4-ARYLOXYMETHYL-CARBOSTYRILS AND THEIR REACTIONS
INTRODUCTION

Chemistry of Tetrazoles in recent years, had undergone a great deal of expansion. Interest in many of these compounds has been stimulated because of their application in Industry, Agriculture and due to their biological and analytical importance\textsuperscript{1-2}.

Tetrazoles are generally regarded as azapyrroles, and are formally derived from pyrrole, by the replacement of three annular carbons by nitrogen atoms and are numbered as below:

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.3\textwidth]{tetrazole_structures.png}};
\end{tikzpicture}
\end{center}

Tetrazoles which can be regarded either as 1H or 2H-Tetrazoles exist in the tautomeric forms (II) and (IIa).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.3\textwidth]{tetrazole_structures.png}};
\end{tikzpicture}
\end{center}

The structural unit, $\text{-C} \ (N^2) = N$, is described either as an azidoazamethine, an iminoazide or an imidoylazide, all
of which terms are used widely in the literature\textsuperscript{3}.

The molecules are planar and exhibit aromatic properties with the sextet, comprising, one electron from carbon, two from the 'pyrrole' nitrogen and one each from the three 'Pyridine' nitrogens. The calculated resonance energy is high (230-250 K.J. mol\textsuperscript{-1}). Although no X-ray study of the parent molecule has been reported, some data are available for the anion\textsuperscript{4}.

\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}

\textbf{Structure of Tetrazole anion}

As expected on the basis of the tautomeric forms, (II) and (IIa), for tetrazole, there are three classes of monosubstituted (III-V) and two classes of disubstituted (VI-VII) derivatives. Fused ring tetrazoles of 1,5-disubstituted class are illustrated by tetrazolo pyridine (VIII).
Tetrazolyl quinoline (IX) falls under the last class, i.e., fused ring tetrazole of 1,5-disubstituted class and is systematically named as Tetrazolo-(1,5-a)-quinoline.5

Tetrazolo -(1,5-a)-quinoline.
TETRAZOLE AND 1,5-a FUSED TETRAZOLES

Eventhough the parent tetrazole itself does not exhibit any pharmacological activity, many nitrogen heterocycles fused with tetrazole moiety have been found to possess interesting biological actions. The tetrazole function is metabolically stable. This feature and a close similarity between the acidic character of the tetrazole group and carboxylic group have inspired synthesis of potential medicinal agents.

The most important tetrazole derivative known for its analeptic activity is pentamethylenetetrazole (X), commonly known as LEPTAZOL.

\[
\text{(X)}
\]

Tetrazoles fused with steroid skeleton has given rise to many antifertility, antispermatogenic agents, and possess normal activity. Many nitrogen heterocycles have been fused with tetrazole and the resulting compounds have a wide variety of medicinal properties which are presented in the following table.
<table>
<thead>
<tr>
<th>Structure</th>
<th>Activity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td>Analgetic</td>
<td>10</td>
</tr>
<tr>
<td><img src="image2" alt="Structure 2" /></td>
<td>Hypnotic</td>
<td>11</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>Bronchodilator, Pesticidal, Fungicidal, Antiulcer</td>
<td>12-15</td>
</tr>
<tr>
<td><img src="image4" alt="Structure 4" /></td>
<td>Antibacterial</td>
<td>16</td>
</tr>
<tr>
<td><img src="image5" alt="Structure 5" /></td>
<td>Analgesic</td>
<td>17</td>
</tr>
<tr>
<td>Structure</td>
<td>Activity</td>
<td>Ref.</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td><img src="image1.png" alt="Structure 6" /></td>
<td>Fungicidal</td>
<td>18</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 7" /></td>
<td>Plant protector</td>
<td>19</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 8" /></td>
<td>Anticancer</td>
<td>20</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 9" /></td>
<td>Antitumor</td>
<td>21</td>
</tr>
</tbody>
</table>
TETRAZOLYL QUINOLINES

The first 1,5-a fused tetrazolyl quinoline (XII) was reported by Marckwald\textsuperscript{22} by the reaction of 2-hydrazinoquinoline (XI) with nitrous acid.

\[
\begin{array}{c}
\text{(XI)} \\
\text{N-NH}_2
\end{array} \xrightarrow{\text{HNO}_2} \begin{array}{c}
\text{(XII)} \\
\text{N=N}
\end{array}
\]

Later Colonna and Risalti\textsuperscript{23} observed the formation of (XII) in the reaction of ethyl-2-quinolylazocarboxylate (XIII) with hydrazoic acid along with a triaziridine (XIV).

\[
\begin{array}{c}
\text{(XIII)} \\
\text{OC}_2\text{H}_5
\end{array} \xrightarrow{2\text{HN}_3} \begin{array}{c}
\text{(XIV)} + \text{(XII)} \\
\text{H}_5\text{C}_2\text{O}-\text{C}=\text{O}
\end{array}
\]

Dreikorn\textsuperscript{24} discovered the utility of tetrazolo-(1,5-a)-quinolines (XV) and their dihydro derivatives (XVI) against phytopathogenic organisms.
Some of them were effective against *Piriculoria Oryzae* at 400 ppm, and others inhibited the growth of *Agrobacterium tumefaciens* on tomato plants at 40 ppm. The dihydro derivatives (XVI) were particularly active against the fungi viz., *Rhizoctonia Erysiphe* and *Collectotrichum*.

Tetrazolyl alkoxy carbostyrils (XVII) and their dihydro derivatives inhibited cyclic AMP and phosphodiesterase and also showed vasodilator activity\(^{25}\).

\[
(XVII) \quad R = R' = R'' = -H, \quad -alkyl, \text{ etc.} \\
Z = \text{alkylene.}
\]
Recently Wright\textsuperscript{26-27} has patented tetrazolyl carbostyrils (XVIII) and tetrazolyl tetrazolo-(1,5-a)-quinolines (XIX) for their marked antiallergic activity.

![Chemical Structures](XVIII)(XIX)

\[ R = R^1 = R^2 = -\text{H}, -\text{alkyl}, \]
\[ \text{alkoxy}, -\text{SCH}_3 \text{ etc.} \]
\[ R^3 = \text{H}, \text{alkyl etc.} \]

**IMPORTANCE OF ARYLETHER LINKAGE IN QUINOLINE AND TETRAZOLE DERIVATIVES**

Various 2-and-4-phenoxyquinolines were reported as useful bactericides against \textit{S.Aureus} and \textit{E.Coli} from this laboratory\textsuperscript{28}.

![Chemical Structure](XX)

\[ R = \text{-Cl, -Br, 3,4-Cl etc.} \]
Many quinolinyl-2-phenoxyalkanoic acids (XXI) have been found to be herbicides.

Some 5-formyl-8-hydroxycarbostyrils (XXII) have been found to exhibit excellent antibacterial, antifungal, and platelet aggregation inhibitory activity.

In their study on potential antiviral agents Reed et al. have found 1-phenoxymethyl isoquinolines (XXIII) to be quite active.
In a closely related study, 2-chloro-3-phenoxymethyl quinolines (XXIV) have recently been reported\textsuperscript{32}.

\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}

(XXIV)

Many 5-phenoxymethyltetrazoles of the general structure (XXV) have been found to be useful as growth hormones for plants\textsuperscript{33}.

\begin{center}
\includegraphics[width=0.5\textwidth]{structure2.png}
\end{center}

(XXV)

\begin{align*}
\text{n} &= 1, 2; \quad R = \text{H, Cl, CH}_3 \text{ etc.}
\end{align*}

Structural variations and lengthening of carbon chain in (XXV) has given rise to many hypocholesterolemic agents\textsuperscript{34}.

Drain et al\textsuperscript{35} have synthesised a series of o-phenoyxcarb amoyl tetrazoles (XXVI) as possible anti-inflammatory agents. The most active compounds were A and B.
Recently a butoxyphenyl tetrazole derivative (XXVII) has been found to be an orally active Leukotriene antagonist.

Fungicidal activity has been claimed for some 2-phenoxy-pyridyl- tetrazoles (XXVIII), and some fused pyridazinyl tetrazoles (XXIX).
In the light of above discussion stressing the importance of phenoxy group in tetrazoles and paucity of literature on 1,5-a fused quinolines it was thought of interest to synthesise some 5-phenoxyethyl-(1,5-a)-tetrazolyl-quinolines (XXX).

\[
\begin{align*}
\text{CH}_2\text{O} & \quad \text{R} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N}
\end{align*}
\]

\[ R = -\text{H}, -4\text{-CH}_3 \text{ etc.} \]

(XXX)

Steps involved in the synthesis of above compounds and their properties will be discussed further.
PRESENT WORK

The work described under this chapter involves a three step synthesis of phenoxy methyl substituted 1,5-a tetrazolyl quinolines (IV) starting from 4-bromomethylcarbostyril (I). Typical reactions of some 4-phenoxy- methylcarbostyrils have also been carried out and the reactions are presented in Scheme-1.

4-bromomethylcarbostyril (I) was prepared by the bromination of acetoacetanilide and cyclising the intermediate w-bromoacetoacetanilide in sulphuric acid. Method reported by earlier workers was found to give low yields. In a slightly modified approach, we have standardized the procedure employing acetoacetanilide (6g) and isolating the intermediate w-bromoderivative as a white solid. This solid (instead of oil as reported) was found to give a better quality of product in good yields.

Bromine at the benzylic carbon in (I) was easily displaced by the strongly nucleophillic phenoxy anions leading to the formation of ethers (II), which react with phosphorous oxychloride at elevated temperatures to give the corresponding low melting 2-chloro compounds (III). These 2-chloro-4-phenoxy methyl quinolines (III) which are cyclic imidic chlorides, act as dipolarophiles and react with sodium azide in ethanol to give fused ring tetrazoles (IV).
Mechanism of tetrazole formation which is an example of 1,3-dipolar addition reaction is shown in Scheme-2.

**Scheme - 2**

First step is the nucleophilic attack of the azide ion to give imide azide (IIIa), as the transient intermediate, which undergoes intramolecular ring closure, involving N-N bond formation to yield the more stable tautomeric form, i.e., tetrazole (IV).

In accordance with the reaction of carbostyrils with compounds containing active methylene groups, the ethers (II), condense with barbituric acid in presence of acetic anhydride and acetic acid mixture (2:1), to give (V), in low yields. In another reaction, the naphthylether (VI),
undergoes azo coupling at the $\alpha$-position of the naphthlene ring, which is supported by the direct synthesis of (VII), by the reaction of (I) with the corresponding azonaphthol.
RESULTS AND DISCUSSION

PHYSICAL PROPERTIES

A preliminary examination of the melting points of the compounds synthesised during the present investigation reveals major differences in the melting points of 4-phenoxy-methylcarbostyrils (II) and the corresponding 2-chloro derivatives (III). This can be attributed to the fact that ethers (II) containing a cyclic amide grouping, can exist as dimers due to intermolecular hydrogen bonding (as shown below), which is characteristic of amides.

Since such a kind of bonding is not possible in the 2-chloro compounds (III), their melting points are lower than the corresponding ethers (Table - 1).
TABLE - 1

<table>
<thead>
<tr>
<th>S.No.</th>
<th>R</th>
<th>Melting Points (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(II)</td>
</tr>
<tr>
<td>1.</td>
<td>-H</td>
<td>198-9</td>
</tr>
<tr>
<td>2.</td>
<td>4'-CH₃</td>
<td>231-32</td>
</tr>
<tr>
<td>3.</td>
<td>4'-Cl</td>
<td>210-11</td>
</tr>
<tr>
<td>4.</td>
<td>2'-Cl</td>
<td>225-26</td>
</tr>
<tr>
<td>5.</td>
<td>2',4'-dichloro</td>
<td>243-4</td>
</tr>
<tr>
<td>6.</td>
<td>2',4',5'-trichloro</td>
<td>262-63</td>
</tr>
<tr>
<td>7.</td>
<td>2',4',6'-tribromo</td>
<td>275-6</td>
</tr>
</tbody>
</table>

SPECTRAL PROPERTIES

The infra-red spectra of 4-phenoxymethylcarboxylic esters were typical of an amide group. The carbonyl stretching frequency was observed around 1670 $\text{cm}^{-1}$. The N-H stretching vibration could not be observed as a sharp band, but a moderately strong hump appeared around 3200-3400 $\text{cm}^{-1}$. Vibrations due to ether linkage were observed as a set of at least three bands in the region of 1100-1270 $\text{cm}^{-1}$ (Fig. 1-2). Ultraviolet spectra of the
above ethers exhibited three bands around 220, 270 and 320 nms respectively, characteristic of 2-hydroxyquinoline derivatives \(^{41-2}\) (Table - 2). In the PMR spectra, all the protons resonated at expected fields. The 3-proton appeared around 6.6 ppm as observed with carbostyril and the N-H proton was observed downfield around 11.5 ppm in accordance with earlier workers\(^{43-4}\). (Fig. 3-4) (Table - 3).

**Infra-red frequencies for the 2-chloro derivatives**

are recorded in (Table - 4). All the compounds showed absence of C=O group and exhibited vibrations typical of 4 and 2-substituted quinolines\(^{45-6}\). In the PMR spectra the methylene protons appeared around 5.4 ppm and the quinoline 3-proton was found to merge in the aromatic multiplet (Fig. 5).

**Infra-red spectra indicated the formation of tetrazoles (IV) from the corresponding 2-chloro-4-phenoxymethylquinolines (III).** In general, 1,5-fused tetrazoles give rise to two principal absorptions\(^{47}\):

\begin{align*}
\text{a) } & 1335-1270 \text{ Cm}^{-1} \text{ (Cyclic } N\equiv N\equiv N) \text{ and} \\
\text{b) } & 1100-980 \text{ Cm}^{-1} \text{ (upto three bands; skeletal vibrations of the tetrazole ring).}
\end{align*}

In a typical case a 2-chloro compound
FIG 3

a = 3.8, OCH₃
b = 5.4, OCH₂
c = 6.65, C-3-H
d = 7.0-7.8, Ar-H
s = solvent

(DMSO-d₆)
FIG. 4

$\alpha = 2.25, \text{CH}_3$

$\beta = 5.36, \text{CH}_5 \text{O}$

$\gamma = 6.61, 3 \text{H}$

$\delta = 6.9-7.8, \text{Ar-H}$

$\epsilon = 11.78, \text{NH}$

$S = \text{Solvent}$

(DMSO-$d_6$)
**TABLE - 2**

**IR & UV Spectral Data of some 4-phenoxy methyl carbostyrils (II)**

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>R</th>
<th>IR (cm⁻¹)</th>
<th>UV (Ethanol) nm (λ max)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C=O</td>
<td>C-O-C</td>
</tr>
<tr>
<td>1.</td>
<td>-H</td>
<td>1660</td>
<td>1150, 1240</td>
</tr>
<tr>
<td>2.</td>
<td>-4-CH₃</td>
<td>1680</td>
<td>1160, 1260</td>
</tr>
<tr>
<td>3.</td>
<td>-4-Cl</td>
<td>1660</td>
<td>1110, 1230</td>
</tr>
<tr>
<td>4.</td>
<td>-2-Cl</td>
<td>1670</td>
<td>1220, 1240</td>
</tr>
<tr>
<td>5.</td>
<td>-2-CH₃</td>
<td>1670</td>
<td>1180, 1250</td>
</tr>
<tr>
<td>6.</td>
<td>-2-OCH₃</td>
<td>1675</td>
<td>1165, 1250</td>
</tr>
<tr>
<td>7.</td>
<td>-2,4-Cl</td>
<td>1660</td>
<td>1240, 1280</td>
</tr>
<tr>
<td>8.</td>
<td>-2,4,5-Cl</td>
<td>1660</td>
<td>1150, 1170</td>
</tr>
<tr>
<td>9.</td>
<td>-2,4,6-Br</td>
<td>1670</td>
<td>1220, 1240</td>
</tr>
<tr>
<td>10.</td>
<td>-2-COCH₃</td>
<td>1680</td>
<td>1230, 1260</td>
</tr>
<tr>
<td></td>
<td>4,6-Br.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### PMR Spectral Data of some 4-phenoxymethylcarbostyrils (II)

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>Solvent</th>
<th>R</th>
<th>3-H</th>
<th>N-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>DMSO-d$_6$</td>
<td>-H</td>
<td>5.3</td>
<td>11.3</td>
</tr>
<tr>
<td>2.</td>
<td>DMSO-d$_6$</td>
<td>4'-CH$_3$</td>
<td>6.6</td>
<td>6.6</td>
</tr>
<tr>
<td>3.</td>
<td>DMSO-d$_6$</td>
<td>2'-CH$_3$</td>
<td>5.3</td>
<td>11.4</td>
</tr>
<tr>
<td>4.</td>
<td>DMSO-d$_6$ + CDC$_3$</td>
<td>2',4'-Cl</td>
<td>6.5</td>
<td>11.5</td>
</tr>
<tr>
<td>5.</td>
<td>DMSO-d$_6$</td>
<td>2',6',-Cl</td>
<td>5.3</td>
<td>11.4</td>
</tr>
</tbody>
</table>

($\delta$ ppm downfield from TMS)
# TABLE - 4

IR Spectral Data of some 2-Chloro-4-phenoxymethylcarbostyrils (III)

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

<table>
<thead>
<tr>
<th>S.No.</th>
<th>R</th>
<th>C=N (Cm⁻¹)</th>
<th>C-O-C (Cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>-H</td>
<td>1600</td>
<td>1245, 1160</td>
</tr>
<tr>
<td>2.</td>
<td>-4'-Cl</td>
<td>1580</td>
<td>1270, 1230, 1160</td>
</tr>
<tr>
<td>3.</td>
<td>-4'-CH₃</td>
<td>1520</td>
<td>1250, 1180, 1140</td>
</tr>
<tr>
<td>4.</td>
<td>-2'-Cl</td>
<td>1590</td>
<td>1240, 1170</td>
</tr>
<tr>
<td>5.</td>
<td>2',4'-Cl</td>
<td>1595</td>
<td>1250, 1270, 1150</td>
</tr>
<tr>
<td>6.</td>
<td>2',4',5'-Cl</td>
<td>1590</td>
<td>1250, 1170, 1150</td>
</tr>
<tr>
<td>7.</td>
<td>2',4',6'-Br</td>
<td>1610</td>
<td>1240, 1190, 1160</td>
</tr>
</tbody>
</table>

54
exhibited two bands at 1285 (m) and 1320 (w) Cm$^{-1}$ respectively. In the same region the corresponding tetrazole showed at least four bands at 1290 (s), 1315 (m) 1325 (s), 1335 (w) Cm$^{-1}$, which indicated the formation of tetrazoles (Fig. 6). Similarly the skeletal vibrations of the tetrazole ring were observed as a set of four bands around 985-1100 Cm$^{-1}$, while their precursors showed only two or three bands in this region, thus supporting the formation of tetrazoles (IV).

In the PMR spectra of tetrazoles, the doublet at the lowest field ($\sim 8.5$ ppm; $\sim 8$ Hz) is expected to be due to H-9, because of its proximity to N-1, which causes deshielding due to anisotropic and lone pair dipole effects. Similar observations for H-9 have been reported for all tetrazolo- (1,5-a)-quinolines$^{48}$ (Table - 5).

In the PMR spectra of the precursors i.e., the 2-chloro derivatives no proton resonates beyond 8.1 ppm which further strengthens the support for the assignment of H-9. Moderate solvent effects are observed for the spectra recorded in deuterochloroform and dimethyl sulphoxide solutions. Positions of H-9 and methylene protons are shifted by about 0.2 ppm and other protons resonate at expected fields (Fig. 7-9).
\[ \text{FIG 7} \]

- \( a = 2.2, \text{CH}_3 \)
- \( b = 555, \text{CH}_2\text{O} \)
- \( c = 6.9-8.3, \text{Ar-H} \)
- \( d = 8.65, 9\text{H} \)
- \( S = \text{Solvent} \)
a = 3, CH₃
b = 55, CH₂O
c = 69-82, A*-H
d = 88, 9'H

FIG. 8
FIG 9

a = 5.5, CH$_2$-O
b = 6.7-7.8, Ar-H
c = 8.4, 9-H
s = solvent

\[
\begin{align*}
\text{(cocl$_2$)}
\end{align*}
\]
<table>
<thead>
<tr>
<th>R</th>
<th>Solvent</th>
<th>-CH₂-0(s)</th>
<th>Ar-H(m)</th>
<th>H-9(d)</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>- H</td>
<td>CDCl₃</td>
<td>5.30</td>
<td>6.8-7.8</td>
<td>8.4 (J=8.5Hz) Ar-H</td>
<td></td>
</tr>
<tr>
<td>- 4'-CH₃</td>
<td>CDCl₃</td>
<td>5.50</td>
<td>6.9-8.1</td>
<td>8.78 (J=8.2Hz) 2.32</td>
<td></td>
</tr>
<tr>
<td>- 4'-CH₃</td>
<td>DMSO-d₆</td>
<td>5.55</td>
<td>6.9-8.2</td>
<td>8.62 (J=8.8Hz) 2.22</td>
<td></td>
</tr>
</tbody>
</table>

MASS SPECTRA

Amongst various compounds reported in this chapter mass spectral fragmentation has been studied for some 4-phenoxymethylcarbostyrils, and one tetrazole derivative.

1) **4-PHENOXYMETHYLCARBOSTYRILS**

(Table-6) shows some important peaks observed in the bar graphs of these compounds.

All these compounds show (M+H) ion as the base peak in the chemical ionisation spectra. Further, it can be seen that the even electron ion at m/e 130 constitutes the base peak in the E.I. spectra of all the ethers. Halogenated ethers show the loss of Cl. and the corresponding even electron ions for(Ib) and(Io) are observed at 250 (15%) and
TABLE 6

Mass Spectral Data of some 4-Phenoxymethylcarbostyrils (II)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>M⁺</th>
<th>M-H</th>
<th>C.I.: (M+H)⁺ Base Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta</td>
<td>-H</td>
<td>251 (21%)</td>
<td>250 (25%)</td>
<td>252 (100%); 288 (29%)</td>
</tr>
<tr>
<td>Tb</td>
<td>2'-Cl</td>
<td>285 (19%)</td>
<td>284 (92%)</td>
<td>286 (23%); 320 (100%); 322 (65%); 324 (9%)</td>
</tr>
<tr>
<td>Tc</td>
<td>2',4'-Cl</td>
<td>319 (10%)</td>
<td>318 (3%)</td>
<td>320 (100%); 322 (2%)</td>
</tr>
</tbody>
</table>

Diagram: Structured representation of the compounds with chemical structure labels.
and 284 (6%); 286 (2%) m/e values respectively. A plausible breaking pattern is proposed for these compounds in the following schemes.

**SCHEME - 1**

The molecular ion can undergo a homolytic fission of the C-O bond to give two daughter ions (II) and (III). The oxygen containing fragment (III) also tries to retain the charge but can easily eliminate a molecule of carbon monoxide through other contributing structures (IVa), to end up in ions of high intensity. This pattern is not observed in the case of (Ic) and in the case of (Ib) this is accompanied by an immediate loss of 60 to give (IVb).

The major fragmentation in all the compounds is by the expulsion of a molecule of carbon monoxide from the carbostyril ion (II) which gives the base peak at m/e 130. This alkylated indole can undergo ring expansion, to the quinolinium ion (Va) which can rearrange to (VB). A molecule of HCN can now be expelled from (VB) to get ion (VI) at m/e 103, which can eliminate a molecule of acetylene to end up in (VII), observed in high intensity in all the cases.

**SCHEME - 2**

In a less favoured route the molecular ion (I) can expel a neutral molecule by an intramolecular hydrogen
SCHEME 1

\[ \text{[Chemical Structures and Reactions]} \]

\[ \text{[Reaction Equations and Percentages]} \]
MASS SPECTRUM
09/26/95 10:18:00 + 0:04
SAMPLE: MUR-MT-3
#1 TO #4 SUMMED
DATA: MP21 #1
CALI. CA22 #1
MASS SPECTRUM
03 22'35 3.52:08 + 0:04
SAMPLE: MUR-MT-4
#1 TO #4 SUMMED

BAAE M'E ...

DATA MR41 #2
CALI. CA42 #1
RIGI. 5134

T SOURCE 250
T PROBE 200
EI 70eV

CH₂-O

Cl

DATA MR41 #2
CALI. CA42 #1
RIGI. 5134

T SOURCE 250
T PROBE 150
CI 70eV

CH₂-O

Cl
transfer leading to an odd electron ion (VIII) at m/e 159. This process is more favoured in the chemical ionisation especially in the case of halogenated ethers (Ib) and (Ic). This ion (VIII) can undergo a loss of carbon monoxide, which is characteristic of carbostyrils to give an alkylated indole (IX) at m/e 131 observed in moderate intensities in all the compounds, and follows the reported fragmentation pattern for alkylindoles (Scheme-1).

In an alternative pathway the molecular ion (I) can also undergo a loss of carbon monoxide and expulsion of a neutral molecule to end up in an odd electron ion (X) corresponding to 3-formyl indole. This proposition is further supported by its characteristic fragmentation from (X → XIII) through (XI) and (XII) by the successive eliminations of H and carbon monoxide, HCN and an acetylene molecule which is observed in the spectra of all the compounds.

ii) 5′-p-TOLYLOXYMETHYL-(1,5-a)-TETRAZOLOQUINOLINE

Bar graph shows the intensities of the various ions produced after electron impact. The fragmentation of this molecule is discussed in the following pages.
SCHEME - 1

The molecular ion (I) can undergo a homolytic fission of the C-O bond to give two daughter ions (II) and (III). The tetrazoloquinolyl ion (II) can eliminate a molecule of nitrogen, undergoing a simultaneous ring contraction to give an 3-alkyl indole -2-nitrile (V) in high intensity. The even electron ion (V) can undergo ring expansion, characteristic of indoles, to the quinolinium ion (Va), which can eliminate a molecule of HCN, which accounts for the base peak in the form of ion (VI), at m/e 128. This ion (VI) follows the breaking pattern for quinoline and eliminates molecules of HCN and acetylene successively to give ions (VII) and (VIII) respectively.

Charge retention in the oxygen containing fragment (III) is associated through rearrangement to the hydroxy tropylium cation (IIIa). The even electron ion (III) can undergo a loss of carbon monoxide via (IIIb) to end up in an hydrocarbon ion (IV) at m/e 79.

SCHEME - 2

In another route the molecular ion (I) can eliminate a molecule of nitrogen to form an odd electron ion (IX) at m/e 262, which undergoes a loss of methyl radical resulting in the formation of an even electron ion (X). This ion (X)
Scheme 2

- N2
- CH3
- CH2-O

I M+ m/e 280 (10%)

IX m/e 262 (6%)

X m/e 247 (4%)

Xa

XI m/e 220 (40%)

XII

not present

m/e 93
can undergo ring expansion (as mentioned in Scheme-1) to the quinolinium ion (Va) which can eliminate a molecule of HCN to end up in an ion of high intensity at m/e 220. In accordance with diaryl ethers the ion (XI) can eliminate a molecule of 4-hydroxyquinoline (XII), the charge being retained entirely by the hydrocarbon part, (VIII) (Scheme-1). The other mode of bond fission, involving the elimination of a heterocyclic benzyne molecule is highly improbable as the corresponding ion at m/e 93 is not seen in the spectrum.

This completes the discussion regarding the spectral properties of the compounds synthesised during the present investigation and the results of the biological studies will be presented in the last chapter.
EXPERIMENTAL

This section has been divided into three parts:

I) Synthesis of 5-(Aryloxymethyl)-Tetrazolo-(1,5-a)-Quinolines (IV)

Synthesis of (IV), involved the following steps:

i) Preparation of 4-bromomethyl carbostyril (I).

ii) Synthesis of 4-(Aryloxymethyl)-Carbostyrils (II).

iii) Conversion of Ethers (II), to the corresponding 2-chloro-4-(Aryloxymethyl)-quinolines (III).

iv) Synthesis of fused tetrazoloquinolines (IV).

II) Reaction of 4-Toluloxymethyl Carbostyril (II, R=4'-CH₃) with Barbituric acid to obtain compound (V)

III) Synthesis of 4-(2'- (1'-p-Tolylazo)-Naphthyloxymethyl)-Carbostyril (VII)

Azoether (VII) can be synthesised by the following two methods:

i) Direct synthesis of (VII), by the condensation of 4-bromomethyl carbostyril (I) with, 1-(p-Tolylazo)-2-naphthol (VIa).

ii) (a) Synthesis of 4-(2'-naphthyloxymethyl)-carbostyril (VI).
b) Coupling of (VI), with p-Toluidine diazonium-chloride to get the azoether (VII).

I) (i) Preparation of 4-Bromomethylcarbostyril \(^{39,53}\) (I)

In a dry 100 ml R.B. flask, Acetoacetanilide (0.034 mole) (6g), in dry chloroform (6 ml), was taken. This was treated dropwise with Bromine (0.034 mole) (5.44g\(\cdot\)2 ml) in chloroform (6 ml) and stirred for 1 hour, till a pale yellow solid was separated. The reaction mixture was then refluxed on a water bath for 3-4 hours. The resulting solid, after the removal of chloroform, was treated with sulphuric acid (20 ml) slowly and heated on a waterbath for 30 min. After cooling, the reaction mixture was poured over 320 ml of ice water. The product, white in colour, was separated and was crystallised from Acetic acid.

- yield - 70\%, M.P - 256°-57°C (d) (Acetic acid).

NMR (\(\delta\)) (CDCl\(_3\)) - CH\(_2\)Br, 4.75 (s); 3-CH, 6.55 (s); Ar-H, 7.1-7.7 (m).

(ii) Synthesis of 4-(Aryloxymethyl)-Carbostyrils (II)

General Method:

To a suspension of 4-bromomethylcarbostyril (0.02 mole), potassium carbonate (0.02 mole), in ethanol (20 ml), contained in a 100 ml R.B. flask, phenol (0.02 mole) was added. The
reaction mixture was refluxed on a water bath for 6 hours. After cooling, it was filtered and the separated solid was treated with dilute hydrochloric acid (1:1). The residual solid was filtered, washed with excess of water and crystallised from suitable solvent. Filtrate was treated with charcoal, concentrated and diluted with water to obtain some more of the condensed product.

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

(iii) Synthesis of 2-Chloro-4-(Aryloxymethyl)-Quinolines (III)

General Method:

In a dry 100 ml R.B. flask, 4-(Aryloxymethyl)-carbostyril (0.02 mole) was taken. To this excess of phosphorous oxychloride (0.03 mole) was added. The reaction mixture was refluxed on an oil bath at 130°-140°C for 2 hours. Excess of phosphorous oxychloride was removed by distillation under reduced pressure. The oily reaction mixture was poured slowly in 300 g of ice. The separated solid was filtered, washed with excess of water and crystallised from suitable solvent.

The compounds prepared with their analytical data are listed in (Table-8).
### TABLE 7

**Analytical Data of some 4-Phenoxymethylcarbostyrils (II)**

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>R</th>
<th>M.P°C</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>-H</td>
<td>198-9</td>
<td>80</td>
<td>C_{16}H_{12}NO_{2}</td>
<td>76.5</td>
</tr>
<tr>
<td>2.</td>
<td>4'-CH_{3}</td>
<td>231-2</td>
<td>80</td>
<td>C_{17}H_{15}NO_{2}</td>
<td>76.99</td>
</tr>
<tr>
<td>3.</td>
<td>4'-Cl</td>
<td>210-11</td>
<td>80</td>
<td>C_{16}H_{12}NO_{2}Cl</td>
<td>67.2</td>
</tr>
<tr>
<td>4.</td>
<td>2'-Cl</td>
<td>225-6</td>
<td>80</td>
<td>C_{16}H_{12}NO_{2}Cl</td>
<td>67.2</td>
</tr>
<tr>
<td>5.</td>
<td>2',4'-Cl</td>
<td>243-4</td>
<td>80</td>
<td>C_{16}H_{14}NO_{2}Cl_{2}</td>
<td>60.00</td>
</tr>
</tbody>
</table>
### Contd. Table - 7.

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>R</th>
<th>M.P°C</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>6.</td>
<td>2',4',5'-Cl</td>
<td>262-3 (c)</td>
<td>80</td>
<td>C₁₀H₁₀N₂O₂Cl₃</td>
<td>54.16</td>
</tr>
<tr>
<td>7.</td>
<td>2',4',6'-Br</td>
<td>275-6 (c)</td>
<td>80</td>
<td>C₁₆H₁₀N₂O₂Br₃</td>
<td>39.3</td>
</tr>
<tr>
<td>8.</td>
<td>2'-OCH₃</td>
<td>195-6 (a)</td>
<td>80</td>
<td>C₁₇H₁₅N₂O₃</td>
<td>72.6</td>
</tr>
<tr>
<td>9.</td>
<td>2'-CH₃</td>
<td>208-9 (a)</td>
<td>80</td>
<td>C₁₇H₁₅NO₂</td>
<td>76.98</td>
</tr>
<tr>
<td>10.</td>
<td>-2'-COCH₃</td>
<td>215-6 (c)</td>
<td>60</td>
<td>C₁₈H₁₃N₂O₃Br₂</td>
<td>47.9</td>
</tr>
</tbody>
</table>

Crystallised from:  
- **a** = Benzene;  
- **b** = Benzene + Pet. Ether;  
- **c** = Acetic acid.
### TABLE 8
Analytical Data of some 2-Chloro-4-Phenoxyethylcarbostyrils (III)

![Chemical Structure]

<table>
<thead>
<tr>
<th>S.No.</th>
<th>R</th>
<th>M.P°C</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>-H</td>
<td>103-4</td>
<td>60</td>
<td>C_{16}H_{12}NOCl</td>
<td>71.24</td>
</tr>
<tr>
<td>2.</td>
<td>4'-CH₃</td>
<td>99-100</td>
<td>65</td>
<td>C_{17}H_{14}NOCl</td>
<td>71.96</td>
</tr>
<tr>
<td>3.</td>
<td>4'-Cl</td>
<td>106-7</td>
<td>60</td>
<td>C_{16}H_{11}NOCl₂</td>
<td>63.16</td>
</tr>
<tr>
<td>4.</td>
<td>2'-Cl</td>
<td>115-16</td>
<td>60</td>
<td>C_{16}H_{11}NOCl₂</td>
<td>63.16</td>
</tr>
<tr>
<td>5.</td>
<td>2',4'-Cl</td>
<td>159-60</td>
<td>70</td>
<td>C_{16}H_{10}NOCl₃</td>
<td>56.77</td>
</tr>
<tr>
<td>6.</td>
<td>2',4',5'-Cl</td>
<td>170-7</td>
<td>50</td>
<td>C_{16}H_{9}NOCl₄</td>
<td>51.47</td>
</tr>
<tr>
<td>7.</td>
<td>2',4',6'-Br</td>
<td>189-90</td>
<td>45</td>
<td>C_{16}H_{9}NOBr₃Cl</td>
<td>37.91</td>
</tr>
</tbody>
</table>

Crystallised from: a = Benzene; b = Ethanol.
(iv) Synthesis of 5\textsuperscript{(Aryloxymethyl)}-Tetrazolo-(1,5-a)-Quinolines (IV)

General Method:

In a 100 ml of R.B. flask, sodium azide (0.02 mole) in a few drops of water was taken. To this, 2-chloro-4-(Aryloxymethyl)-quinoline (0.02 mole) in ethanol (20 ml) was added. The reaction mixture was refluxed on a water bath for 4-5 hours. After cooling the separated solid was filtered, washed with excess of water and crystallised from suitable solvent.

The compounds prepared with their analytical data are listed in (Table-9).

II) Reaction of 4-(Toluloxymethyl)-Carbostyril (II)
\((R=4' - \text{CH}_3)\) With Barbituric acid to obtain compound (V)

Condensation of 4-p-Toluloxymethyl carbostyril with barbituric acid in presence of mixture of Acetic anhydride and Acetic acid (2:1), yielded (V), according to the method of Eiden et al.\textsuperscript{40}

yield - 40\%, M.P. - 245\(^\circ\)(d) (Acetic acid)

\(\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_4\) - Requires - C, 67.20; H, 4.53; N, 11.2

Found - C, 67.02; H, 4.32; N, 10.98

IR (KBr) (Cm\(^{-1}\)) - C=O, 1660.

UV (\text{	extsuperscript{\scriptsize{cCH}}}) (nms) - 510; 475; 380.
**TABLE - 9**

Analytical Data of some Tetrazolo-(1,5-a) quinolines (IV)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>R</th>
<th>M.P°C</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>-H</td>
<td>181-2</td>
<td>60</td>
<td>C₁₆H₁₂N₄O</td>
<td>69.60</td>
</tr>
<tr>
<td>2.</td>
<td>4'-CH₃</td>
<td>206-7</td>
<td>60</td>
<td>C₁₇H₁₄N₄O</td>
<td>70.35</td>
</tr>
<tr>
<td>3.</td>
<td>4'-Cl</td>
<td>184-5</td>
<td>60</td>
<td>C₁₆H₁₁N₄OCl</td>
<td>61.84</td>
</tr>
<tr>
<td>4.</td>
<td>2'-Cl</td>
<td>202-3</td>
<td>60</td>
<td>C₁₆H₁₁N₄OCl</td>
<td>61.84</td>
</tr>
<tr>
<td>5.</td>
<td>2',4',5'-Cl</td>
<td>248-9</td>
<td>60</td>
<td>C₁₆H₉N₄OCl₂</td>
<td>50.59</td>
</tr>
<tr>
<td>6.</td>
<td>2',4',6'-Br</td>
<td>255-6</td>
<td>50</td>
<td>C₁₆H₉N₄OBr₃</td>
<td>37.43</td>
</tr>
</tbody>
</table>

* All the compounds were crystallised from Acetic Acid.
III) (i) Direct Synthesis of (VII), by the condensation of 4-Bromomethyl Carbostyril (I) with 1-(p-Tolylazo)-2-Naphthol (VIa)

To a suspension of 1-(p-Tolylazo)-2-naphthol (0.01 mole) (2.6 g) and powdered, anhydrous potassium carbonate (0.01 mole) (1.38 g) in dry Acetone (20 ml), was added 4-bromomethylcarbostyril (0.01 mole) (2.4 g). The reaction mixture was first stirred for 12 hours and then refluxed on a waterbath for about 14 hours. The reaction mixture was left overnight, to obtain a solid separated, which was treated with dilute hydrochloric acid (1:1), to remove unreacted potassium carbonate. The residual solid was filtered, washed with excess of water and crystallised from Acetic acid.

yield - 30% M.P - 231°-2°C (d) (Acetic acid)

C_{27}H_{21}N_{3}O_{2} - Requires - C, 77.33; H, 5.01; N, 10.02.

Found - C, 77.12; H, 4.85; N, 9.93.

IR (Nujol) (Cm^{-1}) - C=O, 1655, C-O-C, 1100.

(ii) (a) Synthesis of 4-(2'-Naphthyl)oxymethyl)-Carbostyril (VI)

This was prepared according to the general method for 4-Aryloxymethylcarbostyrils (II), mentioned earlier, with the exception that, potassium hydroxide was
used instead of potassium carbonate.

yield - 60%, M.P - 281°-81°C (d) (Toluene),
C_{20}H_{15}NO_2 - Requires - C, 79.73; H, 4.98; N, 4.65.

Found - C, 79.51; H, 4.78; N, 4.40.

b) Coupling of (VI), with p-Toluidine Diazonium-chloride to get the Azoether (VII)

To a suspension of naphthylether (VI), in aqueous sodiumhydroxide (10%, 5ml) at 0°C, was added a solution of p-Toluidine diazoniumchloride (excess), slowly with stirring and the temperature was kept below 0°C throughout. After the addition, the reaction mixture was stirred for 30 min. at room temperature, and then diluted with water, filtered and crystallised from suitable solvent.

Both the azoethers were same as confirmed by their mps, mmps, and IR spectra.
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