Synthesis of Hydroxamic Acids

\[ \text{BENZOYL CHLORIDE} + \text{HYDROXYL AMINE} + \text{NaHCO}_3 \rightarrow \text{ETHER} \rightarrow \text{HYDROXAMIC ACID} \]
This chapter describes the method of synthesis of hydroxamic acids. These were synthesized by acylation of freshly prepared derivatives of hydroxylamine in presence of a base at low temperature. The reaction medium was diethyl ether. The hydroxamic acids prepared were purified thrice with benzene for further use. The purity of these compounds was checked by determining their melting points, UV and IR spectral data. Elemental analysis of these compounds was also performed. These compounds were further used for the evaluation of their physical and diffusion parameters as described in subsequent chapters.
SYNTHESIS OF HYDROXAMIC ACIDS

In recent years, hydroxamic acids and their derivatives have received a lot of attention due to their rich chemistry and biological activities. These are important reagents due to their wide spectrum of applicability as highlighted in chapter I.

In the present investigation, three hydroxamic acids were synthesized.

- N-Phenylbenzohydroxamic Acid (PBHA)
- N-\textit{o}-Tolylbenzohydroxamic Acid (\textit{o}-TBHA)
- N-\textit{p}-Tolylbenzohydroxamic Acid (\textit{p}-TBHA)

The procedure followed for the preparation of these compounds in general was reported in the literature (90). These were prepared by direct coupling of hydroxylamine with benzoyl chloride at low temperature in presence of aqueous sodium bicarbonate suspension. Diethyl ether was the reaction medium. The purity of these compounds was then ascertained by determining their melting points, UV and IR spectral analysis. Elemental analysis of these compounds was also performed.

EXPERIMENTAL SECTION

APPARATUS

- Mechanical stirrer (Remi, RPM 6000).
- Vacuum pump (Basynth, TSRP/30).
- Glass wares.
- IR spectrophotometer (Perkin 1002).

SYNTHESIS OF HYDROXAMIC ACIDS

STEP-I PREPARATION OF N-ARYLHYDROXYLAMINES

Hydroxylamines were prepared by the reduction of corresponding nitro compounds by zinc dust and aqueous ammonium chloride. Preparation of individual hydroxylamine is discussed here.
PHENYLHYDROXYLAMINE

Phenylhydroxylamine was obtained by reduction of nitrobenzene with zinc dust and aqueous ammonium chloride at temperature below 65°C. In one litre plastic jar, 25 ml of nitrobenzene along with 500 ml of distilled water and 12.5 gms. of ammonium chloride were taken. To this, 60 gms. of zinc dust was added in small installments maintaining the temperature below 65°C and solution was stirred mechanically during this period. After complete addition of zinc dust stirring was continued for additional 15 minutes more, to ensure complete reduction of nitrobenzene. The precipitated zinc oxide was filtered and the filtrate was saturated with common salt and kept in freezing mixture for one hour. The shining crystalline flakes of phenylhydroxylamine salted out, were filtered and recrystallized thrice with benzene and petroleum ether (60-80°C).

\[
\text{Reduction} \quad \text{Zn + NH}_4\text{Cl} \quad \rightarrow \quad \text{N} \quad \text{OH}
\]

N- o–TOLYLHYDROXYLAMINE

It is prepared by the reduction of o-nitrotoluene with zinc dust and aqueous ammonium chloride at temperature below 70°C. In preparation flask, 30 gms. of freshly distilled o-nitrotoluene were mixed with 20 ml of water, 30 ml of ethyl alcohol and 2 gms. of ammonium chloride and the mixture was mechanically stirred. Then 30 gms. of zinc dust was added in small lots over a period of 30 minutes. The temperature of reaction mixture was kept below 70°C. The stirring was continued for additional 20 minutes. Zinc oxide was filtered off and the filtrate was used as such for acetylation reaction assuming the 50% yield.

\[
\text{Reduction} \quad \text{Zn + NH}_4\text{Cl} \quad \rightarrow \quad \text{OH}
\]
N-\textit{p}-TOLYLHYDROXYLAMINE

The procedure followed for the preparation of N-\textit{p}-tolylhydroxylamine is similar to that used for the preparation of phenylhydroxylamine except that in place of nitrobenzene, \textit{p}-nitrotoluene was dissolved in hot distilled water (40-50\degree C).

\begin{equation}
\text{CH}_3\text{C}_6\text{H}_4\text{NO}_2 \xrightarrow{\text{Reduction}} \text{CH}_3\text{C}_6\text{H}_4\text{N}=\text{OH} \quad \text{Zn} + \text{NH}_4\text{Cl}
\end{equation}

**STEP – II PREPARATION OF N-ARYLSUBSTITUTED HYDROXAMIC ACIDS**

N-arylsubstituted hydroxamic acids were prepared by coupling of corresponding hydroxylamine with benzoyl chloride (E. MERCK) in presence of sodium bicarbonate slurry in ether medium. All the reacting materials were taken in an equimolar quantity. To the ice-cold solution of freshly crystallized desired hydroxylamine in 1:1 mixture of diethyl ether and petroleum ether, a suspension of sodium bicarbonate (1 mole) in water was added. To this mixture, a solution of benzoyl chloride (1 mole) in diethyl ether was added drop wise over a period of one hour. The solution was stirred throughout and stirring was continued for 15 minutes more. After filtration the products were purified by crystallization thrice with benzene and dried in vacuum over phosphorus pentaoxide for several hours before use.

**N-PHENYLBENZOHYDROXAMIC ACID**

\begin{equation}
\text{N}=\text{OH} \quad \text{H} \quad + \quad \text{C}=\text{O} \quad \text{NaHCO}_3 - \text{HCl}
\end{equation}
GENERAL PROPERTIES OF HYDROXAMIC ACIDS

- Hydroxamic acids are neutral polyfunctional molecules.
- These are white crystalline solids and are highly stable towards heat, light and air.
- They show pharmacophoric activities due to the presence of $-\text{CON (OH)}$ group.
- They are very sparingly soluble in water, but display enhanced solubility in mineral acids solutions.
- These are freely soluble in many organic solvents, viz., acetone, toluene, chloroform, carbon tetrachloride, 1, 2-dichlorobenzene, ethyl acetate and benzene etc.
- These are very weak acidic compounds and do not liberate CO$_2$ from aqueous NaHCO$_3$ solution.
- They serve as weak organic bases in the presence of strong acidic solutions.
Synthesis of Hydroxamic Acids

> They form reddish-violet coloured complex with iron (III) (91) which can be used for the detection of organic functional group, viz., amide, carbonyls, alcohols, phenols, etc. (92, 93)

\[
\text{H-N} \text{OH} + \text{Fe}^{3+} \rightarrow \left(\text{H-N} \text{O}\right)_{\text{Fe}^{2+}} + \text{H}^+ \\
\text{Reddish-violet}
\]

> Hydroxamic acids solutions produce violet colour extracts on treating with vanadium (V) in water immiscible solvents in the presence of hydrochloric acid (94, 90). This reaction is used as detection test for pentavalent vanadium.

\[
\text{H-N} \text{OH} + \text{V} (+5) \text{HCl} \rightarrow \left(\text{H-N} \text{O}\right)_{\text{R'-C=O}} + \text{Cl}^-
\]

Violet coloured vanadium

> Hydroxamic acids form 5-membered ring on chelation with metal ions (95).

> Hydroxamic acids bond is reduced by raney nickel or hydrogen and oxidized in presence of hydroiodic acid, perfomic acid and periodic acid. Periodic acid selectively cleaves the hydroxamic acid linkage while amide and even more sensitive bonds remain unaffected.
TABLE 2.1.

PHYSICAL CHARACTERISTICS OF SYNTHESIZED COMPOUNDS

<table>
<thead>
<tr>
<th>S.No</th>
<th>HYDROXAMIC ACIDS</th>
<th>2D Optimized geometry structure</th>
<th>M.W.</th>
<th>Melting Point</th>
<th>Elemental analysis</th>
<th>IR (cm⁻¹)</th>
<th>UV, λmax (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Observed</td>
<td>Reported</td>
<td>Theoretical</td>
<td>Observed</td>
</tr>
<tr>
<td>I</td>
<td>N-PHENYLBENZO-</td>
<td><img src="image1" alt="Structure" /></td>
<td>213.23</td>
<td>121°C</td>
<td>122°C (96)</td>
<td>73.23</td>
<td>5.20</td>
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<tr>
<td></td>
<td>(C₁₃H₁₁NO₂)</td>
<td></td>
<td></td>
<td>Reported</td>
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</tr>
<tr>
<td>II</td>
<td>N-ο-TOLYLBENZO-</td>
<td><img src="image2" alt="Structure" /></td>
<td>227.09</td>
<td>105°C</td>
<td>105°C (97)</td>
<td>73.99</td>
<td>5.77</td>
</tr>
<tr>
<td></td>
<td>(C₁₄H₁₃NO₂)</td>
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<td>Reported</td>
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</tr>
<tr>
<td>III</td>
<td>N-p-TOLYLBENZO-</td>
<td><img src="image3" alt="Structure" /></td>
<td>227.09</td>
<td>111°C</td>
<td>111°C (96)</td>
<td>73.99</td>
<td>5.77</td>
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