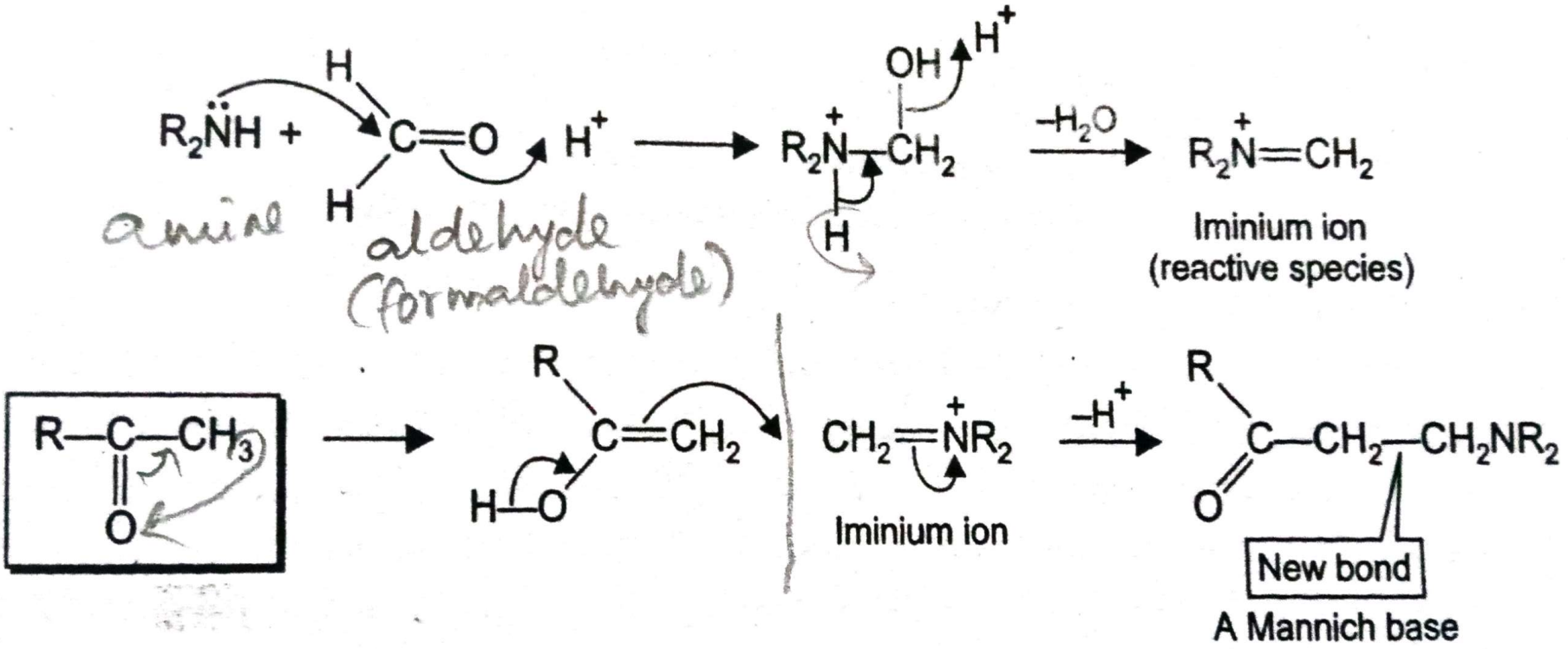
SCHEME 6.48a

(ii) Mannich Reaction

This reaction links together an amine an aldehyde (usually formaldehyde) and the enol of a ketone *i.e.*, a ketone with an α-hydrogen (Scheme 6.49). Thus the net result of Mannich reaction

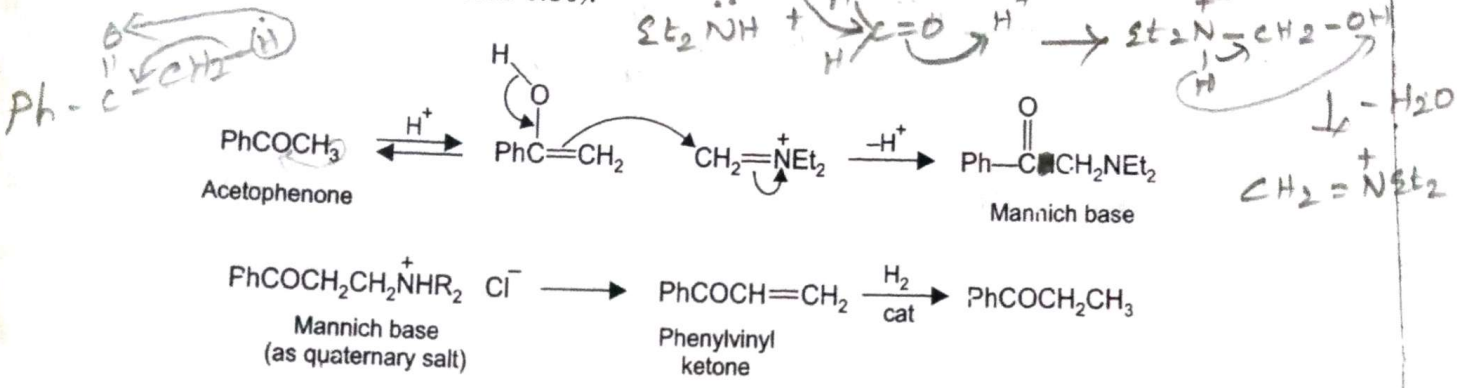


Mechanism of Mannich reaction

SCHEME 6.49

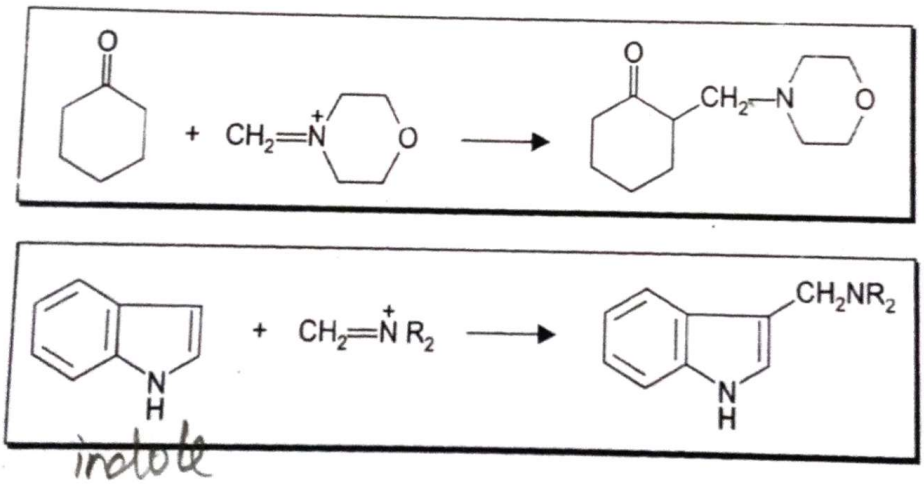
among CH_2O, RNH_2 and $R'COCH_3$ is the extension of the $—CH_3$ of the ketone by $—CH_2NHR$. The products of the Mannich reaction are known as Mannich bases and many are useful as intermediates in synthesis.

The reaction of acetophenone with diethylamine and formaldehyde gives the Mannich base which can be elaborated to a variety of compounds *e.g.*, on Hoffmann elimination (see Scheme 15.29) and so on (Scheme 6.50).



SCHEME 6.50

As seen above (Scheme 6.49) the electrophilic component in a Mannich reaction is the methyleneiminium ion generated from formaldehyde and a secondary amine. The nucleophile may be an enol, an activated arene or a π-excessive heteroarene (Scheme 6.50*a*).

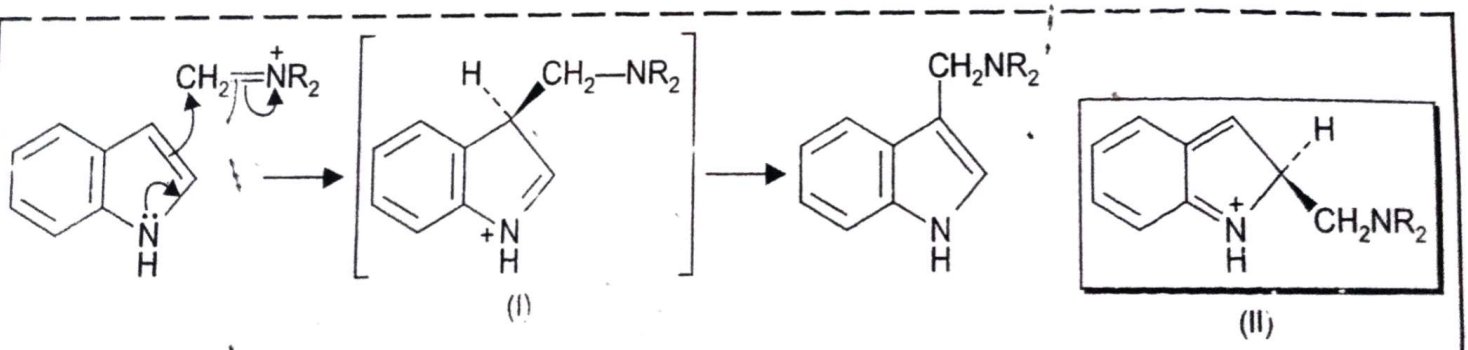


SCHEME 6.50a

EXERCISE 6.6

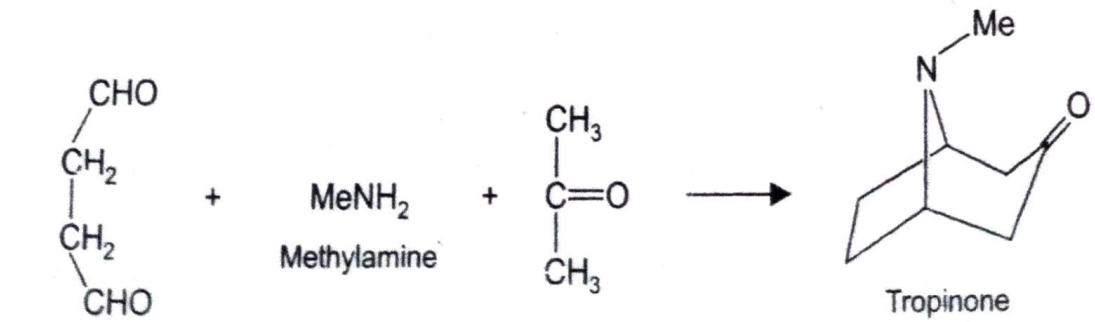
Why in indole (see Scheme 6.50a) the reactive species, the iminium ion reacts at the 3-position and not at position 2?

ANSWER. *The 2, 3-benzo derivatives of pyrrole, furan and thiophene react in the hetero ring. Substitution at the 3-position e.g., in indole generates a transition state (I, Scheme 6.50b) in which the stabilizing effect of N atom on the transition state is more and the appropriate resonance structure is benzenoid. The benzenoid system is disrupted on 2-substitution as shown (II, Scheme 6.50b).*



SCHEME 6.50b

The Mannich reaction is an important synthetic pathway in the biosynthesis of alkaloids, and many such reactions have been duplicated under the laboratory conditions. Thus tropinone can be synthesized from succindialdehyde, methylamine and acetone (Scheme 6.51).



SCHEME 6.51