Organic Pharmaceutical Chemistry IV
1st Semester, Year 5 (2016-2017)
Lecture 2

Organic Pharmaceutical Chemistry: Prodrugs

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This lecture is mainly based on:
Chapter 4, Prodrugs and Drug Latentiation, FORREST T. SMITH AND C. RANDALL CLARK Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 11th ed., 2004, Lippincott Williams & Wilkins, USA.

THE PHARMACOKINETIC PHASE

This phase can be considered as the phase involving absorption, distribution, metabolism and excretion of the drug.

The pharmacokinetic studies provide valuable information regarding the *in vivo* properties of a drug's limitation such as poor absorption, too rapid elimination and pre systemic metabolism.

If these properties can be related back to the physicochemical and dosage form properties of the system, then corrections will require **prodrug** interventions.

What are the principal barriers which identified in the pharmacokinetic?!

1. Incomplete absorption of the drug from the delivery system or across biological barriers such as the gastrointestinal mucosal cells and the blood brain barrier.

2. Incomplete systemic delivery of an agent due to pre-systemic metabolism in the gastrointestinal lumen mucosal cells and liver.

3. Toxicity problems associated with local irritation or distribution into tissue other than the desired target organ.

4. Poor site specificity of the drug.

How Can We Use The Prodrug Approach To Overcome Pharmacokinetic Barriers ?!

1. Absorption Problems:

The drug absorption problems are associated with the **physicochemical** properties of drug itself.

<u>Bioavailability</u> after oral dosing of various **water insoluble** agents is often dissolution rate limited.

On the other hand;

Absorption of **highly polar** agents is often limited by their transport across the GI cell membrane.

Most drugs are absorbed by passive diffusion, therefore, a degree of l**ipophilicity** is necessary for efficient absorption through the GI barrier.

So, **highly polar** compounds (drug molecules) should be converted to less polar and more lipophilic prodrugs to promote GI absorption.

Also, many drugs are poorly absorbed into the central nervous system, eye or through the skin due to their **highly polar** nature.

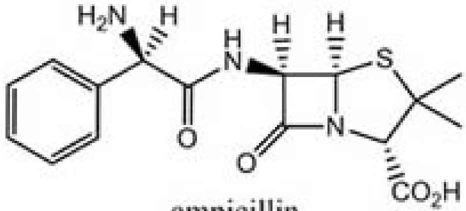
Enhancement of Oral Absorption

Various therapeutic agents such as water soluble vitamins, structural analogues of natural purine and pyrimidine nucleoside, dopamine, antibiotics like ampicillin and carbenicillin, phenytoin and cardiac glycoside such as gitoxin suffers with **poor gastrointestinal absorption**.

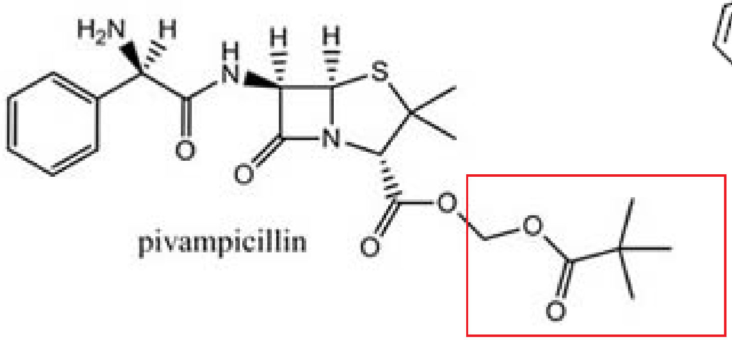
The **prime cause** of the poor absorption of these agents is their **highly polar** nature, **poor lipophilicity and/or metabolism during the absorption process**.

On contrary **gitoxin**, a cardiac glycoside has very **poor oral** bioavailability due to **limited aqueous solubility.**

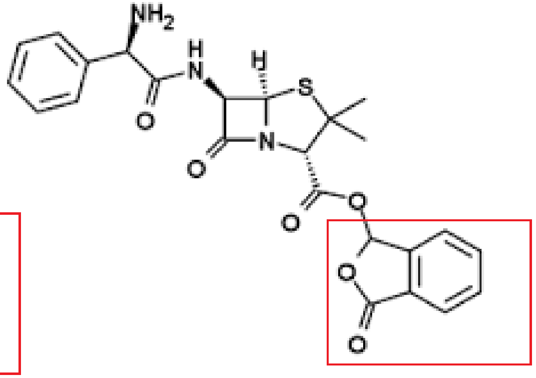
Pivampicillin, talampicillin and bacampicillin are prodrugs of ampicillin, all resulting from the **esterification** of the polar carboxylate group. The absorption of these prodrugs is nearly complete (98-99%) whereas that of ampicillin is < 50%.



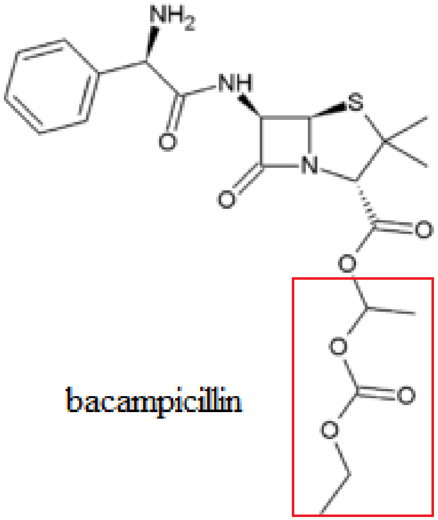
ampicillin



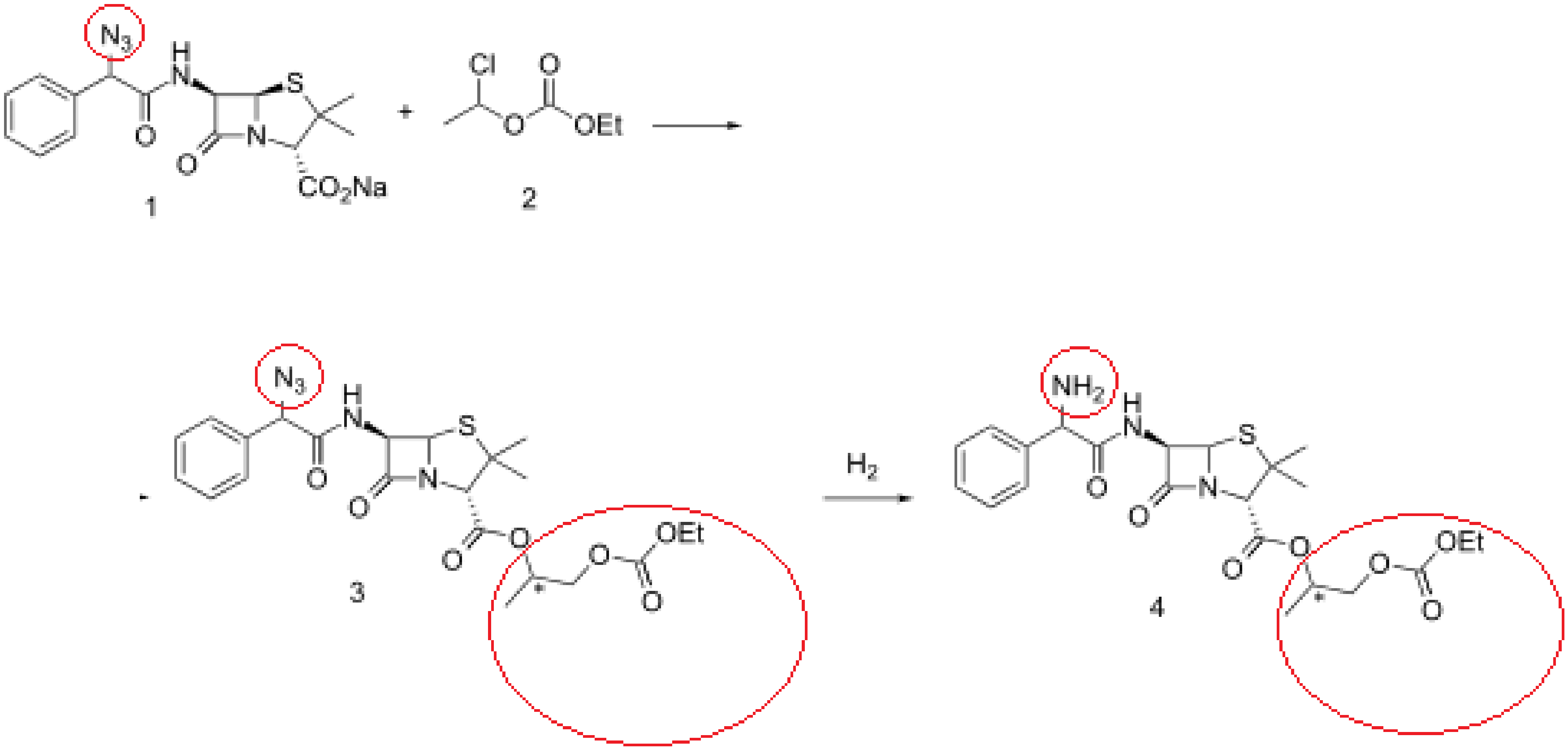
pivampicillin



talampicillin

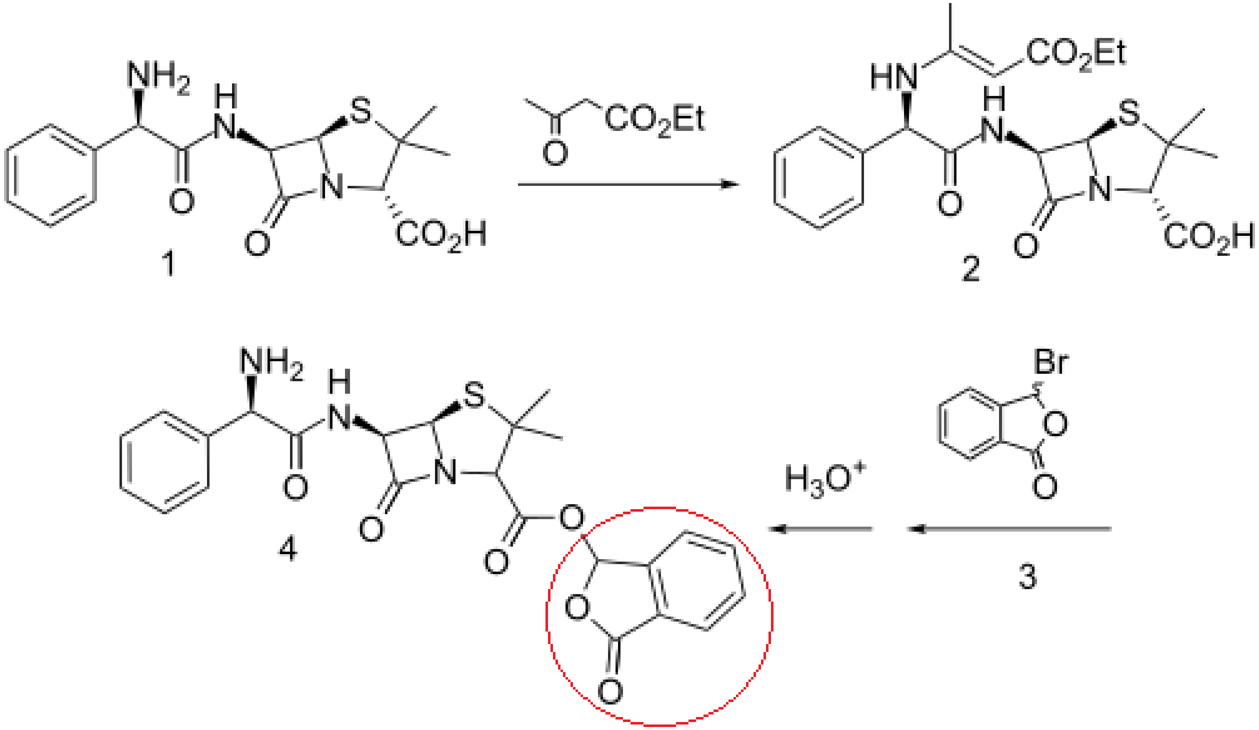


bacampicillin



An azidopenicillin sodium salt (**1**) is reacted with mixed carbonate ester **2** to give ester **3**. Reduction of the azido linkage with hydrogen and a suitable catalyst produces bacampillin (**4**).

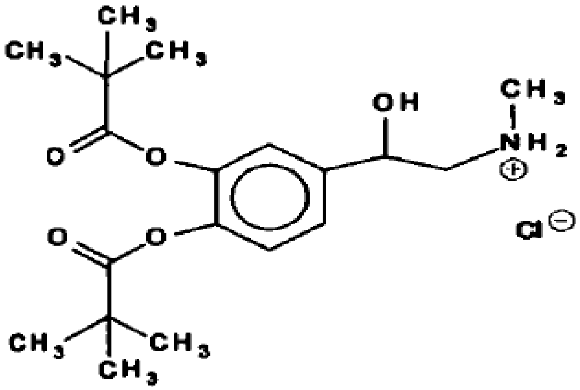
Both enantiomers are active. The drug is rapidly absorbed from the gastrointestinal tract and is quickly cleaved by serum esterases to bioactive ampicillin, acetaldehyde, CO_2 and ethanol.



One synthesis involved protecting the primary amino group of ampicillin (**1**) as the enamine with ethyl acetoacetate (**2**). This was then esterified by reaction with 3-bromopthalide (**3**), and the enamine was carefully hydrolyzed with dilute HCl in acetonitrile to produce talampicillin (**4**).

Enhancement of Ophthalmic Absorption

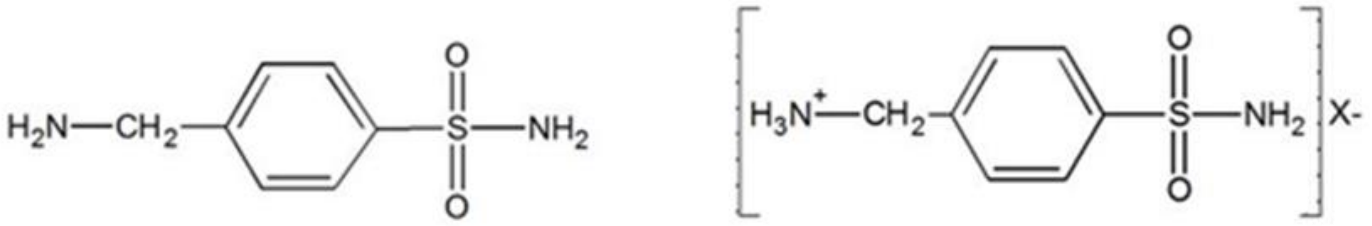
Dipivefrin Hydrochloride is a good example of increased absorption by the addition of a nonpolar (**decreasing the water solubility**) carboxylic acid.



Dipivefrin HCl

Enhancement of Percutaneous Absorption

Mefenide Treating or preventing skin infections in patients with serious burns, to overcome the problem of poor percutaneous absorption its acetae and chloride salts are used as prodrug with enhanced precutaneous adsorption.



Mefenide $X^- = Cl^-$

Mefenide acid salt $X^- = CH_3COO^-$

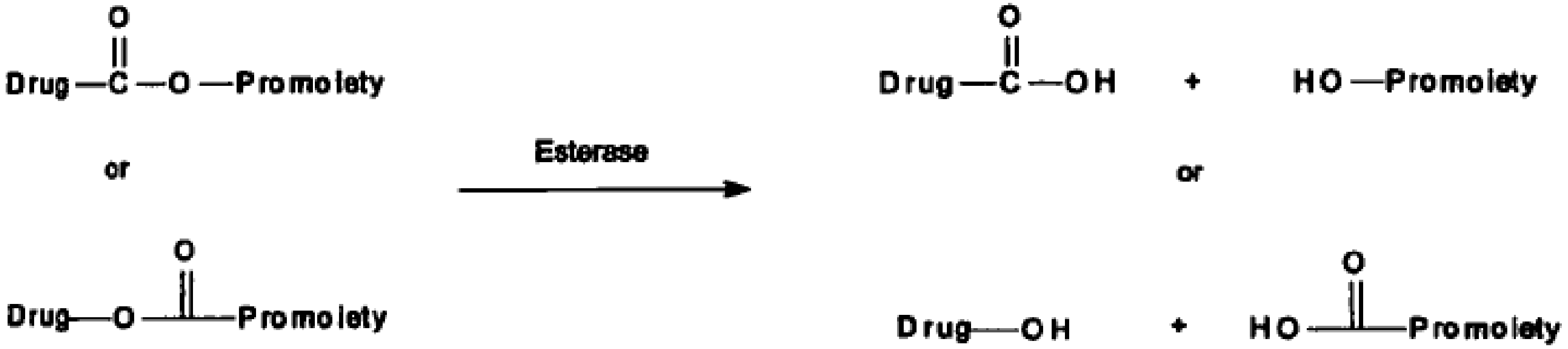
The prodrug approach is also used for prevention of pre-systemic metabolism elongation of the duration of drug action and diminishing local and systemic toxicity of drugs.

Your homework is to look for examples for such prodrugs.

Prodrugs of Functional Groups:

1- Carboxylic Acids and Alcohols

This is the most common type of prodrug because of the ease with which the ester can be hydrolyzed to give the active drug. Hydrolysis is normally accomplished by esterase enzymes present in plasma and other tissues that are capable of hydrolyzing a wide variety of ester linkages. Chemical hydrolysis of the ester function may also occur to some extent.



Below are a number ofi the different types of esterases that prodrugs may use:
Ester hydrolase,
Lipase, Cholesterol esterase,
Acetylchotinesterase,
Carboxypeptidase,
Cholinesterase

What else makes ester prodrugs more popular?!!

An additional factor that has contributed to the popularity of esters as prodrugs is the ease with which they can be formed.

If the drug molecule contains either an alcohol or carboxylic acid functionality, an ester prodrug may be synthesized easily.

The carboxylic or alcohol promoiety can be chosen to provide a wide range of lipophilic or hydrophilic properties to the drug, depending on what is desired.

Manipulation of the steric and electronic properties of the promoiety allows control of the rate and extent of hydrolysis. This can be an important consideration when the active drug must be revealed at the correct point in its movement through the biological system.

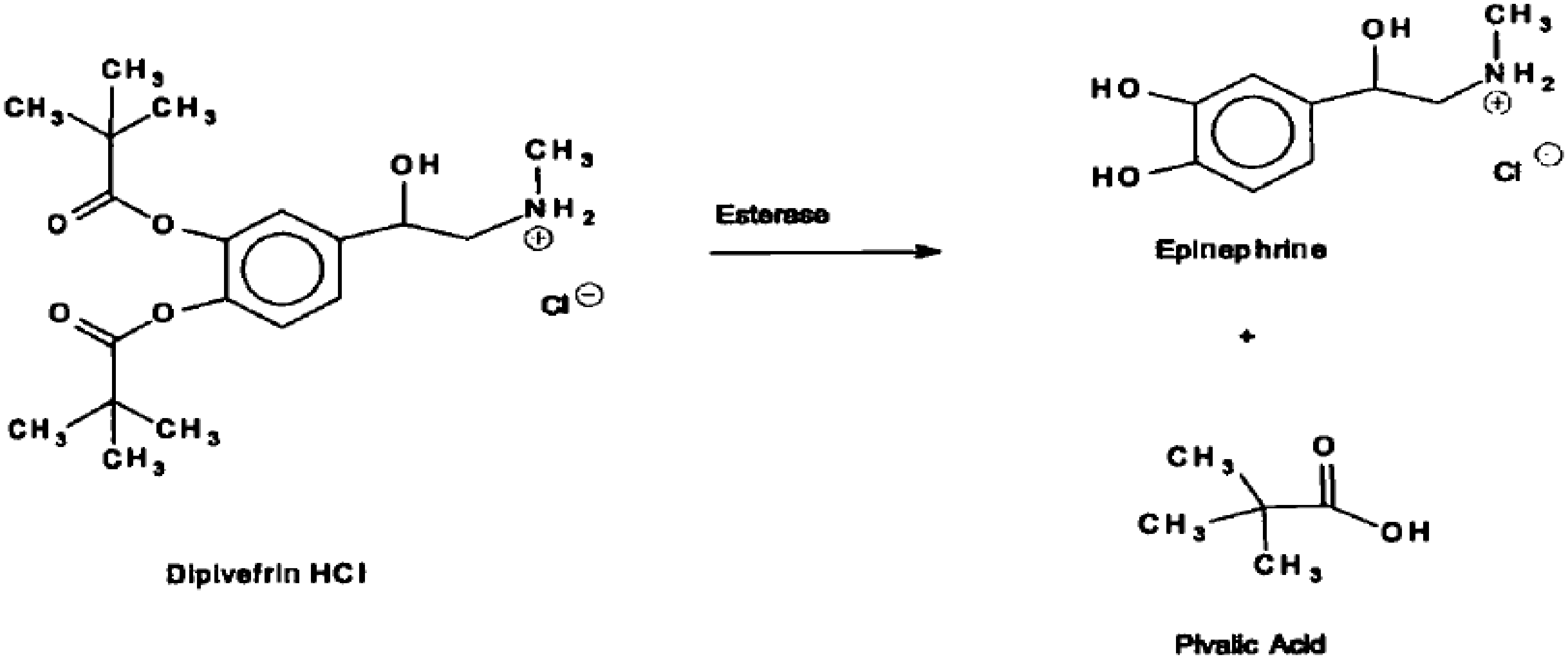
When it is desired to **decrease water solubility**, a nonpolar alcohol or carboxylic acid is chosen as the prodrug moiety. Decreasing the hydrophilicity of the compound may yield a number of **benefits**, including increased absorption, decreased dissolution in the aqueous environment of the stomach, and a longer duration of action.

Dipivefrin Hydrochloride is a good example of increased absorption by the addition of a nonpolar carboxylic acid.

This is a prodrug form of **epinephrine** in which the catechol hydroxyl groups have been used in the formation of an ester linkage with pivalic acid.

The agent is used in controlling inner eye pressure in patients with open-angle glaucoma.

The hydrolysis of Dipivefrin Hydrochloride occur enzymatically by the action of esterase:

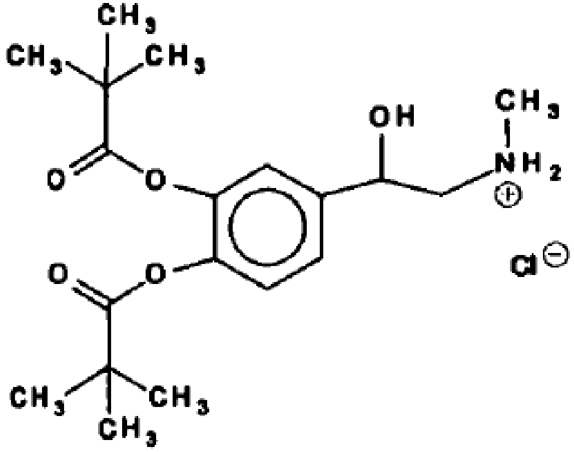


The increased lipophilicity relative to epinephnine allows the agent, when applied to move across the membrane of the eye easily and achieve higher intraocular concentrations.

Hydrolysis of the ester functions then occurs in the cornea, conjunctiva and aqueous humor to generate the active form epinephrine.

Using pivalic acid as the promoiety **increases the steric bulk** around the scissile ester bond, which **slows** the ester hydrolysis relative to less bulky groups, yet still allows this reaction to proceed after the drug has crossed the membrane barriers of the eye.

In addition to this benefit, the catechol system is somewhat susceptible to oxidation, and protecting the catechol as the diester **prevents this oxidation** and the resulting drug inactivation.



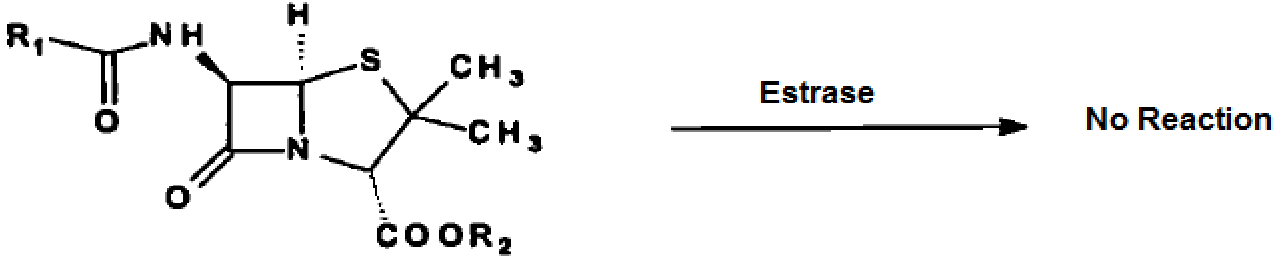
Dipivefrin HCl

The problem of steric inhibition

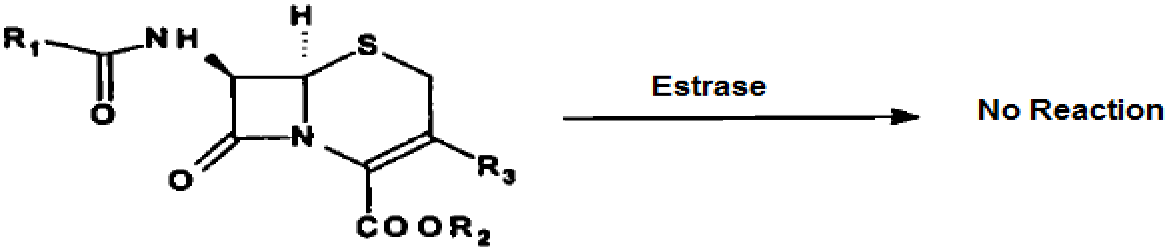
Not all carboxylic esters are easily hydrolyzed *in vivo*. Steric inhibition around the ester in some cases prevents the prodrug from being hydrolyzed.

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.



Peniclin Esters: R_2 Ethyl, Propyl. Butyl, Phenyl



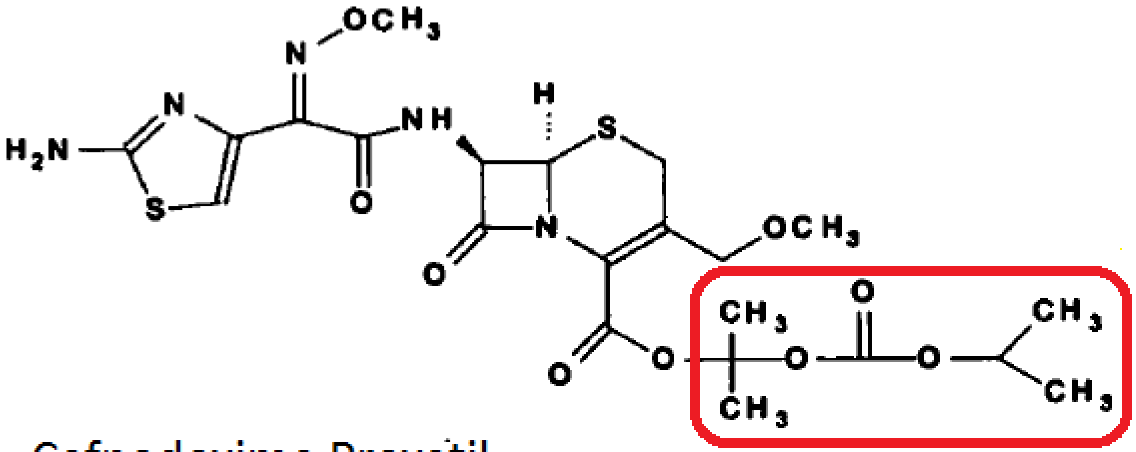
Ciphalosporin Esters: R_2 Ethyl, Propyl. Butyl, Phenyl

Doubleester approach

A solution to this problem (steric inhibition) was to use the so-called **doubleester approach**, in which an additional ester or carbonate function is incorporated into the R_2 substituent further removed from the helerocyclic nucleus.

Hydrolysis of such a function occurred readily, and the moiety was selected that chemical hydrolysis of the second ester occurred quickly.

This is seen in the cephalosporin cefpodoxime proxetil, where a carbonate function was used.



Cefpodoxime Proxetil
(Prodrug)

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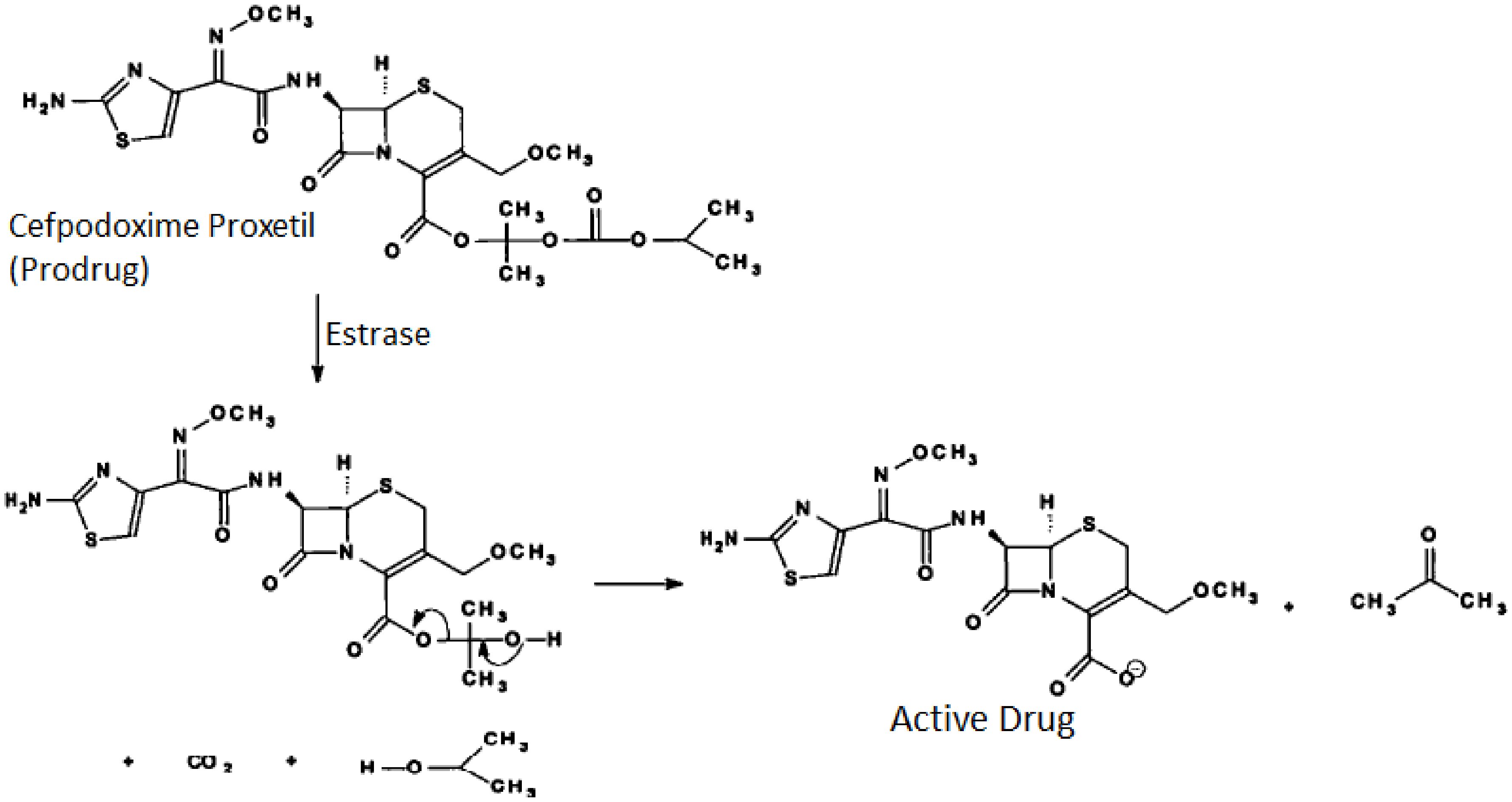
The carbonate is also susceptible to the action of esterase enzymes, and the unstable product undergoes further reaction to give the active carboxylate.

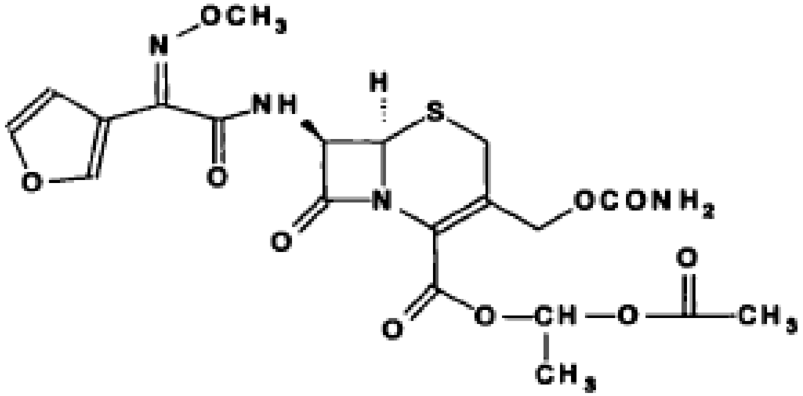


Cefpodoxime Proxetil
(Prodrug)

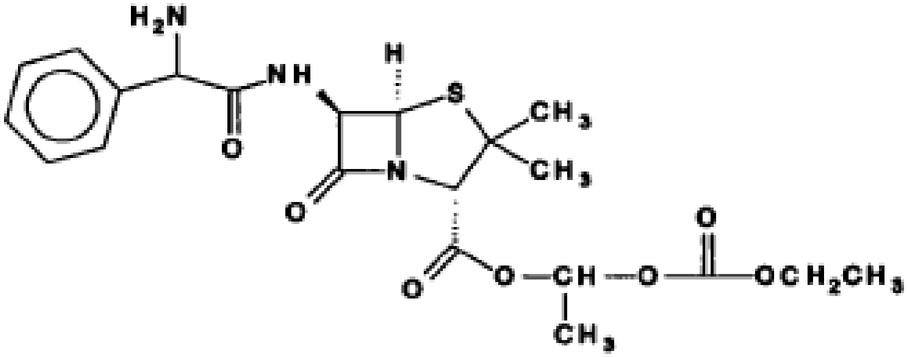
Estrase

Active Drug

The doubleester 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 classified as both a second- and a third-generation agent) so that these agents can be administered orally.



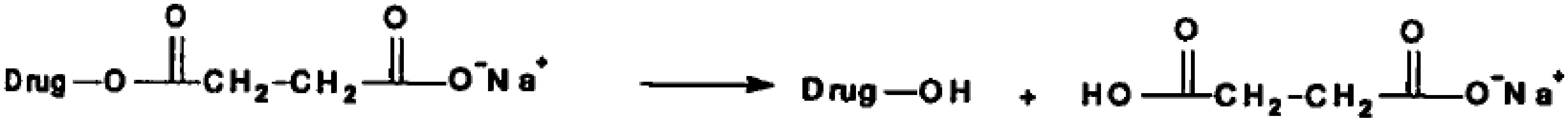
Cefuroxime Axetil



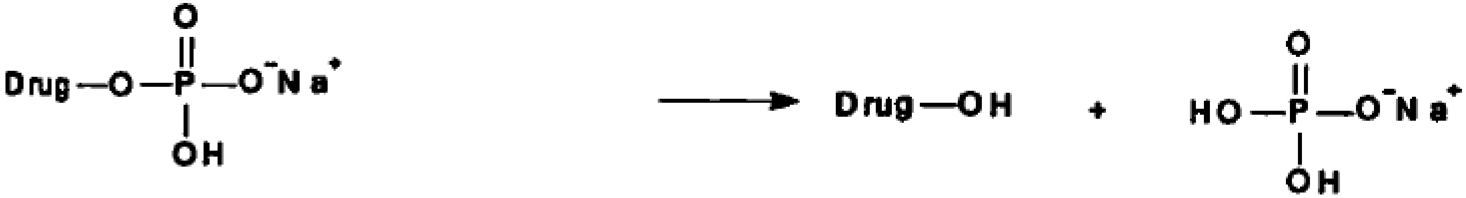
Bacampicillin

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

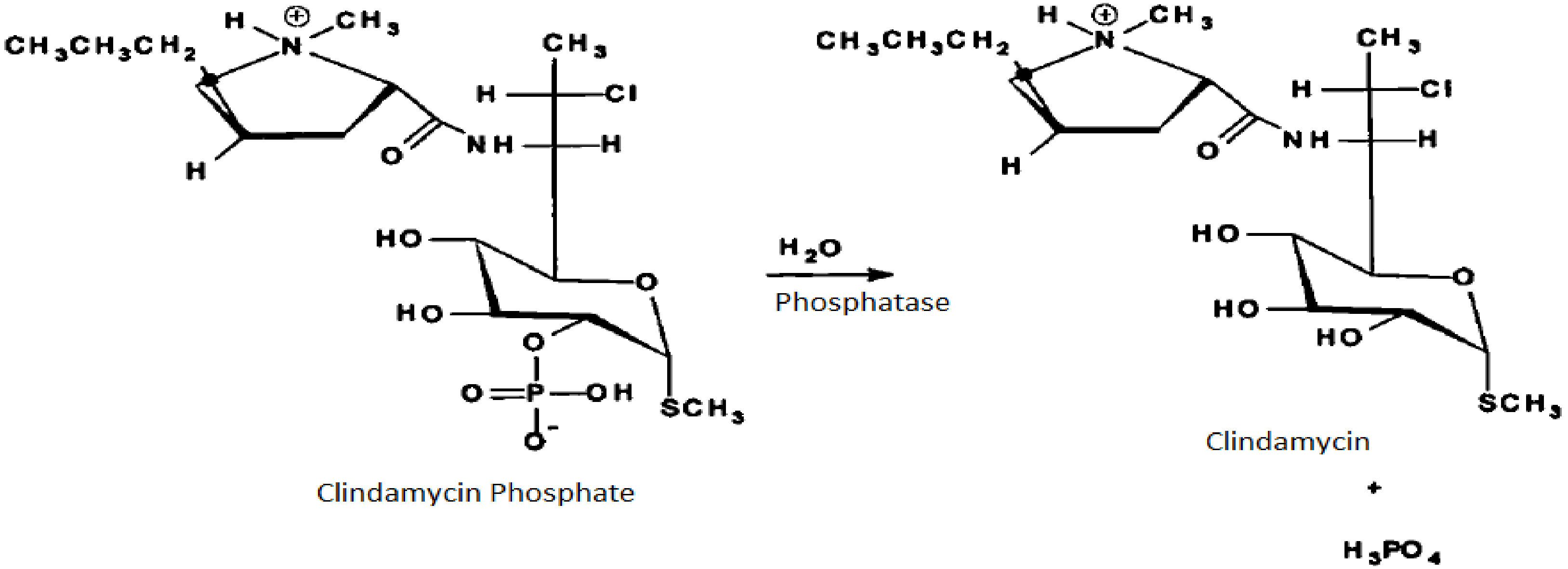


Phosphates

Phosphate esters of alcohols offer another method of increasing the water solubility of an agent. 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 than clindamycin itself.



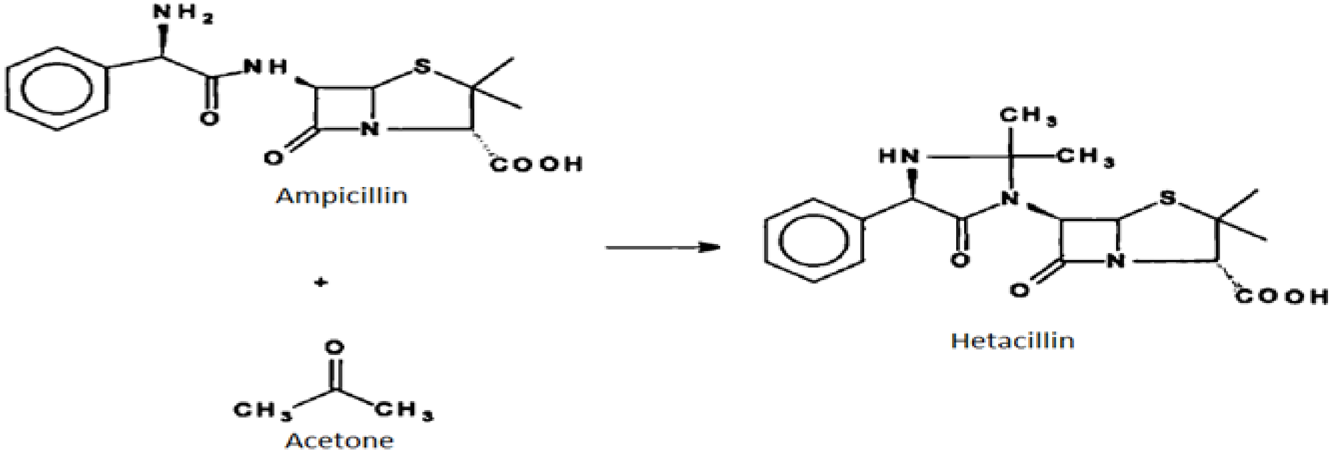
Pain after parenteral administration is associated with local irritation caused by low aqueous solubility or highly acidic or basic solutions. With chindamycin phosphate, the reduction in pain is attributed to the increased water solubility of the agent.

2- Amines

Derivatization of amines to give amides has not been widely used us a prodrug strategy because of the **high chemical stability** of the amide linkage and the **lack of amidase** enzyme necessary for hydrolysis.

There have been efforts at incorporating amines into peptide linkages in which the peptide serves to increase cellular uptake by use an amino acid transporter. The amino acids are then cleaved by specific peptidase enzymes.

A more common approach has been to use **Mannich bases** as a prodrug form of the amines.
Mannich bases result from the reaction of two amines with an aldehyde or ketone as seen with hetacillin.



Ampicillin

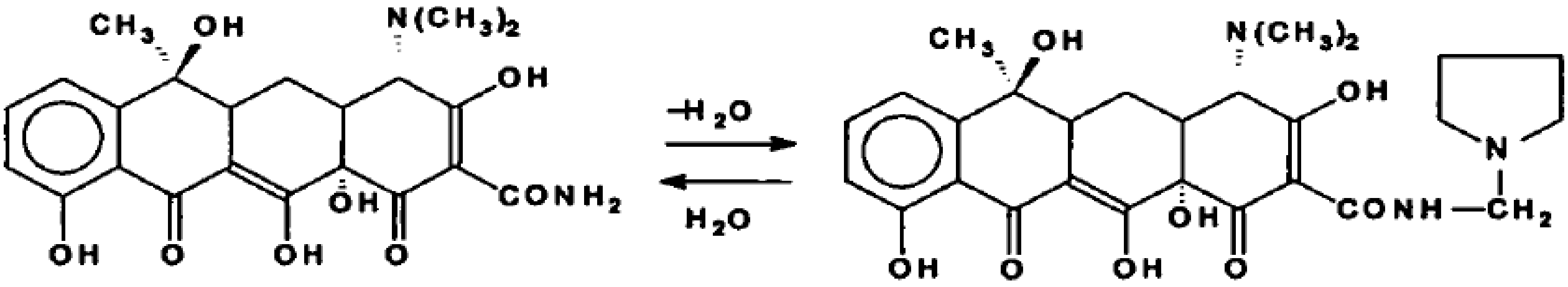
Acetone

Hetacillin

The effect of forming the Mannich base is to lower the basicity of the amine and, thereby, increase lipophilicity and absorption.

When nitrogen is present in an amide linkage, it is sometimes desirable to use the amide nitrogen as one of the amines necessary to form a Mannich base.

This approach was used with the antibiotic tetracycline, the amide nitrogen was allowed to react with formaldehyde and pyrrolidine to give the Mannich base rolitetracycline.



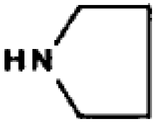
Tetracycline

+

$CH_2{=}O$

Formaldehyde

+



Pyrrolidine

Rolitetracycline
(Prodrug)

In this case, addition of the basic pyrrolidine nitrogen introduces an additional ionizable functionality and increases the water solubility of the parent drug.

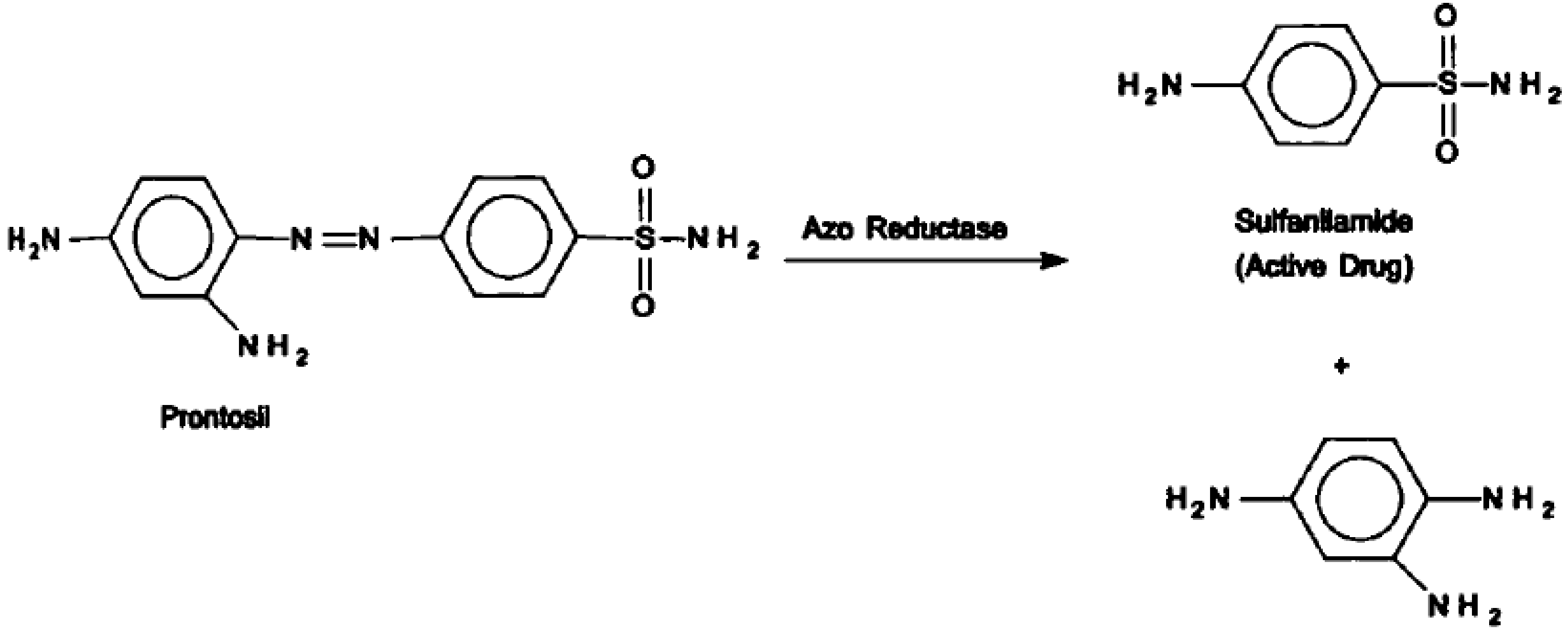
The Mannich base hydrolyzes completely and rapidly in aqueous media to give the active tetracycline.

3- Azo Linkage

Amines are derivatised to azolinkage prodrugs.

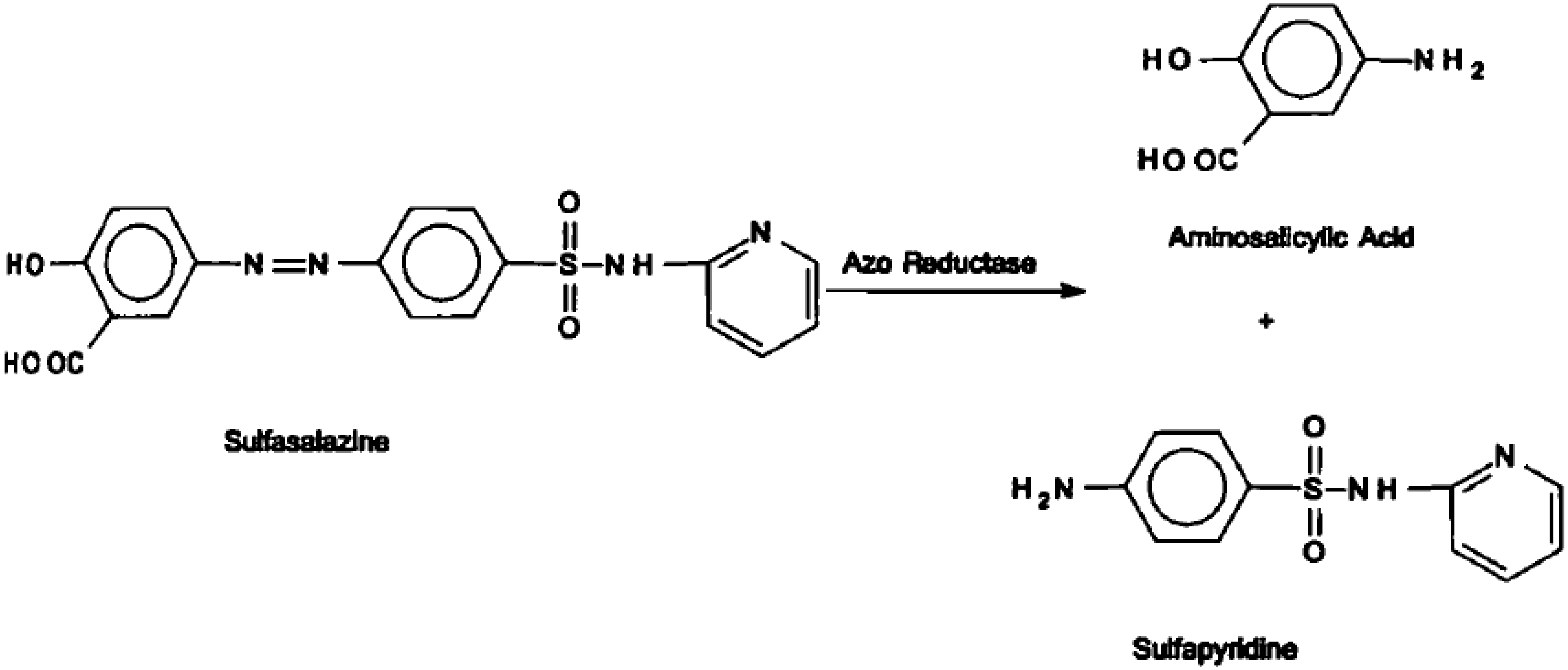
Azo dye prontosil that led to the discovery of the sulfonamides as the first antibacterials to be used to treat systemic infections.

Although prontosil itself was inactive in vitro, it was active in vivo and was converted by azo reductase enzymes in the gut to sutfanilamide the active species.



Although prontosil is no longer used as an antibacterial this type of linkage appears in sulfasalazine which is used in the treatment of ulcerative colitis.

The azo linkage is broken in the gut by the action of azo reductases produced by microflora.



The **advantage** of this prodrug approach is that the combination of cleavage of the azo linkage and generation of aminosalicylic acid prior to absorption prevents the systemic absorption of the agent and helps concentrate the active agent at the site of action.

4- Carbonyl Compounds

A number of different functionalities have been evaluated as prodrug derivatives of carbonyls (e.g., aldehydes and ketones), although this approach has not found wide clinical use.

These have generally involved derivatives in which the *sp*^{2} hybridized carbonyl carbon is converted to an *sp*^{3} hybridised carbon attached to two heteroatoms such as oxygen, nitrogen, or sulfur. These prodrugs are reconverted to the carbonyl compounds by hydrolysis.

Ex: Methenamine releases HCHO in the urine, which acts as an antibacterial agent