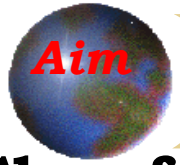
Drug Metabolism (Biotransformation)

- **Drug metabolism is the chemical reactions that are responsible for the conversion of drugs into other products within the body before and after they have reached their sites of action.**

- **Almost all of these reactions are catalyzed by enzymes and so they will exhibit the general characteristics of enzyme-controlled processes.**

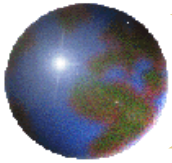
The amount of drug reaching the receptor site depends upon how much of the drug is metabolized before it reaches its site of action.

Drug metabolism is useful in both:
Design of new drugs and development of the existing drugs



The function of biotransformation is conversion of foreign compounds (Xenobiotics) into water-soluble derivatives, which can easily excreted

Xenobiotics are foreign compounds enters to the body such as drugs, pesticides, insecticides, industrial chemicals, pollutants, etc.



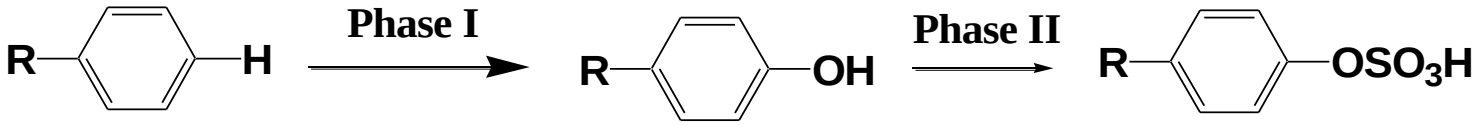
Drug metabolism

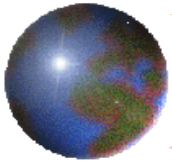
- **Phase I**
  (Asynthetic route)
  Functionalization reactions
- **Phase II**
  (Synthetic route)
  Conjugation reactions

Both types produce metabolites that are more water soluble, more easily excreted than the original drug.

Phase I: will introduce more water soluble functional groups like –COOH, NH_2, and SO_3H. Or unmasking polar water-solubilizing group by reaction like hydrolysis.

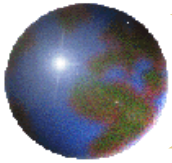
Phase II: The polar groups created in phase I serves as an anchor point for the second metabolic step, where conjugation reactions occur linking an endogenous solubilizing moiety either to the original drug (if a polar groups are already present) or to the phase I metabolite. Common solubilizing groups are glucuronic acid, various amino acids or sulphonate. The conjugate molecule is more polar and easily extracted *via* the renal route.





Drug metabolism occurs in more than one route resulting in compounds (metabolites), that are in most cases, pharmacologically inactive or in little cases pharmacologically active or harmful.

In the development of new drugs, it is important to document behavior of the metabolic product and its parent drug in the body.



- **Phase I metabolites are sometimes excreted prior to conjugation. On the other hand, reactions of functionalization (mainly hydrolysis and oxidation) can occur after conjugation reactions.**

- **Some small molecules like CH_3NH_2, CO_2, some thiols and thioethers are generated due to their gaseous nature can be excreted through the lungs.**

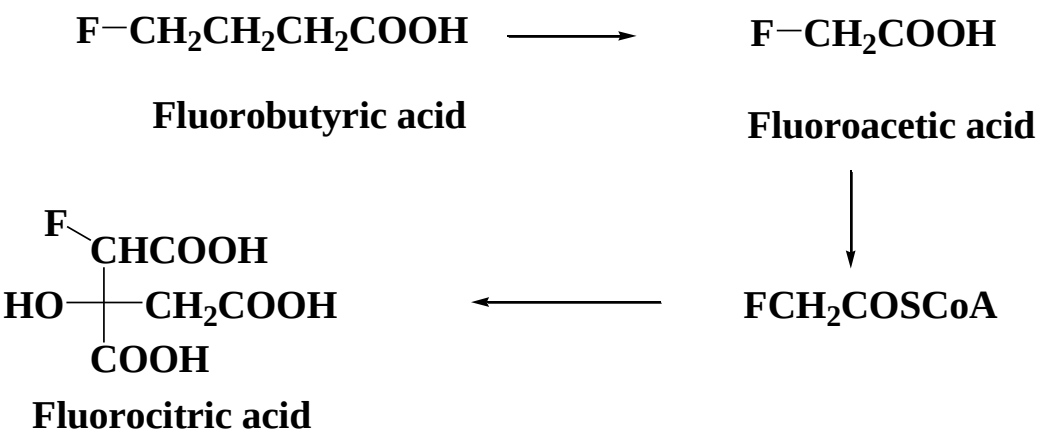
The highly polar compounds (e.g. saccharin, strong acids, strong bases) in addition to the highly lipophilic halogenated xenobiotics like insecticides are not subjected to metabolism.

•In some cases, metabolites retain their activity, which may be similar or different from the parent drug. In cases of "prodrugs", the start drug is inactive, while the metabolite is active.

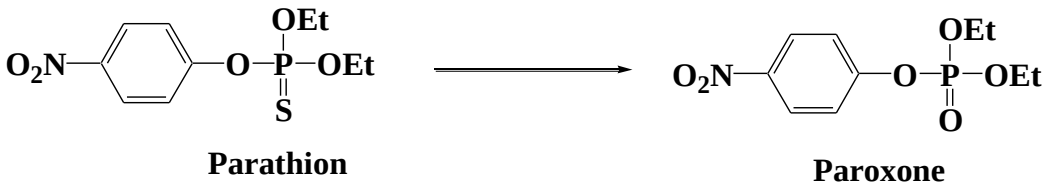
Lethal Synthesis

Some xenobiotics are metabolized to toxic metabolites, this occurs in some insecticides, pollutants and industrial chemicals not in therapeutically used drugs

Examples



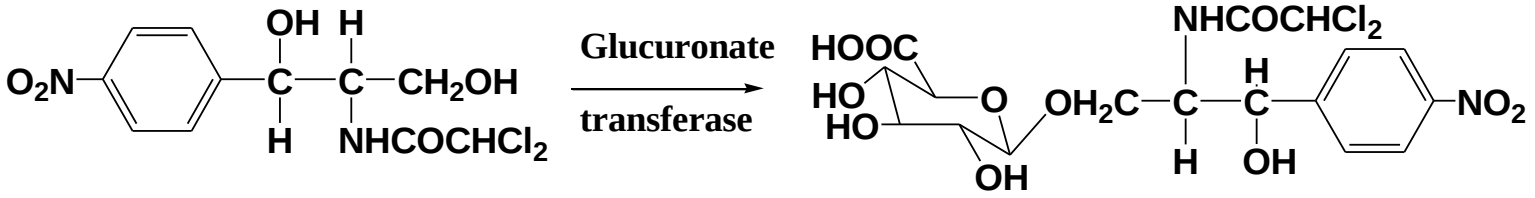
blocks the tricarboxylic acid cycle (Krebs cycle), the essential supplier of energy.



Acetylcholinesterase inhibitor

Biological Factors affecting Metabolism

1-Age

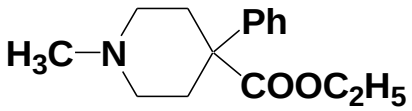


2-Gender

In diazepam

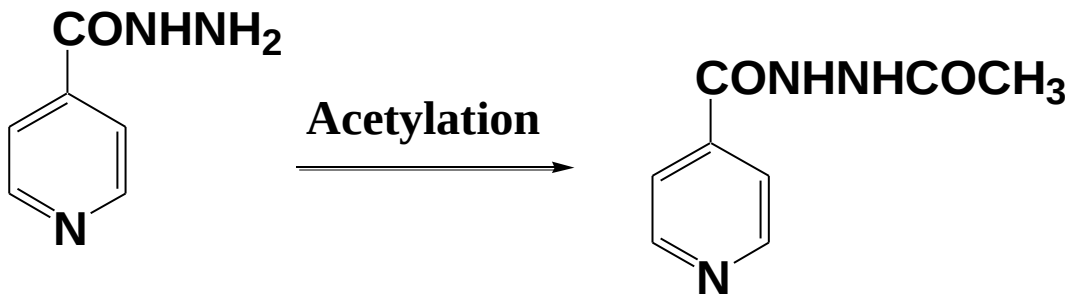
The half-life of 41.9 hr in females but only 32.5 hr in males. Why?

the women exhibit changes in the rate of metabolism of some drugs during pregnancy.e.g:



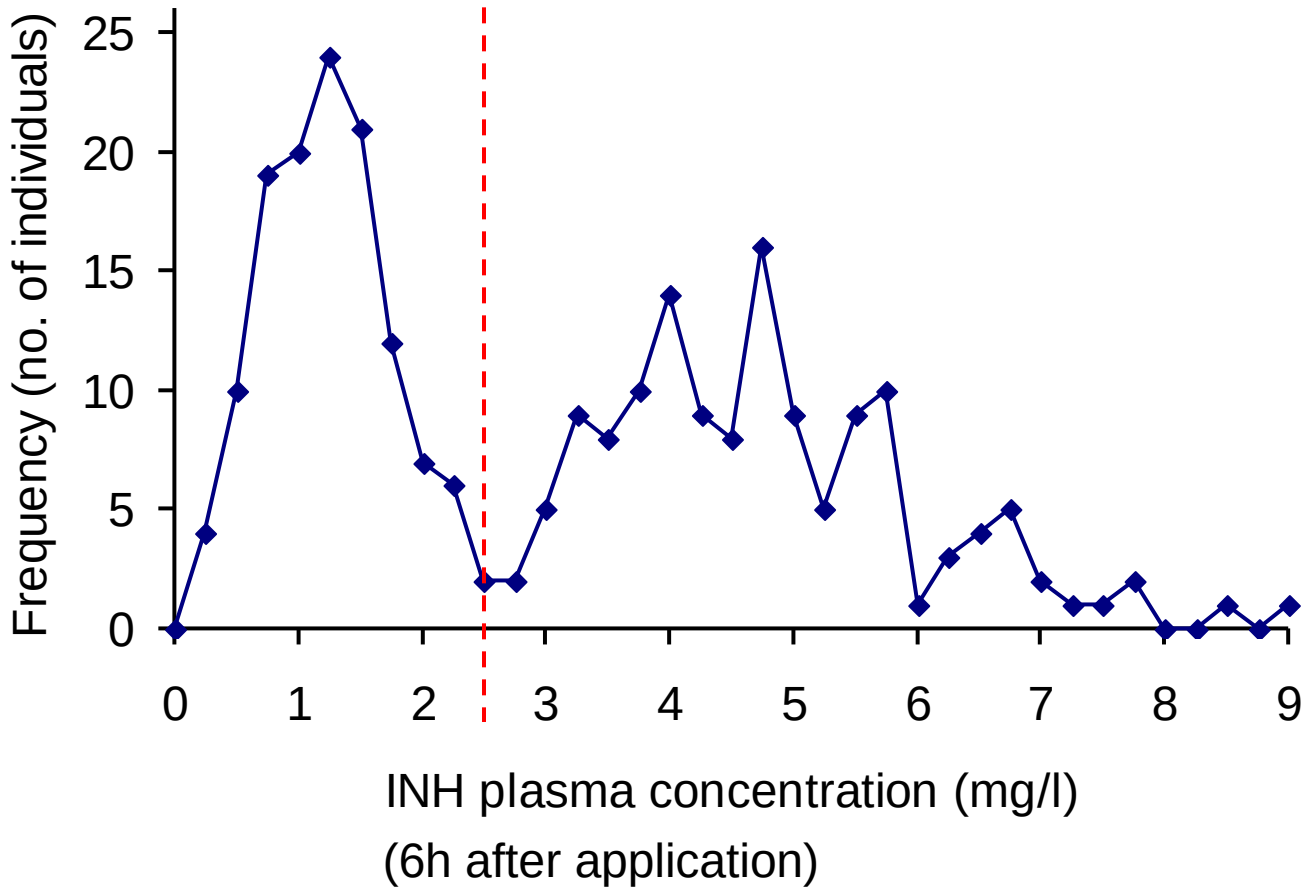
Pethidine

3-Genetic Variations



Genetic variability in INH acetylation

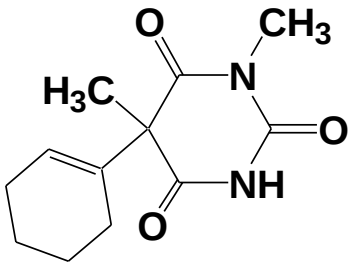
‘fast acetylators’ ‘slow acetylators’



Environmental Factors affecting Metabolism

Species and Metabolism

For instance, a dose of 50 mg/Kg body mass of hexobarbiton will anaesthetize humans for several hours but the same dose will only anaesthetize mice for few minutes.



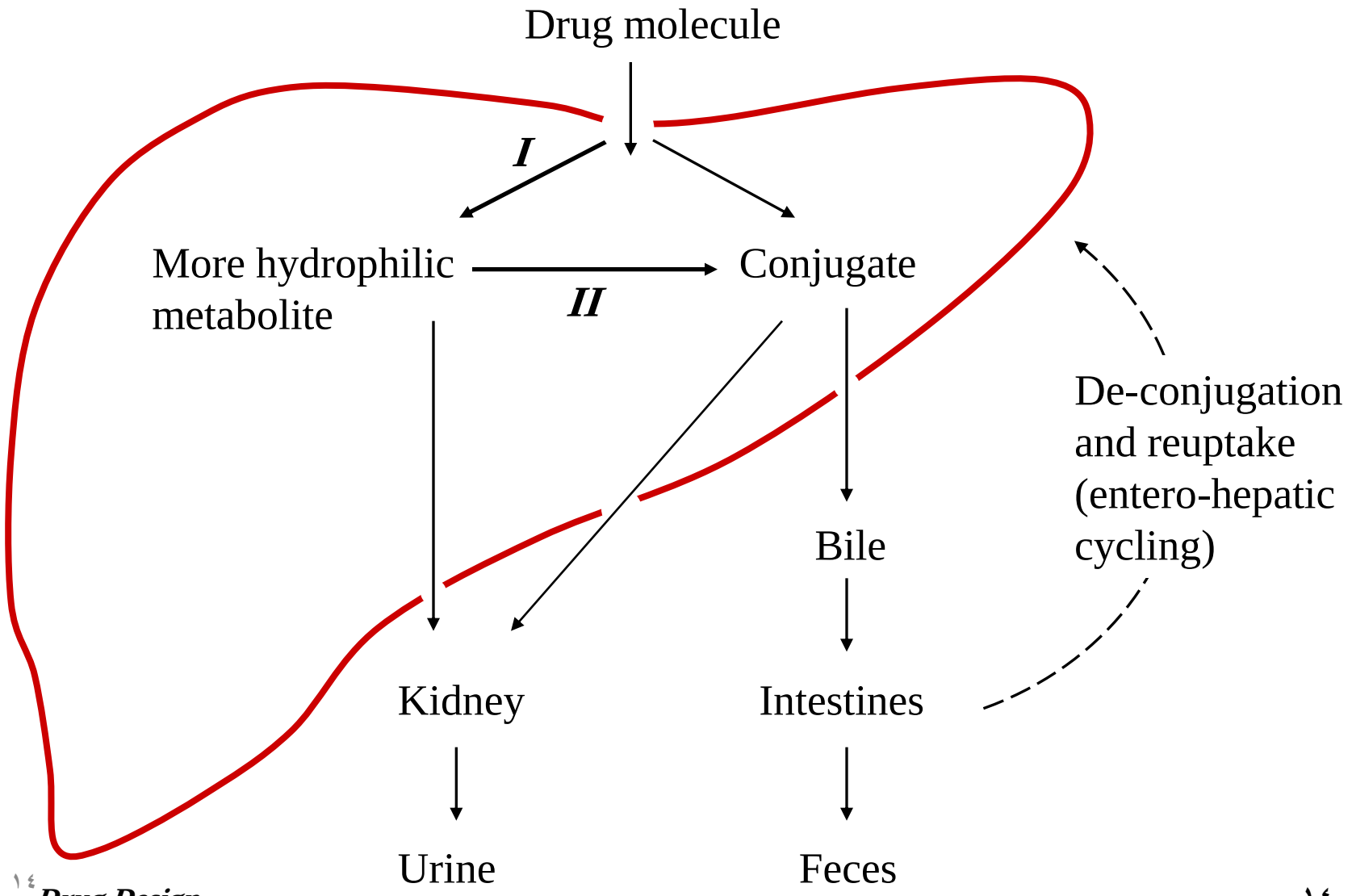
Hexobarbitone

Phase I metabolic reactions

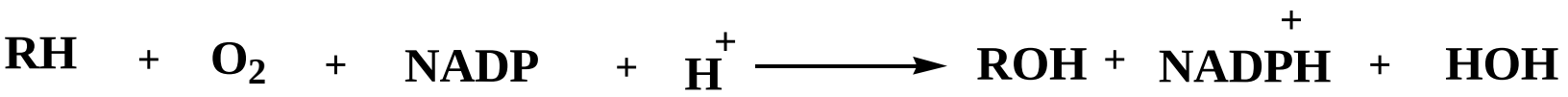
These reactions include oxidation, reduction or hydrolysis. Oxidation involves electron removal, hydrogen removal or hydroxylation. Reduction involves electron donation, hydrogenation or removal of oxygen.

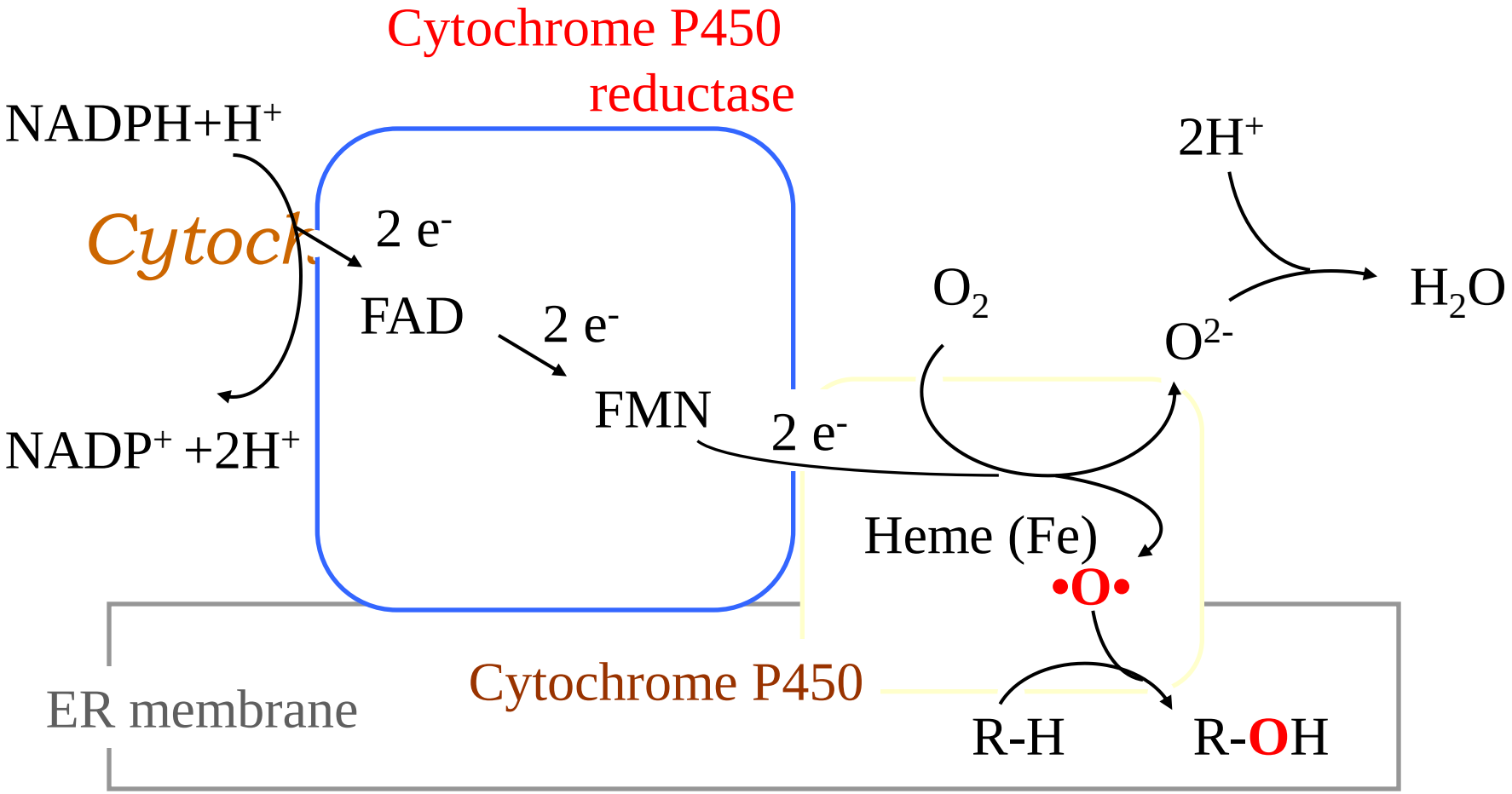
Many metabolic reactions take place in the endoplasmic reticulum of the liver cells, but other organs particularlykidney and lung also participate in drug metabolism.

Drug elimination (2): Liver

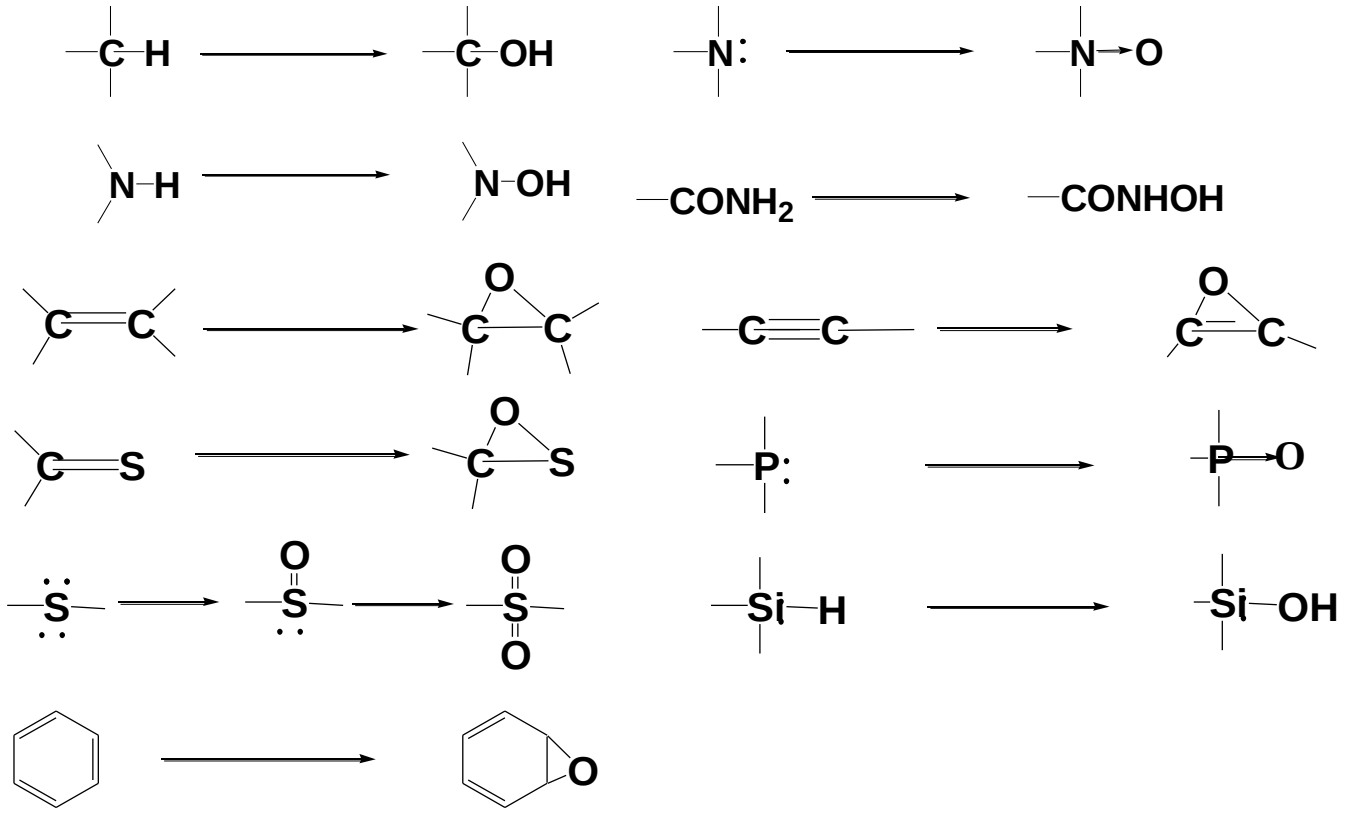


A-Oxidation catalyzed by Monooxygenase




Cytochrome P450
reductase
NADPH+H+
Cytoch
2 e-
FAD
2 e-
FMN
2 e-
NADP+ +2H+
O2
2H+
H2O
O2-
Heme (Fe)
•O•
Cytochrome P450
ER membrane
R-H
R-OH

The Oxidation reaction catalyzed by monooxygenase involves C, Si, N, P, S, Si sand others. Examples

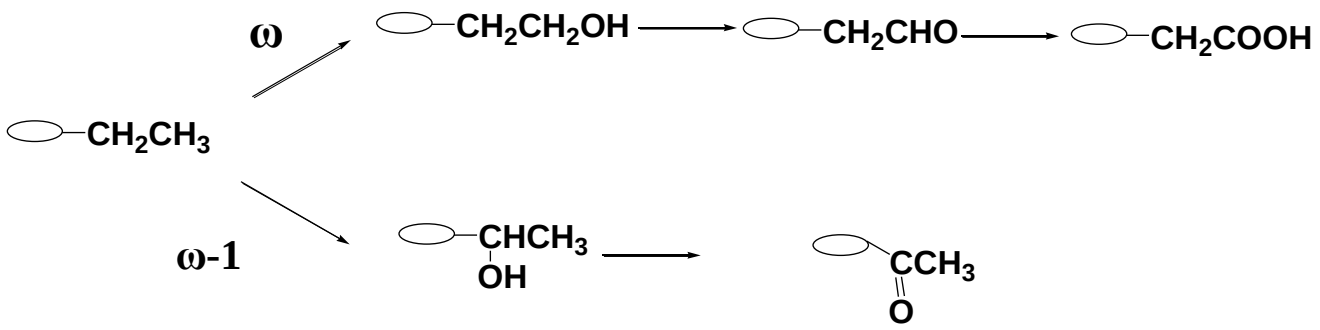


Reactions of Carbon Oxidation

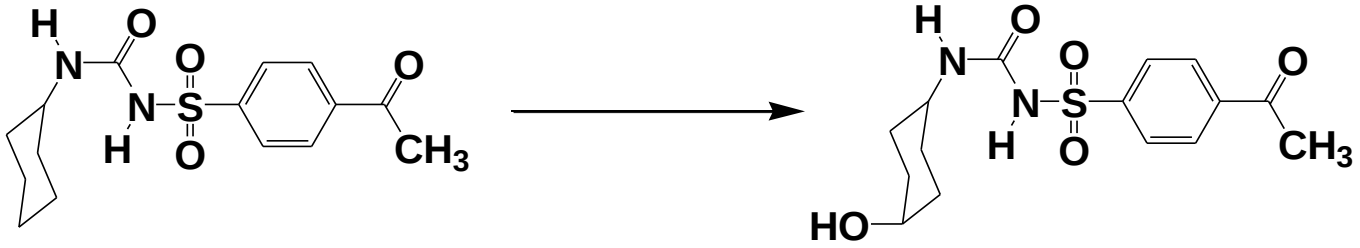
A-Hydroxylation of Saturated Aliphatic C-atoms

Alkanes

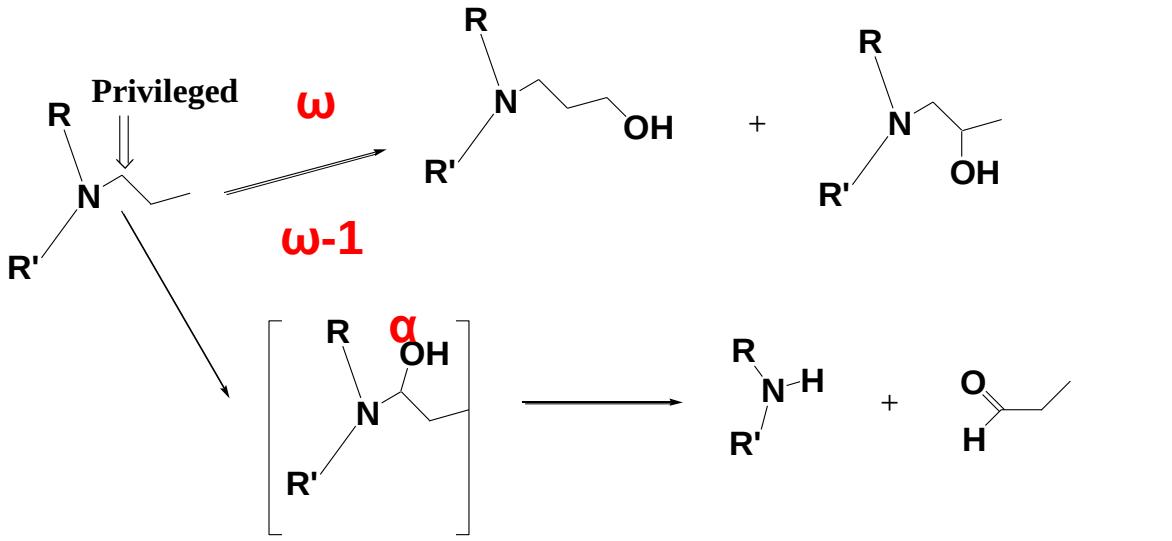
Saturated aliphatic C-H bonds are normally metabolized by Hydroxylation. Hydroxylation normally occurs at either the (ω) and ω-1 C-H bonds or the C-H next to an electron withdrawing group(◌̣◌̣α), such as benzene ring, chloro, aliphatic amino, keto or ester group. The latter oxidation is preferred to the (ω) and ω-1 oxidations.

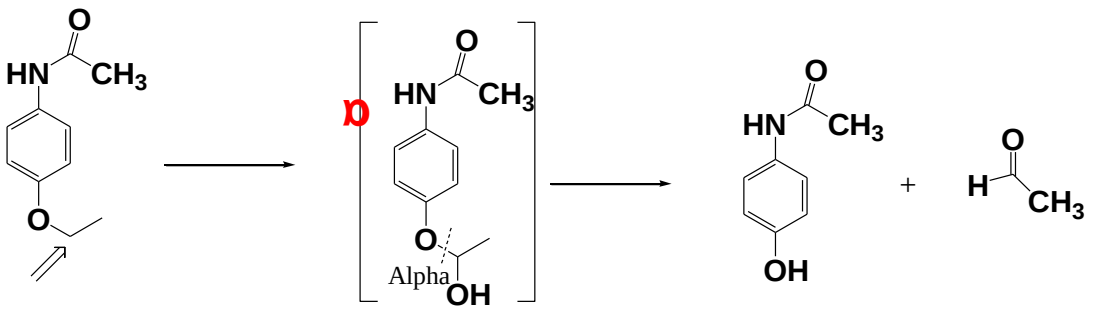


Cyclic aliphatic systems are usually hydroxylated on the least hindered or most activated carbon atom.



The same rules applied to the carbons in the α-position of the heteroatom such as N, O, or S.





Phenacetine (Analgesic)

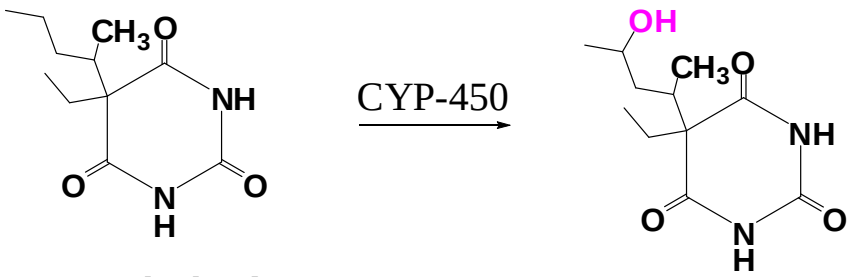
Hemiacetal

Paracetamol (Analgesic)

Toubtamide

Preference position

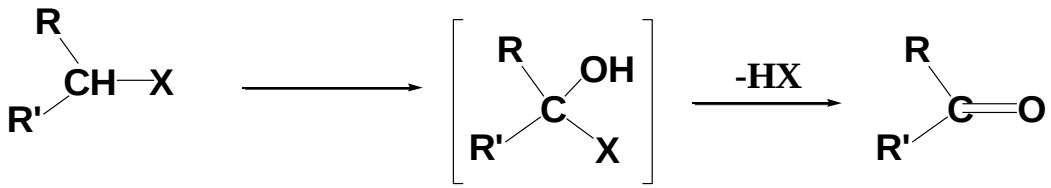
ω-1



ω-1

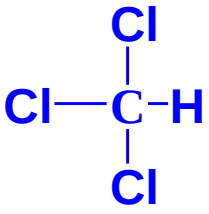
Pentobarbital

Chlorinated or brominated aliphatic derivatives

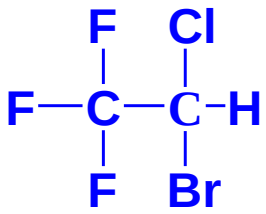


Carbinol Intermediate

What about chloroform and halothane?

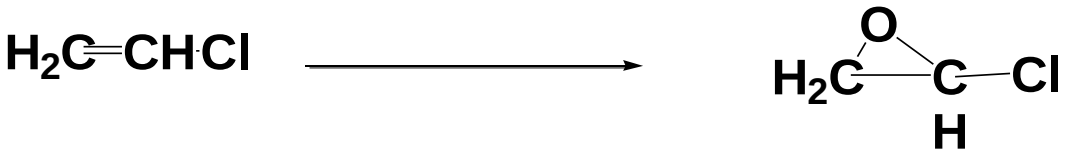


Chloroform



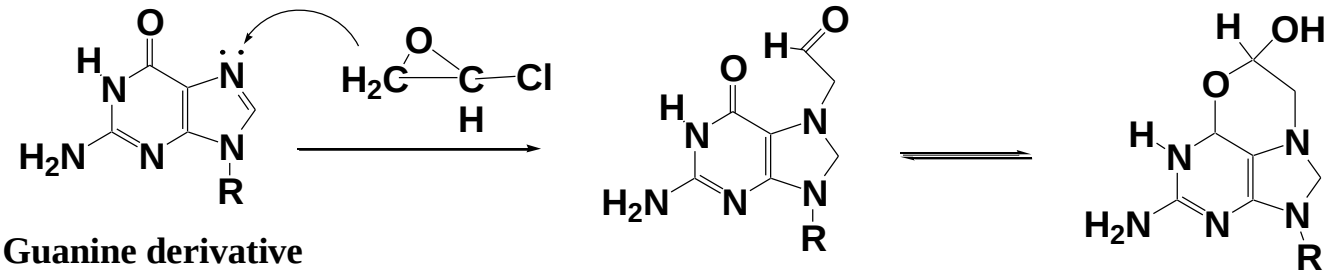
Halothane

Oxidative attack on unsaturated aliphatic systems



Vinyl Chloride

Epoxychloroethane



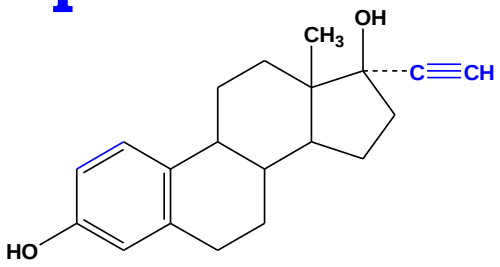
Guanine derivative

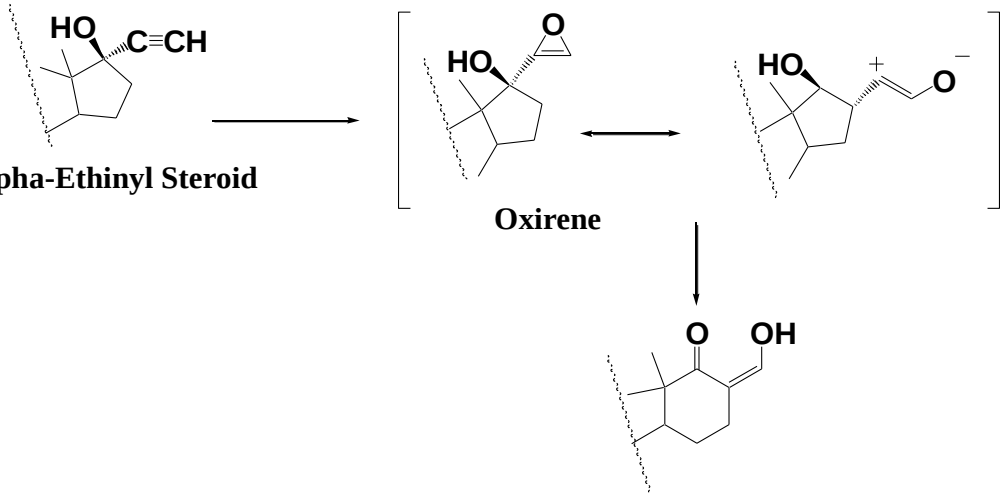
Diethylstilbestrol

Epoxide

With Carbon-carbon triple bond

Ethinyl estradiol

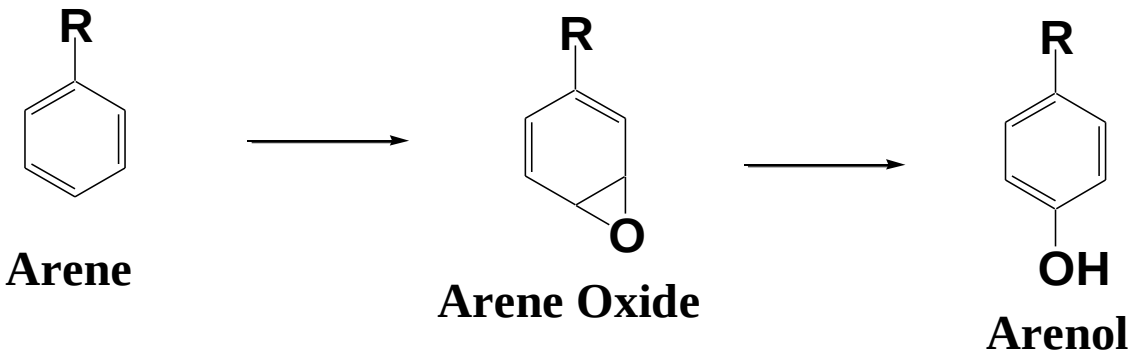




17-Alpha-Ethinyl Steroid

Oxirene

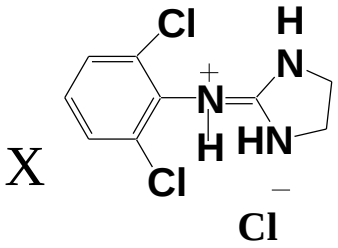
Hydroxylation of aromatic ring



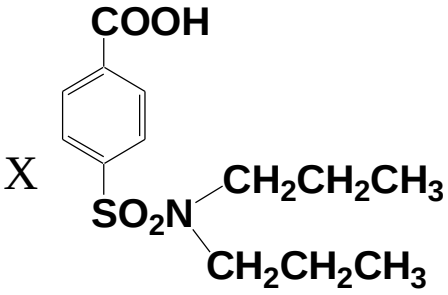
Arene → **Arene Oxide** → **Arenol**

'Highly reactive intermediate'

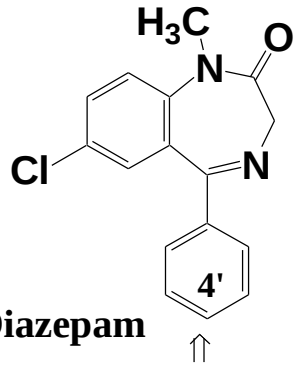
Effect of the substituent



Clonidine Hydrochloride

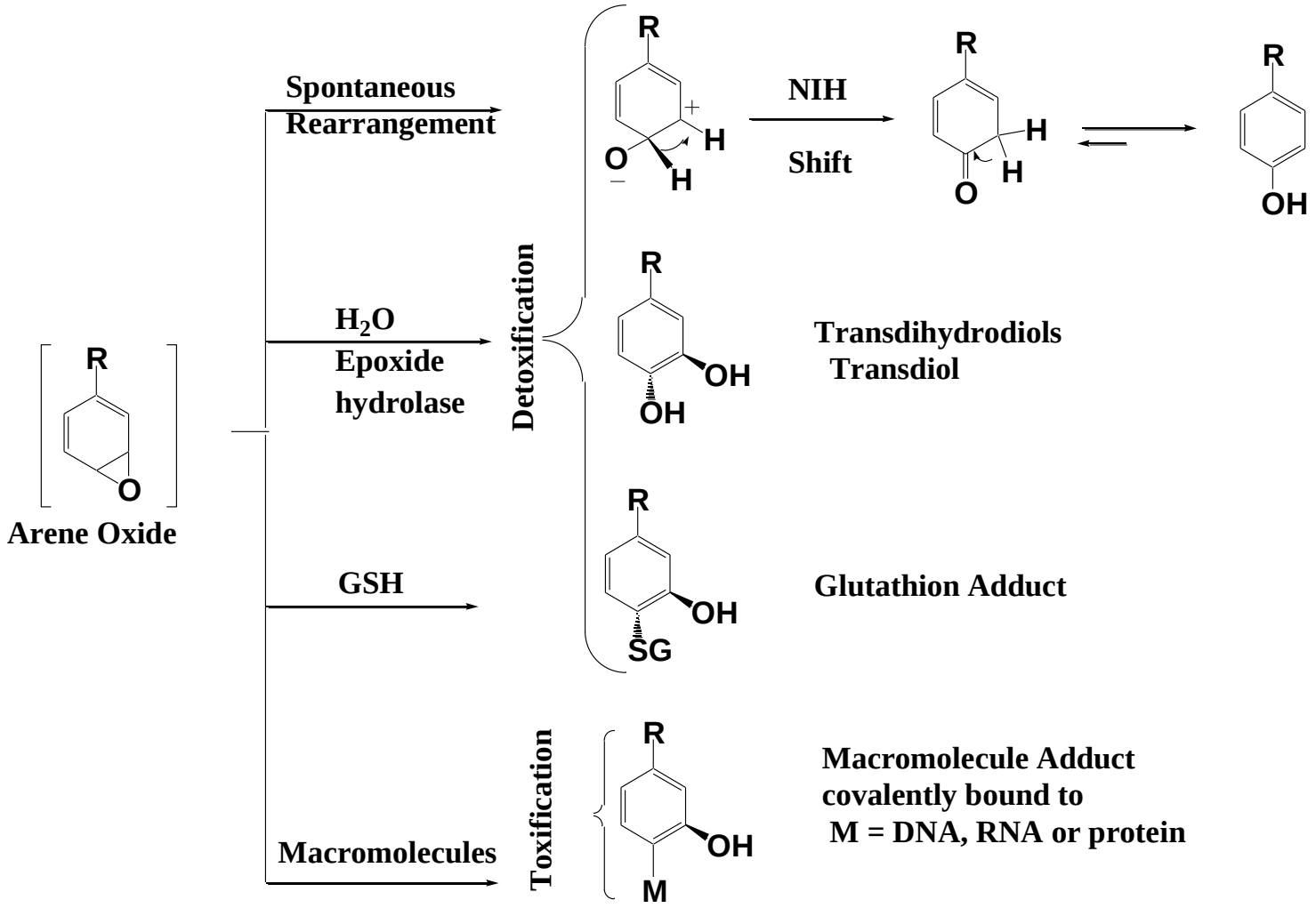


Probencid



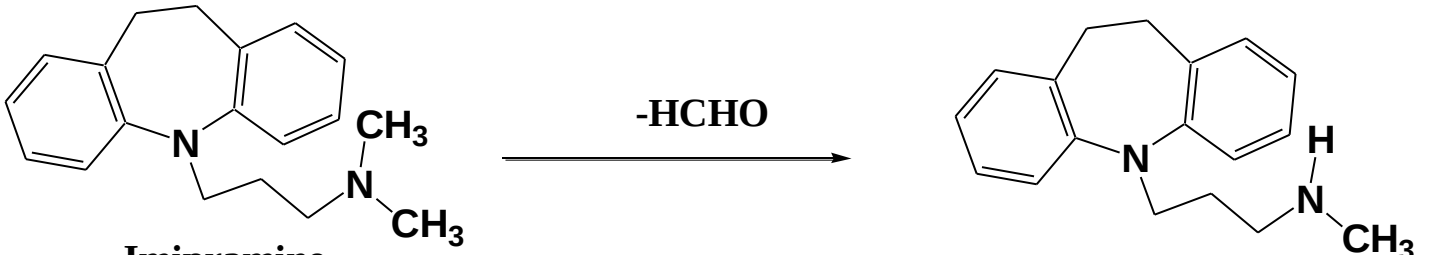
Diazepam

Fate of arene oxides



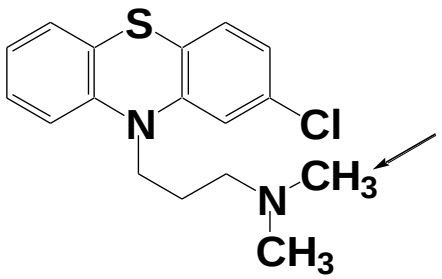
Oxidation Involving C-Nitrogen Systems
Amines and Amides

3˚ Aliphatic & Alicyclic amines

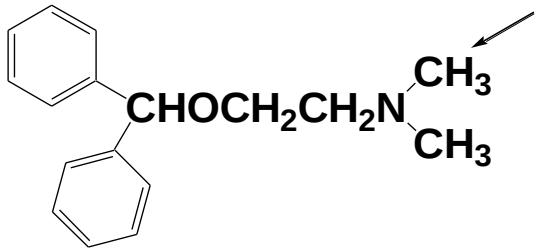


Imipramine

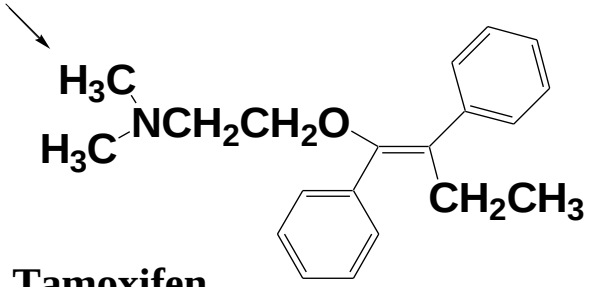
Desmethylimipramine
(Desipramine)



Chlorpromazine

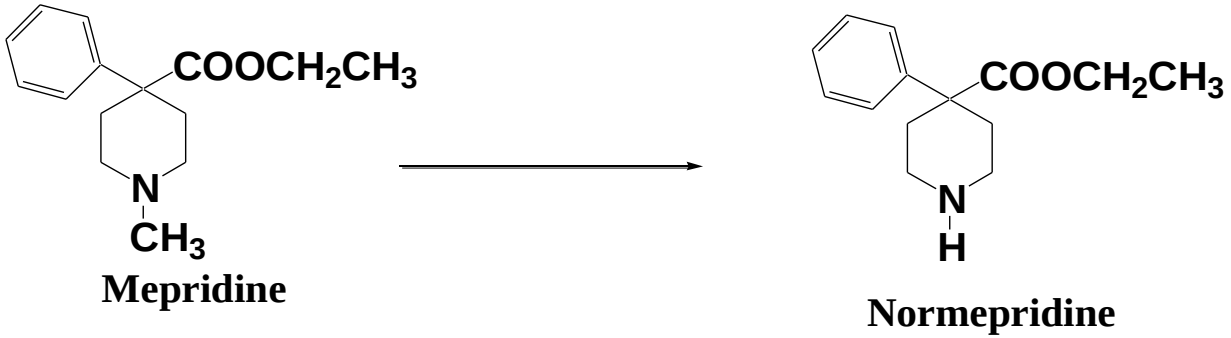


Diphenhydramine



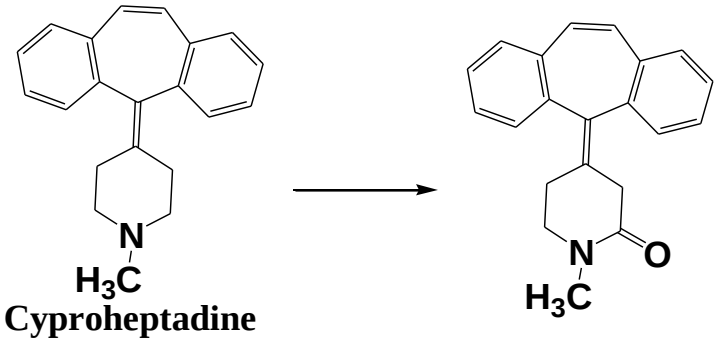
Tamoxifen

The Alicyclic 3˚amines



Mepridine **Normepridine**

Alicyclic tertiary amines often generate lactam metabolites by α-hydroxylation reactions, e.g:



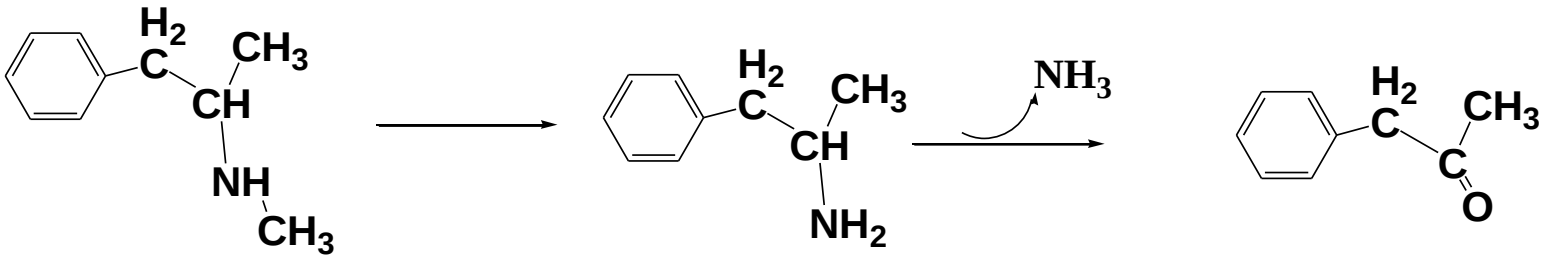
Cyproheptadine

N-Oxidation of tertiary amines

E.g: Morphine, chlorpromazine, imipramine, etc.

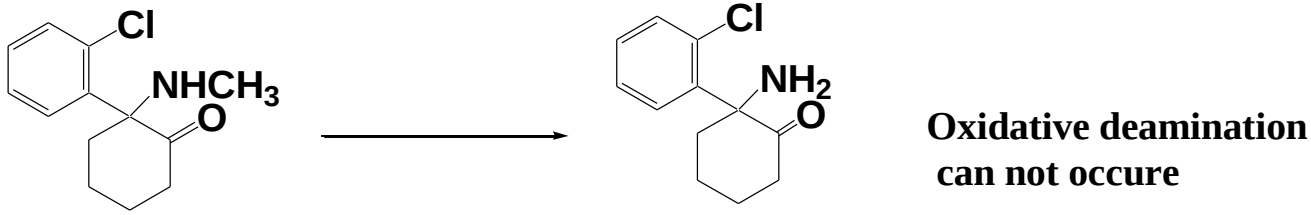
Secondary & Primary Amines

-Oxidative dealkylation
-Oxidative deamination.
-N-Oxidation



Methamphetamine — Amphetamine — Phenylacetone

Ketamine

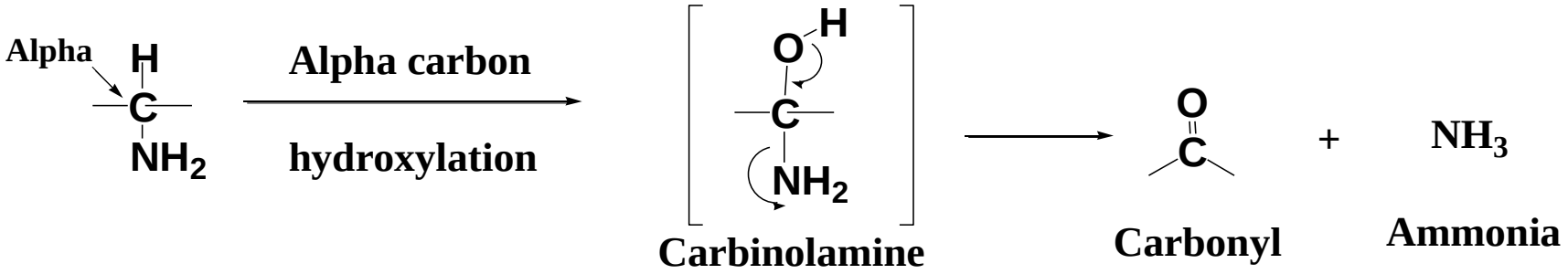


Ketamine

Norketamine

Oxidative deamination can not occure

Oxidative deamination mechanism

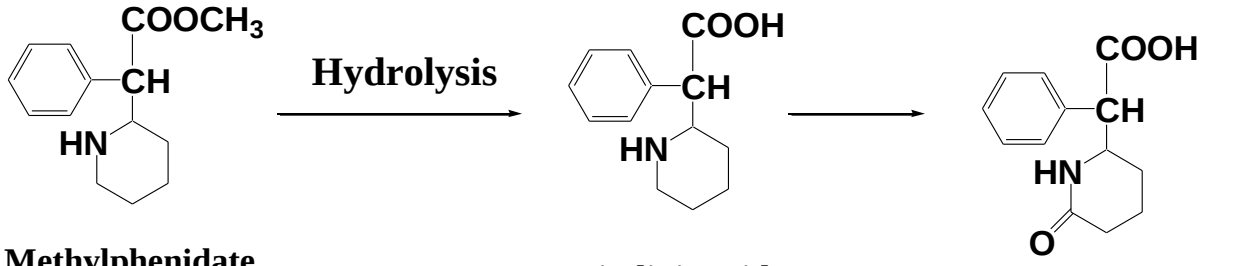


Carbinolamine

Carbonyl

Ammonia

Secondary alicyclic amines

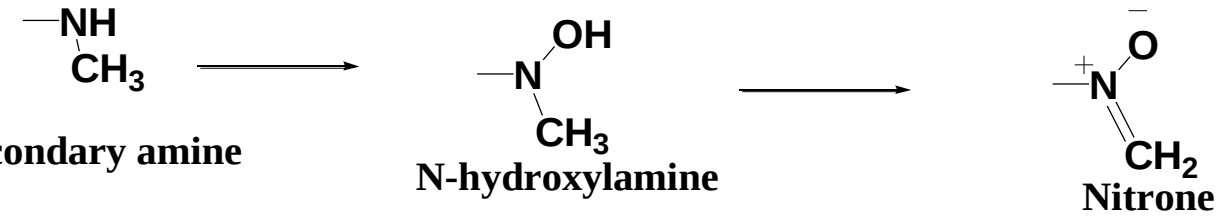


Methylphenidate

Ritalinic acid

6-Oxoritalinic acid

N-oxidation



Secondary amine

N-hydroxylamine

Nitrone

Primary Aliphatic Amines

-Oxidative deamination (carbinolamine pathway).
-N-Oxidation

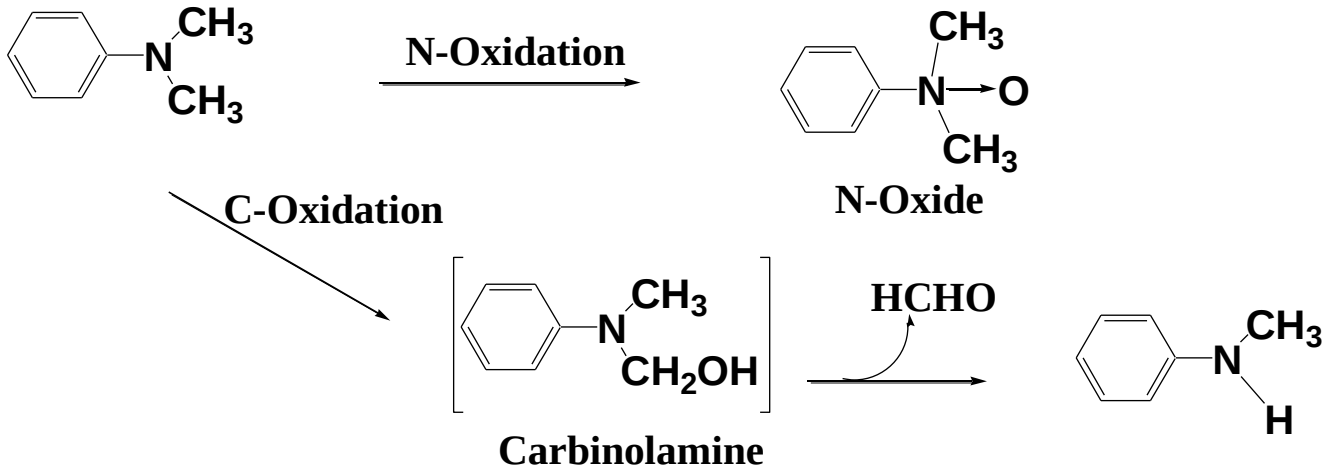
Endogenous primary amines

dopamine, norepinephrine, tryptamine and serotonine are metabolized through oxidative deamination by a specialized family of enzymes called monoamine oxidases (MAO).
MAO apparently plays no role in the metabolism of xenobiotic primary amines.

3˚ Aromatic amines

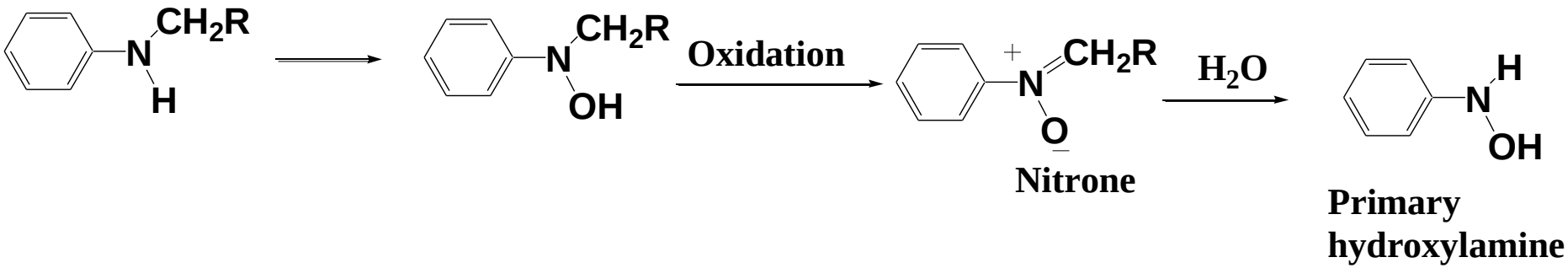
-Oxidative dealkylation

- N-oxidation occur.



2° Aromatic amines

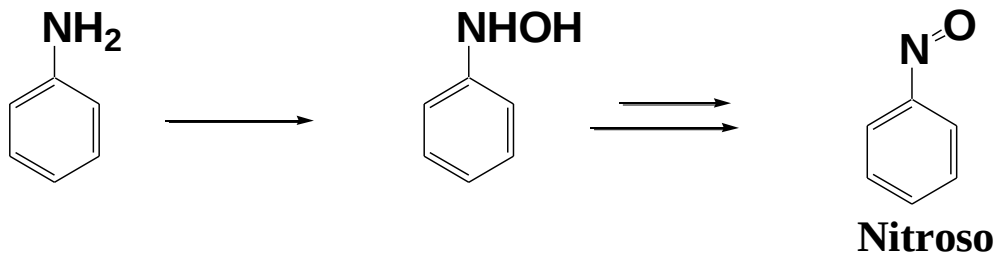
-N-dealkylation or
- N-hydroxylation to give the corresponding N-hydroxylamines.



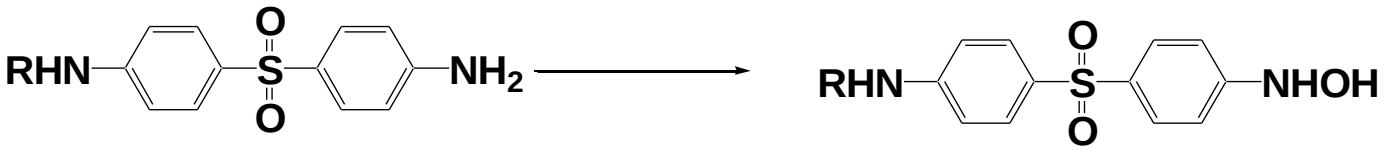
Nitrone

Primary hydroxylamine

1° Aromatic amines



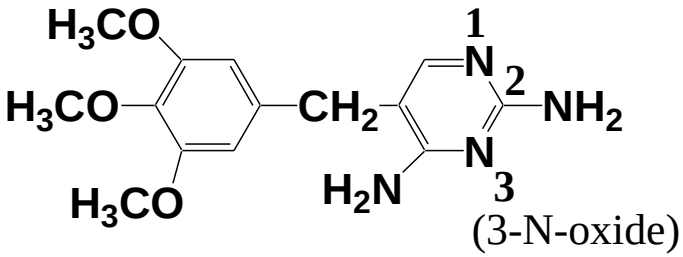
Methemoglobinemia toxicity



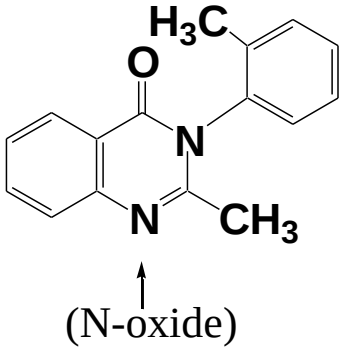
R =H **N-Hydroxydapson**

R = CH_3CO- **N-Acetly-N-hydroxydapson**

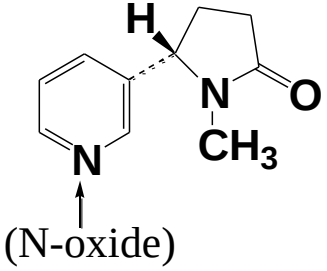
N-Oxidation of the nitrogen atom present in aromatic heterocycles occurs to a minor extent, e.g: trimethoprime, Methaqualone, cotinine, etc.



Trimethoprime



Methaqualone

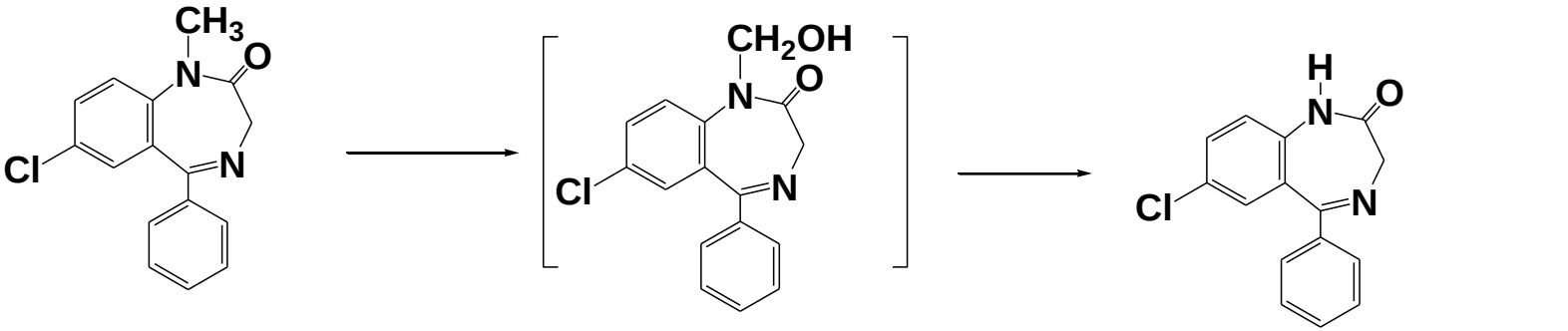


Cotinine

Amides

-Oxidative carbon-nitrogen bond cleavage (by α-carbon hydroxylation).

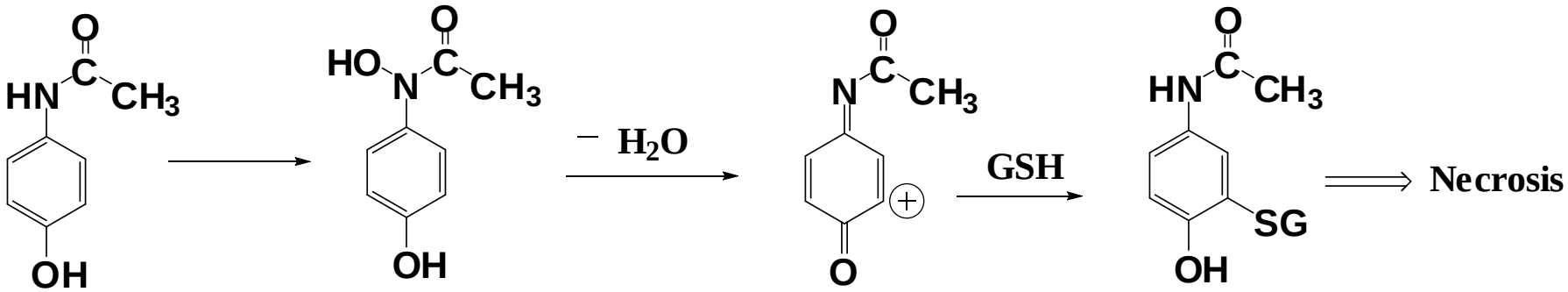
-N-hydroxylation reactions



Carbinolamide

Desmethyldiazepam
Pharmacologically active

N-Hydroxylation of aromatic amides, which occurs to a minor extent, is of some toxicological interest,

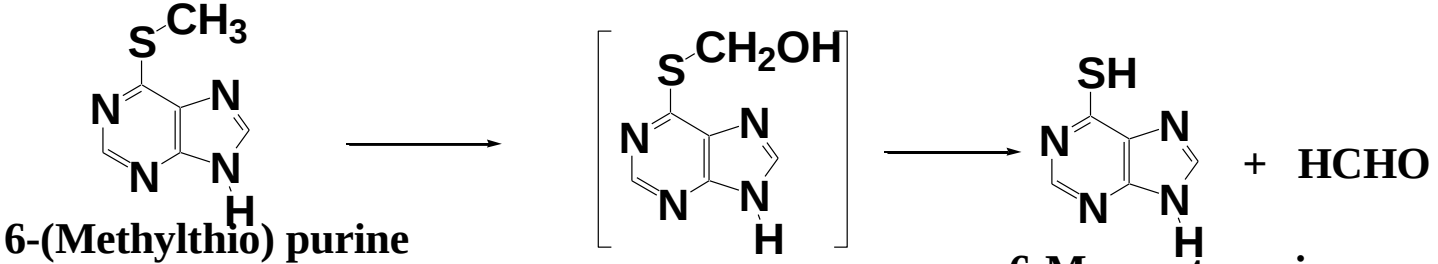


N-Hydroxyacetaminophen N-Acetylimidioquine Glutathion Conjugate

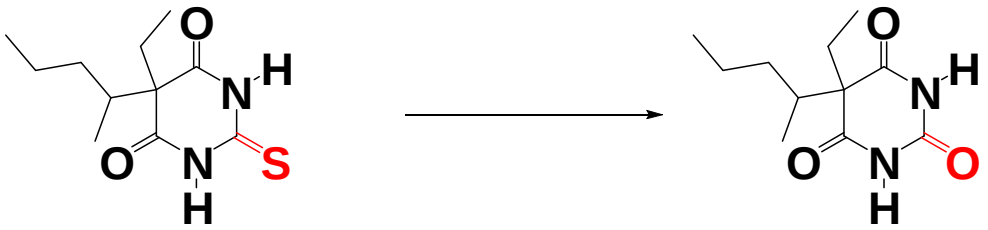
Oxidation Involving Carbon-Sulphur System

-S-Dealkylation
-Desulphonation
-S-Oxidation

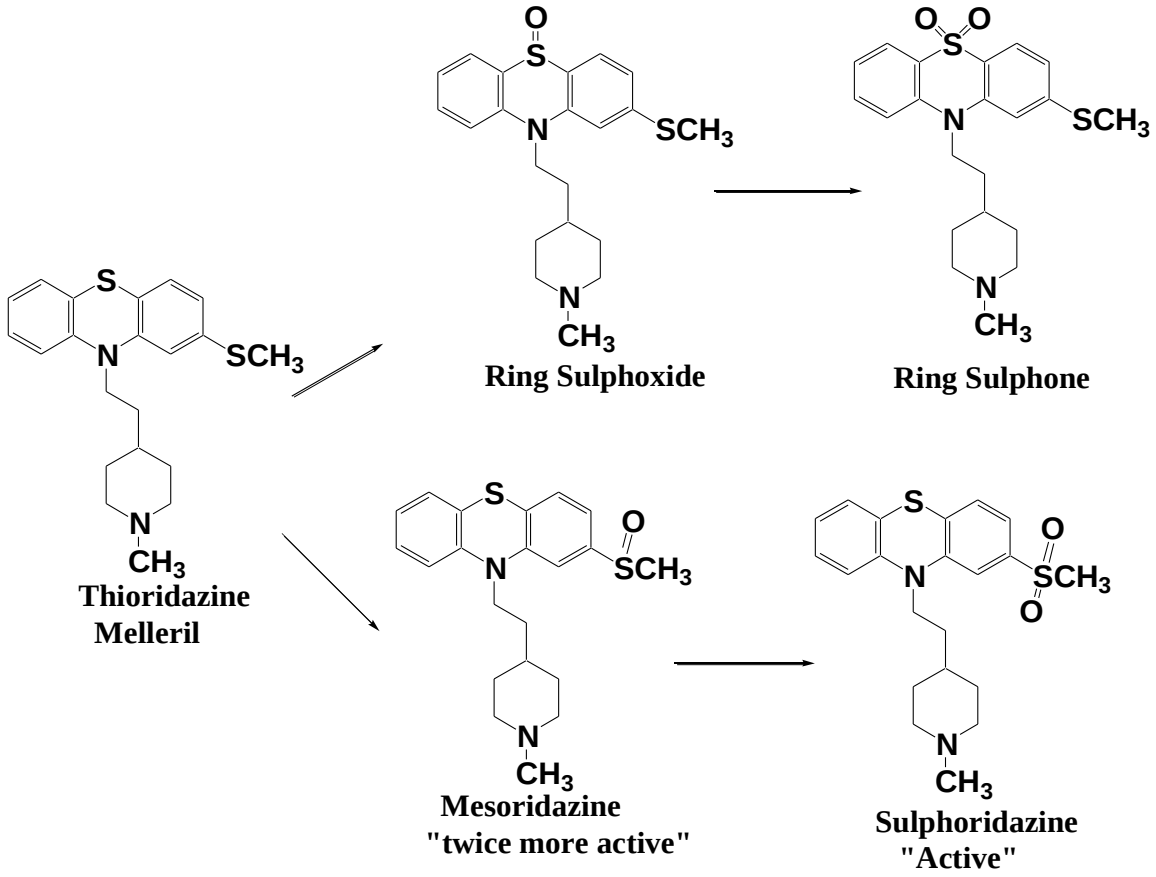
Examples: S-Dealkylation



Oxidative conversion of C=S (thiono) to the corresponding C=O is called desulphonation

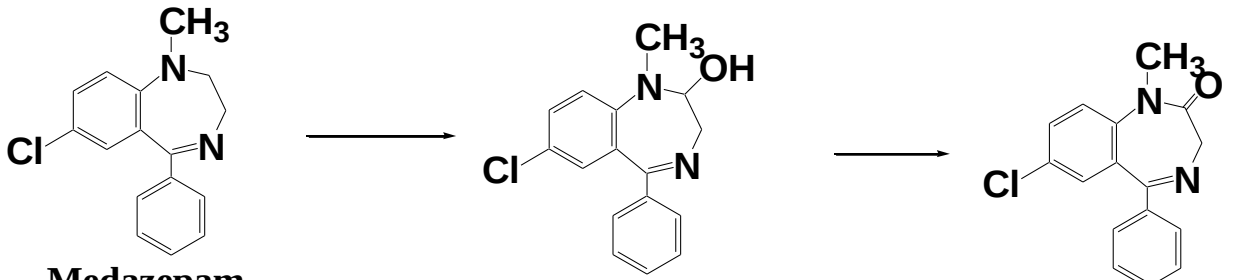


Organosulphur xenobiotics are commonly undergo S-oxidation reaction to yield sulphoxide derivatives, e.g: phenothiazines.



Oxidation of Alcohols and Aldehydes

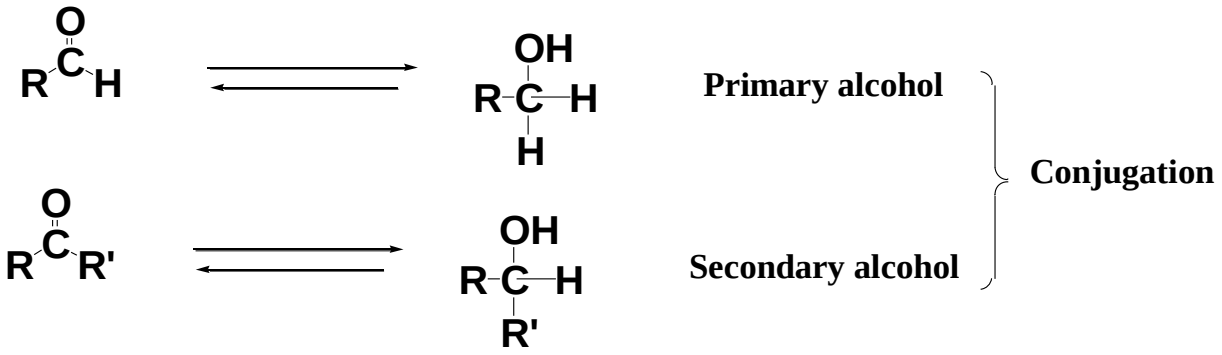
Also, the microsomal dehydrogenases and oxidases are involved in oxidizing the carbinol group of the intermediate carbinolamine into carbonyl moiety. E.g:



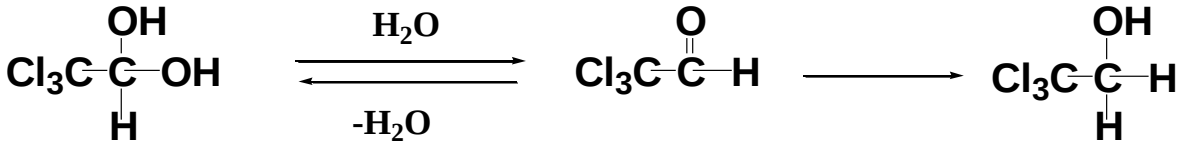
Medazepam → 2-Hydroxymedazepam Alpha-carbinol → Diazepam

Reduction Reactions

Reduction of Aldehydes and Ketones



These reactions are catalyzed by <u>aldoketoreductases</u> (NADPH dependent), which are found in the liver, kidney and other tissues. Also, <u>oxidoreductases</u> are capable (e.g. in the liver). Alcohol dehydrogenase is a NAD+ dependent oxidoreductase converts alcohols into aldehydes and ketones

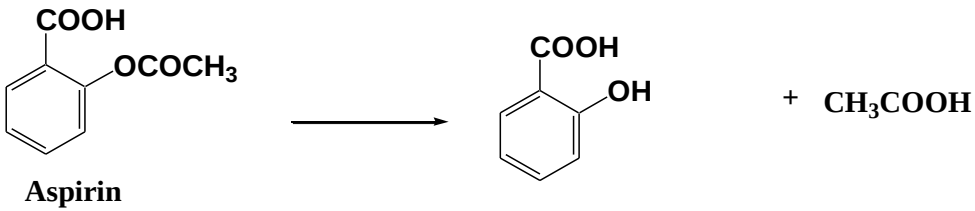


Chloralhydrate

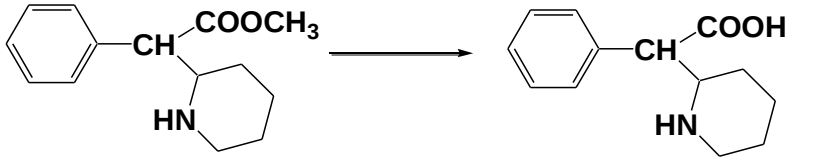
Trichloroethanol
'Active'

Hydrolytic Reactions

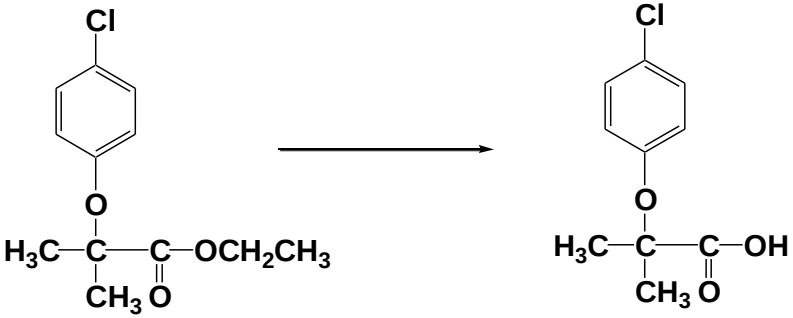
Esters —(Estrases)→ **Acids** + **Phenols** or **Alcohol**



Aspirin



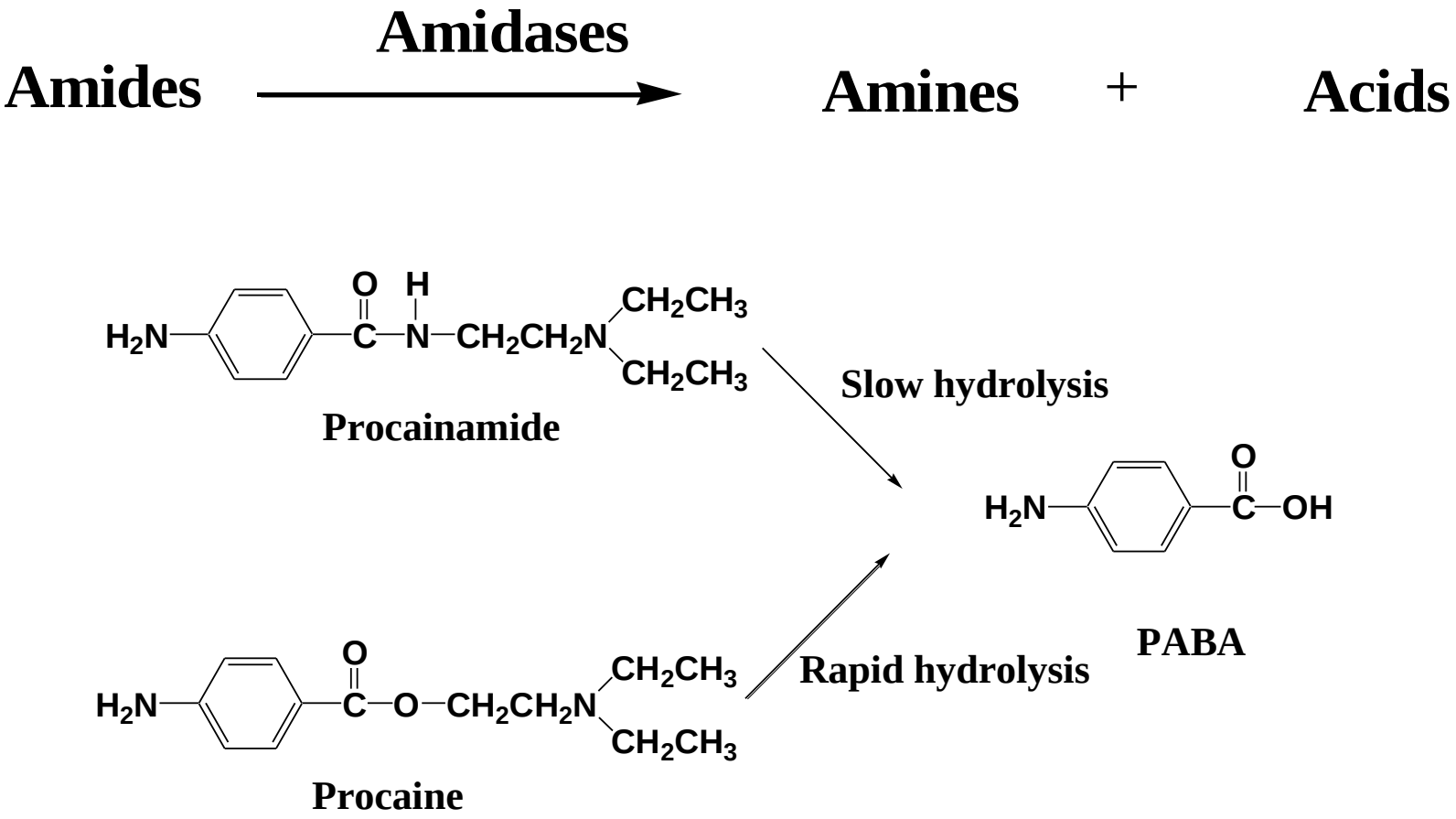
Methylphenidate **Ritlinic acid**



Clofibrate

***p*-Chlorophenoxyisobutyric acid**
Responsible for hypolipodemic effect

Amides


Amides
Amidases
Amines
+
Acids
Procainamide
Slow hydrolysis
PABA
Procaine
Rapid hydrolysis

Phase II metabolic Route (Conjugation Reactions)

Can occur at any point in drug metabolism. However they represent the final step in metabolic pathways before excretion.

Phase II reactions are:
Acetylation, Acylation, sulphate formation and conjugation with amino acids, glucuronic acid and glutathion in addition to methylation.

All phase II reactions are catalyzed by a group of enzymes: known as *Transferases*.

Acetylation

N-Acetylation is the most important route for:

-Primary Amines RNH_2

-Sulphonamides SO_2NH_2

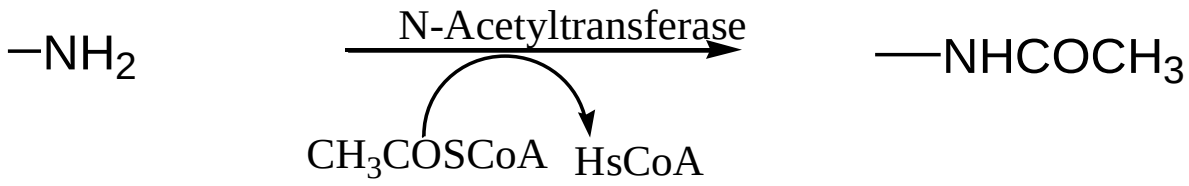
-Hydrazines $-NHNH_2-$

-Hydrazides CONHNH2

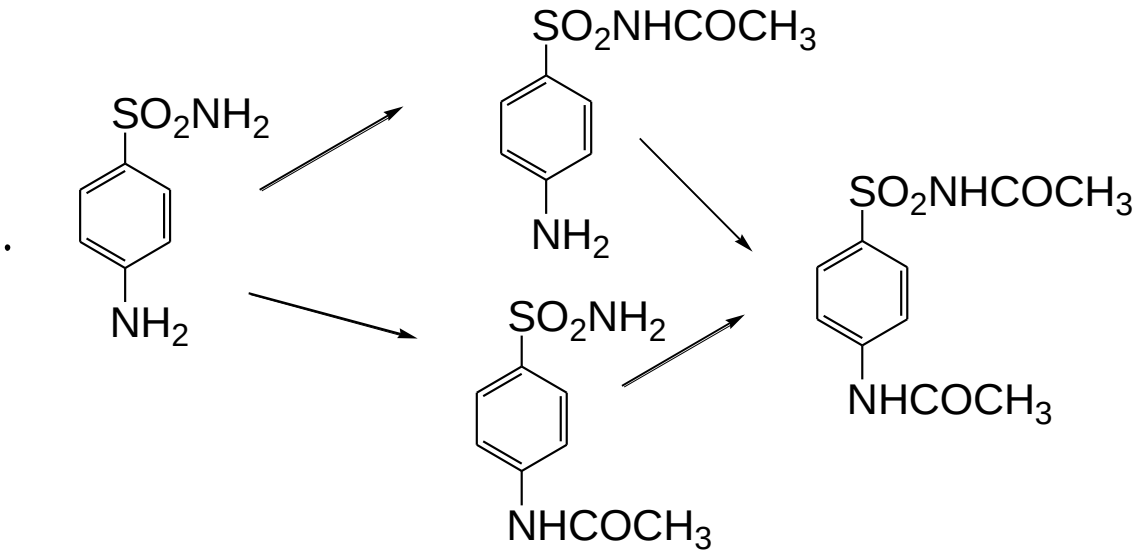
Enzyme catalyzing this reaction is N-acetyltransferase.

with acetyl co-enzyme A supplying the acetyl group.

-The product in this reaction is not more water soluble, but pharmacologically inactive.



Example

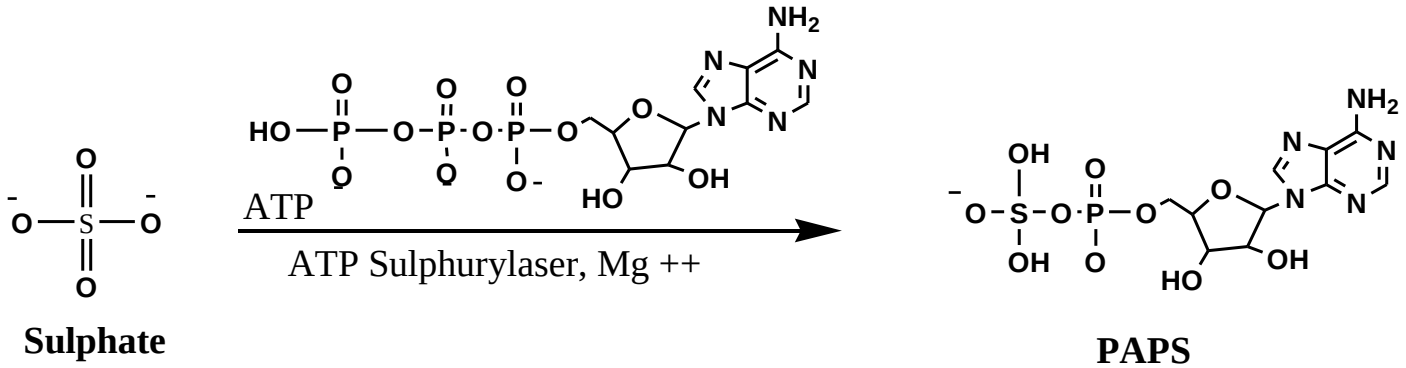


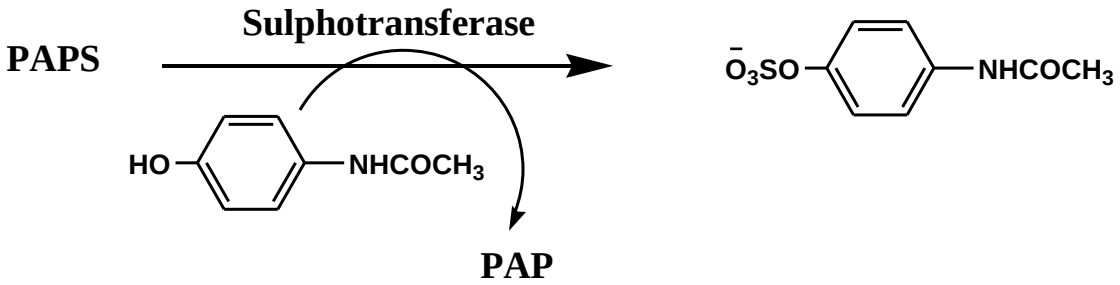
Sulphanilamide
Antibacterial

Sulfate Formation

Sulfate conjugation is an alternative route for phenols and occasionally some alcohols and amines.

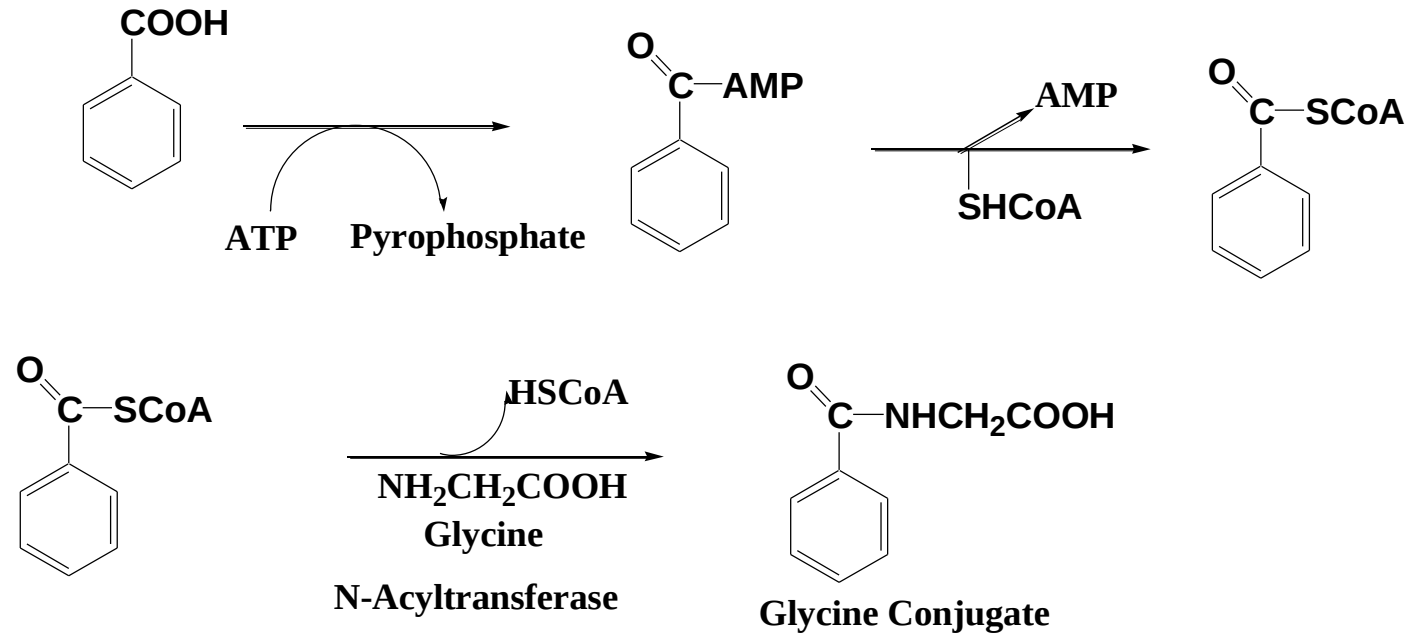
The sulfate originates from the body's sulfate pole. It is believed to be activated by conjugation with ATP to form 3'-phosphoadenosine-5'-phosphosulfate (PAPS).





Conjugation With Amino Acids

Conjugation with amino acids is an important route for the metabolism and conjugation of carboxylic acids. It is thought that the reaction proceeds in a series of steps. Initially, the carboxylic acid reacts with ATP to form monoadenosinphosphate (AMP), Then converted into an active acyl-coenzyme A intermediate by the action of coenzyme A. The coenzyme A intermediate undergoes nucleophilic displacement with the amino acid. All these reactions are catalyzed by various N-acyltransferases. The formed amino acid conjugates are more water soluble than the parent acid and are mainly excreted in the urine.



The quantity of amino acids available for conjugation is limited, so few amino acid conjugates are found in the urine.

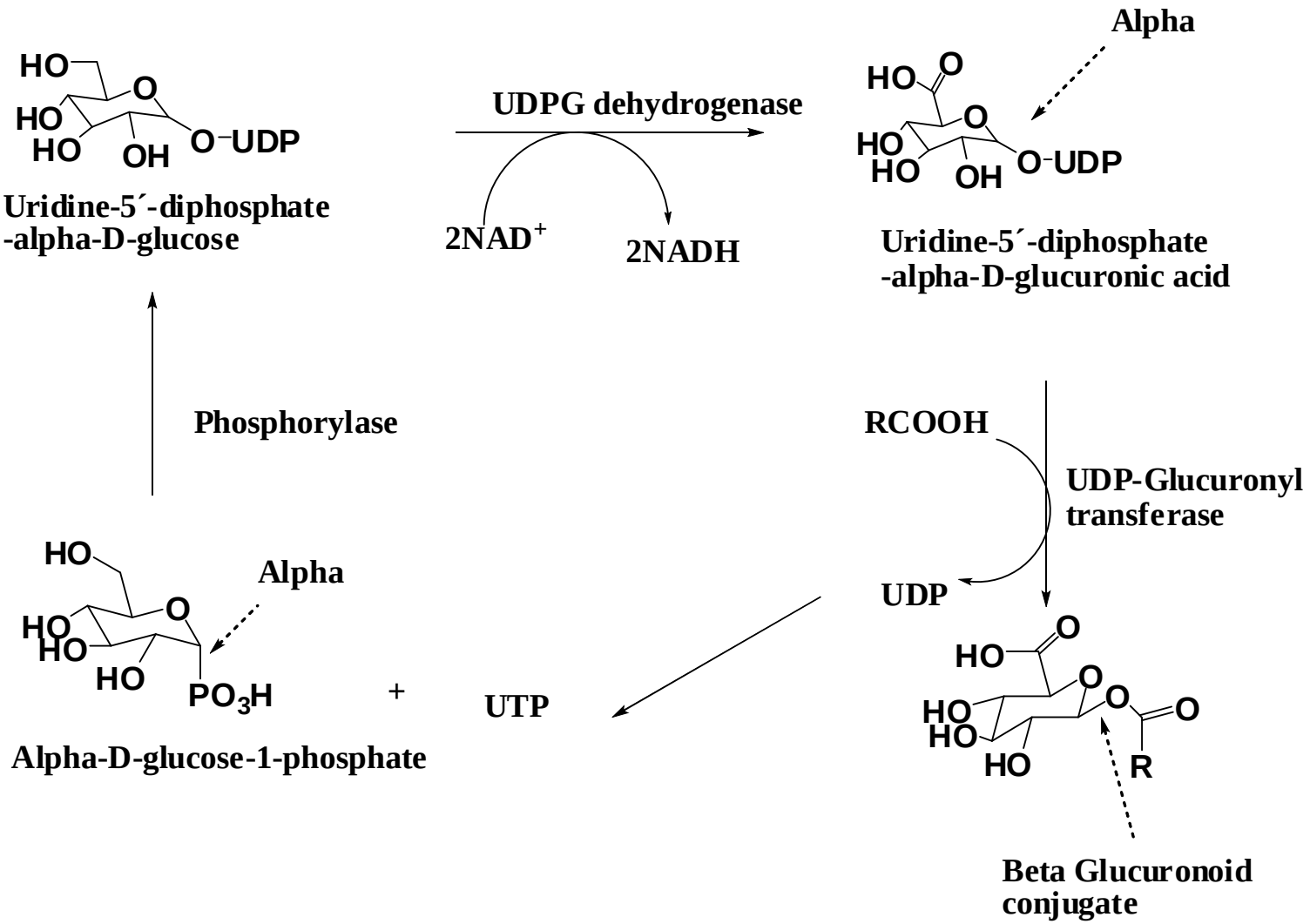
Conjugation With Glucuronic Acid

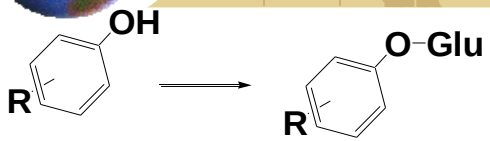
Glucuronic acid conjugation is the most important of all the phase II reactions, this is due to:

1-The presence of good supply of glucuronic acid in the body.
2-Numerous alcohols, phenols, amines, thiols and some carboxylic acids have been found to be metabolized by this route.

The xenobiotic reacts with the activated form of glucuronic acid, uridine diphosphate glucuronic acid (UDPGA) to form highly water soluble glucuronoid conjugate. This reaction is catalyzed by microsomal uridine diphosphate glucuranyl transferase (UDPG-transferase).

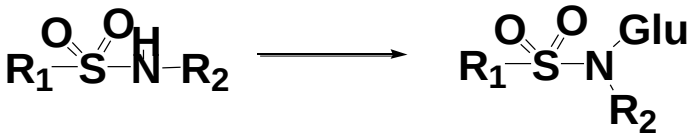
Mechanism

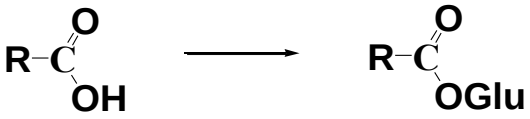

HO
O
HO
HO
OH
O⁻UDP
Uridine-5´-diphosphate
-alpha-D-glucose
UDPG dehydrogenase
2NAD+
2NADH
Alpha
HO
O
HO
HO
OH
O⁻UDP
Uridine-5´-diphosphate
-alpha-D-glucuronic acid
Phosphorylase
RCOOH
UDP-Glucuronyl
transferase
UDP
HO
Alpha
HO
O
HO
HO
PO3H
+
UTP
HO
O
HO
O
HO
O
HO
R
Beta Glucuronoid
conjugate

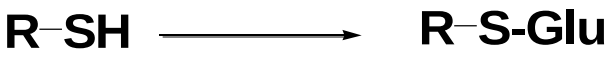

OH
R
O-Glu
R

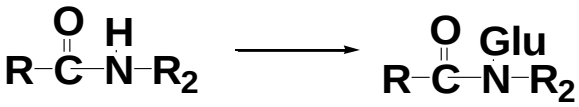

R1
N
C
O
OH
R2
R1
N
C
O
O-Glu
R2

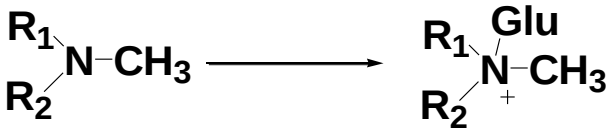

R1
C
OH
R2
R3
R1
C
O-Glu
R2
R3

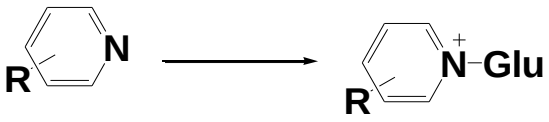

O
O
H
S
N
R1
R2
O
O
Glu
S
N
R1
R2

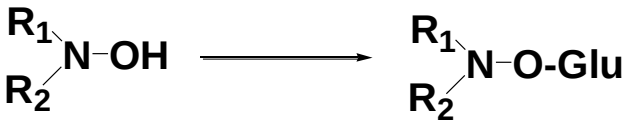

O
R
C
OH
O
R
C
OGlu


R-SH
R-S-Glu


O
H
R
C
N
R2
O
Glu
R
C
N
R2


R1
N
CH3
R2
Glu
R1
N
CH3
R2


N
R
N
Glu
R

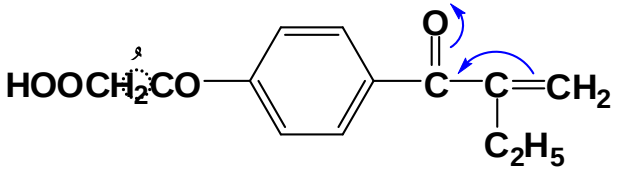

R1
N
OH
R2
R1
N
O-Glu
R2

Conjugation with Glutathione

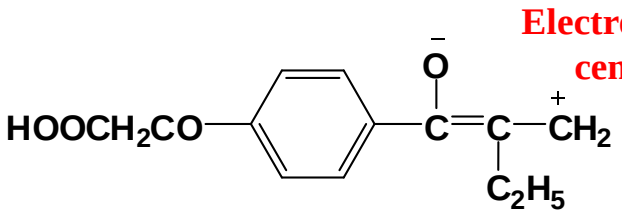
Conjugation with nucleophilic thiol group of glutathione (GSH) is the first step in the elimination of compounds whose structures contain and electrophilic center.

These electrophilic centers are caused by the presence of electron withdrawing groups such as carbonyl, halides, nitro, sulfonate, nitrate, Epoxide and organophosphate groups in the structure

The reaction being catalyzed by a family of enzymes known as glutathione-S-transferases, which are found in most tissues. through substitution, displacement or addition.

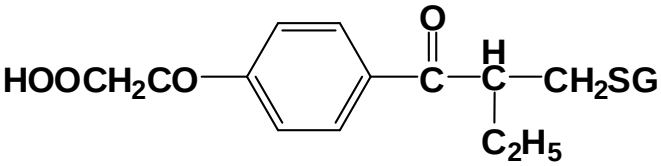


Ethacrynic acid
(Diuretic)



Electrophilic center

Glutathione-S-transferases



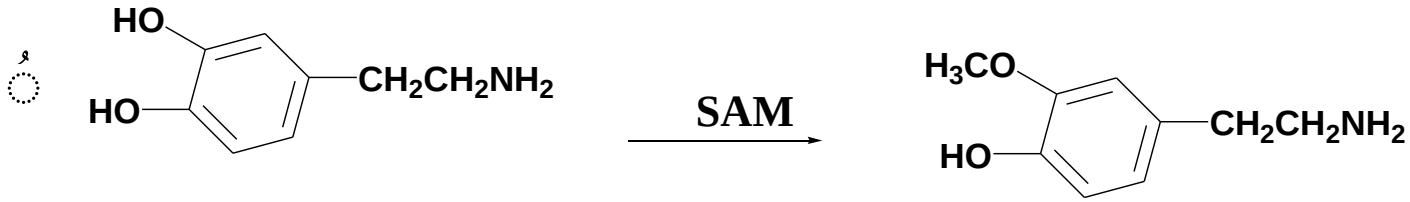
Methylation Reactions

Substrates: **Phenol, thiol, NH_2, some heterocycles are metabolized by this route.**

Catalyzed by specific methyltransferases

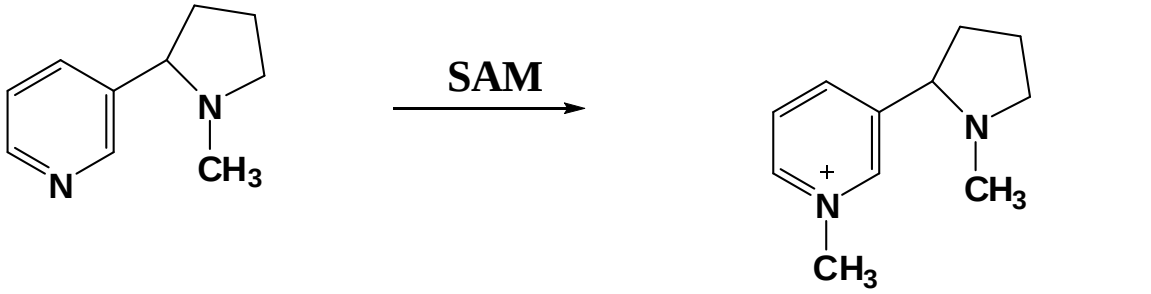
The formed methylated metabolites, except with amines are less water soluble and pharmacologically inactive

The co-enzyme is: S-adenosylmethionine



(Dopamine)
a neurotransmitter

3-Methoxy
(Selective)



Quaternary ammonium salts
(water solube)

N.B: Catechol –O-Methyltransferase COMT is the enzyme responsible for methylation of the *m*-OH group in catechol-type biogenic amines

Drug Metabolism and Drug Design

There is a strong relation between drug design and knowing the metabolic pathway of drugs.

Increasing metabolic and hence duration of the action of a drug is usually achieved by replacing a reactive group by less reactive one.

e.g1:

N-dealkylation could be retarded by replacing the N-CH3 Group by n-t-butyl.

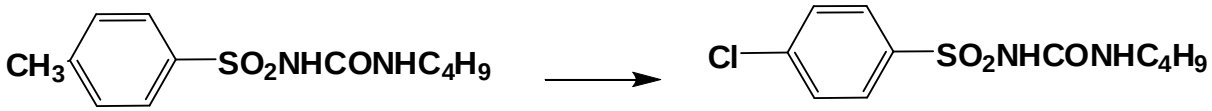
e.g2:

Reactive ester group could be replaced by less reactive amide group

e.g3

Oxidation of the aromatic ring could be retarded by introduction of a strong electronwacceptor group such as -Cl, quaternary amines (-NR_3), -COOH, SO_3R or – SO_2NHR groups.

e.g: Replacement of the arylmethyl substituent of the antidiabetic tolbutamide by Cl yielded the antibiapetic chloropropamide with longer half life (duration of action).



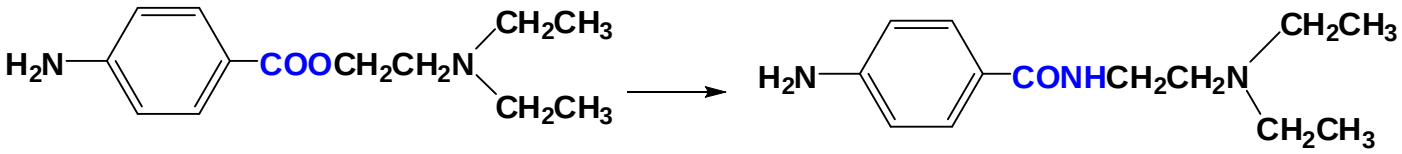
Tolbutamide

t1/2 = 7h

Chlorpropamide

t1/2 = 35h

e.g4: Replacement of the ester group of the local anesthetic procaine by an amide group produced the procainamide with antiarrhythmic acivity



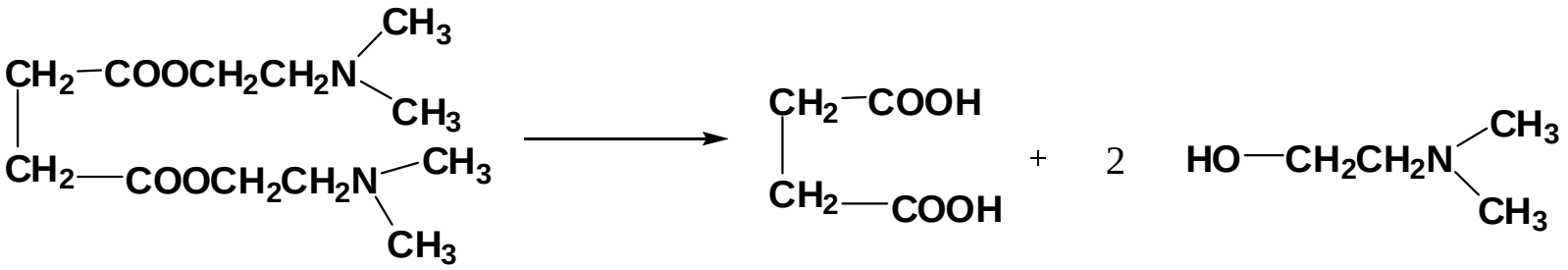
Procaine

(Local anesthetic)

Procainamide

(antiarrhythmic)

e.g5: The labile ester moiety decreased the t1/2 of succinylcholine (neuromuscular blocker) to 10 min. Reducing the chances of fatal overdoses.



Prodrugs

Definition:

Prodrugs are inactive compounds that yield an active compound on metabolism in the body

Classification

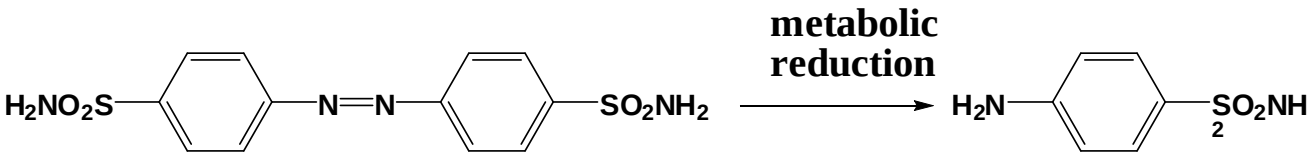
1-Bioprecursor

2-Carrier Prodrugs

1-Bioprecursor Prodrugs

They produce the active species on metabolism

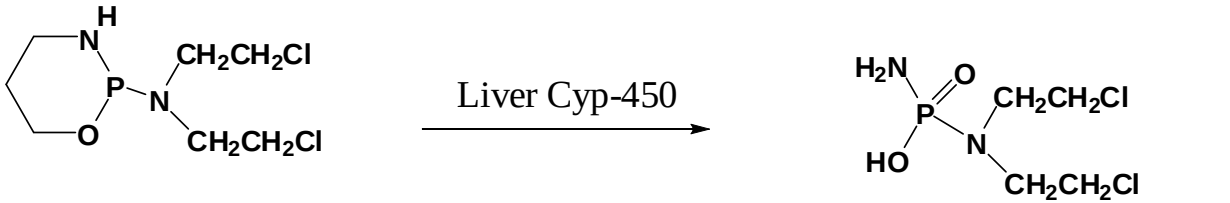
e.g:Prontosil



Prontosil
(Inactive)

Sulphanilamide
(Antibacterial0

e.g:Cyclophosphamide



Cyclophosphamide
(Inactive)

Phosphoramidate mustard

2-Carrier Prodrugs

Carrier prodrugs are formed by combining an active drug with a carrier species to form a compound with the desired chemical and biological characteristics.
e.g: Lipophilic moiety to improve transport across membranes.
The link between the carrier and the active species must be an amide or ester group easily metabolized by esterases or amidases.

Carrier + Active species → Carrier Prodrug

↓

Carrier + Active Species

All types of carrier prodrugs should meet the following criteria:

1-Less toxic than the drug

2-The prodrug should be inactive or significantly less active than the parent drug.

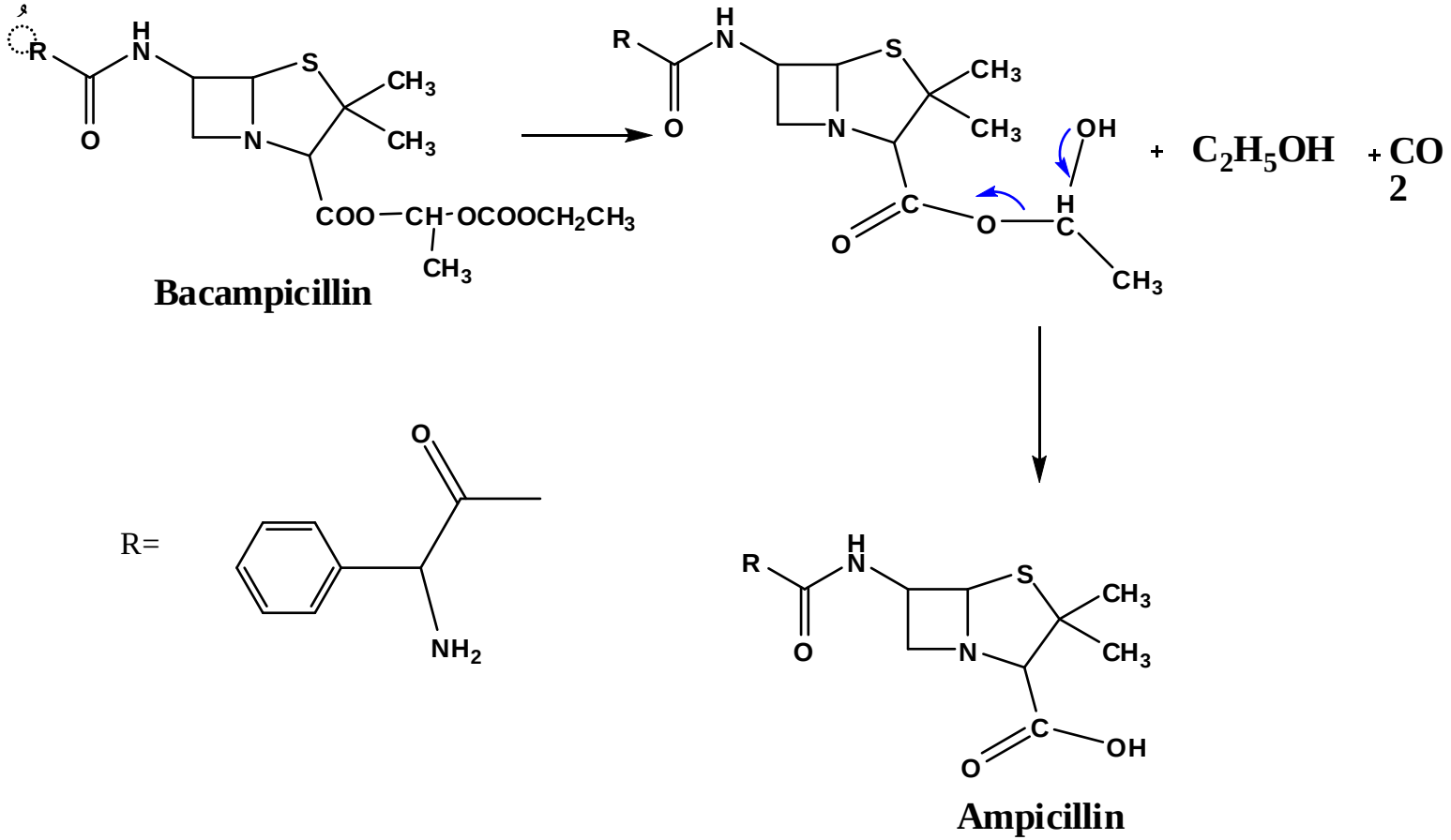
3-The rate of formation of the active drug from the prodrug should be rapid enough to maintain the drug concentration.

4-Prodrug should be with improved bioavailability if administered orally.

5-The prodrug should be site specific.

The ideal prodrugs meeting most of these criteria is **Bacampicillin:** It is a prodrug of ampicillin

Only about 40 % of the orally administered ampicillin is absorbed where the remaining in the GI tract destroys the normal flora. The % of absorption of bacampicillin is 98-99 % where a smaller dose is required to maintain the required concentration of the drug in the blood. The metabolism of the prodrug yields carbon dioxide, ethanal and ethanol, all of which are natural metabolites in the body.

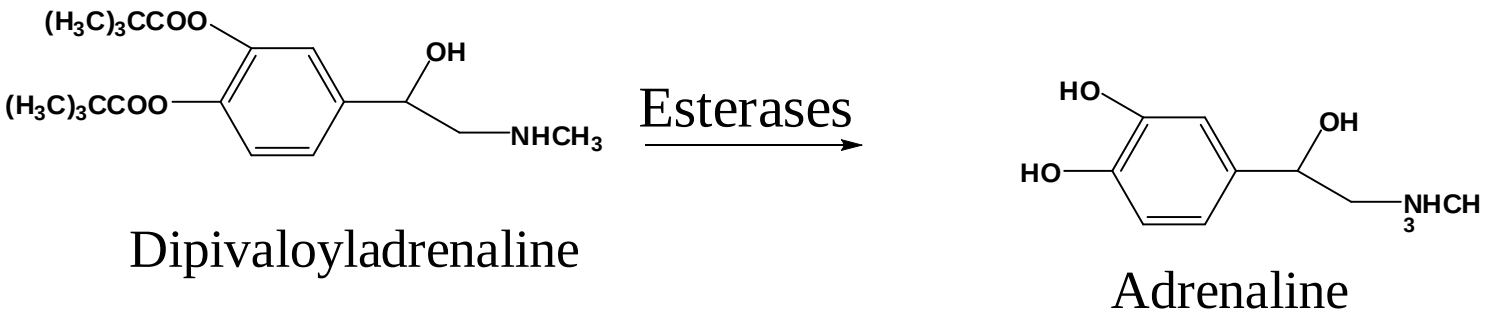

Bacampicillin
+ C_2H_5OH + CO 2
R=
Ampicillin

Design of Prodrug System for Specific Purposes

-Improving Absorption

Lipophilic carriers are used to increase the lipophilic nature and hence the absorption of the drug.

Example: adrenaline when used in treatment of glaucoma is poorly absorbed through the cornea. However the more lipophilic dipivaloyladrenaline increased the absorption.

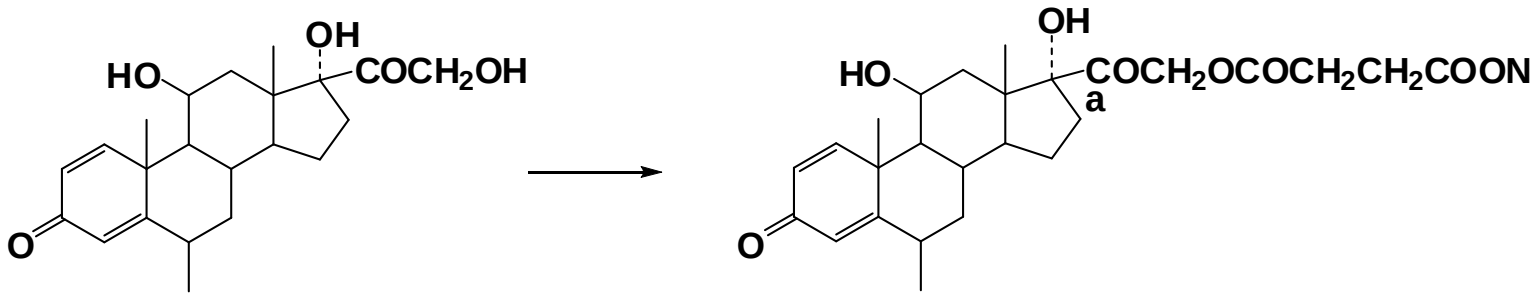


Dipivaloyladrenaline

Adrenaline

Absorption also depends upon water solubility. A drug must have a suitable water solubility if it is transported through membranes by passive diffusion.

e.g:Water soluble carrier sodium succinate is used to increase the water solubility of the glucucorticoid methylprednisolone.

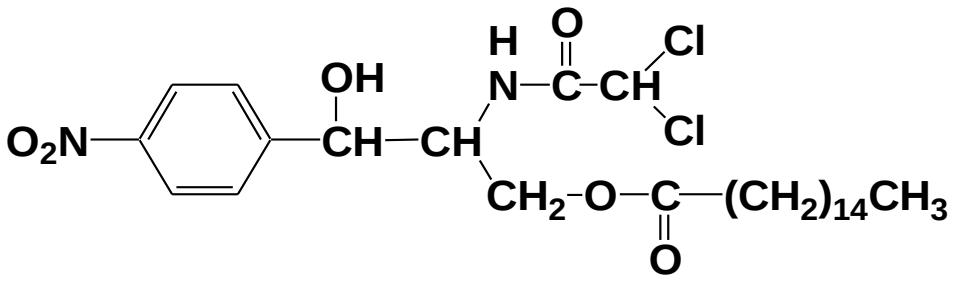


Methylprednisolone

Methylprednisolone sodium succinate

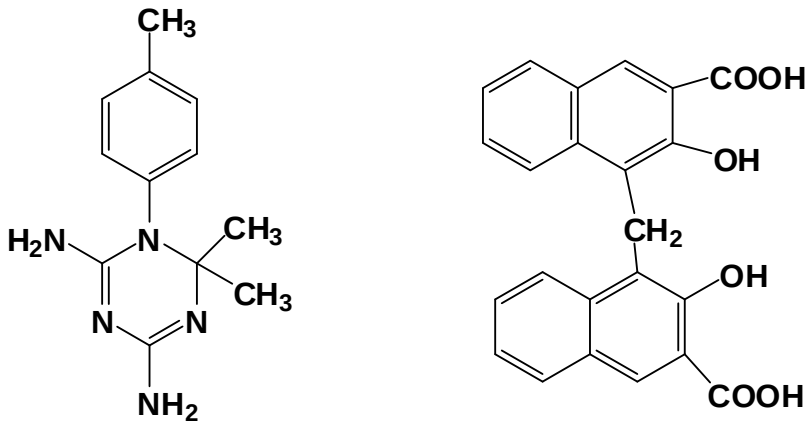
Improving Patient Acceptance

E.g:Chloramphenicol is derivatized as its palmitate ester to overcome its bitter taste to improve its palatability in pediatric liquid suspensions.



Slow Release

The slow release carrier prodrugs are also used as the basis of depot preparations, which are administered by intramuscular injection. E.g The a single dose of the insoluble carrier prodrug cycloguanil embonate will slowly release the antimalarial drug at the therapeutic Level over a period of several months.



Cycloguanil embonate