Lec 2 5th stage

Organic Pharmaceutical Chemistry IV

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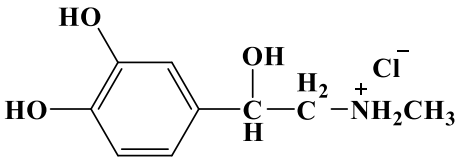
By decreasing the hydrophilicity of the compound, a number of benefits may be achieved, including:-

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

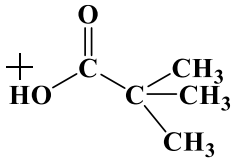
Example of increasing absorption by addition of a nonpolar carboxylic acid



Epinephrine

Use for treatment open angle glucoma

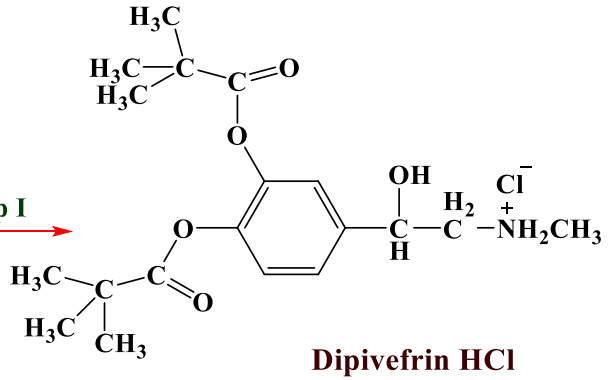
has low lipophilicity (low absorption)



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

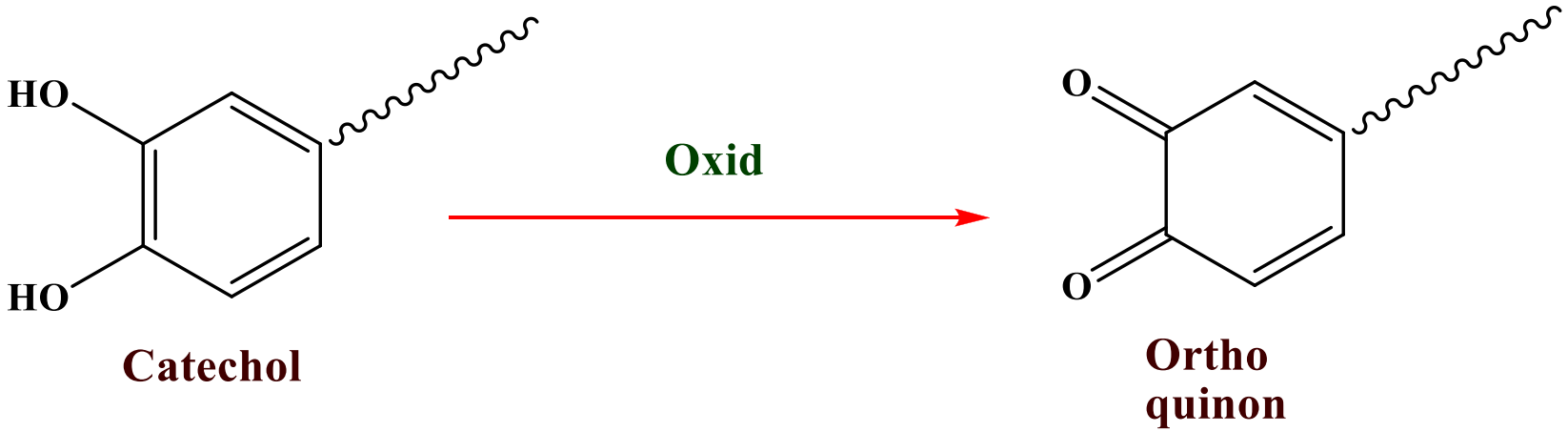
aqueous humor

By utilizing pivalic acid as the promoiety to:-

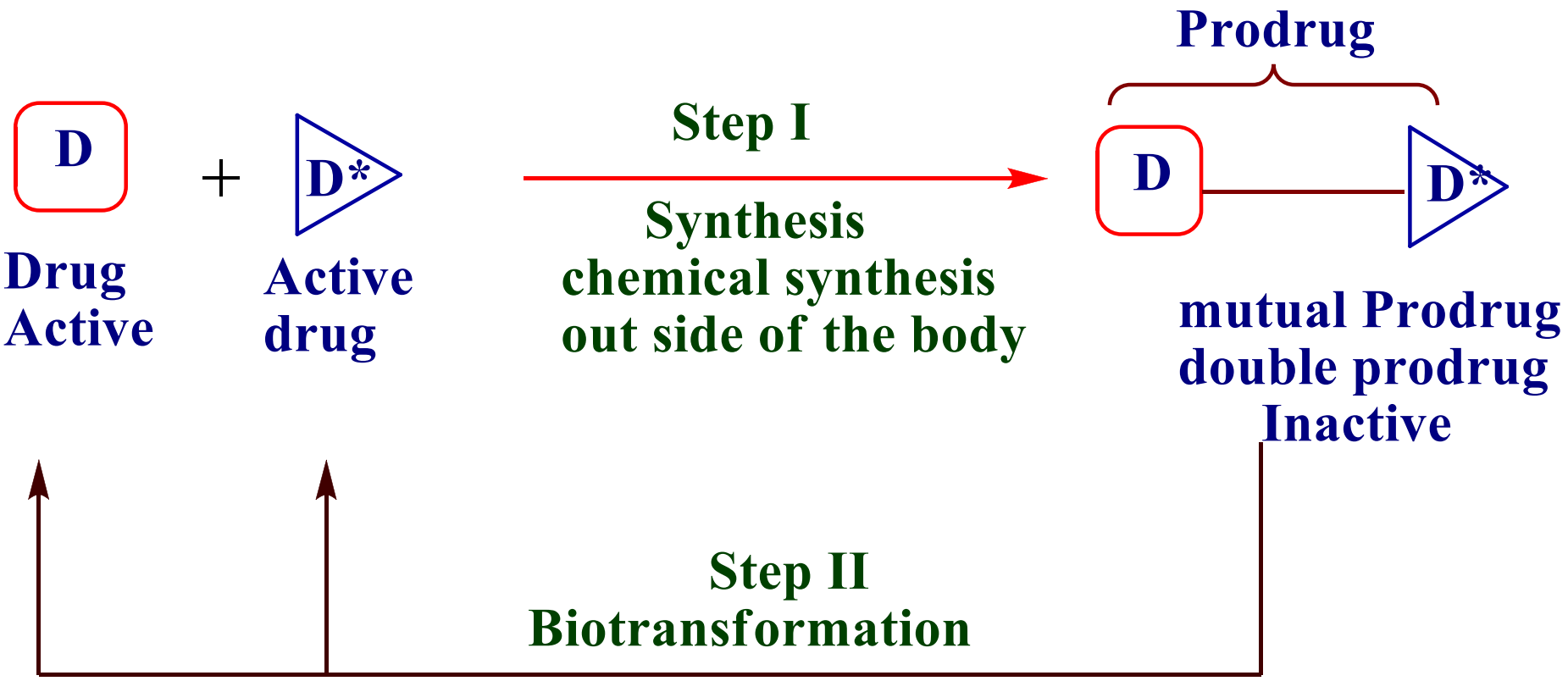
1- Increase the steric bulk around the ester bond lead to slow the ester hydrolysis relative to less bulky groups.

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:-

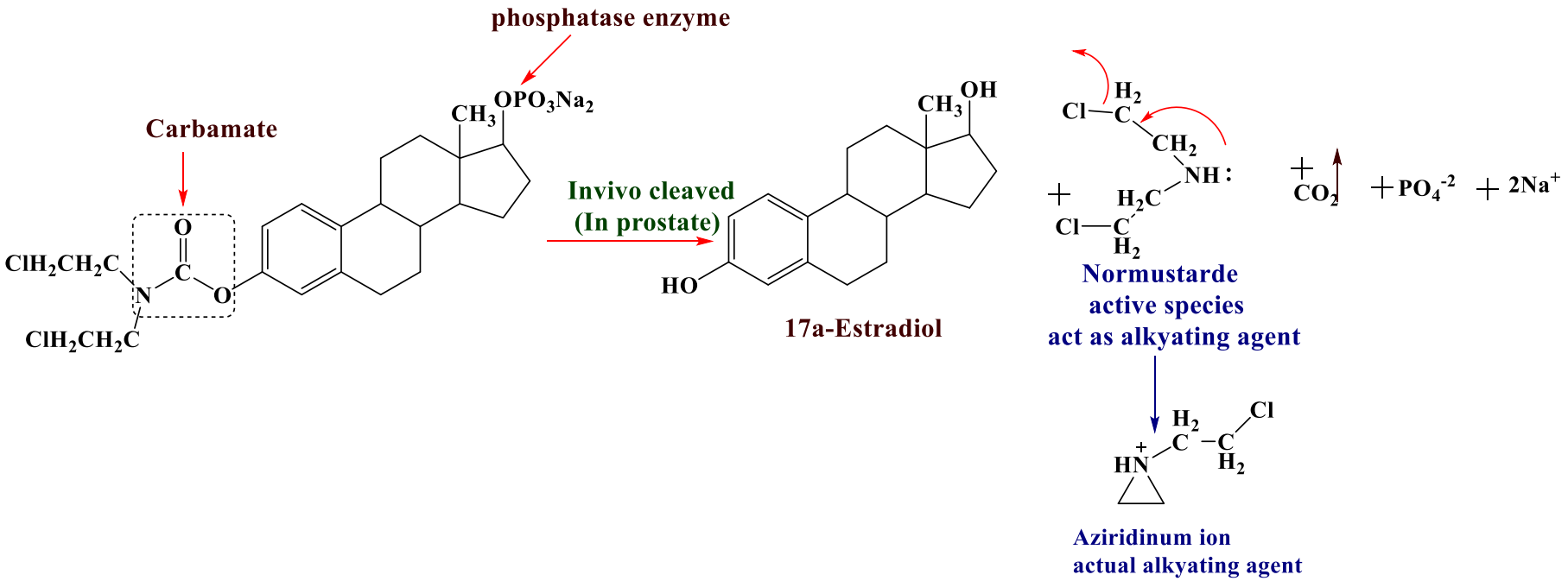
1. **To get synergistic, each one has some activity in certain level. The molecule when cleave, perform its action separately once they are cleave.**

1. **Change physicochemical properties.**

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

Example

Estramustine (mutual prodrug)

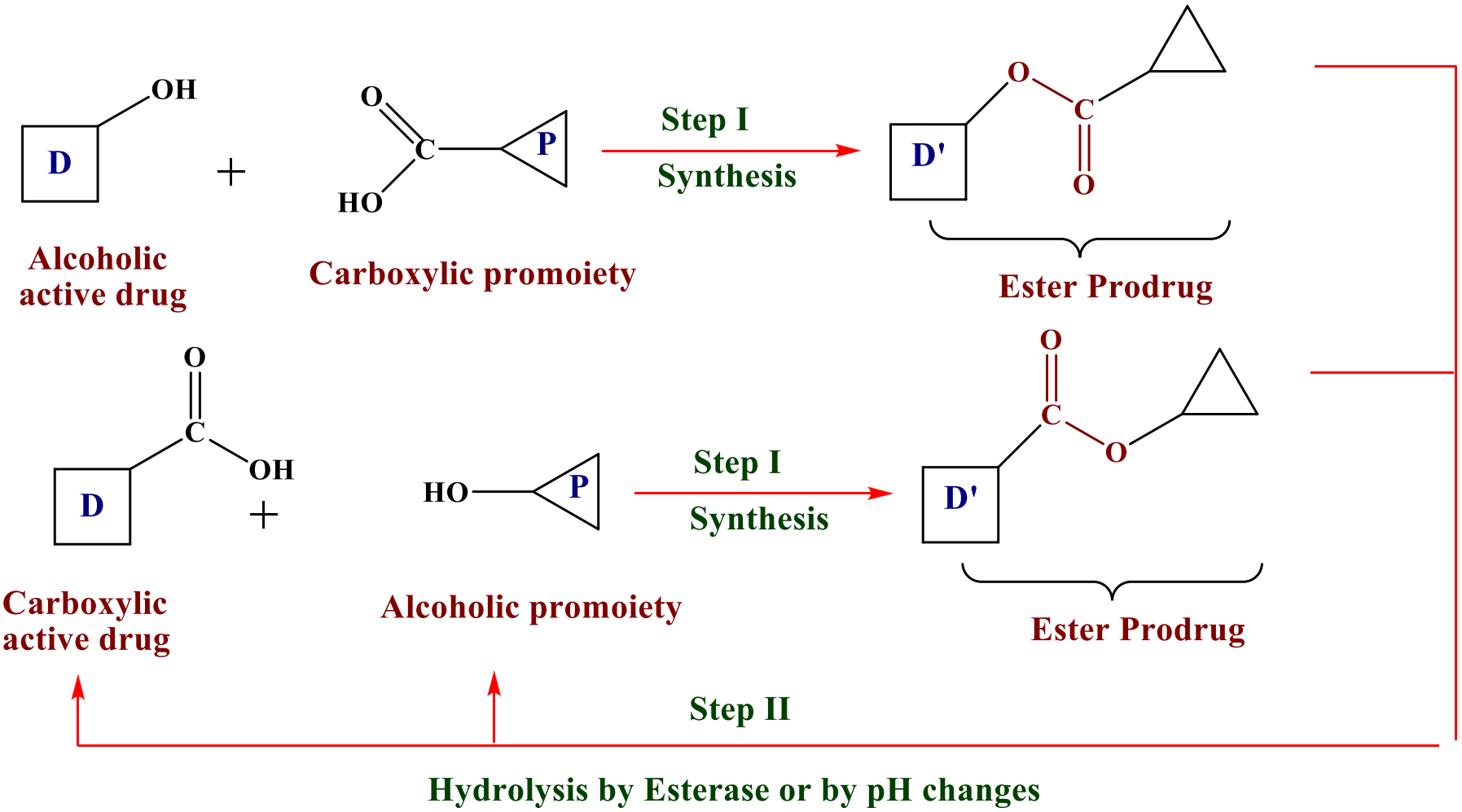


Both carbamate and phosphate are hydrolyse by chemical or enzymatic means

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.

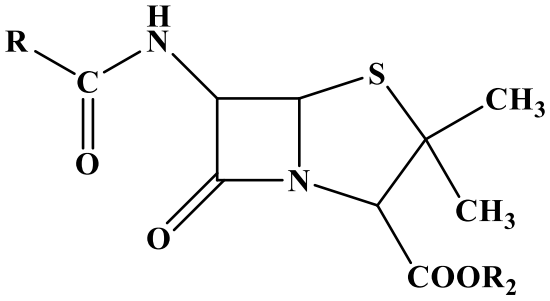

OH
D
O
C
HO
P
Step I
Synthesis
O
C
O
D'
Alcoholic
active drug
Carboxylic promoiety
Ester Prodrug
O
C
OH
D
HO
P
Step I
Synthesis
O
C
O
D'
Carboxylic
active drug
Alcoholic promoiety
Ester Prodrug
Step II
Hydrolysis by Esterase or by pH changes

Esters failure as prodrugs

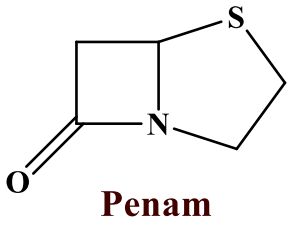
Not all carboxylic esters are easily hydrolyzed in vivo. Steric inhibition around the ester in some cases prevents the prodrug from being hydrolyzed. This is seen in the β-lactams, in which it is often desirable to increase the hydrophobicity of the agent to improve absorption or prevent dissolution 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



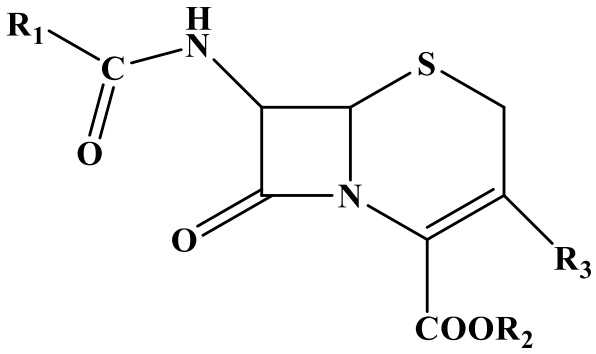
Esterase → No reaction



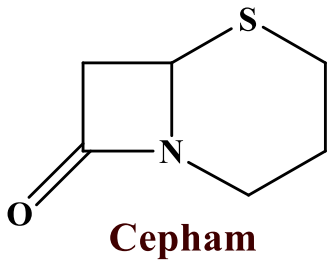
Penam

R_2= Ethyl, propyl, butyl, phenyl.

Cephalosporin ester•



Esterase → No reaction

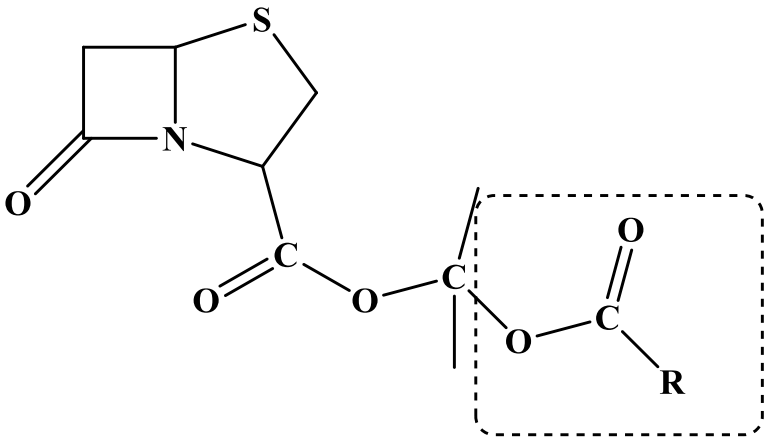


Cepham

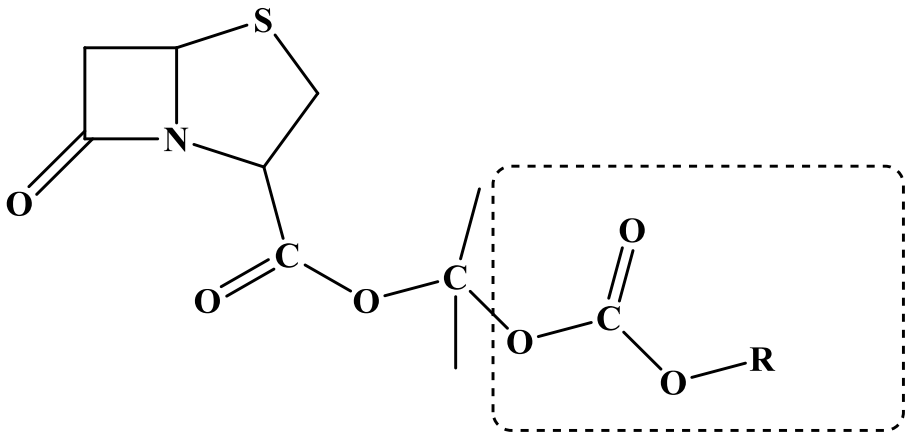
R_2= Ethyl, propyl, butyl, phenyl.

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.



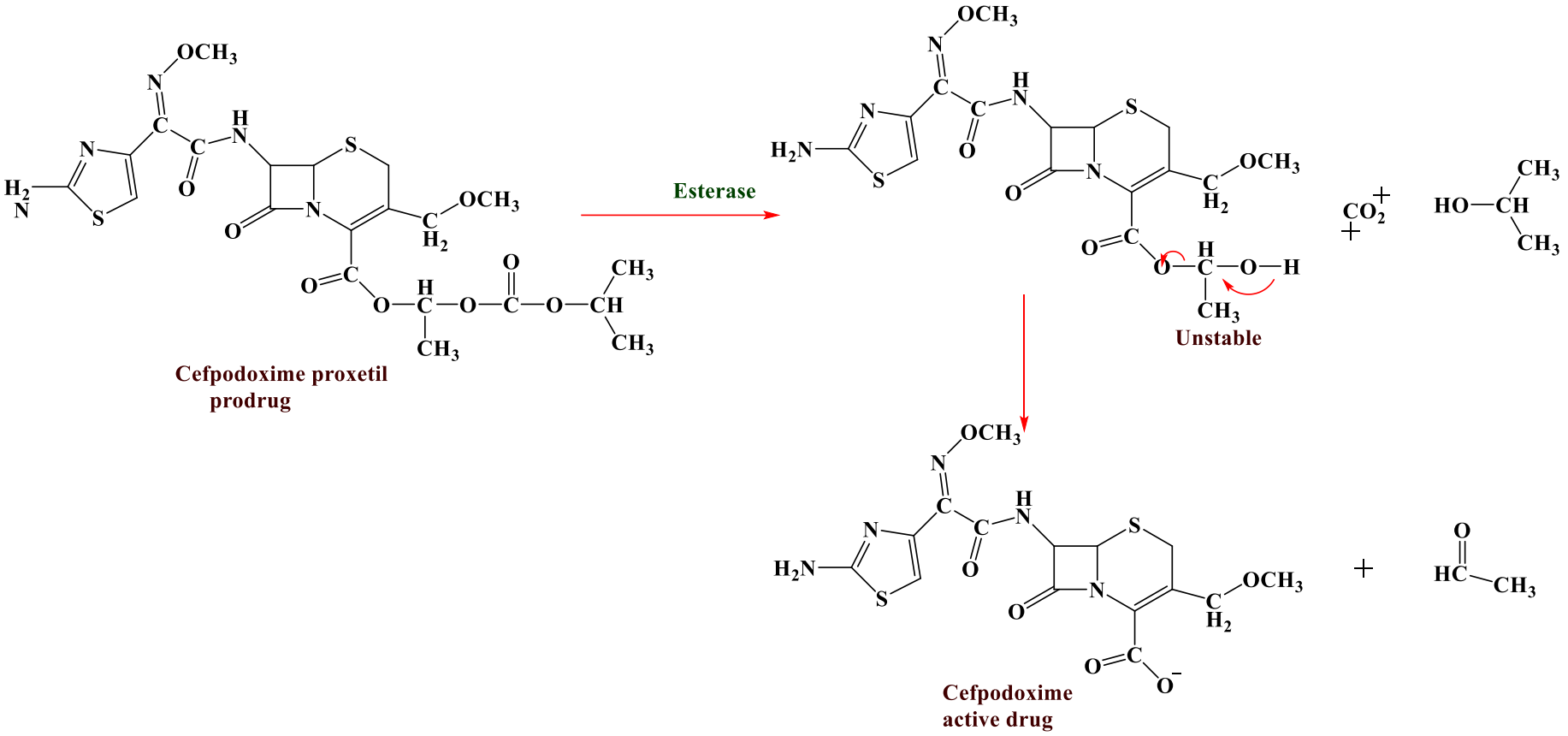
Ester group



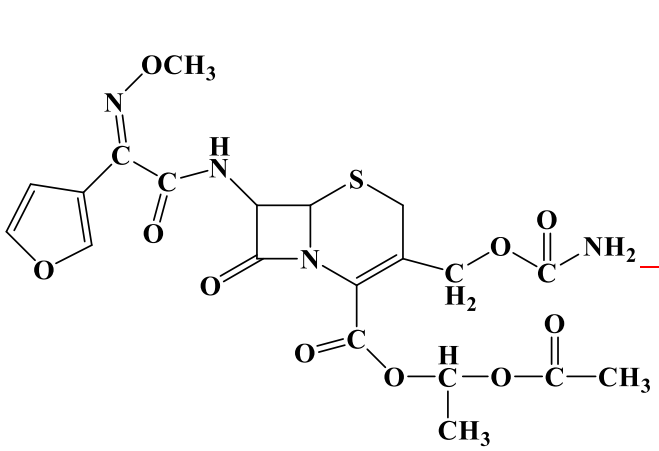
Carbonate group

Example (double ester prodrug)

1)Cefpodoxime proxetile (prodrug)

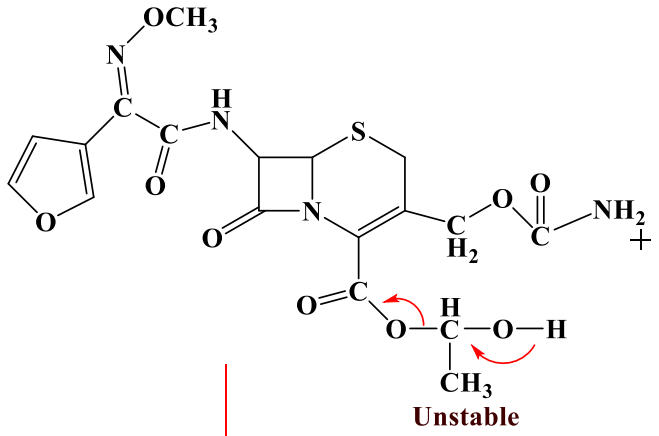


2)cefuroxime axetil (prodrug)

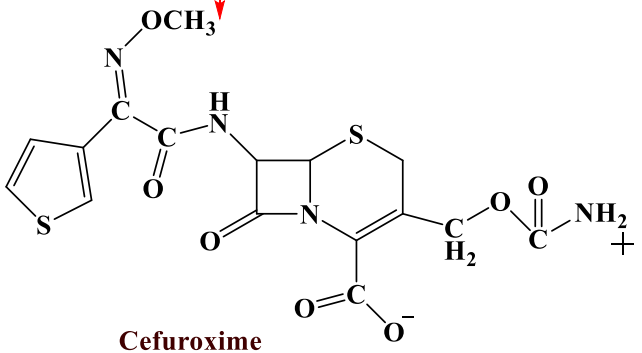


Cefuroxime axetil
prodrug

Esterase

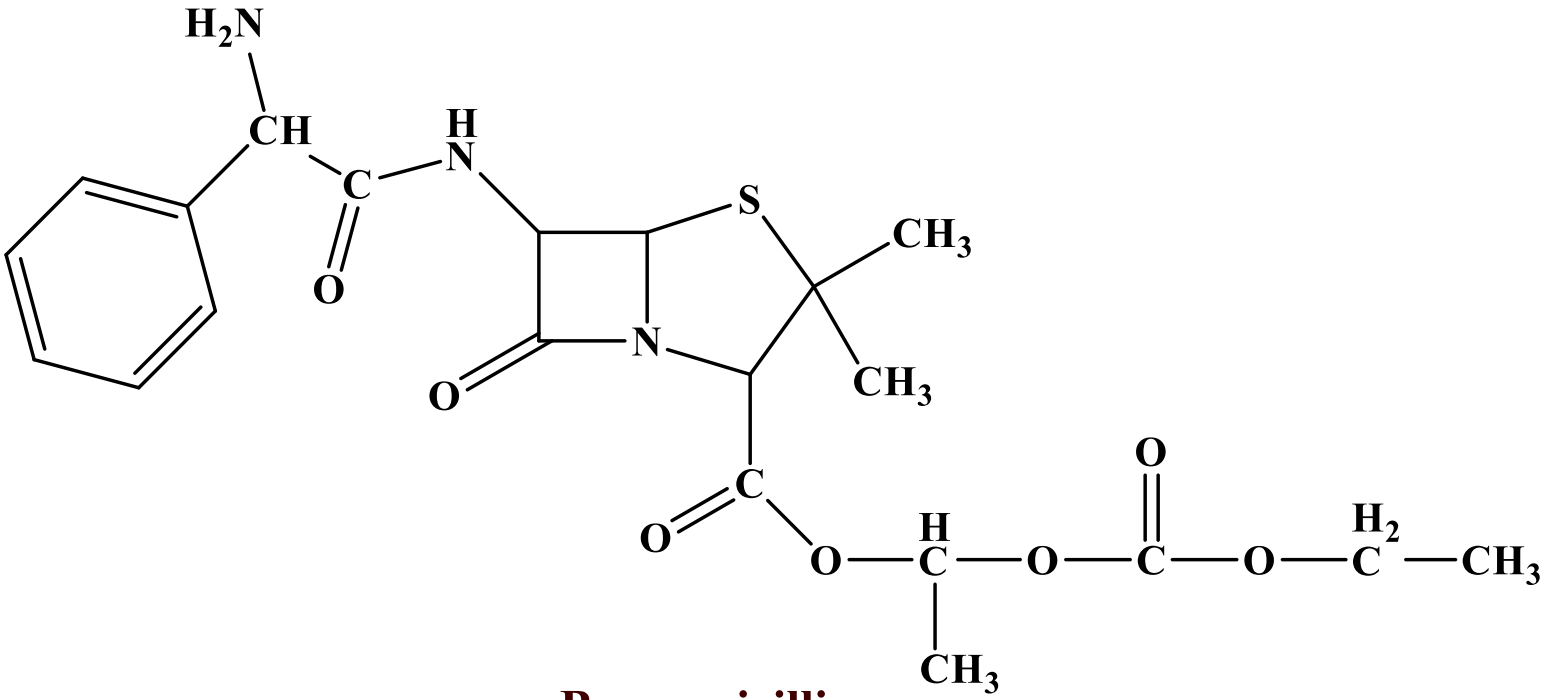


Unstable



Cefuroxime
active drug

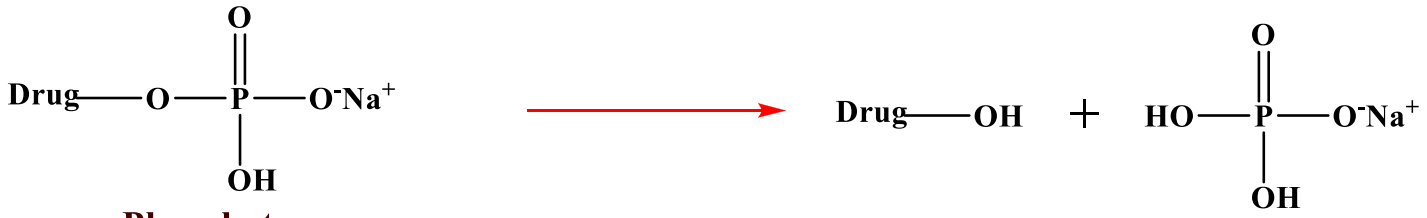
Bacampicillin (prodrug) Homwork •



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.

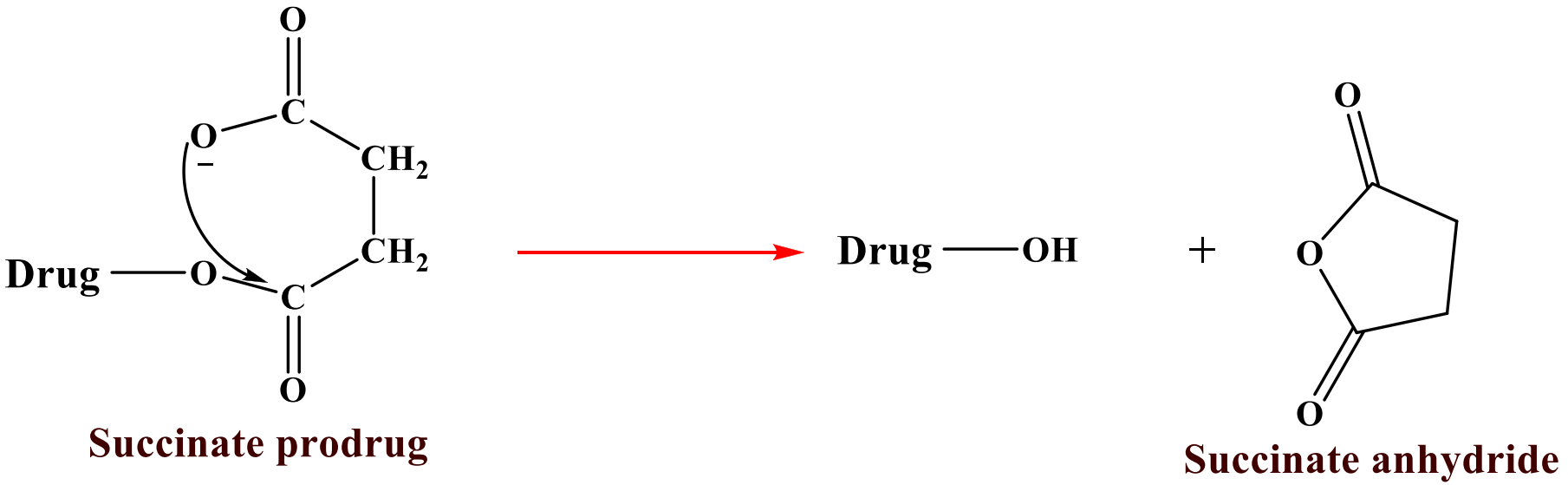
Succinates



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.



Succinate prodrug

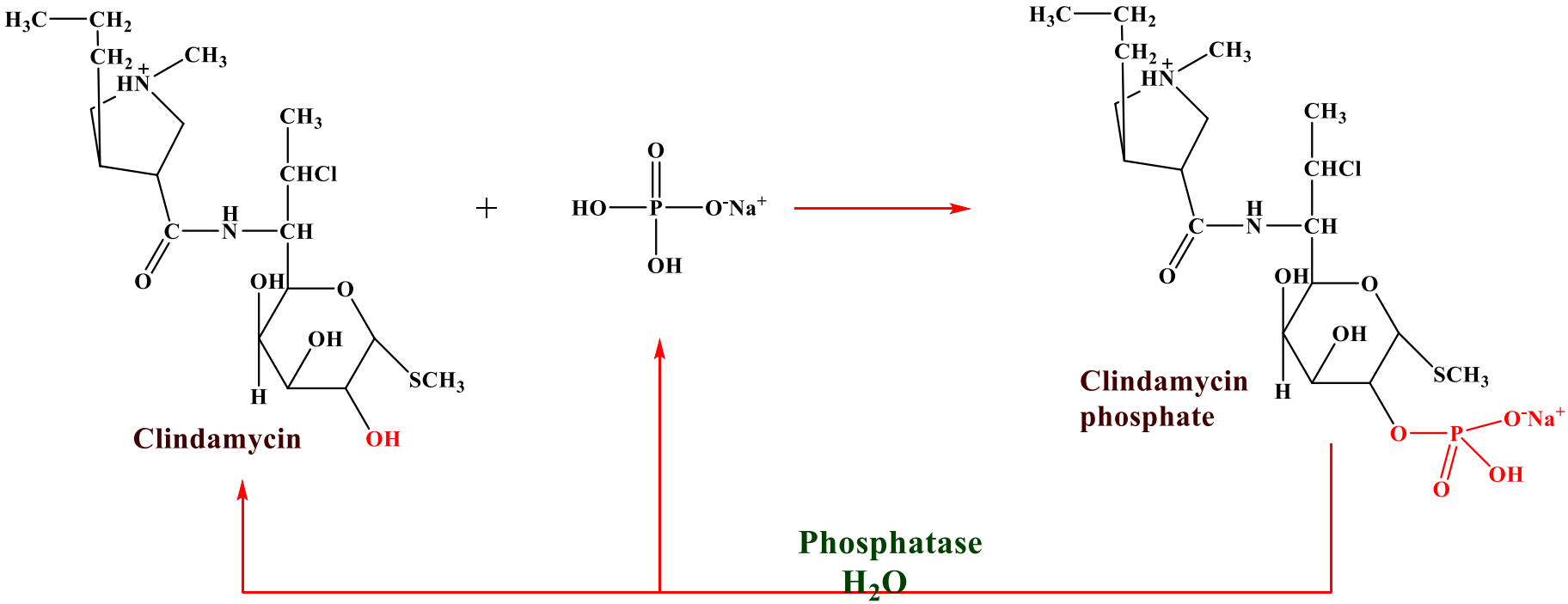
Succinate anhydride

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.