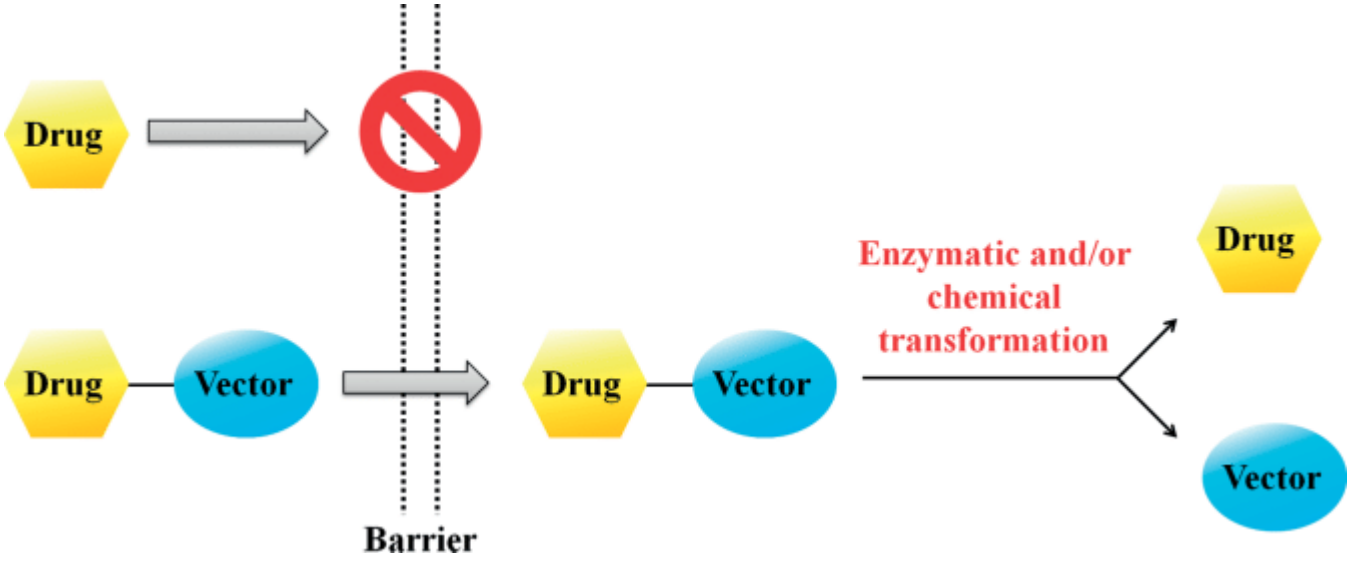
Organic Pharmaceutical Chemistry IV

Lec2: Types of prodrugs

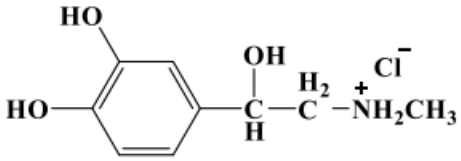
TAMMAR HUSSEIN ALI



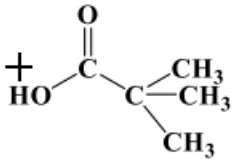
By decreasing the hydrophilicity of the compound, a number of benefits may be achieved, including:-

1. **Increase absorption.**
2. **Decrease dissolution in the aqueous environment of the stomach.**
3. **Prolongation of the duration of action.**

Example of increasing absorption by addition of a nonpolar carboxylic acid

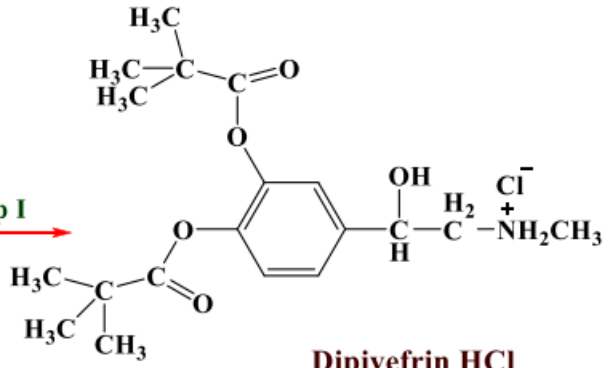


Epinephrine
Use for treatment open angle glucoma
has low lipophilicity (low absorption)



Pivalic acid
Non polar promoiety

Step I



Dipivefrin HCl
inactive
increase lipophilicity
protected catechol group from oxidation
this agent move across the membrane
of eye easily and increase itraocular concentration
increase absorption

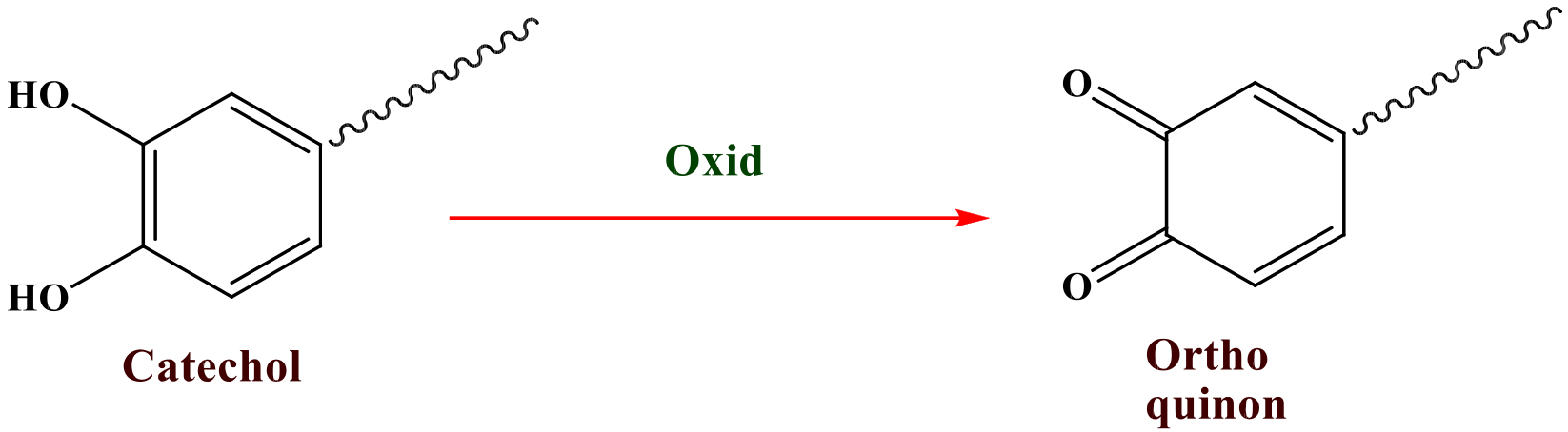
Step II
Esterase or pH changes
cornea,conjunctiva and
aqueous humor

By utilizing pivalic acid as the promoiety to:-

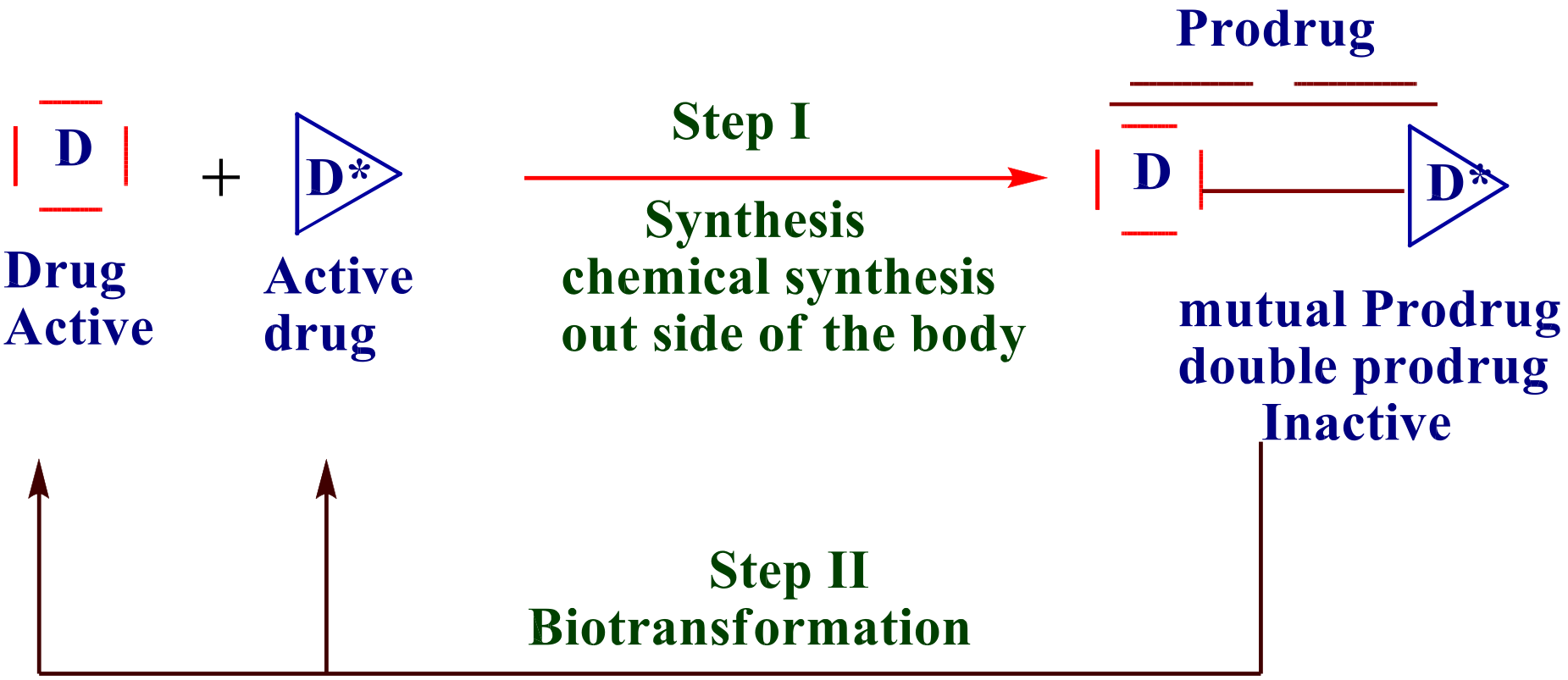
1- Increase the steric bulk around the ester bond lead to slow the ester hydrolysis relative to less bulky groups.

2- Yet still allows this reaction to proceed after the drug has crossed the membrane barriers of the eye.

Note:- The catechol system is somewhat susceptible to oxidation, and protecting the catechol as the diester prevents this oxidation and the resulting drug inactivation.



To be continue with carrier linked prodrug, promoiety which link to the drug may be active or inactive moiety .Now days new approach of (**double prodrug**) or which called (**mutual prodrug**), in which use two drugs link together covalently.



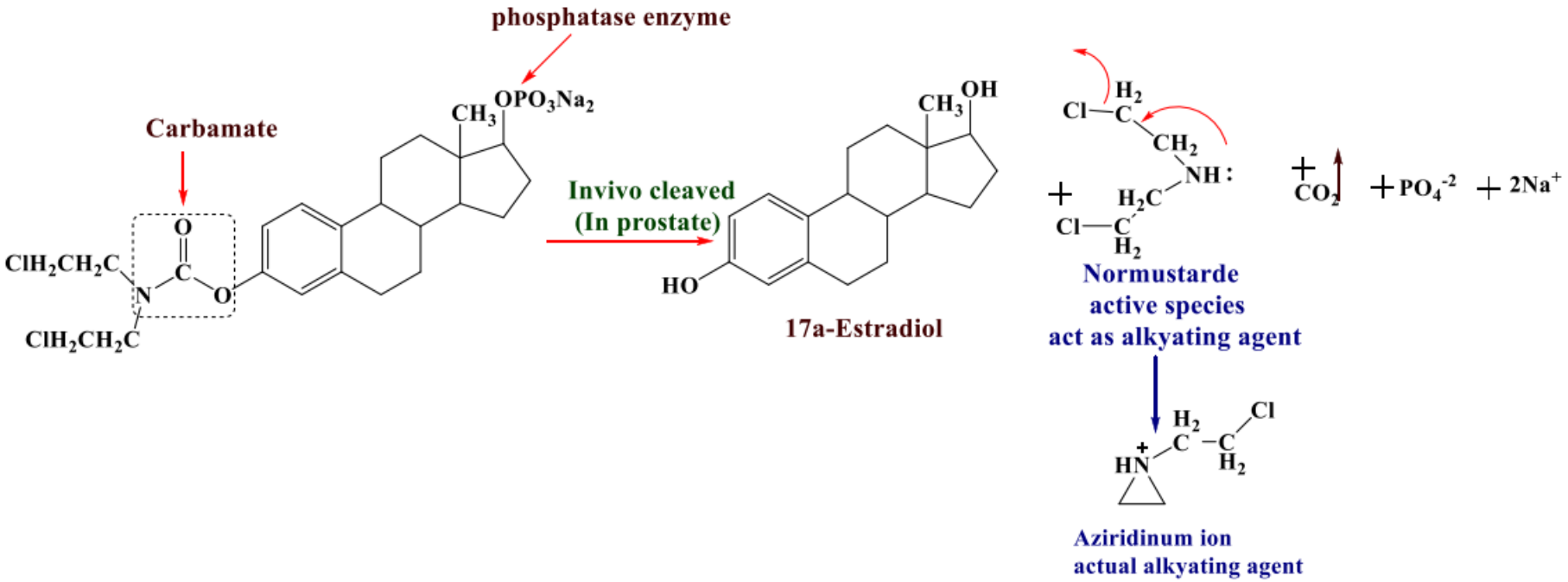
Advantages of double(mutual) prodrug:-

1. To get synergistic, each one has some activity in certain level. The molecule when cleave, perform its action separately once they are cleave.

1. Change physicochemical properties.

1. Change distribution (targeting) or which is called (drug delivery system).

Example
Estramustine (mutual prodrug)

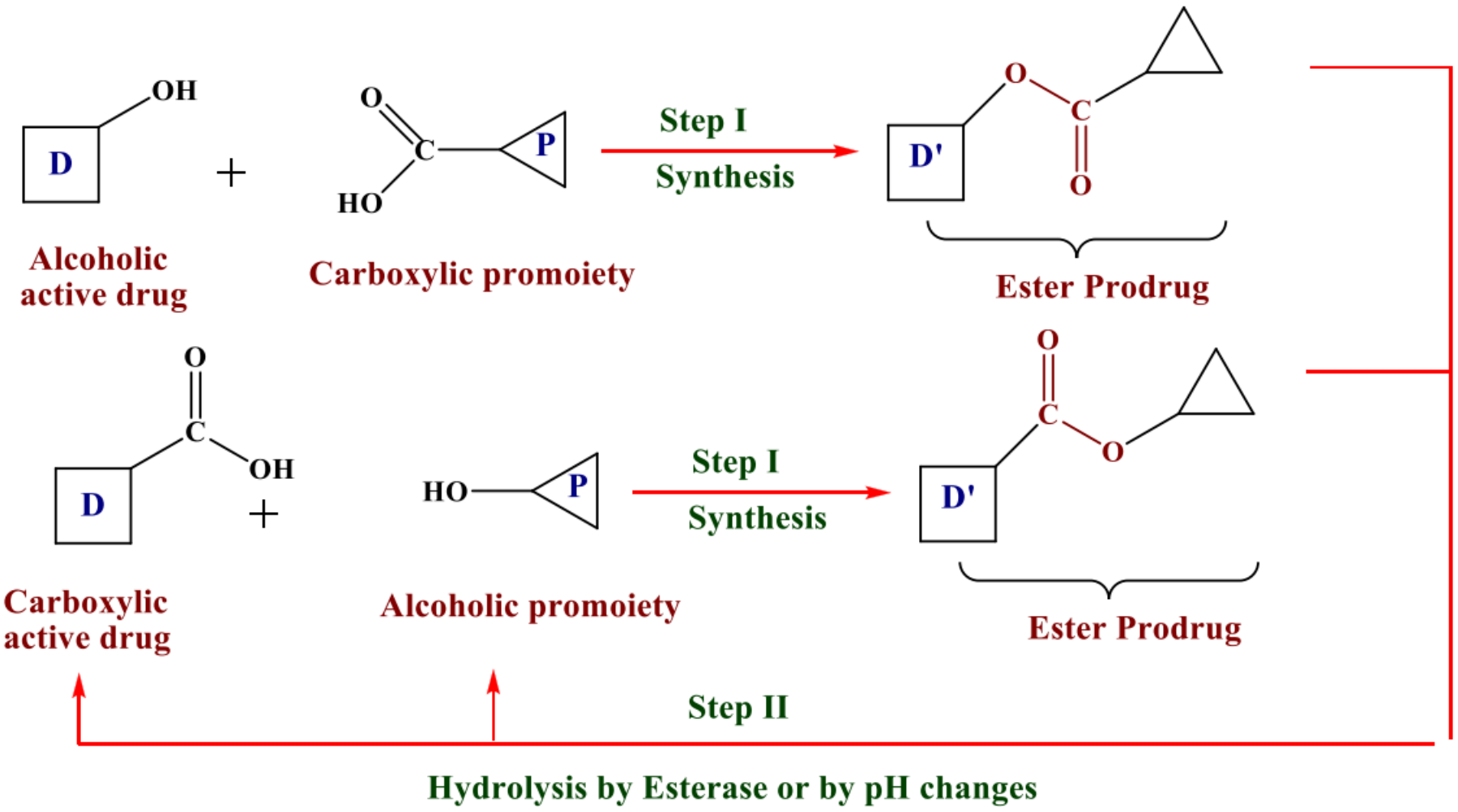


Both carbamate and phosphate are hydrolyse by chemical or enzymatic means

Estramustine is antineoplastic agent use in treatment of prostate cancer, which is composed of phosphorylated steroid (17α- estradiol) linked to normustard by carbamate linkage (N-COO),

The steroid portion help to concentrate the drug in prostate, where the hydrolysis occur to give normustard and CO_2. when normustard act as alkylating agent and exert the cytotoxic effect. In addition 17α- estradiol has anti-androgenic effect, which slows the growth of cancer cells. Since both normustard and steroid have activity so this prodrug is called (mutual prodrug).

Note:- the phosphorylation of the estradiol can be utilized to increase the water solubility, which also constitutes a prodtug modification.

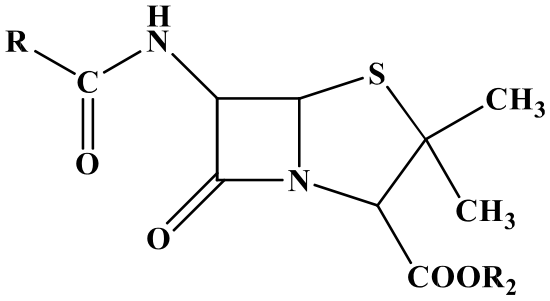

OH
D
+
O
C
HO
P
Step I
Synthesis
O
C
O
D'
Alcoholic
active drug
Carboxylic promoiety
Ester Prodrug
O
C
OH
D
+
HO
P
Step I
Synthesis
O
C
O
D'
Carboxylic
active drug
Alcoholic promoiety
Ester Prodrug
Step II
Hydrolysis by Esterase or by pH changes

Esters failure as prodrugs

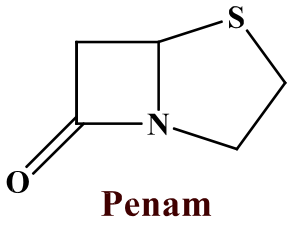
Not all carboxylic esters are easily hydrolyzed in vivo. Steric inhibition around the ester in some cases prevents the prodrug from being hydrolyzed. This is seen in the β-lactams, in which it is often desirable to increase the hydrophobicity of the agent to improve absorption or prevent dissolution in the stomach where acid-catalyzed decomposition may occur. Simple esters of the carboxylic acid moiety, however, are not hydrolyzed in vivo to the active carboxylate.

Example(β-lactams antibiotic)

•penicillin ester



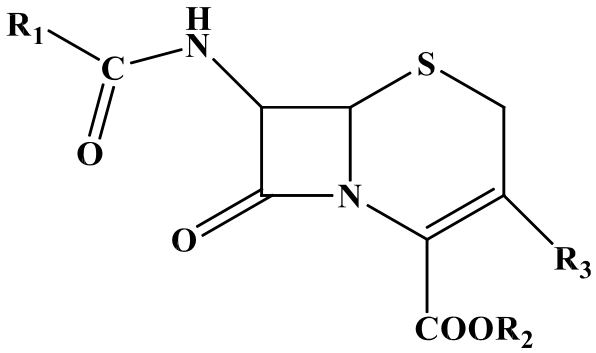
Esterase → No reaction



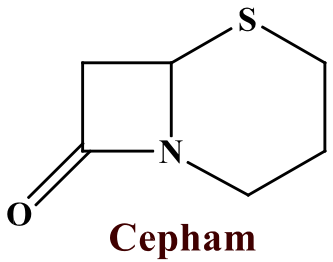
Penam

R_2= Ethyl, propyl, butyl, phenyl.

Cephalosporin ester•



Esterase → No reaction

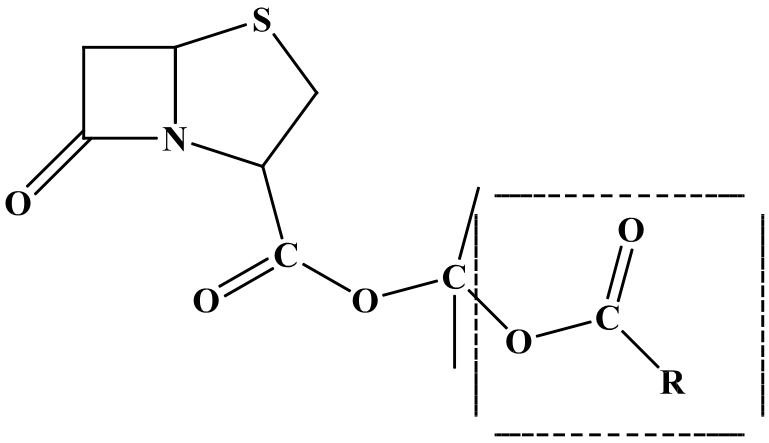


Cepham

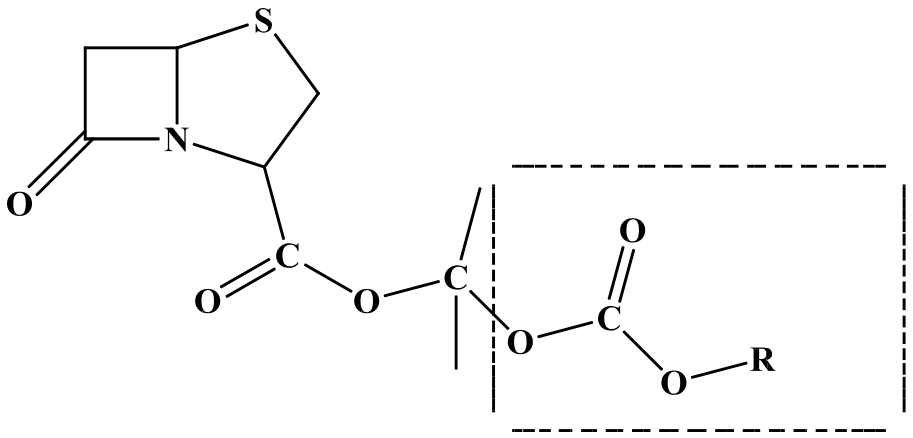
R_2= Ethyl, propyl, butyl, phenyl.

By exposing the penicillin ester and cephalosporin ester to esterase→→ incubation →→waiting → no hydrolysis, because the presence of bulky group (penam and cepham)

Which do not allows ester for binding. While this problem was solved by using double ester prodrug approach, in which the chain was elongated by putting spacer and additional ester or carbonate group is incorporated into the R_2 substituent. So in this case we have two ester groups, The terminal one which is hydrolyzes by esterase and the other near one which cleave by chemical hydrolysis. This approach is frequently used to improve absorption or prevent dissolution in the stomach and the subsequent acid-catalyzed decomposition of aminopenicillins and second- and third-generation cephalosporins (cefpodoxime proxetil has been classilied as both a second- and a third-generation agent) so that these agents can be administered orally.



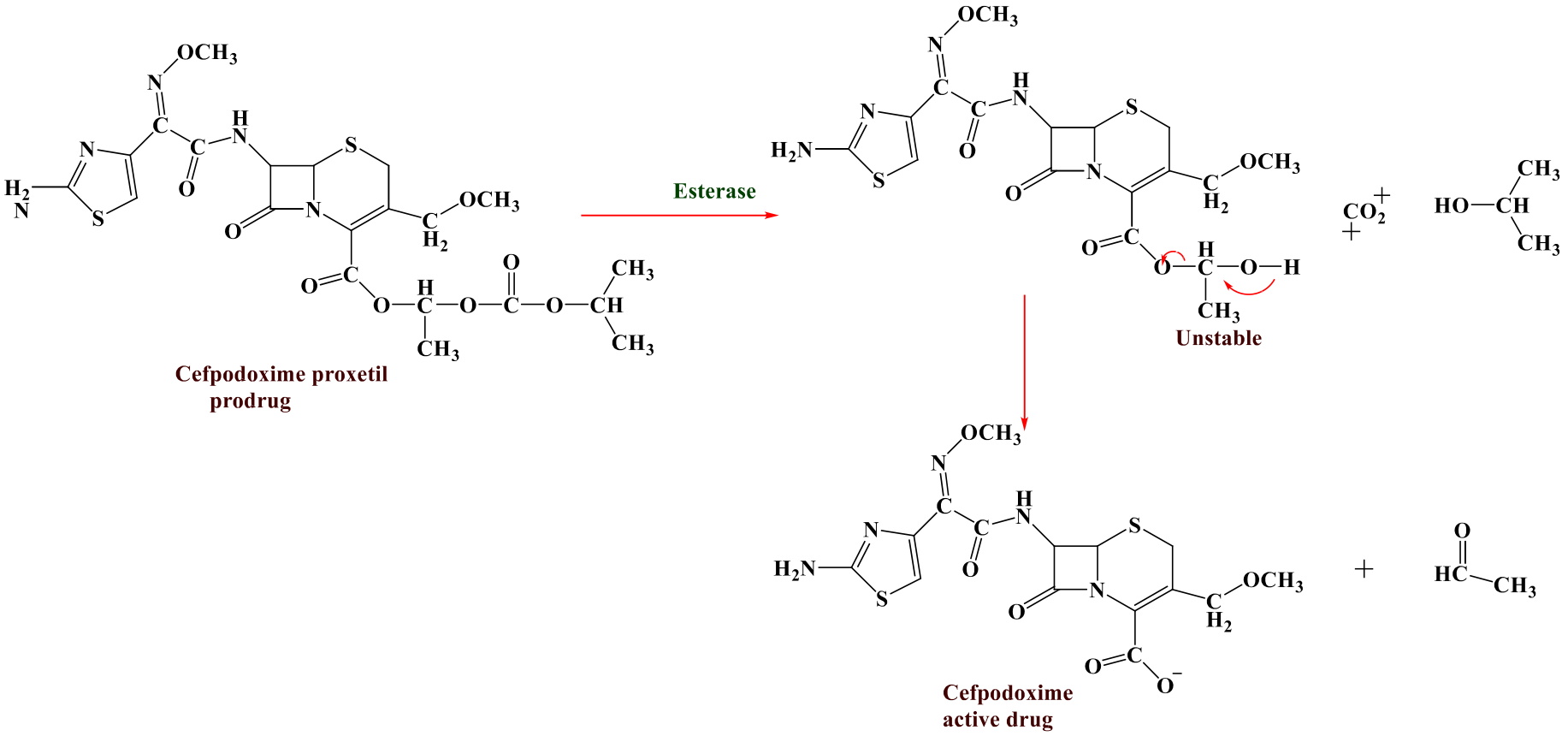
Ester group



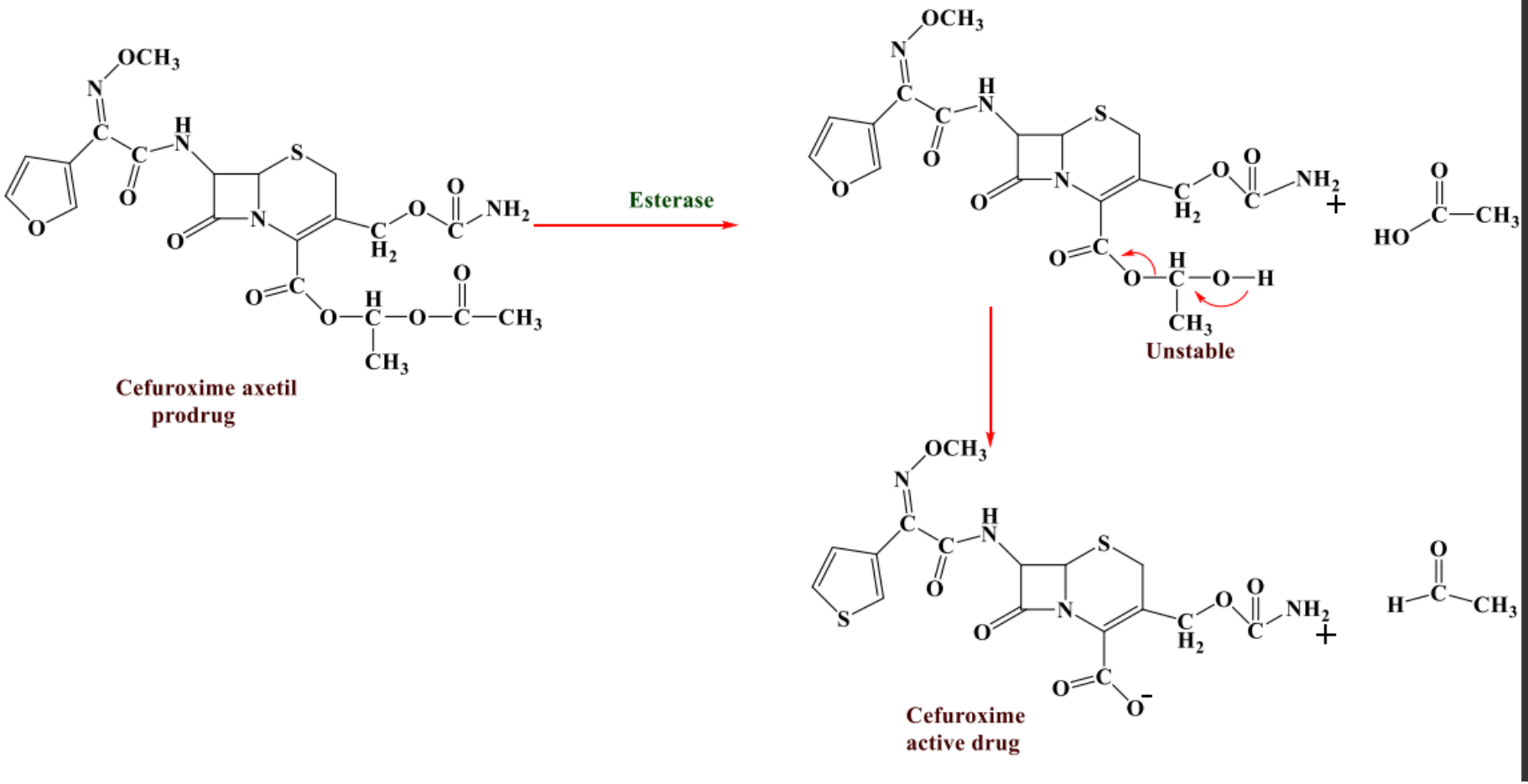
Carbonate group

Example (double ester prodrug)

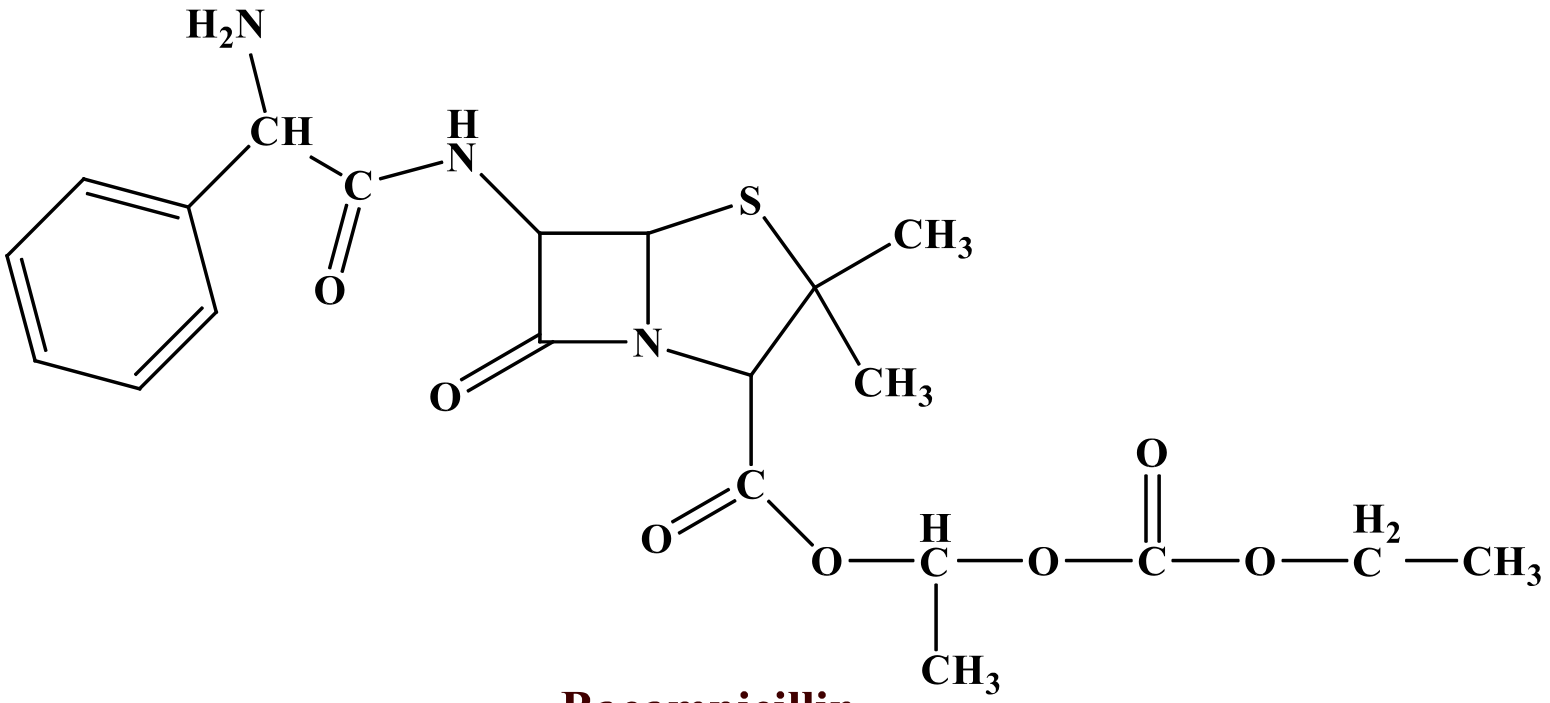
1)Cefpodoxime proxetile (prodrug)



2)cefuroxime axetil (prodrug)



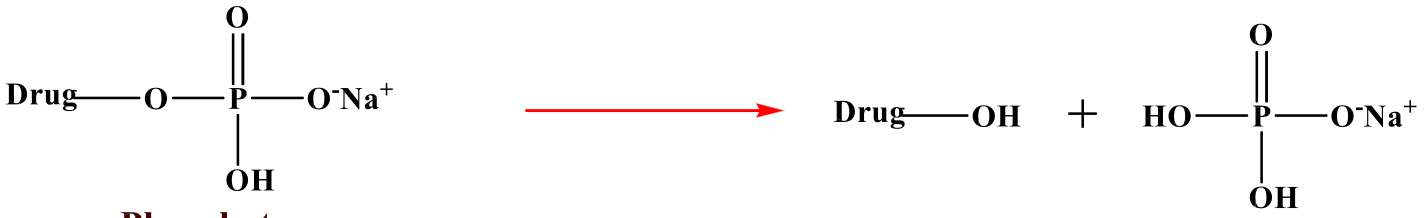
Bacampicillin (prodrug) Homwork •



Bacampicillin

In general to increase the hydrophilicity of an agent, several different types of ester prodrugs have been used, including succinates, Phosphates, and sulfonates. All are ionized at physiological pH and, therefore, increase the water solubility of the agents, making them more suitable for parenteral or oral administration when high water solubility is desirable.

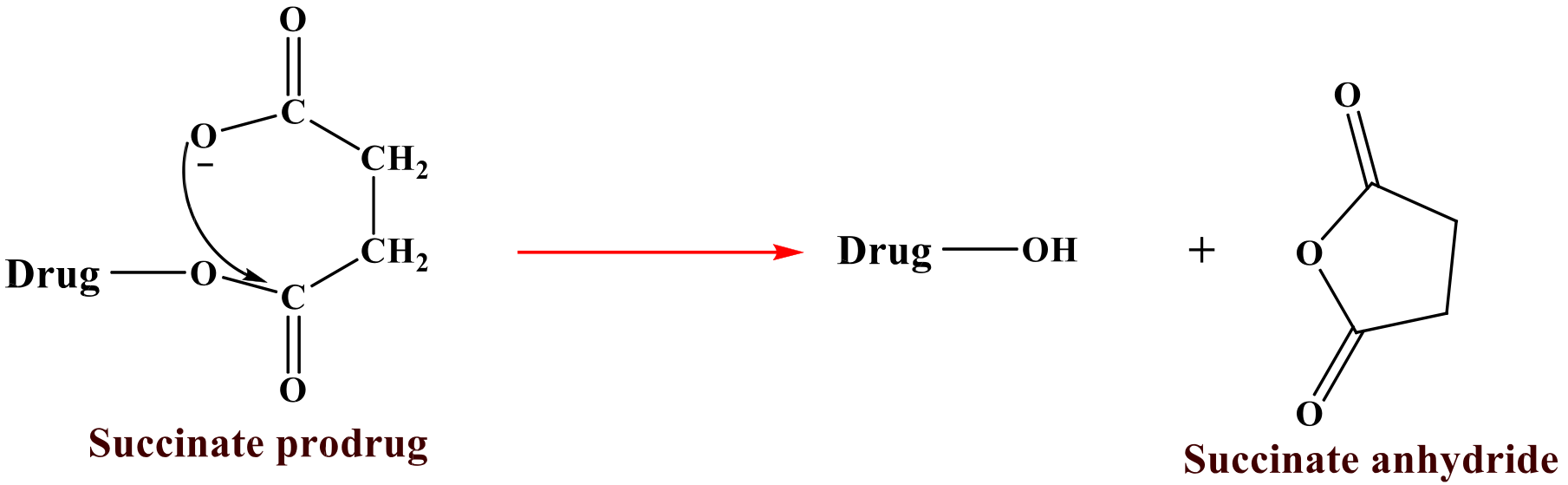
Succinates



Phosphates

Sulfate

Succinate esters containing an ionizable carboxylate are useful when rapid in vivo hydrolysis of the ester functionally is required. The rapid hydrolysis is related to the intramolecular attack of the carboxylate on the ester linkage, which not require the participation of enzymes .As a result, these agents may be somewhat unstable in solution and should he dissolved immediately prior to administration.

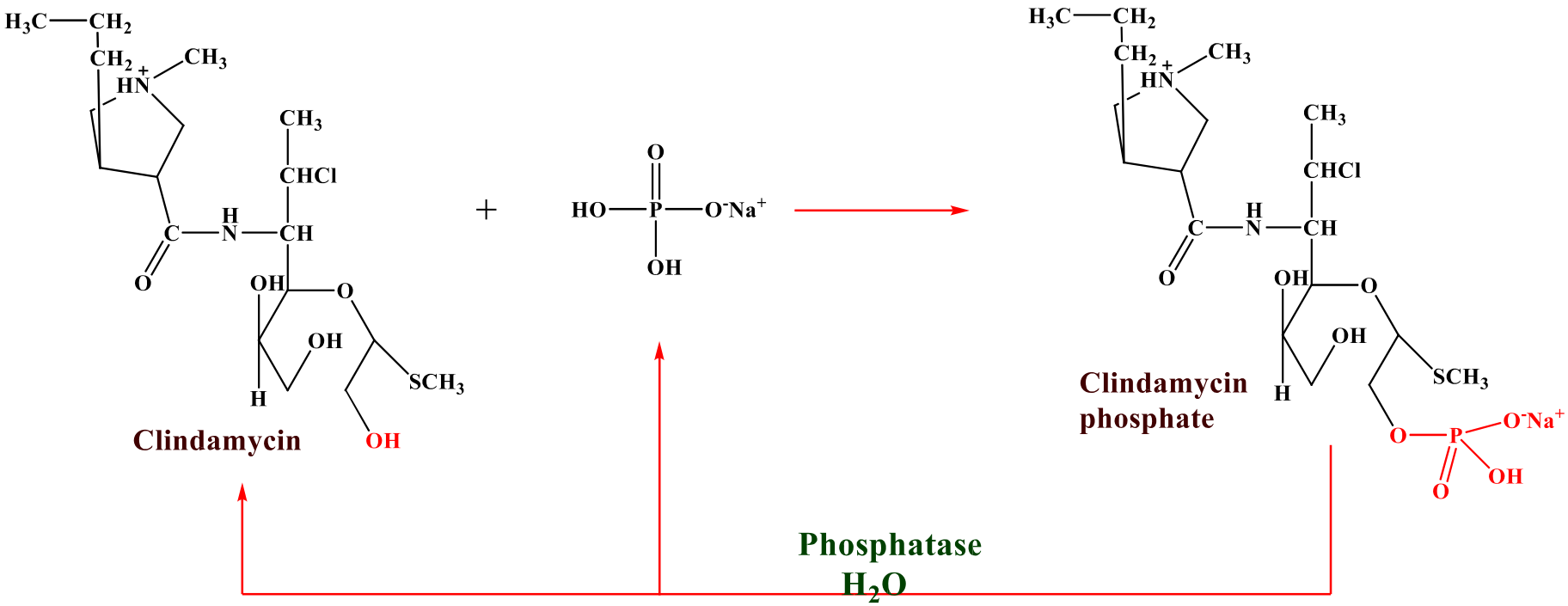


Intramolecular cleavage of Succinate esters

The phosphates are completely ionized at physiological pH and generally hydrolyzed rapidly in vivo by phosphatase enzymes. Ionization of the phosphate function imparts high stability to these derivatives in solution, and solutions for administration can be stored for long periods of time without hydrolysis of the phosphate. Such an approach has been used to produce clindamycin phosphate, which produces less pain at the injection site compared with clindamycin itself.

Pain after parenteral administration is associated with local irritation caused by low aqueous solubility or highly acidic or basic solutions. With clindamycin phosphate, the reduction in pain is attributed to the increased water solubility of the agent.

Clindamycin



Type of esterase

1-Ester hydrolase

2- Lipase

3- Cholesterol esterase

4- Acetyl cholinesterase

5- Carboxypeptidase

6- Cholinesterase.

Types of prodrugs: Current Classifications

1. ***based on*** therapeutic categories; for example, anticancer prodrugs, antiviral prodrugs, antibacterial prodrugs, nonsteroidal anti-inflammatory prodrugs, cardiovascular prodrugs, etc.
2. ***based on*** the categories of chemical linkages or moiety/carriers that attach to the active drug; for example, Esters, Prodrug for Amides, Imides and Other Acidic Compounds, Prodrugs for Amines, and Prodrugs with Carbonyl Groups.
3. ***based on*** functional categories using strategic approaches to circumvent deficiencies inherent to the active drug; for example, prodrugs for improving site specificity, prodrugs to bypass high first-pass metabolism, prodrugs for improving absorption, and prodrugs for reducing adverse effects

Types of prodrugs: New Classification

1. Type I:
    - *i. Type IA*
    - *ii. Type IB*
2. Type II:
    - *i. Type IIA*
    - *ii. Type IIB*
    - *iii. Type IIC*

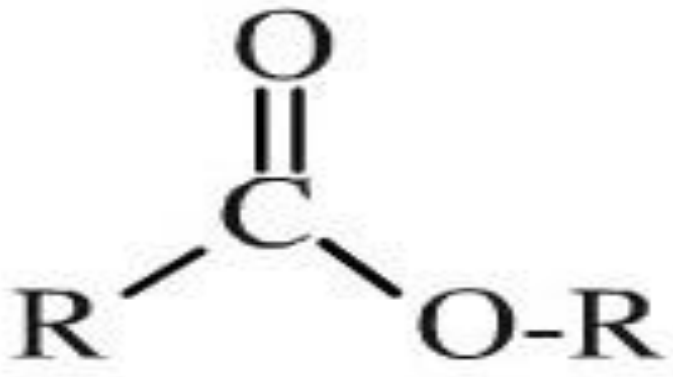
Types of prodrugs: *Based on Chemical linkage.*

- **Bio reversible derivatives for various functional groups:**
- **Various types of functional groups are present in different therapeutic agents.**
- **These functional groups react with other functional groups of nontoxic promoiety to form prodrugs**
- **Various prodrugs belonged to drugs containing different functional groups that 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

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.

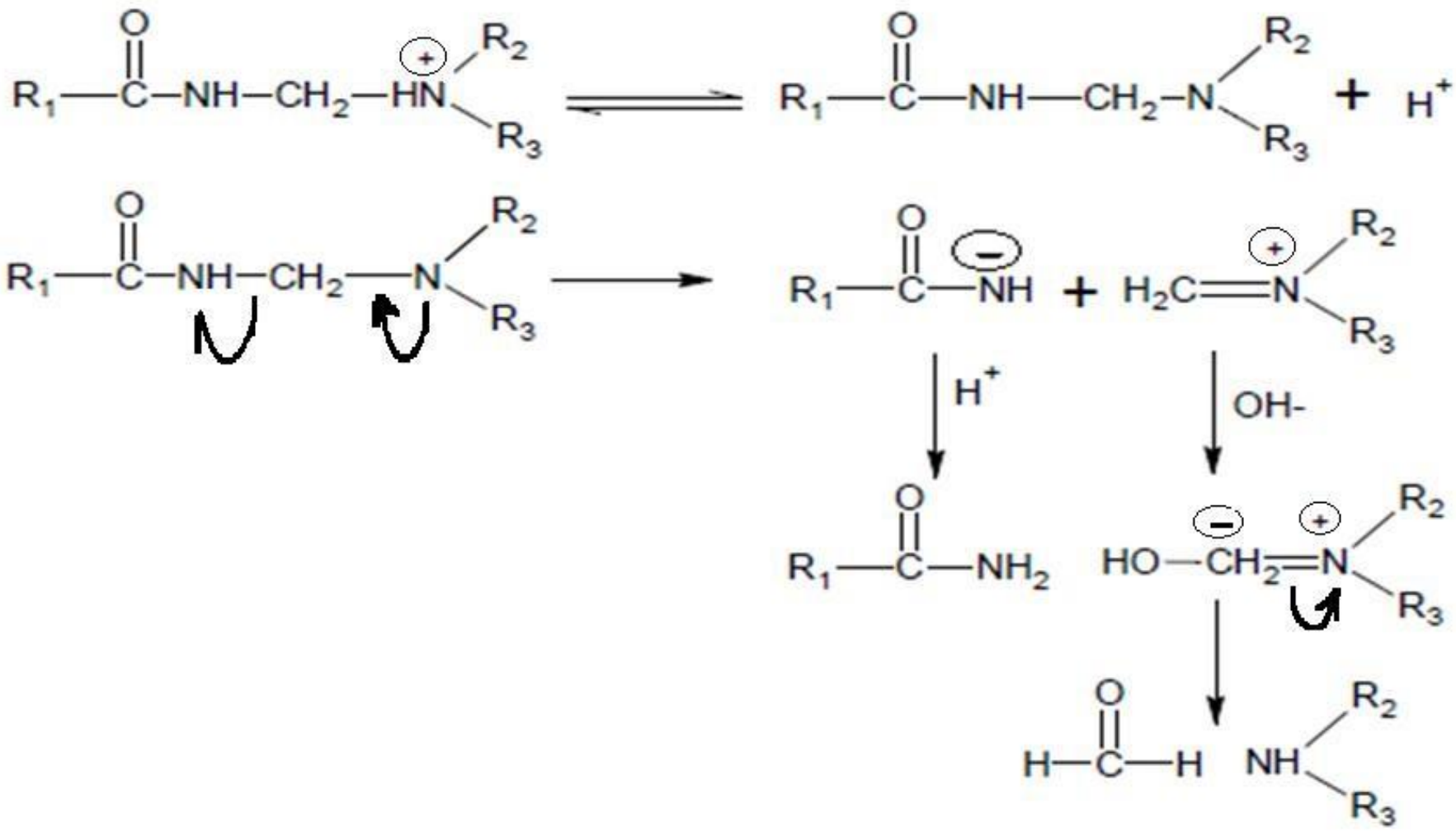
Prodrug for Amides, Imides and Other Acidic Compounds

a) N–Mannich Bases and Acyloxy Derivatives:

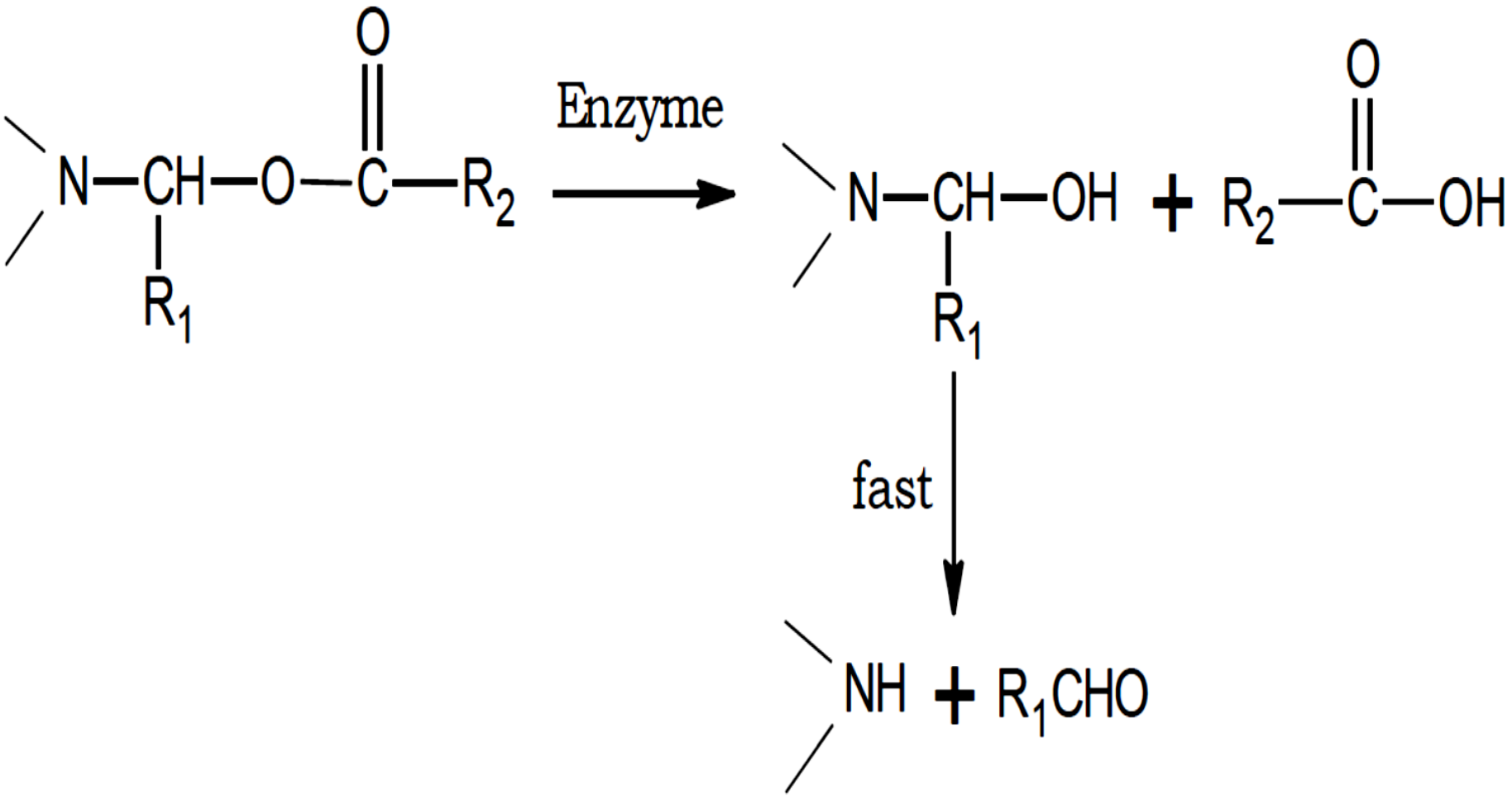
- N–Mannich bases can function as a prodrug candidate for compounds such as amides, imides and urea derivatives.

- The derivatives showed good stability in aqueous solution *in vitro*, they are in general rapidly cleaved *in vivo* by virtue of enzyme mediated hydrolysis.

Reaction Mechanism of Decomposition Of Mannich Bases

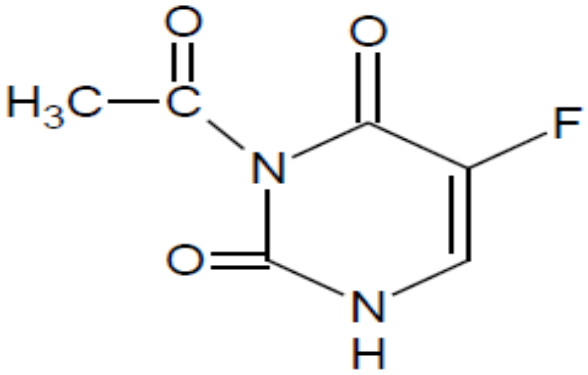


The Regeneration Of NH Group From N-α-acyloxy Alkyl Derivatives

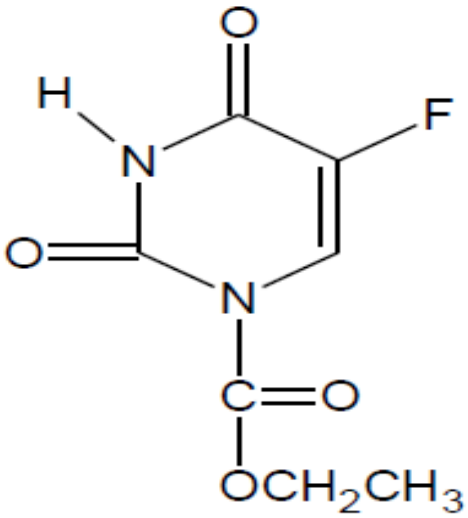


b) N–acyl Derivatives

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

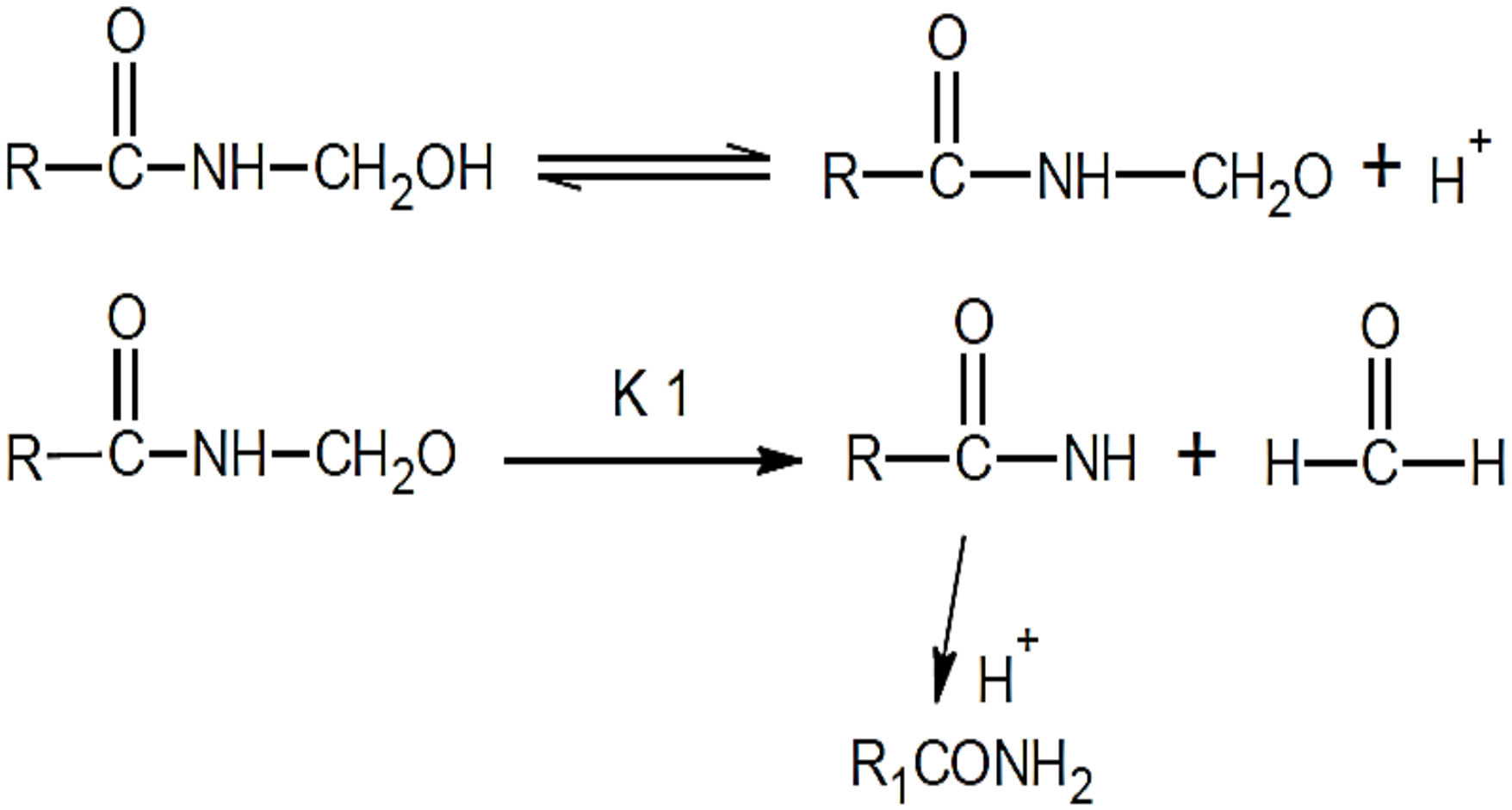
The N–hydroxyl methyl derivatives of amides or imide type compounds are more water soluble than the parent compounds.

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.

Explain why?

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?*

✓ *Due to the resistance to undergo enzymatic cleave.*

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 any given β-amino alcohol.

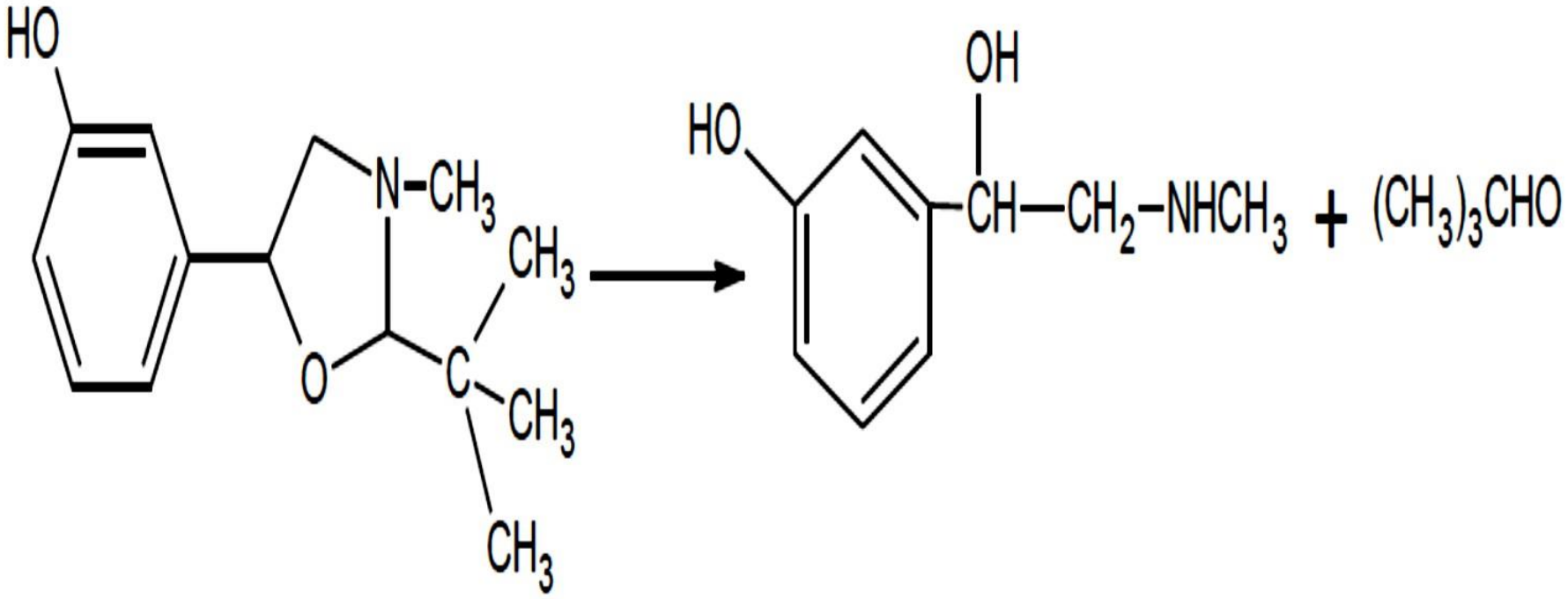
Oxazolidines:

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

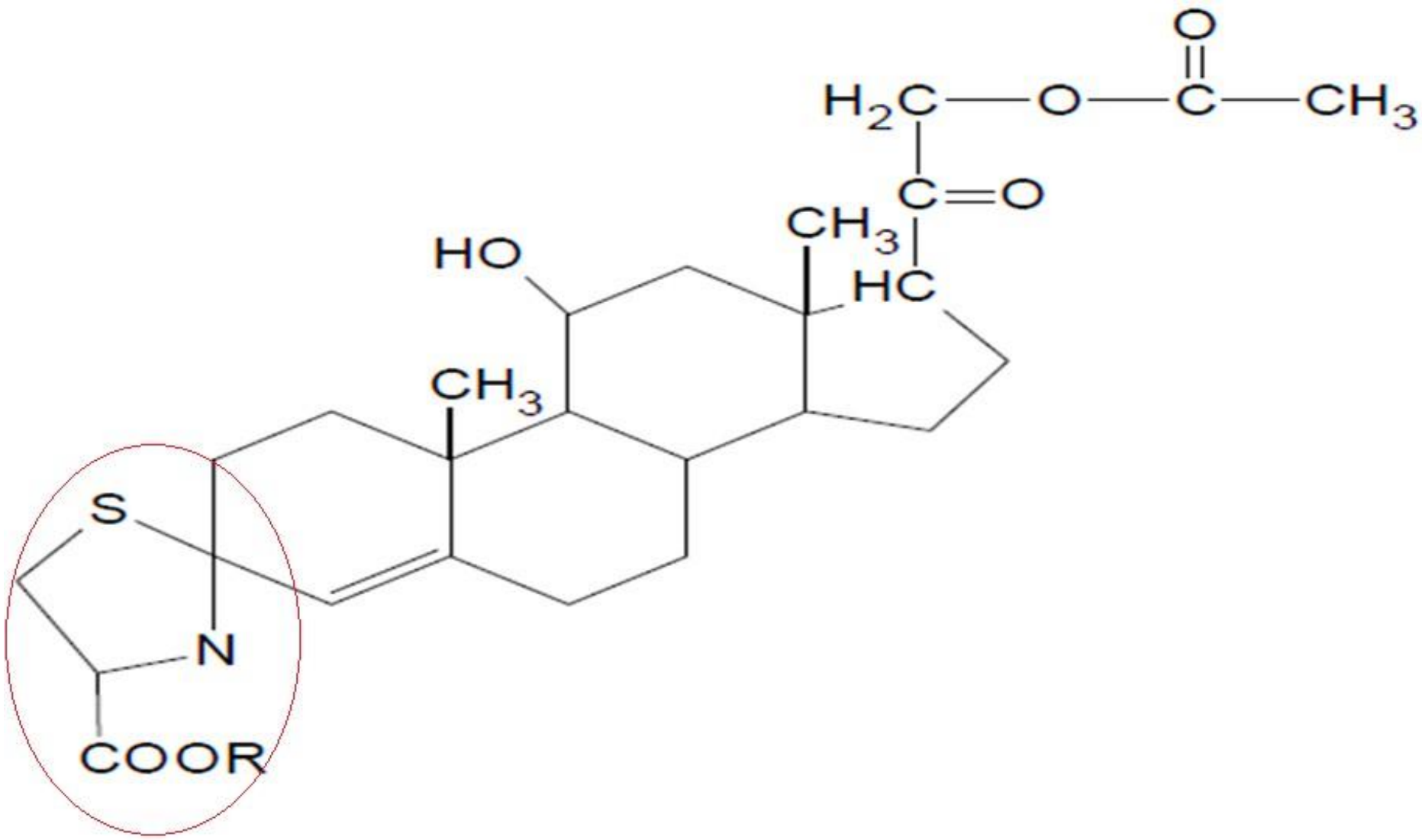
Weakly basic character of carbonyl containing drugs may be advantageous as the transformation of such drugs into oxazolidine, introduces a readily ionisable moiety, which allows the preparation of derivatives with increased aqueous solubilities at acidic pH.

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.

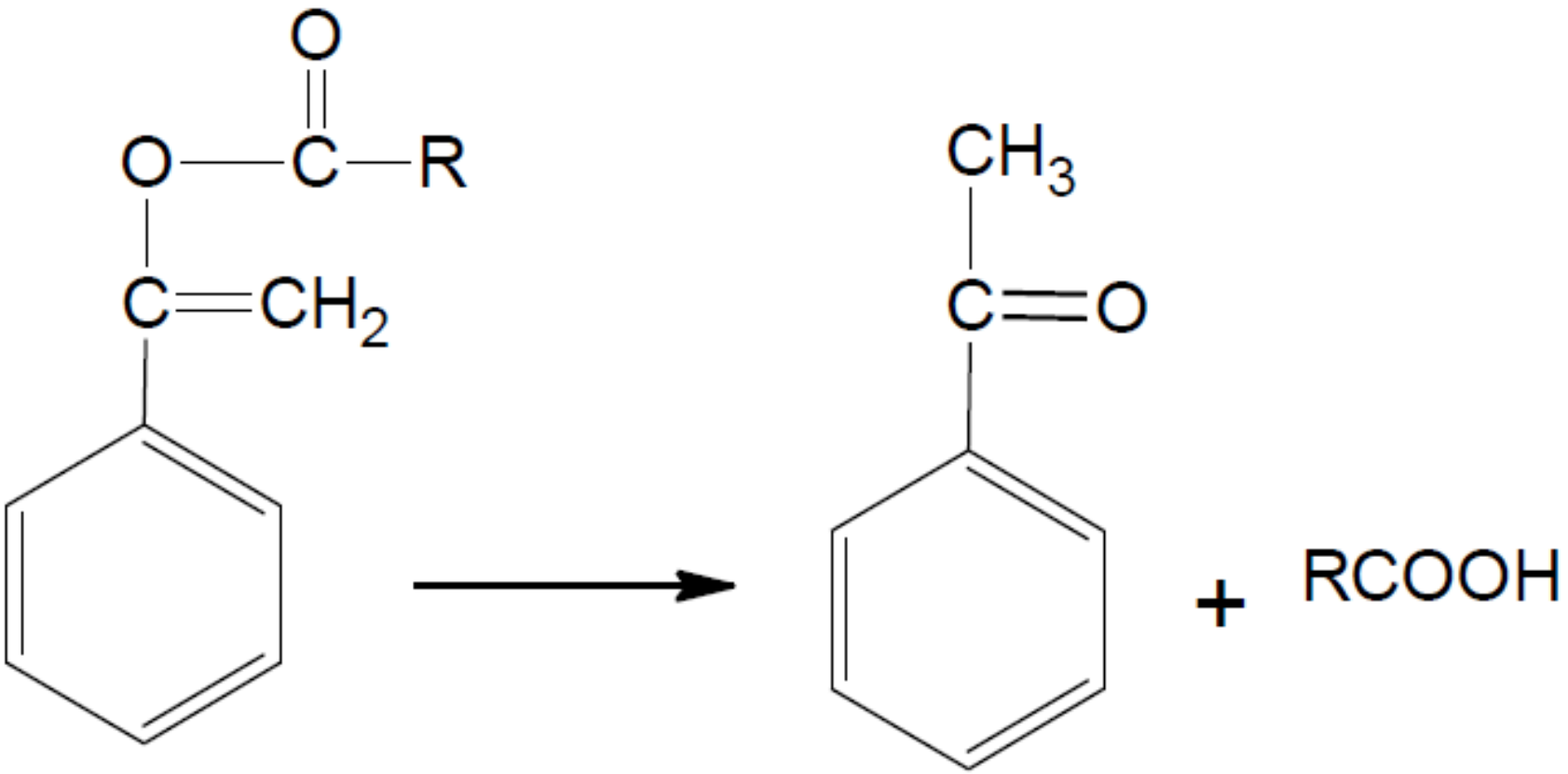
In the presence of plasma or liver enzymes, the enol esters are readily hydrolysed.

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 by plasma and liver enzymes

Enol Ester Of Acetophen



A New Classification of Prodrugs: Regulatory Perspectives

Types of prodrugs:

- Many therapeutic agents are manufactured and administered in prodrug forms.
- A new classification system for prodrugs is proposed to provide useful information about where in the body a prodrug is converted to the active drug.
- In this system, prodrugs are classified into Type I or Type II and the respective Subtypes IA, IB, IIA, IIB or IIC based on their sites of conversion into the final active drug form.

Type I prodrugs:

- Conversion occurs intracellularly (*e.g.*, antiviral nucleoside analogues, lipid-lowering statins).
- Type IA prodrugs refers to those that are converted at the cellular targets of therapeutic actions, whereas
- Type IB prodrugs' conversion occurs in the primary metabolic tissues such as liver, gut, or lung.

Type II prodrugs:

- Conversion occurs extracellularly for examples in digestive fluids, systemic circulation or other extracellular body fluids (*e.g.*, etoposide phosphate, valganciclovir, fosamprenavir).
- For Type IIA prodrugs, the conversion process takes place extracellularly in the milieu of gastrointestinal fluids.
- For Type IIB, the conversion occurs in the systemic circulation and/or other systemic extracellular fluid compartments.
- For Type IIC, the conversion occurs near therapeutical target cells.

Mixed-Type Prodrugs:

- A prodrug may belong to multiple categories and be recognized as a Mixed-Type prodrug.
- For example a prodrug may be converted both in target cells and metabolic tissues such as liver (i.e., named as a Type IA/IB prodrug), or
- one converted in both GI fluids and systemic circulations (i.e., named as a Type IIA/IIB prodrug).