Mannich Reaction.

In Mannich reaction formaldehyde is condensed with ammonia, primary amine or a secondary amine and a compound containing at least one active hydrogen atom. The reaction is acid as well as base catalysed. This product of this reaction is a β-aminocarbonyl compound known as Mannich base.

Following are some compounds which have active hydrogen atom (s)

ketones, β-keto esters, β-cyanoesters, nitroalkanes, alkynes, phenol etc.

(i) $C_6H_5-\overset{O}{\overset{\|}{C}}-CH_3 + CH_2O + (CH_3)_2NH \longrightarrow C_6H_5CO(CH_2)N(CH_3)_2 + H_2O$

Acetophenone — Mannich base

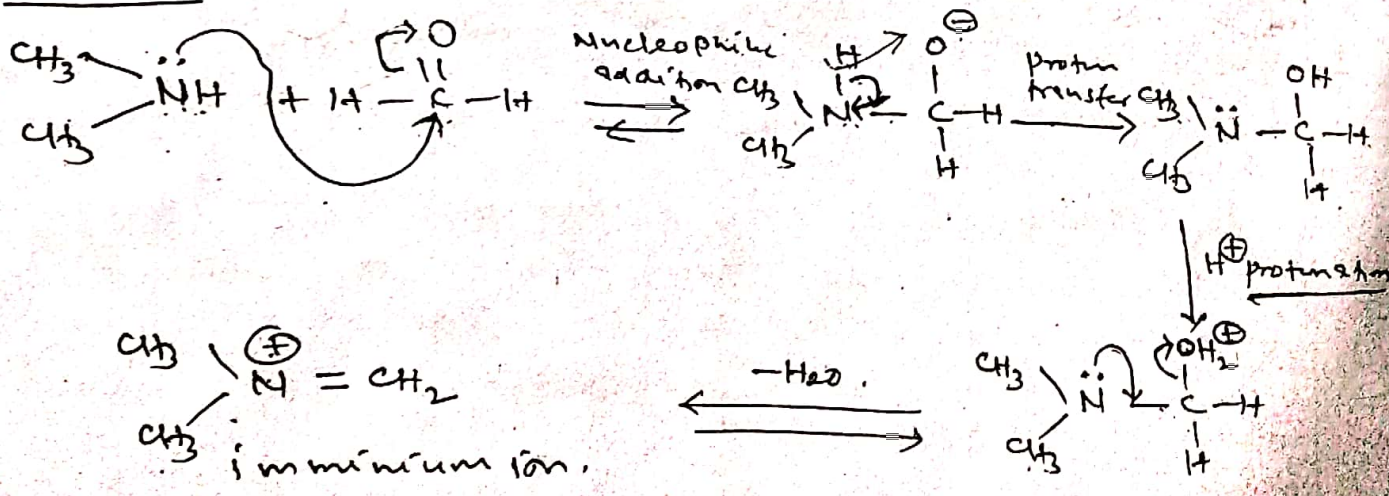
(ii) $CH_3COCH_2CH_3 + CH_2O + (CH_3)_2NH \longrightarrow CH_3CO\overset{\alpha}{C}H(CH_3)\overset{\beta}{C}H_2N(CH_3)_2 + H_2O$

Mannich base

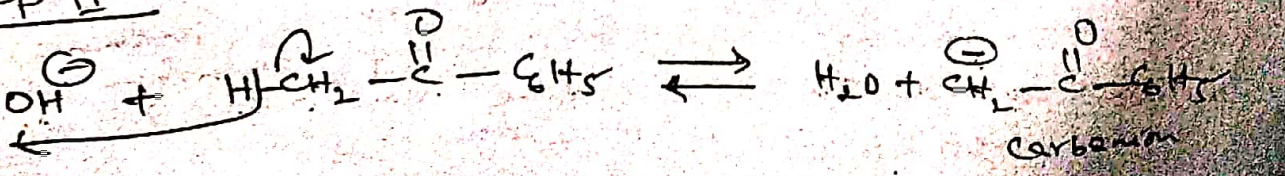
Mechanism.

The initial step of this reaction is involves the formation of the immonium salt by the reaction of formaldehyde with amine which is consequently attacked by the carbanion or the enol.

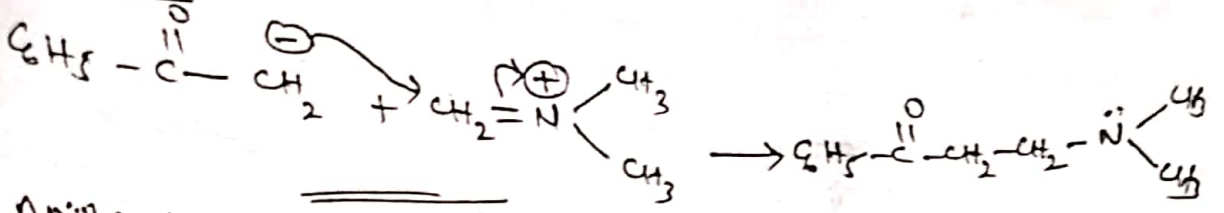
Step I



Step II



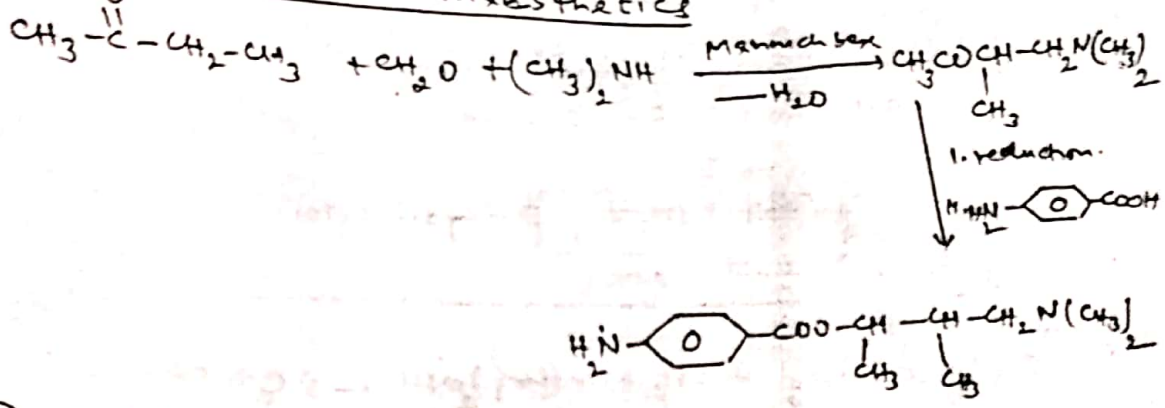
Step iii



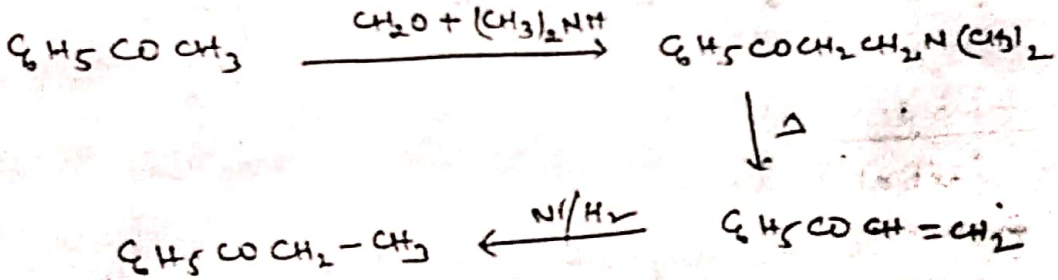
mannich base

Application

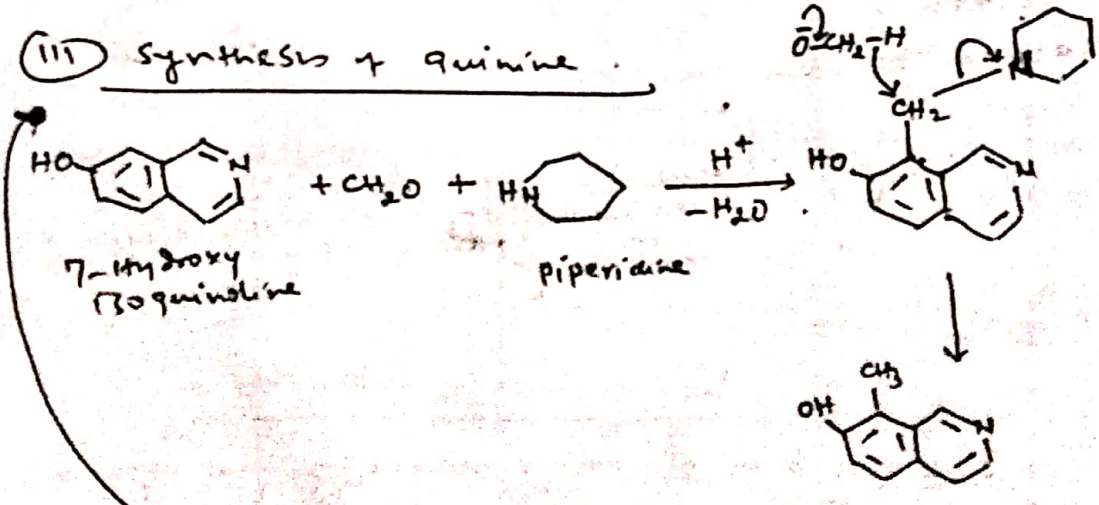
(i) Synthesis of local anaesthetics



(ii) Catalytic reduction of the unsaturated product gives the next higher homologue of ketone from which the mannich base was derived, eg:



(iii) Synthesis of quinine.



7-Hydroxy isoquinoline

piperidine

mannich reaction is applied in synthesis of quinine to introduce a methyl group into 8-position of 7-hydroxy isoquinoline. mannich base is prepared from 7-hydroxy isoquinoline, formaldehyde and piperidine. Now amino group of the base is replaced by hydrogen atom from methoxide ion. (hydride ion transfer).