (m/z):} 211 \ (11.9\%), 166 \ (100\%), \ (M^+) 211.1536; \text{C}_{12}\text{H}_{21}\text{NO}_2 \text{ requires}
211.1572.\)

Preparation of \(N\text{-iso-Propyl-N-(5'\text{-methylfurfuryl})-1\text{-methyl-3\text{-indolylmethylamine}}\) (156)

Chlorotrimethylsilane (1.64g, 11 mmol) was added dropwise to a mixture of \(N\text{-methylindole (1.31g, 10 mmol and N-(5\text{-methylfurfuryl})-N\text{-ethoxymethyl-iso-propylamine}\) (155) (2.32g, 11 mmol) in acetonitrile
(40 ml) at 0°C under nitrogen. The mixture was then stirred at room
temperature for 4 hours. Water (20 ml) was added and the solvent was
removed in vacuo. The residue was washed with ether (3x20 ml) and then
basified to pH14 with 4M sodium hydroxide and extracted with ether
(3x30 ml). The combined organic extracts from the basic solution were
dried and concentrated in vacuo to a brown viscous oil. The crude product
was triturated with ether / pet. ether (40–60 °C) and cooled in the freezer,
crystallising as a brown solid. Recrystallisation from 20% aqueous ethanol
afforded the title compound as a white solid (2.09g, 71%), m.p. 46–48°C.

i.r. (KBr) v max 2964, 1652, 1556, 1470, 1424, 1384, 1360 cm⁻¹

¹H n.m.r. (250 MHz), δ = 1.07 (6H, d, J = 6.5 Hz, CH[CH₃]₂), 2.27
(3H, s, C[5']-CH₃), 3.08 (1H, sept. J = 6.5 Hz), 3.60 (2H, s, C[2']-CH₂N),
3.74 (3H, s, NCH₃), 3.79 (2H, s, C[3]-CH₂N), 5.86–5.87 (1H, m, C[4'] H),
6.04 (1H, d, J = 2.9 Hz, C[3'] H), 7.00 (1H, s, C[2] H), 7.08–7.26
(3H, m, C[4, 5, and 6] H), and 7.74–7.77 (1H, m, C[7] H) ppm.

¹³C n.m.r. (62.9 MHz), δ = 13.6 (C[5']-CH₃), 18.2 (CH[CH₃]₂), 32.4
(NCH₃), 44.6 (C[2']-CH₂N), 46.1 (C[3]-CH₂N), 49.3 (CHMe₂), 105.9
(C[4']), 108.1 (C[3']'), 108.9 (C[7]), 113.2 (C[3]), 118.6 (C[4]), 120.0
(C[5]), 121.4 (C[6]), 127.8 (C[2]), 128.2 (C[3a]), 137.2 (C[7a]), 150.7
(C[2']'), and 152.7 (C[5']) ppm.

M.S. (m/z); 296 (5.9%), 144 (100%), (M⁺) 296.1878; C₁₉H₂₄N₂O requires
296.1888.

C, H, N analysis; Found: C (76.29), H (7.98), N (9.58)%; Requires:
C (75.99), H (8.16), N (9.45) %.
Reactions of \( \text{N-Alkoxymethyl-N-alkyl(methylene)} \)iminium Chlorides with Aromatic Compounds

General Method (M)

As described for General Method (L).

Acetonitrile was used in the reactions carried out above \(-40^\circ\text{C}\) and dichloromethane was used when the reactions were performed at \(-78^\circ\text{C}\).

(1) Furan (1.23g, 18 mmol) was added to the iminium salt [prepared from (149a) (3.51g, 20 mmol) and trichloromethylsilane (3.29g, 22 mmol)] in acetonitrile (60 ml). The mixture was stirred at room temperature for 22 hours yielding, after work-up, and Kugelröhr distillation two products. First product \( \text{N-furfuryl-iso-propylamine (157a)} \) (1.00g, 40%), b.p. 90°C / 15 mmHg, (lit.\(^{167}\), 82–5 °C / 19 mmHg).

i.r. (film) \( \nu_{\text{max}} \) 3320 <\( \nu \rangle, 3112, 2968, 2868, 2828, 2636, 1632, 1600, 1502, 1466, 1442 cm\(^{-1}\)

\(^1\)H n.m.r. (60 MHz), \( \delta = 1.07 \) (6H, d, J = 6 Hz, CH[CH\(_3\)]\(_2\)), 1.50 (1H, br.s, D\(_2\)O ex., NH), 2.80 (1H, sept., J = 6 Hz, CHMe\(_2\)), 3.77 (2H, s, NCH\(_2\)), 6.07–6.37 (2H, m, C[3 and 4] H), and 7.23–7.37 (1H, m, C[5] H) ppm.

\(^{13}\)C n.m.r. (20.1 MHz) \( \delta = 18.8 \) (q, CH[CH\(_3\)]\(_2\)), 46.3 (t, CH\(_2\)N), 50.7 (d, CHMe\(_2\)), 107.9 (d, C[3]), 110.1 (d, C[4]), 141.6 (d, C[5]) and 153.7 (s, C[2]) ppm.

M.S. (m/z); 139 (8.7%), 81 (100%), (M\(^+\)) 139.0973; C\(_9\)H\(_{13}\)NO requires 139.0997.

Second product \( \text{N,N-difurfuryl-iso-propylamine (158a)} \) (0.56g, 30%), b.p. 75°C / 0.05 mmHg.

i.r. (film) \( \nu_{\text{max}} \) 2964, 1598, 1500, 1460, 1382 cm\(^{-1}\)

\(^1\)H n.m.r. (60 MHz), \( \delta = 1.03 \) (6H, d, J = 6 Hz, CH[CH\(_3\)]\(_2\)), 2.93 (1H, sept.,
J = 6 Hz, CHMe₂, 2.63 (4H, s, CH₂N), 6.00–6.30 (4H, m, C [3 and 4] H), and 7.20–7.33 (2H, m, C [5] H) ppm.

13C n.m.r. (20.1 MHz), δ = 22.8 (q, CH[CH₃]₂), 43.9 (t, NCH₂), 47.7 (d, CHMe₂), 106.6 (d, C [3]), 110.2 (d, C [4]), 141.7 (d, C [5]), and 154.5 (s, C [2]) ppm.

M.S. (m/z); 219 (5.6%), 81 (100%), (M⁺) 219.1254; C₁₃H₁₇N₂O₂ requires 219.1259.

(2) The reaction (1) was repeated for 50 hours yielding (157a) (0.70g, 28%) and (158a) (1.10g, 56%).

(3) Furan (1.09g, 16 mmol) was added to the iminium salt (2.93g, 17.6 mmol) (prepared from (149a) and Et₂O.HCl) in acetonitrile (45 ml). The mixture was stirred at room temperature for 2 hours yielding (157a) (1.03g, 46%) and (158a) (0.43g, 24%).

(4) Furan (1.02g, 15 mmol) was added to the iminium salt (2.73g, 16.5 mmol) (prepared from (149c) and Et₂O.HCl) in acetonitrile (45 ml). The mixture was stirred at room temperature for 2 hours affording, after work-up and Kugelröhr distillation, two products. First product N–furfuryl–t–butyl– amine (157b) (0.72g, 31%), b.p. 80°C / 8 mmHg.  
i.r. (film) ν max 3320 (NH), 3130, 2960, 1600, 1505, 1480, 1445, 1390, 1305 cm⁻¹  
1H n.m.r. (60 MHz), δ = 1.10 (9H, s, C [CH₃]₃), 1.17 (1H, br.s. D₂O ex., NH), 3.75 (2H, s, CH₂N), 6.07–6.37 (2H, m, C [3 and 4] H), and 7.27–7.37 (1H, m, C [5] H) ppm.

13C n.m.r. (20.1 MHz), δ = 29.0 (q, C [CH₃]₂), 40.1 (t, CH₂N), 50.5 (s, CMe₃), 106.1 (d, C [3]), 110.2 (d, C [4]), 141.5 (d, C [5]), and 154.9 (s, C [2]) ppm.

M.S. (m/z); 153 (2.7%), 81 (100%), (M⁺) 153.1153; C₉H₁₅NO requires 153.1154.
Second product 2,5-di(N-t-butylaminomethyl)furan (159) (0.39g, 20%), b.p. 80°C / 0.01 mmHg.

d. (film) \(\nu_{\text{max}}\) 3304 (NH), 2964, 2868, 1566, 1478, 1446, 1388, 1362 cm\(^{-1}\)

\(^1\)H n.m.r. (60 MHz), \(\delta = 1.17\) (18H, s, C \(\text{[CH}_3\text{]}\)), 2.33 (2H, br.s, \(\text{D}_2\text{O}\) ex., 2 NHs), 3.73 (4H, s, CH\(_2\text{N}\)), 6.08 (2H, s, C [3 and 4] H) ppm.

\(^1^3\)C n.m.r. (20.1 MHz), \(\delta = 29.0\) (q, C \(\text{[CH}_3\text{]}\)), 40.2 (t, CH\(_2\text{N}\)), 50.5 (s, CMe\(_3\)), 106.9 (d, C [3 and 4]), and 153.9 (s, C [2 and 5]) ppm.

M.S. (m/z); 238 (13.6%), 166 (99%), 110 (100%), (M\(^+\)) 238.2045; C\(_{14}\)H\(_{28}\)N\(_2\)O requires 238.2045.

(5) Furan (13.62g, 0.2 mol) was added to the iminium salt (3.31g, 20 mmol) (prepared from (149c) and Et\(_2\)O.HCl) in acetonitrile (40 ml). The mixture was then stirred at room temperature for 18 hours yielding after work-up and Kugelrohr distillation two products. First product (157b) (0.74g, 24%), b.p. 80°C / 8 mmHg. Second product N,N-di(furfuryl)-t-butylamine (158b) (2.91g, 62%), b.p. 90°C / 0.05 mmHg.

d. (film) \(\nu_{\text{max}}\) 3112, 2972, 1596, 1504, 1364 cm\(^{-1}\)

\(^1\)H n.m.r. (20.1 MHz), \(\delta = 1.13\) (9H, s, C \(\text{[CH}_3\text{]}\)), 3.80 (4H, s, CH\(_2\text{N}\)), 6.07–6.33 (4H, m, C [3 and 4] H), and 7.27–7.40 (2H, m, C [5] H) ppm.

\(^1^3\)C n.m.r. (20.1 MHz), \(\delta = 27.4\) (q, C \(\text{[CH}_3\text{]}\)), 44.4 (t, CH\(_2\text{N}\)), 54.5 (s, CMe\(_3\)), 107.8 (d, C [3]), 110.1 (d, C [4]), 141.3 (d, C [5]), and 154.5 (s, C [2]) ppm.

M.S. (m/z); 233 (22.9%), 218 (90%), 70 (100%), (M\(^+\)) 233.1410; C\(_{14}\)H\(_{19}\)NO\(_2\) requires 233.1416.

(6) Furan (10.89g, 160 mmol) was added to the iminium salt (2.65g, 16 mmol) (prepared from (149c) and Et\(_2\)O.HCl) in acetonitrile (60 ml). The mixture was stirred at room temperature for 1.5 hours yielding (157b) (1.25g, 51%) and (158b) (0.39g, 10%).
(7) Furan (8.85g, 130 mmol) was added to the iminium salt (2.17g, 13 mmol) (prepared from (149c) and Et₂O.HCl) in acetonitrile (50 ml) at -25°C. The mixture was then sealed under nitrogen and kept in the freezer at -22°C for 23 hours. Work-up gave only (157b) (1.01g, 51%).

(8) Furan (0.78g, 11.4 mmol) was added to the iminium salt (3.77g, 22.7 mmol) (prepared from (149c) and Et₂O.HCl) in acetonitrile (50 ml) at -35°C. The mixture was sealed under nitrogen and kept in the freezer at -22°C for 90 hours. Work-up gave only (157b) (1.68g, 50%).

(9) Furan (1.02g, 15 mmol) was added to the iminium salt (4.97g, 30 mmol) (prepared from (149c) and Et₂O.HCl) in acetonitrile (50 ml). The mixture was then stirred at room temperature for 22 hours affording, after work-up, (157a) (1.46g, 63%) and (159) (0.62g, 17%).

(13) N-methylindole (2.36g, 18 mmol) was added to the iminium salt prepared from (149a) (3.51g, 20 mmol) and trichloromethylsilane (3.29g, 22 mmol) in acetonitrile (60 ml) at room temperature for 2 hours. After work-up the crude product was isolated as a yellow crystalline solid. Recrystallisation from 10% aqueous ethanol afforded \( N,N\)-di(1-methyl-3-indolylmethyl)-iso-propylamine (158c) (2.10g, 67.5%) as long white needles, m.p. 119-120°C.

i.r. (KBr) \( \nu_{\text{max}} \) 3052, 2960, 2868, 2808, 1872, 1766, 1616, 1574 cm\(^{-1}\)

\( ^1\)H n.m.r. (60 MHz), \( \delta = 1.10 \) (6H, d, J = 6 Hz, CH[CH₃]₂), 3.20 (1H, sept., J = 6 Hz, CHMe₂), 3.55 (6H, s, NCH₃), 3.77 (4H, s, CH₂N), 6.83 (2H, s, C [2] H), 6.93-7.23 (6H, m, C [4, 5 and 6] H), 7.57-7.83 (2H, m, C [7] H) ppm.

\( ^{13}\)C n.m.r. (20.1 MHz), \( \delta = 17.3 \) (q, CH[CH₃]₃), 32.0 (q, NCH₃), 44.6 (t, CH₂N), 48.0 (d, CHMe₂), 108.9 (d, C [7]), 113.7 (s, C [3]), 118.5 (d, C [5]), 120.1 (d, C [4]), 121.3 (d, C [6]), 127.8 (d, C [2]), 128.2 (s, C [3a]).
and 137.3 (s, C[7α]) ppm.

M.S. (m/z); 345 (6.7%), 144 (100%), (M*) 345.2188; C_{23}H_{27}N_{3} requires 345.2205.

C, H, N analysis; Found: C (80.25), H (8.18), N (12.20)%; Requires: C (79.96), H (7.88), N (12.16)%.

(10) N-methylindole (2.36g, 18 mmol) was added to the iminium salt (3.51g, 20 mmol) (prepared from (149a) and trichloromethylsilane) in acetonitrile (60 ml) at room temperature for 2 hours. After work-up the crude product was isolated as a viscous oil. Kugelröhr distillation gave 3-(N-iso-propylaminomethyl)-1-methylindole (157c) as a pale yellow oil (0.81g, 26%), b.p. 115°C/0.05 mmHg.

i.r. (film) v_max 3376 (NH), 3052, 2960, 2824, 1660, 1614, 1574 cm^{-1}

{H n.m.r. (60 MHz), δ = 1.10 (6H, d, J = 6 Hz, CH[CH_{3}]_{2}), 1.63 (1H, s, D_{2}O ex., NH), 2.90 (1H, sept., J = 6 Hz, CHMe_{2}), 3.60 (3H, s, NCH_{3}), 3.93 (2H, s, CH_{2}N), 6.92 (1H, s, C[2] H), 6.97-7.30 (3H, m, C[4,5 and 6] H), and 7.53-7.73 (1H, m, C[7] H) ppm.

{C n.m.r. (20.1 MHz), δ = 23.0 (q, CH[CH_{3}]_{2}), 32.2 (q, NCH_{3}), 42.4 (t, CH_{2}N), 48.8 (d, CHMe_{2}), 109.1 (d, C[7]), 114.0 (s, C[3]), 118.9 (d, C[4 and 5]), 121.5 (d, C[6]), 126.9 (d, C[2]), 127.6 (s, C[3α]), and 137.2 (s, C[7α]) ppm.

M.S. (m/z); 202 (14.4%), 144 (100%), (M*) 202.1420; C_{13}H_{18}N_{2} requires 202.1470.

The residue after distillation was recrystallised from 10% aqueous ethanol to give (158c) (1.40g, 41%), m.p. 119–121°C.

(11) Reaction (10) was repeated for 22 hours, affording (157c) (1.15g, 32%) and (158c) (1.95g, 63%).
(12) Repeating reaction (10) for 2 hours gave (157c) (0.51g, 14%) and (158c) (1.60g, 51%).

(14) Ethereal hydrogen chloride (1.07M, 15.4 ml, 16.5 mmol) was added to a mixture of N-methylindole (1.97g, 15 mmol) and (149a) (2.89g, 16.5 mmol) in acetonitrile (45 ml). The mixture was stirred at room temperature for 2 hours and, after work-up, gave (157c) (1.94g, 64%) and (158c) (0.79g, 30%).

(15) A solution of N-methylindole (1.84g 14 mmol) in dichloromethane (25 ml) was cooled to -78°C and added via a cannula to a solution of the iminium salt (2.53g, 15.3 mmol) (prepared from (149c) and Et₂O.HCl) in dichloromethane (25 ml) at -78°C. The mixture was then stirred at that temperature for 2 hours affording, after work-up and Kugelröhrr distillation, 3-(N-t-butylaminomethyl)-1-methylindole (157d) (2.42g, 80%), as a pale yellow oil, b.p. 110-120°C / 0.01 mmHg. i.r. (film) ν max 3304 (NH), 3052, 2960, 2876, 2820, 1614, 1556, 1474 cm⁻¹. ¹H n.m.r. (60 MHz), δ = 0.93 (1H, br.s, D₂O ex., NH), 1.20 (9H, s, C[CH₃]₃), 3.50 (3H, s, NCH₃), 3.87 (2H, s, CH₂N), 6.87 (1H, s, C[2] H), 6.97−7.27 (3H, m, C[4,5 and 6] H), 7.47−7.73 (1H, m, C[7] H) ppm. ¹³C n.m.r. (20.1 MHz), δ = 29.1 (q, C[CH₃]₃), 32.3 (q, NCH₃), 37.8 (t, NCH₂), 50.4 (s, CMe₂), 109.2 (d, C[7]), 114.3 (s, C[3]), 118.8 (d, C[4 and 5]), 121.6 (d, C[6]), 127.0 (d, C[2]), 127.5 (s, C[3a]), and 137.2 (s, C[7a]) ppm.

M.S. (m/z); 216 (16.0%), 144 (100%), (M⁺) 216.1618; C₁₄H₂₀N₂ requires 216.1626.

(16) A solution of N-methylindole (1.84g, 14 mmol) in dichloromethane (25 ml) was cooled to -78°C and added via a cannula to a solution of the iminium salt (2.50g, 15.1 mmol) (prepared from (149a) and
Et$_2$O.HCl in dichloromethane (25 ml) at −78°C. The mixture was stirred at that temperature for 2 hours giving, after work-up, (157c) (1.39g, 49%), b.p. 110°C / 0.01 mmHg and (158c) (0.40g, 17%), m.p. 121°C.

(17) Reaction (16) was repeated for 2 hours and yielded (157c) (1.44g, 51%), b.p. 115°C / 0.02 mmHg, and (158c) (0.45g, 19%), m.p. 120–121°C.

(18) N-methylpyrrole (1.46g, 18 mmol) was added to the iminium salt (3.29g, 19.8 mmol) (prepared from (149a) and trichloromethylsilane) in acetonitrile (60 ml). The mixture was stirred at room temperature for 2 hours. The crude product was isolated as a yellow crystalline solid and recrystallised from 10% aqueous ethanol, yielding $N,N$-di-$N$-methyl-2-pyrrolylmethyl-iso-propylamine (158e) (1.49g, 67%) as pale yellow crystals, m.p. 86–88°C.

t.r. (KBr) $\nu_{\text{max}}$ 3100, 2964, 2804, 1634, 1558, 1494 cm$^{-1}$

$^1$H n.m.r. (60 MHz), $\delta$ = 1.03 (6H, d, J = 6 Hz, CH$_2$(CH$_3$)$_2$), 2.97 (1H, sept., J = 6 Hz, CHMe$_2$), 3.40 (6H, s, NCH$_3$), 3.47 (4H, s, NCH$_2$)

$^1^3$C n.m.r. (20.1 MHz), $\delta$ = 16.7 (q, CH$_2$(CH$_3$)$_2$), 33.2 (q, NCH$_3$), 44.4 (t, CH$_2$N), 47.6 (d, CHMe$_2$)

M.S. (m/z); 245 (4.6%), 94 (100%), (M$^+$) 245.1866; C$_{18}$H$_{23}$N$_3$ requires 245.1892.

(19) N-methylpyrrole (1.22g, 15 mmol) was added to the iminium salt (2.89g, 16.5 mmol) (prepared from (149a) and Et$_2$O.HCl) in acetonitrile (45 ml). The mixture was then stirred at room temperature for 2 hours and after work-up the crude product was isolated as a yellow amorphous solid. Trituration with ethyl acetate / hexane gave an amorphous white solid (2.24g). High field $^1$H and $^1^3$C n.m.r. spectra suggested the product was
the polymeric material (160).

$^1$H n.m.r. (250 MHz), $\delta = 0.73-1.11$ (br.d, CH[CH$_3$]$_2$), 2.71-3.03 (br. sept., CHMe$_2$), 3.08-3.27 (br.s, NCH$_3$), 3.27-3.48 (br.s, NCH$_2$), 5.76-5.94 (br.s, C [3 and 4] H) ppm.

$^{13}$C n.m.r. (62.9 MHz), $\delta = 16.8$ (C [CH$_3$]$_2$), 29.8 (NCH$_3$), 45.1 (NCH$_2$), 47.6 (CHMe$_2$), 107.9 (C [3 and 4]), and 130.3 (C [2 and 5]) ppm.

(20) N-methylpyrrole (1.22g, 15 mmol) was added to the iminium salt (2.65g, 16 mmol) (prepared from (149c) and Et$_2$O.HCl) in acetonitrile (40 ml) at -40°C. The mixture was stirred at that temperature for 2 hours yielding, after work-up and Kugelrohr distillation, 2-((N-t-butylamino-methyl)-1-methylpyrrole (157f) (0.55g, 22%), b.p. 110°C / 0.03 mmHg.

i.r. (film) $\nu_{max}$ 3300 (NH), 3100, 2962, 1658, 1497, 1473, 1362 cm$^{-1}$.

$^1$H n.m.r. (60 MHz), $\delta = 0.77$ (1H, br.s, D$_2$O ex., NH), 1.17 (9H, s, C [CH$_3$]$_3$), 3.60 (3H, s, NCH$_3$), 3.63 (2H, s, NCH$_2$), 5.87-6.03 (2H, m, C [3 and 4] H), 6.37-5.53 (1H, m, C [5] H) ppm.

$^{13}$C n.m.r. (20.1 MHz), $\delta = 28.9$ (q, C [CH$_3$]$_3$), 33.4 (q, NCH$_3$), 38.7 (t, CH$_2$N), 50.2 (s, CMe$_3$), 106.4 (d, C [3]), 107.3 (d, C [4]), 122.0 (d, C [5]), and 131.9 (s, C [2]) ppm.

M.S. (m/z; 166 (16.7%), 94 (100%), M$^+$) 166.1448; C$_{10}$H$_{18}$N$_2$ requires 166.1470.

(21) A solution of N-methylpyrrole (1.22g, 15 mmol) in dichloromethane (25 ml) cooled to -78°C was added via a cannula to a solution of the iminium salt (2.73g, 16.5 mmol) (prepared from (149c) and Et$_2$O.HCl) in dichloromethane (25 ml) at -78°C. The mixture was then stirred at that temperature for 2 hours, yielding (157f) (1.14g, 46%), b.p. 80°C / 0.5 mmHg.
(22) Reaction (21) was repeated for 4 hours, affording \(157f\) (1.40g, 56%).

(23) Reaction (21) was also repeated for 8 hours, yielding \(157f\) (1.22g, 59%).

(24) 1,3-Dimethoxybenzene (2.07g, 15 mmol) was added to the iminium salt (2.73g, 16.5 mmol) (prepared from (149c) and Et\(_2\)O.HCl) in acetonitrile (50 ml). The mixture was stirred at room temperature for 24 hours, affording after work-up, unreacted 1,3-dimethoxybenzene (1.08g, 52%) and 2,4-dimethoxy-\(N-t\)-butylbenzylamine \(157g\) (1.08g, 32%), b.p. 115°C / 0.01 mmHg.

i.r. (film) \(\nu_{max}\) 3320 (NH), 2960, 2832, 1614, 1588, 1508, 1466 cm\(^{-1}\).

\(^1H\) n.m.r. (60 MHz), \(\delta\) = 1.18 (9H, s, C[CH\(_3\)]\(_3\)), 1.25 (1H, br.s, D\(_2\)O ex., NH), 3.63 (2H, s, CH\(_2\)N), 3.77 (6H, s, OCH\(_3\)), 6.27–6.60 (2H, m, C[5 and 6] H), and 7.17 (1H, d, \(J_{AB}\) = 9 Hz, C[3] H) ppm.

\(^13C\) n.m.r. (20.1 MHz), \(\delta\) = 29.1 (q, C[CH\(_3\)]\(_3\)), 41.9 (t, CH\(_2\)N), 50.5 (s, CMe\(_3\)), 55.1 (q, OCH\(_3\)), 98.5 (d, C[3]), 104.0 (d, C[5]), 122.1 (s, C[1]), 130.2 (d, C[6]), 158.4 (s, C[4]), and 160.0 (s, C[2]) ppm.

M.S. (m/z); 223 (3.8%), 151 (100%), (M\(^+\)) 223.1572; C\(_{13}\)H\(_{21}\)N\(_2\)O\(_2\) requires 223.1572.

(25) Reaction (24) was repeated at room temperature for 5 days, affording \(157g\) (1.47g, 44%) and unreacted 1,3-dimethoxybenzene (1.10g, 53%).

(26) Reaction (24) was repeated by warming the reagents at 50°C for 2 hours followed by heating under reflux in acetonitrile for 1 hour. The reaction yielded \(157g\) (1.26g, 38%), and unreacted 1,3-dimethoxybenzene (1.03g, 50%) was recovered.
1,3-Dimethoxybenzene (1.036 g, 75 mmol) and the iminium salt (2.48 g, 15 mmol) (prepared from (149c) and Et₂O.HCl) in acetonitrile (75 ml) were stirred at room temperature for 5 days. Work-up gave (157 g) (2.20 g, 66%) and unreacted 1,3-dimethoxybenzene (8.21 g, 79%).

3.6 (a) Reaction of 2-methylfuran with N,N-bis(methoxymethyl)-3,4-dimethoxy-β-phenylethylamine (149 g) and trichloromethylsilane

Trichloromethylsilane (0.90 g, 6 mmol) was added dropwise to a mixture of 2-methylfuran (0.49 g, 6 mmol) and (149 g) (1.62 g, 6 mmol) in acetonitrile (30 ml) at 0°C. The mixture was then stirred at room temperature for 16 hours. Water (20 ml) was added and the solvent removed in vacuo. The residue was then washed with ethyl acetate (3 x 20 ml) and then basified to pH14 with 2 M sodium hydroxide. The aqueous layer was then extracted with ethyl acetate (3 x 40 ml). The combined organic washings from the basic solution were dried and concentrated in vacuo to a viscous immobile oil. The crude product was dissolved in ether triturated with light petroleum ether and cooled to −60°C collapsing to a crystalline solid. Recrystallisation from hexane afforded N-(5-methyl-2-furylmethy)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (162) (1.12 g, 65%) as a white solid, m.p. 93-94°C.

i.r. (KBr) ν max 3020, 2984, 2956, 2912, 2836, 2780, 2660, 1610, 1568, 1518 cm⁻¹

¹H n.m.r. (250 MHz), δ = 2.29 (3H, s, C[5′]-CH₃), 2.74–2.83 (4H, m, C[3 and 4] H), 3.58 (2H, s, C[1] H), 3.65 (2H, s, NCH₂), 3.82 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 5.91–5.93 (1H, m, C[4′] H), 6.14 (1H, d, J = 3 Hz, C[3′] H), 6.50 (1H, s, C[5] H), and 6.58 (1H, s, C[8] H) ppm.

¹³C n.m.r. (62.9 MHz), δ = 13.7 (CH₃), 28.5 (C[4]), 50.4 (C[3]), 54.6 (C[1]), 55.1 (NCH₂), 55.9 (OCH₃), 105.9 (C[4′]), 109.5 (C[3′]), 109.6 (C[8]), 111.5 cm⁻¹
(C[5]), 126.7 (C[4a]), 127.0 (C[8a]), 147.2 and 147.5 (C[6 and 7]), 149.2 (C[2']), and 151.9 (C[5']) ppm.

M.S. (m/z); 287 (25.3%), 95 (100%), (M*) 287.1509; C_{17}H_{21}NO_{3} requires 287.1521.

C, H, N analysis; Found: C (71.33), H (7.44), N (5.05) %; Requires: C (71.05), H (7.37), N (4.87) %.

(b) Preparation of N-Chloromethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and its Related Iminium Chloride (165)

Trichloromethylsilane (29.90g, 0.2 mol) in diethyl ether (100 ml) was added dropwise to a solution of the bis(aminol ether) (149g) (26.94g, 0.1 mol) in diethyl ether (300 ml) cooled to 0°C under a still head of dry nitrogen. The mixture was then stirred at room temperature for 15 minutes and the precipitated solid was filtered under nitrogen, washed with dry ether (3x100 ml) and dried in vacuo. The title compound was isolated as a pale yellow crystalline solid in quantitative yield (24.17g, 100%) and stored under nitrogen.

(c) Preparation of Di(N-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinyl)methane (166)

Trichloromethylsilane (23.92g, 120 mmol) in acetonitrile (50 ml) was added dropwise to a solution of the bis(aminol) ether (149g) (16.16g, 60 mmol) in acetonitrile (150 ml) at 0°C under nitrogen. The mixture was stirred at room temperature for 1 hour. The precipitated solid was dissolved in water (100 ml) and the solvent was removed in vacuo. The aqueous solution was washed with ethyl acetate (3x80 ml) and then basified to pH14 with 2M sodium hydroxide and extracted with ethyl acetate (3x100 ml). The combined organic extracts from the basic solution were dried and concentrated in vacuo to a yellow solid. Recrystallisation from ethyl
acetate / cyclohexane (1:1) gave the title compound (11.35g, 95%) as a white solid, m.p. 131–132°C, (lit.\textsuperscript{168}, m.p. 126–127 °C).

i.r. (KBr) $\nu_{\text{max}}$ 2996, 2780, 1610, 1522, 1464, 1420, 1380, 1368 cm$^{-1}$ \textsuperscript{1}H n.m.r. (250 MHz), $\delta = 2.84$ (8H, s, C[3 and 4] H), 3.27 (2H, s, NCH$_2$N), 3.67 (4H, s, C[1] H), 3.82 (6H, s, OCH$_3$), 3.83 (6H, s, OCH$_3$), 6.55 (2H, s, C[5] H), and 6.61 (2H, s, C[8] H) ppm.

\textsuperscript{13}C n.m.r. (62.9 MHz), $\delta = 28.6$ (C[4]), 49.2 (C[3]), 54.0 (C[1]), 55.92 and 55.95 (OCH$_3$), 80.6 (NCH$_2$N), 109.7 (C[8]), 111.5 (C[5]), 126.7 (C[4a]), 127.0 (C[8a]), 147.2 (C[7]), and 147.5 (C[6]) ppm.

M.S. (m/z): 206 (22.3%), 192 (24.8%), 164 (100%), (M$^+$) (398), not measured. $N$-methylene-$6,7$-dimethoxy-$1,2,3,4$-tetrahydroisoquinolinium ion C$_{12}$H$_{18}$N$_2$O$_2$ measured 206.1101; requires 206.1181.

F.A.B. (M$^+$ + Rb) 483; (398 + 85).

C, H, N analysis: Found: C (69.18), H (7.70), N (7.10) (%); Requires: C (69.32), H (7.59), N (7.03) (%).

(d) Preparation of $N,N,N$-Tris(\textsuperscript{1}phenylethyl)hexahydro-$s$-triazine (167)

Trichloromethylsilane (2.24g, 15 mmol) in acetonitrile (30 ml) was added to a solution of $N,N$-bis(ethoxymethyl)-\textsuperscript{2}phenylethylamine (149f) (3.56g, 15 mmol) in acetonitrile (30 ml) at 0°C. The mixture was then stirred at room temperature for 24 hours. Following the work–up procedure described for the preparation of (166) the title compound was isolated (1.40g, 70%), b.p. 130°C / 0.01 mmHg.

i.r. (film) $\nu_{\text{max}}$ 3080, 3060, 3024, 2928, 2860, 2796, 1676, 1602, 1492, 1452 cm$^{-1}$.

\textsuperscript{1}H n.m.r. (250 MHz), $\delta = 2.56$–2.87 (12H, m, NCH$_2$CH$_2$Ph), 3.42 (6H, br.s, NCH$_2$N), and 7.10–7.29 (15H, m, PhH) ppm.

\textsuperscript{13}C n.m.r. (62.9 MHz), $\delta = 34.5$ (PhCH$_2$), 54.3 (PhCH$_2$CH$_2$N), 74.3 (NCH$_2$N).
(e) Preparation of \(N, N, N\)-Tris[\(\beta\)-(4-methoxyphenyl)ethyl]-hexahydro-\(s\)-triazine (168)

Trichloromethylsilane (2.99 g, 20 mmol) in diethyl ether (25 ml) was added to a solution of \(N, N\)-bis(ethoxymethyl)-\(\beta\)-4-methoxyphenylethylamine (149h) (2.67 g, 10 mmol) in diethyl ether (25 ml) at \(0^\circ C\). The mixture was then stirred at room temperature for 1 hour. Following the work-up procedure described for the preparation of (166) the crude product was isolated as a viscous immobile oil. The product was dissolved in ether, trititated with petroleum ether, and cooled in the freezer overnight, to give pale yellow crystals. Recrystallisation from hexane gave the title compound (1.21 g, 74%), m.p. 53-54°C.

i.r. (Nujol) \(v_{max}\) 3028, 2996, 2932, 2856, 2832, 1610, 1582, 1464 cm\(^{-1}\).

\(^1H\) n.m.r. (250 MHz), \(\delta = 2.63-2.73 (12H, m, NCH_2CH_2Ph), 3.48 (6H, br.s, NCH_2N), 3.78 (9H, OCH_3), 6.80-7.13 (12H, AA' BB', C[2,3,5 and 6] H) ppm.

\(^13C\) n.m.r. (62.9 MHz), \(\delta = 33.6 (PhCH_2), 54.7 (PhCH_2CH_2N), 55.2 (OCH_3), 74.5 (NCH_2N), 113.8 (C[3 and 5]), 129.6 (C[2 and 6]), 132.3 (C[1]), and 157.9 (C[4]) ppm.

M.S. (m/z); 163 (18%), 121 (100%), \(M^+ (489)\) not detected;

4-MeO-C_\(6\)H_\(4\)-CH_2CH_2N^+=CH_2; C_{10}H_{13}NO (\(M^+\) 163.0986; requires 163.0986.
(f) Reaction of the Amlal (166) with Acetyl Chloride

Acetyl chloride (0.43g, 5.5 mmol) in diethyl ether (30 ml) was added dropwise to a solution of the amlal (166) (1.94g, 4.8 mmol) in diethyl ether (30 ml). The mixture was stirred for 24 hours at room temperature and the precipitated solid was filtered, washed with diethyl ether (3x20 ml) and dried in vacuo yielding the chloromethyl derivative (165) (1.11g, 95%). Treatment of the solid (165) with 2-methylfuran (0.31g, 3.8 mmol) in acetonitrile (40 ml), at room temperature for 24 hours, gave the tetrahydroisoquinoline derivative (162) (0.98g, 90%). The filtrate was concentrated in vacuo to give a white solid and recrystallised from cyclohexane to afford 2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.61g, 54%), m.p. 94-95°C, (lit.131, m.p. 94-95°C).

i.r. (Nujol) ν max 1630 (C=O), 1610, 1516 cm⁻¹

1H n.m.r. (250 MHz), (showed 2 rotamers), δ = 2.18 and 2.19 (3H, s, CH₃), 2.75-2.86 (4H, m, C[3 and 4]H), 3.67 (2H, t, J = 6 Hz, C[4]H), 3.81 (2H, t, J = 6 Hz, C[3]H), 3.85 and 3.86 (6H, s, OCH₃), 4.55 and 4.66 (s, C[1]H), 6.59 and 6.64 (2H, s, C[5 and 8]H) ppm.

13C n.m.r. (62.9 MHz) (showed 2 rotamers), δ = 21.59 and 21.94 (CH₃), 28.04 and 28.94 (C[4]), 39.46 and 47.76 (C[1]), 43.72 and 44.10 (C[3]), 55.94 and 56.00 (OCH₃), 108.93 and 109.42 (C[8]), 111.27 and 111.64 (C[5]), 124.23 and 125.38 (C[4a]), 125.76 and 126.97 (C[8a]), 147.68 and 147.73 (C[7]), 147.90 and 147.96 (C[6]), 169.32 and 169.35 (C=O) ppm.

M.S. (m/z); 235 (100%), (M⁺) 235.1213; C₁₃H₁₇NO₃ requires 235.1208.

C, H, N analysis; Found: C (66.46), H (7.27), N (6.32) (%); Requires: C (66.36), H (7.28), N (5.95) (%).
Preparation of \( N\)-Arylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines from the Solid (165)

General Method (N)

An aromatic compound (1.0 equiv.) was added to a solution of the solid (165) (1.0 equiv.) in acetonitrile at room temperature under nitrogen, and the mixture was stirred for a specified period of time. Water (20 ml) was added and the solvent was removed \textit{in vacuo}. The residue was acidified to pH1 with 2M hydrochloric acid and washed with ethyl acetate (3x30 ml). The aqueous layer was then basified to pH14 with 2M sodium hydroxide and extracted with ethyl acetate (3x40 ml). The combined organic washings from the basic solution were dried and concentrated \textit{in vacuo} to a solid or a viscous immobile oil which was triturated with ether to give a solid. The crude products were then purified by recrystallisation from a suitable solvent.

(1) Preparation of \( N\)-furfuryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (169)

Furan (0.68g, 10 mmol) was added to the solid (165) (2.42g, 10 mmol) in acetonitrile (70 ml). The mixture was stirred at room temperature for 72 hours, yielding the title compound, which was recrystallised from hexane, (2.27g, 83%), m.p. 60–62°C.

\( \text{i.r. (KBr)} \ \nu_{\text{max}} \text{ } 3128, 2992, 2956, 2916, 1682, 1644, 1610, 1518, 1462 \text{ cm}^{-1} \)

\( \text{\textsuperscript{1}H n.m.r} \text{ (250 MHz), } \delta = 2.76–2.83 \text{ (4H, m, C} [3 \text{ and 4}] \text{ H)}, 3.58 \text{ (2H, C} [1] \text{ H)}, 3.72 \text{ (2H, s, NCH}_{2}\text{)}, 3.81 \text{ (3H, s, OCH}_{3}\text{)}, 3.83 \text{ (3H, s, OCH}_{3}\text{)}, 6.26–6.35 \text{ (2H, m, C} [3' \text{ and 4'}] \text{ H)}, 6.49 \text{ (1H, s, C} [5] \text{ H)}, 6.58 \text{ (1H, s, C} [8] \text{ H)}, \text{ and 7.40–7.41 (1H, m, C} [5'] \text{ H) ppm.} \)

\( \text{\textsuperscript{13}C n.m.r.} \text{ (62.9 MHz), } \delta = 28.5 \text{ (C} [4]\text{)}, 50.4 \text{ (C} [3]\text{)}, 54.3 \text{ (C} [1]\text{), 54.9} \)
(CH₂N), 55.7 (OCH₃), 108.5 (C[3′]), 109.7 (C[8′]), 111.3 (C[5]), 125.9 (C[4a]), 126.3 (C[8a]), 142.0 (C[5′]), 147.1 (C[7]), 147.4 (C[6]), and 151.8 (C[2′]) ppm.

M.S. (m/z); 273 (12.0%), 164 (100%), (M⁺) 273.1368; C₁₆H₁₉N0₃ requires 273.1365.

C, H, N analysis; Found: C (70.47), H (7.02), N (5.07) (%); Requires: C (70.31), H (7.01), N (5.13) (%).

(2) Preparation of N-(5-Methylfurfuryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (162)

2-Methylfuran (0.49g, 6 mmol) was added to the solid (165) (1.45g, 6 mmol) in acetonitrile (40 ml). The mixture was stirred at room temperature for 24 hours yielding the title compound (162) (1.55g, 90%), m.p. 93–94°C from hexane.

(3) Preparation of N-(2-Pyrrolylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (170)

Pyrrole (0.54g, 8 mmol) was added to the solid (165) (1.93g, 8 mmol) in acetonitrile (60 ml). The mixture was stirred at room temperature for 20 hours, affording the title compound (170) (1.82g, 83%) which was recrystallised from cyclohexane / ethylacetate (1:1), m.p. 146–148°C.

i.r. (KBr) νmax 3396 (NH; pyrrole), 3036, 3000, 2912, 2868, 2832, 2800, 1736, 1692, 1608, 1570, 1518, 1418 cm⁻¹

¹H n.m.r. (250 MHz), δ = 2.70–2.82 (4H, m, C[3 and 4]H), 3.51 (2H, s, C[1]H), 3.67 (2H, s, NCH₂), 3.81 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 6.09–6.15 (2H, m, C[3′ and 4′]H), 6.49 (1H, s, C[5]H), 6.60 (1H, s, C[8]H), 6.72–6.75 (1H, m, C[5′]H), and 8.68 (1H, br.s, D₂O ex. NH) ppm.
$^{13}$C n.m.r. (62.9 MHz), $\delta = 28.4$ ($C[4]$), 50.9 ($C[3]$), 55.2 ($C[1]$), 55.3 ($CH_2N$), 55.8 ($OCH_3$), 107.5 ($C[3']$), 107.9 ($C[4']$), 109.5 ($C[8]$), 111.3 ($C[5]$), 117.9 ($C[5']$), 125.9 ($C[4a]$), 126.3 ($C[8a]$), 128.0 ($C[2']$), 147.2 ($C[7]$) and 147.6 ($C[6]$) ppm.

M.S. (m/z); 272 (1.8%), 192 (97%), 164 (100%), ($M^+$) 272.1531; $C_{18}H_{20}N_2O_2$ requires 272.1525.

C, H, N analysis; Found: C (70.86), H (7.71), N (10.08); (%); Requires: C (70.56), H (7.40), N (10.29) %.

(4) Preparation of $N$-{(5-Methyl-2-pyrrolylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (171)}

$N$-methylpyrrole (0.65g, 8 mmol) was added to the solid (165) (1.93g, 8 mmol) in acetonitrile (60 ml). The mixture was stirred at room temperature for 20 hours, yielding the title compound (171) (2.00g, 87%), recrystallised from hexane, m.p. 77–78°C.

i.r. (KBr) $\nu_{\text{max}}$ 2988, 2952, 2928, 2832, 2704, 1652, 1610, 1518, 1494, 1470 cm$^{-1}$

$^1$H n.m.r. (250 MHz), $\delta = 2.66$–2.80 (4H, m, $C[3$ and 4] H), 3.50 (2H, s, $C[1]$ H), 3.59 (2H, s, NCH$_2$), 3.65 (3H, s, NCH$_3$), 3.81 (3H, OCH$_3$), 3.84 (3H, s, OCH$_3$), 6.05–6.06 (2H, m, $C[3'$ and 4'] H), 6.50 (1H, s, $C[5]$ H), 6.59 (1H, s, $C[8]$ H), 6.60–6.61 (1H, m, $C[5']$ H) ppm.


M.S. (m/z); 192 (93%), 164 (100%), ($M^+$) 286 not detected.

F.A.B. ($M^+$–1); 285 (47%); $C_{17}H_{22}N_2O_2$ measured; $M^+$ + Rb 371.239.

C, H, N analysis; Found: C (71.08), H (7.82), N (9.40) (%); Requires: C (71.30), H (7.74), H (9.78) (%).
(5) Preparation of \( N-(3'-\text{Indolylmethyl})-6,7\text{-dimethoxy-1,2,3,4-}
\text{tetrahydroisoquinoline (172)} \)

Indole (0.82g, 7 mmol) was added to a solution of the solid (165)
(1.69g, 7 mmol) in acetonitrile (70 ml). The mixture was stirred at room
temperature for 22 hours yielding the title compound (172) (2.10g, 93%),
recrystallised from cyclohexane / ethyl acetate (1:1), m.p. 156–7 °C.

\( ^1\text{H n.m.r. (250 MHz), } \delta = 2.80 (4\text{H, br.s., C[3 and 4] H}), 3.62 (2\text{H, s, C[1] H}), 3.79 (3\text{H, s, OCH}_3), 3.83 (3\text{H, s, OCH}_3), 3.89 (2\text{H, s, CH}_2\text{N}), 6.48 (1\text{H, s, C[5] H}), 6.58 (1\text{H, s, C[8] H}), 7.10–7.37 (4\text{H, m, C[2', 4', 5', and 6'] H}), 7.77 (1\text{H, d, J = 7.7 Hz, C[7'] H}), \) and 8.23 (1\text{H, br.s, D}_2\text{O ex. NH) ppm.}

\( ^{13}\text{C n.m.r. (62.9 MHz), } \delta = 28.7 (\text{C[4]}), 50.7 (\text{C[3]}), 53.1 (\text{C[1]}), 55.6 (\text{CH}_2\text{N}), 55.9 (\text{OCH}_3), 109.7 (\text{C[8]}), 111.1, (\text{C[5]}), 111.4 (\text{C[7']}), 112.3 (\text{C[3']}), 119.4 (\text{C[4'] and 6']}), 121.6 (\text{C[5']}), 123.9 (\text{C[2']}), 126.4 (\text{C[4a]}), 126.9 (\text{C[8a]}), 128.0 (\text{C[3a]}), 136.2 (\text{C[7a]}), 147.1 (\text{C[7]}), \) and 147.4 (\text{C[6]}) ppm.

M.S. (m/z); 192 (62%), 164 (100%), \( (M^+ + 1) \) 322 not detected.

F.A.B. \( (M^+ + 1) \) 323 (80.66%); \( C_{20}H_{22}N_2O_2 \); Measured: 323.314.

(6) Preparation of \( N-(1'-\text{Methyl-3'-indolylmethyl})-6,7\text{-dimethoxy-}
\text{1,2,3,4-}
\text{tetrahydroisoquinoline (173)} \)

\( \text{N-methylindole (0.79g, 6 mmol) was added to the solid (165)} \) (1.45g,
6 mmol) in acetonitrile (60 ml). The mixture was stirred at room
temperature for 20 hours affording the title compound (173) (1.79g, 89%),
recrystallised from hexane / cyclohexane (1:1), m.p. 109°C.

\( \text{i.r. (KBr) } \nu_{max} \) 2996, 2964, 2904, 2868, 2788, 1674, 1608, 1566, 1468 \text{ cm}^{-1}. \)
\(^1\)H n.m.r. (250 MHz), \(\delta = 2.79\) (4H, br.s, C[3 and 4] H), 3.60 (2H, C[1] H), 3.76 (3H, s, NCH\(_2\)), 3.79 (3H, s, OCH\(_3\)), 3.83 (3H, s, OCH\(_3\)), 3.87 (2H, s, CH\(_2\)N), 6.47 (1H, s, C[5] H), 6.58 (1H, s, C[8] H), 7.07 (1H, s, C[2'] H), 7.09–7.33 (3H, m, C[4',5', and 6'] H), 7.76 (1H, d, J = 7.8 Hz, C[7] H) ppm.

\(^{13}\)C n.m.r. (62.9 MHz), \(\delta = 28.9\) (C[4]), 32.4 (NCH\(_2\)), 50.6 (C[3]), 53.2 (C[1]), 55.6 (CH\(_2\)N), 55.7 (OCH\(_3\)), 109.0 (C[7']), 109.5 (C[8]), 111.2 (C[5]), 111.3 (C[3']), 118.9 (C[6']), 119.5 (C[4']), 121.1 (C[5']), 126.3 (C[4a]), 127.1 (C[8a]), 128.2 (C[3'a]), 128.4 (C[2]), 136.9 (C[7'a]), 147.0 (C[7]), and 147.3 (C[6]) ppm.

M.S. (m/z); 336 (1.3%), 274 (10%), 144 (37.5%), 56 (100%), \((M^+)\) 336.1850; C\(_2\)H\(_4\)N\(_2\)O\(_2\) requires 336.1838.

C, H, N, analysis; Found: C (74.95), H (7.21), N (8.27) (%); Requires: C (74.97), H (7.19), N (8.33).

(7) Preparation of \(N\)-(2,4-DimethoxybenzyO-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (174)

1,3-Dimethoxybenzene (5.53g, 40 mmol) was added to the solid (165) (1.93g, 8 mmol) in acetonitrile (100 ml) and the mixture was heated under reflux for 72 hours, affording the title compound (174) (2.11g, 77%), recrystallised from hexane, m.p. 88–89°C.

i.r. (KBr) \(\nu_{\text{max}}\) 2996, 2956, 2916, 2836, 2788, 1686, 1610, 1586 cm\(^{-1}\).

\(^1\)H n.m.r. (250 MHz), \(\delta = 2.75–2.81\) (4H, m, C[3 and 4] H), 3.58 (2H, s, C[1] H), 3.65 (2H, s, NCH\(_2\)), 3.802, 3.806, 3.811, and 3.825 (4 x 3H, s, OCH\(_3\)), 6.46–6.48 (2H, m, C[5' and 6'] H), 6.49 (1H, s, C[5] H), 6.58 (1H, s, C[8] H), and 7.31 (1H, d, J = 9 Hz, C[3'] H) ppm.

\(^{13}\)C n.m.r. (62.9 MHz), \(\delta = 28.7\) (C[4]), 50.7 (C[3]), 55.3 (C[1]), 55.4 (CH\(_2\)NAr), 55.5 (C[2']–OCH\(_3\)), 55.6 (C[4']–OCH\(_3\)), 55.9 (C[6] and C[7]–OCH\(_3\)), 98.4 (C[3']), 104.0 (C[5']), 109.6 (C[8]), 111.5 (C[5]), 116.9 (C[1']), 126.4 (C[4a]), 127.1 (C[8a]), 131.2 (C[6']), 147.1 (C[7]), 147.4

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(C\([6]\)), 158.9 (C\([4']\)), and 159.9 (C\([2']\)) ppm.

M.S. (m/z): 343 (21.9%), 151 (100%), (M\(^+\)) 343.1749; \(\text{C}_{20}\text{H}_{25}\text{NO}_{4}\) requires 343.1783.

C, H, N, analysis; Found: C (69.91), H (7.57), N (4.08) (%); Requires: C (69.95), H (7.33), N (4.08) (%).

(8) 2,4-Dimethoxyphenyltributylstannane (1.67g, 3.9 mmol) was added to the solid (165) (0.94g, 3.9 mmol) in acetonitrile (40 ml). The mixture was stirred at room temperature for 48 hours yielding the product (174) (1.17g, 87%), m.p. 88–89°C (from hexane).

(9) Preparation of \(N\)-(4-Methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (175) (Sendaverine Methyl Ether)

4-Methoxyphenyltributylstannane (3.97g, 10 mmol) was added to the solid (165) (2.42g, 10 mmol) in acetonitrile (100 ml). The mixture was then stirred at room temperature for 72 hours yielding the title compound (175) (2.26g, 73%), recrystallised from hexane, m.p. 82–84°C.

i.r. (KBr) \(\nu_{\text{max}}\) 3036, 3004, 2908, 2872, 2836, 2740, 1696, 1630, 1610, 1582, 1518, 1462 cm\(^{-1}\).

\(^1\)H n.m.r. (250 MHz), \(\delta = 2.71–2.83\) (4H, m, C\([3\ and 4]\) H), 3.52 (2H, C\([1]\) H), 3.61 (2H, s, NCH\(_2\)Ar), 3.80, 3.81 and 3.83 (3x3H, s, OCH\(_3\)\), 6.47 (1H, s, C\([5]\) H), 6.58 (1H, s, C\([8]\) H), 6.85–7.32 (4H, AA' BB', C\([2', 3', 5'\ and 6']\) H) ppm.

\(^{13}\)C n.m.r. (62.9 MHz), \(\delta = 28.8\) (C\([4]\)), 50.6 (C\([3]\)), 55.2 (C\([4']\)—OCH\(_3\)\), 55.6 (C\([1]\)), 55.9 (C\([6]\) and C\([7]\)—OCH\(_3\)\), 62.1 (NCH\(_2\)Ar), 109.6 (C\([8]\)), 111.5 (C\([5]\)), 113.6 (C\([3'\ and 5']\)), 126.3 (C\([4a]\)), 126.9 (C\([8a]\)), 130.2 (C\([2'\ and 6']\)), 130.5 (C\([1']\)), 147.2 (C\([7]\)), 147.5 (C\([6]\)), and 158.8 (C\([4']\)) ppm.

M.S. (m/z): 313 (24.1%), 206 (18%), 192 (16%), 164 (87%), 121 (100%),
(M⁺) 313.1699; C₉H₂₉NO₃ requires 313.1678.

C, H, N analysis; Found: C (72.58), H (7.55), N (4.36) (%); Requires: C (72.82), H (7.40), N (4.47) (%).

(10) Preparation of N-(2,4-Dihydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (176)

Resorcinol (0.77g, 7 mmol) was added to the solid (165) (1.69g, 7 mmol) in acetonitrile (60 ml). The mixture was then stirred at room temperature for 16 hours, yielding the title compound (176) (1.76g, 80%), recrystallised from ethyl acetate, m.p. 209–210°C.

I.r. (KBr) νmax 3428 (OH), 1651, 1622, 1517, 1466 cm⁻¹

¹H n.m.r. (250 MHz), (DMSO-d₆), δ = 2.86 (4H, br.s, C[3 and 4] H), 3.66 (2H, s, C[1] H), 3.78 (2H, s, NCH₂Ar), 3.82 and 3.84 (2x3H, s, OCH₃), 6.31–6.34 (2H, m, C[5' and 6'] H), 6.50 (1H, s, C[5] H), 6.59 (1H, s, C[8] H), and 6.66 (1H, d, JAB = 8 Hz, C[3] H) ppm. (OH – not shown)

¹H n.m.r (60 MHz), 6.97 (2H, br.s D₂O ex. OH's) ppm.

¹³C n.m.r. (62.9 MHz), δ = 27.9 (C[4]), 49.4 (C[3]), 54.2 (C[1]), 55.4 (OCH₃), 58.3 (NCH₂Ar), 102.6 (C[3']), 106.6 (C[5']), 110.0 (C[8]), 111.8 (C[5]), 112.8 (C[1']), 125.4 (C[4a]), 125.7 (C[8a]), 129.8 (C[6']), 147.0 (C[7]), 147.4 (C[6]), 157.7 (C[4']), and 157.9 (C[2']) ppm.

M.S. (m/z); 315 (0.6%), 164 (100%), (M⁺) 315.1439; C₁₈H₂₇NO₄ requires 315.1470.

C, H, N analysis; Found: C (68.73), H (6.68), N (4.18) (%); Requires: C (68.55), H (6.71), N (4.44) (%).
Preparation of \(N-(2\text{-Hydroxy-1\text{-naphthylmethyl}})-6,7\text{-dimethoxy-1,2,3,4\text{-tetrahydroisoquinoline}}\) (177)

2-Naphthol (1.44g, 10 mmol) was added to the solid (165g) (2.42g, 10 mmol) in acetonitrile (80 ml). The mixture was stirred at room temperature for 16 hours to yield the title compound (177) (3.19g, 91%, recrystallised from cyclohexane / ethyl acetate (9:1), m.p. 139–140°C.

\[\text{i.r. } (\text{KBr}) \nu_{\text{max}} 3468 (\text{OH}), 2956, 2936, 2832, 1622, 1610, 1520, 1464 \text{ cm}^{-1}\]

\[\text{\(^1H\text{ n.m.r. } (250 \text{ MHz})}, \delta = 2.93 (4\text{H, br.s, C[3 and 4]}\text{H}), 3.79 (2\text{H, s, C[1]}\text{H}), 3.81 (3\text{H, s, OCH}_3), 3.86 (3\text{H, s, OCH}_3), 4.33 (2\text{H, NCH}_2\text{Ar}), 6.50 (1\text{H, s, C[5]}\text{H}), 6.63 (1\text{H, s, C[8]}\text{H}), 7.10 (1\text{H, d, J = 8.9 Hz, C[4']}\text{H}, 7.26–7.80 (4\text{H, m, C[5', 6', 7', and 8']}\text{H}), 7.87 (1\text{H, d, J = 8.9 Hz, C[3']}\text{H}) \text{ppm. (OH not shown)}\]

\[\text{\(^1H\text{ n.m.r. } (60 \text{ MHz}), \delta = 11.03 (1\text{H, br.s, D}_2\text{O ex. OHD}) \text{ppm.}}\]

\[\text{\(^{13}C\text{ n.m.r. } (62.9 \text{ MHz})}, \delta = 28.1 (\text{C[4]}), 50.3 (\text{C[3]}), 55.0 (\text{C[1]}), 55.85 \text{ and 55.88 (OCH}_3), 55.9 (\text{NCH}_2\text{Ar}), 109.4 (\text{C[8]}), 110.8 (\text{C[5]}), 111.3 (\text{C[1']}), 119.3 (\text{C[3']}), 121.0 (\text{C[8']}), 122.4 (\text{C[5']}), 125.0 (\text{C[4a]}), 125.3 (\text{C[8a]}), 126.3 (\text{C[4']}), 128.5 (\text{C[4'a]}), 128.9 and 129.2 (\text{C[6' and 7']}), 132.7 (\text{C[8'a]}), 147.5 (\text{C[7]}), 147.8 (\text{C[6]}), \text{and 156.7 (C[1']} \text{ppm.}}\]

\[\text{M.S. } (m/z); 206 (3%), 192 (76%), 158 (100%); \text{C}_{22}\text{H}_{23}\text{NO}_3 (M^+) 349 \text{not measured.}}\]

\(\text{C, H, N analysis; Found: C (76.01), H (6.74), N (3.85) \% ; Requires: C (75.62), H (6.63), N (4.01) \%} \)
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