

# Hofmann Exhaustive Methylation

Hofmann's exhaustive methylation is a typical nucleophilic  $\beta$ -elimination reaction which is used in the structure determination of amines. When the quaternary ammonium hydroxide is heated, it gives water, a tertiary amine and least substituted alkene as the  $\text{OH}^-$  ion abstracts proton from the least hindered  $\beta$ -position. The reaction ~~can occur~~ leads into following five steps —

Step I

The heterocyclic ring is reduced if unsaturated.

Step II

The reduced ring is methylated with excess of  $\text{CH}_3\text{I}$  to ~~form~~ form quaternary ammonium iodide.

Step III

The quaternary ammonium iodide is converted into corresponding hydroxide with moist  $\text{Ag}_2\text{O}$  ( $\text{Ag}_2\text{O} + \text{H}_2\text{O} \rightarrow 2\text{AgOH}$ )

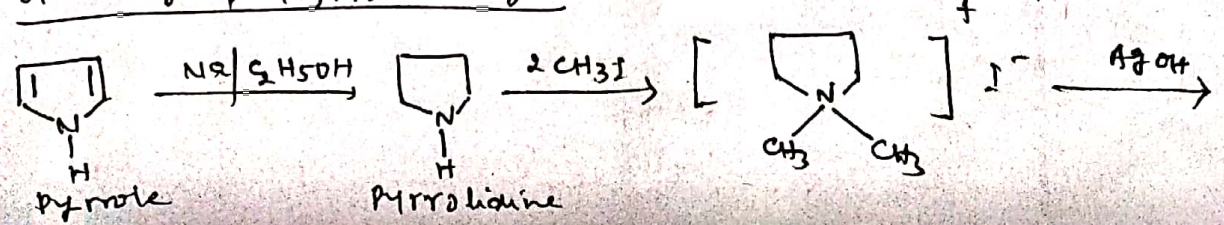
Step IV

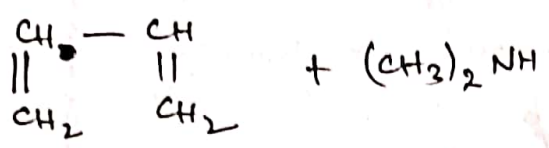
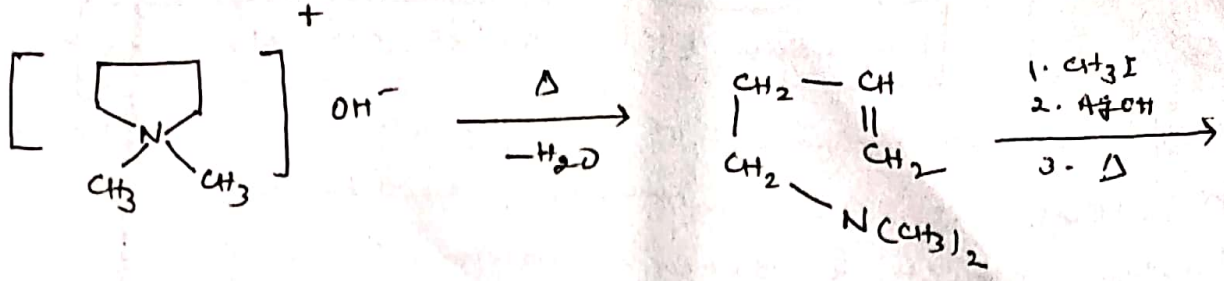
The quaternary ammonium hydroxide undergoes  $\beta$ -elimination on heating where C-N bond on one side of the  $\beta$ -H atom breaks to form an open chain unsaturated 3<sup>o</sup>-amine.

Step V

1-4th steps are repeated when the second C-N bond breaks to give  $(\text{CH}_3)_3\text{N}$  and a diene ~~which~~ which, very often isomerises to a conjugated diene. ~~This is not applicable in case of pyrrolidine and isopiperidine derivatives.~~

opening of pyrrole ring





opening of pyridine ring

