CHAPTER - IV

PYRAZOLYLINDOLES

INTRODUCTION
Pyrazole 335 or 1,2-diazole was first obtained by Knorr in 1883, it exhibits aromatic character with properties resembling both pyridine and pyrrole. Pyrazole can be regarded as overlapping pyrrole and pyridine in order that predictions concerning the reactivities of the ring carbons can be made. The electrophilic substitution reactions occur at position-4, the position of the highest $\pi$ electron density. The annular nitrogen atom reduces electron density at the 3- and 5-positions.

![Pyrazole structure](image)

Pyrazoles exhibit wide number of biological and pharmacological properties$^{374-376}$ such as antipyretic, analgesic, antiarthritic, antiinflammatory and antirheumatic activities. The drug antipyrine (2,3-dimethyl-1-phenyl-5-pyrazolone) or phenazone 336 is an analgesic and antiarthritic.

![Antipyrine structure](image)

El-Kerdawy and associates$^{377}$ have reported the synthesis of 2-(1-phenyl-4,5-dihydro-3-pyrazolyl)benzimidazole 337.

![Benzimidazole structure](image)

$R = C_6H_5, 3,4-(OCH_3)_2C_6H_3, 4-F-C_6H_4, 3$-pyridyl and 2-thienyl
The compound with \( R = 3\)-pyridyl demonstrated vasodilator, anti-inflammatory and analgesic properties while compound with \( R = C_6H_5 \) was vasodilator and compound with \( R = 4\)-F-C\(_6\)H\(_4 \) was hypotensive.

Tripathy et al\(^{378} \) have synthesised pyrazole moiety of the type 338 and reported their monoamine oxidase inhibiting activity.

\[
\begin{align*}
\text{338} \\
\text{R = 2-F, 3-Cl, 2-OCH}_3, \ H
\end{align*}
\]

Thomas and coworkers\(^{379} \) have reported the synthesis and herbicidal activity of 5-hydroxypyrazole derivative 339.

\[
\begin{align*}
\text{339} \\
\text{Et}
\end{align*}
\]

Shibata et al\(^{380} \) have synthesised 3-fluoromethylpyrazole 340 as insecticide.
Lohray and associates have reported 1-aryl-3-fluoromethyl-5-aryl pyrazole 341 as antiinflammatory agent.

The above compound was useful in the treatment of prophylaxis diseases of cyclooxygenase.

Fukuji et al have prepared N-thiadiazolylpyrazolecarboxamides 342 and reported their acaricidal and insecticidal activities.

R¹= H, alkyl, Ph, substituted Ph. R² = alkyl, haloalkyl, cycloalkyl,
X= H, halo, alkyl, alkoxy, NO₂, cyano, Y= alkyl, haloalkythio.
Pimenova and associates\textsuperscript{383} have synthesised 5-aryl-4(arylazo)-1H-pyrazole-3-carboxylic acids \textit{343} and reported their antimicrobial activity.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\text{HOOC}};
  \node (b) at (1,0) {\text{N=N}};
  \node (c) at (2,0) {\text{N}};
  \node (d) at (3,0) {\text{R}};
  \node (e) at (0,-1) {\text{R}^1};
  \node (f) at (1,-1) {\text{N}};
  \node (g) at (2,-1) {\text{N}};
  \node (h) at (3,-1) {\text{R}};
  \node (i) at (3,-2) {\text{R}^2};
  \node (j) at (3,-3) {\text{R}^3};
  \node (k) at (3,-4) {\text{X}};
  \node (l) at (3,-5) {\text{CCR}^3};

\end{tikzpicture}
\end{center}

\textbf{343}

\begin{itemize}
  \item R = H, Me; R, = Cl, Me, OMe
\end{itemize}

Betageri et al\textsuperscript{384} have synthesised pyrazolyl urea of the type \textit{344} and reported them as antiinflammatory agents.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\text{N}};
  \node (b) at (1,0) {\text{O}};
  \node (c) at (2,0) {\text{C}};
  \node (d) at (3,0) {\text{N}};
  \node (e) at (4,0) {\text{H}};
  \node (f) at (5,0) {\text{N}};
  \node (g) at (6,0) {\text{H}};
  \node (h) at (7,0) {\text{O}};
  \node (i) at (8,0) {\text{CH}^3};
  \node (j) at (9,0) {\text{C}};
  \node (k) at (10,0) {\text{H}};
  \node (l) at (11,0) {\text{H}};
  \node (m) at (12,0) {\text{C}};
  \node (n) at (13,0) {\text{H}};
  \node (o) at (14,0) {\text{H}};
  \node (p) at (15,0) {\text{C}};
  \node (q) at (16,0) {\text{H}};
  \node (r) at (17,0) {\text{H}};
  \node (s) at (18,0) {\text{C}};
  \node (t) at (19,0) {\text{H}};
  \node (u) at (20,0) {\text{H}};
  \node (v) at (21,0) {\text{C}};
  \node (w) at (22,0) {\text{H}};
  \node (x) at (23,0) {\text{H}};
  \node (y) at (24,0) {\text{C}};
  \node (z) at (25,0) {\text{H}};
  \node (aa) at (26,0) {\text{H}};

\end{tikzpicture}
\end{center}

\textbf{344}

Okada and associates\textsuperscript{385} have prepared 1-phenylpyrazole-3-carboxamides \textit{345} as fungicides.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\text{R}^2};
  \node (b) at (1,0) {\text{R}^1};
  \node (c) at (2,0) {\text{N}};
  \node (d) at (3,0) {\text{N}};
  \node (e) at (4,0) {\text{X}};
  \node (f) at (5,0) {\text{CCR}^3};

\end{tikzpicture}
\end{center}

\textbf{345}

\begin{itemize}
  \item R¹ = H, alkyl, alkoxy, R² = H, halo, alkyl,
  \item R³ = amino, alkylamino, X = halo, alkyl, allyl
\end{itemize}
Ando and coworkers\textsuperscript{386} have prepared sulfamoylheteroarylpyrazole 346 as antiinflammatory and analgesic agent.

\begin{center}
\includegraphics[width=0.4\textwidth]{346.png}
\end{center}

Cheng and associates\textsuperscript{387} have reported the antiinflammatory and analgesic activity of heterocyclyl-alkylsulfonylpyrazole 347.

\begin{center}
\includegraphics[width=0.2\textwidth]{347.png}
\end{center}

Hiroshi and associates\textsuperscript{388} have reported pyrazolyloxyalkylacetylene 348 as herbicide.

\begin{center}
\includegraphics[width=0.4\textwidth]{348.png}
\end{center}

Kubota et al\textsuperscript{389} have synthesised pyrazoles of the type 349 as calcium channel blockers.

\begin{center}
\includegraphics[width=0.4\textwidth]{349.png}
\end{center}
Fukuchi and associates have reported 4-amino-1-phenyl-3-cyano-pyrazole derivatives 350 as pesticides.

Huber and associates have prepared 1-aryl-3-cyano-pyrazole 351 possessing parasiticidal activity.
Wishart and coworkers\textsuperscript{392} have prepared pyrazoles 352 which are useful in the treatment of glaucoma and multiple sclerosis.

R\textsuperscript{1} = H, alkyl, aryl, alkylaryl;  
R\textsuperscript{2} = aryl, heteroaryl, 3,6-membered heterocycle  
R\textsuperscript{3}, R\textsuperscript{4} = H, alkyl, alkenyl

Sakya et al\textsuperscript{393} have synthesised pyrazole 353 useful for treating Alzheimer's disease.

\begin{equation}
\text{352}
\end{equation}

\begin{equation}
\text{353}
\end{equation}
Present Work

Synthesis of 5-(3-methyl-5-hydroxypyrazol-4-yl)oxyindoles
In the light of wide variety of biological activities\textsuperscript{374-393} associated with pyrazole derivatives and also in continuation of our work on 5-hydroxy indoles, we were encouraged to embark upon the synthesis of hitherto unknown pyrazolylinoles of biological interest.

In the present investigation, synthesis of starting materials viz., 1-substituted-3-acetyl-5-hydroxy-2-methylindoles 327a-c were obtained by adopting Nenitzescu reaction\textsuperscript{329}. 1-Phenyl-3-acetyl-5-hydroxy-2-methylindole 327a was reacted with ethyl $\alpha$-chloroacetoacetate in presence of anhydrous potassium carbonate in refluxing dry acetone but this reaction did not yield the desired 1-phenyl-2-acetyl-5-($\alpha$-acetylethoxycarbonylmethoxy)-2-methylindole 335a in a polar solvent like acetone. Hence, we thought of changing reaction conditions and reacted hydroxyindole 327a with ethyl $\alpha$-chloroacetoacetate and sodium hydride in refluxing dry benzene to secure the desired condensed indole ester 335a in good yield. This ester 335a was further reacted with hydrazine hydrate (99\%) in refluxing ethanol to obtain the required 1-phenyl-3-acetyl-5-(3-methyl-5-hydroxypyrazol-4-yl)oxy-2-methyl-indole 336a [Scheme-19].

IR spectrum (Fig-74) of 335a displayed strong stretching bands at 1760 cm$^{-1}$ and 1733 cm$^{-1}$ due to C$_5$-ester carbonyl and C$_5$-acetyl carbonyl functions respectively. The C$_3$-acetyl carbonyl stretching band was observed at 1622 cm$^{-1}$. $^1$H NMR spectrum (Fig-75) of 335a showed a triplet ($J = 7$ Hz) at 1.24 $\delta$ due to C$_5$-ester methyl protons. Singlet at 2.35 $\delta$ was assigned to C$_3$-acetyl protons and singlet at 2.49$\delta$ was attributed to C$_3$-acetyl protons. The C$_2$-methyl protons resonated as singlet at 2.60 $\delta$ while quartet ($J = 7$ Hz) at 4.22 $\delta$ was accounted for C$_3$-ester methylene protons. A downfield singlet at 5.12 $\delta$ was assigned to CH proton of C$_5$-\(\beta\)-ketoester. Doublet of doublet ($J = 8.5$ Hz and 2.5 Hz) at 6.8 $\delta$ was accounted for C$_6$-proton while C$_7$-proton resonated as doublet ($J = 8.5$ Hz) at 6.85 $\delta$. A multiplet ranging from 7.21 to 7.55 $\delta$ was assigned to five protons of 1-phenyl while C$_4$-proton resonated as doublet ($J = 2.5$ Hz) at 7.56 $\delta$. 

182
Scheme-19

\[ O \quad HN \quad C-CH_3 \quad + \quad H_2C=CH-C-CH_3 \quad \xrightarrow{\text{Acetone} \ \Delta} \quad HO \quad N_2H_4.H_2O \quad (99\%) \quad \text{Ethanol} \]

\[ R \quad 327a-c \quad \xrightarrow{\text{N}_2\text{-atm}} \quad CH_3-C-CH-COOCH_3 \quad \text{NaH}, \quad \text{dry benzene} \quad \Delta \quad 335a-c \]

\[ \Delta \quad NH_2H_2O \quad (99\%) \quad \text{Ethanol} \quad 336a-c \]

<table>
<thead>
<tr>
<th>R</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C_6H_5</td>
</tr>
<tr>
<td>b</td>
<td>C_6H_4OCH_3-p</td>
</tr>
<tr>
<td>c</td>
<td>C_6H_4NHCOH_3-p</td>
</tr>
</tbody>
</table>
IR spectrum (Fig-76) of 336a showed stretching band at 3339 cm\(^{-1}\) due to NH/OH of pyrazole. Strong stretching band at 1610 cm\(^{-1}\) was assigned to C\(_3\)-acetyl carbonyl.

\(^1\)H NMR spectrum (Fig-77) of 336a displayed singlet at 1.98 \(\delta\) due to C\(_3\)-methyl protons of pyrazole, while C\(_2\)-methyl and C\(_3\)-acetyl methyl protons showed a singlet at 2.5 \(\delta\) overlapping the signal of the DMSO methyl protons. The C\(_4\)-proton resonated as doublet \((J = 2.5 \text{ Hz})\) at 7.62 \(\delta\). A multiplet ranging from 6.6 \(\delta\) - 7.80 \(\delta\) corresponded to seven aromatic protons. Broad singlet at 9.63 \(\delta\) was assigned to C\(_5\)-OH of pyrazole while another broad singlet at 11.29 \(\delta\) was attributed to NH of pyrazole. Both these peaks disappeared on D\(_2\)O exchange. The proton decoupled \(^{13}\)C NMR spectrum (Fig-78) of 336a displayed a peak at 8.92 \(\delta\) due to methyl carbon of pyrazole ring while peak due to C\(_2\)-methyl carbon was observed at 13.8 \(\delta\). The peak due to C\(_3\)-acetyl methyl carbon was seen at 32.7 \(\delta\). The peaks of C\(_7\) and C\(_6\) carbons of indole nucleus were observed at 105 \(\delta\) and 110 \(\delta\) respectively. The C\(_4\) carbon of phenyl ring resonated at 111.6 \(\delta\) while C\(_2\) and C\(_6\) carbons of phenyl ring gave peak at 114.4 \(\delta\). The signal of junction carbon [b] was observed at 121.2 \(\delta\) while C\(_3\) and C\(_5\) carbons of phenyl ring showed peak at 126.6 \(\delta\). The C\(_2\)-carbon of indole nucleus resonated at 128.1 \(\delta\) while peak due to C\(_5\) carbon of pyrazole ring was found at 129.12 \(\delta\). The signal of C\(_2\)-carbon of indole nucleus was observed at 129.9 \(\delta\) and the peak due to C\(_1\) carbon of phenyl ring was seen at 130.48 \(\delta\). The junction carbon [a] resonated at 132.8 \(\delta\) while peak due to C\(_4\)-carbon of indole nucleus was observed at 135.7 \(\delta\). The signal of C\(_5\)-carbon of pyrazole ring resonated at 144.9 \(\delta\) while peak of C\(_5\) carbon of indole nucleus was found at 155.17 \(\delta\). The downfield peak due to C\(_3\)-acetyl carbonyl carbon was found at 193.3 \(\delta\).
Fig-76: IR Spectrum

Wavenumbers (cm$^{-1}$)

Inorganic
Fig-77: $^1$H NMR Spectrum
DMSO-\textit{d$_6$}

on D$_2$O exchange

ppm
Experimental
1-Substituted-2-methyl-3-acetyl-5-(α-acetylethoxycarbonylmethoxy)indole: 335a-c

To a suspension of NaH (0.50 g, 0.2 mol) (50% dispersion in mineral oil which had been thoroughly washed with dry hexane) in dry benzene (10 ml) was added a solution 5-hydroxyindoles 327a-c (0.01 mol) in 35 ml of dry benzene and the reaction mixture was stirred under nitrogen at room temperature for 0.5 hours. To this suspension of Na salt of hydroxyindoles was added continuously a solution of ethyl α-chloroacetoacetate (3.30 g, 0.02 mol) in 10 ml of dry benzene and the reaction mixture was stirred at reflux under nitrogen for 16 hours. After cooling to room temperature, the reaction mixture was poured into ice water and extracted with ether and washed with water, 10% aqueous NaOH, brine and dried with sodium sulphate. The ether was evaporated and the residue obtained was recrystallised from ethanol (Table-3).

1-Substituted-3-acetyl-5-(3-methyl-5-hydroxypyrazol-4-yl)oxy-2-methylindoles: 336a-c

To a solution of compounds 335a-c, (0.01 mol) in ethanol (25 ml) was added hydrazine hydrate (99%) (0.5 g, 0.01 mol). The reaction mixture was heated at reflux for 6 hours and the solvent was removed under reduced pressure. The separated solid was recrystallised from ethanol [Table-3].
<table>
<thead>
<tr>
<th>Compd.</th>
<th>Substituent</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Nature (Solvent)</th>
<th>Molecular formula</th>
<th>Elemental analysis found (Calcd.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>335a</td>
<td>-C₆H₅</td>
<td>230</td>
<td>64</td>
<td>Pale yellow granules (ethanol)</td>
<td>C₂₃H₂₅NO₅</td>
<td>C 70.35 (70.21)  H 5.65 (5.89)  N 3.91 (3.56)</td>
</tr>
<tr>
<td>335b</td>
<td>-C₆H₄OCH₃-p</td>
<td>245</td>
<td>68</td>
<td>Brown granules (ethanol)</td>
<td>C₂₄H₂₆NO₆</td>
<td>C 68.25 (68.07)  H 5.88 (5.95)  N 3.41 (3.30)</td>
</tr>
<tr>
<td>335c</td>
<td>-C₆H₄NH-COCH₃-p</td>
<td>257</td>
<td>48</td>
<td>Brown granules (ethanol)</td>
<td>C₂₅H₂₆NO₆</td>
<td>C 66.73 (66.79)  H 5.91 (6.00)  N 3.51 (3.20)</td>
</tr>
<tr>
<td>336a</td>
<td>-C₆H₅</td>
<td>274</td>
<td>55</td>
<td>Yellow needles (ethanol)</td>
<td>C₂₁H₁₅N₃O₃</td>
<td>C 69.93 (69.79)  H 5.35 (5.29)  N 11.83 (11.62)</td>
</tr>
<tr>
<td>336b</td>
<td>-C₆H₄OCH₃-p</td>
<td>259</td>
<td>58</td>
<td>Yellow granules (ethanol)</td>
<td>C₂₂H₂₁N₃O₄</td>
<td>C 67.12 (67.50)  H 5.32 (5.40)  N 10.96 (10.73)</td>
</tr>
<tr>
<td>336c</td>
<td>-C₆H₄NHCOCH₃-p</td>
<td>287</td>
<td>42</td>
<td>Brown powder (ethanol)</td>
<td>C₂₃H₂₂N₄O₄</td>
<td>C 66.35 (66.01)  H 5.34 (5.29)  N 13.66 (13.38)</td>
</tr>
</tbody>
</table>