CHAPTER 3
SYNTHESIS OF 4-[AMINO, PYRIDYL METHYLENE]-2-PYRIDYL-2-IMIDAZOLIN-5-ONES

Introduction

The reaction between benzimidic acid ester and glycine ester yielding red coloured products have been thoroughly investigated.$^{35,37}$ Wieland and Biener$^{109}$ studied the pigment formed by the reaction between benzimidic acid ester and glycine ester and they observed a whole series of red pigments by this study.

Ekeley and Ronzio$^{110,111}$ suggested that the red colour is due to the formation of glyoxaline red with the following structure.

\[
\begin{array}{c}
\text{HN} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{C}_6\text{H}_5 \\
\text{N} \\
\text{C}_6\text{H}_5 \\
\text{HN}
\end{array}
\]

This dye may be formed by the atmospheric oxidation of one molecule of 2-substituted-2-imidazolin-5-one to form a carbonyl compound followed by the condensation with another molecule of 2-substituted-2-imidazolin-5-one. This is just like the formation of indigo from indoxyl by atmospheric oxidation.
A further investigation of the reaction between benzimidic acid ester and glycine ester by Shafi and Sobha\textsuperscript{112} resulted in the isolation and structural elucidation of 4-(amino, arylmethylene)-2-aryl-2-imidazolin-5-one and they prepared the acetylated products of the amino imidazolinones.\textsuperscript{112} In their method imidic acid ester and glycine ester were taken in the molar ratio 2:1 and heated under reflux in toluene in presence of anhydrous sodium acetate as the base. After refluxing for 5 hours the product was filtered, washed with water, ether and dried. From spectral analysis they assigned the structure as

![Chemical structure image]

**Present work**

**III.1. Synthesis of amino imidazolinones**

Shafi and Basheer have reported the antibacterial activity of amino imidazolinones with phenyl groups.\textsuperscript{113} Amino imidazolinones with pyridyl group in place of phenyl group was expected to result in more active derivatives. With this view it was proposed to synthesise this
class of compounds. Two aminoimidazolinones containing pyridyl ring namely 4-[amino,(2-pyridyl) methylene]-2-(2-pyridyl)-2-imidazolin-5-one and 4-[amino,(4-pyridyl) methylene]-2-(4-pyridyl)-2-imidazolin-5-one were synthesised and their structures elucidated by elemental analysis and spectral studies.

Results and discussion

Cyanopyridines (0.04 mol) were converted into the corresponding imidic acid ester in presence of methanol and sodium methoxide as already explained in chapter I. The imidic acid esters formed were then refluxed with glycine ethyl ester hydrochloride (0.02 mol), sodium bicarbonate and toluene for three hours. Then the reaction mixture was cooled and the product formed was filtered. The amino imidazolinones formed were washed with water and then with alcohol and dried.

We tried to prepare aminoimidazolinones from 2-cyanopyridine, 3-cyanopyridine and 4-cyanopyridine. 3-Cyanopyridine did not give the expected product even after trying several different conditions. The amino imidazolinones formed from 2-cyanopyridine and 4-cyanopyridine were obtained in good yield (81% and 75%). The compounds synthesised are given in Table III.1. These compounds are reported for the first time.
TABLE III.1

4-[amino, pyridyl methylene]-2-pyridyl-2-imidazolin-5-one

<table>
<thead>
<tr>
<th>No.</th>
<th>Name of the compound</th>
<th>Yield %</th>
<th>M.P. °C</th>
<th>( \lambda_{\text{max}} ) nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-[amino, (2-pyridyl) methylene]-2-(2-pyridyl)-2-imidazolin-5-one</td>
<td>81</td>
<td>200</td>
<td>411</td>
</tr>
<tr>
<td>2</td>
<td>4-[amino, (4-pyridyl) methylene]-2-(4-pyridyl)-2-imidazolin-5-one</td>
<td>75</td>
<td>330</td>
<td>381</td>
</tr>
</tbody>
</table>

The structures of the compounds were elucidated by spectral and elemental analysis. The structure was arrived at as follows. The mass spectrum of 4-[amino, (2-pyridyl) methylene]-2-(2-pyridyl)-2-imidazolin-5-one had a peak at 265, which is the molecular ion peak corresponding to the proposed structure. The odd mass justified the presence of odd number of nitrogen atoms per molecule. Other important peaks in the mass spectrum were at \( m/z = 237, 133, 105, 78 \), which further supported the proposed structure. The mass peak at 237 units corresponds to the radical ion formed by the elimination of a neutral CO molecule from the molecular ion.
An alternate fragmentation pathway gives rise to the peak at m/z = 187. It is due to the removal of pyridyl radical in the imidazole ring of the molecular ion.

![Diagram 1]

Removal of a neutral cyanopyridine molecule from the molecular ion results in the peak at 161 which eliminates a neutral molecule of CO giving the fragment ion at m/z = 133.

![Diagram 2]

Intense peaks at m/z = 105 and 78 are due to the fragmentations given below.
The \(^1\)H NMR spectrum also supported this structure. The NH proton in the imidazolinone ring absorbed at \(\delta 11.75\).\(^{112}\) It also showed absorptions due to eight aromatic protons in the region \(\delta 7.35\) to \(9.35\). The two hydrogen atoms of the amino group are chemically non equivalent. This happens due to the possible partial double bond character of the C–NH\(_2\) bond as shown below.
In this structure one of the hydrogen atoms of the amino group falls in the deshielding region of the carbonyl group and hence has a higher chemical shift than the other ($\delta 9.25$ and 8.2). The proton absorption integrating to one proton at $\delta 9.35$ is due to the absorption of the proton adjacent to the nitrogen of the pyridyl group at position 2 of the imidazolinone ring. This high chemical shift is observed for this type of hydrogen when the pyridyl group is bonded to electron withdrawing group.\textsuperscript{114}

The $^{13}$C nmr spectrum has 14 peaks in the region $\delta 117.2$ to 170.2. The carbonyl carbon of imidazolinone ring absorbs at $\delta 170.2$. All other carbons absorb between $\delta 117.2$ to 149.7.

IR spectrum also is in consistence with the above observations. Three medium intensity peaks are found in the region 3160 to 3250 which are due to symmetric and antisymmetric vibrations of NH$_2$ and the vibration corresponding to NH of the imidazolinone ring. Non hydrogen bonded NH$_2$ group absorbs at 3336 cm$^{-1}$.\textsuperscript{115} The carbonyl absorption is at 1670 cm$^{-1}$. 

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Mass spectrum of 4-[amino, (2-pyridyl) methylene]-2-(2-pyridyl)-2-imidazolin-5-one
$^1$H NMR spectrum of 4-[amino, (2-pyridyl) methylene]-2-(2-pyridyl)-2-imidazolin-5-one
$^1$H NMR spectrum of 4-[amino, (2-pyrindyl) methylene]-2-(2-pyridyl)-2-imidazolin-5-one (expanded)
$^{13}$C NMR spectrum of 4-[amino, (2-pyridyl) methylene]-2-(2-pyridyl)-2-imidazolin-5-one
Once the structure of the compound was established, the following mechanism could be proposed for its formation.

This type of compounds with phenyl rings at the positions of pyridyl rings in these compounds undergo acetylation and benzoylation very easily giving acetylated and benzoylated products. Therefore we attempted the acetylation and benzoylation but failed.
In order to understand the reason for the failure of these reactions, we calculated the electron density at the N of NH$_2$ group of this compound and the similar compound prepared by Shafi and Sobha with phenyl groups in place of pyridyl group. It was found that the electron density at the nitrogen atom of the amino group in these compounds is very low when compared with the electron density at the nitrogen atom of the amino group in the compounds reported. The contour diagrams of the electron density at various atoms of the two compounds which were compared are given below.

Contour diagram of the electron density at various atoms of 4-[amino,(2-pyridyl) methylene]-2-(2-pyridyl)-2-imidazolin-5-one
The low electron density at the nitrogen atom of the amino group justifies the resistance of these compounds towards acetylation and benzoylation.

III.2. Preparation of metal complexes using aminoimidazolinone as ligand

The structure of these compounds have the amino and carbonyl groups so placed that metal ions can form complexes with these compounds.

We prepared complexes of copper, cobalt and zinc using the compound 4-[amino,(2-pyridyl) methylene]-2(2-pyridyl)-2-imidazolin-5-one as ligand.
Results and discussions

The metal salts (copper acetate, cobalt acetate and zinc acetate) were dissolved in methanol and the amino imidazolinone was dissolved in ethanol. The amino imidazolinone was taken in excess expecting that we can remove the remaining compound after complexation by washing with alcohol. The ligand solution was added to the metal salt solution while the colour of the salt solution was changed immediately and the complex got precipitated. The complexes of Cu, Co and Zn were dark brown, dark purple and yellow in colour respectively.

The complexes of copper and cobalt were highly water soluble and the zinc complex was practically insoluble in water. Because of the high solubility of the complexes of copper and cobalt, we thought of exploiting this property for the colourimetric estimation of these metals. This amino imidazolinone was made soluble in water by converting it into hydrochloride. This was effected by adding concentrated HCl to the imidazolinone and the hydrochloride formed was reprecipitated by adding ethanol drop by drop. The hydrochloride formed was then filtered and washed with ethanol and dried. From the elemental analysis it was clear that the hydrochloride formed was a trihydrochloride. The trihydrochloride was formed by the addition of three molecules of HCl per molecule of the aminoimidazolinone. These HCl molecules might be attached to the nitrogen atoms of the two pyridyl ring and
to the NH₂ group in the molecule. These three nitrogen atoms are more electron rich when compared with the other two nitrogens of the imidazolinone ring. So the structure of the trihydrochloride can be given as follows:

\[
\begin{align*}
&\text{N} & \text{H} & \text{C} & \text{Cl} \\
&\text{N} & \text{H} & \text{N} & \text{O} & \text{N} & \text{H} & \text{2} & \text{H} & \text{C} & \text{Cl} \\
&\text{N} & \text{H} & \text{C} & \text{Cl} \\
&\text{N} & \text{H} & \text{Cl}
\end{align*}
\]

It was readily soluble in water and its solutions of different concentrations can easily be prepared by just adding the required quantity of the compound to water and making up the solution to definite volume.

We were not able to arrive at the structure of the complex formed from the metal and the amino imidazolinone. Therefore, we could not proceed with the quantitative estimation of the metals using this complexation. Once we get the structure of the complex, the colourimetric estimation can also be easily carried out.

**Experimental**

Melting points recorded are uncorrected and carried out on a Toshniwal capillary melting point apparatus. The mass spectrum was recorded on Finnigan MAT 8200 spectrometer. All the \(^1\)H nmr spectra were
recorded on a Brucker AM 360 spectrometer using TMS as reference standard. $^{13}$C nmr spectra were recorded on Brucker AC 250 spectroscope at 90.5 MHz. IR spectra were recorded as KBr pellets using Shimadzu 8101A FTIR equipment. UV-Vis spectra were recorded in ethanol on a Shimadzu 1601 UV-Vis spectrometer.

**Synthesis of the starting materials**

Glycine ethyl ester hydrochloride was prepared as described in chapter I. Imidic acid methyl esters were prepared from cyanopyridines (2-cyanopyridine and 4-cyanopyridine) by Fred and Grace method during the synthesis of each amino imidazolinone.

**Synthesis of aminoimidazolinones**

4-[amino,(2-pyridyl) methylene]-2-(2-pyridyl)-2-imidazolin-5-one

Sodium metal (2 g) was dissolved in 20 ml of absolute methanol in a 100 ml round bottomed flask. 2-Cyanopyridine (4.6 ml, 0.04 mol) was added to it and allowed to stand overnight at room temperature. Acetic acid (1 ml) was then added and boiled on a water bath to remove the excess methyl alcohol present in the reaction mixture. Glycine ethyl ester hydrochloride (2.78 g, 0.02 mol) and sodium bicarbonate (3.5 g) were ground together and added to the imidate formed in the round bottomed flask. Toluene (10 ml) was also added to the round bottomed flask and refluxed for three hours. Yellow
crystals of 4-[amino,(2-pyridyl) methylene]-2-(2-pyridyl)-2-imidazolin-5-one formed were filtered. Washed twice with water and then with ethanol and dried. The yellow product weighed 4.3 g (81%) and melted at 197 °C.

The amino imidazolinone (0.5 g) was recrystallised from ethanol (50 ml) and melted at 200 °C.

Analysis

<table>
<thead>
<tr>
<th></th>
<th>N%</th>
<th>C%</th>
<th>H%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>26.48</td>
<td>63.28</td>
<td>4.12</td>
</tr>
<tr>
<td>Calculated</td>
<td>26.41</td>
<td>63.59</td>
<td>4.15</td>
</tr>
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</table>

C_{14}H_{11}N_{5}O

IR (cm\(^{-1}\)) 3336, 3194, 1670, 1627, 1592

Uv-vis  \(\lambda_{\text{max}} = 411\)

**4-[amino,(4-pyridyl) methylene]-2-(4-pyridyl)-2-imidazolin-5-one**

Sodium metal (2 g) was dissolved in 20 ml of absolute methanol in a 100 ml round bottomed flask. 4-cyanopyridine (4.4 g, 0.04 mol) was added to it and allowed to stand overnight at room temperature. Acetic acid (1 ml) was then added and boiled on a water bath to remove the excess methyl alcohol present in the reaction mixture. Glycine ethyl ester hydrochloride (2.78 g, 0.02 mol) and sodium bicarbonate (3.5 g) were ground together and added to the imidate formed in the round bottomed flask. Toluene (10 ml) was also added to the round bottomed flask and refluxed for three hours. Yellow
crystals of 4-[amino,(4-pyridyl) methylene]-2-(4-pyridyl)-2-imidazolin-5-one formed were filtered. Washed twice with water and then with ethanol and dried. The yellow product weighed 4 g (75%) and melted at 327 °C.

The amino imidazolinone (0.5 g) was recrystallised from ethanol (50 ml) and melted at 330 °C.

**Analysis**

<table>
<thead>
<tr>
<th></th>
<th>N%</th>
<th>C%</th>
<th>H%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>26.37</td>
<td>63.23</td>
<td>4.13</td>
</tr>
<tr>
<td>Calculated</td>
<td>26.41</td>
<td>63.39</td>
<td>4.15</td>
</tr>
</tbody>
</table>

**IR (cm⁻¹)**

3340, 3198, 1652, 1617, 1586

**Uv-vis**

λ<sub>max</sub> = 381

**Preparation of the metal complexes**

Complexes of Co(II), Cu(II) and Zn(II) were prepared by mixing methanolic solutions of the metal acetate (0.005 mol) and ethanolic solutions of the metal acetate (0.005 mol) and ethanolic solution of the amino imidazolinone (0.01 mol) in the presence of sodium acetate. (In the preparation of Cu(II) complex, sodium acetate was not added). On mixing these two solutions, the colour of the solutions changed immediately and the complexes started to precipitate. In order to make the complexation complete, the resulting solution was refluxed for 2 hours, concentrated and
kept overnight in an icebath. The complex formed was filtered using a vacuum pump and washed with ethanol and ether, dried in a desiccator over anhydrous calcium chloride.

**Preparation of trihydrochloride**

The amino imidazolinone (2 g) was taken in a 50 ml beaker. Con. HCl was added to it slowly. On addition of con. HCl the compound got dissolved by the formation of trihydrochloride and a clear solution was resulted. To this solution lime distilled ethanol was added drop by drop to precipitate the trihydrochloride formed. The precipitate was filtered and washed thrice with lime distilled ethanol and dried in a desiccator over anhydrous NaOH pellets.

**Elemental Analysis**

<table>
<thead>
<tr>
<th></th>
<th>N%</th>
<th>C%</th>
<th>H%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>18.52</td>
<td>44.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Calculated</td>
<td>18.7</td>
<td>44.9</td>
<td>4</td>
</tr>
</tbody>
</table>

\[
\text{C}_{14}\text{H}_{14}\text{N}_{3}\text{OCl}_3
\]