CHAPTER-IV

Synthesis and $^{13}$C NMR spectral analysis of 3-(substituted phenyl)pyrazoles and 3-(substituted naphthyl)pyrazoles.
Derivatives of pyrazole have been the essential nucleus of numerous drugs and dyes. A number of pyrazole anaesthetics have also appeared\textsuperscript{228,229}. It was established that pyrazolines are of interest as effective chemical bleaching agents and as luminiscent and fluorescent substances\textsuperscript{230,231}.

The use of pyrazole derivatives in medicine is undoubtedly its principal practical application. Certain pyrazoles have shown quite significant bacterio-ostatic\textsuperscript{232-235}, bactericidal and fungicidal\textsuperscript{236,237} activities. Alkyl-and aryl-pyrazoles themselves have a sharply pronounced sedative action on the central nervous system\textsuperscript{238}. Steroidal compounds, whose structures include pyrazole rings are of interest as possible psychopharmacological agents\textsuperscript{239,240}. Some derivatives are being studied in the fight against cancer\textsuperscript{241}. 3,5-Diethylpyrazole exhibits stimulating action on plants\textsuperscript{242}. Various derivatives of pyrazole have been tested and found to possess analgesic\textsuperscript{243-246}, antiviral\textsuperscript{247,248,249}, anti-inflammatory\textsuperscript{250-54}, antimicrobial\textsuperscript{255}, antibiotic\textsuperscript{256}, antihypertensive\textsuperscript{257}, anti-allergic\textsuperscript{258}, hypoglycemic\textsuperscript{259}, anti-hyperglycemic\textsuperscript{260}, and anthelmintic\textsuperscript{261,262} activities. Some compounds containing pyrazole nucleus have been synthesized and
were found to exhibit antidiabetic properties\textsuperscript{263}.

The use of alkylpyrazoles in perfumery has been suggested\textsuperscript{264}. Unconventional sources of energy like, solar energy have certain problems. Solar cells are uneconomic due to their low quantum efficiency of the solar collectors. So, the 3-(2'-hydroxyphenyl)pyrazoles, which may have large Stoke shift were synthesized so as to be studied for their photochromic properties.

3-(2'-Hydroxyphenyl)-(XXV), 3-(2'-hydroxy-5'-methylphenyl)-(XXVI), 3-(1'-hydroxy-2'-naphthyl)-(XXVII) and 3-(2'-hydroxy-1'-naphthyl)pyrazoles (XXVIII) have been synthesized by following the procedure of Satish and Sharma\textsuperscript{265} with a view that such derivatives are very important as chelating agents, which form very stable complexes with rare metals, very essential for human body. As such, these derivatives will find use in medicinal chemistry as well as dyes for solar collectors.

3-(2'-Hydroxyphenyl)pyrazole (XXV) was prepared by starting from o-hydroxyacetophenone followed by formylation with ethylformate and sodium ethoxide and the resulting $\omega$-formyl-2-hydroxyacetophenone having
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Ar-COCH₃ → Ar-COCH₂CHO

1. HCOOEt / NaOEt
2. NH₂-NH₂·H₂O
been subjected to hydrazine hydrate reaction which resulted in the formation of the title compound (XXV). In a similar fashion, the 3-(2'-hydroxy-5'-methylphenyl)pyrazole (XXVI) was prepared by starting from 2-hydroxy-5-methylacetophenone. The latter was prepared from acetylcresol by Fries rearrangement and subsequently subjected to formylation with ethyl formate and sodium ethoxide followed by hydrazine hydrate treatment to procure the 5'-methyl derivative (XXVI). Following a similar method, 1-hydroxy-2-acetonaphthone was converted into 3-(1'-hydroxy-2'-naphthyl)pyrazole (XXVII) and 2-hydroxy-1-acetonaphthone was converted to 3-(2'-hydroxy-1'-naphthyl)pyrazole (XXVIII) following an analogous method.

The structures of the compounds were confirmed by elemental analysis, IR and PMR spectral data. The compound (XXV) is tautomeric in nature and, therefore, in view of the strong H-bonding it will have the structure given below:

\[
\text{XXIX}
\]

In view of the strong H-bonding, it will behave like a ring cyclic compound and as such there will be a strong ring current...
more than what is expected. The chemical shifts of the various carbon atoms are given in Table-4.1. The assignments are based on OFR, and completely decoupled spectra as well as the substituent shifts in the phenyl ring and the pyrazole ring. Similar assignments have been made by Klienpeter et al.267. These authors have studied the influence of heteroaromatic system on to phenyl carbon and transmission of the electronic effects of m- and p-substituents of the phenyl ring on to the triazole ring carbon atoms.

It has been observed that the most downfield carbon signal in its $^{13}$C NMR spectrum (Fig.4.1) at 168.08$\delta$ belongs to C-3 as is evident from its low intensity as well as non-splitting in the OFR mode. The next upfield signal at 166.83$\delta$ has been assigned to the carbon C-2' both on the basis of its low intensity as well as its non-splitting in the OFR mode of irradiation. The signal at 162.74$\delta$ gives a doublet in the OFR mode and has reasonable intensity which gets enhanced when subjected to NOE mode of irradiation and it has been assigned to the carbon C-5. The signal at 133.41$\delta$ has to be assigned to the carbons C-6' and C-4. Another signal at 130.48$\delta$, in a similar fashion, has been assigned to the carbon C-5'. The small intensity signal at 121.68$\delta$, which remains a singlet in the OFR mode of irradiation has, therefore, been found the responsibility of carbon
Table 4.1

$^{13}$C Chemical shifts of 3-(substituted phenyl)pyrazoles and 3-(substituted naphthyl)pyrazoles in $\delta$ ppm.

<table>
<thead>
<tr>
<th>Carbon atom</th>
<th>XXV</th>
<th>XXVI</th>
<th>XXVII</th>
<th>XXVIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-3</td>
<td>168.08</td>
<td>155.81</td>
<td>169.41</td>
<td>162.94</td>
</tr>
<tr>
<td>C-4</td>
<td>133.41</td>
<td>102.92</td>
<td>119.19</td>
<td>129.50</td>
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<td>C-5</td>
<td>162.74</td>
<td>131.45</td>
<td>137.50</td>
<td>133.98</td>
</tr>
<tr>
<td>C-1'</td>
<td>121.68</td>
<td>118.03</td>
<td>162.12</td>
<td>118.86</td>
</tr>
<tr>
<td>C-2'</td>
<td>166.83</td>
<td>153.41</td>
<td>113.85</td>
<td>159.58</td>
</tr>
<tr>
<td>C-3'</td>
<td>120.08</td>
<td>118.03</td>
<td>126.65</td>
<td>121.26</td>
</tr>
<tr>
<td>C-4'</td>
<td>130.48</td>
<td>131.19</td>
<td>119.19</td>
<td>130.70</td>
</tr>
<tr>
<td>C-5'</td>
<td>119.01</td>
<td>129.40</td>
<td>130.03</td>
<td>129.50</td>
</tr>
<tr>
<td>C-6'</td>
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<td>128.52</td>
<td>129.23</td>
<td>124.46</td>
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<td>C-7'</td>
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<td>126.92</td>
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<td>C-8'</td>
<td>125.68</td>
<td>126.92</td>
<td>156.30</td>
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<td>C-4'a</td>
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<td>C-8'a</td>
<td>127.89</td>
<td>130.70</td>
<td>127.89</td>
<td>130.70</td>
</tr>
</tbody>
</table>
Fig. 4.1: $^{13}$C NMR spectrum of 3-(2’hydroxyphenyl)pyrazole (COM)
Signals at 120.08 and 119.01 have, by similar arguments, been ascribed to carbons C-3' and C-4', respectively.

$^{13}$C NMR spectra of the compound (XXVI) i.e. 3-(2'-hydroxy-5'-methylphenyl)pyrazole in OFR and completely decoupled mode (COM) (Fig. 4.2) have been studied and the most downfield signal at 155.81 has been assigned to the carbon C-3 of the pyrazole ring. The upfield shift of this carbon by calculated 12.27 seems reasonable in view of the fact that the electron-releasing methyl group para to the phenolic group will enhance its $p_k$ (lower the acidity) and, therefore, obviously the strength of H-bonding between the phenolic-OH hydrogen and pyrazole nitrogen will be comparatively far more weaker than in the case of compound (XXV) and consequently, resulting in the lesser ring current as compared to compound (XXV). Thus, one would expect overall shielding of all the carbon atoms in the compound (XXVI) and therefore, rationale for this upfield shift. The carbon resonance at 153.41 has been attributed to the carbon C-2' on the basis of its non-splitting in the OFR mode and poor intensity. The signal at 131.45 has to be assigned to the carbon C-5 which also experiences an upfield shift because of the loss of magnitude of ring current in compound (XXVI) as compared to compound (XXV). The signals at 131.19 , 129.40 and 128.52 have been assigned to the carbons C-4', C-5' and
Fig. 4.2: $^{13}$C NMR spectrum of 3-(2'-hydroxy-5'-methylphenyl)pyrazole (COM)
C-6', respectively. The signal at 129.40δ being lower in intensity and unsplit in the OFR mode of irradiation has been assigned to the carbon C-5'. The carbon resonance at 118.03δ has been assigned to carbons C-1' and C-3' in view of the fact that in the OFR mode this signal gives a doublet as well as a singlet, thereby, confirming our assignment. The most upfield carbon resonance at 102.92δ has been found the responsibility of carbon C-4 of the pyrazole ring. This upfield shift is probably due to electron releasing effect of the methyl group which gets transmitted to pyrazole ring.

The compound (XXVII), like the compound (XXV), will also have very strong H-bonding and, therefore, all the ring carbon atoms will be deshielded, comparatively. The 13C NMR spectra of the compound (XXVII) in the COM (Fig.4.3) and OFR mode of irradiation have helped in deciding the assignments of various carbon resonances. Therefore, the carbon resonance at 169.41δ has been assigned to carbon C-3, which remains unsplit in OFR mode. The signal at 162.12δ also remains singlet in the OFR mode and has been assigned to carbon C-1'. In a similar fashion, the resonance at 137.50δ has been ascribed to the carbons C-4a' and C-5 as it gave a doublet and singlet in the OFR mode. The signals
Fig. 4.3: 13C NMR spectrum of 3-(1-hydroxy-2-naphthyl)pyrazole (CON)
at 130.03, 129.23, 126.92, 126.65, and 125.68 have been assigned to the carbons C-5', C-6', C-7', C-3', and C-8', respectively on the basis of their splitting into doublets as well as their proximity to the calculated values which have been calculated by considering the effect of pyrazole ring on to the naphthol resonances. The signal at 127.89 has been attributed to bridge carbon C-8'a. The signal at 119.19 has been assigned to the carbon C-4 of the pyrazole ring as well as to C-4' of the naphthyl ring, as it splits into a doublet and a singlet in its OFR mode of irradiation. Finally, the resonance at 113.85 has been assigned to C-2' on the basis of its non-splitting in the OFR mode and lower intensity.

In the case of compound (XXVIII) there will be a terrible steric crowding between the hydrogen at C-8' and the C-4 hydrogen resulting into the noncoplanarity of the pyrazole ring. Therefore, one would expect somewhat weaker hydrogen-bonding and overall upfield shift of various carbon resonances in their $^{13}$C NMR spectrum (Fig.4.4) as is evident from table-4.1. The most downfield carbon resonance at 162.94 has been assigned to carbon C-3. The signal at 159.58 has been attributed to carbon C-2', whereas the signal at 156.30 has been assigned to the carbon C-8', as it splits into a doublet in the OFR mode and one would expect the
Fig. 4.4: $^{13}$C NMR spectrum of 3-(2'-hydroxy-1'-naphthyl)pyrazole (COM)
carbons C-8' and C-4 to be reasonably downfield due to the
van der Waal effects. The signal at $133.98\delta$ has been assigned
to carbon C-5 as is evident from the OFR mode of irradiation
splitting this resonance into a doublet. The signal at
$130.70\delta$ in its OFR mode splits into a doublet and one singlet
still remains there, thereby, suggesting that there are two
carbon resonances and these have been assigned to carbons
C-4' and C-8'a. This downfield shift of carbon C-4' is due
to the substituent effects and is very close to the calcu-
lated value of $129.06\delta$. The carbon resonance at $129.50\delta$
has been assigned to the carbons C-5' and C-4, as this signal
gave two nearly overlapping doublets. The signal at $128.54\delta$
has been attributed to the carbon C-7' on the basis of its
OFR spectrum. The carbons C-6' and C-3' have been found
to resonate at $124.46$ and $121.26\delta$, respectively, as the same
get split into doublet each in the OFR mode of irradiation.
The signals at $120.54$ and $118.86\delta$, which remain unsplit in the
OFR mode of recording have been ascribed to the carbons C-4'a
and C-1', respectively which are also close to the calculated
values.