CHAPTER IV

DIHETEROARYL SULFIDES
INTRODUCTION

Interest in the chemistry of diaryl, heteroarylsulphides and related compounds was developed mainly because of the discovery of diaminodiphenylsulfone (DADS), as a potential antileprosy drug. Later many sulphur containing aminoacids and proteins revealed the importance of sulphides, disulphides etc., in biological systems. In recent years diaryl and heteroaryl sulphides have been found to be useful in the areas of agriculture, medicine and industry. The compound S-adenosylmethionine is a methylating agent in biochemical $S_N^2$ reactions, which are catalysed by appropriate enzymes.

During the present investigation a variety of heteroarylsulphides containing biologically important systems like benzimidazole and coumarin have been synthesised starting from 4-bromomethylcarbostyril. In view of this a brief review of the structurally related sulphides will be presented.
As early as in the year 1945, Shinkle\textsuperscript{2} found the insect repellant property of 4-methyl-2-mercaptoquinoline (I). This compound was also found to be active against insect larvae, acarids and arachnids. The patent further claims the utility of this as a constituent of other insecticides, flysprays etc.

The parent thiocarbostyril (II) was described by Nakanishi et al\textsuperscript{3}, who showed that the compound exists in the thione form (II).

During their study on pyridyl and quinolyl sulphides
as possible antibacterial agents, Surrey and Lindwall\textsuperscript{4} synthesised a bisquinolylsulphide (III).

![Chemical Structure](III)

Nargund et al\textsuperscript{5} reported the synthesis of some new 2- and 4-arylquinolyl sulphides (IV). They found that the sulphides (IV) had growth inhibitory action against \textit{S. Aureus} and \textit{E. Coli}.

![Chemical Structure](IV)

Thioethers of 4-quinaldine derivatives (V) were synthesised as possible radioprotective agents\textsuperscript{6}.

![Chemical Structure](V)
Quinolinylthiophenoxy alkanoic acids and their derivatives (VI) have been patented for their herbicidal activity. Some compounds (VI) were effective in preemergence control of barnyard grass and crabgrass.

An interesting polycyclic quinoline system (VII) containing the diaryl sulphide moiety has been reported by Russian Workers.

![Chemical Structures]

(VI) $R = R^1 = F, Cl, Br, CF_3$
$R^2 = -CO_{2}H, CO_{2}Na, CO_{2}K.$
Nesynov et al. have reported that 2-p-methoxyphenyl-thiobenzimidazole (VIII) was effective against cucumber mildew.

\[ \text{Nesynov et al.} \]

Strong fungicidal activity for 2-S-alkylbenzimidazoles was reported by Nakajima et al. against Trichophyton interdigitale at a dilution of 1 : 291,900. The most effective amongst these were (IX)

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\[ \begin{align*}
R^1 = H, & R = n\text{-propyl} \\
& \text{isopropyl} \\
R^1 = Cl, & R = \text{Benzyl}
\end{align*} \]

Metabolic studies of compounds (IX) indicate the intervention of a desulphurisation enzymic system which probably releases hydrogen sulphide in the tissues.

Fungitoxicity of some 2-halogenonitrophenylthiobenzimidazoles (X) against A. Niger, F. Oxysporum H. Sativum and A. Tenuis was reported by Gupta and Rani.

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Among various benzimidazoles tested for their analgesic activity in mice, rabbits and dogs the most effective compound was 1-(β-diethylaminoethyl)-2-benzyl-5-nitrobenzimidazole (XI). These compounds were respiratory depressants offering little advantage over morphine.

Watanabe et al. reported the powerful analgesic effects of 1-(dialkylaminoethyl)-2-arylthio, 2-arylxyloxy and 2-pyridylthiobenzimidazoles (XII) which were patented for their excellent analgesic activity.
2-Alkylbenzimidazoles when treated with formaldehyde and an aromatic amine gave 1-arylaminoderivatives (XIII). These compounds were screened against *E. Coli*, *B. Megatarium* and *S. Aureus*.

\[
\begin{align*}
\text{R} &= -\text{CH}_3, -\text{C}_2\text{H}_5 \\
\text{ar} &= -\text{Ph}, -\text{Ph-CH}_3 \text{ etc.}
\end{align*}
\]

(XIII)

Hydrobromides of benzimidazolyl-2-thioacetyl-γ-valerolactones (XIV) have been patented for their muscle relaxant and analgesic activities.

\[
\begin{align*}
\text{R} &= -\text{H}, \text{CO}_2\text{C}_2\text{H}_5; \quad \text{R}^1 = \text{n-butyl, amyl etc.}
\end{align*}
\]

(XIV)

During their study on stomach acid secretion inhibitors, Berntsson et al. have found that compound (XV) inhibited acid secretion by 80% at a dose level of 10 mg/Kg, (orally) in dogs.
2-Carbamate esters of benzimidazole containing an alkylthio or an arylthio grouping are known for their anthelmintic activity. Recently Vishwanathan et al. have reported the anthelmintic activity of some 5-bisbenzimidazolyl sulphides (XVI).

Arylsulphides (XVII) and benzimidazolylsulphides (XVIII) obtained by the reaction of 4-bromomethylcoumarins with thiophenol and 5,6-dimethyl-2-mercaptobenzimidazole respectively, have been reported from this laboratory.
Recently Merchant et al.\textsuperscript{26} have reported the synthesis and antitubercular activity of arylsulphides derived from pyranobenzopyrandones (XIX).

2,4-Dichlorophenoxyacetic acid is a widely known growth hormone for plants. Further the bisaryl sulphide (XX) containing the 2,4-dichlorophenol moiety, known as \textsc{Bithionol} is effective against \textit{F. hepatica} in Cattle\textsuperscript{27}.
Recently Schmitt and Luerssen\textsuperscript{28} found that arylsulphides (XXI) linked to 2,4-dichlorophenoxyethyl moiety stimulate nitrogen fixation in soyabeans and retard the growth of barley.

It is interesting to note that the lactone (XXII) and the thiolactone (XXIII) formed during the acid hydrolysis of the naturally occurring antibiotic, Cephalosporin C also contain the \(-\text{CH}_2\text{-S-CH}_2\)-moiety.
Heteroarylsulphides of the type (XXIV) synthesised during the present investigation also contain a \( \text{CH}_2\text{S-CH}_2\) moiety in which the two end methylene groups are linked to a lactone and a lactam, present in the form of coumarin and carbostyril rings.

This brief survey underlines the importance of:

(a) Quinolylsulphides

(b) Benzimidazolylsulphides

(c) Coumarinylsulphides

(d) 2,4-dichlorophenoxy group.

Hence the following sulphides (XXIV→XXVI) have been synthesised during the present investigation.

(XXIV): \[
\begin{align*}
\text{CH}_2\text{S-CH}_2 \\
\text{(XXIV)}
\end{align*}
\]

(XXV): \[
\begin{align*}
\text{CH}_2\text{S-CH}_2 \\
\text{(XXV)}
\end{align*}
\]

(XXVI): \[
\begin{align*}
\text{R}^1\text{O-CH}_2 \\
\text{(XXVI)}
\end{align*}
\]

(XXVI): \( R^1 = 2,4\text{-dichlorophenyl} \).
The steps involved in the synthesis of sulphides are outlined in Schemes-1 and 2.

2-Mercaptobenzimidazole reacted with (I) in alcohol in presence of potassium hydroxide to give the sulphide (II) in good yields. Further compound (II) underwent Mannich reaction with formaldehyde and secondary amines to give the Mannich bases (III). Similarly the aryl sulphide (VI) was obtained by the reaction of thiophenol with (I). Reaction of (I) with thiourea in ethanol afforded the 4-mercaptomethyl carbostyril (IV), which condensed with 4-bromomethyl coumarins (IVA) to give the heteroarylsulphides (V). All the compounds were colourless solids, easily crystallisable from ethanol or acetic acid. Mechanism of Mannich reaction is well established29.

In another route (Scheme-2) 4-bromomethylcarbostyril (I) reacted with phenols to give 4-phenoxy methylcarbostyrils (VII) which were converted to the corresponding 2-chloroquinolines (VIII) by their reaction with phosphorus oxychloride. These compounds which are intermediates in the synthesis of tetrazoles have already been described in Chapter II. Some of the 2-chloro-4-phenoxy methyl quinolines (VIII) were reacted with thiourea, according to an earlier method30 to get the key intermediates 4-phenoxy methyl-2-mercaptoquinolines (I' ).
Scheme 1

- **I**: Thiourea in ethanol
- **II**: 2-Mercapto benzimidazole
- **III**: 
  - R = R' = Morpholino
  - Pyrididino
  - Dimethylamino
- **IV**: 4-Bromomethyl Coumarins
- **V**: R = 6-CH₃, 7-CH₃, 7-OCH₃, 5,6-Benzo
- **VI**: Other structures

**Equations and Reactions**

1. **I** + **II** → **III**
2. **III** + CH₂/S - CH₂ → **IV**
3. **IV** + Thiophenol → **V**
Bisaumolylsulphides (X) were synthesised by the reaction of (IX) with 2-chloroquinolines (VIII).

In an attempted synthesis of thienoquinolines (XII), intermediates (XI) were obtained by the reaction of an \( \alpha \)-haloketone with (IX). However, the intermediate (XI) did not undergo dehydration in polyphosphoric acid, phosphorous oxychloride etc., at elevated temperatures and even when kept for longer hours. Mercaptoacetic acid (XIII) obtained by the reaction of (IX) with monochloroacetic acid in dilute aqueous sodium hydroxide solution underwent cyclisation in pyridine and acetic anhydride to give the red mesoionic compound (XIV). Cyclisations to such mesoionic systems in similar nitrogen heterocycles have been reported in the literature\(^{31-2}\).

Mannich bases (III) have been screened for their pharmacological activity and some of the sulphides have been subjected to antibacterial testing, the results of which are presented in the last chapter (VI).
RESULTS AND DISCUSSION

The intermediate 4-mercaptomethylcarbostyril (IV) required for the synthesis of coumarinylsulphides (V) exhibited S-H stretching vibration around 2520 cm⁻¹ and carbonyl stretching band of the carbostyril moiety was observed at 1660 cm⁻¹. Further the SH proton appeared around 1.6 ppm and the CH₂ protons appeared as a doublet (J = 6 Hz) centered at 3.75 ppm. The SH proton got exchanged in D₂O and the methylene protons collapsed into a sharp singlet at 3.7 ppm. The carbostyril 3-proton appeared as a singlet at 6.45 ppm while the aromatic protons appeared as a multiplet between 6.9 and 7.5 ppm. (Figs. 1-3). Coumarinylsulphides (V) exhibited stretching vibrations due to amide and lactone carbonyl groups at 1670 and 1720 cm⁻¹ respectively, in the IR spectra. (Table - 1). Compound (V) R = 6-CH₃, showed the presence of -CH₃ protons at 2.3 ppm while the methylene protons attached to coumarin and carbostyril rings are seen as singlets at 4.15 and 3.90 ppm respectively. Further the coumarin 3-proton and the carbostyril 3-proton appear as singlets at 5.45 and 6.65 ppm respectively. Aromatic protons appear around 7.4 to 8.1 ppm. (Fig.4-5).

Arylsulphide (VI) was characterised by IR and PMR spectra. The IR spectrum showed the presence of amide carbonyl around 1680 cm⁻¹. PMR spectrum (DMSO-d₆) showed the presence of S-CH₂, ²-H, and aromatic protons at expected resonances while the NH proton appeared at 11.77 ppm. (Fig. 6).
FIG 1

CH$_2$-SH

H

CH$_2$-SH

(CDC$_3$)

a = 1.6, S-H
b = 3.75, 3.95, CH$_2$
c = 6.45, 3-CH
d = 6.9-7.45, Ar-H
a = 3.7, 3.9, CH₂
b = 6.45, 3-CH
C = 6.9-7.4, Ar-H

FIG 2

(D₂O exchange)
FIG 4

a = 2.33, CH₃
b = 3.9, CH₂-S
   (carbostyril)
c = 4.15, CH₂-S
   (coumarin)
d = 6.4, 3-H
   (carbostyril)
e = 6.6, 3-H (coumarin)
f = 7.3-8.1, Ar-H

(TFA)

PPM (δ)
FIG. 6

$\alpha = 4.47, \text{CH}_2\text{-S}$

$\beta = 6.4, \text{3H}$

$c = 7.2-7.9, \text{Ar-H}$

$d = 11.47, \text{NH}$

$S = \text{Solvent}$
TABLE - 1

IR Spectral Data of Coumarinylsulphides (V)

![Chemical Structure]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>R</th>
<th>$C = O$ (Amide) ($\text{cm}^{-1}$)</th>
<th>$C = O$ (Lactone) ($\text{cm}^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>6-Ci$_2$</td>
<td>1670</td>
<td>1720</td>
</tr>
<tr>
<td>2.</td>
<td>7-CH$_3$</td>
<td>1670</td>
<td>1730</td>
</tr>
<tr>
<td>3.</td>
<td>6-OCH$_3$</td>
<td>1670</td>
<td>1720</td>
</tr>
<tr>
<td>4.</td>
<td>7-OCH$_3$</td>
<td>1670</td>
<td>1725</td>
</tr>
<tr>
<td>5.</td>
<td>5,6-Benzo</td>
<td>1660</td>
<td>1720</td>
</tr>
</tbody>
</table>
**TABLE - 2**

IR Spectral Data of Bisquinolylsulphides (X)

![Chemical Structure]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>R</th>
<th>C = N (Cm(^{-1}))</th>
<th>C-O-C (Cm(^{-1}))</th>
<th>C-Cl (Cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>-H</td>
<td>1600</td>
<td>1100, 1150</td>
<td>870</td>
</tr>
<tr>
<td>2.</td>
<td>4-Cl</td>
<td>1600</td>
<td>1090, 1110</td>
<td>860</td>
</tr>
<tr>
<td>3.</td>
<td>4-CH(_3)</td>
<td>1600</td>
<td>1100, 1160</td>
<td>860</td>
</tr>
<tr>
<td>4.</td>
<td>2-Cl</td>
<td>1590</td>
<td>1105, 1150</td>
<td>880</td>
</tr>
<tr>
<td>5.</td>
<td>2,4,5-Cl</td>
<td>1590</td>
<td>1140, 1090</td>
<td>860</td>
</tr>
<tr>
<td>6.</td>
<td>2,4-Cl</td>
<td>1600</td>
<td>1120, 1170</td>
<td>870</td>
</tr>
</tbody>
</table>
Synthesis and characterisation of 4-phenoxymethyl-carbostyrils (VII) and 2-chloro-4-phenoxymethylquinolines (VIII) has already been described in chapter-II. Some of the 2-chloro compounds were converted to 2-mercapto-4-phenoxymethylquinolines (IX). In accordance with the observation of earlier workers about 2-mercaptoquinoline, compounds (IX) also exist mainly in the thione form. The IR spectra showed strong bands around 1580 cm\(^{-1}\) due to C=S stretching vibrations. In the PMR spectra the 3-proton was deshielded and appeared as a part of the aromatic multiplet. Compound IX (R" = 2,4-Cl) was reacted with different 2-chloroquinolines (VIII) to get the bissulphides (X). The IR spectral data for compounds (X) is presented in (Table - 2) in which stretching vibrations of C=N, C-Cl and C-O-C bonds are assigned. PMR spectrum of the symmetrical sulphide X (R=R' = 2,4-Cl) shows the presence of -CH\(_2\) protons at 5.4 ppm while quinoline 3 protons resonate at 5.8 ppm and the aromatic multiplet is seen around 7.0-8.1 ppm (Fig. 7-g).

In an attempted synthesis of the thienoquinolines (XII) the 2-mercapto-4-phenoxymethylcarbostyrils (IX) (R = 2, 4-Cl; 4-CH\(_3\)) were reacted with \(\chi^2\) haloketones (R' = Ph; 3-coumarinyl). PMR spectrum of the thione (IX) (R = 4-CH\(_3\)) shows the presence of -CH\(_3\) protons at 2.3 ppm while the other protons resonate at expected fields. Condensation of 3-bromoacetyl coumarin with (IX) (R = 4-CH\(_3\)) afforded (XI) (R' = 3-coumarinyl). IR spectrum of the compound showed the vibrations due to lactone carbonyl of coumarin around 1705 cm\(^{-1}\). PMR spectrum (DMSO\(_d_6\)) showed
CH\textsubscript{3}- protons as a singlet at 2.3 ppm. CH\textsubscript{2}-O- and -S-CH\textsubscript{2}-C-protons appeared as singlets at 5.4 and 6.2 ppm respectively. The quinoline 3-proton appears deshielded at 6.7 ppm while the coumarin 4-proton was found to resonate at 8.5 ppm. The aromatic multiplet was observed in between 7.0 to 8.0 ppm. (Fig.10) condensation products (XI) (R= 2,4 -Cl R' = - Ph; 3-coumarinyl) also exhibited similar IR spectral properties. None of the intermediates (XI) could be cyclised to the thieno-quinolines (XII). Various cyclising agents like polyphosphoric acid, phosphorous oxychloride, titanium tetrachloride etc., were tried unsuccessfully. Thienoquinolines of the type (XII) have been synthesised from 3-vinylcarbostyrils\textsuperscript{32}.

Mercaptoacetic acid (XIII) was easily converted to the mesoionic system (XIV) in presence of pyridine and acetic anhydride. Compound (XIV) (R = 2,4-CI) showed the presence of C=O group around 1720 Cm\textsuperscript{-1}.

The benzimidazolylsulphide (II) showed the presence of amide carboxyl group in the IR spectrum at 1650 Cm\textsuperscript{-1}. IR spectrum showed - S- CH\textsubscript{2} protons as a singlet at 4.75 ppm while the carbostryil -3- proton appeared at 6.6 ppm. Aromatic protons were found to resonate at 7-8 ppm (Fig.11).

Mannich bases (III) obtained by the reaction of benzimidazolyl sulphide (II) with various secondaryamines and formaldehyde, showed the presence of amide carboxyl group around
FIG. 10

a = 2.3, CH₃
b = 5.4, O-CH₂
c = 6.2, S-CH₂-CO
d = 6.7, C-3-H
e = 7.0-8.0, Ar-H
f = 8.6 Coumarin 4-H
s = solvent

(DMSO-d₆)
### TABLE 3
IR Spectral Date of Mannich Bases (III)

![Chemical Structure]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>R</th>
<th>R¹</th>
<th>C = N (Cm⁻¹)</th>
<th>C = O (Cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CH₃</td>
<td>CH₃</td>
<td>1620</td>
<td>1680</td>
</tr>
<tr>
<td>2.</td>
<td>CH₃</td>
<td>C₆H₅</td>
<td>1605</td>
<td>1660</td>
</tr>
<tr>
<td>3.</td>
<td>iornholino</td>
<td></td>
<td>1610</td>
<td>1655</td>
</tr>
<tr>
<td>4.</td>
<td>liperidino</td>
<td></td>
<td>1615</td>
<td>1680</td>
</tr>
<tr>
<td>5.</td>
<td>Tyrrolidino</td>
<td></td>
<td>1616</td>
<td>1670</td>
</tr>
</tbody>
</table>
TABLE 4

PMR Spectral Data of Mannich Bases (III) in (CCl₄ + DMSO₆)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>R</th>
<th>R'</th>
<th>S-CH₂-C</th>
<th>N-CH₂-N</th>
<th>3-H</th>
<th>Ar-H</th>
<th>n</th>
<th>R'</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>-CH₃</td>
<td>⁻C₆H₅</td>
<td>4.65</td>
<td>5.35</td>
<td>6.4</td>
<td>6.5-7.5</td>
<td>2.9</td>
<td>Ar-H</td>
</tr>
<tr>
<td>2.</td>
<td>-CH₃</td>
<td>-CH₃</td>
<td>4.6</td>
<td>5.15</td>
<td>6.4</td>
<td>6.7-7.5</td>
<td>Merged in solvent</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Piperidino</td>
<td></td>
<td>4.6</td>
<td>4.4</td>
<td>6.35</td>
<td>6.7-7.5</td>
<td>1.4</td>
<td>2.8</td>
</tr>
<tr>
<td>4.</td>
<td>Morfolino</td>
<td></td>
<td>4.6</td>
<td>6.4</td>
<td>6.7-7.5</td>
<td>Merged in solvent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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FIG 13

- a = 1.4, C-(CH₂)₃-C
- b = 2.8, CH₂-N-CH₂ ring
- c = 4.4, N-CH₂-N
- d = 4.6, S-CH₂
- e = 6.35, C-3-H
- f = 6.8-7.5, Ar-H
- s = solvent

(CCl₄-DMSO-d₆)
1670 cm$^{-1}$ and vibrations due to C = N group were found around 1610-20 cm$^{-1}$, (Table - 3) (Fig. 12).

PMR spectra of the manich bases has been recorded in CCl$_4$ and D$_2$SO$_6$ mixture, (Table - 4). It can be seen from the Table that the S-CH$_2$ protons resonate around 4.6 ppm while the methylene protons between two nitrogens show a broader range of resonances reflecting the effect of substituents present. Carbostyril 3-proton shows an upfield shift from its precursor sulphide (II) by about 0.25 ppm. Other protons occur at expected fields. The N-CH$_3$ protons in case of dimethylamino group and the N-CH$_2$ protons of morpholino have merged in the solvent taking into consideration the values for the parent secondary amine or the nearest model to the same. (Fig. 13).
Of the various sulphides synthesised during the present investigation mass spectral fragmentation of the coumarin-1 sulphide (V) ($R = \text{6-CH}_2$) has been elucidated.

**Scheme - 1**

From the bar graph it can be seen that the molecular ion $M^+$ (I) is seen in about 20% intensity. The main fragmentation of this molecule probably can occur by the transfer of hydrogen from either of the methylene groups to obtain four fragments (II) $\rightarrow$ (V) in which the coumarin thioaldehyde (IV) is eliminated as a neutral molecule and the other sulphur containing fragment acquires less charge in accordance with the fragmentation pattern of dibenzylsulphide. The base peak (II) is obtained by the hydrogen transfer of a methylene proton from coumarin to carbostyril and expulsion of 6 methylcoumarin-4-thioaldehyde as a neutral molecule. This proposition is further supported by the appearance of another ion at $m/e$ 131, expected by the loss of carbon monoxide from (II), which is characteristic of carbostyrils. The 3-alkylindole ion (VI) further follows the indole breaking pattern. The odd electron ion (III) can expel a molecule of CS resulting in ion (VII) of high intensity, which can easily expel a molecule of carbon monoxide to give indole (VIII) the fragmentation of which is well established.
SCHEME 1

I. M^+ m/e 363 (20%)

II. m/e 159 (100%) → CO^-

III. m/e 189 (47%) → S^2^+

IV. m/e 174 (27%) → CO^-

V. m/e 146 (18%) → CO^-

VI. m/e 204 (neutral)

VII. m/e 117 (10%)
SCHEME - 2
The dialkylcoumarin (V) can undergo a loss of carbon monoxide to end up in the odd electron ion (IX) which further follows the breaking pattern for 3-alkylbenzofurans.

**Scheme - 2**

Another probable route for the fragmentation of the molecular ion (I) is through the homolytic fission of either of \( \text{CH}_2\text{-S-} \) bonds. In one path the two even electron ions (X) and (XI) are expected. The sulphur containing coumarin ion (XI) undergoes ring contraction due to loss of carbon monoxide to give benzofuran moiety (XIV). The ion (XIV) can undergo ring expansion as observed for other alkylbenzofurans and expel a molecule of CS to end up in dihydrobenzofuran (XVI), through the resonance forms (XV) and (XVa).

Carbostyril even electron ion (X) shows the loss of carbon monoxide to give another alkylindole ion in high intensity which can eliminate a molecule of HCN after ring expansion which is characteristic of indoles to end up in an even electron hydrocarbon ion (XIII).

**Scheme - 3**

In another possible homolytic cleavage two even electron ions (XVII) and (XVIII) can be formed. The sulphur containing carbostyril moiety (XVII) can eliminate a molecule of carbon monoxide to give the 2-mercaptomethyl indole ion (IX).
in low intensity. Ion (XIX) expels a molecule of CS through the ring expanded forms (XX) and (X'α). The resulting dihydroindole can expel a molecule of HCN to end up in an ion (X'II) at m/e 91.

The alkylcoumarin (XVIII) apart from its usual pattern can also eliminate a molecule of carbon dioxide to give the 5'-methyl indene ion (XXIII).
EXPERIMENTAL

This section has been divided mainly into four parts:

Part I: Synthesis of 4-(4'-S-Coumarinomethyl)-Mercaptomethylcarbostyrils (V)

i) Synthesis of 4-mercaptomethylcarbostyril (IV).

ii) Preparation of substituted 4-bromomethylcoumarins (IVa).

iii) Condensation of (IVa) with (IV) to get the sulphides (V).

i) Synthesis of 4-Mercaptomethylcarbostyrils (IV)

To a suspension of 4-bromomethylcarbostyril (0.0042 mole) (1.0g), in a mixture of ethanol and ether (12 + 8 ml), was added, Thiourea (0.0042 mole) (400 mg) and stirred for 2 hours. This was then refluxed on steam bath for 4 hours and left overnight. The separated solid was filtered and washed with excess of water. The solid was dissolved in a solution of sodium hydroxide (5%) (15 ml), treated with charcoal and filtered. The compound was reprecipitated by the careful addition of Hydrochloric acid. The compound, white in colour was crystallised from acetie acid.

yield - 80%, M.P - 180°-9°C (Acetic acid),

$C_{10}H_{9}NOS$ - Requires - C, 62.82; H, 4.71; N, 7.33

Found - C, 62.70; H, 4.50; N, 7.20
IR (KBr) (cm⁻¹) - S-H, 2520; C=O, 1660.

NMR (DCl₃) - SH, 1.6 (s); S-CH₂, 3.75 (d); 3-H, 5.45 (s); nr-H, 6.9-7.4 (m).

(iii) Preparation of Substituted 4-Bromomethylcoumarins (IVa)

The following substituted 4-bromomethyl coumarins were prepared:

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>M.P°C</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>6-Methyl-4-bromomethylcoumarin</td>
<td>176</td>
<td>39</td>
</tr>
<tr>
<td>2.</td>
<td>7-Methyl-4-bromomethylcoumarin</td>
<td>234</td>
<td>40</td>
</tr>
<tr>
<td>3.</td>
<td>6-Methoxy-4-bromomethylcoumarin</td>
<td>175</td>
<td>41</td>
</tr>
<tr>
<td>4.</td>
<td>7-Methoxy-4-bromomethylcoumarin</td>
<td>206</td>
<td>41</td>
</tr>
<tr>
<td>5.</td>
<td>5,6-benzo-4-bromomethylcoumarin</td>
<td>195</td>
<td>39</td>
</tr>
</tbody>
</table>

(iii) Condensation of 4-Bromomethylcoumarin (IVa) with 4-Mercaptomethylcarbostyril (IV) to get the Sulphides (V)

General Method:

In a dry 100 ml R.B. Flask, 4-mercaptomethylcarbostyril (0.002 mole), 4-bromomethylcoumarin (0.002 mole) in ab. ethanol (15 ml) were taken and powdered, anhydrous potassium carbonate (0.002 mole) was added to it. This was refluxed for 6 hours on a waterbath. After cooling,
the separated solid was filtered, treated with dilute hydrochloric acid to neutralise the unreacted potassium carbonate. The residual solid was filtered and washed with excess of water. The filtrate was concentrated and diluted with water to obtain some more of the sulphide (V), which was crystallised from acetic acid.

The compounds thus prepared, with their analytical data are listed in (Table - 5).

**Part II : Synthesis of 4-((1'-Dialkylaminomethyl-2'-S-Benzimidazolyl) Mercaptomethylcarbostyrils (III)

Steps involved are as follows:

1) Synthesis of 4-(2'-S-Benzimidazolyl)-mercaptomethyl-carbostyril (II).

2) Synthesis of Mannich bases (III).

i) Synthesis of 4-(2'-S-Benzimidazolyl)-mercaptomethyl-carbostyril (II).

To a suspension of 4-bromomethylcarbostyril (0.004 mole) (960 mg), and 2-mercaptobenzimidazole (0.004 mole) (600 mg), in ab. ethanol (20 ml), was added potassium hydroxide (0.004 mole) (240 mg). The reaction mixture was refluxed on a waterbath for 6 hours. After cooling, the solid separated was filtered and washed with excess of water and crystallised from acetic acid.
**TABLE - 5**

Analytical Data of Coumarinyl Sulphides (V)

![Chemical Structure](chart.png)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>R</th>
<th>M.P., °C (d)*</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Analysis %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Required</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>1.</td>
<td>6-Methyl</td>
<td>264-5</td>
<td>70</td>
<td>C₂₁H₁₇NO₃₂S</td>
<td>69.42</td>
</tr>
<tr>
<td>2.</td>
<td>6-Methoxy</td>
<td>251-2</td>
<td>70</td>
<td>C₂₁H₁₇NO₄₂S</td>
<td>66.49</td>
</tr>
<tr>
<td>3.</td>
<td>7-Methyl</td>
<td>281-2</td>
<td>70</td>
<td>C₂₁H₁₇NO₃₂S</td>
<td>69.42</td>
</tr>
<tr>
<td>4.</td>
<td>7-Methoxy</td>
<td>245-6</td>
<td>40</td>
<td>C₂₁H₁₇NO₄₂S</td>
<td>66.49</td>
</tr>
<tr>
<td>5.</td>
<td>5,6-Dienzo</td>
<td>262-3</td>
<td>70</td>
<td>C₂₄H₁₇NO₃₂S</td>
<td>72.13</td>
</tr>
</tbody>
</table>

*All the compounds were crystallised from Acetic Acid.*
# TABLE - 6
Analytical Data of Mannich Bases (III)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>R</th>
<th>M.°C</th>
<th>Yield</th>
<th>Mol. Formula</th>
<th>Analysis Required</th>
<th>Analysis Found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>%</td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>1.</td>
<td>Piperidino</td>
<td>200-201</td>
<td>80</td>
<td>C_{23}H_{24}N_{4}O_{2}S</td>
<td>68.31</td>
<td>5.94</td>
</tr>
<tr>
<td>2.</td>
<td>Nornholino</td>
<td>231-2</td>
<td>80</td>
<td>C_{22}H_{22}N_{4}O_{2}S</td>
<td>65.02</td>
<td>5.42</td>
</tr>
<tr>
<td>3.</td>
<td>Dimethylamino</td>
<td>211-2</td>
<td>60</td>
<td>C_{20}H_{20}N_{4}O_{2}S</td>
<td>65.93</td>
<td>5.5</td>
</tr>
<tr>
<td>4.</td>
<td>4-Methylani-</td>
<td>184-2</td>
<td>80</td>
<td>C_{29}H_{22}N_{4}O_{2}S</td>
<td>70.42</td>
<td>5.16</td>
</tr>
<tr>
<td>5.</td>
<td>Pyrrolidino</td>
<td>184-5</td>
<td>70</td>
<td>C_{22}H_{22}N_{4}O_{2}S</td>
<td>67.69</td>
<td>5.64</td>
</tr>
</tbody>
</table>

Crystallised form: a = Benzene; b = Ethanol.
yield - 80%, M.P - 231°C - 32°C (Acetic acid)

C₁₇H₁₃N₃O₅ S - Requires - C, 65.45; H, 4.25; N, 13.68.

Found - C, 66.33; H, 4.21; N, 13.52.

IR (KBr) (cm⁻¹) - C=O, 1650;

N'-R (δ) (DMSO₆ + CDCl₃) - H₂C=S, 4.8 (s) ; 3.H, 6.62 (s);

Ar-H, 7.0-8.2 (m).

11) **Synthesis of Mannich Bases (III)**

**General Method:**

In a dry 100 ml R. B. Flask, 4-benzimidazolylsulphide (II), (0.001 mole), a secondary amine (0.001 mole), and formalin (37%) (0.005 mole) in ab. ethanol (15 ml) were taken. This was refluxed on a steam bath for 6 hours. The reaction mixture was concentrated and left overnight, to get the crystals of the compound separated. This was filtered and washed with water. The motherliquor was concentrated and diluted with water to obtain a second crop of the compound. This was crystallised from a suitable solvent.

The compounds prepared in this manner, are listed with their analytical data in (Table - 6).

**Part III : Synthesis of 4,4'-Aryloxymethyl-2,2'-Bisquinoxalylsulphides (X)**

The steps involved are as shown below:

1) Synthesis of 4-Aryloxymethyl carbostyrils (VII).
ii) Conversion of ethers (VII) into their 2-chloro derivatives (VIII).

iii) Synthesis of 2-mercapto-4-Aryloxymethylquinolines (IX).

iv) Synthesis of bisquinolylsulphides (X).

i) Synthesis of 4-Aryloxymethyl Carbostyrils (VII)

These are prepared by the reaction of 4-bromomethylcarbostyril with substituted phenols in presence of a base and the details of the procedure are mentioned in Chapter II.

ii) Synthesis of 2-Chloro-4-Aryloxymethylquinolines (VIII)

General procedure for the conversion of ethers, into their corresponding 2-chloro derivatives by using phosphorous oxychloride, has been given in Chapter II.

iii) Synthesis of 2-Mercapto-4-Aryloxymethylquinolines (IX)

General Method:

In a 100 ml R. B. Flask, 2-chloro-4-Aryloxymethylquinoline (VIII) ($R'' = 2''$, $4''$-dichloro, and $4'' - CH_3$) (0.003 mole) and thiourea (0.003 mole), in a mixture of ethanol and ether (12 + 8) ml, were taken. The reaction mixture was first stirred for 2 hours and then refluxed on a waterbath for 5 hours. The yellow solid separated after filtration, was decomposed in a solution of sodium hydroxide(5%, 25 ml).
This was filtered, washed with excess of water and crystallised from suitable solvent.

1. \( R'' = 2'', 4'' \)-dichloro -
   yield - 80%, M.P - 229°-30°C (Acetic acid)

\[ \text{C}_{16}	ext{H}_{11}	ext{NO}_{2} \text{SCl}_2 \] - Requires - C, 57.14; H, 3.27; N, 4.16.
   Found - C, 57.00; H, 3.20; N, 4.20.

IR (KBr) (Cm\(^{-1}\)) - C=O-C, 1250.

NMR (\(^{1}H\)) (DMSO\(_d_6 + CDCl_3\)) - CH\(_2\), 5.2 (s);
   Ar-H, 7.0-7.5 (m).

2. \( R'' = 4'' - CH_3 \)-
   yield - 80%, M.P - 231°-2°C (Benzene),

\[ \text{C}_{17}	ext{H}_{15}	ext{NO}_{2} \] - Requires - C, 72.60; H, 5.33; N, 4.98.
   Found - C, 71.56; H, 5.28; N, 4.89.

IR (KBr) (Cm\(^{-1}\)) - C=O-C, 1250.

NMR (\(^{1}H\)) (DMSO\(_d_6\)) - CH\(_3\), 2.3 (s); CH\(_2\), 5.3 (s);
   Ar-H, 7.0 - 7.90 (m).

(iv) **Synthesis of Bisquinolinyl sulphides (X)**

**General Method:**

To a suspension of 2-mercapto compound (IX)
(\( \text{R} = 2', 4' \)-dichloro) (0.002 mole), and 2-chloroquinoline
 derivative (\( \text{VIII} \)) (0.002 mole), in ab. ethanol (25 ml) was added, anhydrous potassium carbonate (0.002 mole). The mixture
was refluxed on a steam bath for 6 hours. The reaction mixture was concentrated and poured into water to obtain a pasty mass, which was treated with dilute hydrochloric acid (1:1), to remove unreacted potassium carbonate. The compound was extracted with carbon tetrachloride. The organic layer was dried, treated with charcoal, filtered, concentrated and treated with dropwise addition of petroleum ether to get a white solid, which was recrystallised from a suitable solvent.

The compounds prepared with their analytical data are listed in (Table - 7).

Part IV(i) Synthesis of 4-Thiophenoxymethylcarbostyrils (VI)

In a 100 ml R.B. Flask, 4-bromomethylcarbostyril (I) (0.01 mole) (2.4g), and thiophenol (0.01 mole) (1.2 ml), in ab. ethanol (25 ml) were taken. To this, anhydrous powdered potassium carbonate (0.01 mole) (1.4g), was added. The reaction mixture was refluxed on a water bath for about 4-6 hours. After cooling, the solid separated was filtered and treated with dilute hydrochloric acid (1:1), to remove unreacted potassium carbonate. The compound, white in colour, was filtered and washed thoroughly with water and crystallised from ethanol.

yield - 80%, M. P - 215-6°C (d) (Ethanol)

C_{16}H_{15}NO - Requires - C, 71.91; H, 4.87; N, 5.24.

Found - C, 71.80; H, 4.35; N, 5.20.
## TABLE - 7

### Analytical Data of Bisquinolyl Sulphides (X)

![Chemical Structure](image.png)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>R</th>
<th>M.P°C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Required</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>1.</td>
<td>-H</td>
<td>92-93</td>
<td>60</td>
<td>C\textsubscript{32}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2}SCl\textsubscript{2}</td>
<td>67.48 3.36 4.92</td>
<td>67.36 3.83 4.85</td>
</tr>
<tr>
<td>2.</td>
<td>4-Methyl</td>
<td>102-103</td>
<td>60</td>
<td>C\textsubscript{33}H\textsubscript{24}N\textsubscript{2}O\textsubscript{2}SCl\textsubscript{2}</td>
<td>67.92 4.11 4.80</td>
<td>67.80 4.15 4.82</td>
</tr>
<tr>
<td>3.</td>
<td>4-Chloro</td>
<td>183-4</td>
<td>70</td>
<td>C\textsubscript{32}H\textsubscript{21}N\textsubscript{2}O\textsubscript{2}SCl\textsubscript{3}</td>
<td>67.63 3.48 4.64</td>
<td>63.65 3.50 4.56</td>
</tr>
<tr>
<td>4.</td>
<td>2-Chloro</td>
<td>129-30</td>
<td>70</td>
<td>C\textsubscript{32}H\textsubscript{21}N\textsubscript{2}O\textsubscript{2}SCl\textsubscript{3}</td>
<td>63.62 3.48 4.64</td>
<td>63.60 3.52 4.52</td>
</tr>
<tr>
<td>5.</td>
<td>2,4-Dichloro</td>
<td>154-5</td>
<td>70</td>
<td>C\textsubscript{32}H\textsubscript{20}N\textsubscript{2}O\textsubscript{2}SCl\textsubscript{4}</td>
<td>60.19 3.13 4.39</td>
<td>60.22 3.10 4.36</td>
</tr>
<tr>
<td>6.</td>
<td>2,4,5-Trichloro</td>
<td>179-80</td>
<td>70</td>
<td>C\textsubscript{32}H\textsubscript{19}N\textsubscript{2}O\textsubscript{2}SCl\textsubscript{5}</td>
<td>57.10 2.82 4.16</td>
<td>56.89 2.84 4.21</td>
</tr>
</tbody>
</table>

Crystallised from: a = Carbon tetrachloride; b = Carbon tetrachloride + pet. ether; c = Benzene + Pet. Ether.
178

IR (\text{Br}) (cm\textsuperscript{-1}) - C = O, 1660;
\\text{IR} (\delta) (\nu \text{SOD}G) - \text{CH}_2, 4.47 \text{ (s)}; 3-H, .53 \text{ (s)}
\nhr-H 7.20-7.90 \text{ (m)}; \text{NH}, 11.77.

11) \textbf{Synthesis of Hesolonic 1,3-Thiazolo-(3,2-a)-4-(2',4'-Dichloro)-Phenoxymethylquinoline (XIV)}

This involves, two step reaction from the 2-mercapto
4-(2',4'-dichloro)-phenoxymethylquinoline compound (IX):

a) \textbf{Preparation of 2-Carboxymethylthio-4-(2',4'-dichloro)-phenoxymethylquinoline (XIII) from the mercapto}
compound (R = 2',4'-dichloro) (IX)

A mixture of 2-mercapto compound (IX) (0.004 mole)
(1.240 g) and monochloroacetic acid (0.004 mole) (400 mg)
in sodiumhydroxide solution (5\%) (40 ml), was refluxed directly
on wire gauge, for 3 to 4 hours. After cooling, the reaction
mixture was treated with charcoal, filtered and neutralised
with hydrochloric acid to obtain a white solid compound. It
was recrystallised from Acetic acid.

yield - 80\%, M. P - 173\textdegree-4\textdegree C (d) (Acetic acid)
\text{C}_{18}H_{13}NC_{3} \text{SCl}_2 - \text{Requir s - C, 74.82; H, 3.30; N, 3.55.}
\text{Found - C, 74.72; H, 3.25; N, 3.60.}

b) \textbf{Synthesis of Hesolonic Thiazolyquinoline (XIV)}

To a solution of 2-mercaptoacetic acid (XIII) (0.0015-
mole) (640 mg), in acetic anhydride (7 ml), Pyridine (6 ml)
was added and the mixture was refluxed on a waterbath for
3 h. and left overnight. Separate dark coloured compound
was filtered, washed with excess of water to remove the unreacted
acetic anhydride and crystallised from Benzene and Petroleum ether.

\[ \text{yield} = 40\% ; \quad P = 115^\circ-116^\circ C \text{ (d) (Benzene+Pet. ether)} \]

\[ \text{C}_{18}H_{12}NO_2 \text{SCl}_2 \text{ - Requires - } C, 57.29; H, 3.18; N, 3.71. \]

\[ \text{Found - } C, 57.32; H, 3.15; N, 3.72. \]

\[ \text{IR (KBr) (Cm}^{-1}) \text{ - C=O, 1720; C-O-C, 1250.} \]

iii) Reaction of 2-Mercapto-4-aryloxymethylquinoline (IX)
with \( \alpha \)-Haloketones to get Thioacetylquinolines (XI)

General Method:

To a suspension of 2-mercapto-4-aryloxymethylquinoline
(IX) (Where \( R' = 2'' , 4'' \)-dichloro, and 4''-CH\(_3\)) (0.002 mole) in
absolute ethanol (20 ml), \( \alpha \)-haloketone \( ^{42-3} \) (\( R' = \text{Ph} \& 3\text{-coumarmyl} \)) (0.002 mole) was added and the reaction mixture was
refluxed on a waterbath for 5 hours. After cooling, it was
filtered, washed with excess of water and crystallised from
suitable solvent.

The following compounds were prepared:

1) \[ \text{XI - } R'' = 4'' \text{-CH}_3, \text{R'} = 3'\text{-coumarinyl} \]

\[ \text{yield} = 70\%; \quad P = 170^\circ-1^\circ C \text{ (Benzene)} \]

\[ \text{C}_{27}H_{21}NO_4S \text{ - Requires - } C, 71.70; H, 4.61; N, 3.07. \]

\[ \text{Found - } C, 71.12; H, 4.58; N, 3.12. \]
IR (FIR) (cm\(^{-1}\)) - C=O, 1710 (br).

IR (\(\delta\)) (DMSO\(_d_6\)) - CH\(_3\), 2.3 (s); CH\(_2\)=O, 3.4 (s);
S-CH\(_2\)=O, 5.2 (s); 3-H, 6.7 (s); 4-H, 7.0 (m);
Coumarin 4-H, 8.5 (s).

2) XI - R''-2", 4", dichloro, R' = Phenyl.
Yield - 70%, M.P - 181°-82°C (Benzene)
C\(_{23}\)H\(_{17}\)N\(_2\)O\(_2\)SCl\(_2\) - Requires - C, 62.44; H, 3.84; N, 3.16.
Found - C, 62.32; H, 3.92; N, 3.18.
IR (KBr) (cm\(^{-1}\)) - C=O, 1725.

3) XI - R'' - 2", 4" - dichloro, R' = 3'-Coumarinyl
Yield - 70%, M.P - 229°-30°C (Benzene).
C\(_{26}\)H\(_{17}\)N\(_4\)SCl\(_2\) - Requires - C, 61.17; H, 3.33; N, 2.74.
Found - C, 61.23; H, 3.28; N, 2.82.
IR (KBr) (cm\(^{-1}\)) - C=O, 1720 (br).

(iv) Attempted Synthesis of Thienoquinolines (XII)

Attempts were made to cyclise thioacetylquinoline compound (XI) to obtain thienoquinolines (XII), through various cyclodehydrating agents. The cyclising agents used were Polyphosphoric acid, Titanium tetrachloride and phosphorous oxychloride. However, the cyclisation did not occur and the thioacetyl compounds were obtained back.
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