STUDIES IN PYRROLE CHEMISTRY:


PART II. Application of the Pschorr Reaction to the Synthesis of Heterocycles based on the Pyrrole Ring System.

A thesis presented for the Degree of Master of Science in the Department of Chemistry, School of General Studies, Australian National University

By

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Except where it is acknowledged to have been performed by others, all the work described in this thesis was performed by me.

Susan Beveridge
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I also wish to thank Professor W.D. Crow, and members of the staff in the Chemistry Department for their help during my visits there.
SUMMARY

PART I.

The oxidation of aliphatic, aromatic and heterocyclic thiols
in the presence of pyrroles with iodine-potassium iodide gives pyrrolyl
alkyl, aryl or hetaryl sulphinic acid 

A mechanism is proposed which involves initial reaction of the
thiol and iodine to give a sulphenyl iodide species followed by
electrophilic attack of this species on the pyrrole nucleus.

Several of the pyrrolyl alkyl and aryl sulphenic acids were cyclised
to give new heterocyclic ring systems - e.g. 2,5-dimethylpyrrolo(3,4-f)-
benzo(b) 1',4'-thiazepine-5'-one (73).

The chemistry of 3-indolylthiol, prepared by alkaline hydrolysis of
S-(3-indolyl) iso-thiouronium iodide, has been examined and a number of
derivatives have been prepared for an examination of their biological
activity.

PART II.

The Pschorr reaction applied to certain pyrrole derivatives has
been examined.

1-(2-Nitrophenyl)-1-(3',5'-dimethyl-4'-ethoxycarbonylpyrrolyl)-
ethylene (31) was reduced to the corresponding amine (31A), which was
reacted under Pschorr conditions, but failed to yield identifiable products.

The copper-catalysed decomposition of the diazonium chloride derived
from H-(3,5-dithoxycarbonyl-4-methyl-2-pyrrolylmethyl)-3-methanesulphonyl-
2-phenylenediamine (37) gave spiroy l-methanesulphonyl-3H-indoline-3,2'-
(3',5'-dithoxycarbonyl-4-methyl-2'H-pyrrole) (51), in high yield.
However thermal decomposition of the diazonium salt gave 2,4-diethoxycarbonyl-3-methyl-5-(N-methanesulphonyl-o-aminophenyl)pyrrole (50) as the major product.

The spiro compound (51) gave the phenyl pyrrole (50) in almost quantitative yield on treatment with concentrated hydrochloric acid, while treatment with 100% phosphoric acid or 60% sulphuric acid converted the spiro compound (51) to 1,3-diethoxycarbonyl-5-methanesulphonyl-2-methyl-1,5-dihydropyrrole (1,2-c) quinazoline (52). Treatment of the spiro compound (51) in methanol or ethanol with catalytic amounts of concentrated sulphuric acid gave 2-(2'-N-methanesulphonyl-N-methoxymethyl-aminophenyl)-3,5-diethoxycarbonyl-4-methylpyrrole (61A) and the corresponding ethoxy derivative (61B). Possible mechanisms for the acid-catalysed reactions of the spiro-indoline are discussed.

The diazonium chloride derived from N-(2-ethoxycarbonyl-3-methyl-1-acetyl-5-pyrrolylmethyl)-N-methanesulphonyl-o-phenylenediamine (39) gave the spiro-indoline (62) on copper-catalysed decomposition. Thermal decomposition of the diazonium salt failed to give any recognizable products in this case.

The copper-catalysed decomposition of the diazonium chloride derived from N-(2-ethoxycarbonyl-3,4-dimethyl-5-pyrrolylmethyl)-N-methanesulphonyl-o-phenylenediamine (39) also failed to yield identifiable products.
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INTRODUCTION.

In the recent literature there have appeared examples of organic thiocyanano-compounds which have been patented for their pharmacological, fungicidal and insecticidal activity. Such compounds include the benzimidazole (1A), the benzoazole (1B) and the benzthiazole (1C). Even more recently the pyrrolyl thiocyanates (2)\(^1\) and (3)\(^2\) have been patented as fungicides.

One theory to be considered for the activity of these compounds is that they are in fact protected thiols. Therefore there are at least two biological pathways with which these compounds may be interfering; they may react or compete with sulphhydril groups or they may act as chelating agents, forming either irreversible or toxic complexes with essential metals in the cell. A similar mode of activity has been proposed for the fungicidal effects of the dithiocarbamate group\(^4\), for example in tetramethylthiurian disulphide (4).

It was thought that a process for the synthesis of other protected pyrrolyl thiols may lead to compounds with some interesting biological effects. Because of the widespread occurrence of the indole nucleus in natural products, a protected indolethiol would be of particular interest, as penetration into the biological system may be more efficient in this case. With this idea in mind several pyrrolyl alkyl sulphides and a series of pyrrolyl aryl sulphides were synthesised. These compounds have been tested for herbicidal and fungicidal activity in a primary screen and the results are reported. (Chapter 1)

The preparation of 3-indolethiol by Harris\(^5\) by cleavage of \(S-[3-\text{Indoly}]-\text{isothiuronium salts}\) enabled a more varied series of derivatives to be prepared. The preparation and biological activity of some indolyl thioesters, thio- and dithiocarbamates, as well as alkyl sulphides prepared from the thiol are reported. (Chapter 1)
A  \( X = \text{NH} \)

B  \( X = \text{O} \)

C  \( X = \text{S} \)
CHAPTER I.

Oxidation of Thiophenols and Thiols in the presence of Pyrroles.

A novel electrophilic substitution of pyrroles has been described recently, involving oxidation of thiourea in the presence of pyrroles, under acidic conditions, to give S-pyrrolyl isothiouronium salts, e.g. (5). The reaction is thought to proceed via formation of an intermediate sulphenyl cation, e.g. (6), which reacts with the pyrrole nucleus to give the isothiouronium salt.

Extensions of this reaction have been considered in which the pyrroles are replaced by other reactive aromatic and heterocyclic ring systems, and the thioureas are replaced by other sulphur compounds capable of generating a sulphur cation. The present section is confined to reactions in which the thioureas are replaced by thiophenols and thiols.

 Aryl sulphenyl halides are well known, and their reactions with pyrroles to give pyrrolyl aryl sulphides were reported by Fischer as early as 1922. In this work the relatively stable sulphenyl chlorides, o-nitrophenyl sulphenyl chloride (7, X=N=O) and phenyl sulphenyl chloride (7, X=H) were prepared by the chlorination of the corresponding disulphides and then reacted with several pyrroles unsubstituted in the α- and β-positions to give pyrrolyl aryl sulphides (e.g. 8, X=N=O,H) in good yield. This method is limited because of the number of sulphenyl halides known, and their high reactivity. Their synthesis in general involves cleavage of the appropriate disulphide by either chlorine or bromine, or reaction of the appropriate thiophenol with halogen.

It was considered that by analogy with the substitution reaction using thiourea, pyrrolyl aryl sulphides might be formed directly when the diaryl disulphide, or better, the thiophenol, was oxidized under acidic conditions in the presence of a pyrrole.
The reaction in the title compounds, in which the anion is formed by the reaction of the halogen with a thiol, was found to be rapid and quantitative. In the title compounds, the reaction is accelerated by the presence of a halogen, which facilitates the formation of the anion.

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Accordingly, a number of thiophenols were oxidized by iodine in aqueous-ethanolic solution in the presence of a number of pyrroles with an unsubstituted α- or β- position (e.g. Reaction 1). Table 1 summarizes the results of these reactions and shows the extent of pyrrolyl aryl sulphide formation in comparison with the corresponding disulphide formation.

The reactions in Table 1 were all carried out under standard conditions (aqueous-ethanolic solutions; 25-35°C) with the exception of reactions 11-15 where the temperature was kept below 15°C because of the higher reactivity of the alkyl pyrroles involved.

In reactions 1-6, in which 2,4-dimethyl-3-ethoxycarbonylpyrrole (10) was used, there appears to be no trend in the yields obtained. However no attempt was made to establish the optimum conditions for any of the reactions.

In the indole series, substitution is considered to have occurred in the 3-position by analogy with other electrophilic substitution reactions in the indole nucleus. Jardine and Brown, in an N.M.R. study, have shown that in a variety of solvents, the maximum chemical shift of the α-proton of indole and of 3-substituted indoles is of the order of 0.7 ppm, whereas the β-proton of indole and 2-substituted indoles, in the same variety of solvents, varies by only 0.2 ppm. The N.M.R. spectrum of p-tolyl 3-indolyl sulphide (12), in carbon tetrachloride and dimethyl sulfoxide, showed a chemical shift for the heterocyclic ring proton of 0.67 ppm. The similarity between this chemical shift and the shift of the α-proton reported supports, but does not prove, that 3-substitution has occurred, because the correlation made is not with a sulphur substituted indole. However the formation of 3-indolyl isothiouronium iodide (14) in the related reaction in which thiourea is oxidized by iodine in the presence of indole has been rigorously established and will be discussed in Chapter 3.
Reaction 1.
Table 1. The oxidation reaction of thiophenols in the presence of pyrroles to form pyrrolyl aryl sulphides.

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Thiophenol</th>
<th>Pyrrole</th>
<th>Pyrrolyl Aryl Sulphide</th>
<th>% Pyrrolyl Aryl Sulphide</th>
<th>% Disulphide</th>
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<td>66.5</td>
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<td>EtO₂C(CH₃)CH(CH₃)NC₂H₃S(C₂H₅)N(CH₃)₂ (17)</td>
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<td>12</td>
</tr>
<tr>
<td>5</td>
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<td></td>
<td>EtO₂C(CH₃)CH(CH₃)NC₂H₃S(C₂H₅)MeO₂C (19)</td>
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<td><img src="sulphide" alt="" /></td>
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<tr>
<td>Exp. No.</td>
<td>Thiophenol</td>
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<td>Pyrrolyl Aryl Sulphide</td>
<td>% Pyrrolyl Aryl Sulphide</td>
<td>% Disulphide</td>
</tr>
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The Mechanism of the Reaction.

The Classical Nucleophilic Displacement Mechanism.

The nucleophilic displacement of halogens by thiophenols involves attack by the species $\text{ArS}^-\text{ with displacement of the halide X}^-$. Similarly it is well established that the iodination of pyrroles is a facile reaction.

It may be possible in the reaction being considered, that initially iodine and the pyrrole (10) form the iodopyrrole (51), which subsequently may be attacked by the nucleophile $\text{ArS}^-\text{ with the expulsion of I}^-\text{, forming the pyrrolyl aryl sulphide (8, }X=\text{H})$. (Scheme A).

\[
\begin{align*}
* \text{pyH} + \text{I}_2 & \rightarrow \text{pyI} + \text{HI} \\
\text{ArS}^- + \text{pyI} & \rightarrow \text{ArSpy} + \text{I}^-
\end{align*}
\]

Scheme A.

Woodbridge and Dougherty$^{13}$ have proposed this nucleophilic mechanism in a similar reaction of thiourea, iodine and certain pyrroles to give dipyrrolyl disulphides, via the intermediate $S-(\text{pyrrolyl})\text{isothiouronium salt}$. However Harris$^6$ has shown that under the same conditions used for the formation of the $S-(\text{pyrrolyl})\text{isothiouronium salt (5)}$ from thiourea, iodine and the pyrrole (10), the iodopyrrole (51) and thiourea can be substantially recovered without reaction having occurred.

The work of Treibs also disputes the possibility of this mechanism operating. In an extensive study of iodopyrroles he has found no examples of the nucleophilic displacement of iodide from iodopyrroles, even under strongly alkaline conditions.$^{14}$ In fact the only displacements recorded from an iodopyrrole have been by an electrophile expelling $\text{I}^+\text{(equ.24)}$.

* pyH = A pyrrole with an unsubstituted position.
Equation 24.

\[
\begin{align*}
\text{EtO}_2C & \quad \text{CH}_3 \\
\text{H}_3C & \quad \text{N} \\
\text{I} & \quad \text{N}\end{align*}
\]
In order to test the possible occurrence of the nucleophilic mechanism, the iodopyrrole (51) and thiophenol were subjected to the reaction conditions used for the series of reactions in Table 1. No pyrrolyl aryl sulphide (8, X=H) was obtained, and diphenyl disulphide and thiophenol (isolated as the lead salt) were recovered, accounting for 93% of the original thiophenol. It is therefore apparent that this mechanism cannot be important under the reaction conditions used.

The Proposed Electrophilic Mechanism.

The mechanism proposed for the formation of pyrrolyl aryl sulphides in the reaction of iodine, a pyrrole and thiophenols is summarized in Scheme B.

\[
\begin{align*}
\text{ArSH} + I_2 & \rightarrow [\text{ArS}^+ I^-] + HI \\
\text{pyH} & \quad \text{pySAr} + HI \\
\text{ArSH} & \quad \text{ArSSAr} + HI
\end{align*}
\]

Scheme B.

The thiophenol, ArSH, reacts initially with the iodine to form the unstable sulphenyl iodide, ArSI, which can then react with either the pyrrole pyH, to form a pyrrolyl aryl sulphide or with unreacted thiophenol to form the disulphide. If the reaction occurred solely along path A, then one mole of iodine per mole of thiophenol would be consumed, and if reaction occurred only along path B, then one half mole of iodine per mole of thiophenol is consumed. In all the reactions discussed more than one half mole of iodine was consumed.

Few sulphenyl iodides have been isolated but they have been postulated as reactive intermediates in certain reactions.\textsuperscript{15} Messer\textsuperscript{16} obtained the only reported crystalline sulphenyl iodide, 2-benzothiazole sulphenyl iodide (52), but his only published evidence is an indefinite melting point of 105-125°C. This is the only reported synthesis of a sulphenyl iodide by cleavage of the corresponding disulphide with iodine.
\[
\begin{align*}
\text{(52)} & \quad \text{[Diagram]} \\
\text{(53)} & \quad \text{[Diagram]} \\
\text{(54)} & \quad \text{[Diagram]}
\end{align*}
\]

\[
[(\text{CH}_3\text{CS})_2\text{Hg}] + 2\text{I}_2 \rightarrow 2(\text{CH}_3\text{CSI}) + \text{HgI}_2
\]

\[
\text{(55)} \quad \text{(56)}
\]
Burrawoy et al.\textsuperscript{17} have prepared "azobenzene-2-sulphenyl iodide" (53) analytically pure by the double decomposition of the corresponding bromide. In view of the exceptional stability of this compound the structure (54) was proposed. Rheinboldt and hotzkus\textsuperscript{18} have obtained trimethylmethanesulphenyl iodide (56) from tert-butyl mercury mercaptide (55). Although the sulphenyl iodide was not isolated, its existence in solution has been well established.

The oxidation reaction of thiols to disulphides by iodine has long been known\textsuperscript{19}, although only recently has a mechanism, involving sulphenyl iodides, been proposed by Kharash\textsuperscript{20} (Scheme C).

\[
\begin{align*}
\text{RSH} + \text{I}_2 & \rightarrow \text{RSI} + \text{HI} \\
\text{RSH} + \text{RSI} & \rightarrow \text{RSSR} + \text{HI}
\end{align*}
\]

(Scheme C).

Thus the proposed intermediacy of the sulphenyl iodide in Scheme B is not without precedent.

A closer examination of the reactivity of the iodopyrrole (51) towards thiophenol, showed that a high yield of pyrrolyl aryl sulphide (8, X=H) was obtained when an equimolar solution of the iodopyrrole and thiophenol were refluxed for twelve hours. Refluxing a similar solution for fifteen minutes gave a 60\% yield of pyrrolyl aryl sulphide. Thus the nucleophilic mechanism could be operative under these more vigorous conditions, but is still considered to be unlikely in the light of the known lack of reactivity towards nucleophilic attack in halopyrroles\textsuperscript{17}.

An alternative explanation of these observations is that the iodopyrrole may undergo electrophilic displacement by a proton and subsequent reaction of the pyrrole with the species ArS\textsuperscript{+} as in Scheme B. (Scheme C).
\[
\begin{align*}
\text{pyI} + \text{H}^+ & \rightarrow \text{pyH} + I^+ \\
I^+ + \text{ArSH} & \rightarrow \text{ArS}^+ + \text{HI} \\
\text{pyH} + \text{ArS}^+ & \rightarrow \text{pySAr} + \text{H}^+
\end{align*}
\]

Scheme C.

If this mechanism is operating under reflux conditions, then the addition of strong acid to the solution, thereby increasing the proportion of the pyrrole pyH and of the species ArS\(^+\), would be expected to facilitate the reaction. A molar equivalent solution of thiophenol, the iodopyrrole (51) and sulphuric acid in aqueous ethanol was stirred at room temperature, and from this solution was obtained the pyrrolyl aryl sulphide (8, X=H) in 62\% yield. Under these same conditions the iodopyrrole and thiophenol do not react. (c.f. page 11)

The nucleophilic displacement of iodide from the iodopyrrole by the species ArS\(^-\) has been shown to be unimportant under the reaction conditions used in Table 1. However under forcing conditions the iodine is displaced. Therefore considering the work of Treibs\(^1\) and Harris\(^5\) and the acid catalysis of the reaction it is thought to proceed via the electrophilic displacement of I\(^+\).

**Pyrrolyl Alkyl Sulphides.**

The oxidation reaction of thiophenols was extended to certain thiols, and Table 2 shows the reactions which were carried out and the yields of products isolated. In the case of benzyl thiol (57) and methyl thioglycollate (56) the expected pyrrolyl alkyl sulphides (53) and (60) respectively were isolated in low yields. It is postulated that the alkyl sulphenium iodide is more unstable than the ring stabilised phenylsulphonyl iodide and reacts more readily with the solvent to form the highly unstable sulphonic acid which in turn will be further oxidized by the iodine present to sulphonic acids etc. or react with thiol to form the disulphide.\(^2\)
TABLE 2. The oxidation reaction of thiols in the presence of pyrroles.

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Thiol</th>
<th>Pyrrole</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
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<td>H$_3$C[CH=[N[CH$_3$]CO$_2$Et</td>
<td>CH$_3$C[CH$_2$S[N[CH$_3$]CO$_2$Et</td>
<td>17</td>
</tr>
<tr>
<td>25</td>
<td>CH$_3$O$_2$CCH$_2$SH</td>
<td></td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>26</td>
<td>CH$_3$COSH</td>
<td></td>
<td></td>
<td>57</td>
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</tbody>
</table>
The oxidation of methyl thioglycollate in the presence of the pyrrole (10) gave a crude mixture of the pyrrole and methyl S-(2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl) thioglycollate (60) which could not be purified satisfactorily by chromatography. The methyl ester (60) was hydrolysed to the acid (63) which was obtained in a pure state.

The product obtained from the reaction of thiolacetic acid (61) and the pyrrole (10) was di-(2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl) sulphide (62). A plausible explanation (Scheme D) is that initially S-(2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl) thioacetate (64) is formed by a mechanism analogous to that previously discussed in the thiophenol series which is then hydrolysed under the acidic conditions of the reaction medium to form the thiol (65). Iodine in the reaction medium converts this to the sulphenyl iodide (66) which then attacks the unreacted pyrrole to give the dipyrrolyl sulphide (62).

This mechanism is supported by a reaction carried out in which equimolar amounts of the pyrrole (10), the pyrrolyl thioacetate (64), iodine and hydriodic acid were stirred at room temperature under the standard set of conditions. From this reaction was isolated the monosulphide (62) identical to that previously isolated, and also identical to an authentic sample supplied by Harris.
Scheme D.
CHAPTER II.

Cyclisation of some Pyrrolyl Aryl and Alkyl Sulphides.

The oxidative coupling of thiophenols and thiols with pyrroles has opened a synthetic route to some pyrrolyl aryl and alkyl sulphides suitable for cyclisation to a variety of new fused heterocyclic ring systems. Experiments leading to several such compounds are discussed in this chapter.

Cyclisation of Pyrrolyl o-Methoxycarbonylphenyl Sulphides.

The facile conversion of pyrrole \( \omega \)-carboxylic acids to pyrrocols (e.g. 68) is known to occur under acidic conditions \(^{23}\) (equation 27). By analogy it was thought that the pyrrolyl \( \omega \)-methoxycarbonylphenyl sulphide (19) might cyclise under similar conditions to give the pyrrolobenzothiazinone (76).

Initial experiments, utilizing acid conditions (e.g. polyphosphoric acid, acetic anhydride) were unsuccessful. However the cyclisation was accomplished smoothly in 78\% yield when the methyl ester (19) was refluxed with sodium hydride in benzene. The pyrrolobenzothiazinone (69) was obtained as yellow fluorescent needles. The N.M.R. spectrum of this compound in comparison with that of the starting material (19), shows a loss of the exchangeable \( N-H \) of the pyrrole and of the methyl from the methyl ester. In addition, the \( \omega \)-methyl group of the pyrrole ring moves from 2.55 ppm to 3.1 ppm in the cyclised product (76) due to the deshielding effect of the carbonyl group.

The mass spectrum of this compound (69) showed the molecular ion at \( m/e \) 301. Peaks also occur at 282 (loss of 29, \( C_2H_5 \)), 256 (loss of 45, \( C_2H_4O \)) and at 228 (loss of 73, \( COOEt \)). The loss of these fragments from 2,1-dimethyl-3-ethoxycarbonyl pyrrole (10) have been previously reported\(^{24}\) (Scheme H). In addition the high resolution mass spectrum of this compound determined that the peak at 282 was due to the loss of \( C_2H_5 \) and not CHO.
Equation 27.
Scheme 124
The o-methoxycarbonylphenyl 3-pyrrolyl sulphide (32) which was obtained in 92% yield from 2,5-dimethylpyrrole and o-methoxycarbonylthiophenol, has a centre of high activity towards electrophilic attack at C-4 in the pyrrole ring, and facile acylation at this centre by the phenyl ester could be expected under Friedel-Craft conditions. Cyclisation did in fact occur readily when the sulphide (32), was heated briefly in polyphosphoric acid at 120°C. The product, benzo[b]2',5'-dimethylpyrrolo[3',4'-e]-5,6-dihydro-4H-thiopyran-4-one (70), was obtained in 65% yield. The structure was evident from the isolation of the same compound in 51% yield by cyclisation of the ethoxycarbonylpyrrolyl phenyl sulphide (25) under similar conditions, and was confirmed by physical data.

The mass spectrum of the cyclised product (70) establishes the molecular weight as 229 which is the m/e value of the parent peak of the spectrum. The N.M.R. spectrum also supports the structure (70). In comparison with the spectrum of the ester (32), loss of the methyl group of the ester and the β-H of the pyrrole ring in the cyclised compound has occurred. The ultraviolet spectrum of the product (70) shows an extended fused ring absorption pattern.

Cyclisation of Pyrrolyl o-Aminophenyl Sulphides.

The cyclisations so far described have given rise to compounds in which the sulphide linkage becomes part of a new six-membered heterocyclic ring formed by cyclisation of an ester substituent in either the phenyl or pyrrole ring, this cyclisation occurring onto either carbon (equation 28,29) or nitrogen (equation 30), depending on the sulphide used.
Equation 28.

Equation 29.

Equation 30.
Attempts have also been made to cyclise o-aminophenyl pyrrolyl sulphides. In the initial experiments the amine (21) was diazotised and subjected to the conditions of the Pschorr cyclisation\textsuperscript{25} in an attempt to form the compound (71). Decomposition of the diazonium salt from the amine (21) was carried out both by the addition of copper and by heating. However in neither case could any identifiable products be isolated.

Harris\textsuperscript{5} found that diazotisation of the amine (72) is complicated by competing nitrosation of the free $\beta$-position of the pyrrole ring and no identifiable products could be recovered from a Pschorr reaction of this compound.

It was thought the diazonium salt from the amine (26) with the $\beta$-position of the pyrrole blocked to prevent nitrosation, but with the C-1 carbon to which the ester is attached susceptible to attack by the diazonium salt, might cyclise under Pschorr conditions with the elimination of the $\beta$-ester group. The Pschorr cyclisation of the diazonium salt was carried out with copper, but the product (isolated in 73\% yield) was the deaminated compound (25). The compound (25) is obtained by a reductive process similar to that which has previously been reported from a copper suspension in aqueous media even though obvious hydrogen sources such as the alcohols are absent.\textsuperscript{26}

The aminophenyl pyrrolyl sulphide (26) was converted by heating in polyphosphoric acid to a compound to which the seven-membered lactam ring structure (73) was assigned. The N.M.R. spectrum of this compound showed two N-H protons (broad singlets, and in comparison with the spectrum of the starting material (26), the ethyl group of the ester had disappeared.

The mass spectrum showed that the molecular weight of the compound is 211, as required. Two other peaks occurred in the spectrum at 229 (N-CH$_3$) and at 211 (N-SH). The loss of SH can be rationalized in Scheme (F). The ultraviolet spectrum of the lactam showed peaks at 228\textmu and 280\textmu. 
Scheme F.
Earlier attempts to form the lactam (73) by refluxing the amine (26) in o-dichlorobenzene led to the deaminated sulphide (25), a surprising result which so far cannot be explained.

Cyclisation of some Pyrrolyl Alkyl Sulphides.

It was thought that the thioacetic acid (63) (formed by the oxidation of methyl thioglycollate and the pyrrole (10), with subsequent hydrolysis of the methyl ester (60)) might cyclise to give the hitherto unreported type of lactam (71). Initial experiments were carried out using the acid (63), in acetic anhydride and in polyphosphoric acid, without cyclisation occurring. However in refluxing acetic anhydride/pyridine mixture cyclisation did occur and the product (71) was obtained in 13% yield. The N.M.R. spectrum supports the structure of this compound by the absence of the N-H proton and the O-H proton of the acid. The -CH= of the thiazolidinone has shifted from 3.38 ppm in the acid (63) to 4.35 ppm in the cyclised product. The mass spectrum showed molecular ion at m/e 239 and subsequent fragmentation gave ions at m/e 210 (loss of 29, C₂H₅), m/e 182 (loss of 23 from m/e 210, CO), m/e 164 (loss of 45, C₂H₅O) and m/e 166 (loss of 23, CO).

The success of this cyclisation in acetic anhydride/pyridine led to an attempt to prepare the compound (76) from the thiopropionic acid (22) (75). The cyclised product (76) was in fact obtained by the same method although in only 15% yield.

The N.M.R. spectrum was first run in acetone-D₆ and the spectrum obtained was consistent with the structure (76) except that the two -CH₂- groups of the six membered ring occurred as a singlet at 3.15 ppm. The spectrum was then run in CDCl₃ where again these four protons occurred as a singlet at 3.1 ppm. In the propionic acid (75) these protons appear as a multiplet centred at 2.6 ppm. The structure (76) is further supported by the mass spectrum, which shows the molecular ion at m/e 253, which is the molecular weight of the structure (76).
Peaks also occur at 208 (M-45, C₂H₂O), at 198 (M-55, C₃H₂O), at 55 (M-198, C₉H₁₂NO₂S), and at m/e 152, a loss of 46 from the ion at m/e 198 (C₂H₅OH), (not CH₂S as S is still present in the ion, from the examination of the M+2 peak).
In Chapter I it was shown that the oxidation of thiophenols in the presence of indole gave reasonable yields of the corresponding indolyl aryl sulphones. Harris has found that under similar reaction conditions to those used for the preparation of the pyrrolyl isothiouronium salt (5), the oxidation of thiourea in the presence of indole gave almost quantitative yields of the isothiouronium salt (77). In the case of the pyrrolyl isothiouronium salt (5), hydrolysis by strong base led to the unstable thiol (78) which could be generated in situ and acylated or alkylated. For example, reaction with 3-chloropropionic acid gave the thiopropionic acid (75).

The indolyl isothiouronium salt could be hydrolysed by strong base under nitrogen to give 3-indolethiol (79) which was more stable and could be isolated in 0.5% yield as colourless plates, m.p. 107-108°C. This compound could be stored at 5°C for several weeks without oxidation by air to the disulphide. This method makes 3-indolethiol (79) available for the first time. The thiol is soluble in alkaline solution, and is readily oxidized in air. The N.M.R. spectrum of the compound shows two exchangeable protons, and the mass spectrum has a base peak at m/e 146, the molecular weight of the thiol (79).

Previous attempts at making 3-indolethiol have been unsatisfactory. When indole magnesium bromide was treated with sulphur, 3,3'-diindolyl disulphide (80) was obtained rather than the expected 3-indolethiol.27 Oddo and Mingoa have reported the preparation of 3-benzoylthioindole (81) when indole magnesium bromide was allowed to react with sulphur and then benzoyl chloride. Hydrolysis of the thioester led to 3-indolethiol. However the melting point recorded for this compound was 235°C which is similar to the melting point of 3,3'-diindolyl disulphide (217-218°C)10 recorded by Grant and Snyder. This disulphide was obtained from 3-thiocyanatoindole (85) which was prepared by the thiocyanation of indole with potassium isothiocyanate in the presence of bromine.
The 3,3'-substitution pattern has been unequivocally established\textsuperscript{10} by the oxidation of 3-thiocyano-2-carboxyindole (86) to the disulphide, which was then decarboxylated, and proved identical to the previously prepared samples.

Grant and Snyder\textsuperscript{10} reduced 3,3'-diindolyl disulphide (80) with lithium aluminium hydride followed by addition of 2,4-dinitrochlorobenzene and readily obtained 3-(2,4-dinitrophenylthio) indole (82). When ethyl bromoacetate was added, however, mainly unchanged disulphide (80) was obtained with only a trace of 3-indolylthioacetic acid (83). The same authors failed to isolate 3-indolethiol, presumably because of the ease of oxidation back to the disulphide (80).

Jardine and Brown\textsuperscript{11} have prepared 3-ethylthioindole (84) in poor yield from the reaction of indole magnesium bromide and ethanesulphenyl chloride. Another product obtained from the reaction was the diindolyl disulphide identical to that previously reported\textsuperscript{27,10} A study of the infra-red and N.M.R. spectra of this compound has corroborated the 3,3'-substitution previously established\textsuperscript{10}.

The disulphide obtained by the oxidation of the thiol (79) has a melting point of 218-220\degree C which is almost identical to that found previously for the disulphide (80). The $\alpha$-proton of the 3,3'-diindolyl disulphide occurs in the N.M.R. spectrum as a doublet which collapses to a singlet on deuteration of the sample. Jardine and Brown\textsuperscript{12} have tabulated the position of the $\alpha$-proton in the N.M.R. spectrum of the disulphide (80); in acetone, a doublet at 2.80, 2.83 ppm, and in dimethylsulphoxide at 2.62, 2.66 ppm. The N.M.R. spectrum of the disulphide obtained showed a doublet at 2.80, 2.85 ppm in acetone, and in dimethyl sulphoxide at 2.65, 2.69 ppm. Further evidence for the structure of 3-indolethiol is given by the melting point 176-178\degree C of the 2,4-dinitrophenyl derivative, which is similar to that obtained by Grant and Snyder\textsuperscript{10} (176\degree C) for the compound (82).
The acylation of 3-indolethiol was the first reaction to be considered. Indolyl aryl thioesters ([3, 37-39]) were prepared from the thiol and the appropriate benzoyl chloride in either aqueous alkali or in benzene to which a two molar excess of pyridine or triethylamine had been added. The thiobenzoate prepared in this manner was obtained as pale yellow plates, m.p. 141-142°C, whereas the sample prepared by Oddo and Mingoa was dark red, m.p. 157°C. The mass spectrum of this compound has a molecular ion at 253, and the N.M.R. spectrum supports the structure ([31]).

The reactions, under the conditions described above, between butyryl chloride and the thiol (79) were unsuccessful. S-(3-Indolyl) thiobutyrate ([92]) was finally prepared by heating a solution of the thiol, pyridine and butyric anhydride on a water bath for fifteen to thirty minutes. These conditions were also the most successful for the preparation of the thiopropionate (91) and the thiohexanoate (93) from the appropriate anhydride. The thioacetate ([90]) however was prepared by adding excess acetic anhydride to an alkaline solution of the thiol (79).

The reaction of alkyl haloacids, e.g. chloroacetic acid, with 3-indolethiol would lead to thiohomologues of indoleacetic acid ([34]) which has been the subject of a great deal of study because of its hormonal effect on plants. S-(3-Indolyl) thioacetic acid ([83]) was prepared in high yield by addition of chloroacetic acid to an alkaline solution of the thiol (79). In a similar reaction with p-propiolactone, S-(3-indolyl) thiopropionic acid ([95]) was obtained.

Another compound which could be included in this series as a derivative of a homologue of indoleacetic acid, and which was prepared under similar conditions to the thioacetic acid ([83]) is 3-indolyl 4'-cyanopropyl sulphide ([96]). The thio acrylic acid ([97]) was prepared by addition of the thiol (79) to the triple bond of propiolic acid.
\[ R = H \quad (81) \]
\[ R = \text{OCH}_3 \quad (87) \]
\[ R = \text{NO}_2 \quad (88) \]
\[ R = \text{3,4-di Cl} \quad (89) \]
$R' = \text{CH}_3$ (90)

$R' = \text{CH}_2\text{CH}_3$ (91)

$R' = (\text{CH}_2)_2 - \text{CH}_3$ (92)

$R' = (\text{CH}_2)_4 - \text{CH}_3$ (93)
The antifungal effects of some dithiocarbamates suggested that the indolyl dithiocarbamates and thiocarbamates would be of biological interest. Addition of the thiol to the isothiocyanates and isocyanates was in all cases a very efficient reaction, and the thio-and dithiocarbamates were prepared. Again three methods were used in the preparation of these compounds. Reaction of the thiol and the isothiocyanate or the isocyanate were carried out in neutral aqueous solution (e.g. 101), in benzene/triethylamine solution (e.g. 98, 100, 102) or in pyridine (100, 103).
\[ \text{R} = \text{phenyl (08)} \]

\[ \text{R} = \text{\( \rho \)-tolyl (00)} \]

\[ \text{R} = \text{\( \rho \)-chlorophenyl (100)} \]
$R' = \text{phenyl (101)}$

$R' = \text{cyclohexyl (102)}$

$R' = \text{methyl (103)}$
Herbicidal and Antifungal Activity of some Pyrrolylthio-Compounds.

The Plant Chemotherapy group at C.S.I.R.O. in Canberra has established a routine pre- and post-emergent herbicidal screen and an antifungal screen for novel compounds.

Herbicidal Testing.

In the pre-emergence testing, six species of plants (peas, mustard, barley, maize, linseed, ryegrass) are planted in soil which is then treated with a solution of the compound under test at a concentration equivalent to 8 kgm/hectare. For the post-emergent testing six species of plants (linseed, buckwheat, mustard, peas, silver beet, barley) are sprayed with a solution of the compound at a concentration of 8 kgm/hectare, 14 days after the emergence of the plants. The herbicidal effect of the applied compound is scored after a further seven days, by comparison with the control plants, on a 0-10 scale, where 0 is no effect and 10 is complete kill. If a score of 8, 9 or 10 is obtained, then the compound is retested at half concentration until a score less than 8 is obtained.

The lowest concentration of the applied compounds where the score is 8, 9 or 10, is then rated on a more convenient scale as shown below.

A score of < 8 at 8 kgm/hectare rates 0
   ≥ 8 " 8 kgm/hectare rates 1
   ≥ 8 " 4 kgm/hectare rates 2
   ≥ 8 " 2 kgm/hectare rates 3
   ≥ 8 " 1 kgm/hectare rates 4
   ≥ 8 " ½ kgm/hectare rates 5, etc.
i.e. A compound which is not active (scores less than 8 at 8 kgm/hectare), is given a rating of 0, and a score of 8 at 8 kgm/hectare but of less than 8 at 4 kgm/hectare rates 1. Commercial preparations of herbicides are used roughly in the range 2 kgm/hectare to ½ kgm/hectare which are ratings of 3 to 5 on this scale.

Antifungal Testing.

The in vitro antifungal testing is carried out on three germinating organisms, Monilinia fructicola (brown rot), Peronospora tabacina (blue mould) and Aspergillus Nidulans, and two growth organisms Phytophthora palmivora and Alternaria solani.

The germination ratings are determined by the lowest concentration of the applied compounds which score a 50% germination inhibition in comparison with control cultures, i.e. an L.D. 50. This rating system is shown in the following table.

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<td>15-50 ppm</td>
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<tr>
<td>5-15 ppm</td>
<td>3</td>
</tr>
<tr>
<td>1-5 ppm</td>
<td>4 etc.</td>
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</table>

The growth assay ratings are determined by the percentage inhibition of growth in comparison with the control cultures as follows.

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<td>&gt; 80%</td>
<td>+</td>
</tr>
<tr>
<td>&gt; 90%</td>
<td>++</td>
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<tr>
<td>&gt; 95%</td>
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Table 3 shows the herbicidal and antifungal effects of most of the pyrrolylthio compounds reported here.
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<th>Aspergillus</th>
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The pyrrolyl aryl sulphides were, in general, not active on the primary screen. Slight antifungal activity was found in several reactive pyrroles with an unsubstituted position (e.g., 32, 35 and 37), and with the indolyl aryl sulphides, but the herbicidal activity of the group was negligible. The cyclised products 69, 70, were quite inactive.

However the indolylthio-compounds were in most cases active as antifungal agents, with the thioesters (83, 97, 98, 100) and the thiocarbamates being the most active. The thioesters, (97, 98, 99, 100) showed post-emergent but no pre-emergent activity. It is considered that in the pre-emergent tests the esters may be broken down by the soil before they can become incorporated into the plant, whereas in the post-emergent test, the compounds may be incorporated before decomposition occurs.
EXPERIMENTAL.

General.

The microanalyses reported were performed by the Australian Microanalytical Service. All melting points were recorded on a Büchi melting point apparatus.

The U.V. spectra were recorded on a Bausch and Lomb, Spectronic 505 instrument, and the N.M.R. spectra were measured on a Varian A60 instrument. The mass spectra were kindly recorded by Dr. J. H. Lewis on an AEI, MS9 instrument at 70 e.v.

Starting Materials.

Pyroroles.

2,4-Dimethyl-3-ethoxycarbonylpyrrole (10) was prepared from 2,4-dimethyl-3,5-diethoxycarbonylpyrrole by selective hydrolysis of the $\alpha$-ester followed by decarboxylation of the acid m.p. 74-75°C (lit. m.p. 75-76°C).

2,4-Dimethyl-3-ethoxycarbonyl-5-iodopyrrole (11) was prepared by iodination of 2,4-dimethyl-3-ethoxycarbonylpyrrole, m.p. 145-146°C (lit. m.p. 145°C).

2,4-Dimethyl-5-ethoxycarbonylpyrrole (22) was prepared from 2,4-dimethyl-3,5-diethoxycarbonylpyrrole by selective hydrolysis of the $\beta$-ester followed by decarboxylation of the acid m.p. 123-124°C (lit. m.p. 124.5-125°C).

2,5-Dimethyl-3-ethoxycarbonylpyrrole (24) was prepared by the method of Hantzsch, m.p. 114-116°C (lit. m.p. 116-117°C) 2,5-Dimethylpyrrole (30) was prepared by the method of Vogel b.p. 75-78°C/25 mm. (lit. b.p. 78-80°C/25 mm).

2,4-Dimethyl-2-acetylpyrrole (27) was prepared from 2,4-dimethyl-3-acetyl-5-ethoxycarbonylpyrrole by hydrolysis of the ester followed by decarboxylation of the resulting acid m.p. 136-137°C (lit. m.p. 139°C).

S-(3-Indolyl) isothiouronium iodide (77) was prepared according to the method of Harris.
Thiophenols.

o-Nethoxycarbonyl thiophenol (12) was prepared by the esterification of thiosalicylic acid, b.p. 142-145°C (lit. b.p. 143-145°C).\(^4\)

p-(N-Dimethylamino) thiophenol (16) was prepared from p-thiocyanodimethylaniline\(^1\) by reduction with sodium sulphide\(^2\)
Pyrrolyl aryl sulphides.

General procedure.

A stirred solution of the pyrrole (10 m.mole) and the thiophenol (10 m.mole) in 50% aqueous ethanol (50 ml) was treated dropwise at a temperature < 50°C with a solution of iodine (10 m.mole) in ethanol (20 ml) or I2 iodine - potassium iodide reagent (10 ml). After one hour the solution was diluted with water (150 ml) and the product collected and purified by chromatography. In this manner, thiophenol and 2,4-dimethyl-3-ethoxycarbonylpyrrole (10) gave diphenyl disulphide (5.5%), colourless needles, m.p. 59-61°C (lit. m.p. 61.5°C)\(^4\) and phenyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulphide (8, R=H) (80%), colourless plates from ethanol-water m.p. 109-111°C (lit. m.p. 111°C)\(^3\), which was separated by chromatography on silicic acid in chloroform.

Similarly, 4-chlorothiophenol and 2,4-dimethyl-3-ethoxycarbonylpyrrole gave di(4-chlorophenyl) disulphide (23%), pale yellow plates, m.p. 69-71°C (lit. m.p. 70-71°C)\(^6\) and 3'-chlorophenyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulphide (13) (72%), colourless prisms from ethanol-water, m.p. 151-153°C, (Found C, 58.1; H, 5.4; S, 10.1. C\(_{15}\)H\(_{16}\)Cl NO\(_2\) S requires C, 58.2; H, 5.2; S, 10.1%), after separation by chromatography on alumina in benzene.

4-Nitrothiophenol and 2,4-dimethyl-3-ethoxycarbonylpyrrole gave di(4-nitrophenyl) disulphide (16%), buff prisms, m.p. 166-168°C (lit. m.p. 168-169°C)\(^1\) and 4'-nitrophenyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulphide (15) (66.5%), pale yellow prisms from ethanol-water m.p. 152-154°C (Found C, 56.1; H, 5.3; S, 9.6. C\(_{15}\)H\(_{16}\)NO\(_2\) 2 S requires C, 56.3; H, 5.0; S, 9.9%),. These were separated by chromatography on alumina in petroleum ether b.p. 60-80°C (50%) - chloroform (50%).
4-Dimethylaminothiophenol and 2,4-dimethyl-3-ethoxycarbonylpyrrole gave di(4-dimethylaminophenyl) disulphide (12%), buff needles, m.p. 116-117°C (lit. m.p. 118°C)\textsuperscript{16} and 4'-dimethylaminophenyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulphone (17) (62%), colourless prisms from ethanol-water, m.p. 111-113°C, (Found C, 64.0; H, 7.0; N, 8.5. C\textsubscript{17}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2}S requires C, 64.1; H, 7.0; N, 8.8%).

Which were separated by chromatography on silicic acid in benzene (50%)-petroleum ether b.p. 60-90°C (50%).

2-Methoxycarbonylthiophenol and 2,4-dimethyl-3-ethoxycarbonylpyrrole gave di(2-methoxycarbonylphenyl) disulphide (13%), colourless prisms, m.p. 130-131°C (lit. m.p. 130-135°C)\textsuperscript{40} and 2'-methoxycarbonylphenyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulphone (19) (17%), colourless needles from ethanol-water, m.p. 154-156°C (Found C, 61.0; H, 5.9; N, 4.1. C\textsubscript{17}H\textsubscript{19}N\textsubscript{2}O\textsubscript{2}S requires C, 61.3; H, 5.8; N, 4.2%), which were separated by chromatography on alumina in benzene (90%)-petroleum ether b.p. 40-60°C (10%). N.M.R. (CDCl\textsubscript{3}). 1.3 ppm (Triplet, \textit{JH}, -CH\textsubscript{3} of ethyl ester) 2.25 ppm. (Singlet, \textit{JH}, -CH\textsubscript{3} of pyrrole), 2.55 ppm. (Singlet, \textit{JH}, -CH\textsubscript{3} of methyl ester), 4.25 ppm. (Quartet, \textit{JH}, -CH\textsubscript{2} of ethyl ester), 6.5-8.0 ppm. (Complex multiplet, \textit{JH}, phenyl protons), 12.1 ppm. (Singlet, 1H, NH).

2-Aminothiophenol and 2,4-dimethyl-3-ethoxycarbonylpyrrole gave di(2-aminophenyl) disulphide (27%), buff needles, m.p. 92-93°C (lit. m.p. 93°C)\textsuperscript{47} and 2'-aminophenyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulphone (21) (60%) colourless needles from ethanol-water, m.p. 133-134°C, (Found C, 62.3; H, 6.5; N, 9.7%. C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2} requires C, 62.1; H, 6.3; N, 9.7%) which were separated by chromatography on silicic acid in chloroform (80%)-benzene (20%).

Thiophenol and 3,5-dimethyl-2-ethoxyacarbonylpyrrole gave diamphenyl disulphide (20%), colourless needles, m.p. 50-61°C (lit. m.p. 61.5°C)\textsuperscript{13} and phenyl 3,5-dimethyl-2-ethoxycarbonyl-4-pyrrolyl sulphone\textsuperscript{23} (11%), colourless needles from ethanol-water m.p. 155-157°C (lit. m.p. 157°C)\textsuperscript{3} which were separated by chromatography on silicic acid in benzene.
Thiophenol and 2,5-dimethyl-3-ethoxycarbonylpyrrole gave
diphenyl disulphide (5%), m.p. 59-61°C (lit. m.p. 61.5°C),43 and
phenyl 2,5-dimethyl-3-ethoxycarbonyl-4-pyrrolyl sulphone (25) (9%),
colourless prisms, m.p. 142-143°C (lit. m.p. 115°C) from ethanol-water,
which were separated by chromatography on silicic acid in chloroform.

N.M.R. (DMSO-D$_6$). 1.0 ppm (Triplet, 3H, -CH$_3$ of ethyl ester),
2.1 ppm (Singlet, 3H, -CH$_3$ of pyrrole), 2.45 ppm (Singlet, 3H, -CH$_3$
of pyrrole), 4.0 ppm (Quartet, 2H, -CH$_2$ of ethyl ester), 6.8-7.3 ppm
(Complex multiplet, 5H, phenyl protons), 12.2 ppm (Singlet, 1H, NH).

Thiophenol and 2,4-dimethyl-3-acetylpyrrole, gave diphenyl
disulphide (8%), m.p. 59-61°C (lit. m.p. 61.5°C) and phenyl 2,4-dimethyl-
3-acetyl-5-pyrrolyl sulphone (23) (8%), colourless needles from ethanol-
water, m.p. 135-140°C, (Found C, 68.5; H, 6.1; N, 5.5. C$_{14}$H$_{15}$N$_2$S requires C, 68.5; H, 6.2; N, 5.7%) which were separated by chromatography
on silicic acid in chloroform.

2-Aminothiophenol and 2,5-dimethyl-3-ethoxycarbonylpyrrole gave
2'-aminothienyl 2,5-dimethyl-3-ethoxycarbonyl-4-pyrrolyl sulphon (26) (8%),
colourless prisms from ethanol-water, m.p. 155-157°C (Found C, 61.3; H, 6.4;
N, 9.6. C$_{15}$H$_{13}$N$_2$S requires C, 62.1; H, 6.3; N, 9.7%). N.M.R. (Acetone-d$_6$)
1.2 ppm (Triplet, 3H, -CH$_3$ of ethyl ester), 2.2 ppm (Singlet, 3H, -CH$_3$ of
pyrrole), 3.45 ppm (Singlet, 3H, -CH$_3$ of pyrrole), 3.2 ppm (Singlet, 2H, NH$_2$),
4.15 ppm (Quartet, 2H, -CH$_2$- of ethyl ester), 4.8 ppm (Singlet broad band,
1H, NH), 6.2-7.1 ppm (Complex multiplet, 1H, phenyl protons).

A stirred solution of 2-aminothiophenol (20 m.mole) and 2,5-dimethyl-
pyrrole in 50% aqueous ethanol (50 ml) at 5°C in an ice bath was treated
dropwise with stirring, with a solution of IN iodine-potassium iodide
reagent (<40 ml) until the iodine colour persisted. After stirring for
one hour at room temperature, the solution was diluted with water (100 ml).
The product was collected, dried and purified by crystallisation from ethanol-water giving 2,5-dimethyl-3,4-di-(2'-aminophenylthio) pyrrole (31) (61%), buff prisms, m.p. 135-137°C. (Found C, 63.0; H, 5.7; N, 12.1. C₁₈H₁₇N₃S₂ requires C, 63.3; H, 5.6; N, 12.3%).

Similarly 2-methoxycarbonyl thiophenol and 2,5-dimethylpyrrole gave 2'-methoxycarbonyl 2,5-dimethyl-3-pyrrolyl sulphide (32) (92%), colourless needles, m.p. 112-114°C. (Found C, 64.0; H, 5.6; N, 5.3. C₁₄H₁₅NO₂S requires C, 64.4; H, 5.5; N, 5.1%). N.M.R. (CDCl₃). 2.1 ppm. (Singlet, 3H, -CH₂), 2.2 ppm. (Singlet, 3H, -CH₃), 3.9 ppm. (Singlet, 3H, -CH₃ of methyl ester), 5.8 ppm. (1H, β-H of pyrrole), 6.8-80 ppm. (Complex multiplet, 1H, phenyl protons) 8.5 ppm (1H, NH).

L-Aminothiophenol and pyrrole gave di(L-aminophenyl)disulphide (51%), m.p. 71-73°C (lit. m.p. 76-77°C) and L'-aminophenyl 2-pyrrolyl sulphide (30) (26%), colourless prisms from ethanol-water, m.p. 92-93°C, (Found C, 63.0; H, 5.5; N, 14.63. C₁₀H₁₀N₂S requires C, 63.15; H, 5.3; N, 14.7%).

which were separated by chromatography on silicic acid in chloroform (90%) - acetone (10%).

2-Aminothiophenol and pyrrole gave 2'-aminophenyl 2-pyrrolyl sulphide (35) (75%), pink plates from ethanol-water, m.p. 76-77°C, (Found C, 63.1; H, 5.4; N, 14.5. C₁₀H₁₀N₂S requires C, 63.2; H, 5.3; N, 14.7%), which were purified by chromatography on silicic acid in chloroform.

By the general procedure described on page 53, 2-aminothiophenol and indole gave 3-indolyl 2'-aminophenyl sulphide (39) (60%), colourless prisms, from ethanol-water, m.p. 93-95°C, (Found C, 70.0; H, 5.2; N, 12.0. C₁₄H₁₂N₂S requires C, 70.0; H, 5.0; N, 11.7%), which was separated from unreacted indole and di(2'-aminophenyl) disulphide by chromatography on silicic acid in chloroform.
4-Chlorothiophenol and indole gave 3-indolyl 4'-chlorophenyl sulphone (40) (83%), colourless needles, from ethanol-water, m.p. 134-135°C, (Found C, 64.4; H, 3.8; N, 5.0. C₁₄H₁₀ClNS requires C, 64.7; H, 3.9; N, 5.1%) which was separated from di-(4-chlorophenyl) disulphide by chromatography on silicic acid in benzene.

p-Thiocresol and indole gave 3-indolyl p-tolyl sulphone (42) (8%) , colourless prisms from ethanol-water, m.p. 128-129°C, (Found C, 74.0; H, 5.4; N, 5.0. C₁₅H₁₃NS requires C, 75.3; H, 5.5; N, 5.3%) which was purified by chromatography on silicic acid with benzene (50%) - chloroform (50%) as eluent.

m-Thiocresol and indole gave 3-indolyl m-tolyl sulphone (44) (62%), colourless needles from ethanol-water, m.p. 115-117°C (Found C, 75.0; H, 5.1; N, 11.6. C₁₄H₉₂N₂S requires C, 76.0; H, 5.0; N, 11.7%).

4-Aminothiophenol and indole gave 3-indolyl 4'-aminophenyl sulphone (45) (78%), pink prisms, from ethanol-water, m.p. 124-125°C (Found C, 70.2; H, 5.1; N, 11.6. C₁₄H₁₂₂N₂₂S₂ requires C, 70.0; H, 5.0; N, 11.7%).

Pentafluorothiophenol and indole gave 3-indolyl pentafluorophenyl sulphone (46) (76%), buff prisms, from ethanol-water, m.p. 86-88°C (Found C, 53.1; H, 1.7; N, 4.0. C₁₃H₆F₅NS requires C, 53.3; H, 1.9; N, 4.1%).

1-Methyl-2-mercaptothiazole and indole gave 2-(3'-indolylthio)-1-methylthiazole (48) (81%), colourless needles from ethanol-water, m.p. 163-165°C (Found C, 58.3; H, 4.4; N, 11.0. C₁₃H₁₀N₂S₂ requires C, 58.5; H, 4.1; N, 11.3%).

2-Methyl-5-mercaptotriazole and indole gave 2-Methyl-5-(3'-indolylthio)triazole (50) (82%), colourless needles, from ethanol-water, m.p. 224-225°C (Found C, 57.2; H, 4.1; N, 24.5. C₁₁H₁₀N₄S requires C, 57.4; H, 4.4; N, 24.3%).
Mechanistic Studies.

1. 2,4-Dimethyl-3-ethoxycarbonyl-5-iodo[pyrrole] and thiophenol.
   a) A solution of 2,4-dimethyl-3-ethoxycarbonyl-5-iodo[pyrrole] (1 m. mole) and thiophenol (1 m. mole) in 50% aqueous ethanol was stirred for 30 minutes. The solution was poured into water and lead acetate added. The solid lead salt of thiophenol (63%) was filtered off. The solution was extracted with ether, the ether dried and removed. Thin layer chromatography showed no phenyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulphide. Chromatography on silicic acid with chloroform as eluent gave diphényl disulphide (30%) and a mixture of 2,4-dimethyl-3-ethoxycarbonyl-5-iodopyrrole (60%) and 2,4-dimethyl-3-ethoxycarbonylnpyrrole (35%), the quantities of each present being established by N.M.R.
   b) When the reactants were refluxed for 15 minutes, the product obtained was identified as phenyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulphide (3, X=H) (60%), m.p. 103-110°C, mixed m.p. with a sample prepared by the oxidation of thiophenol in the presence of 2,4-dimethyl-3-ethoxycarbonyln pyrrole 103-110°C.
   c) The above reactants were refluxed for twelve hours. Phenyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulphide (3, X=H) (90%), m.p. 103-110°C was obtained.

2. A solution of 2,4-dimethyl-3-ethoxycarbonyl-5-iodo[pyrrole] (5 m. mole), thiophenol (5 m. mole) and concentrated sulphuric acid (5 m. mole) was stirred at room temperature for three hours. The solution was poured into water, and the solid filtered. Chromatography on silicic acid gave phenyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulphide (3, X=H), (62%), m.p. 103-110°C. lit. m.p. 111°C.
3. Reaction of S-(2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl) thioacetate with iodine/hydriodic acid in the presence of 2,4-dimethyl-3-ethoxycarbonylpyrrole.

a) A solution of 2,4-dimethyl-3-ethoxycarbonylpyrrole (5 m.mole), S-(2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl) thioacetate (64) (5 m.mole), hydriodic acid (5 m.mole) and iodine (5 m.mole) in ethanol water (30 ml) was stirred for 30 minutes and poured into water (150 ml). Solid sodium metabisulphite was added to remove unreacted iodine. The solution was extracted with ether, the ether dried and removed. Chromatography on silicic acid with chloroform as eluent gave di-(2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl) sulphide (5%), m.p. 107-108°C, mixed m.p. with di(2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl) sulphide22 109-200°C; mixed m.p. with di(2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl)disulphide22 173-175°C.

The mass spectrum shows a molecular ion at m/e 364.

b) The above reaction was repeated by refluxing the reactants for 30 minutes. Chromatography gave di(2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl) sulphide m.p. 104-106°C, supported by mixed melting points and mass spectra.
Pyrrolyl Alkyl Sulphides.

By the general procedure described above for pyrrolyl aryl sulphides, benzyl mercaptan and 2,4-dimethyl-3-ethoxycarbonylpyrrole gave dibenzyl disulphide (30%) m.p. 71-73°C (lit. m.p. 71-72°C) and benzyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulphide (58) (17%), pale pink plates from ethanol-water, m.p. 81-86°C, (Found C, 66.0; H, 6.7; S, 11.0.

C\(_{16}\)H\(_{19}\)NO\(_{3}\)S requires C, 66.3; H, 6.6; S, 11.1%), which were separated by chromatography on alumina in benzene (70%)-petroleum ether b.p. 10-60°C (30%).

Oxidation of methyl thioglycollate in the presence of 2,4-dimethyl-3-ethoxycarbonylpyrrole as described in the general procedure gave a crude product which could not be purified satisfactorily by chromatography. This product was dissolved in ethanol, sodium hydroxide (11 m.mole) was added and the solution heated on a water bath for 15 minutes. The solution was extracted with ether to remove 2,4-dimethyl-3-ethoxycarbonylpyrrole, acidified and re-extracted. The ether was dried and removed giving S-(2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl) thioglycollic acid (63) (23%), pale pink prisms from benzene-petroleum ether b.p. 60-80°C, m.p. 123-124°C (Found C, 51.5; H, 5.0; N, 5.1. C\(_{11}\)H\(_{15}\)NO\(_{4}\)S requires C, 51.4; H, 5.0; N, 5.1%). H-N.M.R. (CDCl\(_3\)) 1.3 ppm (Triplet, 3H, -CH\(_3\) of methyl ester), 2.3 ppm (Singlet, 3H, -CH\(_3\) of pyrrole), 3.4 ppm (Singlet, 3H, -CH\(_3\) of pyrrole) 3.3 ppm (Singlet, 2H, -CH\(_2\) attached to sulphur), 4.2 ppm (Quartet, 2H, ethyl ester) 9.55, 11.3 ppm (Singlets, 1H each, NH and OH). The acid was esterified by dissolving in methanol saturated with hydrogen chloride, stirring for twelve hours at room temperature. The solution was poured into water and extracted with ether. The ether was dried and removed giving methyl S-(2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl) thioglycollate (60), colourless needles from ethanol-water, m.p. 63-65°C. (Found C, 53.0; H, 6.4; S, 11.4.

C\(_{12}\)H\(_{17}\)NO\(_{4}\)S requires C, 53.2; H, 6.3; S, 11.8%).
Thiolacetic acid and 2,4-dimethyl-3-ethoxycarbonylpyrrole gave 

\[
di(2,4\text{-dimethyl-3-ethoxycarbonyl-5-pyrrolyl}) \text{ sulphide (6)} (57\%),
\]

colourless needles, m.p. 107-108°C (lit. m.p. 107°C)\(^3\). The mass spectrum shows a molecular ion at m/e 364 (base peak). The mixed m.p. with an authentic sample\(^22\) was 196-197°C. The mixed m.p. with an authentic sample of 

\[
di(2,4\text{-dimethyl-3-ethoxycarbonyl-5-pyrrolyl}) \text{ disulphide}\]

was 175-176°C.
Cyclisations and Attempted Cyclisations.

1. Cyclisation of 2'-methoxycarbonylphenyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulhide (19). Sodium hydride (0.2 g, 50% suspension in mineral oil) was washed three times with dry benzene, and suspended in benzene (20 ml).

To the resulting suspension was added 2'-methoxycarbonylphenyl 2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulhide (1.0 g). The solution was refluxed for one hour, and washed with water. The benzene was dried and removed. Chromatography on silicic acid with chloroform as eluent gave 2',4'-dimethyl-3'-ethoxycarbonyl-5'-pyrrole [2,3]benzo [3,4] -2,3-dihydro-1H-1,3-thiazin-4-one (69), (78%) fluorescent yellow needles from ethanol-water, m.p. 103-109°C. (Found C, 63.9; H, 5.2; N, 4.5. C_{16}H_{15}NO_{3}S requires C, 63.8; H, 5.0; N, 4.6%)

N.M.R. (CDCl₃) 1.4 ppm (Triplet, 3H, -CH₃ of ethyl ester) 2.23 ppm (Singlet, 3H, β-CH₃ of pyrrole) 3.1 ppm (Singlet, 3H, α-CH₃), 4.4 ppm (Quartet, 2H, -CH₂- of ethyl ester), 7.1-7.7 ppm. (Multiplet, 4H, phenyl protons) U.V. λ = 213 μm (ε = 56,600), 235 μm (ε = 64,600), shoulder at 270 μm (ε = 14,230) 315 μm (ε = 2,800).

Mass spectrum. Base peak at m/e 301. Peaks at 273, loss of 29 (C₂H₅); at 256, loss of 15 (C₂H₅O); at 228, loss of 73 (C₂H₄CO₂).

2. Cyclisation of o-methoxycarbonylphenyl 2,5-dimethyl-3-pyrrolyl sulhide. o-Methoxycarbonylphenyl 2,5-dimethyl-3-pyrrolyl sulhide (32) (1 g) in polyphosphoric acid (10 g) was heated at 120°C for 15 minutes. The solution was allowed to cool and diluted with water. The yellow precipitate was filtered and washed with water. Crystallisation from ethanol-water gave benzo[b]2',5',6'-dimethylpyrrolo [3', 4'-] 5,6-dihydro-1H-thiopyran-4-one (70) (65%), yellow prisms, m.p. 211-216°C with decomposition. (Found C, 67.6%; H, 4.9; N, 6.0; C₁₂H₁₃NO₃S requires C, 68.1; H, 4.3; N, 6.1%).
N.M.R. \((\text{DMSO-d}_6)\) 2.2 ppm. (Singlet, 3H, \(-\text{CH}_3\) of nyrrole), 2.65 ppm
(Singlet, 3H, \(-\text{CH}_3\) of nyrrole), 7.3-8.1 ppm (Multiplet, 4H, phenyl protons)
11.8 ppm. (Singlet, 1H, NH).

U.V. \(\lambda = 234 \text{ m}\mu (\epsilon = 12,370), 253 \text{ m}\mu (13,330), 270 \text{ m}\mu (7,150), 280 \text{ m}\mu (6,870),
314 \text{ m}\mu (1,030), 354 \text{ m}\mu (1,710).\)

Mass spectrum: Base peak m/e 229.

3. **Cyclisation of phenyl 2,5-dimethyl-3-ethoxycarbonyl-4-nyrrolyl sulphide**

Phenyl 2,4-dimethyl-3-ethoxycarbonyl-5-nyrrolyl sulphide \((15)\) in polyphosphoric acid \((10 \text{ g})\) was heated in an oil bath at 120°C for fifteen minutes. The solution was cooled to 60°C and diluted with water. The yellow solid was filtered off. Crystallisation from ethanol-water gave benzo[b]1,5,2'-
dimethylnyrrolo[2',1'-e]5,6-dihydro-4H-thiopyran-4-one \((70)\) \((5.4\%),\) yellow
prisms, m.p. 214-216°C (with decomposition); mixed m.p. with sample prepared in previous experiment was undepressed.

4. **Pechmann cyclisation of \(\phi\)-aminophenyl 2,4-dimethyl-3-ethoxycarbonyl-
5-nyrrolyl sulphide** \((21).\)

a) Sodium nitrite \((0.3 \text{ g})\) was added to a solution of acetic acid \((3 \text{ ml})\) and
sulphuric acid \((2 \text{ ml})\) at 0°C. \(\phi\)-aminophenyl 2,4-dimethyl-3-ethoxycarbonyl-5-nyrrolyl sulphide \((1 \text{ g})\) in acetic acid \((30 \text{ ml})-
sulphuric acid \((7.5 \text{ ml})\) cooled to 0°C was added dropwise over 1.5 minutes.
The solution was stirred for 30 minutes, sulphamic acid \((0.1 \text{ g})\) added
and the solution was stirred a further 30 minutes. During this time
the copper sulphate pentahydrate \((1 \text{ g})\) in water \((20 \text{ ml})\) at 40°C
was treated with powdered zinc \((1.4 \text{ g})\). The precipitated copper was
washed by decantation with water and then stirred with 10% hydrochloric
acid until hydrogen evolution ceased. The copper was rinsed with acetic
acid and added in a moist condition to the solution of the diazonium salt.

After the addition of the copper catalyst the solution was stirred
for one hour in ice and two hours at room temperature.
The reaction mixture was then poured into ice water and basified with ammonia. The solution was extracted thoroughly with ether, the ether dried and removed. The resulting oil was chromatographed on silicic acid with chloroform as eluent but no identifiable products were obtained.

b) The experiment above was repeated but instead of decomposing the diazonium salt with copper, the reaction mixture was heated for one hour on a boiling water bath. Again an intractable black tar was obtained.

c) The reaction was repeated using 20% hydrochloric acid (20 ml) and acetic acid (75 ml) as solvent. However in this case the amine hydrochloride was formed and precipitated from solution. Treatment with base regenerated the starting material (identified by m.p. 133-135°C and mixed m.p. undepressed).

5. Pscchorr cyclisation of o-aminophenyl 2,5-dimethyl-3-ethoxycarbonyl-4-pyrrolyl sulphide (26).

The Pschorr cyclisation of o-aminophenyl 2,5-dimethyl-3-ethoxycarbonyl-4-pyrrolyl sulphide (1 g) was carried out in acetic acid/sulphuric acid mixture by the same procedure as described in (4a). Chromatography of the resulting oil on silicic acid with chloroform as eluent gave the de-amminated product phenyl 2,5-dimethyl-3-ethoxycarbonyl-5-pyrrolyl sulphide (75) (62%), m.p. 141-143°C (lit. m.p. 143°C)8 mixed m.p. with sample prepared by the oxidation of thiophenol in the presence of 2,5-dimethyl-3-ethoxycarbonylpyrrole was undepressed.

6. Cyclisation of o-aminophenyl 2,5-dimethyl-3-ethoxycarbonyl-4-pyrrolyl sulphide (26)

The amine (1 g) in polyphosphoric acid (10 g) was heated at 100°C for fifteen minutes. The solution was cooled and diluted with water. The solid was filtered off and crystallised from chloroform/petroleum ether b.p. 10-60°C to give 2,5-dimethylpyrrole\[3,1-\text{f}]benzo[b]1', 1'-thiazepin-5'-one (73), (35%)
buff prisms, m.p. 235°C (Found C, 64.0; H, 5.0; N, 11.6. \( \text{C}_{13}\text{H}_{12}\text{O}_{3} \) requires C, 65.0; H, 4.8; N, 11.5%).

H.H.R. (DMSO-d_6). 2.15 ppm (Singlet, 3H, -CH_3 of pyrrole), 2.3 ppm (Singlet, 3H, -CH_3 of pyrrole), 7.2 ppm (Complex multiplet, 1H, phenyl protons), 10.1 ppm (Broad singlet, 1H, NH of 7-membered ring), 11.3 ppm (Broad singlet, 1H, NH of pyrrole ring).

U.V. 230 m\( \mu \) (\( \varepsilon = 8,420 \)), 279 (3,510).

Mass spectrum. Base peak m/e 244. Peaks at 229 (loss of 15, CH_3), at 211 (loss of 33, SH).

7. De-amination of \( \alpha \)-aminophenyl 2,5-dimethyl-3-ethoxycarbonyl-4-yrrolyl sulphide (26).

\( \alpha \)-Aminophenyl 2,5-dimethyl-3-ethoxycarbonyl-4-yrrolyl sulphide (0.1 g) was refluxed in \( \alpha \)-dichlorobenzene (5 ml) for 1/2 hours. The solution was chromatographed on silicic acid with chloroform as eluent. The product obtained was \( \alpha \)-phenyl 2,5-dimethyl-3-ethoxycarbonyl-4-yrrolyl sulphide (25) (70%), m.p. 143°C (lit. m.p. 143°C). The mass spectrum showed a molecular ion at m/e = 275 which was the base peak.

8. Cyclisation of 3-(\( \alpha \),\( \alpha \)-dimethyl-5-ethoxycarbonyl-5-yrrolyl)-thiazolidin-5-one (31) (43%), buff prisms, m.p. 224-226°C from ethanol-water. (Found C, 55.4; H, 5.5; N, 5.9. \( \text{C}_{11}\text{H}_{13}\text{O}_{3} \) requires C, 55.2; H, 5.5; N, 5.8%).
H.M.R. (DMSO-d$_6$). 1.25 ppm (Triplet, 3H, -CH$_3$ of ethyl ester), 1.95 ppm (Singlet, 3H, -CH$_3$ of pyrrole), 2.6 ppm (Singlet, 3H, -CH$_3$ of pyrrole), 4.2 ppm (Quartet, 1H, -CH$_2$- of ethyl ester), 4.35 ppm (Singlet, 2H, -CH$_2$- of thiazolidine ring). U.V. $\lambda$ = 218 m$\mu$, ($\epsilon$ = 15,220), 238 m$\mu$ ($\epsilon$ = 13,520), 340 m$\mu$ ($\epsilon$ = 1,180).

Mass spectrum. Base peak m/e 239. Peaks at 210 (loss of 29, C$_2$H$_5$), 182 (loss of 23 from peak at 210, CO), 194 (loss of 45 from the molecular ion, C$_2$H$_7$O) and 166 (loss of 29 from peak at 194 (CO).

Cyclisation of (2,4-dimethyl-3-ethoxycarbonyl-5-pyrrolylthio) propionic acid (75).

The acid (0.5 g) in pyridine (5 ml) and acetic anhydride (0.75 ml) was refluxed for one hour. The solution was poured into water and extracted with chloroform. The chloroform was removed and the resulting oil was chromatographed on silicic acid in chloroform. The product obtained was 2,4-dimethyl-3-ethoxycarbonylpyrrollo[1,2-b]tetrahydro-1,3-thiazin-4-one (76) (15%), buff prisms from ethanol-water, m.p. 89-90°C. H.M.R. Acetone-d$_6$. 1.3 ppm (Triplet, 3H, -CH$_3$ of ethyl ester), 2.1 ppm (Singlet, 3H, -CH$_3$ of pyrrole), 2.75 ppm (Singlet, 3H, -CH$_3$ of pyrrole), 3.1 ppm (Singlet, 1H, -CH$_2$-CH$_2$-), 4.2 ppm (Quartet, 2H, -CH$_2$- of ethyl ester). The N.M.R. spectrum was also run in CDCl$_3$ and the 4 methylene protons, -CH$_2$-CH$_2$- again appeared as a singlet at 3.1 ppm.

Mass spectrum. Base peak m/e 253, peaks at 208 (loss of 45, C$_2$H$_5$O), 193 (loss of 55, C$_3$H$_7$O), 55 (loss of 158, C$_2$H$_{12}$O$_2$S) and 152 (loss of 16 from the ion at 198, C$_2$H$_5$OH).
Preparation of 3,3'-diindolyl disulphide (80).

3-Indolethiol (10 m.mole) was dissolved in ethanol and IN iodine/potassium iodide reagent (5 ml) was added. The solution was stirred for one hour and poured into water. The solid was filtered and crystallised from ethanol-water. 3,3'-Diindolyl disulphide (80) (95%) was obtained as yellow prisms, m.p. 213-220°C, (lit. m.p. 217°C).^10

3-Indolyl 2,4-dinitrophenyl sulphide (82).

A solution of 1-chloro-2,4-dinitrobenzene (10 m.mole), 3-Indolethiol (10 m.mole) and triethylamine (1 ml) in anhydrous benzene (40 ml) was stoppered and stirred overnight. The solution was filtered and the benzene removed. Chromatography of the resulting yellow oil gave 3-indolyl 2,4-dinitrophenyl sulphide (82), (91%), yellow needles, m.p. 176-178°C (lit. m.p. 175°C) from ethanol-water.

Preparation of Indolyl thioesters.

S-(3-Indolyl) isothiouronium iodide (10 m.mole) in water (100 ml) was heated to 80°C under butane. 10% Sodium hydroxide solution (20 ml) was added. After ten minutes benzoyl chloride (12.5 m.mole) was added and the solution stoppered and shaken until a solid separated. The solution was allowed to stand for one hour, the solid was filtered, washed and crystallised from ethanol-water giving S-(3-indolyl) thiobenzoate (81) (67%), yellow plates, m.p. 141-142°C. (Found C, 71.1; H, 4.3; N, 5.4. C_{15}H_{11}NOS requires C, 71.1; H, 4.4; N, 5.5%). N.M.R. (CDCl₃). 6.0 ppm (Doublet, 1H, 2H of indole ring), 7.0-7.6 ppm (Multiplet, 7H, phenyl protons), 8.0-8.3 ppm (2 protons, 2H's of phenyl ring adjacent to carbonyl). 8.7 ppm (Singlet, 1H, NH).
To a solution of 2-methoxybenzoyl chloride (10 m.mole) and triethylamine (3 ml) in benzene (20 ml) under butane was added 3-indolethioli (10 m.mole). The solution was allowed to stand for two hours, and the solid filtered off. The benzene was removed yielding a yellow solid, S-(3-indolyl) 2'-methoxythiobenzoate (87) (70%), colourless plates from ethanol-water, m.p. 128-129°C. (Found C, 67.7; H, 4.9. C_{16}H_{14}NO_2S requires C, 67.6; H, 5.0; N, 4.9%).

Similarly 4-nitrobenzoyl chloride and 3-indolethioli gave S-(3-indolyl) 4'-nitrothiobenzoate (88) (53%), yellow needles, m.p. 234-236°C from ethanol-water. (Found C, 60.1; N, 9.3; H, 3.4. C_{15}H_{10}NO_3S requires C, 60.4; H, 3.0; N, 9.7%).

Similarly 3,4-dichlorobenzoyl chloride and 3-indolethioli gave S-(3-indolyl) 3',4'-dichlorothiobenzoate (89) (80%), yellow plates, m.p. 193-195°C from ethanol-water. (Found C, 56.1; H, 2.8; N, 7.1. C_{15}H_{9}Cl_2NOS requires C, 56.4; H, 2.9; N, 7.0%).

S-(3-indolyl) thiaoacetate.

By the method of preparation of S-(3-indolyl) thiobenzoate, the isothiouronium salt (77) and acetic anhydride gave S-(3-indolyl) thiaoacetate (90) (77%), colourless prisms, m.p. 110-113°C. (Found C, 62.7; H, 4.7; N, 7.1. C_{10}H_{8}NOS requires C, 62.8; H, 4.8; N, 7.3%).

β-S-(3-Indolyl) thiopropionate.

To a solution of propionic anhydride (10 ml) under butane was added 3-indolethioli (10 m.mole). The solution was heated on a water bath for 15 minutes and poured into hot water to hydrolyse the anhydride. The solution was cooled and the solid filtered off and crystallised from ethanol-water giving β-S-(3-indolyl) thiopropionate (91) (65%), colourless prisms, m.p. 70-80°C. (Found C, 64.1; H, 5.5; N, 6.7. C_{11}H_{11}NO_3S requires C, 64.38; H, 5.4; N, 6.3%).
Similarly butyric anhydride (10 ml) and 3-indolethiol (10 m.mole) gave S-(3-indolyl) thiobutyrate (62) (94%), colourless prisms, m.p. 50-60°C, from ethanol-water. (Found C, 65.5; H, 6.0; N, 6.4. \( \text{C}_{12} \text{H}_{13} \text{NOS} \) requires C, 65.7; H, 6.0; N, 6.5%).

n-Hexanoic anhydride (1.4 ml), 3-indolethiol (1 g) in pyridine (20 ml) under butane were heated on a water-bath for 30 minutes and poured into hot water. The solution was cooled and the solid filtered off, washed and crystallised from ethanol-water giving S-(3-indolyl) n-thiohexanoate (63) (48%), colourless prisms, m.p. 58-59°C. (Found C, 67.6; H, 6.9; N, 5.8. \( \text{C}_{14} \text{H}_{17} \text{NOS} \) requires C, 67.9; H, 6.9; N, 5.7%).

S-(3-indolyl) thioacetic acid.

A solution of S-(3-indolyl) isothiouronium iodide (10 m.mole) in water (100 ml) at 80°C was flushed with butane and 10% sodium hydroxide solution (15 ml) added. After 10 minutes chloroacetic acid (12 m.mole) was added. The solution was refluxed for five minutes, cooled and extracted with chloroform. The aqueous phase was acidified and re-extracted. This extract was then extracted with sodium bicarbonate solution which was acidified, and the product filtered, washed and dried. Crystallisation from chloroform-petroleum ether b.p. 40-60°C gave S-(3-indolyl) thioacetic acid (83) (62%), colourless prisms, m.p. 107-109°C (Found C, 57.7; H, 4.6; N, 6.7. \( \text{C}_{10} \text{H}_{20} \text{NOS} \) requires C, 58.0; H, 4.1; N, 6.7%).

\( \beta \)-S-(3-indolyl) thionoproionic acid.

In a similar manner, S-(3-indolyl) isothiouronium iodide and \( \beta \)-propiolactone gave \( \beta \)-S-(3-indolyl) thionoproionic acid (65) (60%), colourless prisms, from chloroform-petroleum ether b.p. 40-60°C, m.p. 134-136°C. (Found C, 50.8; H, 5.1; N, 6.3. \( \text{C}_{11} \text{H}_{11} \text{NOS} \) requires C, 50.7; H, 5.0; N, 6.3%).
2-S-(3-indolyl) thioacrylic acid.

Similarly S-(3-indolyl) isothiouronium iodide and propanic acid gave 2-S-(3-indolyl) thioacrylic acid (97) (65%), colourless prisms, m.p. 170-171°C with decomposition, from chloroform-petroleum ether b.p. 40-60°C. (Found C, 60.3; H, 4.4; N, 6.2. C_{11}H_{9}NO_{2}S requires C, 60.3; H, 4.2; N, 6.4%).

2-Indolyl 4'-cyanopropyl sulphide.

By the method used to prepare S-(3-indolyl) thiobenzoate, the isothiouronium salt (81) and 4'-bromobutryronitrile gave 2-Indolyl 4'-cyanopropyl sulphide (96) (65%), buff needles, m.p. 48-50°C, from ethanol-water. (Found C, 66.7; H, 5.6; N, 12.9. C_{12}H_{12}N_{2}S requires C, 66.7; H, 5.6; N, 13.0%).
To a solution of phenyl isocyanate (10 m. mole) and triethylamine (0.1 ml) in anhydrous benzene (50 ml) was added 3-indolethiol (10 m. mole). The solution was allowed to stand for thirty minutes and the benzene was removed. The resulting solid was S-(3'-indolyl) N-phenyl thiocarbamate (98) (93%), colourless prisms, from ethanol-water, m.p. 73-75°C. (Found C, 67·0; H, 4·8; N, 10·5. \( \text{C}_{15}\text{H}_{12}\text{N}_{2}\text{S} \) requires C, 67·2; H, 4·5; N, 10·4%).

Similarly cyclohexyl isothiocyanate and 3-indolethiol gave S-(3-indolyl) N-cyclohexyl dithiocarbamate (102) (90%), colourless prisms from ethanol-water, m.p. 137-138°C. (Found C, 61·8; H, 6·1; N, 9·6. \( \text{C}_{15}\text{H}_{18}\text{N}_{2}\text{S} \) requires C, 62·0; H, 6·3; N, 9·7%).

Similarly -tolylisocyanate and 3-indolethiol gave S-(3'-indolyl) N-4-tolylthiocarbamate (101) (86%), colourless needles from ethanol-water, m.p. 173-174°C. (Found C, 68·1; H, 5·3; N, 9·7. \( \text{C}_{16}\text{H}_{14}\text{N}_{2}\text{S} \) requires C, 68·1; H, 5·0; N, 9·9%).

S-(3-Indolyl) isothiouronium iodide (10 m. mole) was dissolved in water at 80°C under butane. Sodium hydroxide solution (10%, 15 ml) was added. After ten minutes the solution was neutralized with acetic acid and phenyl isothiocyanate (10 m. mole) added. The solution was shaken and the resulting yellow oil extracted with chloroform. The chloroform was dried (MgSO\(_4\)) and removed and the oil was purified by chromatography on silica gel in chloroform. Crystallisation from ethanol-water gave S-(3-indolyl) N-phenyl dithiocarbamate (101) (86%), colourless prisms, m.p. 197-198°C. (Found C, 63·6; H, 4·3; N, 9·6. \( \text{C}_{15}\text{H}_{12}\text{N}_{2}\text{S} \) requires C, 63·4; H, 4·3; N, 9·8%).
A solution of isothiocyanato-methane (10 m.mole) and 3-indolethiol (10 m.mole) in pyridine (20 ml) under butane was heated on a water bath for one hour. The solution was poured into water, acidified and extracted with chloroform. The chloroform was removed and the solid obtained was S-(3-indoly) N-methyl dithiocarbamate (103) (90%), colourless prisms from ethanol-water, m.p. 140-151°C. (Found C, 54.2; H, 4.5; N, 12.4. \( \text{C}_{10}\text{H}_{10}\text{N}_2\text{S}_2 \) requires C, 54.1; H, 4.5; N, 12.6%).

Similarly p-chlorophenyl isocyanate and 3-indolethiol gave S-(3-indoly) N-p-chlorophenyl thiocarbamate (100) (65%), colourless prisms from ethanol-water, m.p. 156-158°C. (Found C, 59.2; H, 3.7; N, 9.1. \( \text{C}_{15}\text{H}_{11}\text{ClN}_2\text{S} \) requires C, 59.5; H, 3.7; N, 9.3%).
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PART II. Application of the Pschorr Reaction to the Synthesis of Heterocycles based on the Pyrrole Ring System.
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INTRODUCTION.

The synthesis of compounds related to known antibiotics, fungicides and herbicides, may produce compounds with high activity in these fields, as well as being of interest in the study of structure-activity relationships.

The important mitomycin antibiotics have the aziridinopyrrolo-(1,2-a)indoloquinone structure of mitomycin C (1).

Patrick and co-workers\(^1\) have found that the related indoloquinone (2) retains the high antibacterial activity of the parent antibiotics (1) while the deaziridinopyrroloindoloquinone (3) retains a significant degree of antibacterial activity.

An approach by Mazzolo and workers\(^2\) to the synthesis of mitomycin antibiotics was envisaged by using 9-H-pyrrolo(1,2-a) indole as a basis for further work.

The work described herein is concerned with the possibility of employing the Pschorr reaction in the synthesis of pyrrolo(1,2-a) indoles (4) and pyrrolo(1,2-a) quinoxalines (5).

The Pschorr reaction is an intramolecular cyclisation reaction of a diazonium salt under acid conditions, usually effected in the presence of copper powder.

Pschorr\(^3\) reacted the diazonium salt derived from trans-2-\(\alpha\)-phenylcinnamic acid (6) to obtain phenanthrine-9-carboxylic acid (7). Although Pschorr was not the first\(^4\) to use the reaction, he was the first to synthesise a large number of substituted ring structures in which the position of the substituents were known.
Image 1

Image 2

Image 3
The synthesis of 1-alkan-1-one 10-carboxylic acid amides was accomplished by the reaction of 2-aminobenzyl alcohol with formic acid and sodium formate. The compound was purified by column chromatography and recrystallization from ethanol.

Reactions:

- Reaction (4) with compound (5)
- Reaction (6) with compound (7)
- Reaction (8) with compound (9-11)

![Chemical Structures](image)

(4)
(5)
(6)
(7)
(8)
(9-11)

(9) $X = O^6$
(10) $X = S^7$
(11) $X = NCH_3^8$
The synthesis of heterocycles by the Pschorr reaction is well established. The reaction has been carried out with compounds having a number of different types of bridging atoms (9-11).

The earliest application of the Pschorr reaction to phenanthridone synthesis was reported by Pictet and Gonset with the formation of N-methylphenanthridone (13) from o-amino-N-methylbenzanilide (12).

Hey and Heacock investigated the scope and limitations of the reaction in the formation of substituted phenanthridones. The highest yield of N-methylphenanthridone (13) from (12) was 53%. Lower yields were obtained from the substituted phenylenediamine (14) and a further complication arose from its tendency to form the benzimidazole (15).

It was found that the N-alkyl group of the compound (12) was necessary to prevent formation of a triazole on diazotisation.

Huppatz and Sasse utilized the Pschorr reaction in a new synthesis of phenanthridines (17) from N-substituted N-benzyl-α-phenylenediamines (16). A blocking group (N-methyl, N-benzenesulphonyl or N-methanesulphonyl) was again necessary to prevent the formation of the benzotriazole (13).

Unequivocal syntheses of 7-bromophenanthridine and 9-bromophenanthridine were carried out by the Pschorr reaction from suitably substituted starting materials.

There are two separate instances, in which intramolecular cyclisation onto a nitrogen atom are known to occur. If a secondary amine (19) is in a position to form a five or six membered ring, the coupling of the diazonium salt is preferred to the loss of nitrogen.
A similar intramolecular reaction, in this case involving prior loss of $\text{N}_2$, was reported by Hey and co-workers. The formation of 5-methylpyrido (1,2-a)benzimidazolium chloride (22) from 2-amino-2'-methyl-2'-pyridylaniline (21) occurred as a side reaction in the synthesis of ind-$\text{H}$-methyl-$\alpha$-carboline (23).

It was hoped that the use of suitably substituted pyrrolic intermediates in Pechmann cyclisation reactions would prove an alternative route to the pyrrolo (1,2-a)indole (4) and pyrrolo(1,2-a)quinoxaline (5) ring systems.
In an alternative procedure (20), the pyrrole (19) was employed in the nitration of dimethylamine to obtain the pyrrole (20) and subsequent reduction of the pyrrole using metallic sodium to generate the pyrrole (21) with an additional methyl group. The failure of the pyrrole (21) to react with acetic anhydride was noted, indicating a possible steric hindrance or other factors. In contrast, the pyrrole (23) with an additional methyl group exhibited reactivity with acetic anhydride, suggesting a structural change affecting reactivity. Further experiments were required to determine the exact mechanism of reaction.
CHAPTER I.

The Attempted Synthesis of the Pyrrolo(1,2-a)indole Ring System.

The Pschorr cyclisation reaction first considered, was an attempt to form a $\text{C-N}$ bond onto the nitrogen of the pyrrole ring of the amine (25) to give the pyrrolo (1,2-a)indol-9-one (26).

In a preliminary investigation of the initial condensation reaction, 2-benzoyl-3,5-dimethyl-4-ethoxycarbonylpyrrole (27) was obtained in reasonable yield from the Friedel-Crafts reaction of benzoyl chloride and 2,4-dimethyl-3-ethoxycarbonylpyrrole (28). In an alternative procedure, $\text{N,N}$-dimethylbenzamide was reacted with the pyrrole (23) and phosphoryl chloride under similar conditions to those described by Anthony for the extension of the Vilsmeier-Haak reaction of $\text{N,N}$-dimethyl arylamides. The product obtained was again the benzoylpyrrole (27).

In order to prepare the nitro compound (24), the Friedel-Crafts reaction of $\text{O}$-nitrobenzoyl chloride and the pyrrole (23) was attempted but only intractable oils resulted. $\text{O}$-Nitro-$\text{N,N}$-dimethylbenzamide, the pyrrole (23) and phosphoryl chloride were reacted under milder Vilsmeier-Haak conditions than those used for the formation of the benzoylpyrrole (27) but again only black oils were obtained.

The failure of the condensation reaction in the case of the $\text{O}$-nitro compounds may be due to the possible competing reactions of the nitro group.

In a further attempt to form 2-$\text{(O}$-nitrobenzoyl-3,5-dimethyl-$\text{L}$-ethoxycarbonylpyrrole (24), the pyrrole (23) and $\text{O}$-nitrobenzaldehyde were stirred in ethanol containing hydrochloric acid.
\[ (24) \quad X = O \]

\[ (25) \quad X = H \]

\[ (26) \]

\[ (27) \]

\[ (28) \]
The product obtained was the dipyrromethane (2°). This compound crystallised out of the reaction mixture quantitatively and was found to be only sparingly soluble in solvents suitable for hydrogenation of the nitro group. The N.M.R. spectrum of the compound shows the presence of the two pyrrole rings and the -CH- of the pyrrole bridge (6.24 ppm).

By replacing the pyrromethane bridge hydrogen (2°) by a methyl group, it was hoped that the resulting compound might be more soluble in suitable hydrogenating solvents. \( \text{\textsuperscript{2}} \text{Nitroacetophenone} \) \( ^{20} \) and the pyrrole (23) were therefore subjected to the conditions for the preparation of the dipyrromethane (2°), but no reaction occurred. However in ethylene dichloride with phosphoryl chloride as condensing agent, a green-red dichroic oil which is believed to be the dichlorophosphate salt (30), was obtained. This on treatment with base yielded the yellow compound \( 1-(\text{\textsuperscript{2}} \text{nitrophenyl})-1-(3',5'-\text{dimethyl-4'ethoxycarbonyl-2'-pyrrolyl})- \) ethylene (31). The vinylic protons of this compound occurred in the N.M.R. spectrum as a doublet which was unchanged when the temperature was raised to 65°C. The structure (31) is supported by the work of Treibs and co-workers, who reported that pyrromethenes exist mainly in the conjugated form (32) except when both rings carry electron withdrawing substituents, in which case the predominant form (33) has an exocyclic methylene group. The nitro compound would be expected to exist in the form (31) due to the electron withdrawing effects of the ester and nitro groups.

Hydrogenation of the nitro compound (31) reduced both the ethylenic double bond and the nitro group, giving the amine (34). The methine proton occurs in the N.M.R. spectrum as a triplet and the methyl group of the bridge occurs as a doublet.
The amine (34) was diazotised in dilute hydrochloric acid solution with sodium nitrite. The diazonium salt solution was treated with copper powder, but the resulting dark oil yielded no isolable products.

An unsuccessful attempt was made to prepare the nitro compound \( (35) \) from 3,4-dimethyl-2-ethoxycarbonylpyrrole\(^{22,27}(36) \) and 2-nitroacetophenone, but condensation failed under the reaction conditions used for the preparation of the ethylene (31).

In view of the unsuccessful attempts described above, this approach to the pyrrolo (1,2-\(a \)) indole ring was abandoned.
CHAPTER II.

The Attempted Synthesis of the Pyrrolo(1,2-a)Quinoxaline Ring System.

The Pschorr cyclisation reaction of a suitably substituted pyrrole (e.g. 37) was considered to be a feasible and efficient method for the synthesis of the pyrrolo(1,2-a)quinoxaline ring system (5). Formation of a C-N bond by intramolecular cyclisation onto a pyridine nitrogen has been reported previously (c.f. page 86, compound 22). It was hoped that, by fully substituting the pyrrole amine of the amine precursor (37), the decomposition of the diazonium salt would result in C-N bond formation with elimination of nitrogen.

The initial experiments were carried out with the amine (37). 2,4-Diethoxycarbonyl-3-methyl-5-chloromethylpyrrole (40) and N-methanesulphonyl-2-nitroaniline (41) were condensed under basic conditions to form the nitro-compound (42) which on reduction with tin and hydrochloric acid gave the amine (37). The amine was first recrystallised from benzene-petroleum ether and had a melting point of 130-132°C. The N.M.R. spectrum showed that one mole of benzene was incorporated into the crystal structure. Recrystallisation from ethanol removed the benzene and the melting point increased to 150-152°C.

The acetyl pyrrole (46) was converted to the chloromethyl derivative (47) which was condensed with N-methanesulphonyl o-nitroaniline (41) to give the nitro-compound (48). Reduction of (48) with tin and hydrochloric acid gave the amine (38).

The chloromethyl derivative (48) of 2,3,4-trimethyl-5-ethoxycarbonylpyrrole (27) was prepared by the method for chloromethyl-cryptopyrrole (46) condensed with N-methanesulphonyl o-nitroaniline in benzene-triethylamine solution, and the resulting nitro-compound (45) was converted to the amine (39) by hydrogenation at atmospheric temperature and pressure using palladium on charcoal as catalyst. The tin and hydrochloric acid method failed to give the desired amine.
(37) $R = \text{CO}_2\text{Et}$

(38) $R = \text{COCH}_3$

(39) $R = \text{CH}_3$

(40)

(41)

(42) $R = \text{CO}_2\text{Et}$

(43) $R = \text{COCH}_3$

(44) $R = \text{CH}_3$
The γ-phenylpropionic group was incorporated into the acyclic compound (e.g., 20) as a protecting group to restrict the formation of the final product (27) by attack of the diisocyanate only. In this case, the product is the desired compound, and the acyclic amide may be selectively cleaved from the cyclic amide (20) by reaction with hydroxylamine, with a small quantity of hydrochloric acid affecting the complete solution of the amide and subsequent thermal decomposition of the diisocyanate amide.

Thermal decompositions of the acyclic amides were carried out in vacuo, producing 1,2,4-triazole (49) in 60% yield. The compound was used without further purification, indicating no molecular weight at 7]. The compound was used without further purification, indicating the presence of no acidic hydrogen. The making reaction (Table 1) showed the presence of a new product, 52, failed to show one signal corresponding to the pyrazole ring of either amide (48).

The above data suggested that the product of thermal decomposition was the phenylpyrazine (49) which could only be formed by attack at the position of attachment of the acyclic group to the pyrazine ring. Subsequent reactions of this product were followed by elimination of the ethylidyne group and ring opening to the acyclic amide, as in Scheme 1. A similar reaction has been reported by Suppels and Sanner, as a cine reaction in the case of the 3-benzyl γ-phenylpropionic amides.

For convenience the reacting centre is represented above, to indicate that a cation or radical may be involved.
The N-methanesulphonyl group was incorporated into the amines (e.g. 37) as a protecting group to prevent the formation of the triazine\textsuperscript{10} (49) by attack of the diazonium salt.

Cyclisation of the amine (37) was attempted by two methods commonly used to effect cyclisation of diazonium salts:

\textbf{a)} diazotisation of the amine in dilute hydrochloric acid (in this case, with a small quantity of acetic acid to effect complete solution of the amine) and subsequent thermal decomposition of the diazonium salt,

\textbf{b)} diazotisation of the amine in the same medium followed by decomposition of the diazonium salt with copper powder.

Thermal decomposition of the amine (37) gave a product, m.p. 186-187\textsuperscript{0} in 63\% yield. The compound was shown by analysis to have the molecular formula \(C_{18}H_{22}N_{2}O_{6}\) and the mass spectrum indicated a molecular weight of 394. The compound was soluble in sodium carbonate solution, indicating the presence of an acidic hydrogen. The N.M.R. spectrum (Table 1) showed the presence of two N-H groups, but failed to show any signal corresponding to the methylene group of the amine (33).

The above data suggested that the product of thermal decomposition was the phenylpyrrole (50) which could only be formed by attack at the position of attachment of the methylene group to the pyrrole ring. Subsequent breakdown of the spiro intermediate, followed by elimination of the methylene group, presumably as formaldehyde\textsuperscript{11} can be rationalized as in Scheme 1. A similar rearrangement was reported by Huppatz and Sasse\textsuperscript{11} as a side reaction in the case of the \(N\)-benzyl \(o\)-phenylenediamine derivatives.

For convenience the reactive centre is represented thus:*, to indicate that a cation or radical may be involved.
Scheme 1.

\[ R = \text{CO}_2\text{Et} \]
\[ R' = \text{CH}_3 \]
Scheme 211
However it is generally accepted that the thermal decomposition of diazonium salts involves carbonium ion intermediates\(^5\) (Scheme 1).

The copper-catalysed decomposition of the diazonium salt derived from the amine (37) gave a compound, m.p. 121-122.5\(^\circ\)C, in 81\% yield, together with a small amount of the phenylpyrrole (50). The product was shown to have the molecular formula \(\text{C}_{19}\text{H}_{22}\text{N}_{2}\text{O}_{6}\text{S}\) by elemental analysis and a molecular weight of 406 (mass spectrum).

Treatment of the product with hot concentrated hydrochloric acid afforded the phenylpyrrole (50) in almost quantitative yield. This facile conversion suggested that this compound, \(\text{C}_{19}\text{H}_{22}\text{N}_{2}\text{O}_{6}\text{S}\), was the spiroindoline (51), the precursor of the phenylpyrrole (50), formed by the thermal decomposition of the diazonium salt.

Support for the spiroindoline structure was provided by spectral data and the reactions of the compound. The infra-red spectrum showed no absorption in the N-H region, but absorption at 1710, and 1728 cm\(^{-1}\) (carbonyl groups, c.f. the amine (37) which exhibited a single broad band at 1670 cm\(^{-1}\)) and 1350 and 1150 cm\(^{-1}\) (the sulphone group) was observed. A band of medium intensity, which was not present in the parent amine occurred at 1507 cm\(^{-1}\).

Although C=N stretching frequencies occur over a wide range depending on environment, it is possible to assign this band to C=N absorption by analogy with the pyrrole (52) in which C=N absorption is reported\(^29\) to occur at 1588 cm\(^{-1}\).\(^31\)

The most significant feature of the N.M.R. spectrum (Table 1) is the upfield shift of the methylene signal with respect to the amine (37). This is consistent with the absence of the deshielding influence of the pyrrole ring on the methylene group. The bands in the ultraviolet spectrum (Table 2) were significantly lower in intensity than the corresponding maxima in the spectrum of the phenyl pyrrole (50), due to the lower degree of conjugation in the spiroindoline.
The reaction currently under study is similar to an earlier reaction described for the synthesis of tetrahydrocarbazole (51), a reaction which involves the cyclocondensation of 1-methylthiophene to an arylmagnesium halide in the presence of a base. The present authors have described a novel method for the synthesis of tetrahydrocarbazole (51), which involves the reaction of 1-methylthiophene with an arylmagnesium halide in the presence of a base.

In addition, the authors have also described the synthesis of tetrahydrocarbazole (52), which involves the reaction of 1-methylthiophene with an arylmagnesium halide in the presence of a base. The authors have also described the synthesis of tetrahydrocarbazole (53), which involves the reaction of 1-methylthiophene with an arylmagnesium halide in the presence of a base.

Similarly, the authors have described the synthesis of tetrahydrocarbazole (54), which involves the reaction of 1-methylthiophene with an arylmagnesium halide in the presence of a base. The authors have also described the synthesis of tetrahydrocarbazole (55), which involves the reaction of 1-methylthiophene with an arylmagnesium halide in the presence of a base.

Finally, the authors have described the synthesis of tetrahydrocarbazole (56), which involves the reaction of 1-methylthiophene with an arylmagnesium halide in the presence of a base.
The reaction described above is similar to an anomalous Pschorr reaction reported by Hey and his co-workers. They described the thermal decomposition of the diazoniium sulphate from 2-amino-4-ethylethyloxybenzanilide (53), a reaction which failed to give the expected cyclisation product (54). The compound isolated was identified as the spiroadienone (55).

In Pschorr cyclisations in which phenyl migrations have previously been described, the spirane intermediates are represented as either radical or cationic species (c.f. Scheme 2). However, in this case formation of the stable dienone system allowed isolation of the spiroadienone (55). Similarly the spiroindoline (51) was stabilised by formation of the 2-H-pyrrole system.

Hey found that the spiroadienone (55) underwent a dienone-phenol rearrangement to the N-ethylphenanthridone (56) when treated with 100% phosphoric acid at 170°C. Under much milder conditions the spiroindoline (51) underwent rearrangement when treated with 60% sulphuric acid, or 100% phosphoric acid. The product (58) obtained was an example of the previously unreported pyrrolo(1,2-c)quinazoline ring system.

The N.M.R. spectrum (Table 1) showed absorption due to the methylene protons at unusually low field (5.97 ppm). Although no examples of a similar grouping could be found in the literature, low field absorption may be expected because of the heavy deshielding of the methylene group in such a position. The ultraviolet spectrum (Table 2) was consistent with the increased conjugation of the compound (58), resulting from the enforced coplanarity of the system.
\[ R = \text{COOEt} \]
A plausible mechanism for the acid-catalysed reactions of the spiroindoline (51) involves the initial protonation of the 2H-pyrrole nitrogen (57). Under the anhydrous conditions of 100% phosphoric acid, the protonated intermediate undergoes an intramolecular rearrangement to form a C-N bond. When water is present, as in the case of hydrochloric acid, nucleophilic attack by water is considered to occur at the methylene group (59) followed by ring opening. The resulting hydroxymethyl compound (60) then decomposes further with the elimination of formaldehyde to give the final product, the phenylpyrrole (50).

When 60% sulphuric acid was used to effect the rearrangement a lower yield of the pyrrolo(1,2-c)quinazoline (58) was formed, due to the competing reaction of nucleophilic attack by water at the methylene group to form the phenylpyrrole.

More recent evidence that two mechanisms are responsible for the acid-catalysed reactions of the spiroindoline (51), was provided by the formation of ethanol and methanol "adducts". Analysis showed the addition of the elements of methanol and ethanol respectively, to the spiroindoline when the compound was heated in these solvents containing catalytic amounts of concentrated sulphuric acid. The infra-red absorption of the two products showed the appearance of a broad NH absorption at 3330 cm\(^{-1}\), while the C\(_N\) absorption (1597 cm\(^{-1}\)) of the spiroindoline was absent. The ultraviolet spectra (Table 2) were virtually identical to that of the phenylpyrrole (50) and hence the compounds were formulated as 2-(2'\(-\text{N-methanesulphonyl-N-methoxymethylaminophenyl})-3,5-diethoxycarbonyl-L-methylpyrrole (61A) and the corresponding ethoxy derivative (61B).

These structures were supported by the N.M.R. spectra of the compounds (Table 1) and confirmed by an independent synthesis of the methoxy derivative (61A). The phenylpyrrole (50) when treated in benzene with triethylamine and chloromethyl methyl ether, gave the methoxy compound (61A) in good yield.
\[ R = \text{CO}_2\text{Et} \]

(62)
It is probable that the ethers (61A) and 61B) are formed by a mechanism similar to that described for the hydrolytic fission of the spiroindoline (51) except that, in this case, the formation of the ether linkage renders the products isolable.

The diazonium salt of the corresponding acetyl amine (33) was prepared in dilute hydrochloric acid and was decomposed by the same two methods employed for the amine (37). The thermal decomposition of the amine yielded only black intractable tars, but on decomposition by copper powder, the product obtained in good yield was the spiroindoline (62). This structure was supported by the mass spectrum (molecular weight 376) and the N.M.R. spectrum (Table 1) which contains no exchangeable proton signals.

When the spiroindoline (62) was heated in 100% phosphoric acid, a mixture of compounds was obtained, and this reaction was not investigated further.

\[ \text{N-(3,4-Dimethyl-5-ethoxycarbonyl-2-pyrrolylmethyl)} \text{-2-phenyl} \text{enediamine (30) was diazotised and the diazonium salt decomposed with copper powder. However the resulting black oil yielded no identifiable products. It is thought that the N-CH}_2 \text{ bond in the molecule is very susceptible to cleavage in acid media, rendering Pschorr cyclisation of this compound impractical.} \]
### TABLE I. Nuclear Magnetic Resonance Spectral Data. (nm)

<table>
<thead>
<tr>
<th>Compound</th>
<th>NH</th>
<th>Aromatic 4 protons</th>
<th>- CH₂ -</th>
<th>- COOCH₂CH₃</th>
<th>- SO₂CH₃</th>
<th>- CH₃</th>
<th>- COOCH₂CH₃</th>
<th>Other Signals</th>
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<tr>
<td>37</td>
<td>11.4</td>
<td>6.3-7.2</td>
<td>5.12</td>
<td>4.33 (q)</td>
<td>3.05</td>
<td>2.53</td>
<td></td>
<td>(1.33(t))</td>
</tr>
<tr>
<td></td>
<td>~4.4</td>
<td></td>
<td>5.10</td>
<td>4.37 (q)</td>
<td></td>
<td></td>
<td></td>
<td>(1.38(t))</td>
</tr>
<tr>
<td>50</td>
<td>9.05*</td>
<td>7.18-7.7</td>
<td>-</td>
<td>4.10-4.20</td>
<td>2.80</td>
<td>2.60</td>
<td></td>
<td>(1.17(t))</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.30(t))</td>
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<tr>
<td>51</td>
<td>-</td>
<td>6.55-7.7</td>
<td>4.0-</td>
<td>4.7 (m)</td>
<td>3.05</td>
<td>2.60</td>
<td></td>
<td>(1.17(t))</td>
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<tr>
<td>58</td>
<td>-</td>
<td>7.2-3.1</td>
<td>5.97</td>
<td>4.32 (q)</td>
<td>2.50</td>
<td>2.30</td>
<td></td>
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<td>(1.30(t))</td>
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<tr>
<td>61A</td>
<td>0.05*</td>
<td>7.2-7.5</td>
<td>4.65</td>
<td>4.04 (q)</td>
<td>3.02</td>
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<td></td>
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<td>(1.33(t))</td>
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<td>6.8-7.4</td>
<td>5.32 (d)</td>
<td>4.31 (q)</td>
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<td>-</td>
<td>6.4-7.3</td>
<td>4.0-4.62 (m)</td>
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<td>3.05</td>
<td>2.55</td>
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(d) doublet  
(t) triplet  
(q) quartet  
(m) multiplet

* pyrrolic NH  
† broad band NH₂  
‡ an exchangeable proton NH in this region.
### Table 2.

**Ultraviolet Spectral Data**

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EXPERIMENTAL.

1. 2-Benzoyl-3,5-dimethyl-4-ethoxycarbonylpyrrole (27)

a) Friedel-Crafts Acylation Reaction.

2,4-Dimethyl-3-ethoxycarbonylpyrrole<sup>15,16,17</sup>(28) (1.67 g) and benzoyl chloride (1.4 g) in carbon disulfide (40 ml) were placed in a dry 100 ml 3-necked flask with a sealed stirrer, a reflux condenser and drying tube and a rubber tube attached to a flask containing aluminium chloride (1.33 g). The solution was cooled in an ice bath to 5°C. The aluminium chloride was added through the rubber tube in six portions over thirty minutes. The solution was brought to room temperature and treated with concentrated hydrochloric acid/ice mixture. The solution was extracted with ether. The combined ether extracts were dried (MgSO₄) and the ether removed, whereupon the resulting brown oil solidified. Crystallisation from ethanol gave yellow prisms of 2-benzoyl-3,5-dimethyl-4-ethoxycarbonylpyrrole (27), (70%), m.p. 105-107°C, lit. m.p. 105-106°C<sup>33</sup>.

b) Vilsmeier-Haak Reaction.

N,N-Dimethylbenzamide (1.5 g), 2,4-dimethyl-3-ethoxycarbonylpyrrole (1.67 g) and phosphoryl chloride (1.2 g) in ethylene dichloride (30 ml), were refluxed for thirty minutes. Sodium hydroxide solution (20 ml, 10%) was added and the solution refluxed for a further fifteen minutes. The organic layer was removed, dried (MgSO₄) and the solvent evaporated. The resulting brown oil solidified and gave on crystallisation from ethanol 2-benzoyl-3,5-dimethyl-4-ethoxycarbonylpyrrole (27), (75%), m.p. 107-109°C, identical with the sample obtained in (a) above.
2. Attempted preparation of 2-(o-nitrobenzoyl)-3,5-dimethyl-4-ethoxycarbonylpyrrole (24).

a) Friedel-Crafts Acylation Reaction.

2,4-Dimethyl-3-ethoxycarbonylpyrrole (1.67 g) and o-nitrobenzoyl chloride (1.85 g) in carbon disulphide (40 ml) were reacted as in (1a) above. An intractable black tar was obtained.

The Friedel-Crafts acylation was repeated using stannic chloride as the Lewis acid and ethylene dichloride as solvent. Again an intractable black tar resulted from the reaction.

b) Vilsmeier-Haak Reaction.

N,N-Dimethyl-o-nitrobenzamide (1.9 g) and phosphoryl chloride (1.2 g) in ethylene dichloride (20 ml) was cooled to 5°C.

2,4-Dimethyl-3-ethoxycarbonylpyrrole (1.67 g) in ethylene dichloride (10 ml) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. Sodium hydroxide (10 ml, 10%) was added. The organic layer was dried (MgSO₄) and the solvent removed. Again brown intractable oils only were obtained.

3. Reaction of 2,4-dimethyl-3-ethoxycarbonylpyrrole with o-nitrobenzaldehyde.

2,4-Dimethyl-3-ethoxycarbonylpyrrole (1.67 g) and o-nitrobenzaldehyde (0.75 g) were dissolved in ethanol (30 ml) at room temperature.

Concentrated hydrochloric acid (0.5 ml) was added to the stirred solution. A yellow precipitate of m (o-nitrophosphoryl)-3,3'-dithoxycarbonyl-2,2',4,4'-tetramethyl-dipyrrromethane (20) (95%) precipitated from the reaction mixture, m.p. 221-223°C. (Found: C, 64.6; H, 6.4; N, 8.8. C₂₆H₃₁N₃O₆ requires C, 64.8; H, 6.5; N, 8.7%). N.M.R. (CDCl₃/acetone) 1.3 ppm (triplet, 6H, 2x -CH₂CH₂CO₂) 2.0 ppm and 2.38 ppm (Each a singlet, 6H, 2x -CH₃ of pyrrole ring) 4.23 ppm (Quartet, 3H, -CO₂CH₂CH₃) 6.25 ppm (Singlet, 1H, CH) 7.0-8.0 ppm (Multiple t, 3H, phenyl protons) 8.7 ppm (1H, NH).
4. 2,4-Dimethyl-3-ethoxycarbonyl-4 Pyrrole and o-Nitroacetophenone.

a) o-Nitroacetophenone (0.83 g) and the pyrrole (1.67 g) were stirred for 48 hours in ethanol (30 ml) to which concentrated hydrochloric acid (0.5 ml) was added. Starting materials were recovered.

b) o-Nitroacetophenone (1.65 g), the pyrrole (1.67 g) and phosphoryl chloride (1.2 g) in ethylene dichloride were stirred overnight at room temperature. The green solution was washed with water, dried (MgSO₄) and the solvent removed. The red-green oil was treated with sodium hydroxide solution (20 ml, 10%). Yellow crystals of 1-(o-Nitrophenyl)-1-(3',5'-dimethyl-4'-ethoxycarbonyl-2'-pyrrolyl)-ethylene (31) (81%) were obtained which was crystallised from chloroform-petroleum ether (b.p. 40-60°C), m.p. 150-152°C. (Found: C, 64.9; H, 5.7; N, 8.6. C₁₇H₁₈O₄N₂ requires C, 64.6; H, 5.7; N, 8.9%).

N.M.R. (CDCl₃) 1.3 ppm (Triplet, 3H, -CH₃ of ethyl ester), 1.98 and 2.45 ppm (Each singlet, 3H, -CH₃ of pyrrole), 4.2 ppm (Quartet, 2H, -CH₂ of ethyl ester), 5.3 ppm (Doublet, 2H, ethylenic protons, peaks do not change at 65°C), 7.2-7.9 (Multiplet, 4H, phenyl protons), 8.4 ppm (Singlet, 1H, NH).

5. Reduction of the nitro compound in (4) above.

1-(o-Nitrophenyl)-1-(3',5'-dimethyl-4'-ethoxycarbonyl-2'-pyrrolyl)-ethylene (31) (5 g) was dissolved in ethanol (50 ml) and palladium on charcoal catalyst (1 g) added. The hydrogenation was carried out at atmospheric temperature and pressure. At the end of the reduction, the solution was filtered and the solvent removed. Crystallisation from ethanol gave colourless needles of 1-(o-Aminophenyl)-1-(3',5'-dimethyl-4'-ethoxycarbonyl-2'-pyrrolyl)-ethane (3₄) (85%) m.p. 110-112°C.
(Found: C, 71.2; H, 7.8; N, 9.6. $\text{C}_{17}\text{H}_{25}\text{N}_{2}\text{O}_{2}$ requires C, 71.3; H, 7.7; N, 9.8%).

N.M.R. (CDCl$_3$) 1.33 ppm (Triplet, 3H, -CH$_3$ of ethyl ester), 1.5 ppm (Doublet, 3H, -CH$_3$ of methylene bridge), 2.3 ppm (Broad singlet, 6H, 2X-CH$_3$ of nyrrole), 3.9-4.5 ppm (Multiplet, 3H, CH$_2$ of ethyl ester and CH of methylene bridge), 3.5 ppm (Singlet, 2H, exchangeable, -NH$_2$), 6.5-7.4 ppm (Multiplet, 4H, phenyl protons), 7.8 ppm (1H, NH).

6. Attempted cyclisation of 1-(o-aminophenyl)-1-(3',5'-dimethyl-4'-ethoxycarbonyl-2'-pyrrolyl)-ethane (3l).

The amine (2.5 g) was dissolved with heating in hydrochloric acid (100 ml, 10%). The solution was cooled to 0°C in an ice bath. Sodium nitrite (0.75 g, 30% excess) in water (10 ml) was added to the stirred solution over thirty minutes, the temperature being kept between 0° and 5°C. The solution was then stirred for one hour in an ice bath.

A solution of copper sulphate pentahydrate (7 g) in water (40 ml) at 40°C was treated with powdered zinc (2.5 g) with stirring.

The precipitated copper was washed with water, and then stirred with dilute hydrochloric acid (10%) until the evolution of hydrogen ceased. The copper was again washed and drained. The copper was added in a moist condition to the solution of the diazonium salt.

After the addition of the copper catalyst, the reaction mixture was stirred for one hour in the ice bath followed by one hour at room temperature. The reaction was completed by stirring the mixture for three hours while it was being kept at 40-50°C.

The mixture was poured onto ice and the solution basified with NH$_3$ (d.0.88). The mixture was thoroughly extracted with chloroform, the chloroform dried and removed to give a brown oil which contained no identifiable products.
7. Reaction of 2-ethoxycarbonyl-3,4-dimethylpyrrole and o-nitroacetophenone.

a) 2-Ethoxycarbonyl-3,4-dimethylpyrrole (36) (1.67 g), o-nitroacetophenone (1.5 g) and phosphoryl chloride (1.2 g) were reacted under the conditions described in 1(a) above. The resulting red oil when chromatographed on silicic acid gave back the pyrrole and an intractable oil.

b) 2-Ethoxycarbonyl-3,4-dimethylpyrrole (36) (1.67 g), o-nitroacetophenone (1.5 g) and phosphoryl chloride (1.2 g) in ethylene chloride (30 ml) was refluxed overnight. The solvent was removed and ethanol (10 ml) added to the brown oil. Sodium hydroxide solution (10 ml, 10%) was added to the ethanolic solution and this was extracted with ether. The ether extracts were dried (MgSO₄) and the ether removed. The brown oil failed to give any identifiable products.

8. 2-Ethoxycarbonyl-3,4-dimethylpyrrole (36)

2-Ethoxycarbonyl-3,4-dimethyl-5-iodopyrrole (20 g), ammonium chloride (40 g) and powdered zinc (20 g) in aqueous ethanol (100 ml) was refluxed for fifteen minutes. Powdered zinc (5 g) was added and the hot solution filtered. The ethanol was removed and the pyrrole crystallised out. Crystallisation from ethanol gave the product 2-ethoxycarbonyl-3,4-dimethylpyrrole (73%) m.p. 96-97°C.

9. N-(2,4-Diethoxycarbonyl-3,5-diethyl-5-pyrrol methyl)-4-methanesulphonyl-2-phenylenediamine (37).

a) 2-Chloromethyl-3,5-diethoxycarbonyl-4-methylpyrrole²³ (5.5 g) was added in portions to a solution of N-methanesulphonyl-2-nitroaniline¹¹ (4.3 g) in ethanol (20 ml) and water (10 ml) containing sodium hydroxide (0.8 g). After the addition the mixture was stirred for a further thirty minutes.
The pale yellow precipitate was filtered, washed with water and crystallised from ethanol. \( \text{N-(2,4-Diethoxycarbonyl-3-methyl-5-pyrrolylmethyl)-N'-methanesulphonyl-o-nitroaniline (42)} \) (96%) was obtained as pale yellow prisms, m.p. 154-155°C.

Found: C, 50.3; H, 5.1; N, 9.2; S, 7.6. \( \text{C}_{19}\text{H}_{23}\text{N}_{3}\text{O}_{8}\text{S} \) requires

C, 50.3; H, 5.1; N, 9.2; S, 7.6.

b) The nitro compound (42) (10 g) was reduced with tin and hydrochloric acid by the method of Hubatsch. \( \text{N-(2,4-Diethoxycarbonyl-3-methyl-5-pyrrolylmethyl)-N'-methanesulphonyl-o-phenylenediamine (37)} \) (90%) was obtained as colourless prisms from ethanol, m.p. 150-151°C.

Found: C, 53.6; H, 5.9; N, 10.3; S, 7.3. \( \text{C}_{19}\text{H}_{25}\text{N}_{3}\text{O}_{8} \) requires

C, 53.6; H, 5.9; N, 10.3; S, 7.6.

**Infra-red spectrum.**

\[
\begin{align*}
3145 \text{ cm}^{-1} & \quad \text{NH (Broad)} \\
3340 \text{ cm}^{-1} & \quad \text{NH} \\
3430 \text{ cm}^{-1} & \quad \text{NH} \\
1679 \text{ cm}^{-1} & \quad \text{C=O} \\
1342 \text{ cm}^{-1} & \quad \text{SO}_{2} \\
1151 \text{ cm}^{-1} & \quad \\
\end{align*}
\]

When crystallised from benzene this compound had a m.p. 130-132°C (frothing). The N.M.R. spectrum showed that one mole of benzene of crystallisation has been incorporated.

10. \( \text{N-(3-acetyl-5-ethoxycarbonyl-4-methyl-2-pyrrolylmethyl)-N'-methanesulphonyl-o-phenylenediamine (38)} \).

a) 3-Acetyl-5-ethoxycarbonyl-2,4-dimethylpyrrole\( ^{24} \) (16) (10.5 g) was suspended in dry ether (50 ml) and sulphuryl chloride (7.5 g) added drowsily with stirring, the temperature being kept at 0°C. The solution was stirred for a further thirty minutes.
The precipitate was filtered, washed with petroleum ether (b.p. 60-80°C). 3-Acetyl-5-ethoxycarbonyl-2-chloromethyl-4-methylpyrrole (79%) was obtained as colourless prisms, m.p. 117-118°C, (lit. m.p. 119°C) from benzene.

b) 3-Acetyl-5-ethoxycarbonyl-2-chloromethyl-4-methylpyrrole and N-methanesulphonyl-o-nitroaniline were condensed by the same method as (9a) above. N-(3-Acetyl-5-ethoxycarbonyl-4-methyl-2-pyrrolylmethyl)-o-methanesulphonyl-o-nitroaniline (13) (71%) was obtained as pale yellow prisms, m.p. 175-176°C. (Found:
C, 50.8; H, 5.1; N, 10.0; S, 7.3. \( \text{C}_{13}\text{H}_{21}\text{N}_{3}\text{O}_{7}\text{S} \) requires C, 51.0; H, 5.0; N, 9.9; S, 7.6%).

c) The above nitro compound (13) was reduced with tin and hydrochloric acid. 11 N-(3-Acetyl-5-ethoxycarbonyl-4-methyl-2-pyrrolylmethyl)-N-methanesulphonyl-o-phenylenediamine (38) (91%), was obtained as colourless prisms, m.p. 165-166°C from ethanol. (Found:
C, 54.9; H, 5.9; N, 10.6; S, 8.0. \( \text{C}_{18}\text{H}_{23}\text{N}_{3}\text{O}_{5}\text{S} \) requires C, 54.9; H, 5.9; N, 10.7; S, 8.1%).

Infra-red spectrum.

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<th>Wave Number (cm(^{-1}))</th>
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<td>-NH</td>
</tr>
<tr>
<td>3342</td>
<td>-NH</td>
</tr>
<tr>
<td>3140</td>
<td>N(\text{H} ) (broad)</td>
</tr>
<tr>
<td>1683 (\text{cm}^{-1})</td>
<td>(\text{C=O} )</td>
</tr>
<tr>
<td>1639 (\text{cm}^{-1})</td>
<td>(\text{SO}_{2} )</td>
</tr>
<tr>
<td>1340 (\text{cm}^{-1})</td>
<td></td>
</tr>
<tr>
<td>1150 (\text{cm}^{-1})</td>
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</table>


a) Sulphuryl chloride (6.8 g) was added dropwise with stirring to a solution of 2-ethoxycarbonyl-3,4,5-trimethylpyrrole\(^{27}\) (9.0 g) in ether (50 ml), the temperature being maintained at 0°C.
The solution was stirred for a further fifteen minutes, whereupon a solution of N-methanesulphonyl-o-nitroaniline (9.0 g) and triethylamine (20 g) in benzene (200 ml) was added. The solution was then refluxed for 3-4 hours. The reaction was allowed to cool and water (200 ml) was added. The organic layer was separated and washed with sodium hydroxide solution (5%), sodium chloride solution, and finally, with water, and then dried (MgSO₄). The solvent was removed leaving a dark red oil which was dissolved in hot ethanol (approx. 100 ml). The crude product separated on standing and was filtered, and washed with cold ethanol. Crystallisation from ethanol gave N-[(3,4-dimethyl-5-ethoxycarbonyl-2-pyrrolylmethyl)-N-methanesulphonyl-o-nitroaniline (45) (43%), m.p. 161-163°C. (Found: C, 51.6; H, 5.4; N, 11.0; S, 7.9. \( \text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_6\text{S} \) requires C, 51.6; H, 5.1; N, 11.6; S, 8.1%).

b) The above nitro compound (45) (3g) in ethanol (150 ml) was hydrogenated at atmospheric temperature and pressure using palladium on charcoal as the catalyst. After the required amount of hydrogen had been absorbed, the solution was filtered, and the solvent evaporated. The residue, a colourless oil, subsequently solidified. Crystallisation from 50% aqueous ethanol gave N-[(3,4-dimethyl-5-ethoxycarbonyl-2-pyrrolylmethyl)-N-methanesulphinyl-o-phenylenediamine (3%) (8%) as colourless prisms, m.p. 97-98°C. (Found: C, 55.0; H, 6.5; N, 11.3; S, 8.7. \( \text{C}_{17}\text{H}_{23}\text{N}_3\text{O}_4\text{S} \) requires C, 55.0; H, 6.4; N, 11.5; S, 8.8%).

Infra-red spectrum.

\[
\begin{align*}
3428 \text{ cm}^{-1} & \quad \text{NH (broad)} \\
3200 \text{ cm}^{-1} & \quad \text{NH (broad)} \\
1682 \text{ cm}^{-1} & \quad \text{CO} \\
1380 \text{ cm}^{-1} \} & \quad -\text{SO}_2 \\
1146 \text{ cm}^{-1} \} & \quad -\text{SO}_2 
\end{align*}
\]
Cyclisations.

12. \(N-(2,4\text{-Dithoxycarbonyl-3-methyl-5-\text{pyrrolylmethyl}})\text{-N-methanesulphonyl-2-phenylenediamine} \) (37).

\(a\) The amine (37) was dissolved in dilute hydrochloric acid (100 ml, 10%) and glacial acetic acid (20 ml) and the solution cooled to 0-5°C. A solution of sodium nitrite (0.4 g) in water (100 ml) was added dropwise and the solution stirred for a further thirty minutes in the ice bath. The solution was then heated for one hour on a boiling water bath after which the evolution of nitrogen was complete. The mixture was diluted with water (100 ml) and extracted with chloroform (3 x 100 ml). The combined extracts were washed with water, dried (MgSO₄) and the chloroform evaporated.

The dark red oil (1.7 g) was then chromatographed on a silicic acid column (20 x 3 cm) using chloroform as eluent. The first band was collected, and the product was crystallised from ethanol. \(2,4\text{-Dithoxycarbonyl-3-methyl-5-(N-methanesulphonyl-2-aminophenyl) pyrrole} \) (50) (6%) was obtained as colourless prisms, m.p. 186-187°C. (Found: C, 54.9; H, 5.8; N, 7.3; S, 7.9. C₁₃H₂₂N₂O₆S requires C, 54.8; H, 5.6; N, 7.1; S, 8.0%).

Infra-red spectrum.

\[\begin{align*}
3420 \text{ cm}^{-1} & \quad \text{NH} \\
3340 \text{ cm}^{-1} & \quad \text{NH} \\
3263 \text{ cm}^{-1} & \quad \text{NH} \\
1678 \text{ cm}^{-1} & \quad \text{CO (Broad)} \\
1335 \text{ cm}^{-1} & \quad \text{SO}_2^- \\
1156 \text{ cm}^{-1} & \quad \text{SO}_2^- 
\end{align*}\]
b) The amine (37) (2.2 g) was diazotised as described in (12a) above. After the diazonium salt solution had been stirred for thirty minutes in an ice bath, copper powder (1.5 g) (See (6) above) was added and the mixture stirred for three hours at room temperature. The mixture was diluted with water (100 ml) and extracted with chloroform as above (12a). The dark red oil (2.0 g) obtained was chromatographed on a short silicic acid column (20 x 3 cm). The first band was collected, the solvent removed and the product obtained as a pale yellow oil. Crystallisation from ethanol gave spiro \([1\text{-methanesulphonyl-3\text{-H-indoline-3,2'\text{-diethoxycarbonyl-}}\]
\[4\text{'-methyl-2\text{'-H-pyrrole}] (51) (81\%) as colourless prisms, m.p. 121-122.5°C (Found: C, 56.1; H, 5.5; N, 7.4; S, 7.7. C\(_{19}\)H\(_{22}\)N\(_2\)O\(_6\)S requires C, 56.1; H, 5.5; N, 6.9; S, 7.9%).

Infra-red spectrum:

\[
\begin{align*}
1725 \text{ cm}^{-1} & \quad \text{CO} \\
1703 \text{ cm}^{-1} & \\
1352 \text{ cm}^{-1} & \quad \text{SO}_2^-
\end{align*}
\]

Further elution of the column with chloroform afforded 2,4-diethoxycarbonyl-3-methyl-5-(\(\text{N-methanesulphonyl-2-}
\text{aminophenyl) pyrrole (50) (7\%)}, which had m.p. 135-137°C, alone and when mixed with the compound obtained in (12a) above.

13. \(\text{N-(2-ethoxycarbonyl-3-methyl-4-acetyl-5-pyrrolyl)-N-}
\text{methanesulphonyl-2-phenylenediamine (38) }
\]

a) The amine (38) was diazotised and the diazonium salt decomposed thermally by the method described in (12a). No recognizable products were obtained from the reaction.
b) The amine (38) was diazotised and the diazonium salt decomposed with copper by the method in (12b). Chromatography on silicic acid of the resulting oil gave spiro[1-methanesulphonyl-3-
indoline-3,2'(5'-ethoxycarbonyl-1'-methyl-3'-acetyl-2'H-pyrrole)]
(62) (76%) m.p. 93-95°C from ethanol. (Found: C, 57.1; H, 5.6;
N, 7.1; S, 8.2. C$_{18}$H$_{20}$N$_2$O$_5$ requires C, 57.4; H, 5.4; N, 7.4;
S, 8.5%).

14. N-(2-ethoxycarbonyl-3,4-dimethyl-5-pyrrolylmethyl)-1-
methanesulphonyl-o-phenylenediamine (39).

The amine (39) was diazotised by the method described in (12b)
and the diazonium salt decomposed by copper powder. The resulting
black oil was chromatographed on silicic acid but no recognizable
products were isolated.

15. Reactions of the spiroindoline (51).

a) With concentrated hydrochloric acid.

The spiroindoline (1 g) was suspended in concentrated hydrochloric
acid (10 ml) and heated on a water bath for fifteen minutes.
The mixture was diluted with water (50 ml) and the solid material
was filtered, and washed thoroughly with water. Crystallisation
of the product from ethanol gave 2,4-diethoxycarbonyl-3-methyl-
5-(N-methanesulphonyl-o-aminophenyl) pyrrole (50), (90%) as colourless
prisms, m.p. 185-187°C, alone and when mixed with the compound
in (12a) above.

b) With 100% phosphoric acid.

The spiroindoline (51) (1 g) was treated with 100% phosphoric
acid (5 g) and the solution warmed on a boiling water bath for
fifteen minutes. The solution was poured into water and the
mixture extracted with chloroform. The chloroform extracts were
washed with water, dried (MgSO$_4$) and the solvent removed.
The colourless oil solidified and was crystallised from ethanol. A small amount of insoluble material was removed by filtration. This was not further investigated. 1,3-Diethoxycarbonyl-5-methanesulphonyl-2-methyl-4,5-dihydropyrrolo(1,2-c)quinazoline (58) (70%) was obtained as colourless prisms, m.p. 111-112°C. (Found: C, 55.9; H, 5.6; N, 6.8; S, 7.6. \( \text{C}_{19} \text{H}_{22} \text{N}_{2} \text{O}_{5} \) S requires C, 56.2; H, 5.5; N, 6.9; S, 7.8%).

Infra-red spectrum.

\[
\begin{align*}
1695 \text{ cm}^{-1} & \quad \text{CO} \\
1356 \text{ cm}^{-1} & \quad \text{SO}_2^- \\
1177 \text{ cm}^{-1} & \\
1161 \text{ cm}^{-1} &
\end{align*}
\]

c) With 60% sulphuric acid.

The spirindoline (51) (2 g) was treated with 60% sulphuric acid (20 ml) and the red solution was warmed on a water bath until a yellow, oil precipitate formed, (4-5 minutes). The mixture was poured into water (100 ml) and the solution was extracted with chloroform (3 x 50 ml). The combined extracts were washed with water, dried (\( \text{MgSO}_4 \)) and the chloroform removed. The residual pale yellow oil (2.0 g) was chromatographed on a silicic acid column (20 x 3 cm) with chloroform as eluent. The first band, which was fluorescent under ultraviolet light, was collected. The solvent was evaporated and the resulting colourless oil solidified and was crystallised from ethanol. 1,3-Diethoxycarbonyl-5-methanesulphonyl-2-methyl-4,5-dihydropyrrolo(1,2-c)quinazoline (58) (50%) as colourless prisms, m.p. 111-112°C, alone and when mixed with the compound obtained in (15b) above.
Further elution of the column with chloroform and evaporation of the solvent gave a yellow oil (0.8 g) which failed to crystallise. T.L.C. on silicic acid plates showed that the oil was a complex mixture and it was not examined further.

d) With methanol/sulphuric acid

The spiroindoline (1 g) was dissolved in methanol (10 ml) and two drops of concentrated sulphuric acid were added. The solution was boiled under reflux for ten minutes, during which time the original yellow colour of the solution disappeared. The solution was poured into water (100 ml) and extracted with chloroform (3 x 50 ml). The chloroform extracts were washed with water, dried (MgSO₄) and the chloroform evaporated. The residue was a colourless oil (1.1 g) which subsequently solidified. Crystallisation from ethanol afforded 2-(2'-N-methanesulphonyl-N-ethoxymethylaminoethyl)-3,5-diethoxycarbonyl-4-methylpyrrole (61A) (88%), as colourless prisms, m.p. 112-113°C. (Found: C, 54.8; H, 6.0; N, 6.4; S, 7.3.

C₂₀H₂₆N₂O₇ requires C, 54.8; H, 6.1; N, 6.3; S, 7.4%).

Infra-red spectrum.

<table>
<thead>
<tr>
<th>Wavenumber</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3330 cm⁻¹</td>
<td>NH (broad)</td>
</tr>
<tr>
<td>1700 cm⁻¹</td>
<td>C = O</td>
</tr>
<tr>
<td>1683 cm⁻¹</td>
<td></td>
</tr>
<tr>
<td>1340 cm⁻¹</td>
<td>-SO₂-</td>
</tr>
<tr>
<td>1155</td>
<td></td>
</tr>
</tbody>
</table>

e) With ethanol/sulphuric acid

The spiroindole (1 g) was dissolved in ethanol (10 ml) containing two drops of concentrated sulphuric acid and reacted as described in (d) above. Crystallisation of the product from ethanol gave 2-(2'-N-methanesulphonyl-N-ethoxymethylaminophenyl)-3,5-diethoxycarbonyl-4-methylpyrrole (61B) (90%) as colourless prisms, m.p. 141-142°C.
(Found: C, 55.7; H, 6.2; N, 6.2; S, 7.1. \( \text{C}_{21} \text{H}_{28} \text{N}_2 \text{O}_f \text{S} \) requires C, 55.6; H, 6.3; N, 6.2; S, 7.1%).

**Infra-red spectrum.**

\[ \begin{align*}
3330 \text{ cm}^{-1} & \quad \text{NH (broad)} \\
1700 \text{ cm}^{-1} & \quad (\text{shoulder}) \\
1688 \text{ cm}^{-1} & \quad \text{CO} \\
1340 \text{ cm}^{-1} & \quad \text{SO}_2^- \\
1155 \text{ cm}^{-1} & \quad \\
\end{align*} \]

16. **Synthesis of the methanol "adduct" (61A).**

2,4-Diethoxycarbonyl-3-methyl-5-(\( \text{N} \)-methanesulphonyl-\( \text{N} \)-aminophenyl) pyrrole (50) (0.4 g) was suspended in benzene (5 ml) and triethylamine (0.15 g) was added. The solution was warmed and chloromethyl methyl ether (0.1 g) in benzene (5 ml) was added. The mixture was boiled gently under reflux for one hour. After cooling the mixture, water (20 ml) was added, and the benzene layer was separated. The benzene solution was washed with water, dried (\( \text{MgSO}_4 \)) and the benzene removed. The residue was a colourless oil which subsequently crystallised. Crystallisation from ethanol gave 2-(\( \text{N} \)-methanesulphonyl-\( \text{N} \)-methoxymethylaminophenyl)-3,5-diethoxycarbonyl-\( \text{N} \)-methylpyrrole (61A) (86%), as colourless prisms, m.p. 111-113°C, alone, or when mixed with the sample obtained in (d) above.

17. **Reaction of the Acetyl Spiroindoline (62) with 100% Phosphoric Acid.**

Spiro[\( \text{N} \)-methanesulphonyl-\( \text{N} \)-indoline-3,2'(5'-ethoxycarbonyl-\( \text{N} \)-methyl-3'-acetyl-2'H-pyrrole)] (62) (1 g) and 100% phosphoric acid (5 g) were reacted as in (15b) above. T.L.C. of the resulting oil showed it to be a mixture of at least three compounds, and this reaction was not investigated further.
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