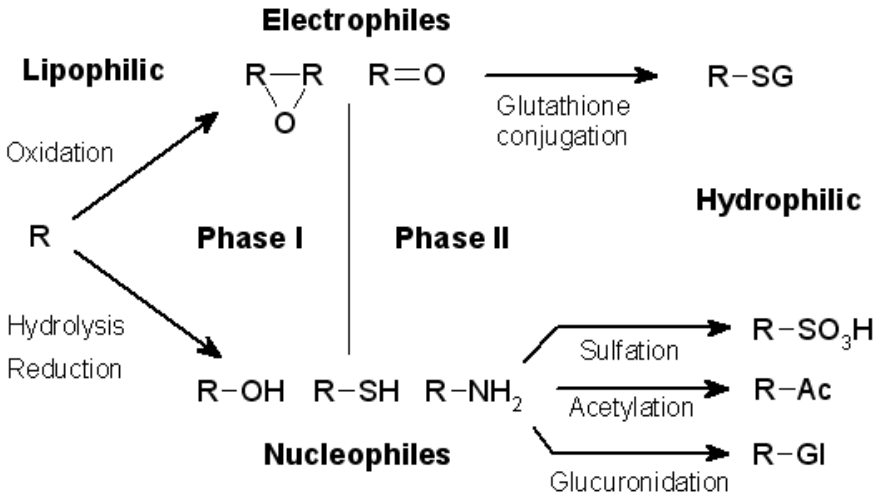
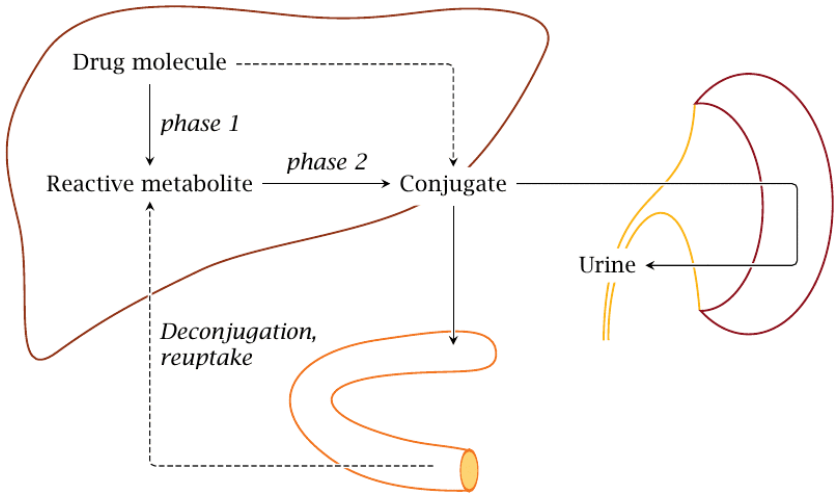
Drug Metabolism: Phase-I





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Learning Outcomes

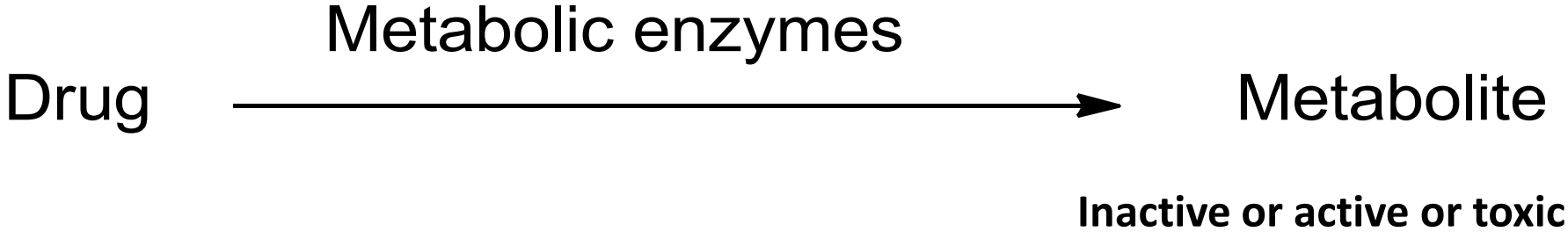
At the end of this lesson, students will be able to:

- Explain the drug metabolism.
- Demonstrate the different routes of Phase-I metabolism.
- Explain the effect of drug metabolism on duration of action and activity of drugs.
- Explain different mechanisms of drug metabolism-Phase-I such as oxidation, reduction and hydrolysis.

Drug metabolism

Drug metabolism is the metabolic breakdown of drugs through specialized enzymatic systems.

It refers to enzyme-mediated biotransformations (detoxification) that alters the pharmacological activity.



Drug metabolism

- Drugs undergo a variety of chemical changes by enzymes of the liver, intestine, kidney, lung, plasma and other tissues.

- Many enzymes take place in such biotransformations; oxidase, hydrolase, lipase, synthetase, dehydrogenase, …etc.

- Metabolism may result in:-
  - Pharmacologically inactive drug (detoxification).
  - Pharmacologically active drug (bioactivation…prodrug approach).
  - Change in the pharmacological activity (toxic effect).

The importance of studying the drug metabolism

- Understanding the pharmacological and toxicological activity of drugs.
- The importance of shortening the drug's duration of action.
- The complications of drug-drug interactions mainly depends on the induction or inhibition of metabolic enzymes.

Pathways of Drug metabolism

- Can be divided into two distinct categories:

  - Phase-I: Functionalization reactions

    Reactions which introduce or unmask hydrophilic groups in the drug structure.

  - Phase-II: Conjugation reactions

    Reactions which conjugate the drug or its metabolite from phase-I to a hydrophilic, endogenous species.

Phase-I Metabolism or Functionalization Reactions

- Oxidation Reactions:-
  - Oxidation of aromatic moieties.
  - Oxidation of olefins.
  - Oxidation at benzylic, allylic carbon atoms, and carbon atoms α to carbonyl and imines
  - Oxidation at aliphatic and alicyclic carbon atoms or Aliphatic hydroxylation.
  - Oxidation involving carbon–heteroatom systems (Oxidative dealkylation, Oxidative deamination, *N-, S-* oxidation, N-hydroxylation and N-oxide formation.
  - Oxidation of alcohol and aldehydes.
  - Other oxidations.

- Reduction Reactions:-
  - Reduction of aldehydes and ketones.
  - Reduction of nitro and azo compounds.
  - Other reductions.

- Hydrolysis or Hydrolytic Reactions:-
  - Hydrolysis of esters and amides.
  - Hydration of epoxides and arene oxides by epoxide hydrase.

Phase-II Metabolism or Conjugation Reactions

It involves the following conjugation reactions that are catalyzed by transferase enzymes:-

- Glucuronic acid conjugation or Glucuronidation.
- Sulfate conjugation or sulfation.
- Amino acid conjugation (Glycine, Glutamine).
- Glutathione conjugation.
- Methylation.
- Acetylation.

Phase-I Reactions

Two general types of enzyme systems take part in these reactions:-

- Microsomal Mixed Function Oxidases (MFOs)
  - Flavoprotein, NADPH-monooxygenase
  - Cytochrome P450
- Non-cytochrome oxidizing enzymes
  - Xanthine oxidase
  - Alcohol/aldehyde dehydrogenase

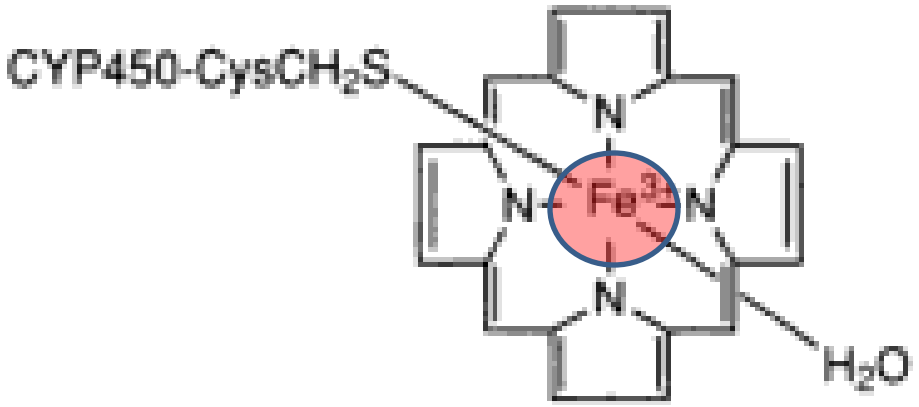
General Features of Cytochrome P-450

- A large number of families (at least 18 in mammals) of cytochrome P-450 (abbreviated "CYP") enzymes exists as well as many subfamilies.
- Total of 300 different CYP available and each member catalyzes the biotransformation of a unique group of drugs.
- CYP can transfer oxygen atom to the substrate.

R-H ⟶ R-OH

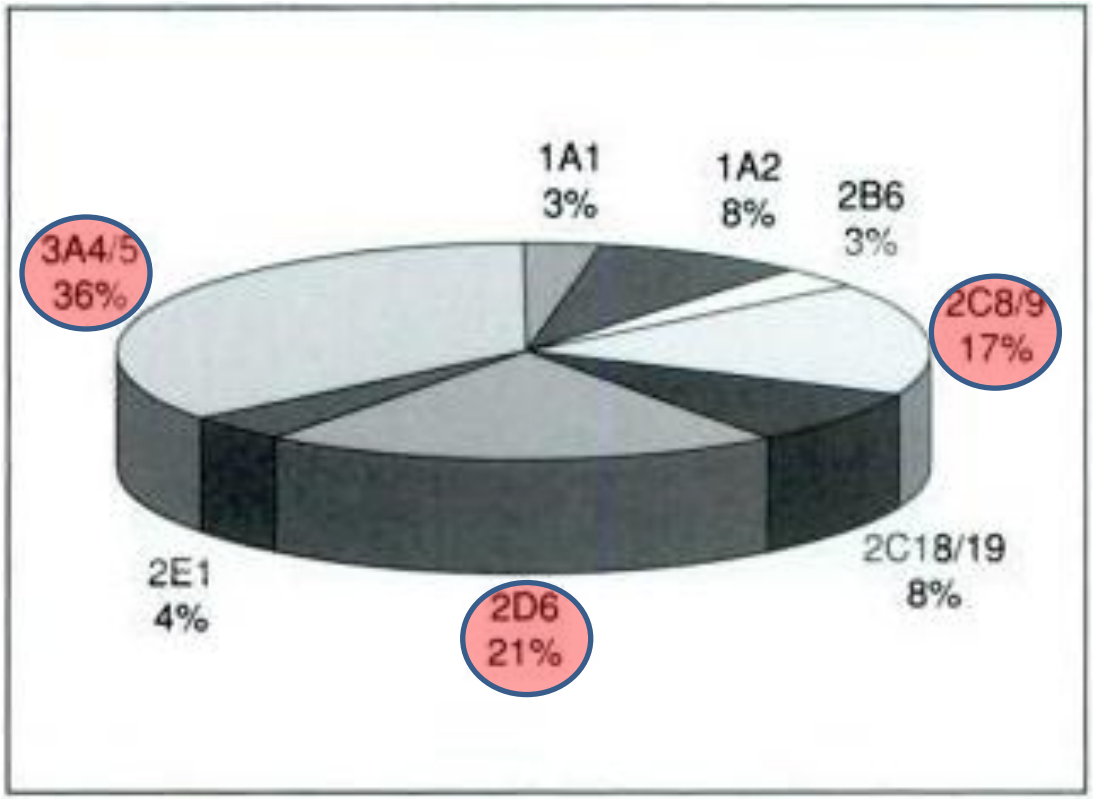
(Substrate/drug) (Product/metabolite)

- More than 75% of drug metabolism are mediated by CYPs.



CYP 450

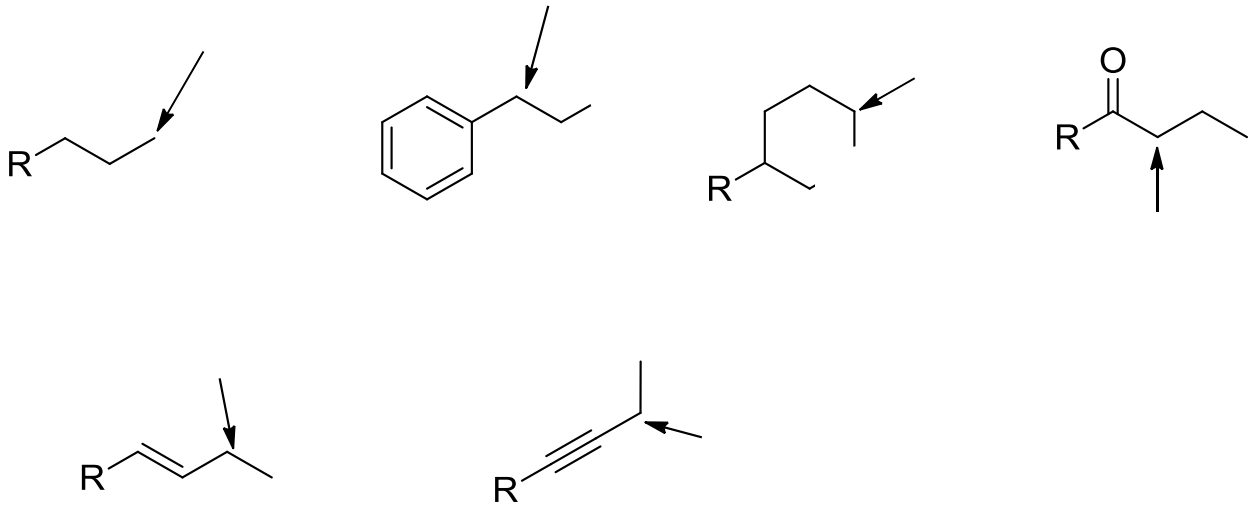
Families and subfamilies



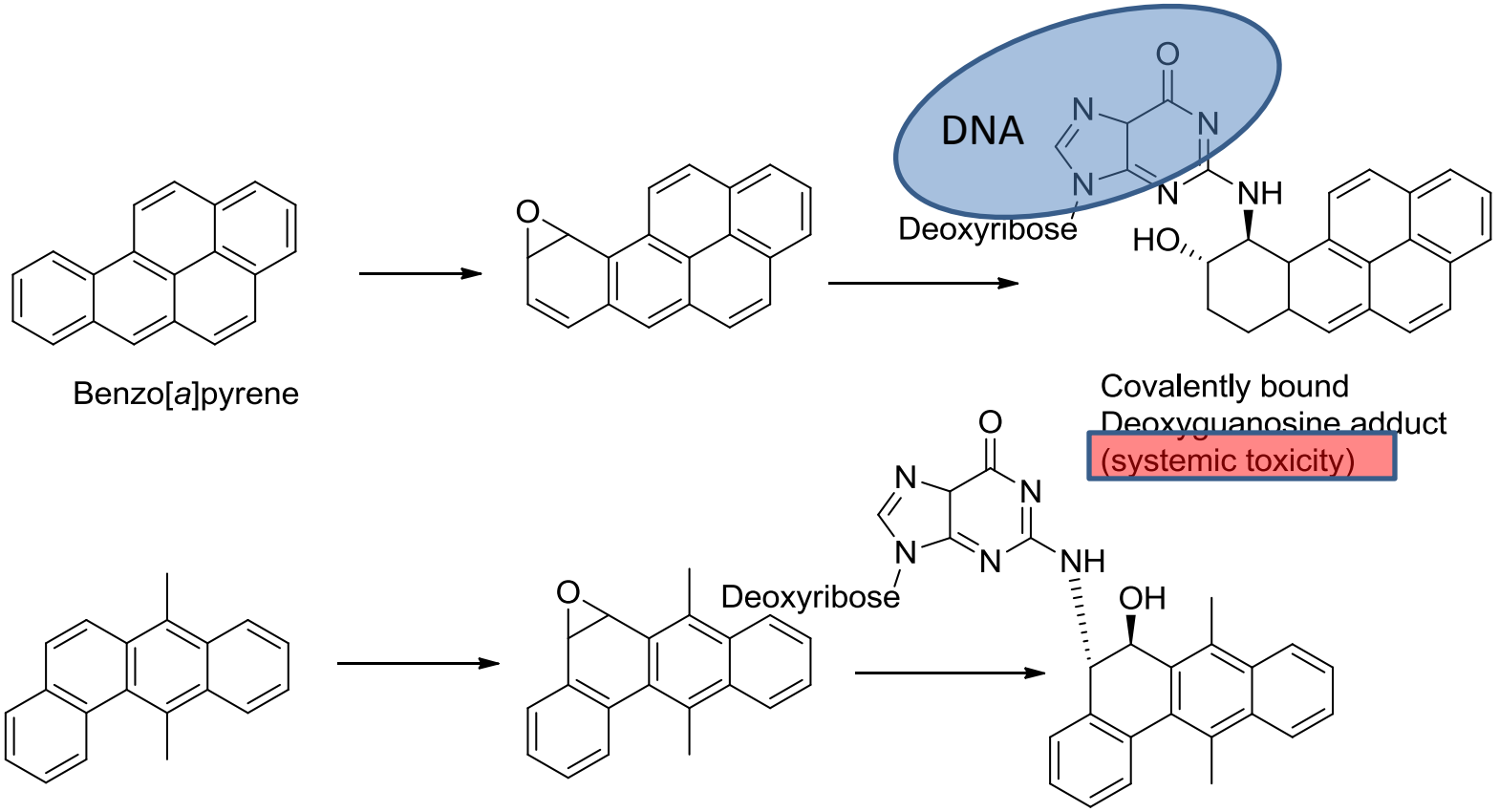
Phase-I: Functionalization Reactions

Oxidation

- **Aliphatic hydroxylation:-**
  - Mainly occur on the ultimate (ω) or penultimate (ω-1) carbon atom in the structure.
  - Also it occurs at an activated carbon atom, that is next to sp , sp^2 carbons.

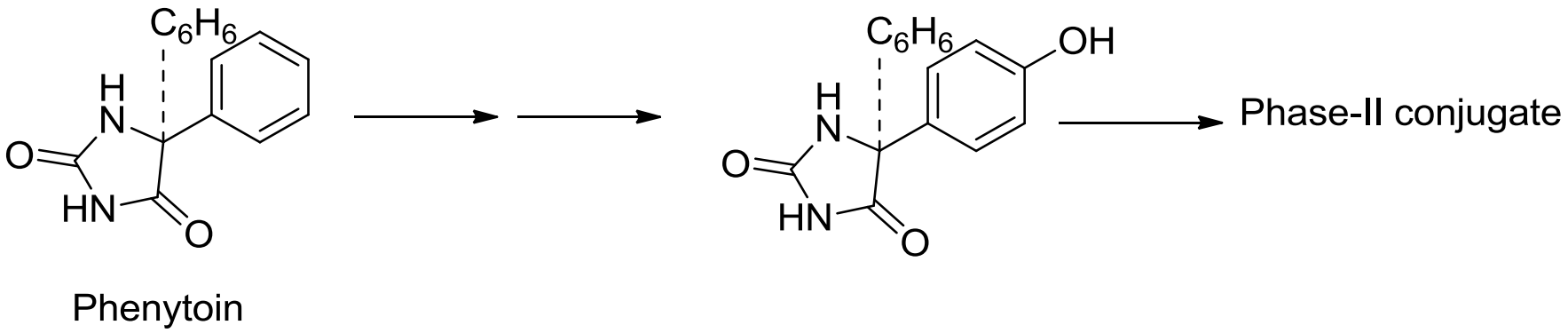


Aromatic epoxidation:-



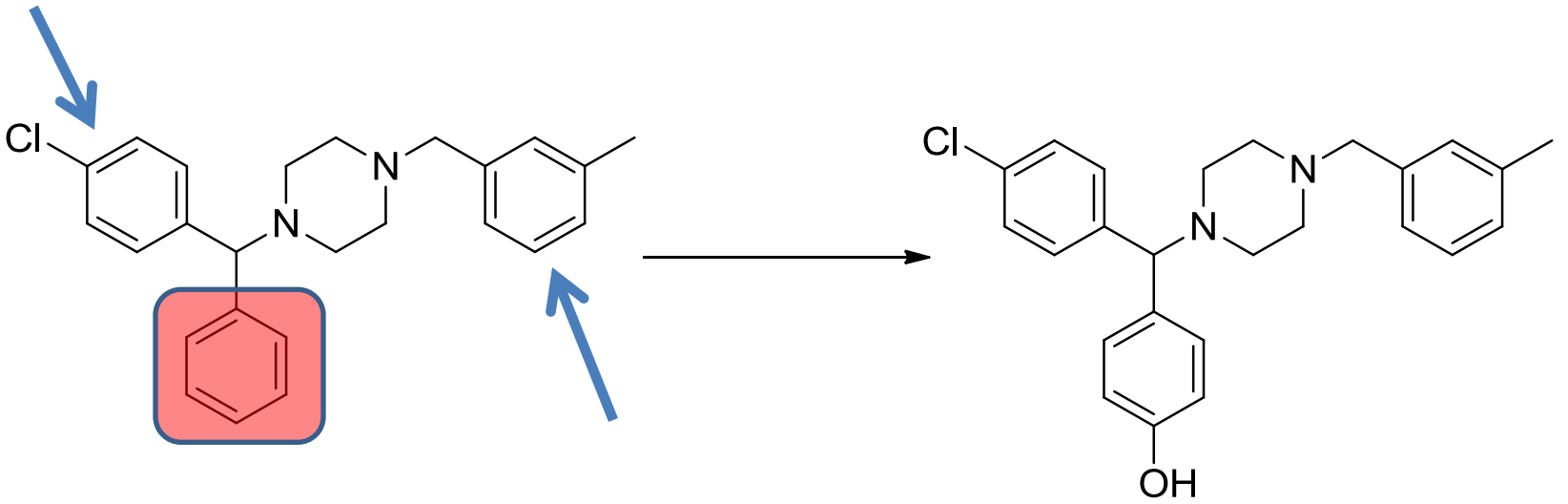
Aromatic hydroxylation:-

1. The least substituted aromatic ring will be favorably oxidized, especially at the least hindered carbon atom.
2. The activated ring will be better oxidized (the ring bearing an electron donating group).



Phenytoin

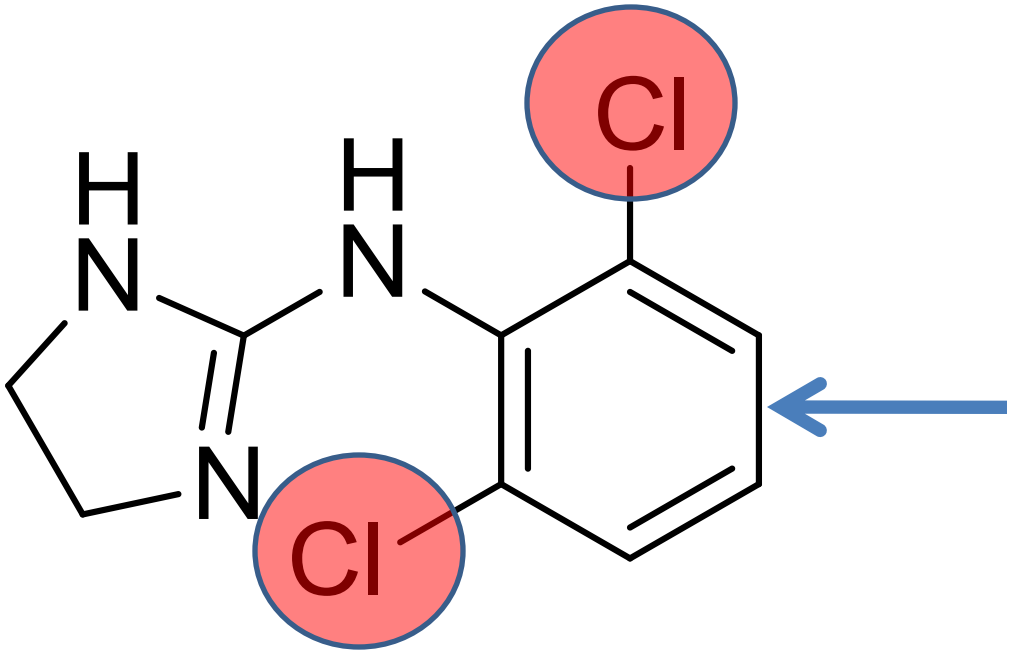
1. The least substituted aromatic ring will be favorably oxidized, especially at the least hindered carbon atom.



Meclizine
Antiemetic agent

Major metabolite

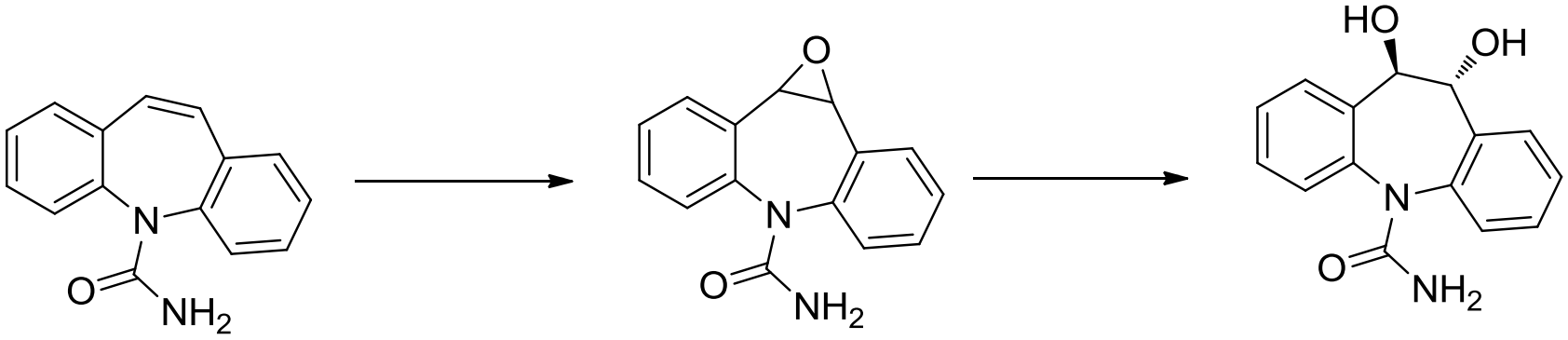
2. The activated ring will be better oxidized (the ring bearing an electron donating group)



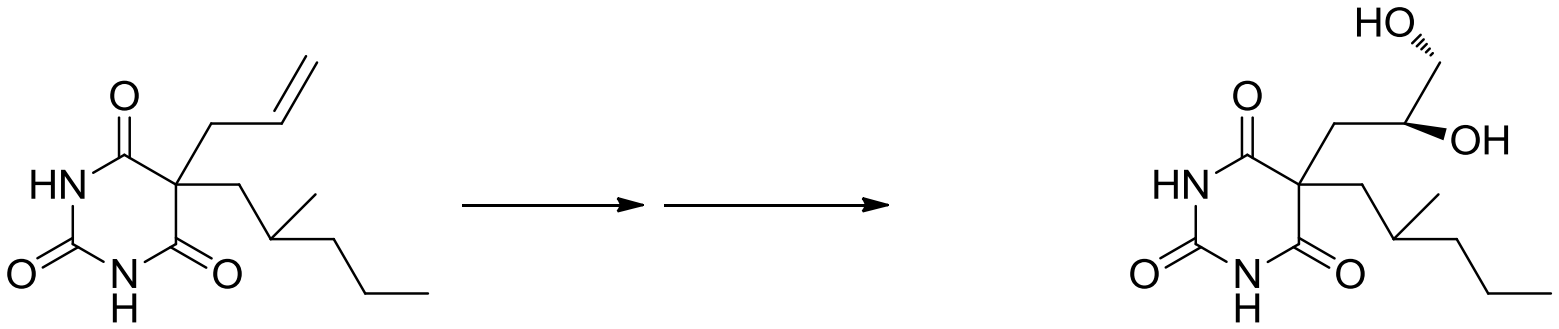
No aromatic hydroxylation

Clonidine

- Alkene oxidation or epoxidation:-



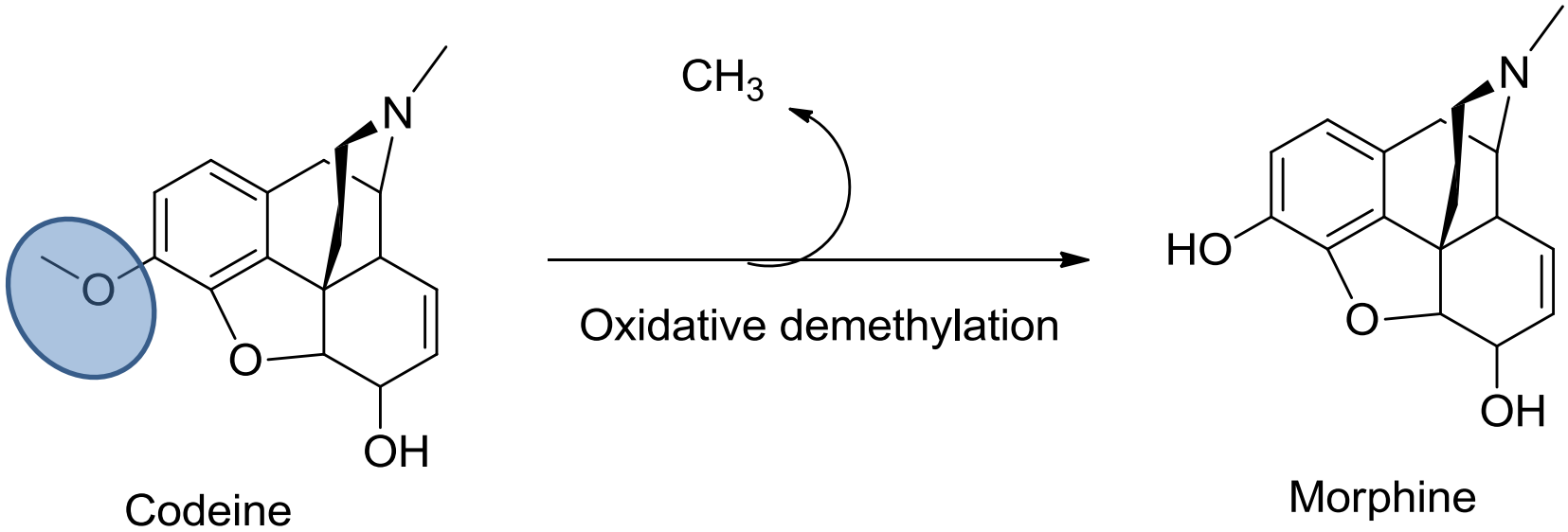
Carbamazipine



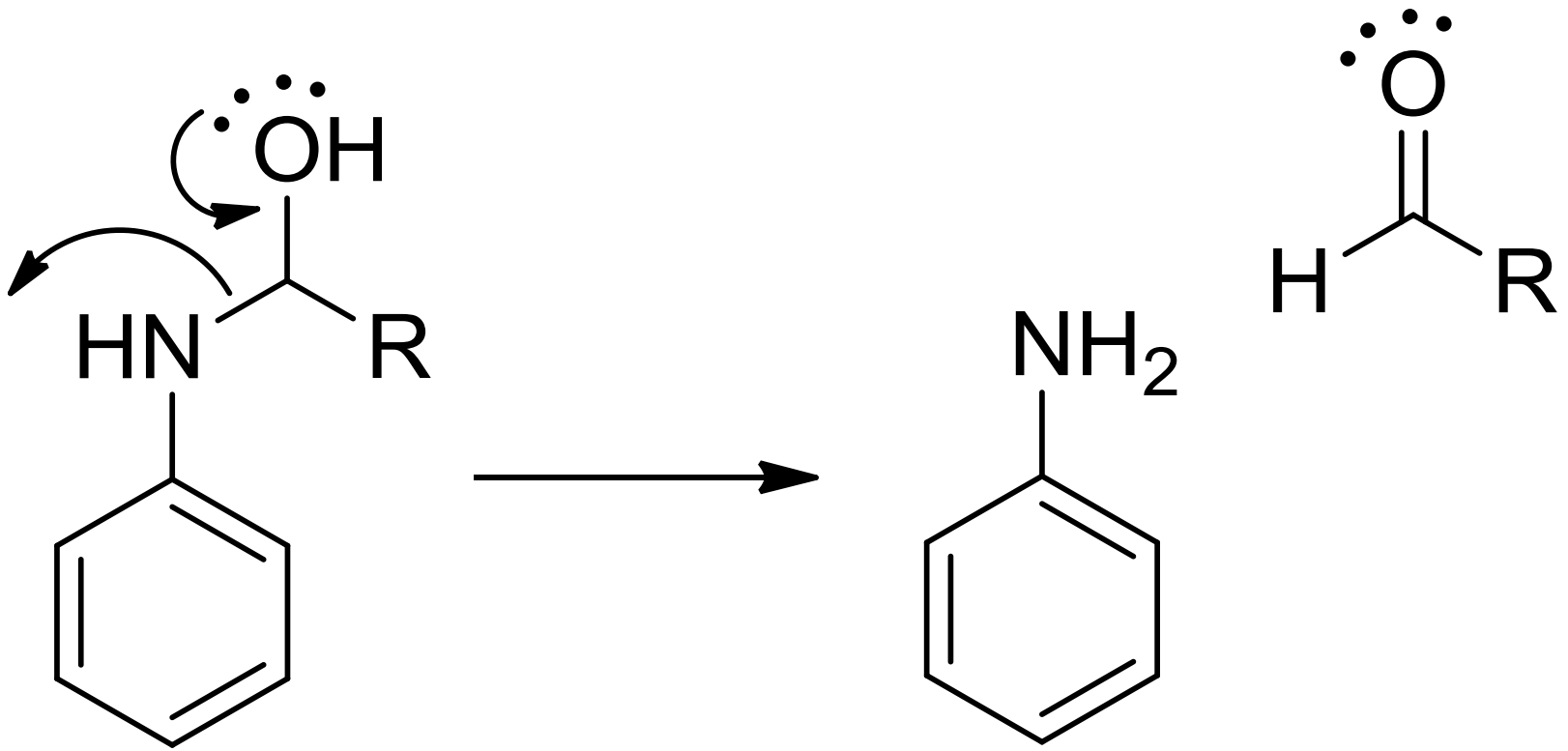
Secobarbital

Secodiol

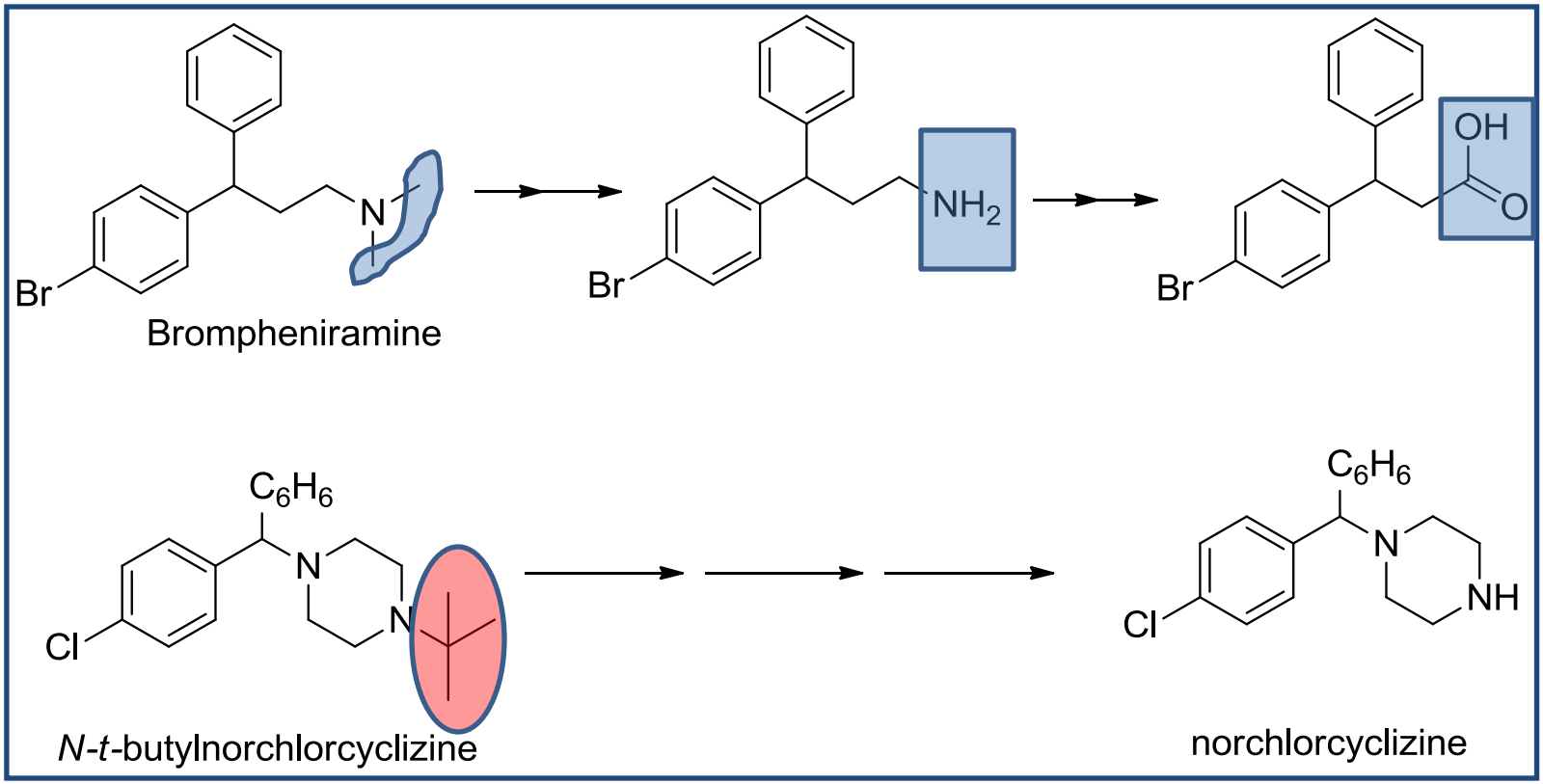
- *O*-dealkylation:-



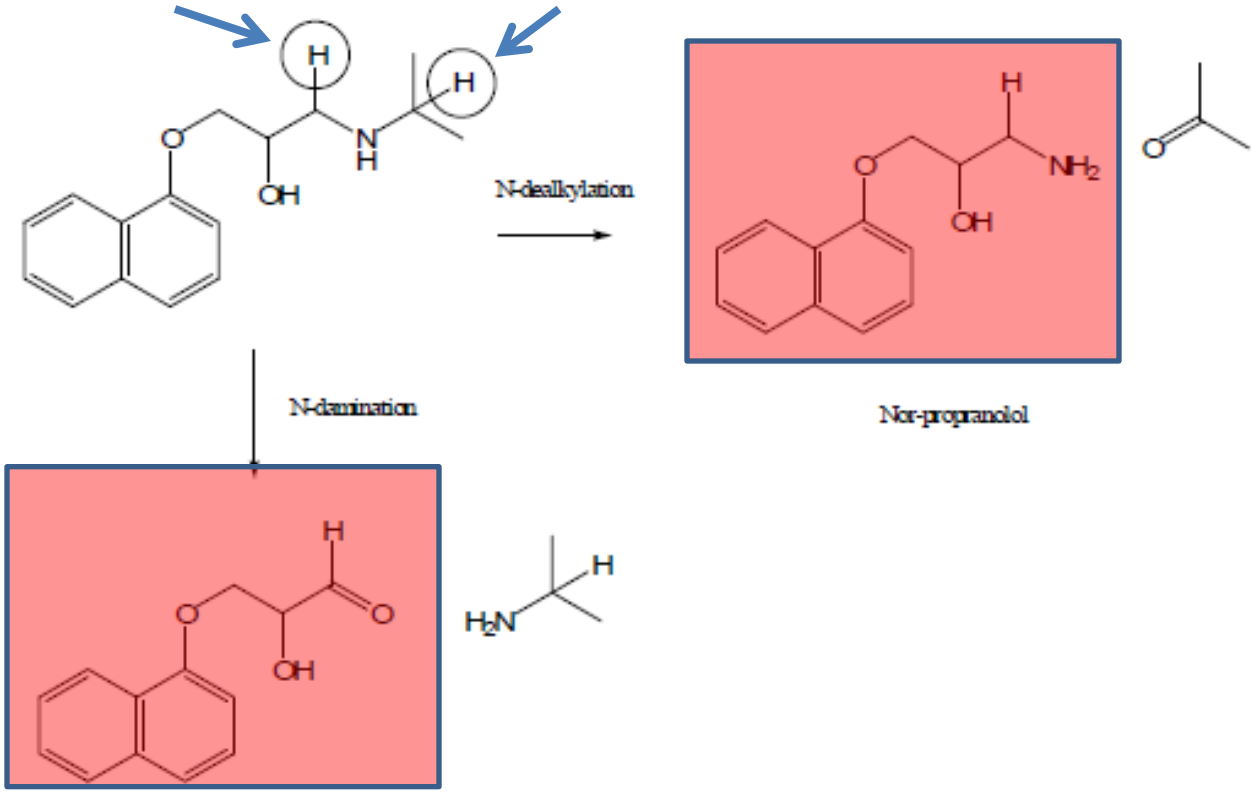
- *N*-dealkylation:-



N-dealkylation

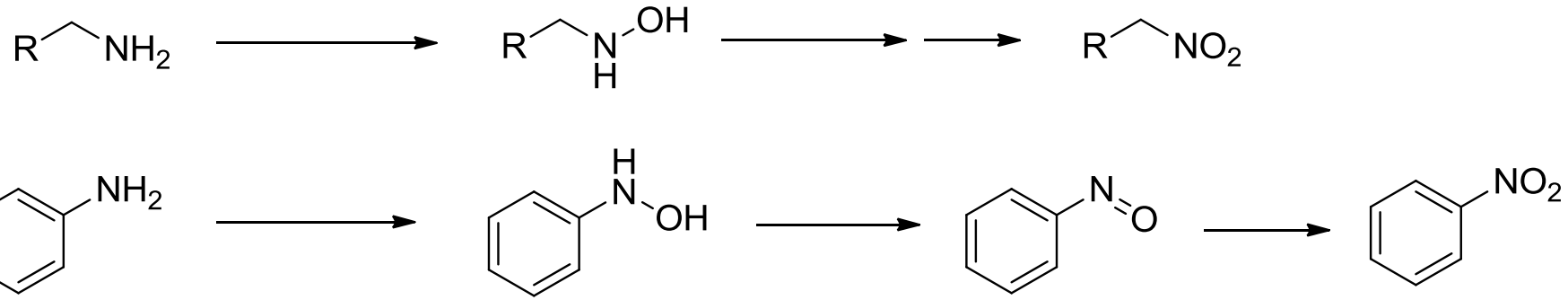


- Oxidative deamination:-

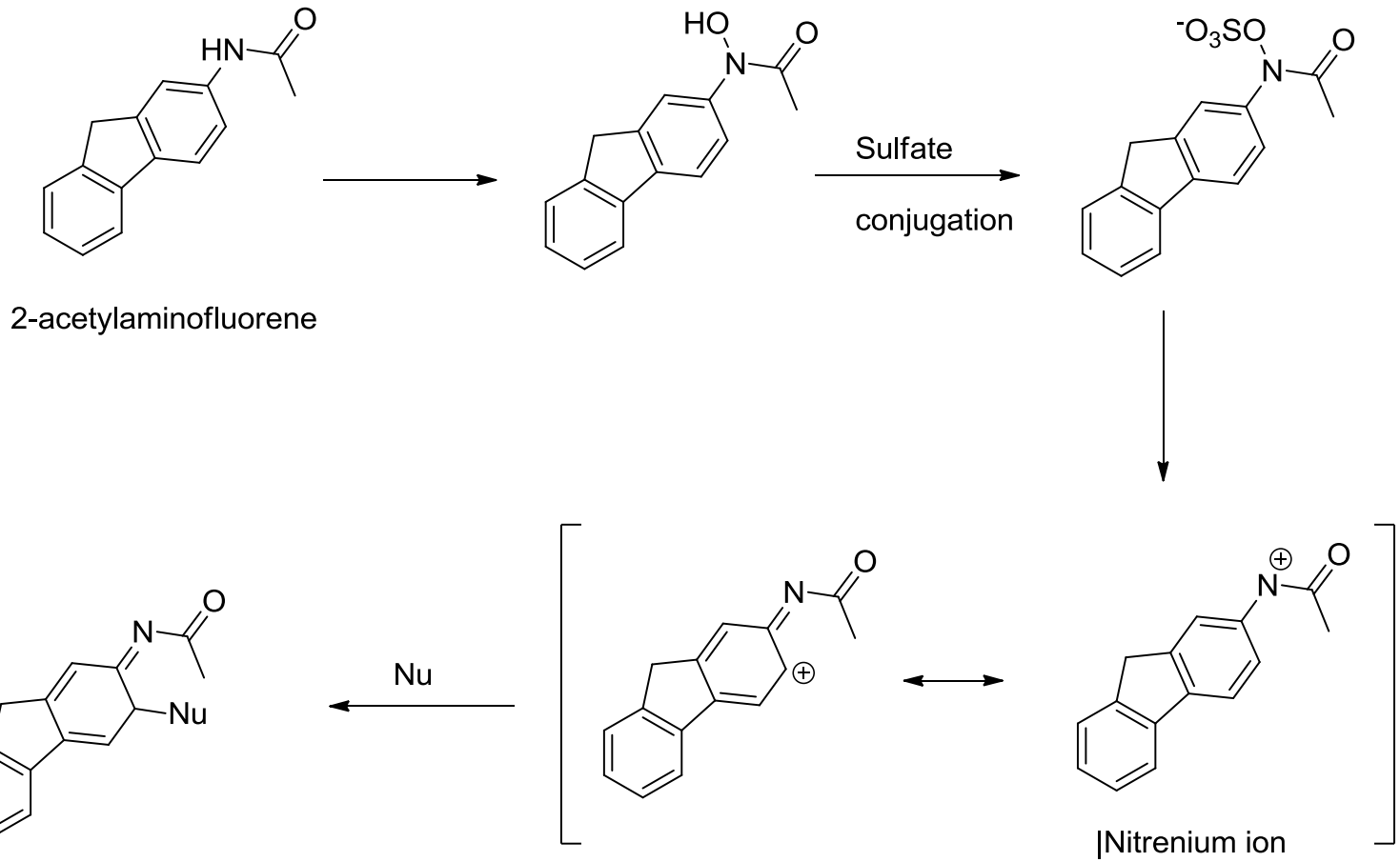


Nor-propranolol

- *N*-oxidation:-
  - Mostly for primary and secondary amines as well as aromatic amines:
  - This gives N-oxide that will be rapidly converted to hydroxylamines.

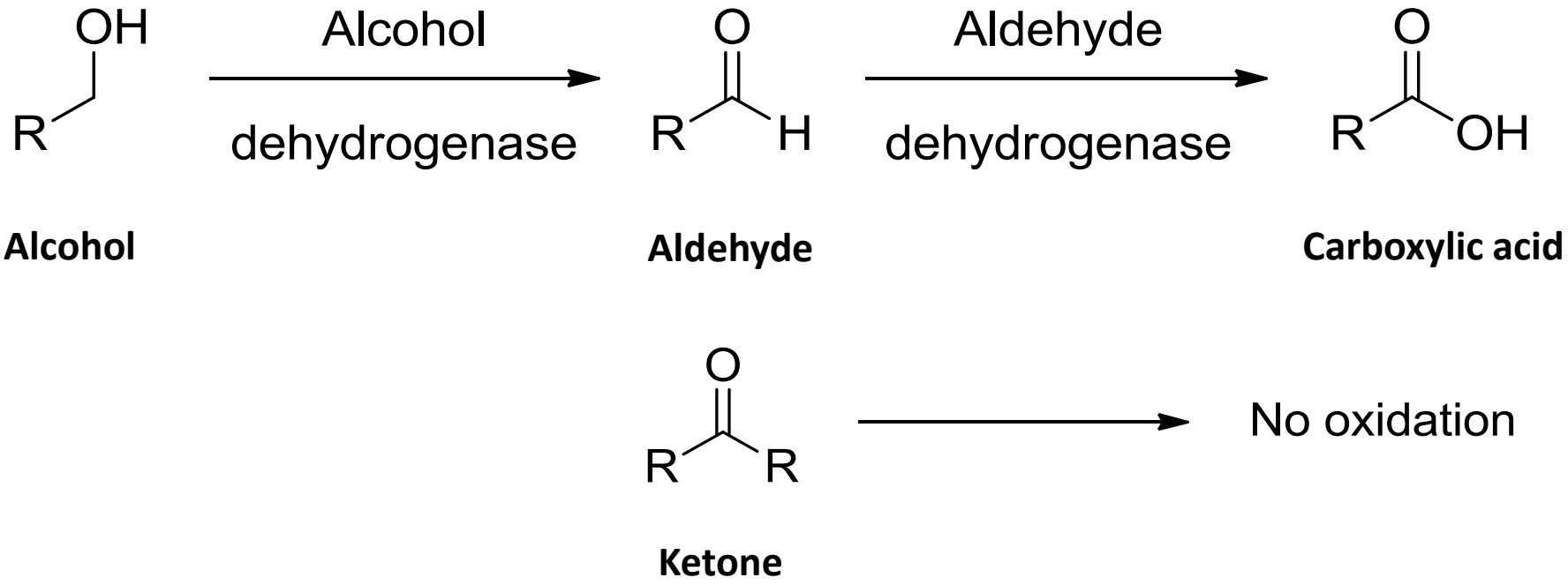


N-oxidation:-


HN
O
HO
N
O
Sulfate
conjugation
$^{-}O_3SO$
N
O
2-acetylaminofluorene
N
O
Nu
Nu
N
O
N
O
|Nitrenium ion

Oxidation of alcohols and aldehydes:-

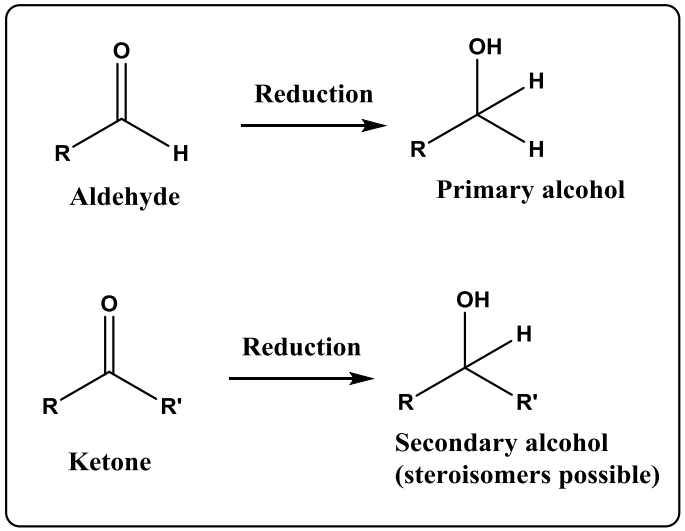
- Alcohol dehydrogenase and aldehyde dehydrogenase enzymes are involved.



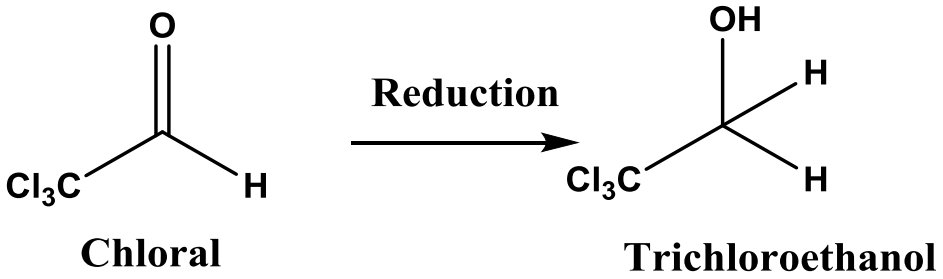
Reduction

Bioreduction of carbonyl compounds give alcohols, whereas the azo or nitro reduction lead to amines.

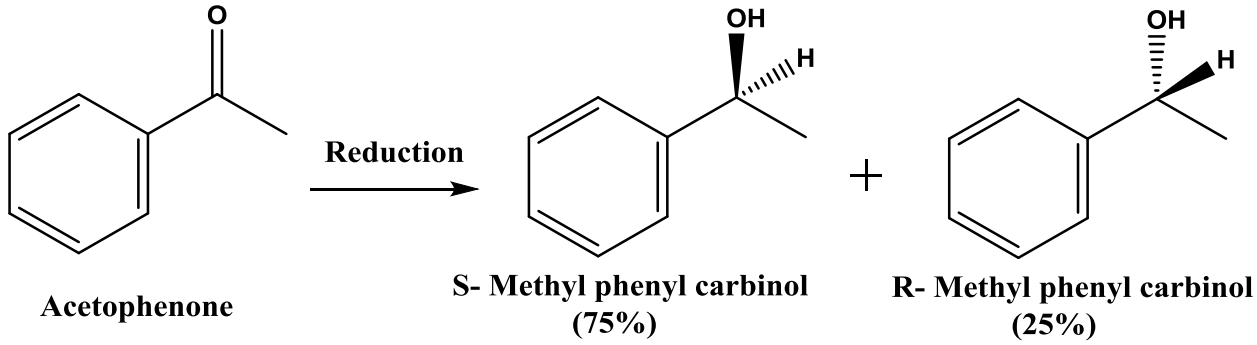
Reduction of aldehydes and ketones



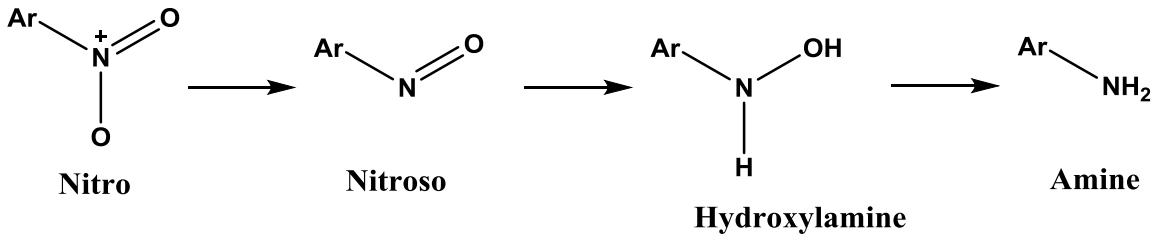
Example of aldehyde containing drug

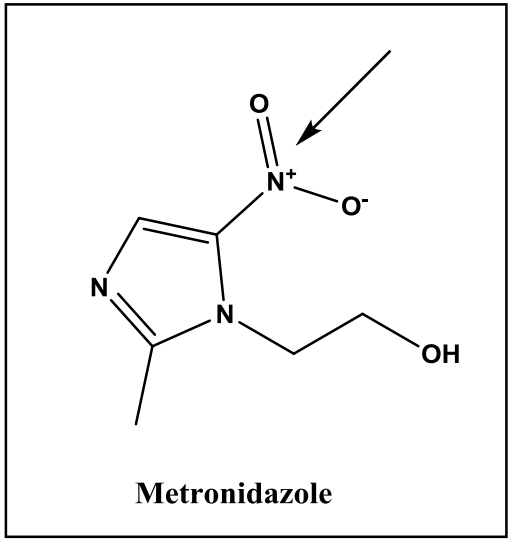


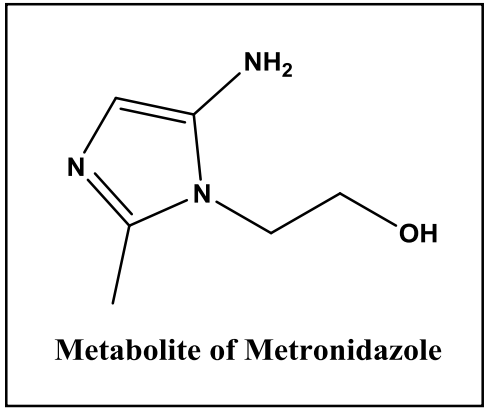
Example of Ketone containing compound



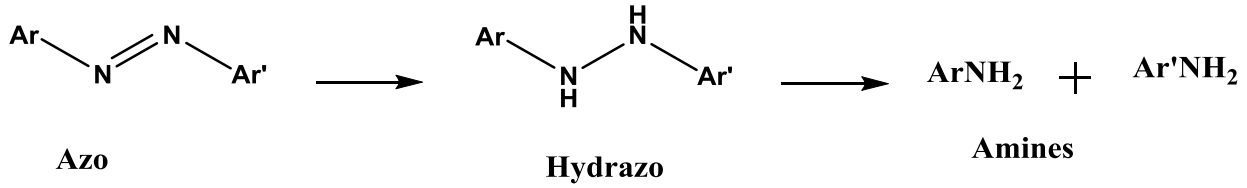
Reduction of Nitro containing compounds

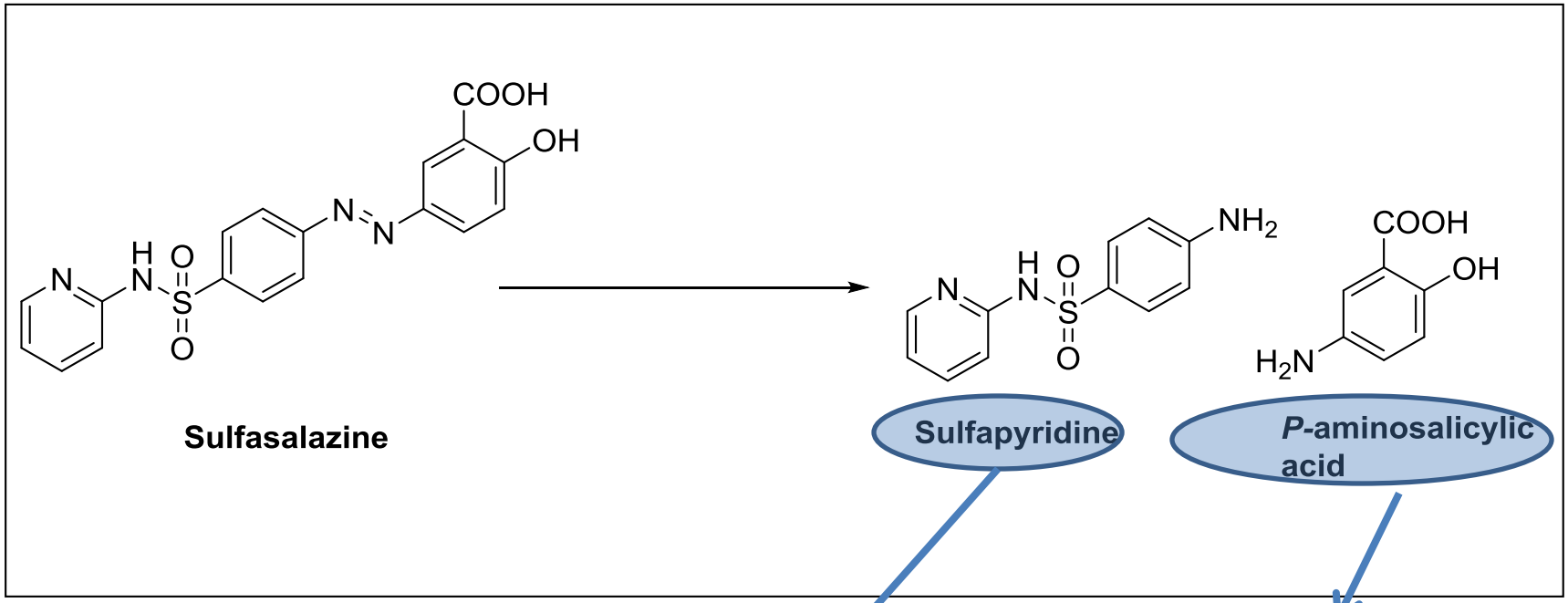






Reduction of Azo containing compounds





Hydrolysis

- By non-specific esterase and amidase enzymes present in plasma, gut, liver and kidney.

- It has a beneficial role in most of the prodrugs that after hydrolysis inside the body release the active form of the drug.

- Hydrolysis is a major biotransformation pathway for drugs containing an ester or an amide functionality.

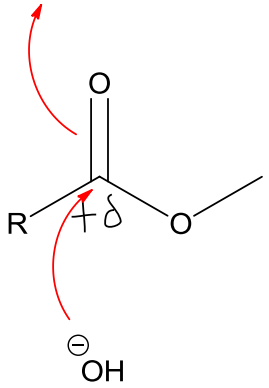
Ester Vs Amide

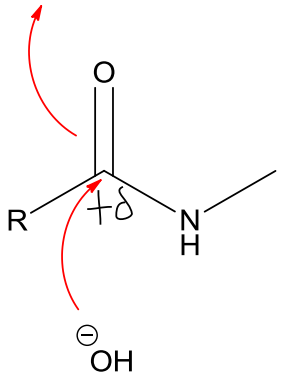
Ester bond is relatively weaker than amide bond, and rapidly hydrolyzed by esterase enzyme.

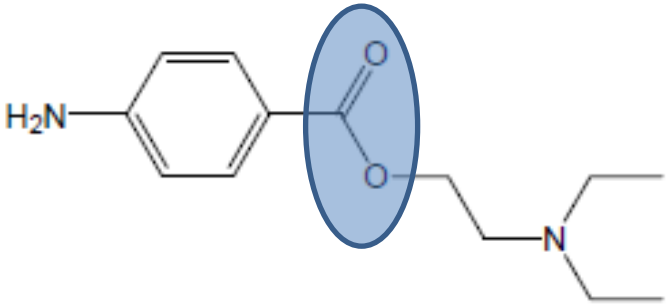
The reactivity of ester and amide bond depends on how much the carbonyl carbon is electropositive.

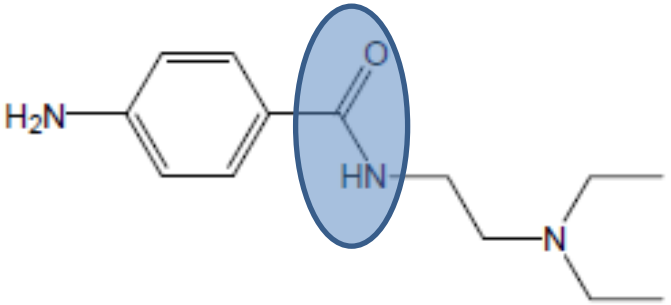
Nitrogen atom is less electronegative than oxygen, so it will be weaker electron withdrawing atom.
therefore, the carbonyl carbon attached to oxygen atom will be more electropositive, and more reactive towards nucleophilic attack of water molecule during hydrolysis.

Nucleophilic attack of hydroxide anion on ester and amide









Procaine

Short acting local anesthetic

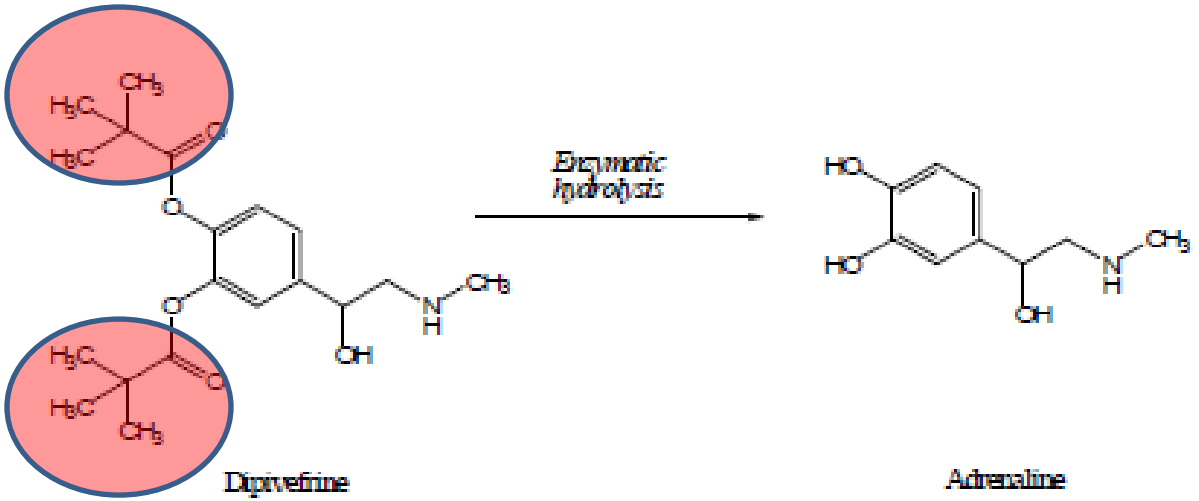
$T_{1/2}$ = 40-84 second

Procainamide

Long acting antiarrhythmic

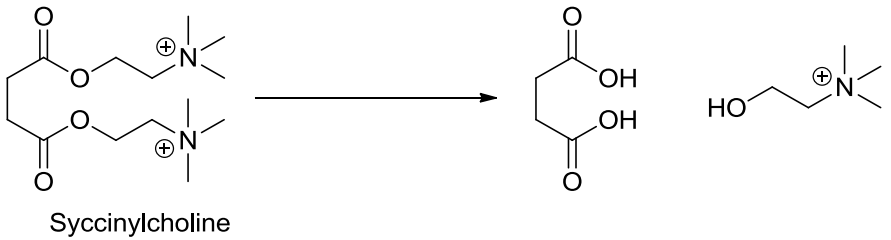
$T_{1/2}$ = 2.5-4.5 hr

Example of prodrugs activated by hydrolytic enzymes:-



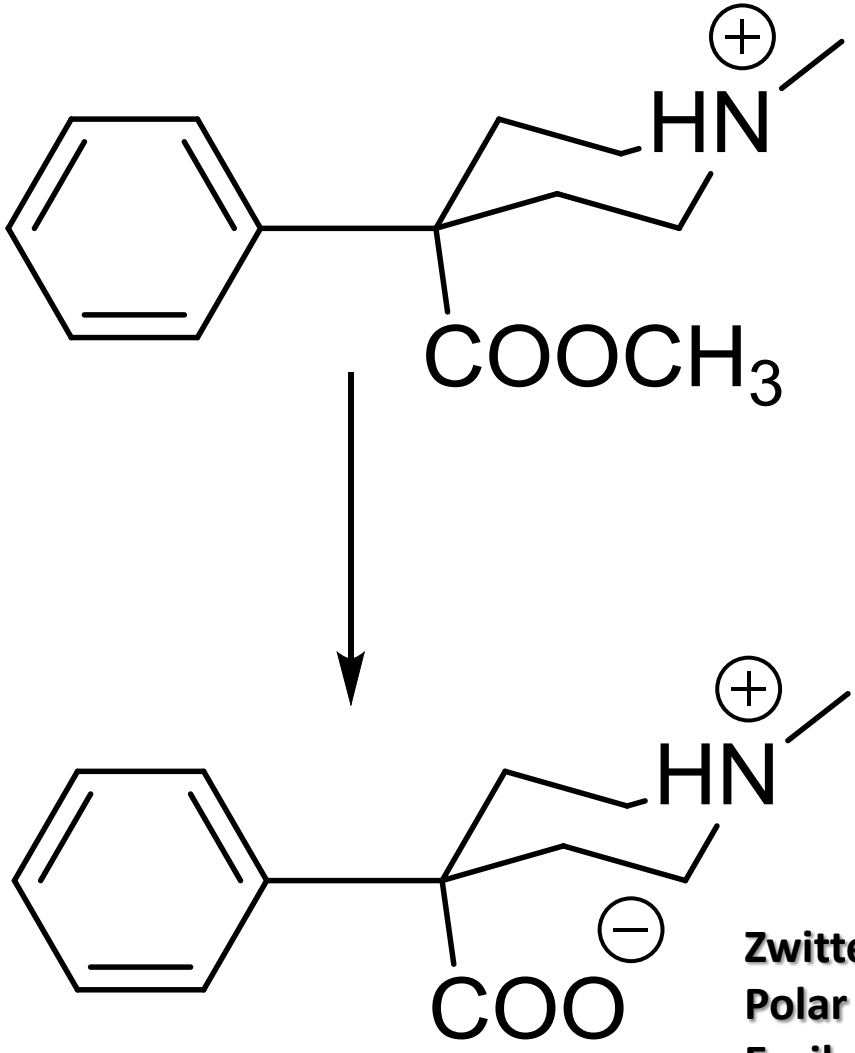
- Dipivefrine (prodrug): is a di-tertbutylcarboxy ester of adrenaline…. More lipophilic… better penetration through the corneal membrane….then will be hydrolyzed to give the active form (adrenaline) to treat glaucoma.
- Adrenaline (drug) is a polar drug….difficulty in access into the ocular cavity. Adrenaline has a generalized adrenergic effect…. Many side effects such as increases blood pressure, heart rate and bronchodilation.

- Hydrolysis normally catalyzed by carboxy-esterases:-
  - Cholinesterase…. Hydrolyzes choline-like esters (such as succinylcholine), procaine and acetylsalicylic acid.



Syccinylcholine

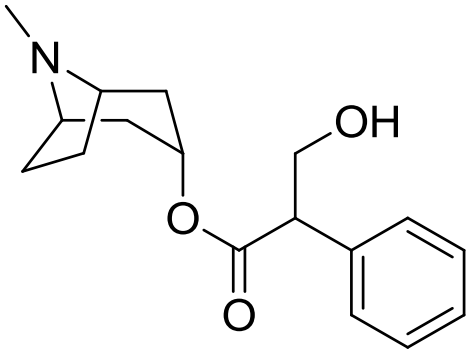
  - Aryl carboxyesterase
  - Liver carboxyesterase



Zwitter ionic
Polar
Easily excreted

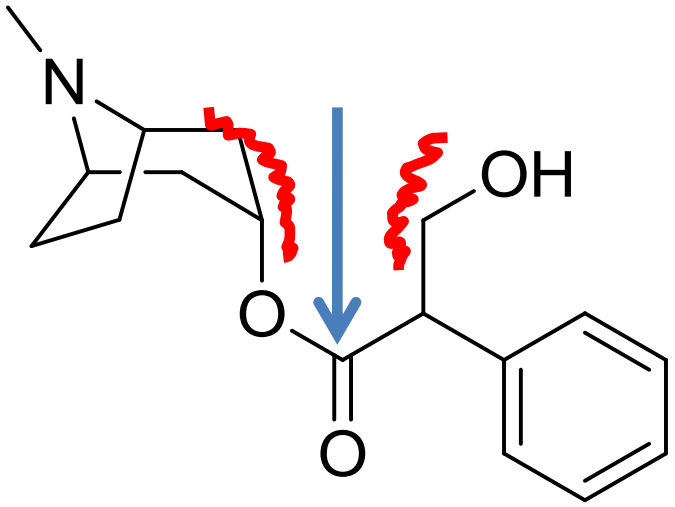
Pethidine Drug

- Esters that are sterically hindered are hydrolyzed more slowly and may be appeared unchanged in urine.



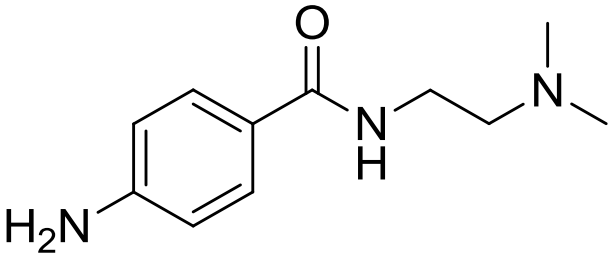
Atropine

50% excreted unchanged in urine



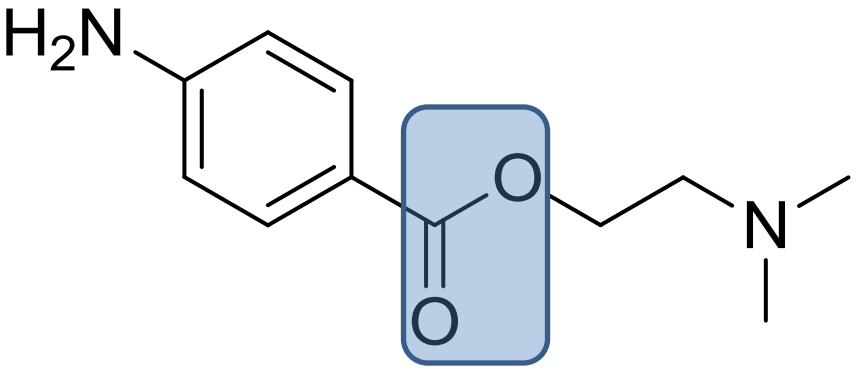
Atropine

- Amides are more stable to hydrolysis than esters….large fraction of amide containing drugs are normally excreted unchanged.

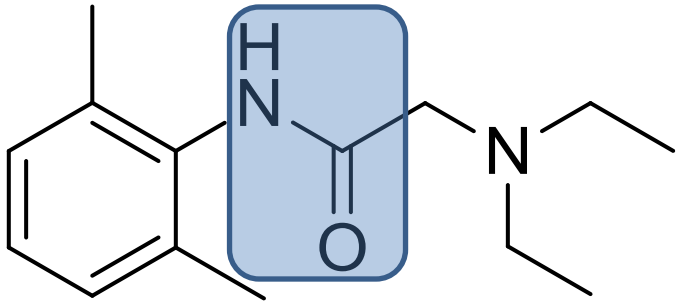


Procainamide

60% excreted unchanged in urine



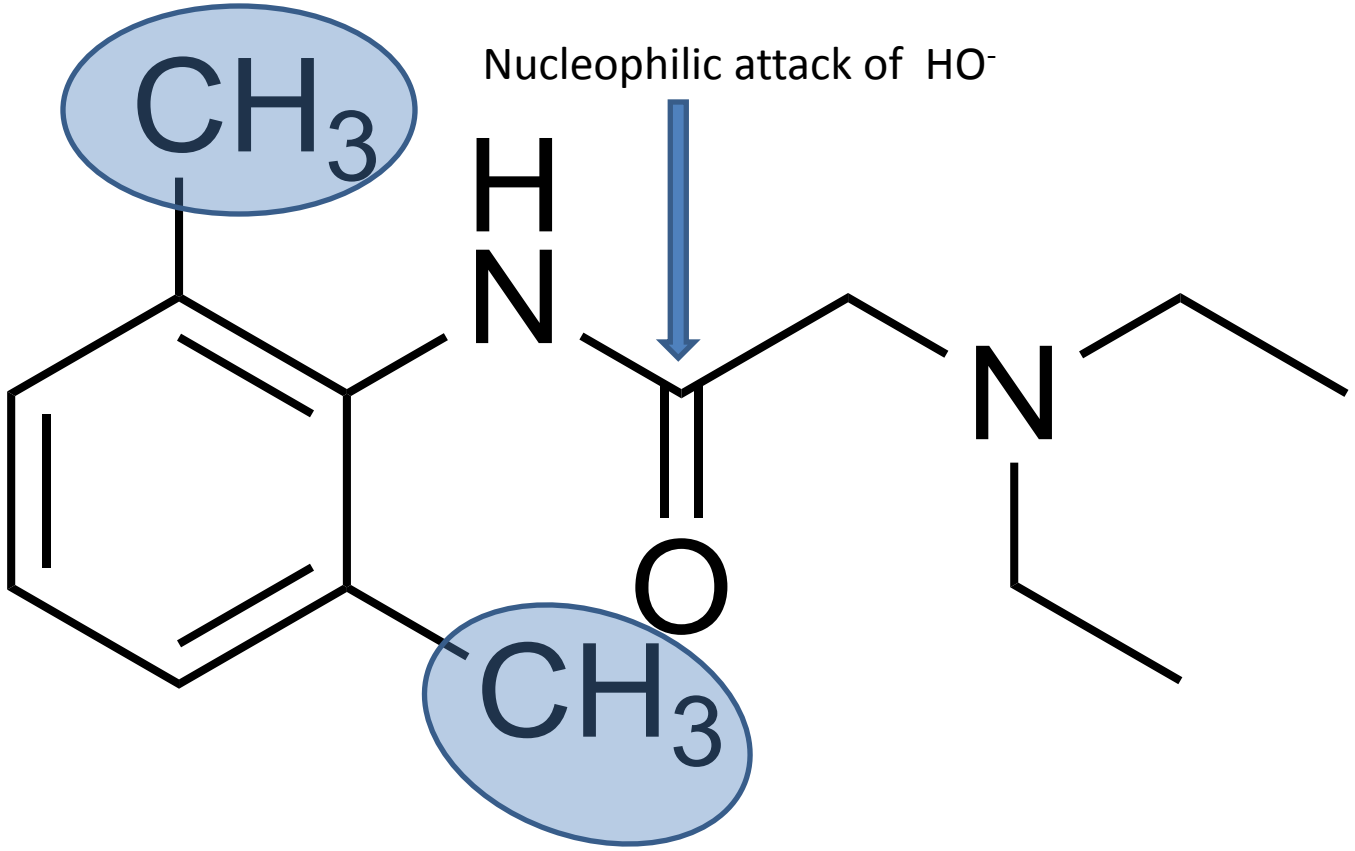
Procaine



Lidocaine

Procaine has a short duration of anesthesia

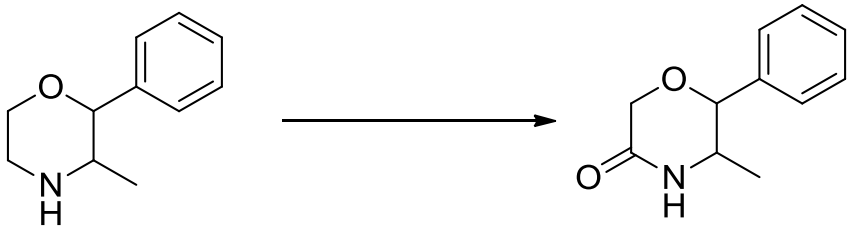
lidocaine has a long duration of anesthesia



Lidocaine

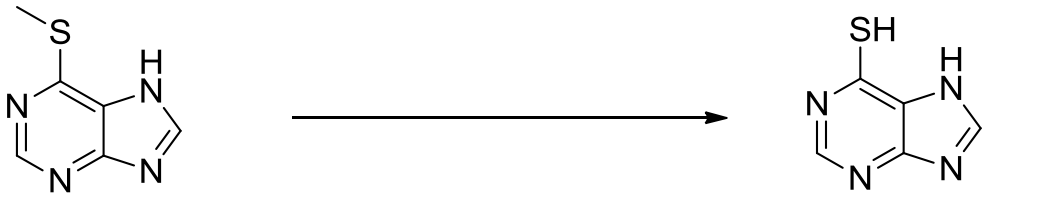
Other Phase-I Reactions

- Heterocyclic ring oxidation:-



Phenmetrazine

- S-dealkylation:-

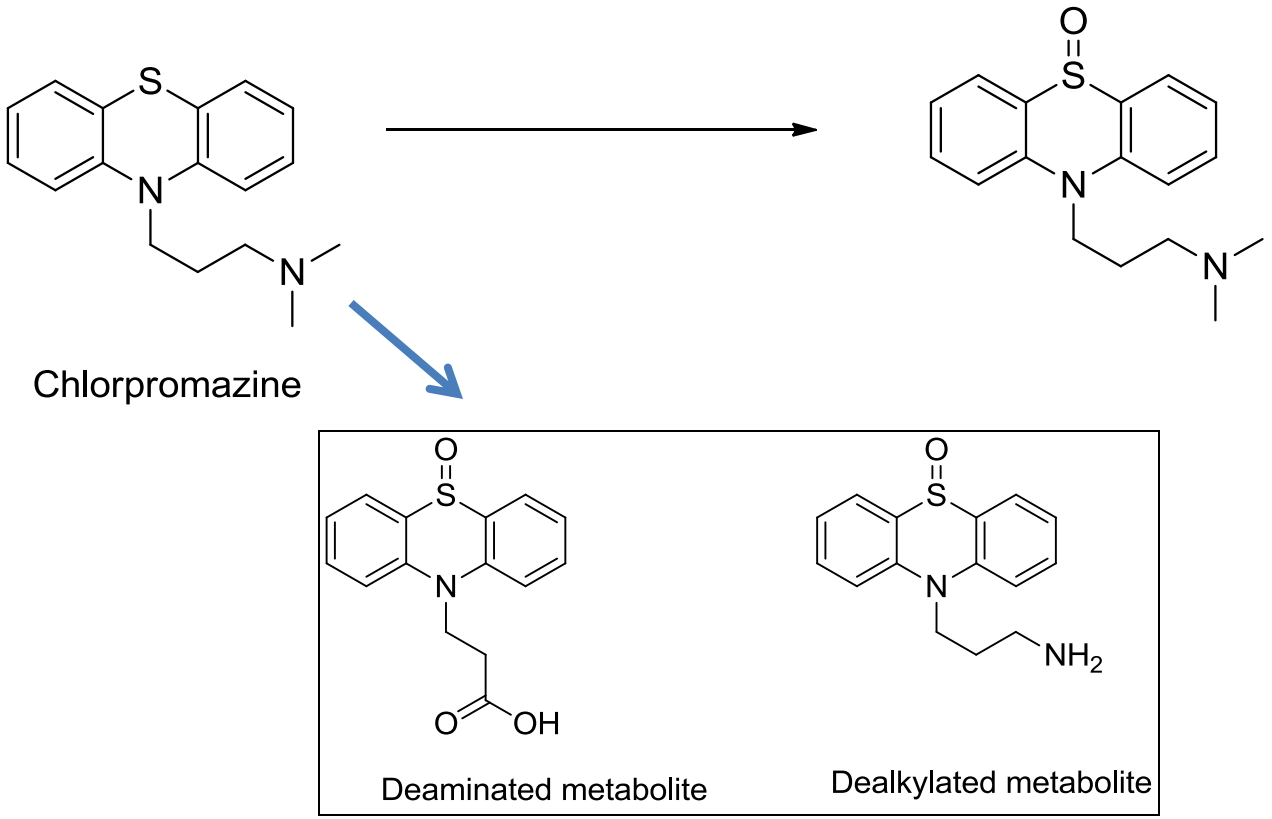


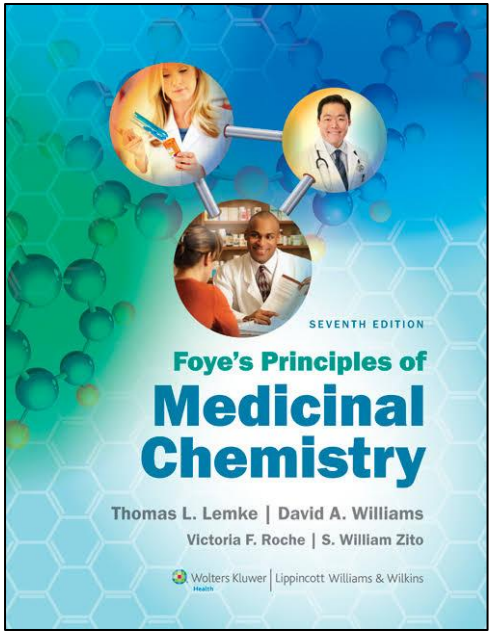
6-methylmercapropurine

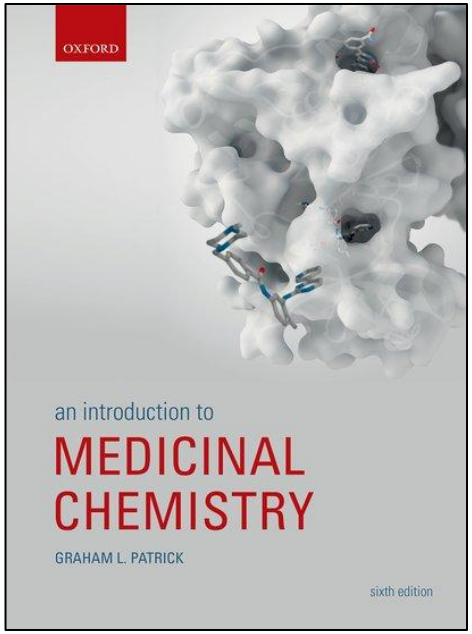
6-mercapropurine

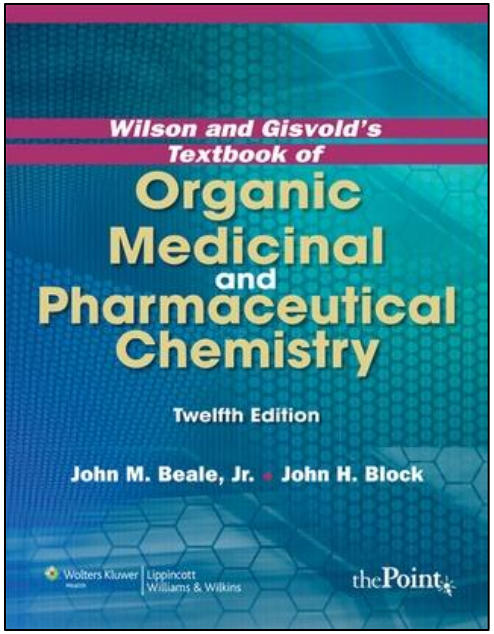
Other Phase-I Reactions

- Sulfoxidation:- By flavin monooxygenase









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Thank
You