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A REVIEW ANALYSIS ON MECHANISM OF THE AMIDOALKYLATION REACTIONS

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ABSTRACT

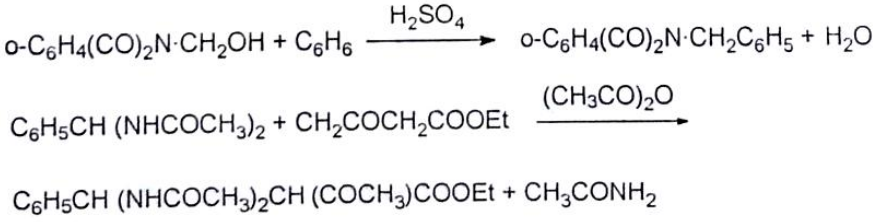
α-Amidoalkylation reaction is a powerful tool of modern organic synthesis for carbon-carbon or carbon-heteroatom bond formation. The distinguishing features of amidoalkylating reagents are higher electrophilicity and wider structural diversity compared with those of reagents involved in aminoalkylation reactions. Therefore, amidoalkylation has been extensively applied in the synthesis of various nitrogencontaining acyclic and heterocyclic compounds including bioactive natural products (e.g., alkaloids, antibiotics, toxins, vitamins) and pharmaceuticals. Recently, some enantioselective variants of this reaction employing catalytic amounts of chiral auxiliaries has also been described.

Keywords: *α-amidoalkylation; nucleophiles, aromatic compounds and aliphatic compounds*

INTRODUCTION

a-Amido alkylation reaction leads to the formation of a new carbon-carbon bond by replacement of X from the electrophilic reagent RCON (R'), CH (R") X, where X is halogen, -OH, -OR, -OCOR, -NHCOR, -NR, or -NR,. The group R' may be hydrogen or alkyl or, in important instances a second acyl group, as in the corresponding derivatives of phthalimide, o-C,H. (CO), N.CH(R')X. In a few cases a sulphonyl group may replace the acyl group of the electrophilic reagent.

The nucleophilies that react with these reagents fall into two broad groups - aromatic compounds and aliphatic compounds containing reactive methylene or methine groups. The first may be illustrated by the phthalimidomethylation of benzene and the second by the reaction of ethyl acetoacetate and N, N'-benzylidene bis acetamide.



Compounds sufficiently nucleophilic to undergo attack by the amido alkylating agents include aromatic compounds, olefins, acetylenes, ketones, carbenoid compounds derived from active methylenes, Grignard reagents, and other organomethallics. Amidoalkylation of conjugated dienes, a hetero-Diels-Alder reaction has received much attention recently. Four other areas are :

1. Intramolecular amidoalkylations have received much attention especially in connection with new approaches to alkaloid synthesis.

2. The heteroarylation reaction of N-acyl pyridinium, quinolinium, and isoquinolinium salts and moreover is more logically related to the exhaustively reviewed reaction of Reissert compounds4.

3. The few reported amido alkylations occuring through homolytic mechanisms and

4. Finally the umpolung equivalent of cationic aamido alkylation, viz; the utilization of dipole stabilized carbanions derived by abstraction of a proton from the N-methyl or N-methylene group attached to amide nitrogeno.

The amido alkylation reaction provides valuable alternative to the very useful Mannich reaction?. In addition to furnishing ready access cens: to primary and secondary amines, it generates a spectrum of reactivity considerably broader than that of the Mannich reaction. The electrophilic reactivity of the N-acylmethylene immonium ion 1 is generally greater than that of the methylene immonium ion 2.

(1)

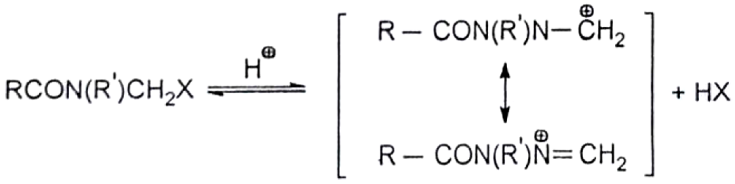
(2)

Furthermore by varying the structures of R-CO in 1 together with the reaction conditions, a broader range of reactivity in 1 is obtainable. It is not surprising then, that recent work involving amidoalkylations encompasses a large segment of synthetic organic chemistry. Biologically important areas include new synthesis of a and B-aminoacids8,10, B-amino-ketones", application to the

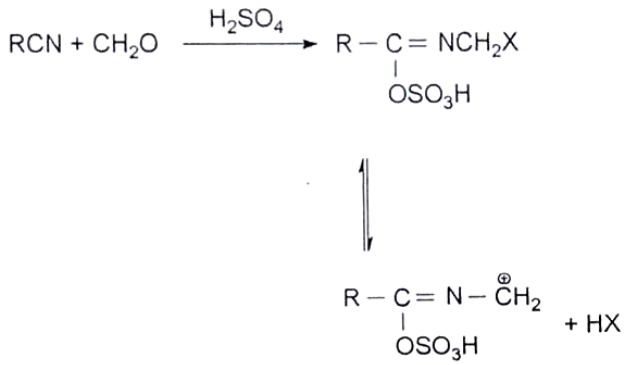
synthesis of B-lactam antibiotics12,13, the corrin skeleton of vitamin B.214, and other porphyrinsls, pyridoxinel6 and other alkaloids'? And the synthesis of a series of aminomethylphenol diuretics18. Other areas of potential commercial value comprise the application of amidoalkylation to improve the efficiency of the polymers used in solid-phase peptide synthesis", to improve certain dye characteristics20, and to serve as cross-linking agents for the crease-proofing of cotton21, 22 (amido alkylation of oxygen).

Mechanism of the reaction:

The reactions considered include acids catalyzed, basecatalyzed and thermally induced processes. They like the corresponding a-aminoalkylation reactions probably encompass a considerable portion of the mechanistic spectrum of heterolytic organic chemistry. Detailed studies are almost completely locking. Nevertheless, some general outlines of the mechanistic possibilities can be drawn23. Although cryoscopic studies in 100% sulphuric acid have yet to be reported, it seems likely that in very strong acid of high dielectric constant electrophiles lacking a hydrogen atom on the nitrogen atom undergo appreciable dissociation to a carbonium-immonium ion. In the presence of weak nucleophile (e.g. aromatic rings) bimolecular displacement (SN) of protons from C-H bond usually follows.

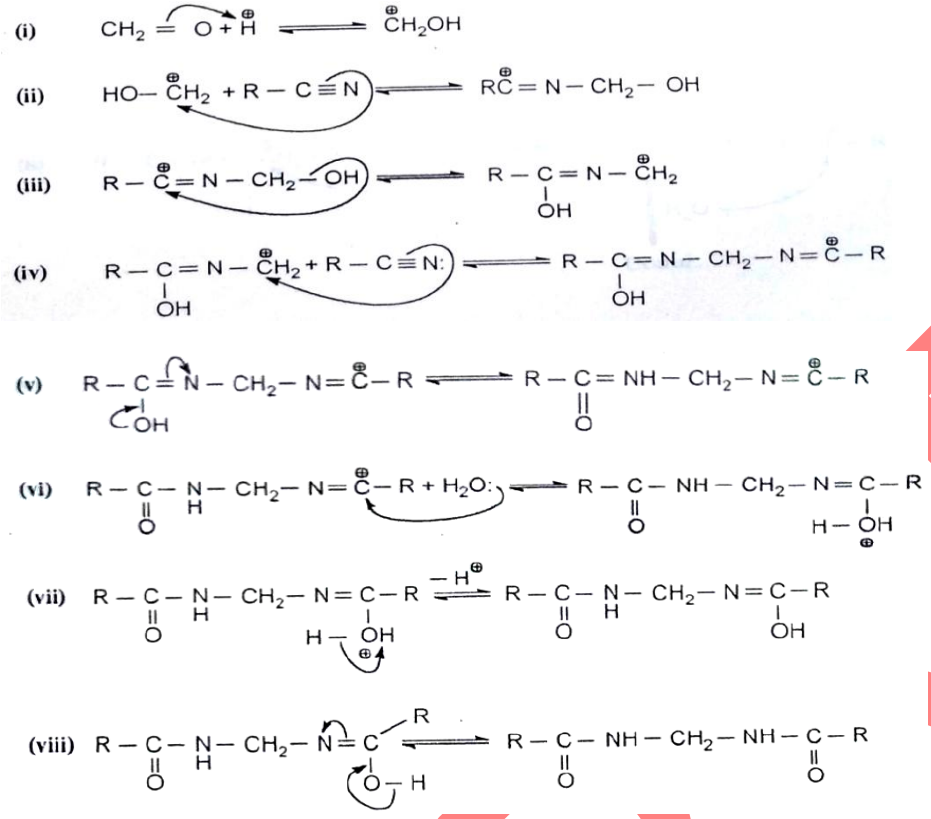


Under the same conditions amide derivative having a hydrogen atom attached to the nitrogen atom (R' = H) may give the analogous cation but the other forms are more likely. Thus, when nitriles are treated with formaldehyde in strong H,SO, sulpher containing intermediates have been isolated24,25. Evidence indicates that these are sulphate esters which in strong acid equilibrate with their corresponding carbonium ions26. Granting the existence of these structures, identical species should, of course, be formed, when the amide, RCONHCH,X is dissolved in strong H,SO

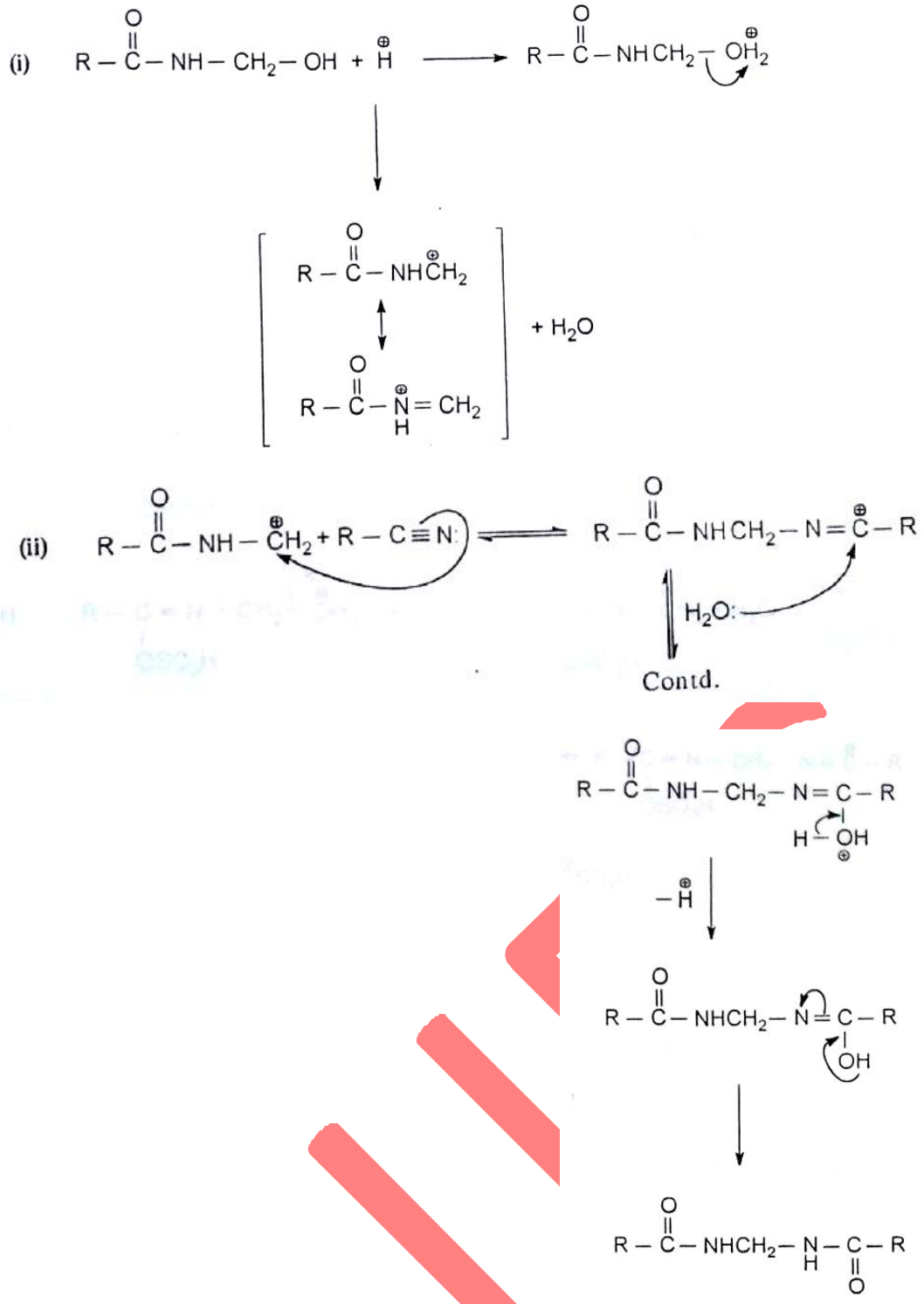


That such a common intermediate is present, is supported by the recent findings that nitriles and formaldehyde in either strong H_2SO_4 or strong H_3PO_4 can substitute effectively for the corresponding methyloamides in the amdiomethylation of aromatic compounds.

The overall mechanistic steps in acid-catalysed a-amido alkylation can be represented as follows:



The mechanism of the reaction of methylolamides and nitriles may be represented by the series of equations.



In the presence of H, 90, the principal reaction possibly proceeds through the following mechanism.

(i) $CH_2=O^{+}H \rightleftharpoons {}^{\oplus}CH_2-OH$

(ii) $R-C\equiv N + {}^{\oplus}CH_2-OH \rightleftharpoons R-{}^{\oplus}C=N-CH_2OH$

(iii) $R-{}^{\oplus}C=N-CH_2OH + {}^{\ominus}OSO_3H \rightleftharpoons R-\underset{\displaystyle OSO_3H}{\overset{\displaystyle |}{C}}=N-CH_2OH$

(iv) $R-\underset{\displaystyle OSO_3H}{\overset{\displaystyle |}{C}}=N-CH_2-OH + {}^{\oplus}H \rightleftharpoons R-\underset{\displaystyle OSO_3H}{\overset{\displaystyle |}{C}}=N-CH_2-{}^{\oplus}OH_2$

(v) $R-\underset{\displaystyle OSO_3H}{\overset{\displaystyle |}{C}}=N-CH_2-{}^{\oplus}OH_2 \rightleftharpoons R-\underset{\displaystyle OSO_3H}{\overset{\displaystyle |}{C}}=N-{}^{\oplus}CH_2 + H_2O$

(vii) $R-\underset{\displaystyle OSO_3H}{\overset{\displaystyle |}{C}}=N-CH_2-N=\overset{\oplus}{C}-R + {}^{\ominus}OSO_3H$

$\rightleftharpoons R-\underset{\displaystyle OSO_3H}{\overset{\displaystyle |}{C}}=N-CH_2-N=\underset{\displaystyle OSO_3H}{\overset{\displaystyle |}{C}}-R$

(viii) $R-\underset{\displaystyle OSO_3H}{\overset{\displaystyle |}{C}}=N-CH_2-N=\underset{\displaystyle OSO_3H}{\overset{\displaystyle |}{C}}-R \xrightarrow{H_2O} R-\underset{\displaystyle OH}{\overset{\displaystyle |}{C}}=N-CH_2-N=\underset{\displaystyle OH}{\overset{\displaystyle |}{C}}-R$ (imide)

$\rightleftharpoons R-\underset{\displaystyle O}{\overset{\displaystyle ||}{C}}-NHCH_2NH-\underset{\displaystyle O}{\overset{\displaystyle ||}{C}}-R$ amide

Some amidoalkylation reactions are expected to proceed via a cyclic intermediate as suggested below.

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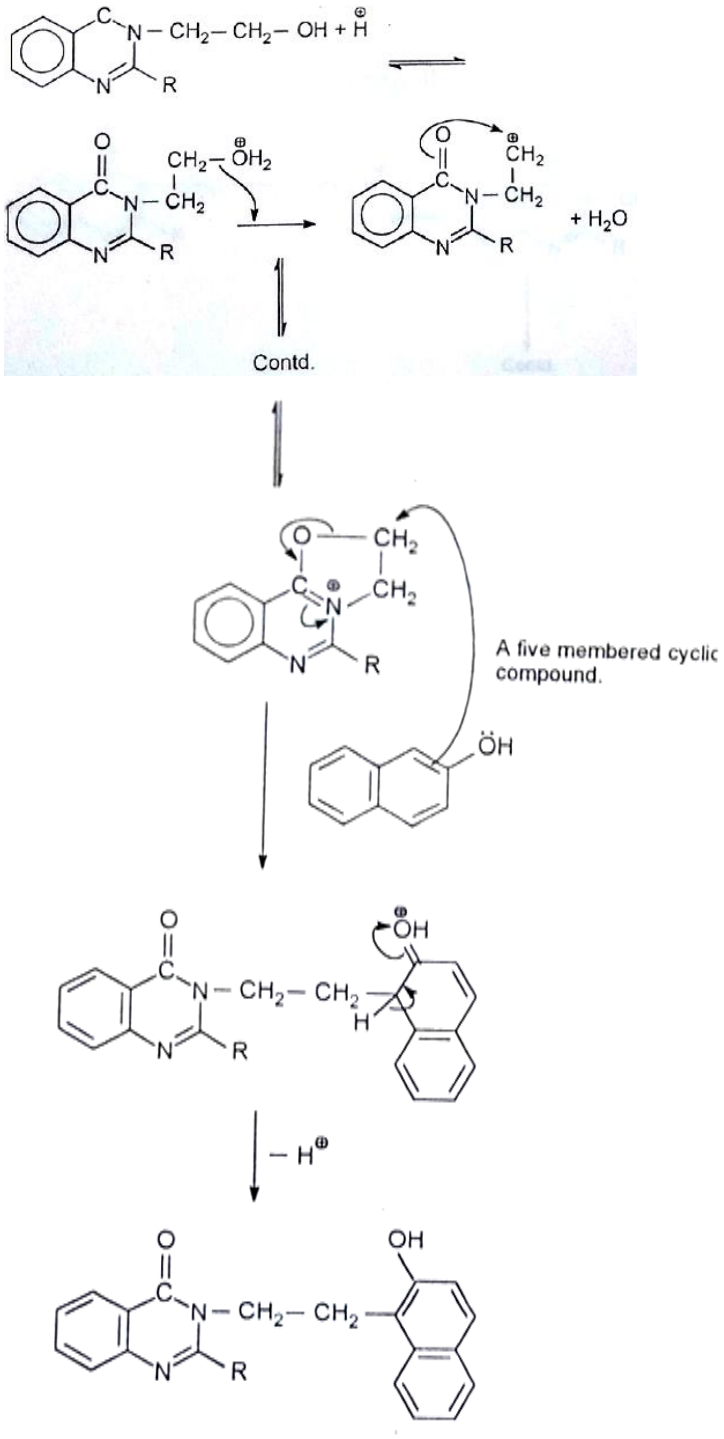
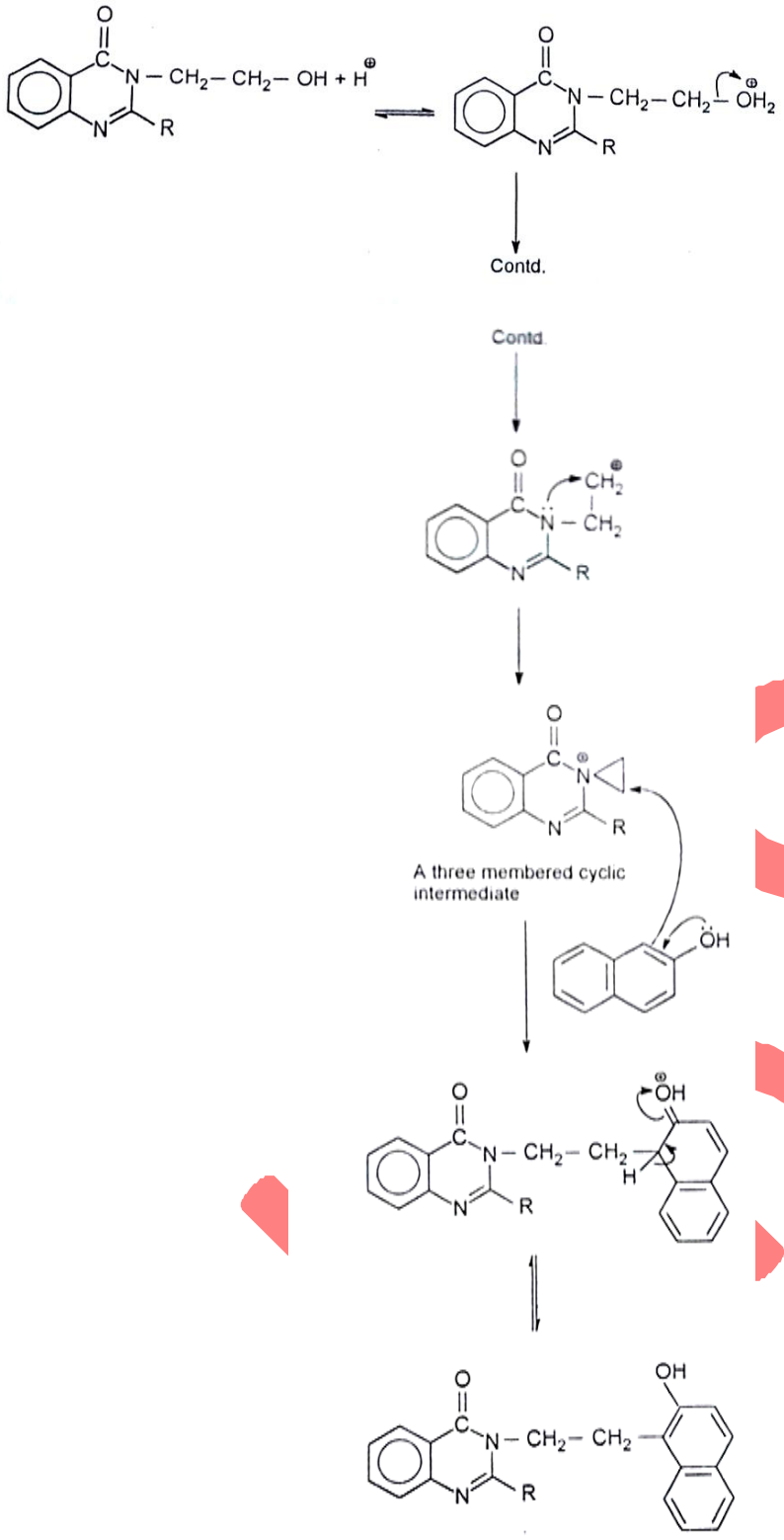
Path A



Path B



Most probably the reaction proceeds via a five membered cyclic intermediate because of its greater stability than a three membered cyclic intermediate.

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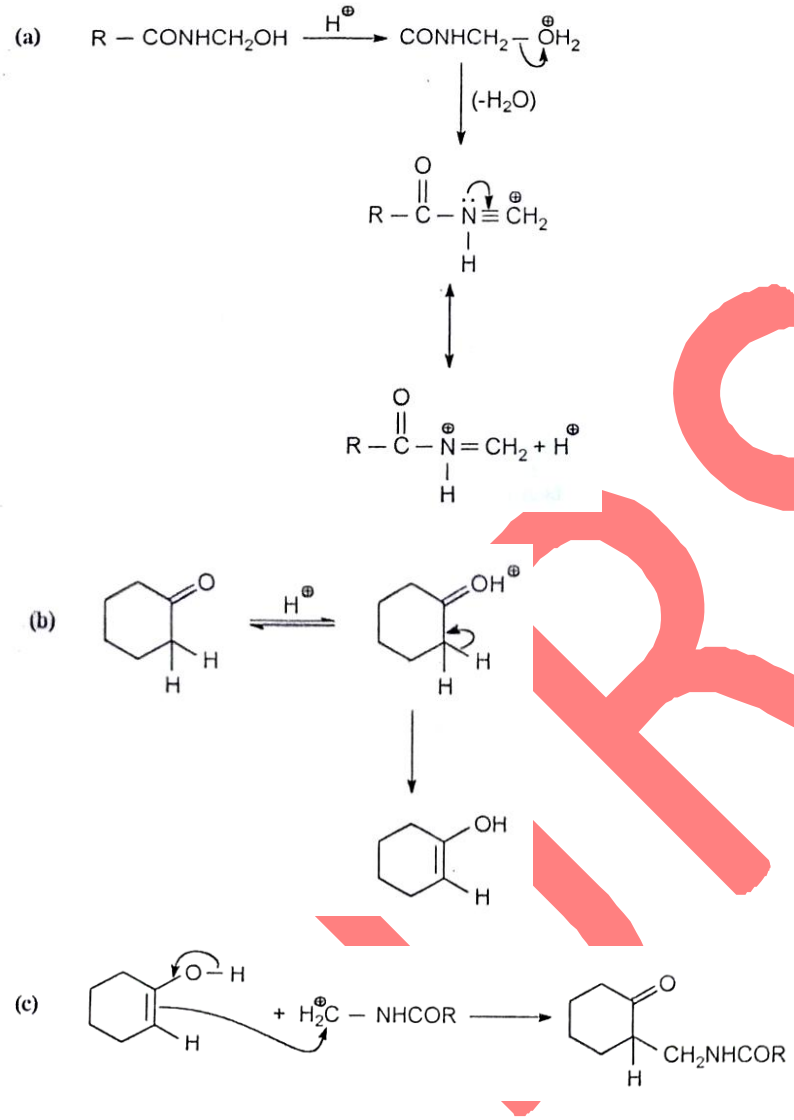
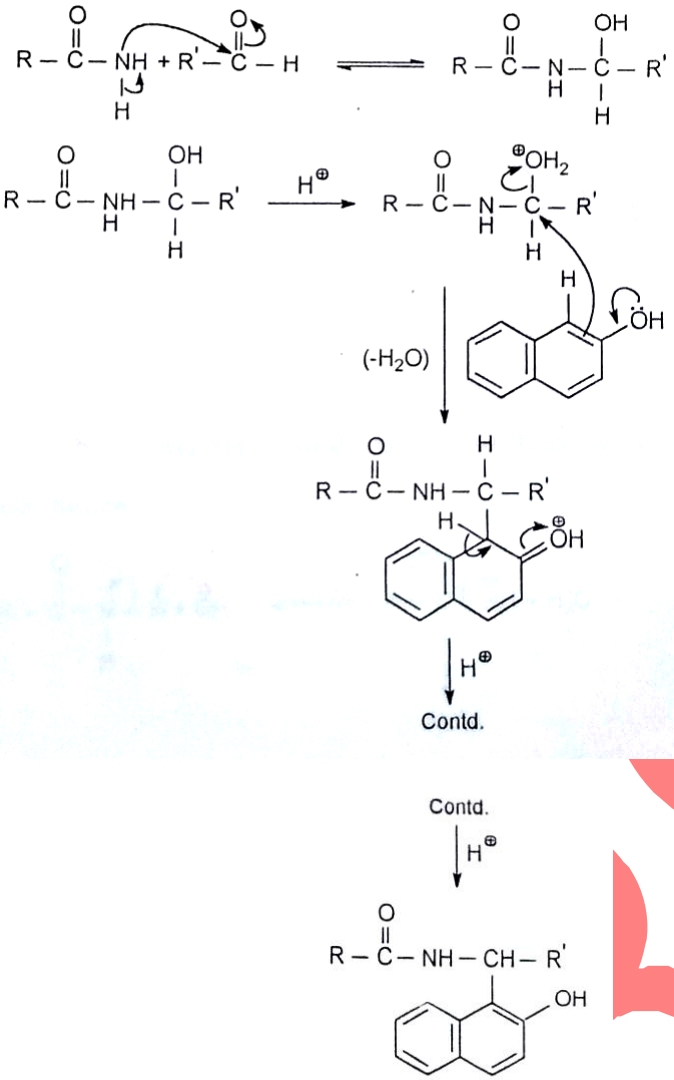
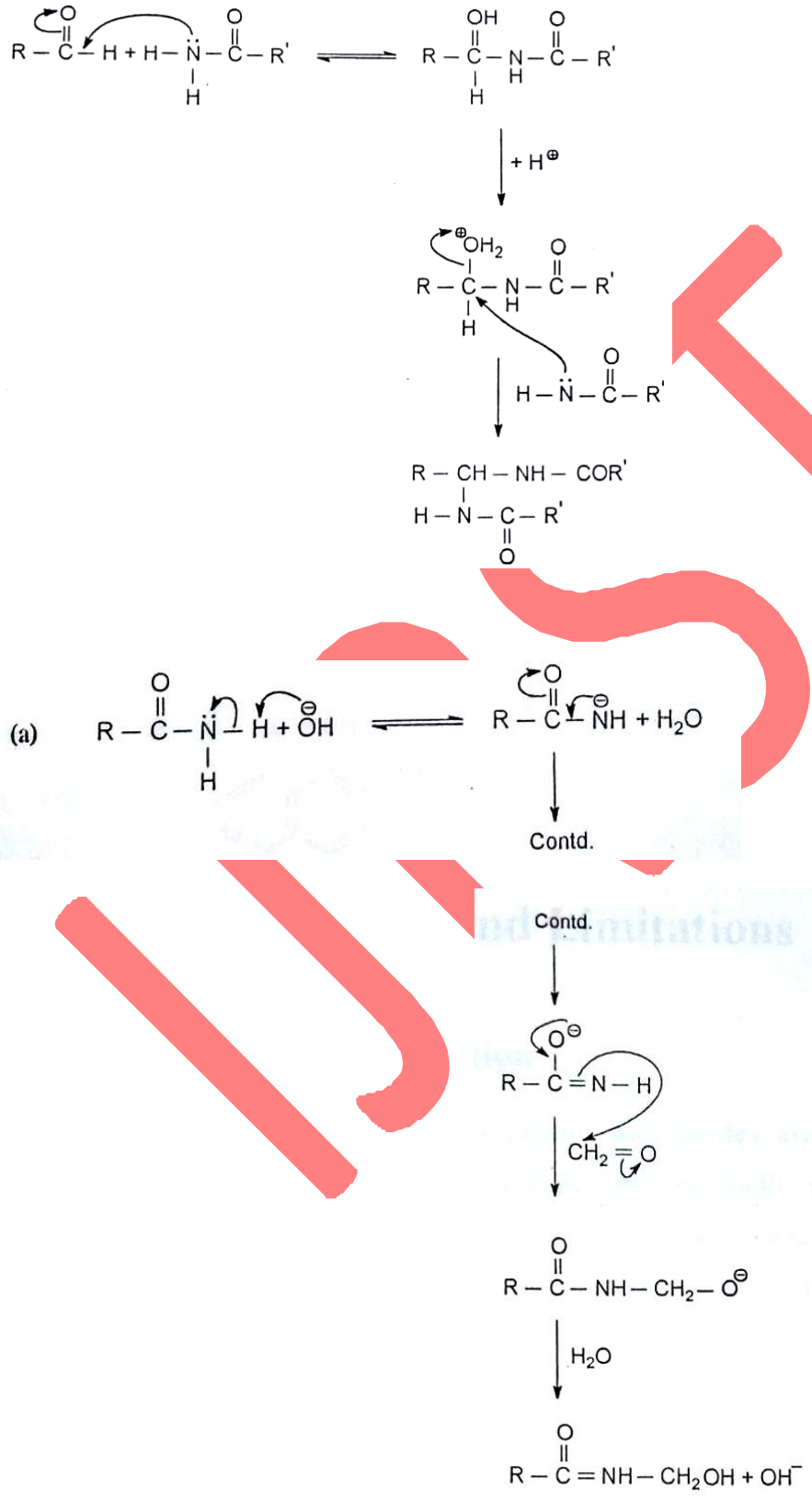
In addition, a-amido alkylation reaction in cyclohexanone which is a weak nucleophile has been shown to be very much similar to the acid-catalyzed bromination of cyclohexanone, where the rate determining step has been shown to be the production of the enol of the ketones as the result of carbonyl protonation followed by proton removal by a basic species such as water. The reversible formation of an oxonium ion or oxonium salt intermediate by the protonation of the oxygen atom takes place which is then followed by the loss of a water molecule from the intermediate ion to form a immonium carbonium ion which then reacts with the enal of ketone to give the a-amido alkylated product.

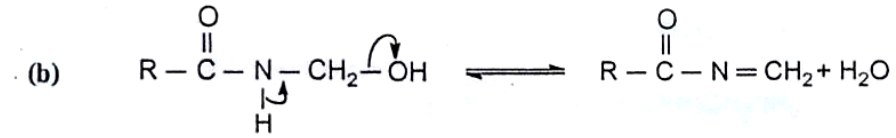


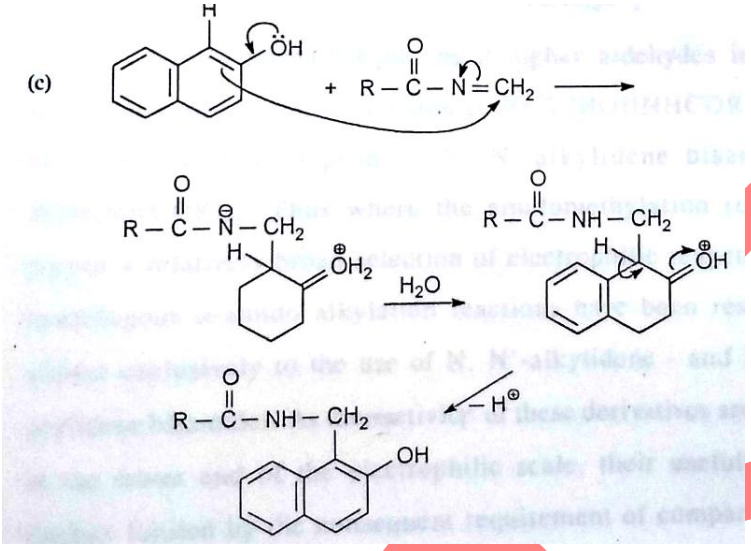
With aldehydes other than formaldehyde reaction may proceed as follows:



If however two equivalents of amide for one equivalent of an aldehyde is treated, the final product is amidoalkylamide.


+ H⊕
H – N – C – R'
R – CH – NH – COR'
H – N – C – R'
(a)
Contd.
Contd.
CH2 = O
H2O





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