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Dep. of Pharmaceutical Chemistry
Organic Pharmaceutical Chemistry IV

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Types of prodrugs:

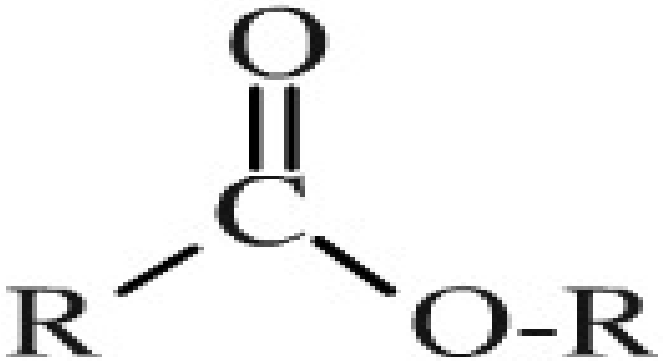
- Various prodrugs for drugs containing different functional groups are listed below:

1. **Esters.**
2. **Prodrug for Amides, Imides and Other Acidic Compounds.**
3. **Prodrugs for Amines, and.**
4. **Prodrugs with Carbonyl Groups.**

Esters

Esters

- Ester derivatives are suitable prodrug for therapeutic agents containing carboxyl and hydroxyl functional groups.



Esters

- Chemical reactivity of esters is readily predictable on the basis of the steric and electronic properties of the substitutes in both the acyl and alcohol molecules.

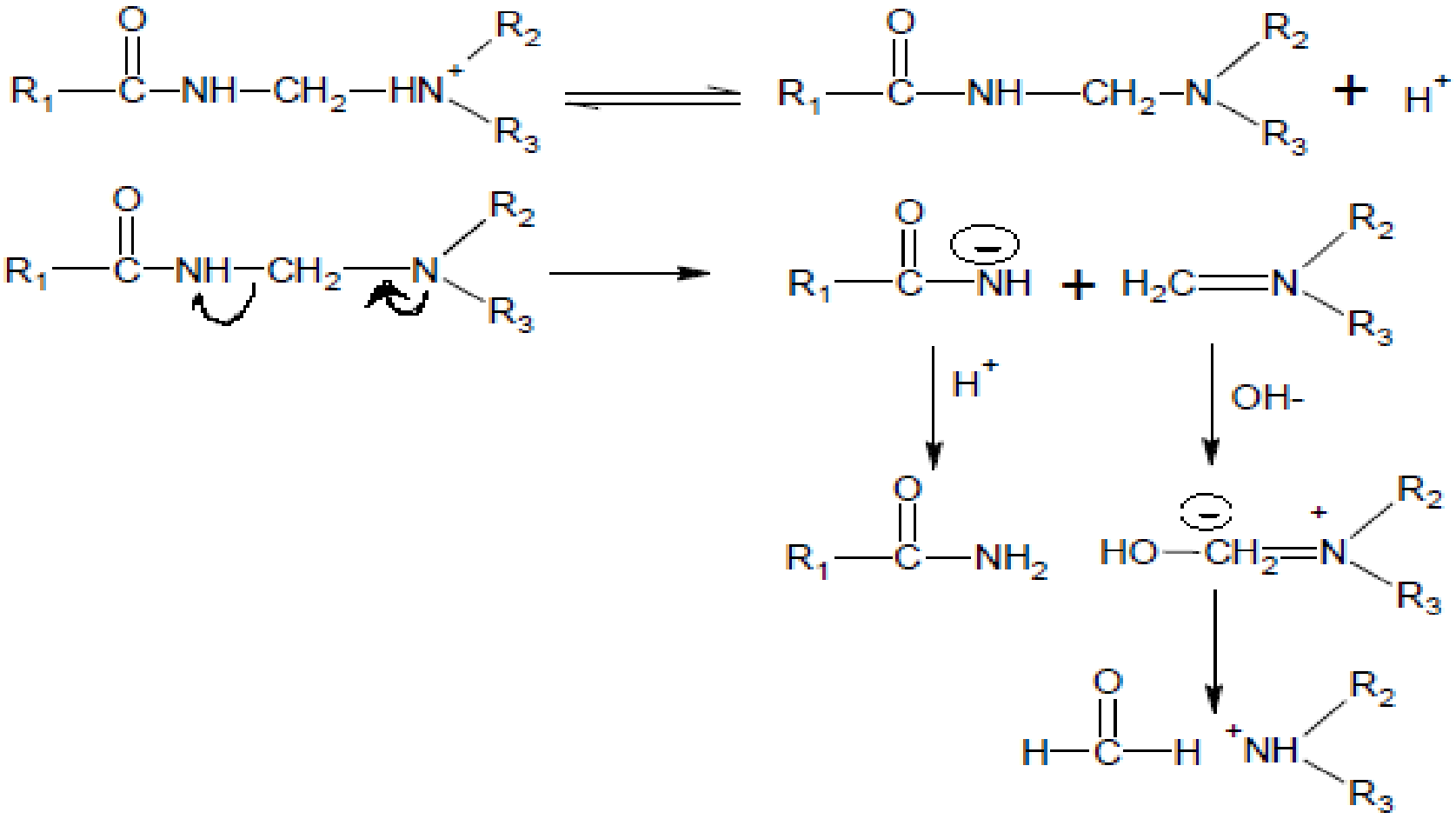
- However, hydrophilic properties and charge of ester may play a major role in enzyme-facilitated hydrolysis.

Prodrug for Amides, Imides and Other Acidic Compounds

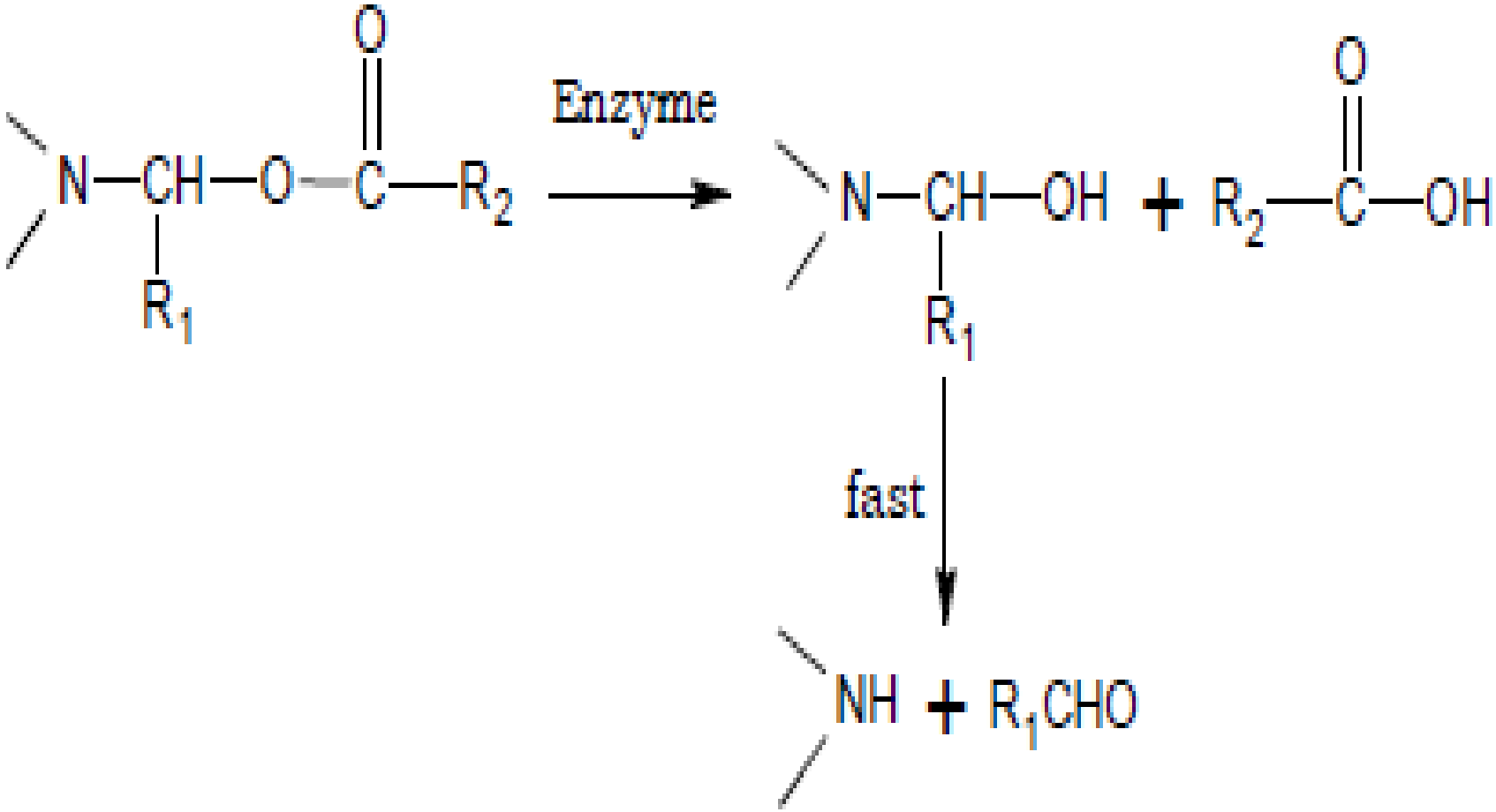
a) N–Mannich Bases and Acyloxy Derivatives:

- N–Mannich bases can function as a prodrug candidate for compounds such as amides, imides and urea derivatives.

Reaction mechanism of decomposition of Mannich bases

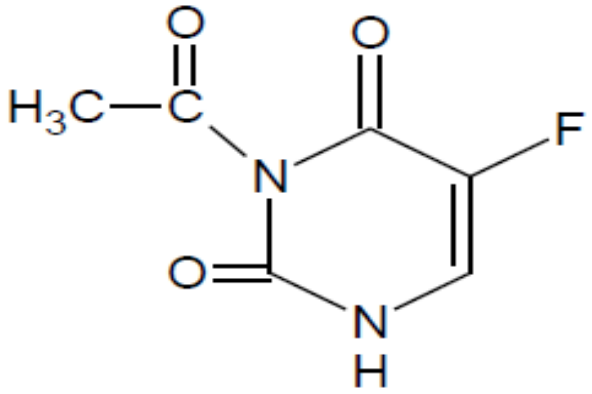


The regeneration of NH group from N-α-acyloxy alkyl derivatives

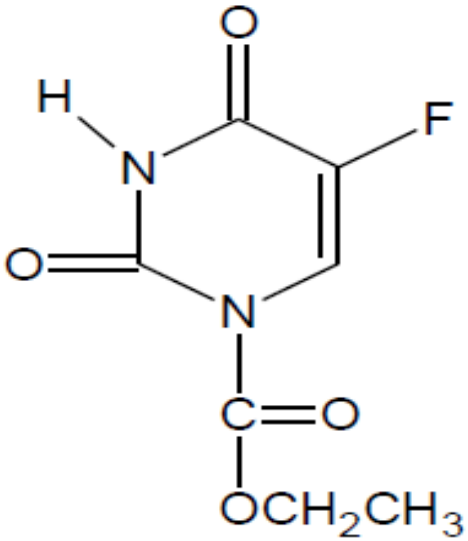


b) N–Acyl Derivatives

- Plasma enzyme catalysed hydrolysis of the N–acyl derivatives makes N–acylation of amide or imide fruitful in some cases such as N– acetyl–5–fluorouracil and N-ethoxy carbonyl–2-fluorouracil.



N_3-acetyl-5-fluorouracil



N_1-ethoxycarbonyl-5-fluorouracil

N–Acyl Derivatives

- Improved physicochemical properties and easy bioconversion of N–acyl derivative of 5–fluorouracil enhances the oral and rectal absorption of the parent drug

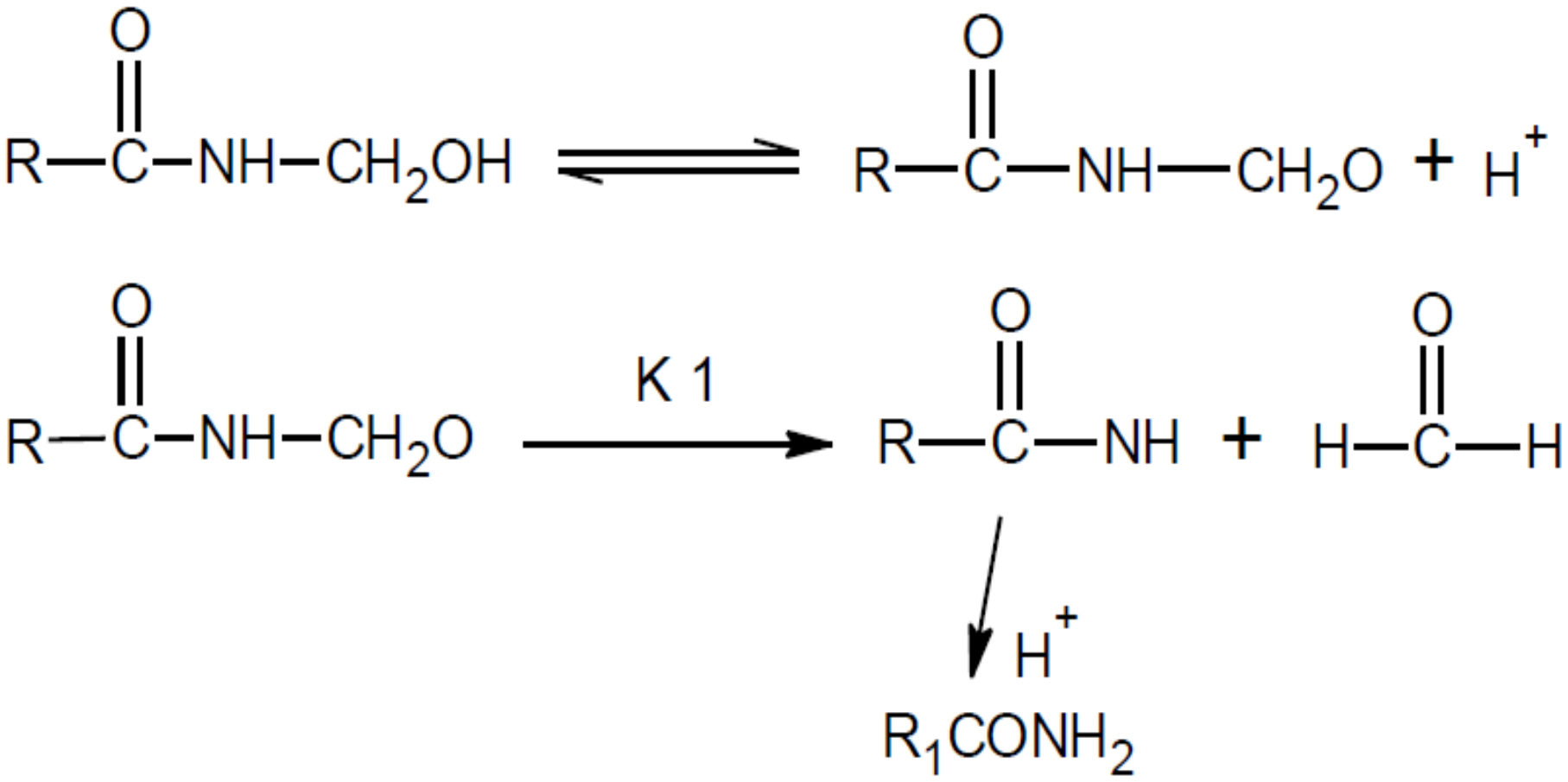
c) N–Hydroxy Methyl Derivatives

- The N–hydroxyl methyl derivatives of amides or imide type compounds are more water soluble than the parent compounds.

N–Hydroxy Methyl Derivatives

- By replacing a proton bind to nitrogen atom by a hydroxyl methyl group, intra- or inter-molecular hydrogen bonding in such molecules may be increased resulting in a decrease in melting point and increase in water solubility

The mechanism for the decomposition of N-hydroxyl methyl derivatives



Prodrugs for Amines:

Prodrugs for Amines:

- Prodrugs of amines are generally designed by making their amide, N–(acyloxy alkoxy carbonyl) derivatives and oxazolidine derivatives.

a) N–(Acyloxy alkoxy carbonyl) Derivatives and Amide Derivatives:

- The utility of the N–(acyloxy alkoxy carbonyl) derivative is limited *in vivo.* *Explain why?* Nevertheless, certain activated amides are chemically labile and also certain amides formed with amino acids may undergo enzymatic cleavage.

N–(Acyloxy alkoxy carbonyl) Derivatives and Amide Derivatives:

- For example the γ-glutamyl derivatives of dopamine, L-Dopa and sulfamethoxazole are rapidly hydrolyzed by γ-glutamyl transpeptidase *in vivo.*

b) Oxazolidines:

- Oxazolidines are cyclic condensation products of β-amino alcohols and aldehydes or ketone, and they undergo a facile and complete, hydrolysis in aqueous solution.

- Alteration in carbonyl moiety controls the rate of formation of given β-amino alcohol.

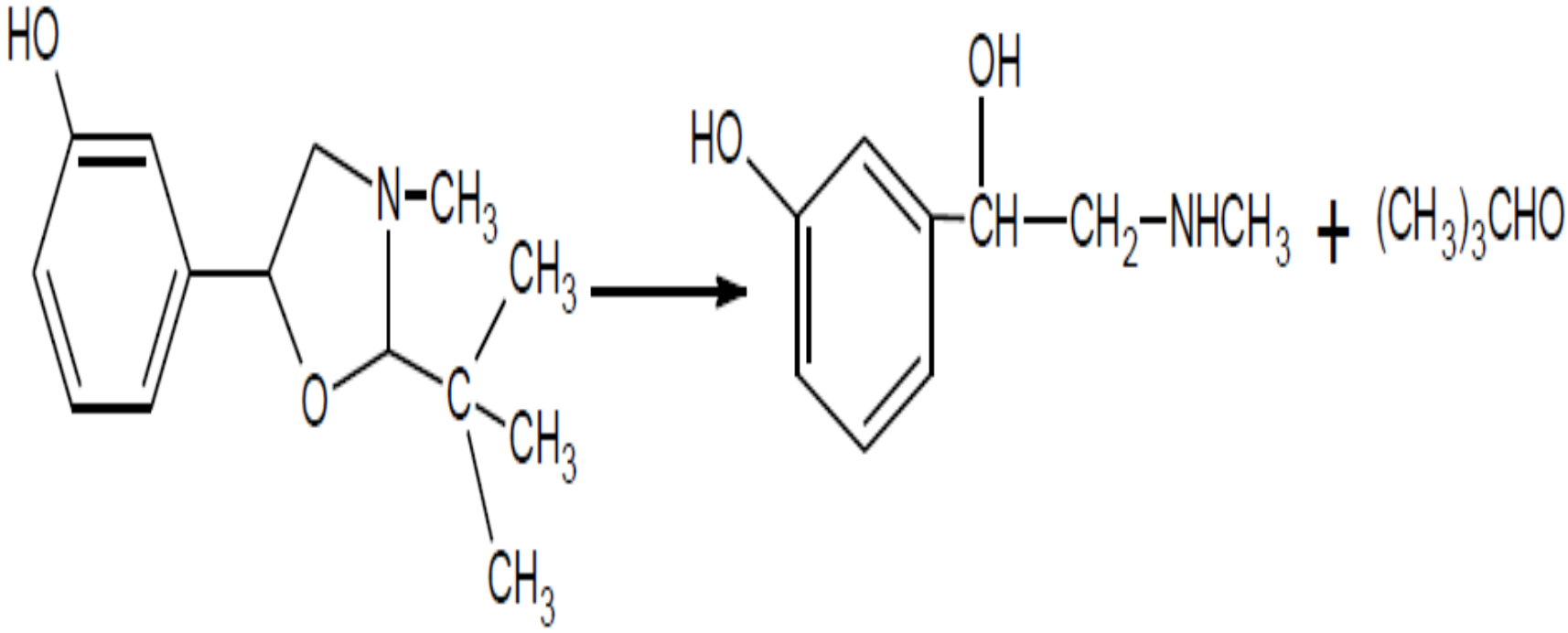
Oxazolidines:

- Oxazolidines are weaker bases (pKa 6–7) than parent β-amino alcohols and found as more lipophilic than the parent compound at physiological pH.

Oxazolidines:

- For example the oxazolidine prodrug of phenylephrine prepared from pivaldehyde has penetrated the cornea much more easily than the parent drug as a result of increased lipophilicity

Oxazolidine prodrug of phenylephrine



Prodrugs with Carbonyl Groups:

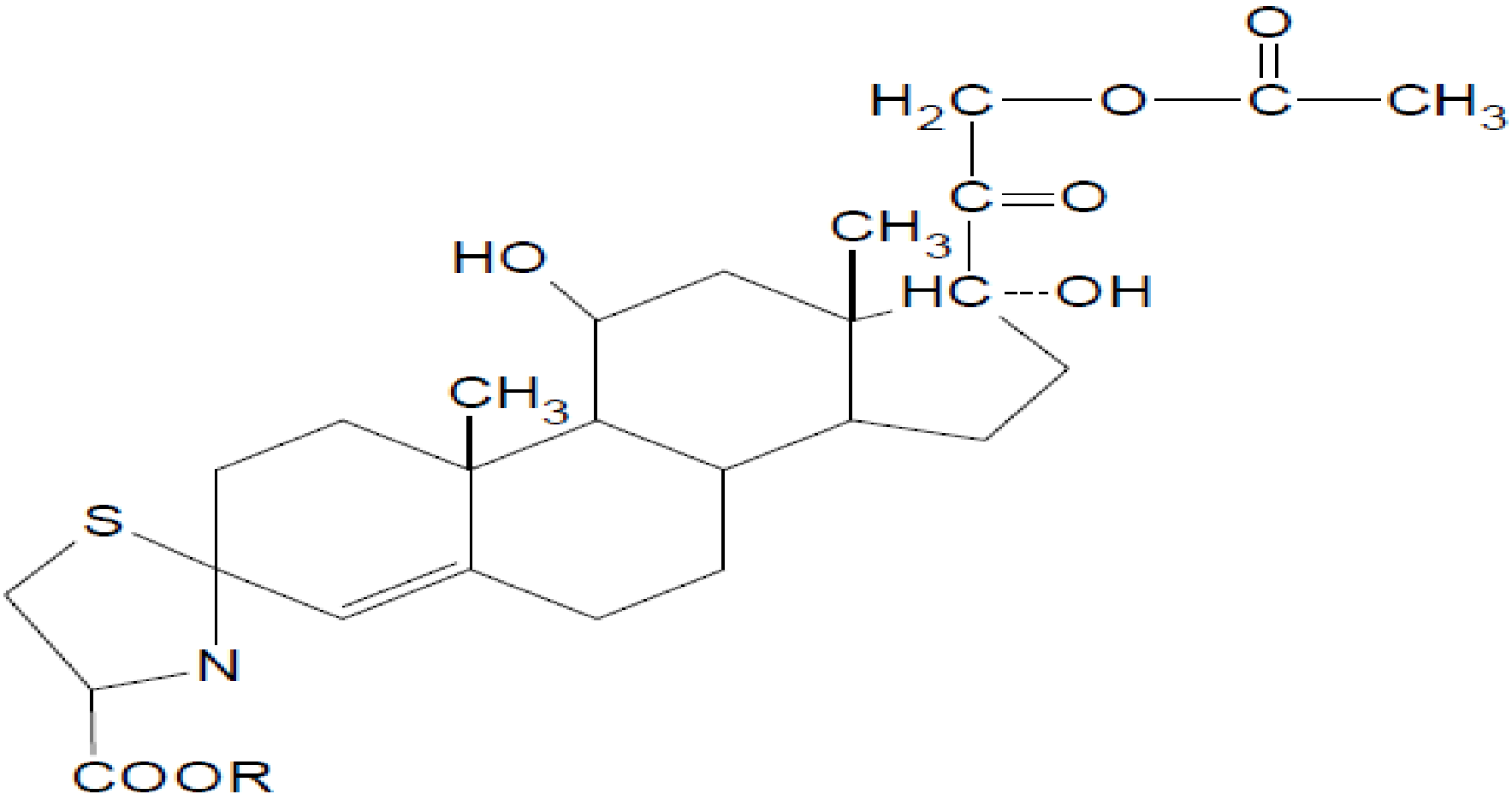
Prodrugs with Carbonyl Groups

- Weakly basic character of carbonyl containing drugs may be advantageous as the transformation of such drugs into oxazolidine, introduces a readily ionisable moiety, which allows the preparation of derivatives with increased aqueous solubilities at acidic pH.

a) Thiazolidines:

- Applied as prodrug for various steroids to improve their topical anti-inflammatory activity.
- Thiazolidine derivatives of hydrocortisone and hydrocortisone 21-acetate have been shown to be readily converted to the parent corticosteroids at conditions similar to those in the skin.

Thiazolidine prodrug



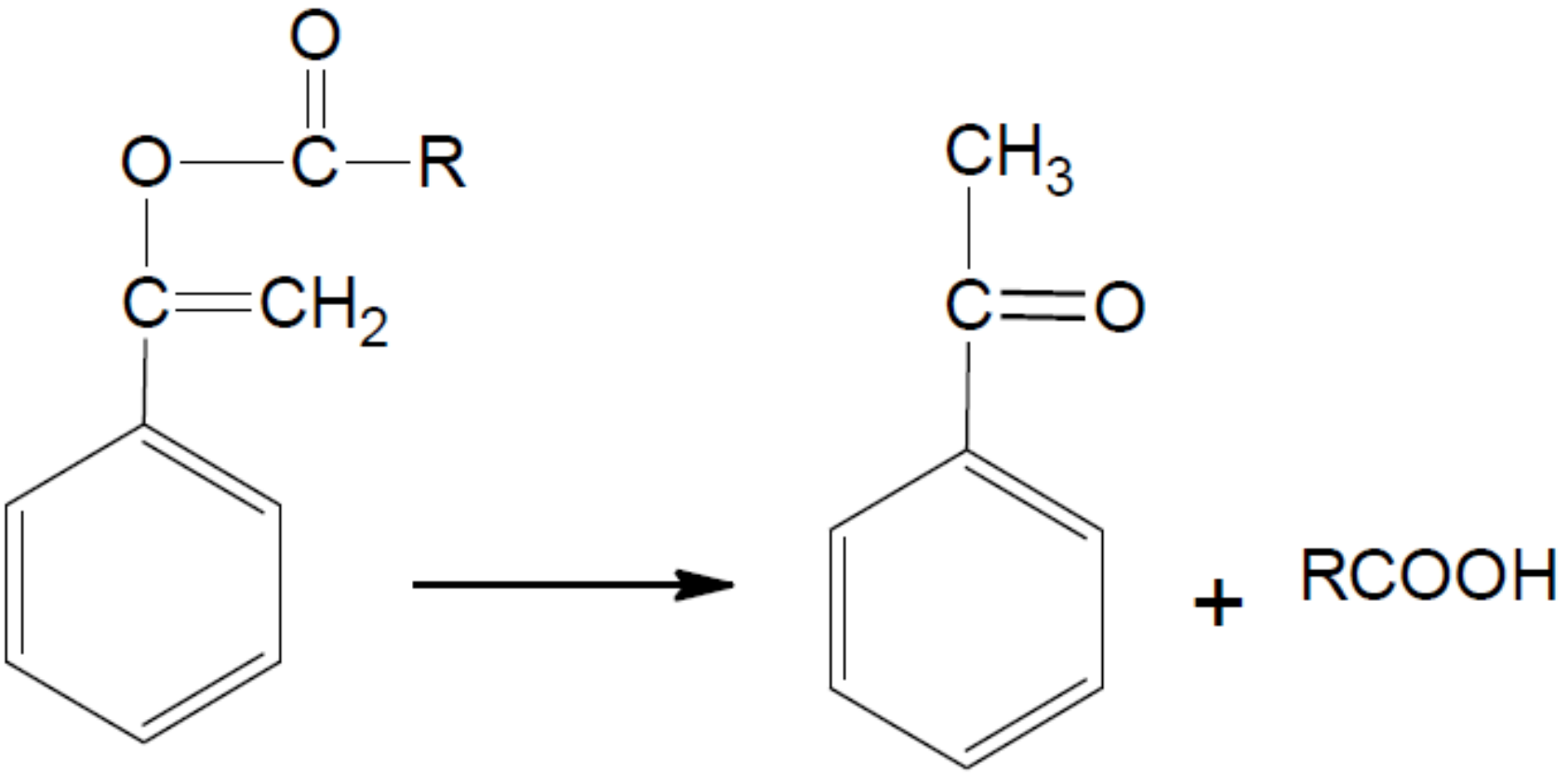
b) Enol Esters:

- Enol form (of keto–enol equilibrium) can be trapped by alkylation or acylation.
- Such enol esters and ethers undergo hydrolysis with liberation of free enol, which then reverts to the keto form.
- In the presence of plasma or liver enzymes, the enol esters are readily hydrolysed.

Enol Esters

- For example the chemical stability of enol ester of acetophen is similar to that of phenol ester with maximum stability at pH 3.3. On contrary it is rapidly hydrolysable in plasma and liver enzymes

Enol ester of acetophen



References:

- Wilson and Gisvold Textbook of Organic Medicinal and Pharmaceutical Chemistry; Delgado JN, Remers WA, (Eds.); 12th ed., 2011.
- http://shodhganga.inflibnet.ac.in/bitstream/10603/3457/10/10_chapter%201.pdf

Thank you for your listening