CHAPTER FIVE

THEORETICAL III

A) Attempted Synthesis of Isoxazoloindole and Stereochemistry of Indole-2-aldoximes

B) Synthesis of 3(3'-Isoxazoly1)indoles
A) Attempted Synthesis of Isoxazoloindole and Stereochemistry of Indole-2-aldoximes

When indole was brominated with pyridinium bromideperbromide\textsuperscript{136} or dioxane dibromide\textsuperscript{137} 3-bromoindole was obtained in good yield. Kunori\textsuperscript{138} brominated indole-2-carboxylic acid and ethyl indole-2-carboxylate with bromine in acetic acid to get the 3-bromo derivatives. DaSettimo and coworkers\textsuperscript{139} have carried out bromination of indole-3-carboxaldehyde with bromine in acetic acid or bromine in refluxing carbon tetrachloride to obtain a mixture of 5- and 6-bromo derivatives. However, no report has appeared in literature about the bromination of indole-2-carboxaldehyde. So, in order to study this reaction, 5-methyl-7-bromindole-2-carboxaldehyde (30a) was treated with N-bromosuccinimide in refluxing carbon tetrachloride. The hot reaction mixture was separated by filtration from succinimide and the filtrate worked out to yield pink flakes which melted at 190-2° (the parent aldehyde 30a melted at 119°). Its ir spectrum (Fig.23) showed characteristic bands at 3230\textsuperscript{m} (NH) and 1686\textsuperscript{s} (C=O). Its nmr spectrum (CDCl\textsubscript{3}) (Fig.22) showed a singlet in the downfield at 10.3 due to aldehydic proton. A peak due to indole NH appeared at 9.2. Two aromatic protons at position 6 and 4 have resonated at 7.54 and 7.4, respectively,
while the 5-methyl group appeared as a sharp singlet at 2.5. The absence of C-3 proton proves that bromine has entered at position 3 of the indole nucleus and thus the compound was given the structure 5-methyl-3,7-dibromoindole-2-carboxaldehyde (68a). The nmr spectrum (Fig. 21) of the parent aldehyde 30a was as follows: 6 ppm (CDCl₃) 9.8 (1H, S, CHO), 9.16 (1H, S, NH), 7.36 (1H, S, 6-H), 7.32 (1H, S, 4-H), 7.12 (1H, S, 3-H), 2.38 (3H, S, 5-CH₃).
68a was refluxed for 4 h with equimolar quantity of hydroxylamine hydrochloride in alcoholic KOH (50%). The resulting product, after purification, melted at 212-214°. It would have either of the following two structures -(i) 5-bromo-7-methylisoxazolo(4,5-b)Indole (70a) or 5-methyl-3,7-dibromoindole-2-aldoxime (69a). Its ir spectrum (Fig.23) exhibited a medium absorption band at 3382 cm\(^{-1}\) due to OH stretching vibration. Bands appeared at 3280m cm\(^{-1}\) and 1625m cm\(^{-1}\) could be easily assigned to NH and C=N groups, respectively, thus pointing out that the compound had the oxime structure 69a. The conclusive evidence came from the mass spectrum (Fig.24) wherein the molecular ion peak appeared at m/e 330. Isotopic peaks due to the presence
of two bromine atoms appeared at 332 and 334. The relative intensities of M, M+2 and M+4 peaks were 48.98: 100: 51.28, coincident as demanded by theory. The molecular ion then lost a hydroxyl group giving 73 which gave isotopic peaks at m/e 313, 315 and 317.

Peaks due to the loss of 3-Br appeared at m/e 235, 237 (one bromine present) to give 74. Further, loss of another bromine gave a peak at m/e 157 (structure 75). The fragmentation pattern is depicted below:

![Fragmentation Diagram](image-url)
Dehydrobromination of 69a was tried by refluxing it with alcoholic potassium hydroxide, potassium carbonate in ethanol and pyridine but no isoxazoloindole (70a) could be formed, 69a was recovered unchanged.

Similarly, 5-methylindole-2-carboxaldehyde 30e was brominated with NBS in refluxing CCl₄ to obtain 5-methyl-3-bromoindole-2-carboxaldehyde (68e), which was converted into the corresponding oxime, viz., 5-methyl-3-bromoindole-2-aldoxime (69e). It could not be converted into the corresponding isoxazoloindole (70e).

The failure of dehydrobromination of 69a and e to give isoxazoloindole prompted us to study the stereochemistry of these oximes. It was contemplated that they might exist in anti form with respect to 3-bromo substituent thus preventing the dehydrobromination.

It was decided to prepare variously substituted indole-2-aldoximes for studying their geometrical isomerism. Thus several indole-2-aldoximes (72a-j) were prepared from the corresponding indole-2-carboxaldehydes (71a-j) which are summerised in Table XII.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Substituents</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>ir cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>72a</td>
<td>5-Me-7-Br</td>
<td>170-3</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>72b</td>
<td>3,5-diMe-7-Br</td>
<td>203-5</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>72c</td>
<td>5-Me</td>
<td>204-6</td>
<td>57</td>
<td>3410m (OH), 3235m (NH), 1647m (C=N)</td>
</tr>
<tr>
<td>72d</td>
<td>5-Cl</td>
<td>162-4</td>
<td>64</td>
<td>3283s (OH/NH), 1690m (C=N)</td>
</tr>
<tr>
<td>72e</td>
<td>3-Me-5-Cl</td>
<td>205-6</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>72f</td>
<td>5-Br</td>
<td>215</td>
<td>72</td>
<td>3399m (OH), 3200w (NH), 1635w (C=N)</td>
</tr>
<tr>
<td>72g</td>
<td>3-Me-5,7-diCl</td>
<td>117-9</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>72h</td>
<td>3-Me</td>
<td>149-50</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>72i</td>
<td>5-OBz</td>
<td>192-4</td>
<td>66</td>
<td>3404m (OH), 3160m (NH), 1627m (C=N)</td>
</tr>
<tr>
<td>72j</td>
<td>3,7-diMe-5-Cl</td>
<td>205-7</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>69a</td>
<td>5-Me-3,7-diBr</td>
<td>212-4</td>
<td>76</td>
<td>3382m (OH), 3280m (NH), 1625m (C=N)</td>
</tr>
<tr>
<td>69e</td>
<td>5-Me-3-Br</td>
<td>208-10</td>
<td>75</td>
<td>3385m (OH), 3200w (NH), 1650m (C=N)</td>
</tr>
</tbody>
</table>
Various methods are available to determine the stereochemistry of oximes. A classical method for determining the stereochemistry of ketoximes is based upon the preferential migration of the group anti to the oximino hydroxyl group during the Beckmann rearrangement. The shortcomings of this method for stereochemical assignment are well known.\textsuperscript{140,141} Recent nmr studies have provided alternate and more generally reliable techniques for assigning configuration. In the method of Karabatsos and Teller\textsuperscript{142} nmr spectra were obtained in CCl\textsubscript{4} and C\textsubscript{6}H\textsubscript{6}. The magnitude of the benzene-induced changes in chemical shifts were then taken as indication of configuration.

Fox and coworkers\textsuperscript{143} have made an important observation, using benzene solutions of several ketoximes of known configuration, that in all cases investigated, the addition of small amount of concentrated hydrochloric acid vapour to a nmr sample caused the \(\alpha\)-protons syn to the hydroxyl group to shift to higher field, while the \(\text{anti}\ \alpha\)-protons were shifted to lower field. This method could not be employed due to the poor solubility of the oximes under investigation in benzene.

Recently, Lehn and Crepiaux\textsuperscript{144} have used nuclear spin-spin interaction nitrogen-15-proton coupling constants in the determination of oxime configurations. These
authors have obtained nmr spectra of $^{15}N$-enriched heterocyclic aldoximes and the geminal $^{15}N$-H coupling constants in $RCH=^{15}NOH$ fragmented. The configurations of the oximes were unambiguously assigned from the above coupling constants. Indole-3- and pyrrolo-2- and thiophene-2-aldoximes and furfuraldoxime existed predominantly in the anti form whereas oximes of pyridoxal and its phosphate existed predominantly in the syn form. Pyridine-2-, -3- and -4-aldoximes existed in the syn form whereas the corresponding methiodides were obtained in both forms. This method involves the use of $^{15}N$ enriched hydroxyalmine which was not available to us. Moreover, it requires a sophisticated Fourier transform nmr spectrometer which was also not easily accessible in India.

Another sophisticated technique for structural studies is $^{13}C$ nmr. Levy and Nelson, Roberts and coworkers have applied this method for determination of configurations and composition of syn and anti isomers of aldoximes and ketoximes. The latter workers have examined several $^{13}C$ nmr spectra of oximes and their parent aldehydes or ketones and concluded that the substituent shifts for the change $C\beta C\alpha CH=0 \rightarrow C\beta C\alpha CH=NOH$ for aldehydes are sufficiently regular to be quite helpful in making assignments. The $\alpha$-carbon substituent shifts for aldoximes,
as measured by $\Delta_{\text{syn}}$ and $\Delta_{\text{anti}}$, fall into two ranges. If there is one substituent on the $\alpha$-carbon, then $\Delta_{\text{syn}} = -18.8$ ppm and $\Delta_{\text{anti}} = 14.4$ ppm, while with two substituents on the $\alpha$-carbon $\Delta_{\alpha-\text{syn}} = -16.6$ ppm and $\Delta_{\alpha-\text{anti}} = -11.6$ ppm. The authors claimed these differences to be regular enough to have diagnostic value.

It was thought that this method would be useful in determining the configuration of the oximes under investigation. The following three pairs of aldehydes and aldoximes were selected for this purpose.

$$
\begin{align*}
\text{H}_2\text{C} & \quad \text{H}_2\text{C} \\
\text{Br} & \quad \text{Br} \\
\text{N} & \quad \text{N} \\
\text{CHO} & \quad \text{CHNOH} \\
\text{R} & \quad \text{R} \\
\text{76} & \quad \text{77}
\end{align*}
$$

$a$, H  
$b$, Br  
$c$, CH$_3$

It was easy to see from the FT $^{13}$C nmr spectra of these oximes ($77a-c$) that they were mixtures of syn and anti forms, the number of peaks being more than the number...
of carbon atoms present in the molecule.

Roberts and Parker\textsuperscript{149} have obtained $^{13}$C nmr spectra of indole, all methylindoles and many dimethylindoles and interpreted them. This data was advantageously used in making assignments for different spectra obtained by us.

In compound 76b, (Fig.26) a doublet at 181.37 ppm represented the aldehydic\textsuperscript{148} carbon and a quartet at 20.43 ppm the methyl group. The remaining eight peaks were due to ring carbon atoms. The two low-field singlets at 133.89 ppm and 132.33 ppm could be assigned to C$_9$ and C$_8$, respectively. The lower-field singlet at 133.89 ppm was assigned to C$_9$ since carbon adjacent to nitrogen in pyrroles\textsuperscript{150} and pyridines\textsuperscript{151} had been shown to appear at lower field than those in a $\beta$-position. The other singlet at 132.33 ppm was due to C$_8$.

C$_5$ in 5-methylindole\textsuperscript{149} appeared at 128.90 ppm.

The effect of meta bromo substitution viz., +1.7 makes 130.6. So, a peak at 132.27 which is at low-field, out of the remaining ones, could be assigned to C$_5$. Two singlets appeared in the high-field at 105.21 ppm and 99.98 ppm. In 5-methylindole C$_3$ appeared at 102.11 ppm, subtracting 5.5 for the self bromo substitution and adding 1.3 for the
ortho formyl group\textsuperscript{145,146,152} made 97.91 and thus a peak observed at 99.98 ppm must be due to C\textsubscript{3}. In 5-methylindole C\textsubscript{7} was detected at 111.30 ppm; subtracting 5.8 for bromo substitution made 106.30. So, 105.21 ppm peak could be certainly due to C\textsubscript{7}. A doublet at 118.98 ppm and a peak at 127 ppm (should be a doublet) could be due to C\textsubscript{6} and C\textsubscript{4'} respectively, in analogy with the nmr spectrum. This left only one peak at 131.62 to be assigned and it must be due to C\textsubscript{2}.

5-Methyl-3,7-dibromoindole-2-aldoxime (77b)

Here the absence of the peak around 180 ppm indicated that aldehydic group had been derivatised. The spectrum (Fig.26) consisted of 10 pairs of lines pointing out that this oxime was a mixture of syn and anti forms. The CH-N=O carbon appeared at 139.34, 134.74\textsuperscript{148} C\textsubscript{3} had shifted upfield by about 6 ppm (99.98 \rightarrow 93.58, 91.41). The other part of the spectrum was similar to that of 76b and summarised in Table XIII.

5-Methyl-7-bromoindole-2-carboxaldehyde (76a)

This spectrum was almost similar to that of 76b except the downfield shift of 5.14 ppm of C\textsubscript{3} due to the absence of 3-Br substitution (Table XIII).
5-Methyl-7-bromoindole-2-aldoxime (77a)

This spectrum could be compared to those of 76a and 77b and assignments made for different peaks are summarised in Table XIV.

3,5-Dimethylindole-2-carboxaldehyde (76c)

It differs from the spectra of other aldehydes as the aldehydic carbon has absorbed at two frequencies, viz., 183.05 and 181.79 ppm. (Fig. 27). This suggested that the aldehyde 76c existed in two geometrical isomers 76c₁ and 76c₂ owing to the presence of 3-CH₃ substituent as given below.

\[ \begin{array}{c}
\text{CH₃} \\
\text{H₃C} \\
\text{Br} \\
\text{N} \\
\text{C=O} \\
\text{CH₃} \\
\text{H} \\
\text{H}
\end{array} \quad \begin{array}{c}
\text{CH₃} \\
\text{H₃C} \\
\text{Br} \\
\text{N} \\
\text{C=}H \\
\text{CH₃} \\
\text{H} \\
\text{0}
\end{array} \]

\[ 76c₁ \quad 76c₂ \]

C₃ shifted towards lowfield by 16.8 due to the methyl substitution. This was rather more than expected. The two methyl groups at positions 3 and 5 appeared at 8.57 and 20.48 ppm, respectively.
<table>
<thead>
<tr>
<th>Comp</th>
<th>C12</th>
<th>C11</th>
<th>C10</th>
<th>C9</th>
<th>C8</th>
<th>C7</th>
<th>C6</th>
<th>C5</th>
<th>C4</th>
<th>C3</th>
<th>C2</th>
<th>C1</th>
<th>C0</th>
<th>Cn</th>
<th>Cmp</th>
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</tr>
</tbody>
</table>

Table XII

Spectral Data of some Indole-2-carboxaldehydes and their Oximes

For 13C NMR spectral data of some Indole-2-carboxaldehydes and their oximes

<table>
<thead>
<tr>
<th>Comp</th>
<th>C12</th>
<th>C11</th>
<th>C10</th>
<th>C9</th>
<th>C8</th>
<th>C7</th>
<th>C6</th>
<th>C5</th>
<th>C4</th>
<th>C3</th>
<th>C2</th>
<th>C1</th>
<th>C0</th>
<th>Cn</th>
<th>Cmp</th>
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<tr>
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</tr>
</tbody>
</table>

Table XIII
3,5-Dimethyl-7-bromoindole-2-aldoxime (77c)

This spectrum could be compared to that of its parent 76c. Here C_3 absorbed at 114.90 which was very close to the predicted theoretical value, viz. 114.28 ppm (104.98 + 9.3). 3-CH_3 group was observed as two peaks at 9.37 and 8.62 ppm (Table XIII).

Unsuccessful dehydrobromination of 3-bromoaldoximes (69a and e) could be explained only on the basis of a strong C-Br bond that exists.

B) Synthesis of 3(3'-isoxazoly)indoles

Isoxazoles are found to possess good biological properties. The most interesting compound of this series, 4-aminoisoxazolid-3-one, first isolated from Streptomyces possesses strong antituberculosis activity^{154}. The penicillin derivatives, acylated with isoxazole carboxylic acids, are known to possess antibacterial activity against resistant species^{155}. Amongst the hydrazides of isoxazole carboxylic acids, the hydrazide of 5-methylisoxazole-3-carboxylic acid was reported to show high antilepratic activity^{156}. The corresponding benzyl hydrazide, known as marplane, is a strong inhibitor of monoaminoxidase and is being used in psychotherapy^{157} and in the treatment of angina pectoris^{158}.
In recent years much attention has been focussed on the steroids involving an isoxazole ring in the 2,3-position because of their anabolic activity. In view of these observations it was planned to synthesise 3-indolyl substituted isoxazoles which may exhibit some interesting biological activity.

The synthesis of isoxazoles from hydroximic chlorides was found to be a convenient method. Quilico and Fusco have reported the synthesis of several isoxazoles by the reaction between hydroximic chloride and compounds containing active methylene group in alkaline medium. The condensation of ethyl cyanoacetate with benz-hydroximic chloride was reported to yield ethyl 5-amino-3-phenylisoxazole-4-carboxylate in 80% yield. In the present investigation also indole-3-hydroximic chlorides were synthesised from the readily available aldoximes and allowed to react with ethyl cyanoacetate in alkaline medium to get 3-(5'-amino-4'-carbethoxyisoxazolyl)indoles in good yields.

Indole-, 2-phenylindole- and N-methylindole-3-aldoximes (79a-c) were prepared as per the literature methods. These oximes were chlorinated with chlorine in HCl-methanol medium and when hydroximic chlorides (80a-c) were obtained. These are summed up in Table XIV.
\[ \text{88} \xrightarrow{\text{NH}_2\text{OH}} \text{79} \]

\[ \text{78} \xrightarrow{\text{Cl}_2, \text{HCl, CH}_2\text{OH}} \text{80} \]

\[ \text{81} \xrightarrow{\text{CNCH}_2\text{CO}_2\text{C}_2\text{H}_5} \text{80} \]

\[ R \quad R_1 \]

\[ \begin{align*}
a. & \quad \text{H} & \quad \text{H} \\
b. & \quad \text{H} & \quad \text{C}_6\text{H}_5 \\
c. & \quad \text{CH}_3 & \quad \text{H} \\
\end{align*} \]
Table XIV

Indole-3-hydroximic chlorides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Substitution</th>
<th>M.P. °C</th>
<th>Nature (solvent)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>80a</td>
<td>None</td>
<td>180</td>
<td>Orange needles</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(benzene)</td>
<td></td>
</tr>
<tr>
<td>80b</td>
<td>2-Ph</td>
<td>107-10</td>
<td>-do-</td>
<td>64</td>
</tr>
<tr>
<td>80c</td>
<td>1-Me</td>
<td>128-30</td>
<td>Yellow needles</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(chloroform, pet ether, 60-80°)</td>
<td></td>
</tr>
</tbody>
</table>

These hydroximic chlorides (80a–c) were then condensed with ethyl cyanoacetate in sodium ethoxide-ethanol medium when carban ion addition with reductive cyclisation took place yielding 3-(5'-amino-4'-carbethoxy-3'-isoxazolyl)indoles 81a–c. These compounds exhibited characteristic NH₂ absorption around 3500 cm⁻¹ and C=O around 1600 cm⁻¹ which substantiates their structures. These are summarised in Table XV.
Table XV

3-(5'-amino-4'-carbethoxyisoxazolyl)indoles

<table>
<thead>
<tr>
<th>Compound</th>
<th>Substituents</th>
<th>M.P. °C</th>
<th>Nature (solvent)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>81a</td>
<td>None</td>
<td>&gt;360°</td>
<td>Brown tiny needles (aq. ethanol)</td>
<td>50</td>
</tr>
<tr>
<td>81b</td>
<td>2-Ph</td>
<td>&quot;</td>
<td>Yellowish brown needles (aq. ethanol)</td>
<td>60</td>
</tr>
<tr>
<td>81c</td>
<td>1-Me</td>
<td>&quot;</td>
<td>-do-</td>
<td>65</td>
</tr>
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</table>