Chemistry
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For B.Sc. 4th Semester

(Alkaloids)
Module-VI

Structure Elucidation and Synthesis of Hygrine

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**Hygrine: Occurrence**

**Hygrine**, is a pyrrolidene alkaloid with molecular formula $\text{C}_8\text{H}_{15}\text{NO}$.

It is a natural product **occurring** in the coca leaves along with cocaine. It is a thick oil having pungent smell and odour. Boiling point 193 -195 °C.

Coca leaves

- Hygrine is used as a sedative, hypnotic, laxative and diuretic.
Mol formula was determined as \( C_8H_{15}NO \) and it shows the presence of a keto group and a tertiary N-atom.

On oxidation with Chromic acid, hygrinic acid is formed.

\[
\begin{align*}
C_8H_{15}NO + O & \rightarrow C_6H_{11}NO_2 \\
\end{align*}
\]

On dry distillation, hygrinic acid gives N-methyl pyrrolidine. This shows that hygrinic acid is an N-methyl pyrrolidine carboxylic acid.

Hygrinic acid undergoes decarboxylation very rapidly indicating that the \(-\text{COOH}\) group is present at 2-position.

This structure is confirmed by Wilstatter synthesis.
Formation of Hygrinic acid on oxidation of hygrine shows that in hygrine a side chain of C3H5O must be present at C-2 position of N-methyl pyrrolidine nucleus.
Upon oxidation, this side chain nicotine methiodide gives hygrinic acid.

\[
\text{C}_{10}\text{H}_{14}\text{N}_{2}\text{CH}_{3}\text{I} \xrightarrow{\text{O}} \begin{array}{c}
\text{N-methyl-pyrrolidine-2-carboxylic acid} \\
\text{Hygrinic acid}
\end{array}
\]

This suggests that 2-position of N-methylpyrrolidine ring is attached to 3-position of pyridine nucleus.

Upon drastic oxidation, the side chain gives only one carbon containing carboxylic acid (hygrinic acid). So the side chain must contain a keto group.

The structures proposed for Hygrine by Hess (1913) are A and B.
Structure A for Hygrine is finally confirmed by its synthesis from the condensation reaction of $\gamma$-methylaminobutyraldehyde with ethyl acetoacetate at pH 7.

The product resembles in structure to natural Hygrine and gives all the reactions discussed earlier.
References

1. K.D Sharma and Y. R. Sharma, Kalyani Publishers, Unit-III page-319;