Pharmaceutical chemistry Metabolic Changes of Drugs and Related Organic Compounds "Oxidation Involving Carbon–Heteroatom Systems"

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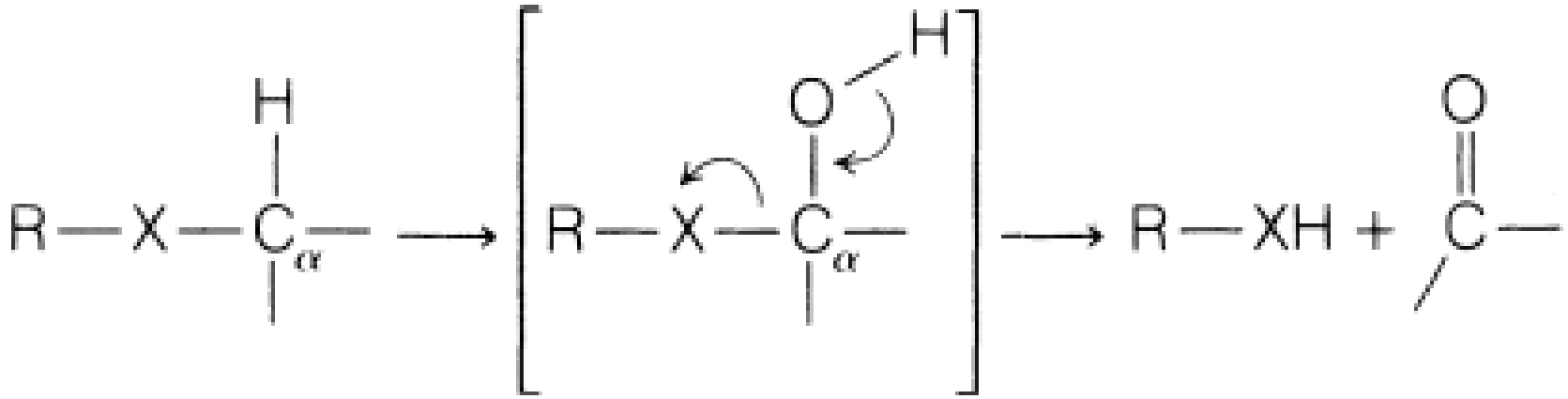
Oxidation Involving Carbon–Heteroatom Systems

- Nitrogen and oxygen functionalities are commonly found in most drugs and foreign compounds; sulfur functionalities occur only occasionally. Metabolic oxidation of carbon–nitrogen, carbon–oxygen, and carbon–sulfur systems principally involves two basic types of biotransformation processes:

1. Hydroxylation of the α-carbon atom attached directly to the heteroatom (N, O, S).

- The resulting intermediate is often unstable and decomposes with the cleavage of the carbon–heteroatom bond:

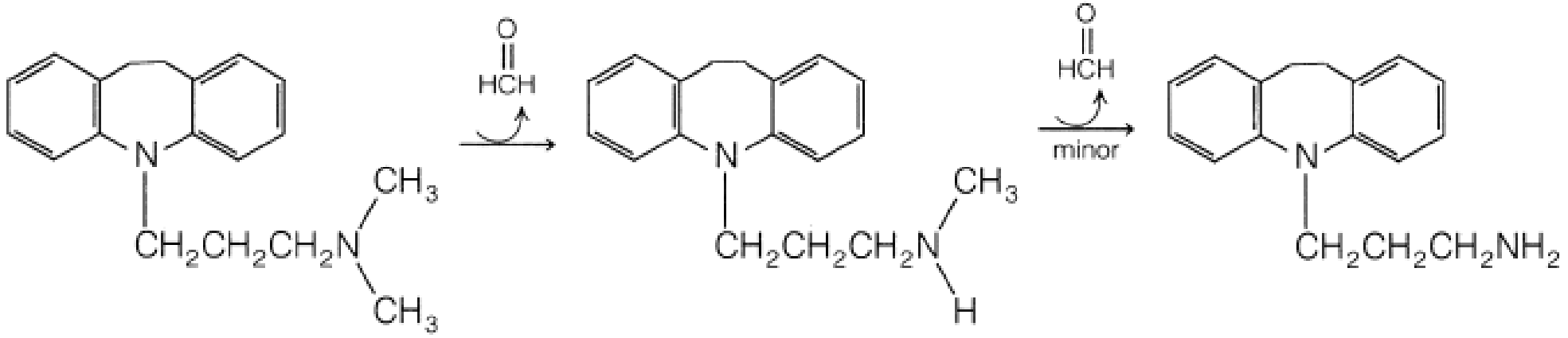


2. Hydroxylation or oxidation of the heteroatom (N, S only, e.g., N-hydroxylation, N-oxide formation, sulfoxide, and sulfone formation).

- Other oxidative processes that do not fall under these two basic categories are discussed individually in the appropriate carbon–heteroatom section.

OXIDATION INVOLVING CARBON–NITROGEN SYSTEMS

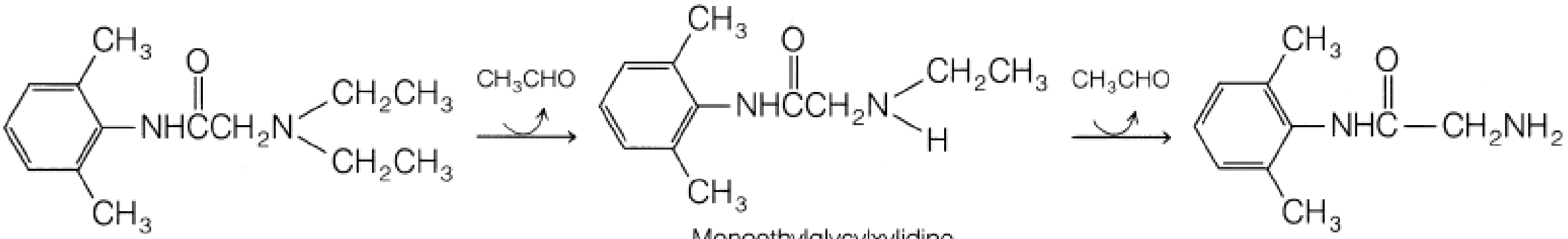
- Metabolism of nitrogen functionalities (e.g., amines, amides) is important because such functional groups are found in many natural products (e.g., morphine, cocaine, nicotine) and in numerous important drugs.
- **A) tertiary and secondary oxidative amine dealkylation:** amine dealkylation occur by oxidation of α carbon atom.



Imipramine

Desmethylimipramine
(desipramine)

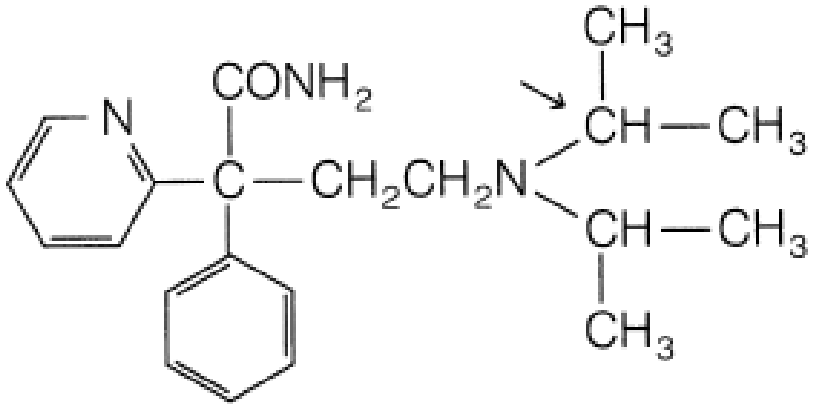
Bisdesmethylimipramine



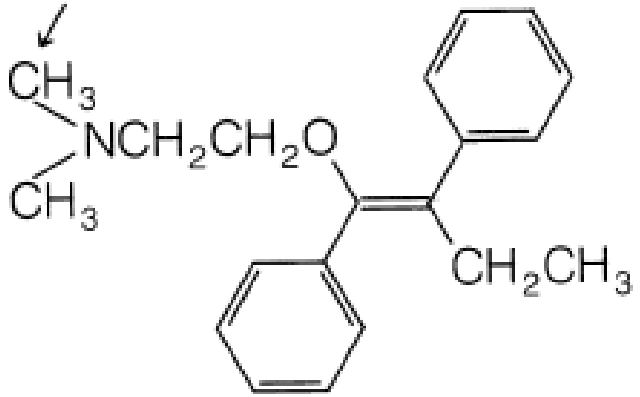
Lidocaine

Monoethylglycylxylidine
(MEGX)

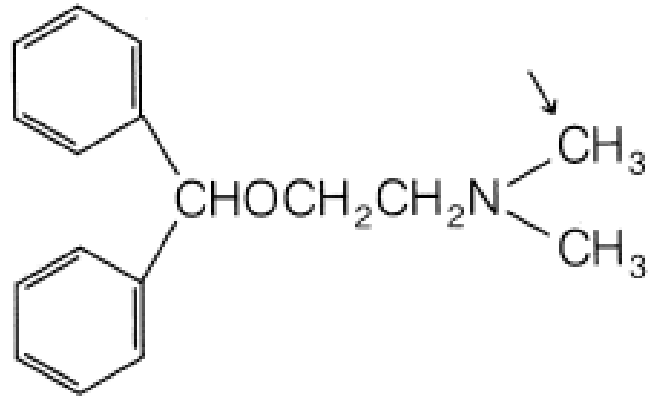
Glycyl-2,6-xylidine



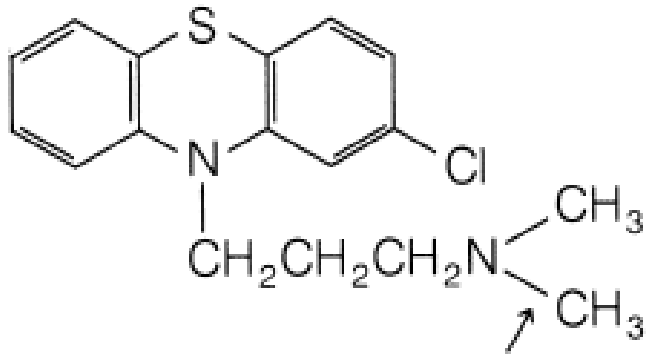
Disopyramide



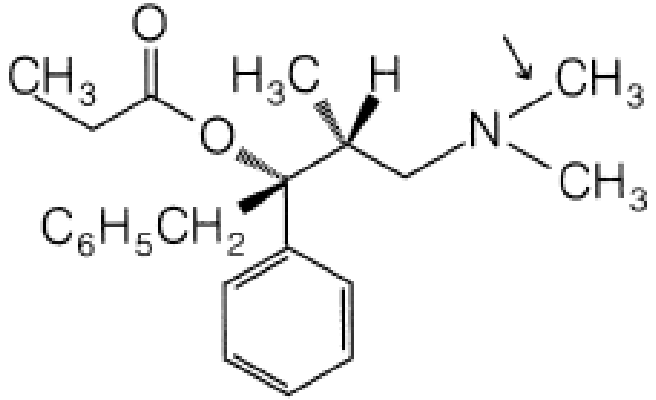
Tamoxifen



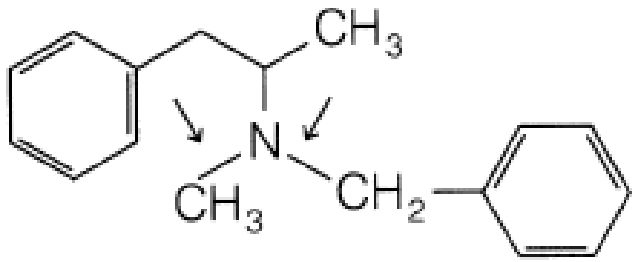
Diphenhydramine



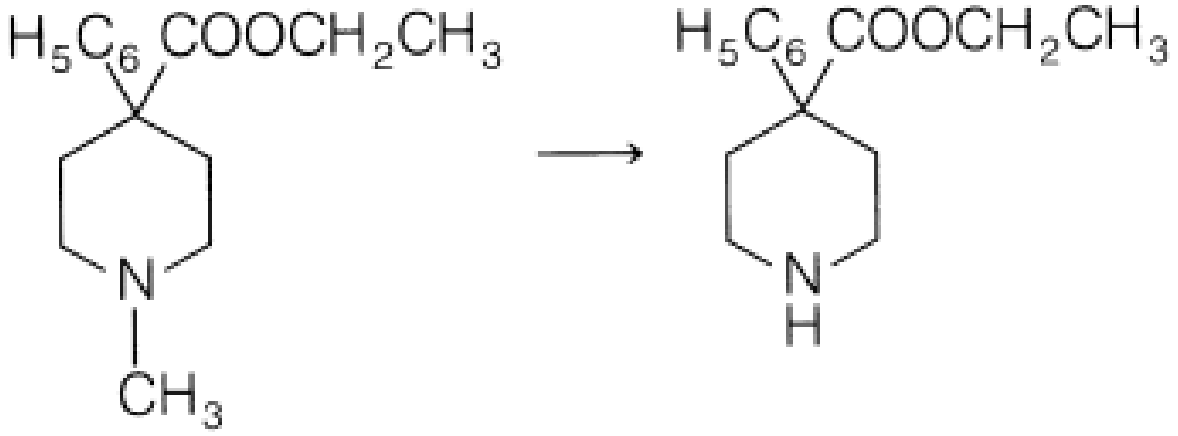
Chlorpromazine



(+)-α-Propoxyphene

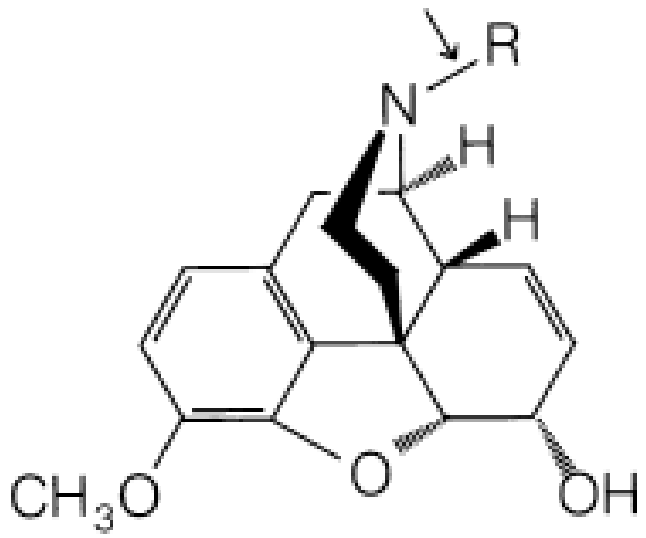


Benzphetamine
(N-demethylation
and N-debenzylation)



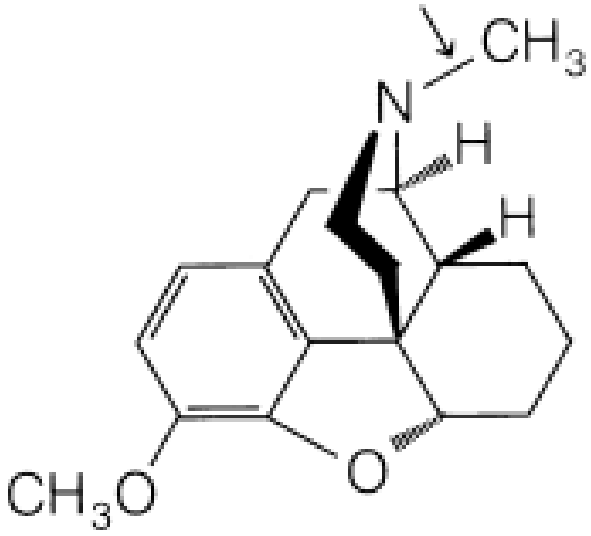
Meperidine

Normeperidine

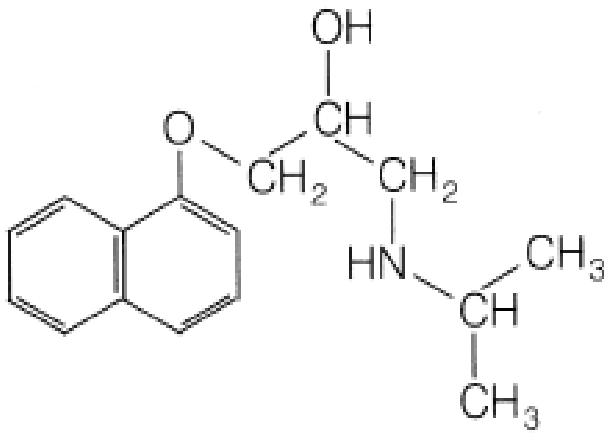


Morphine R = CH_3

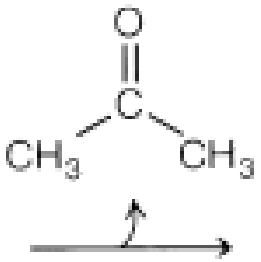
N-Ethylnormorphine R = CH_2CH_3

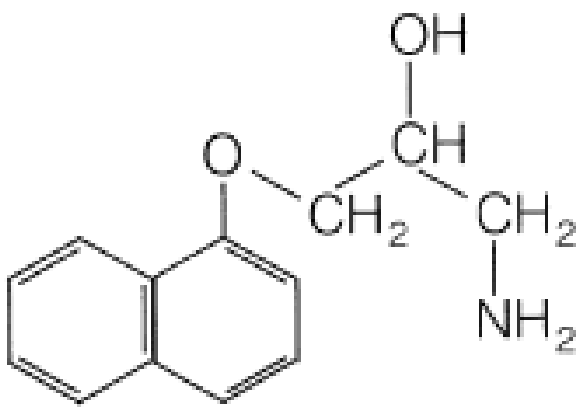


Dextromethorphan



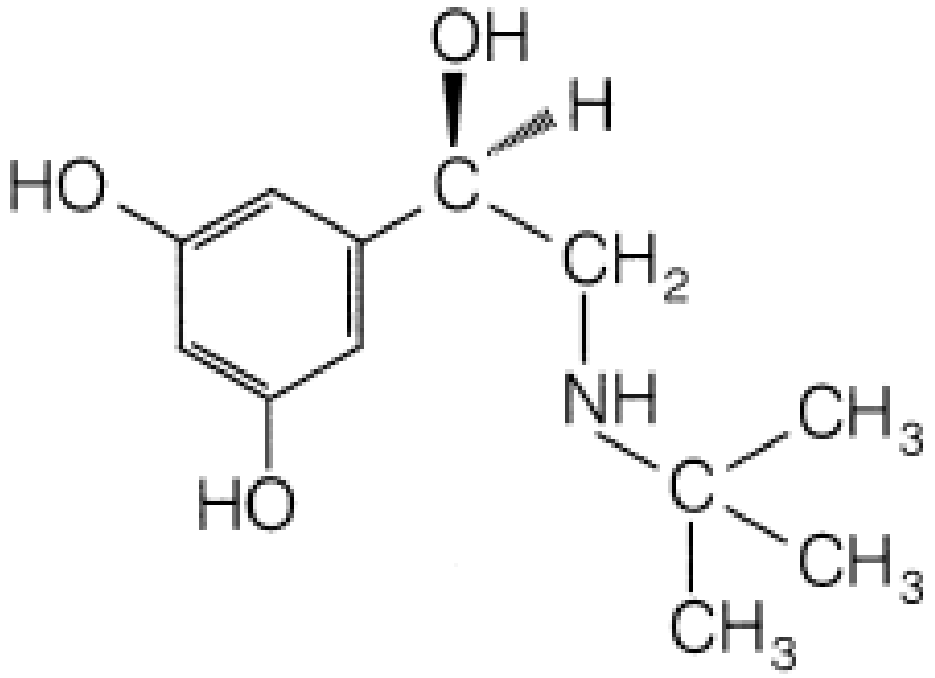
Propranolol



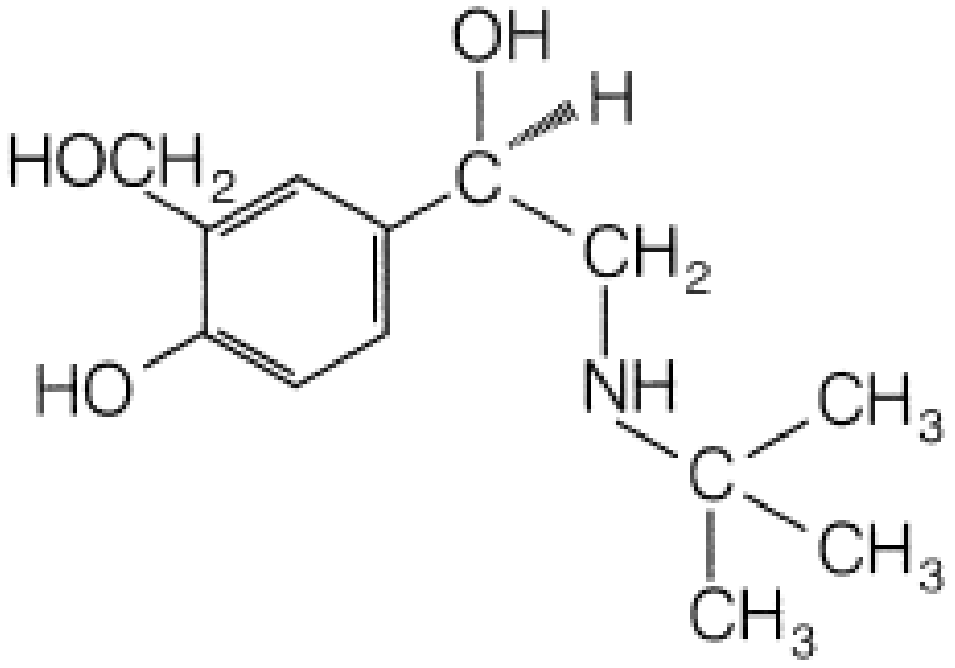


Primary Amine Metabolite
(Desisopropyl Propranolol)

- The *N*-*t*-butyl group present in many -adrenergic antagonists, such as terbutaline and salbutamol, remains intact and does not appear to undergo any significant metabolism.

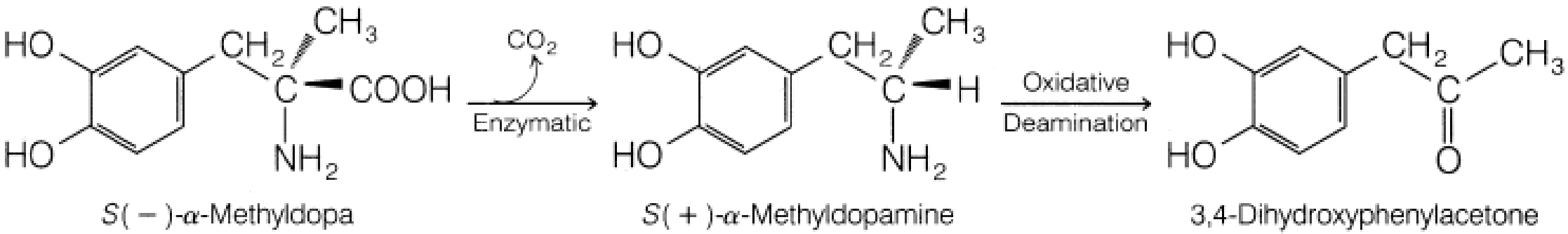


Terbutaline



Salbutamol

B) oxidative deamination:

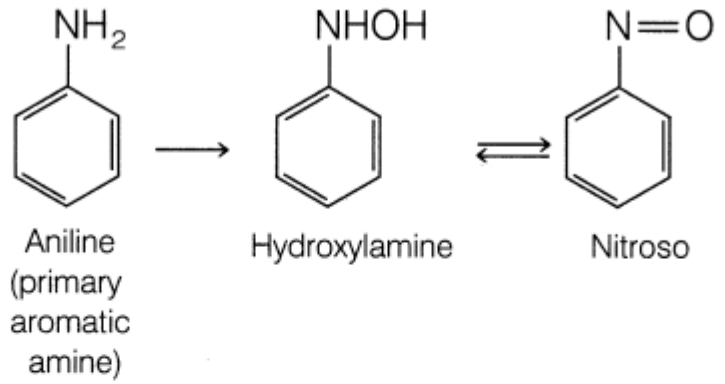


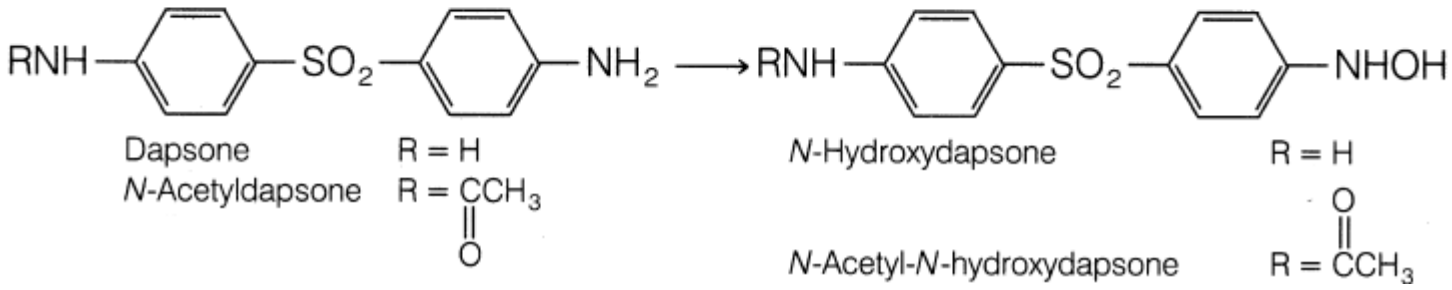
S(−)-α-Methyldopa

S(+)-α-Methyldopamine

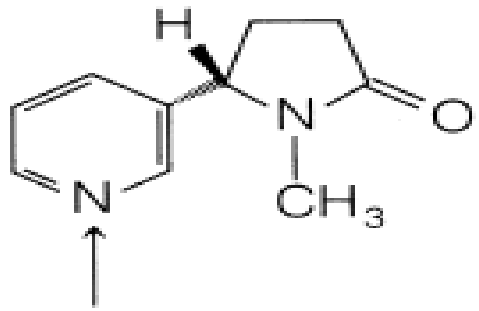
3,4-Dihydroxyphenylacetone

- The biotransformation of aromatic amines parallels the carbon and nitrogen oxidation reactions seen for aliphatic amines.
- Methemoglobinemia toxicity is caused by several aromatic amines, including aniline and dapsone, and is a result of the bioconversion of the aromatic amine to its N-hydroxy derivative.

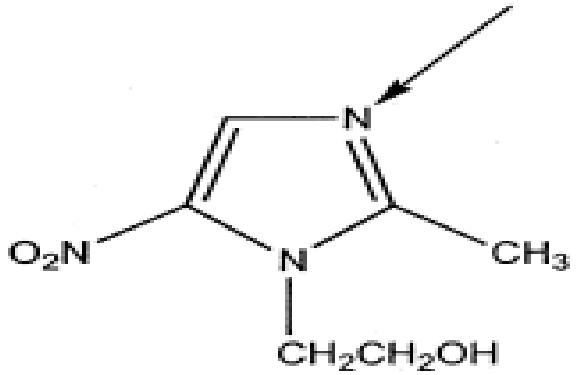




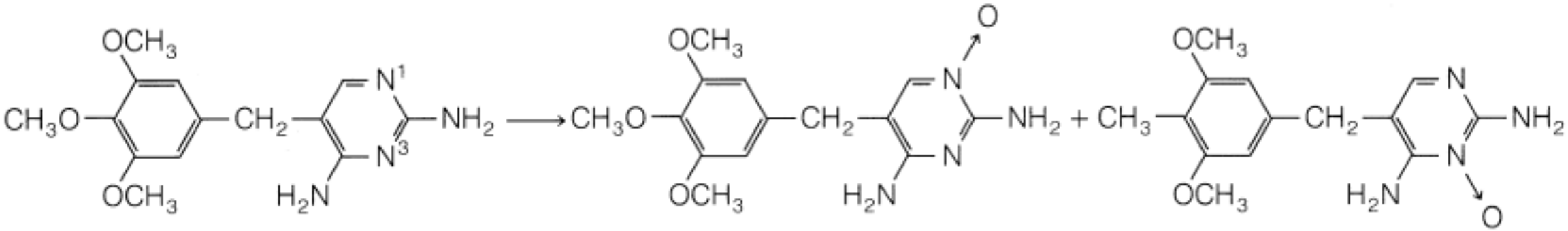
- Apparently, the N-hydroxylamine oxidizes the Fe+2 form of hemoglobin to its Fe+3 form. This oxidized (Fe+3) state of hemoglobin (called methemoglobin or ferrihemoglobin) can no longer transport oxygen, which leads to serious hypoxia or anemia, a unique type of chemical suffocation.
- Diverse aromatic amines (especially azoamino dyes) are known to be carcinogenic.
- N-oxidation plays an important role in bioactivating these aromatic amines to potentially reactive electrophilic species that covalently bind to cellular protein, DNA, or RNA.



Cotinine



Metronidazole



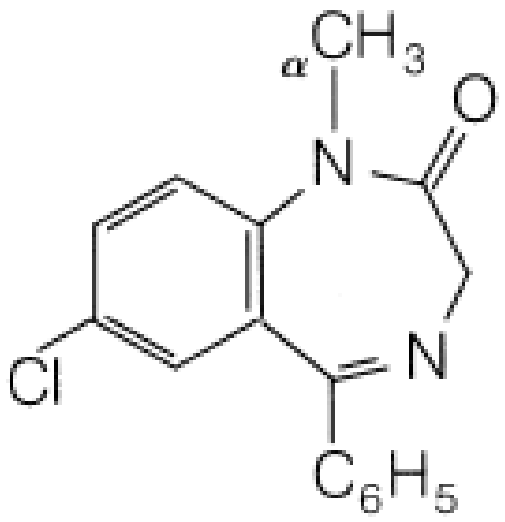
Trimethoprim

1-*N*-Oxide

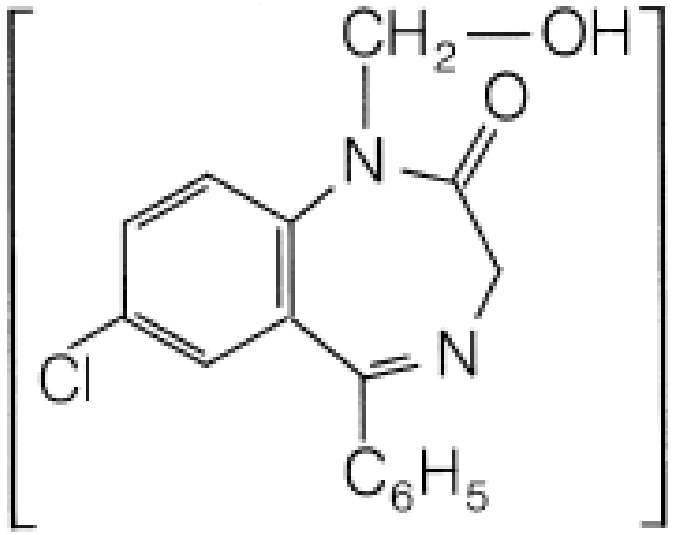
3-*N*-Oxide

C) Amides:

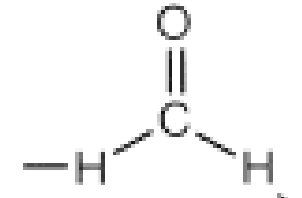
- Amide functionalities are susceptible to oxidative carbon–nitrogen bond cleavage (via α-carbon hydroxylation) and N-hydroxylation reactions.
- Oxidative dealkylation of many N-substituted amide drugs and xenobiotics has been reported. For example, diazepam undergoes extensive N-demethylation.

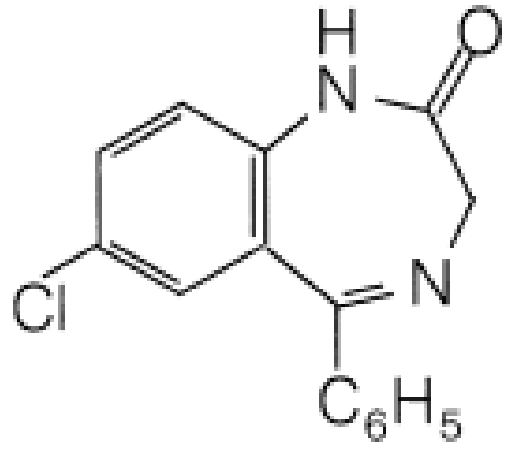


Diazepam

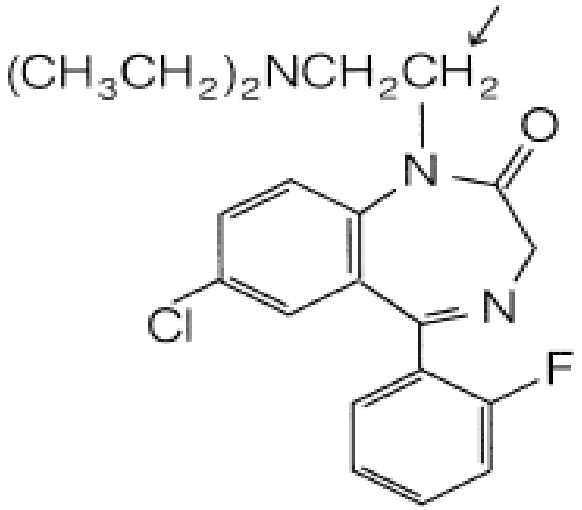


Carbinolamide

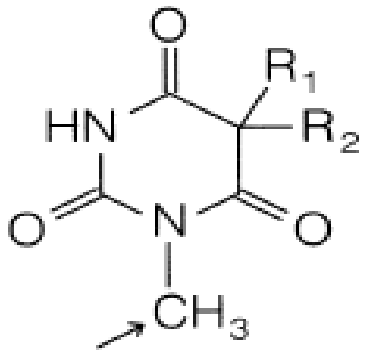


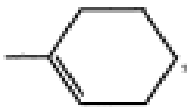


Desmethyldiazepam

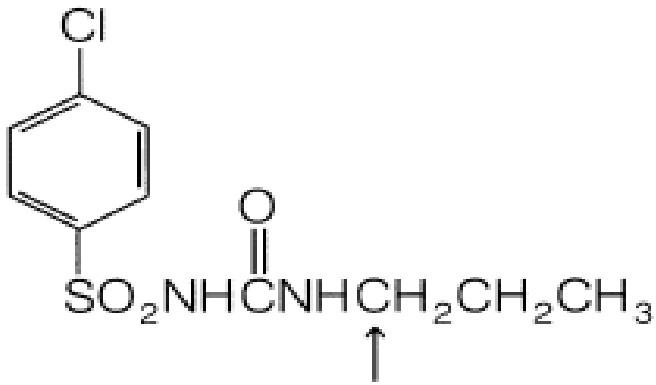


Flurazepam



Hexobarbital R_1 =  , $R_2 = CH_3$

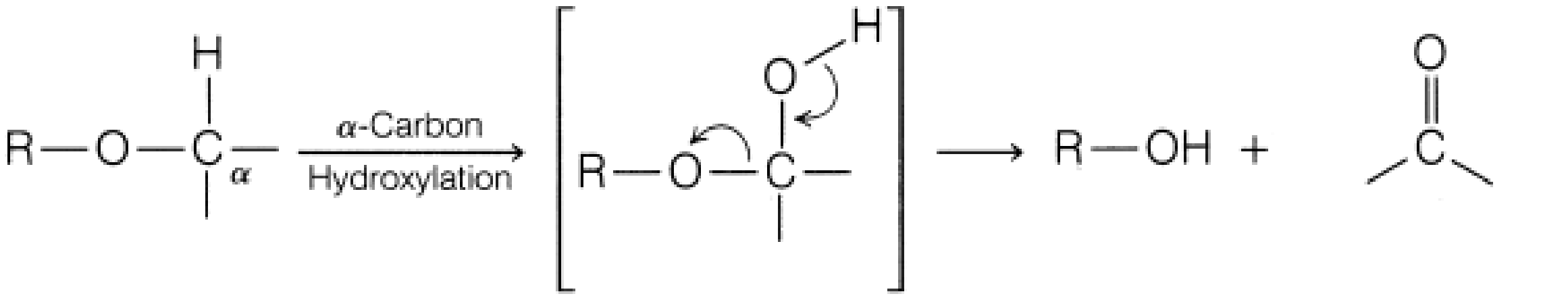
Mephobarbital $R_1 = C_6H_5$, $R_2 = CH_2CH_3$



Chlorpropamide

OXIDATION INVOLVING CARBON–OXYGEN SYSTEMS

- Oxidative O-dealkylation of carbon–oxygen systems (principally ethers) is catalyzed by microsomal mixed function oxidases.
- Mechanistically, the biotransformation involves an initial α-carbon hydroxylation to form either a hemiacetal or a hemiketal, which undergoes spontaneous carbon–oxygen bond cleavage to yield the dealkylated oxygen species (phenol or alcohol) and a carbon moiety (aldehyde or ketone).
- Small alkyl groups (e.g., methyl or ethyl) attached to oxygen are O-dealkylated rapidly. For example, morphine is the metabolic product of O-demethylation of codeine. The antipyretic and analgesic activities of phenacetin in humans appear to be a consequence of O-deethylation to the active metabolite acetaminophen.

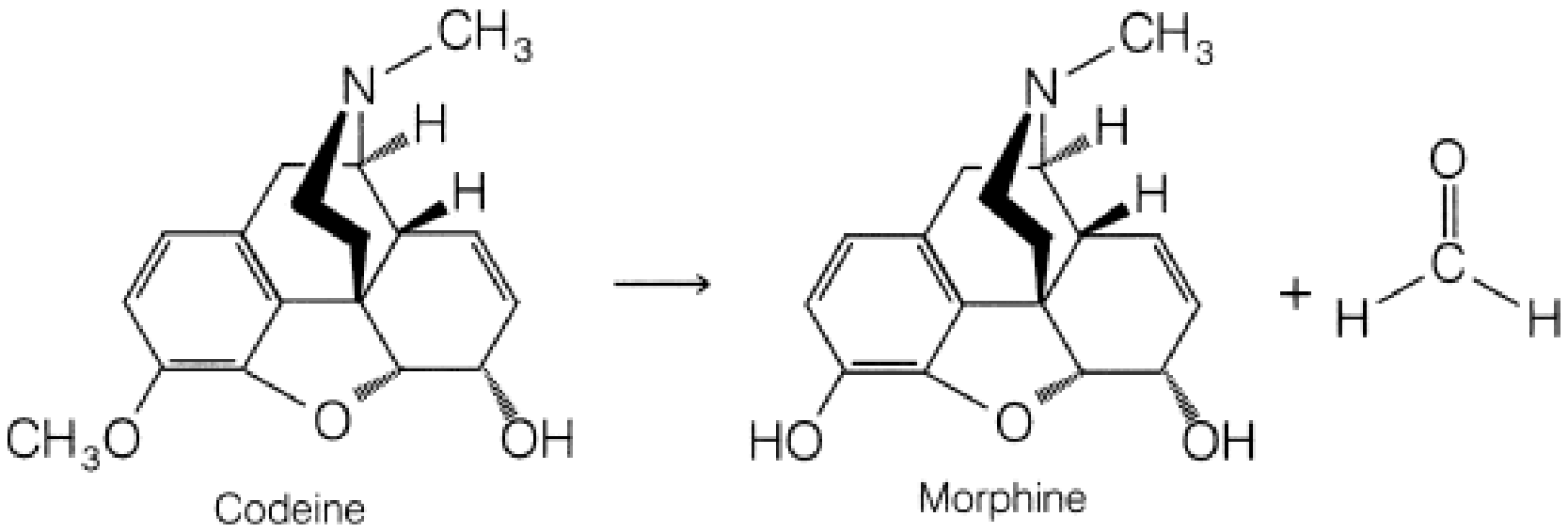


Ether

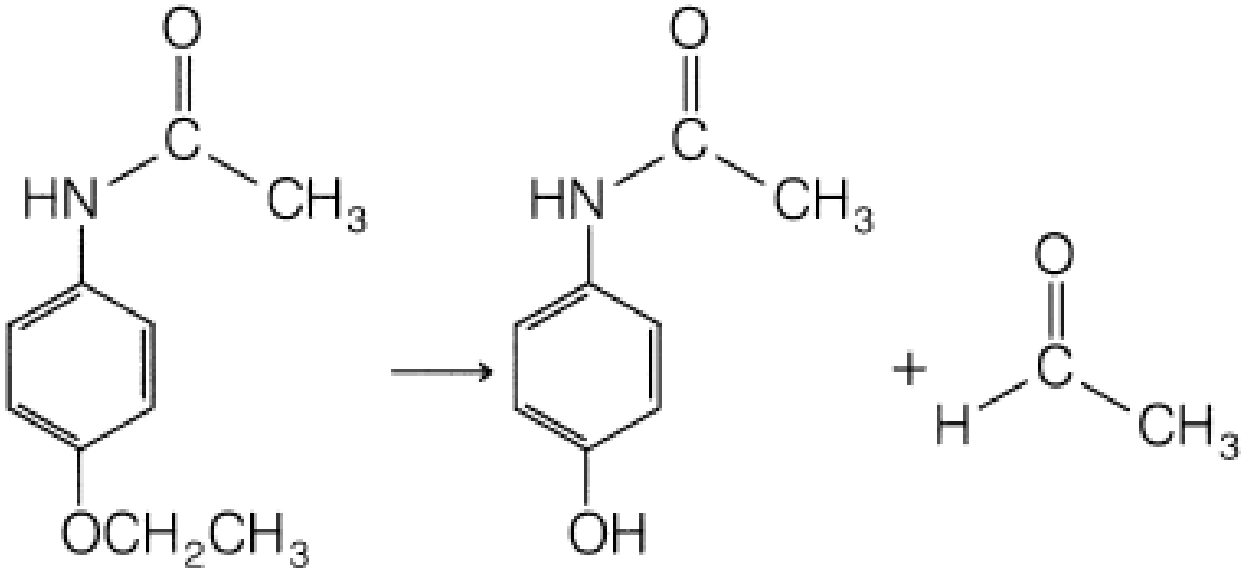
Hemiacetal or Hemiketal

Phenol or Alcohol

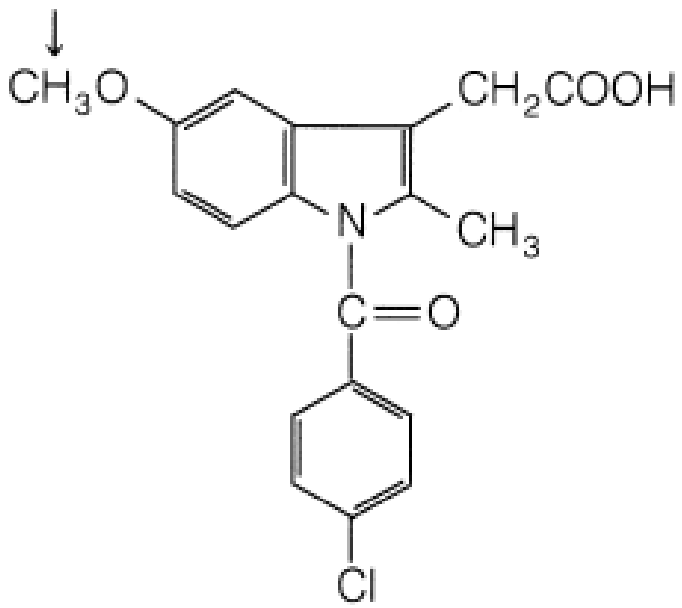
Carbonyl Moiety (aldehyde or ketone)



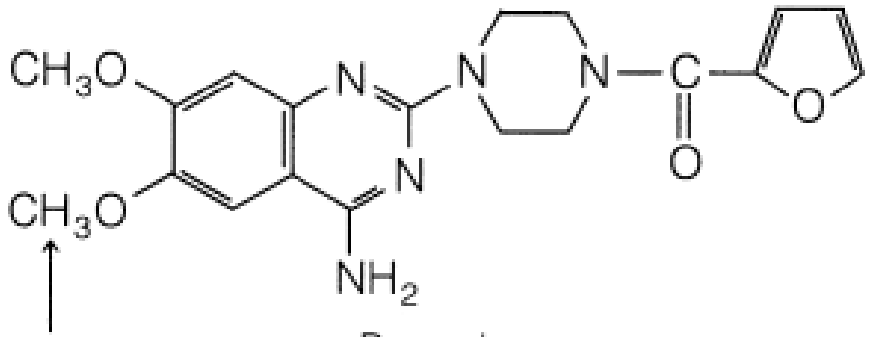
Codeine Morphine



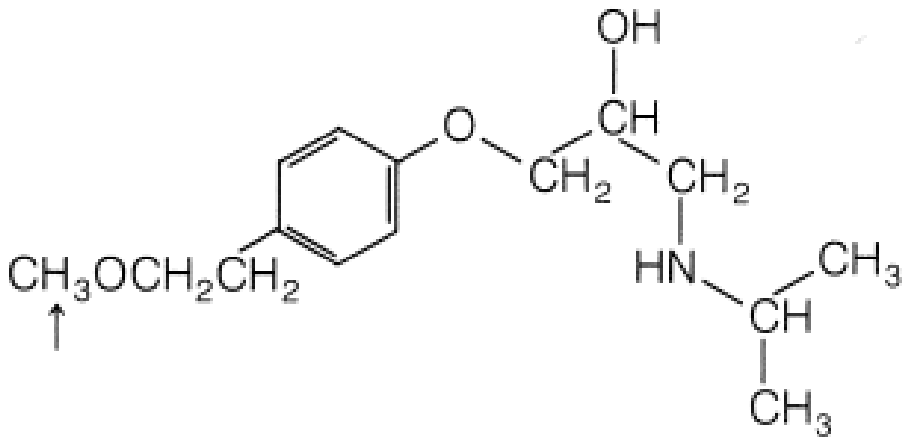
Phenacetin Acetaminophen



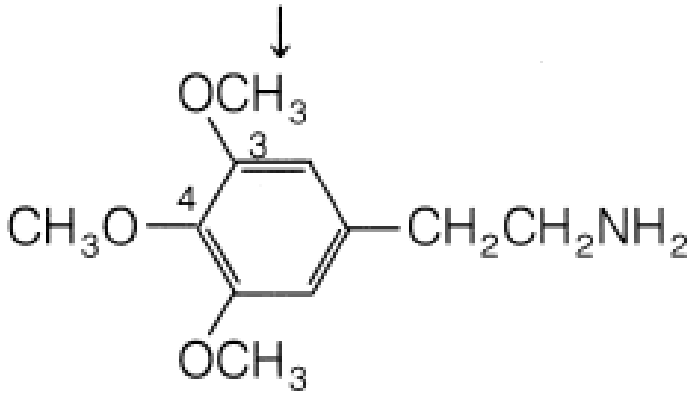
Indomethacin



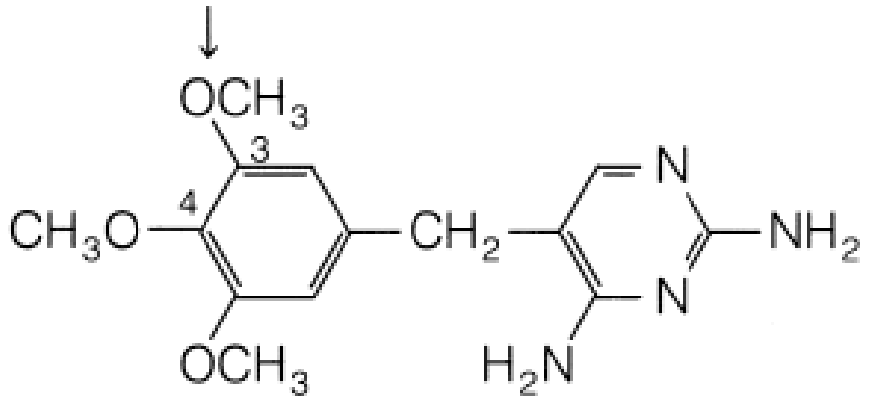
Prazosin



Metoprolol



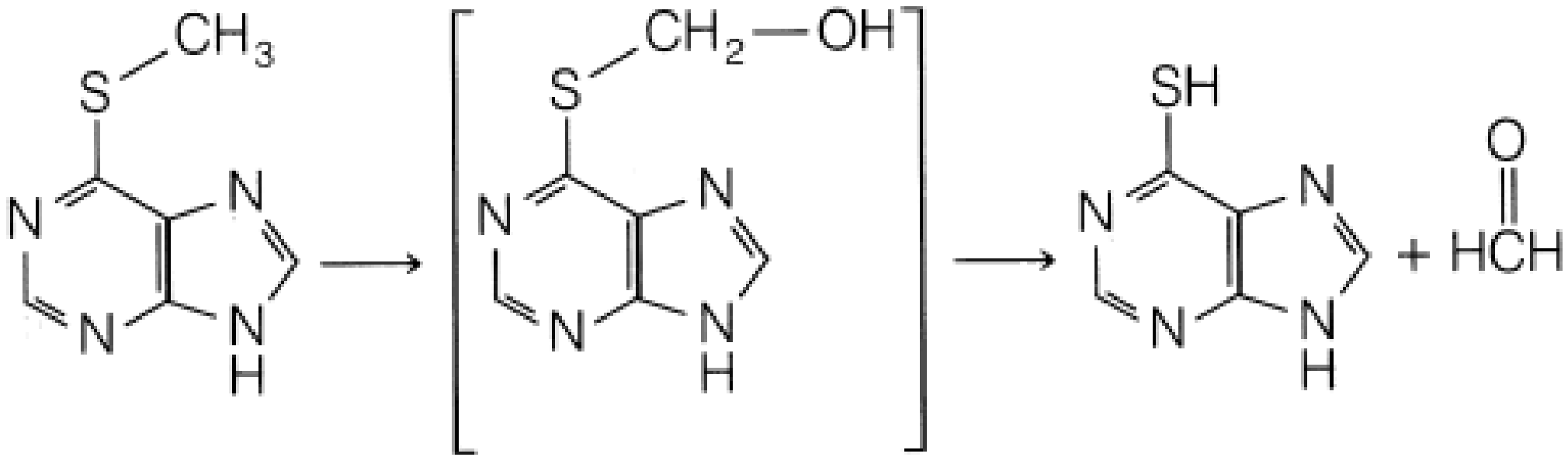
Mescaline



Trimethoprim

OXIDATION INVOLVING CARBON–SULFUR SYSTEMS

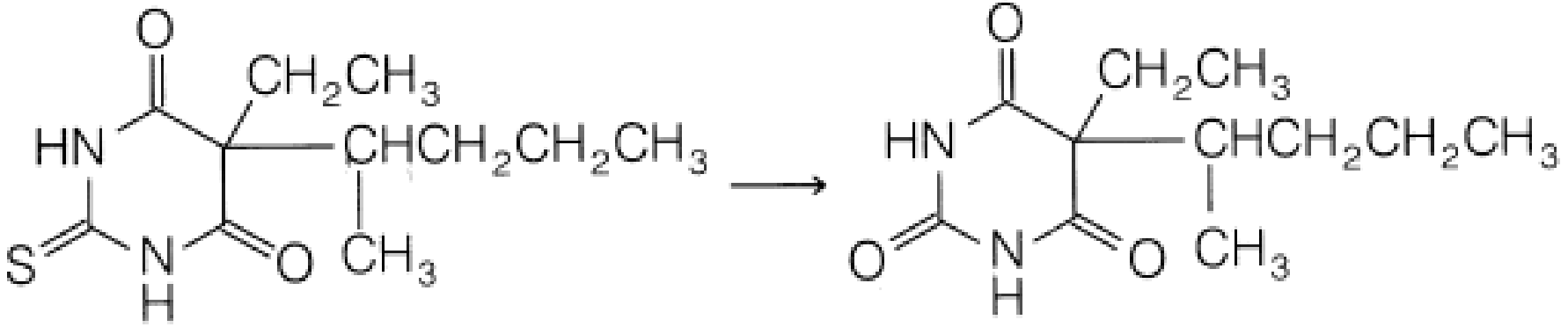
- Carbon–sulfur functional groups are susceptible to metabolic S-dealkylation, desulfuration, and S-oxidation reactions.
- The first two processes involve oxidative carbon–sulfur bond cleavage.
- S-dealkylation is analogous to O- and N-dealkylation mechanistically (i.e., it involves α-carbon hydroxylation) and has been observed for various sulfur xenobiotics. For example, 6- (methylthio)purine is demethylated oxidatively in rats to 6-mercaptopurine.



6-(Methylthio)-purine

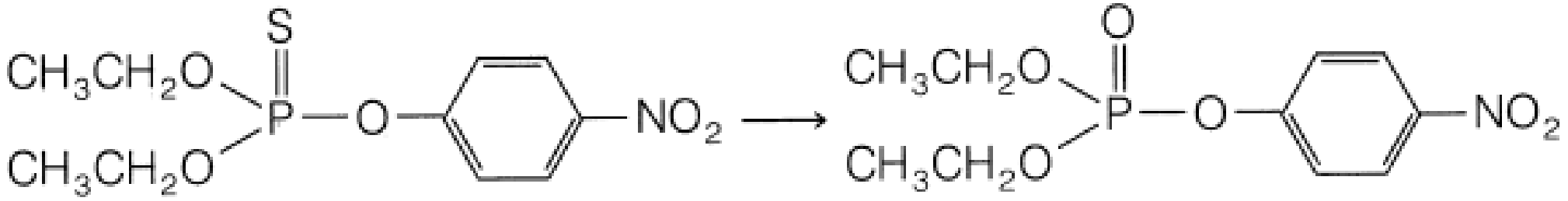
6-Mercaptopurine

- Oxidative conversion of carbon–sulfur double bonds (C=S) (thiono) to the corresponding carbon–oxygen double bond (C=O) is called desulfuration.
- A well-known drug example of this metabolic process is the biotransformation of thiopental to its corresponding oxygen analog pentobarbital.
- An analogous desulfuration reaction also occurs with the P=S moiety present in several organophosphate insecticides, such as parathion. Desulfuration of parathion leads to the formation of paraoxon, which is the active metabolite responsible for the anticholinesterase activity of the parent drug.



Thiopental

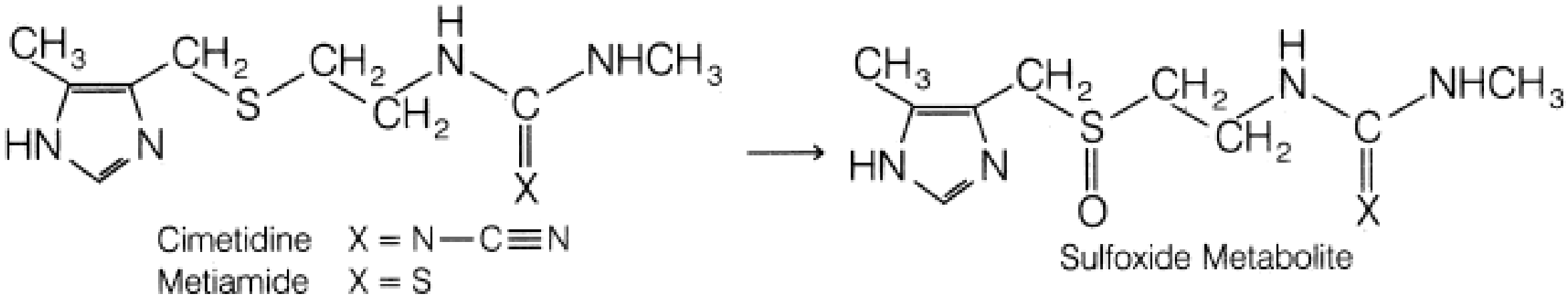
Pentobarbital



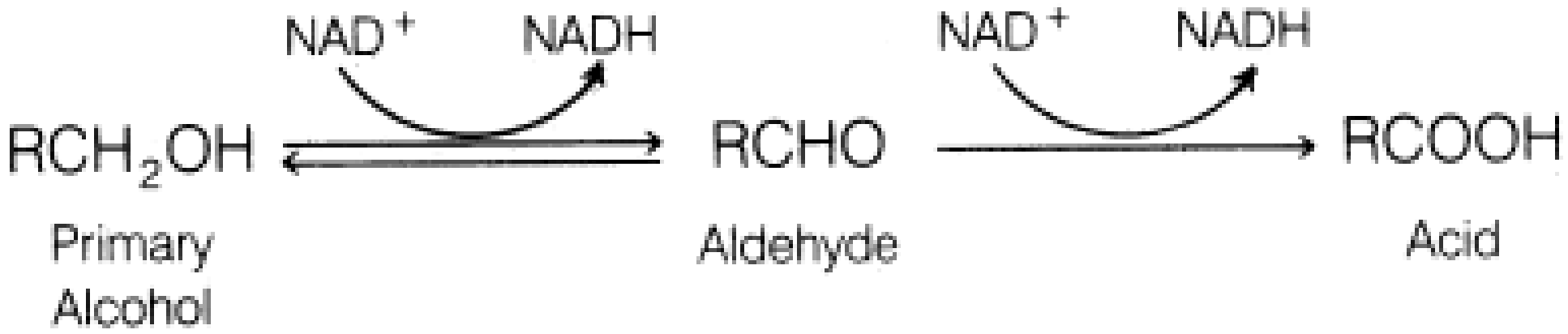
Parathion

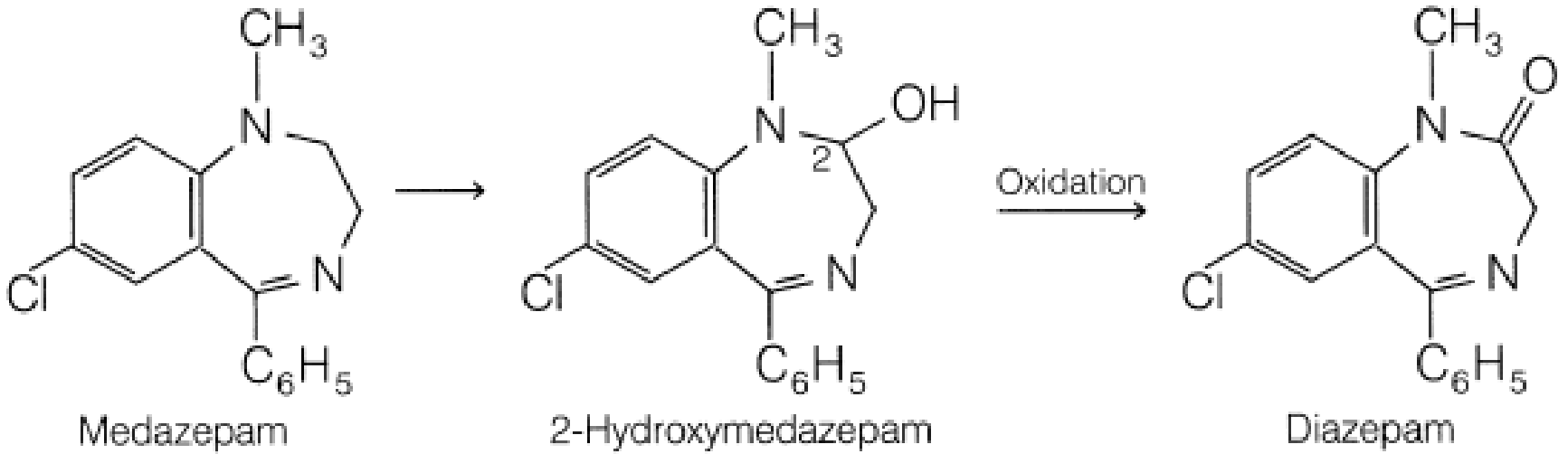
Paraoxon

- S-oxidation constitutes an important pathway in the metabolism of the H2-histamine antagonists cimetidine and metiamide. The corresponding sulfoxide derivatives are the major human urinary metabolites.



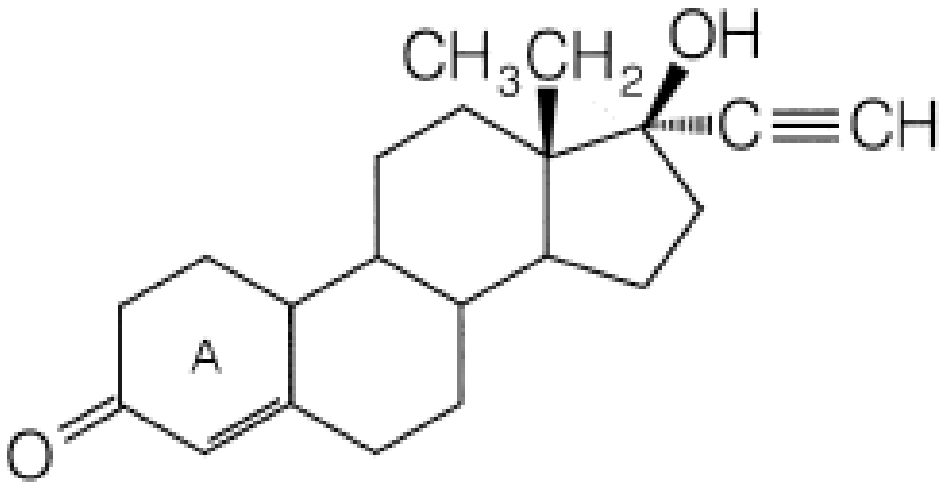
Oxidation of Alcohols and Aldehydes



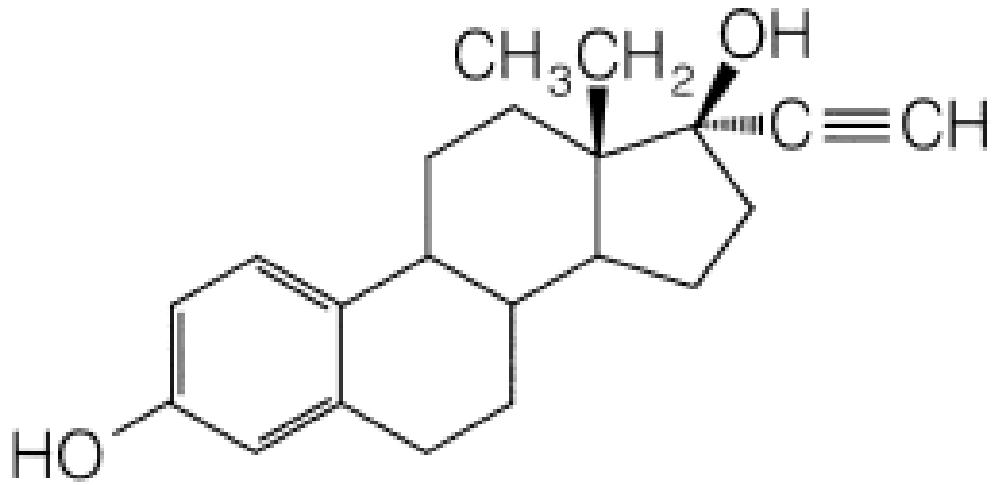


REDUCTIVE REACTIONS

- Reductive processes play an important role in the metabolism of many compounds containing carbonyl, nitro, and azo groups.
- Bioreduction of **carbonyl** compounds generates alcohol derivatives, whereas nitro and azo reductions lead to amino derivatives.
- The hydroxyl and amino moieties of the metabolites are much more susceptible to conjugation than the functional groups of the parent compounds. Hence, reductive processes, as such, facilitate drug elimination.



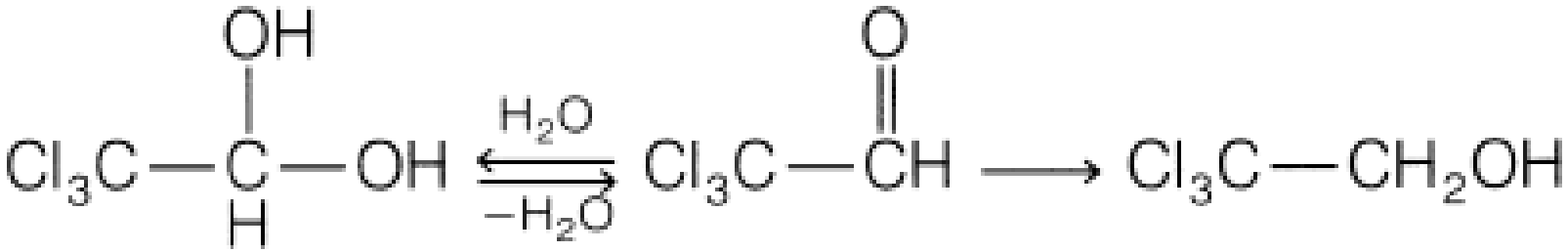
Norgestrel



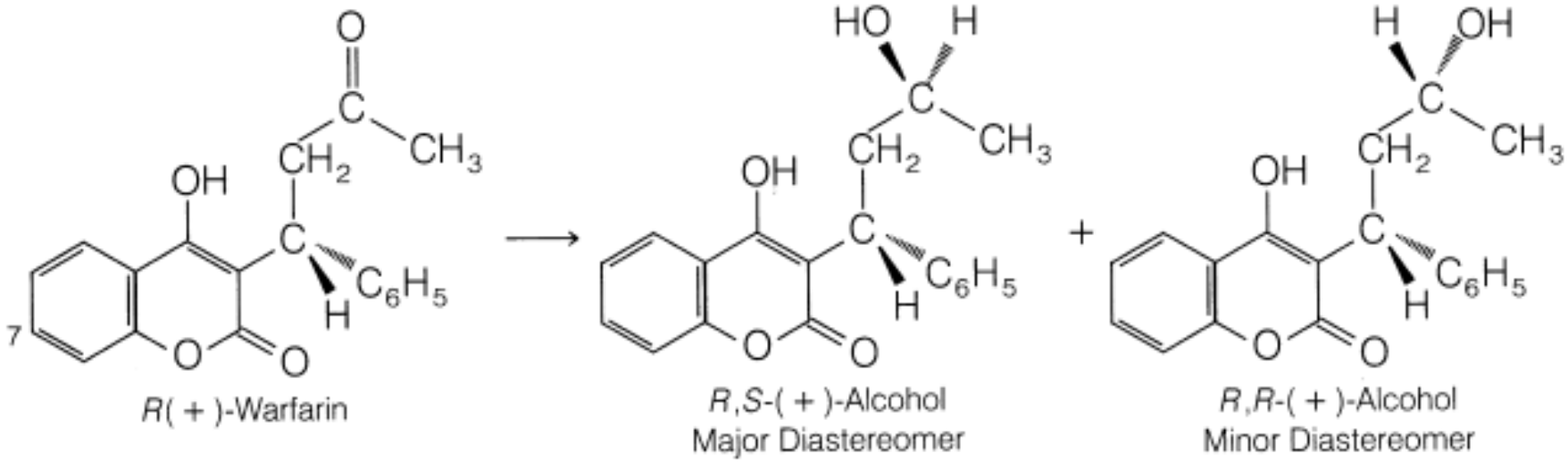
17α-Ethinyl-18-homoestradiol

Reduction of Aldehyde and Ketone Carbonyls

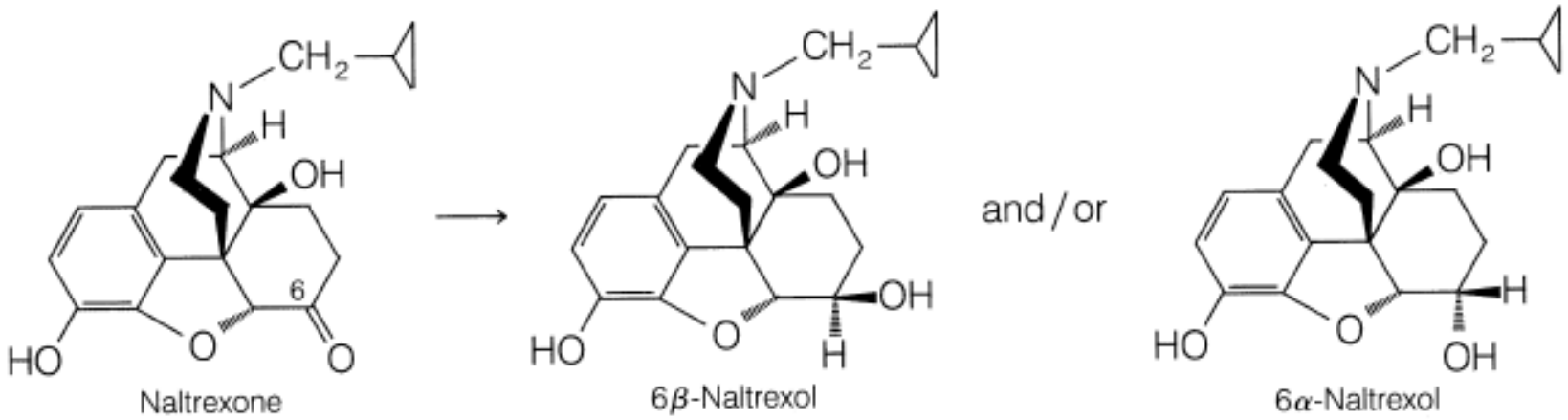
- Diverse soluble enzymes, called aldo-keto reductases, carry out bioreduction of aldehydes and ketones. They are found in the liver and other tissues (e.g., kidney). Few aldehydes undergo bioreduction because of the relative ease of oxidation of aldehydes to carboxylic acids. However, one frequently cited example of a parent aldehyde drug undergoing extensive enzymatic reduction is the sedative–hypnotic chloral hydrate. Further glucuronidation of the alcohol leads to an inactive conjugated product that is readily excreted in the urine.



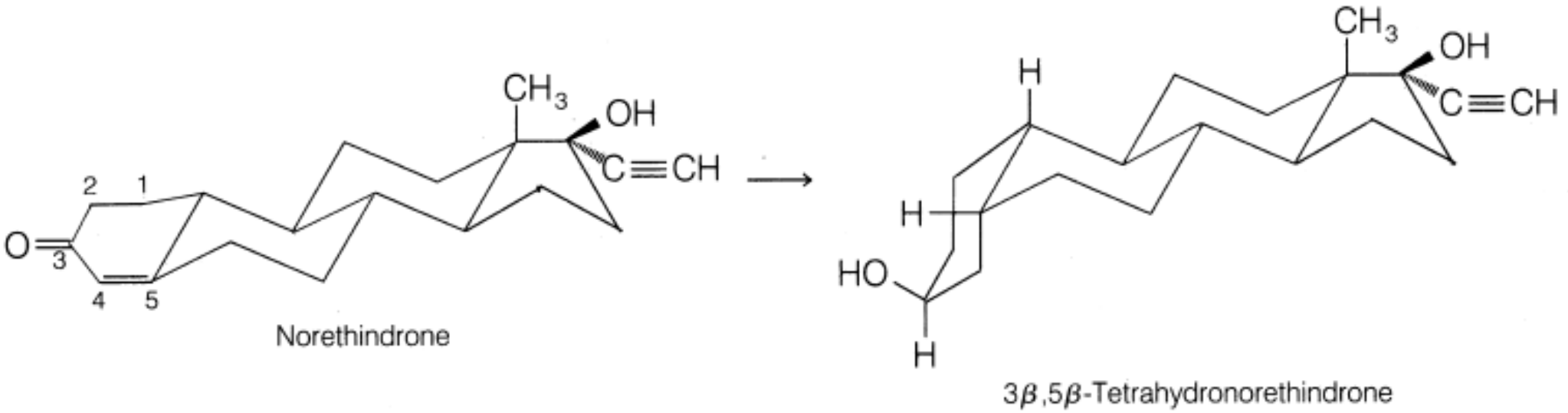
- When chiral ketones are reduced, they yield two possible diastereomeric or epimeric alcohols. For example, the (R)(+) enantiomer of the oral anticoagulant warfarin undergoes extensive reduction of its side chain keto group to generate the (R,S)(+) alcohol as the major plasma metabolite in humans. Small amounts of the (R,R)(+) diastereomer are also formed. In contrast, the (S)(-) enantiomer undergoes little ketone reduction and is primarily 7-hydroxylated (i.e., aromatic hydroxylation) in humans.



- Reduction of the 6-keto functionality in the naltrexone can lead to either the epimeric 6α- or 6β-hydroxy metabolites, depending on the animal species. In humans and rabbits, bioreduction of naltrexone is highly stereoselective and generates only 6 β -naltrexol.



- Reduction of α,β-unsaturated ketones results in reduction not only of the ketone group but of the carbon–carbon double bond as well.
- Steroidal drugs often fall into this class, including norethindrone, the major plasma and urinary metabolite of norethindrone is the 3β,5β-tetrahydro derivative.

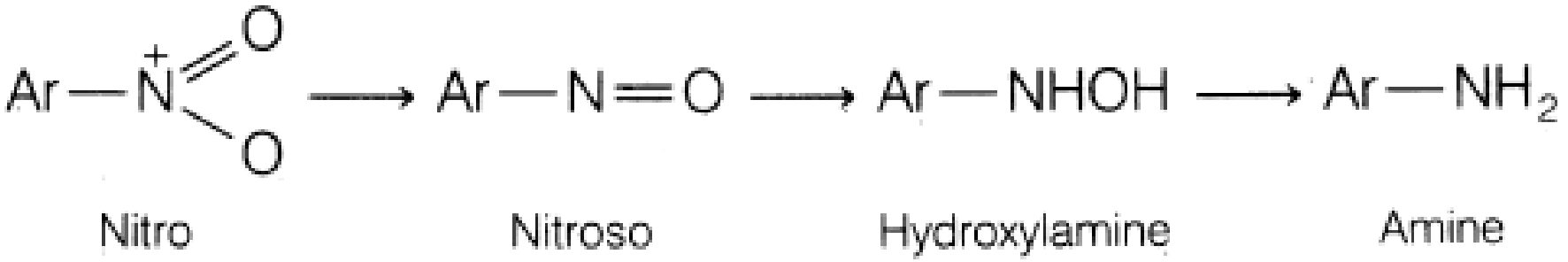


Norethindrone

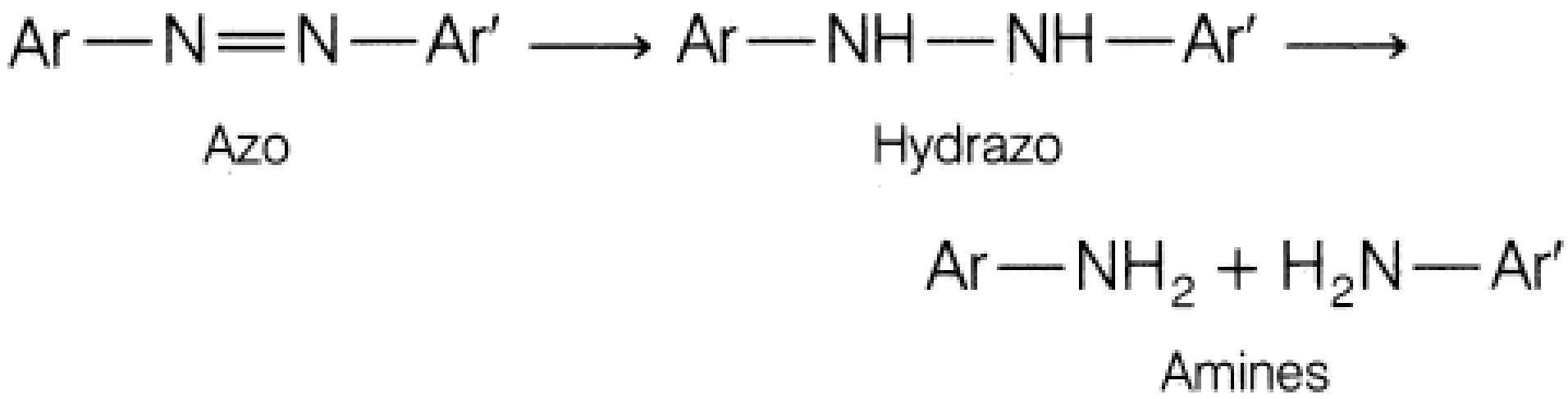
3β,5β-Tetrahydronorethindrone

Reduction of Nitro and Azo Compounds

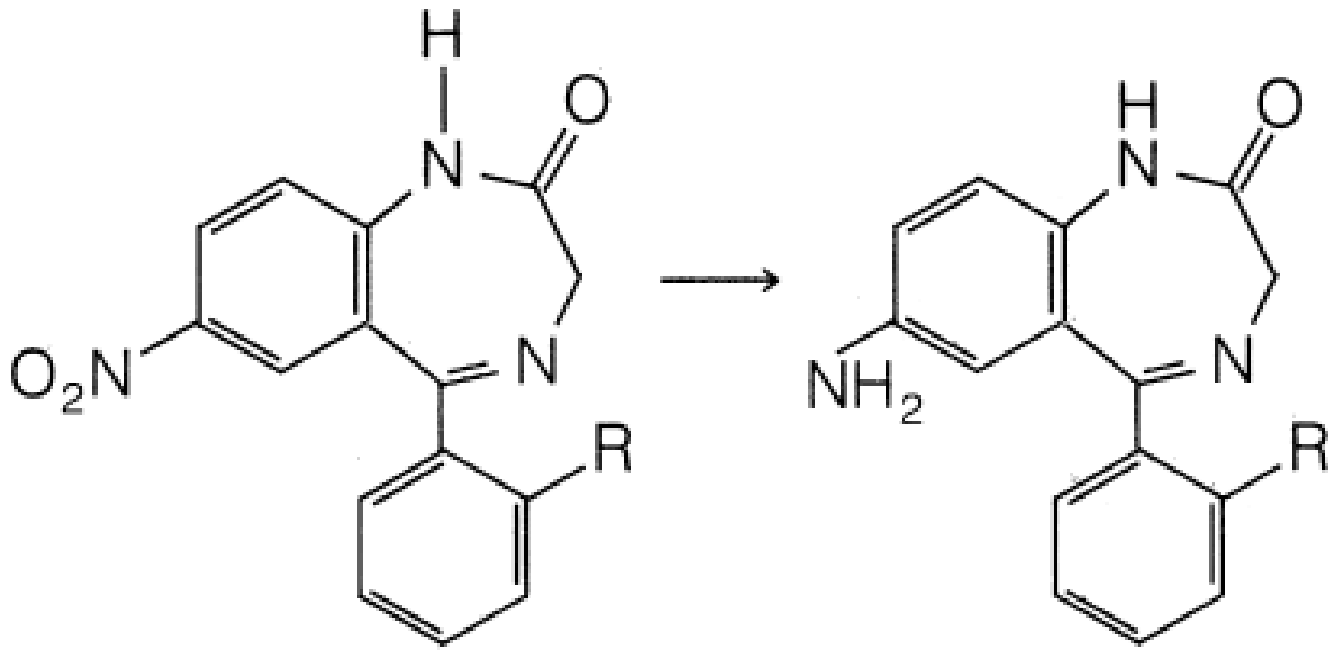
- The reduction of aromatic nitro and azo xenobiotics leads to aromatic primary amine metabolites. Aromatic nitro compounds are reduced initially to the nitroso and hydroxylamine intermediates, as shown in the following metabolic sequence:



- Azo reduction, however, is believed to proceed via a hydrazo intermediate (-NH-NH-) that subsequently is cleaved reductively to yield the corresponding aromatic amines:



- Bioreduction of nitro compounds is carried out by NADPH-dependent microsomal and soluble nitro reductases present in the liver.
- In addition, bacterial reductases present in the intestine can reduce nitro and azo compounds, especially those that are absorbed poorly or excreted mainly in the bile.
- Various aromatic nitro drugs undergo enzymatic reduction to the corresponding aromatic amines. For example, the 7-nitro benzodiazepine derivatives clonazepam and nitrazepam are metabolized extensively to their respective 7-amino metabolites in humans.

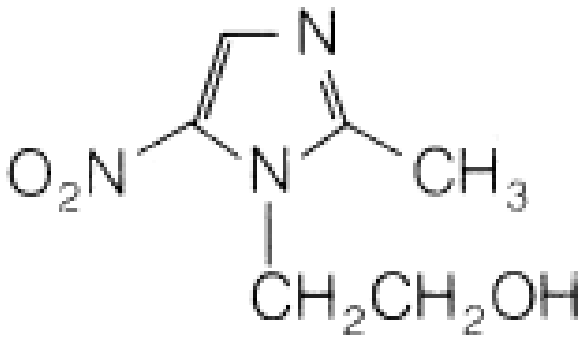


Clonazepam, R = Cl
Nitrazepam, R = H

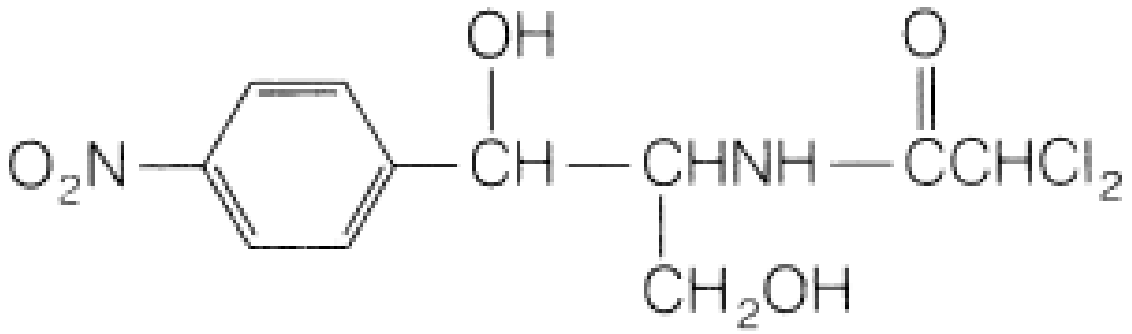
7-Amino Metabolite

- For some nitro xenobiotics, bioreduction appears to be a minor metabolic pathway in vivo, because of competing oxidative and conjugative reactions.
- Under artificial anaerobic in vitro incubation conditions, however, these same nitro xenobiotics are enzymatically reduced rapidly. For example, most of the urinary metabolites of metronidazole found in humans are either oxidation or conjugation products. Reduced metabolites of metronidazole have not been detected. When incubated anaerobically with guinea pig liver preparations, however, metronidazole undergoes considerable nitro reduction.

- Bacterial reductase present in the intestine also tends to complicate in vivo interpretations of nitro reduction. For example, in rats, the antibiotic chloramphenicol is not reduced in vivo by the liver but is excreted in the bile and, subsequently, reduced by intestinal flora to form the amino metabolite.

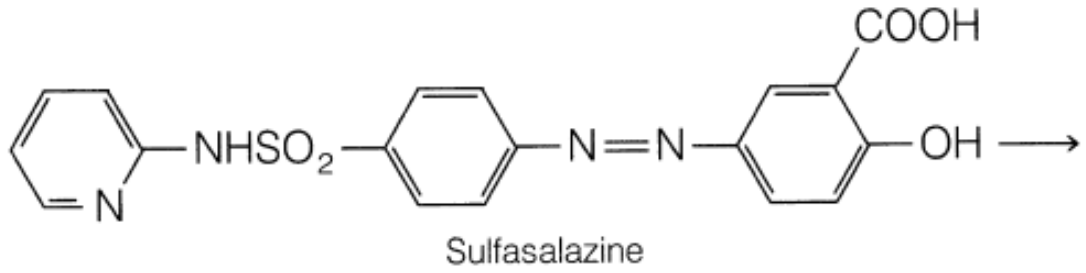


Metronidazole



Chloramphenicol

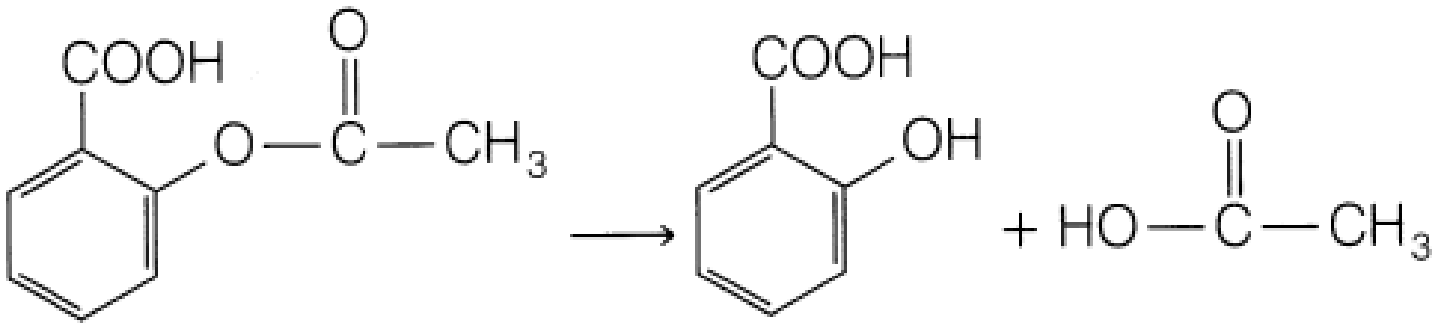
- The importance of intestinal reduction is further revealed in the metabolism of sulfasalazine, a drug used in the treatment of ulcerative colitis. The drug is absorbed poorly and undergoes reductive cleavage of the azo linkage to yield sulfapyridine and 5-aminosalicylic acid. The reaction occurs primarily in the colon and is carried out principally by intestinal bacteria.



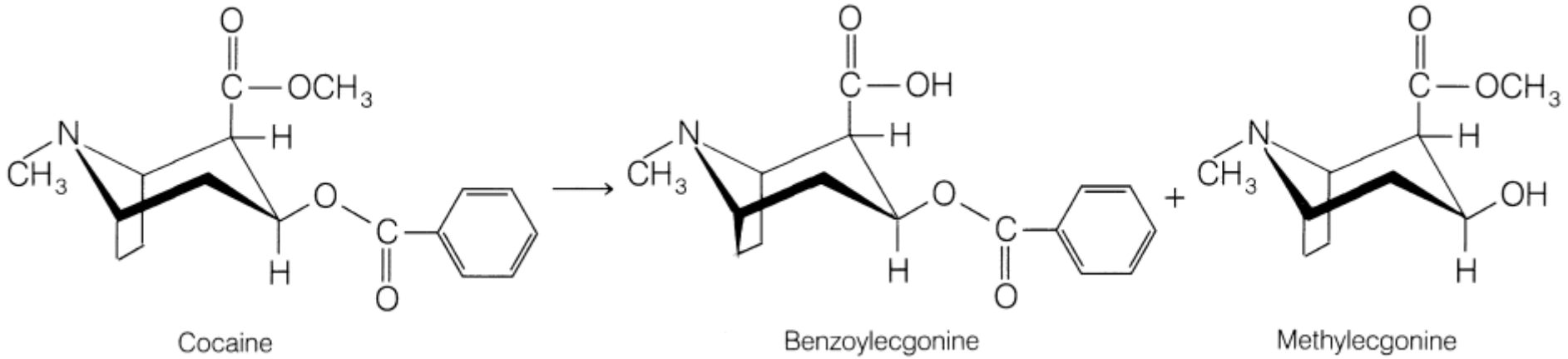
HYDROLYTIC REACTIONS
Hydrolysis of Esters and Amides

- The metabolism of ester and amide linkages in many drugs is catalyzed by hydrolytic enzymes present in various tissues and in plasma.
- The metabolic products formed (carboxylic acids, alcohols, phenols, and amines) generally are polar and functionally more susceptible to conjugation and excretion than the parent ester or amide drugs.
- The enzymes carrying out ester hydrolysis include several nonspecific esterases found in the liver, kidney, and intestine as well as the pseudocholinesterases present in plasma.
- Amide hydrolysis appears to be mediated by liver microsomal amidases, esterases, and deacylases.

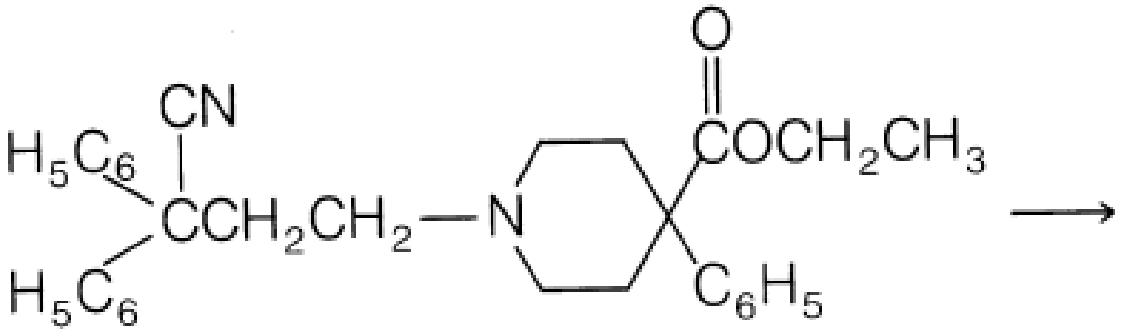
- A classic example of ester hydrolysis is the metabolic conversion of aspirin (acetylsalicylic acid) to salicylic acid.



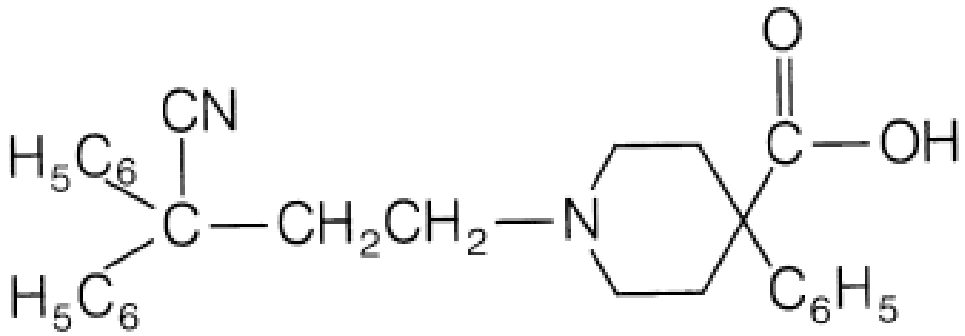
- Of the two ester moieties present in cocaine, it appears that, in general, the methyl group is hydrolyzed preferentially to yield benzoylecgonine as the major human urinary metabolite.
- The hydrolysis of cocaine to methyl ecgonine, however, also occurs in plasma and, to a minor extent, blood.



- Often, ester hydrolysis of the parent drug leads to pharmacologically active metabolites. For example, hydrolysis of diphenoxylate in humans leads to diphenoxylic acid, which is 5 times more potent an antidiarrheal agent than the parent ester.



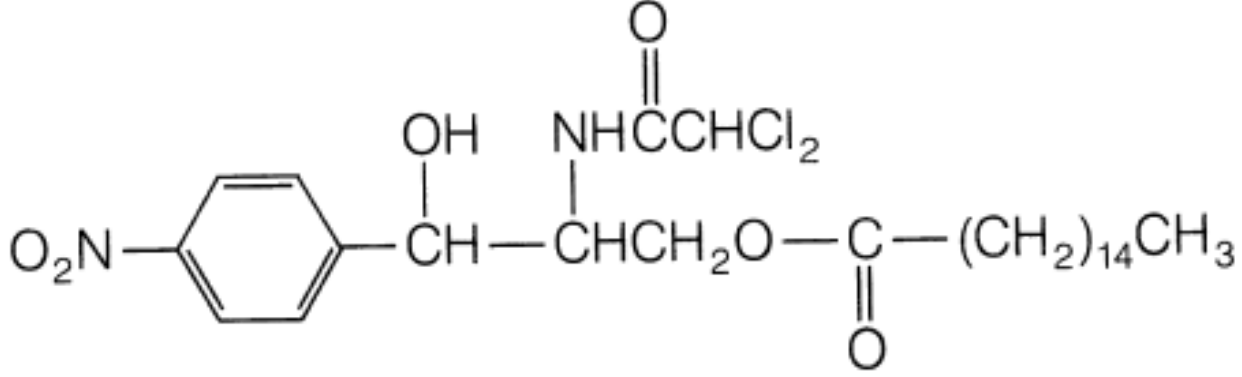
Diphenoxylate



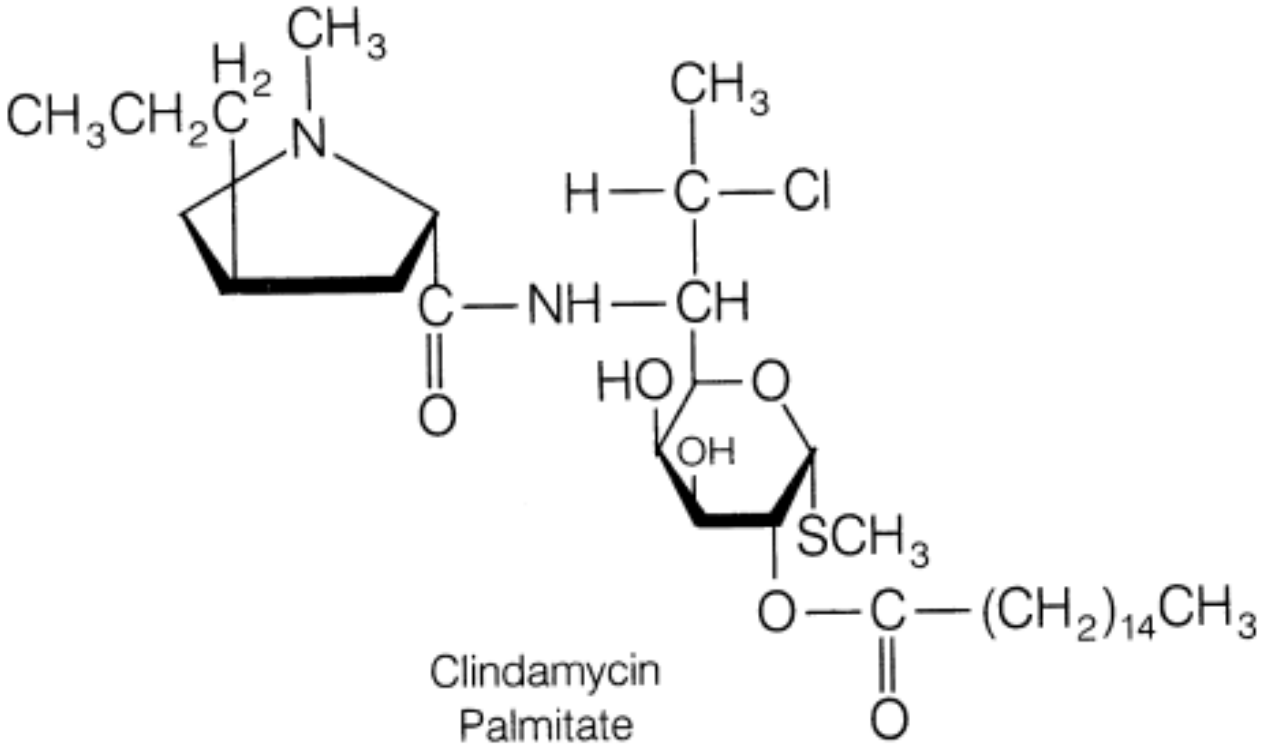
Diphenoxylic Acid
(Difenoxin)

- Many parent drugs have been chemically modified or derivatized to generate so-called prodrugs to overcome some undesirable property (e.g., bitter taste, poor absorption, poor solubility, irritation at site of injection).
- The rationale behind the prodrug concept was to develop an agent that, once inside the biological system, would be biotransformed to the active parent drug.
- The presence of esterases in many tissues and plasma makes ester derivatives logical prodrug candidates, because hydrolysis would cause the ester prodrug to revert to the parent compound.

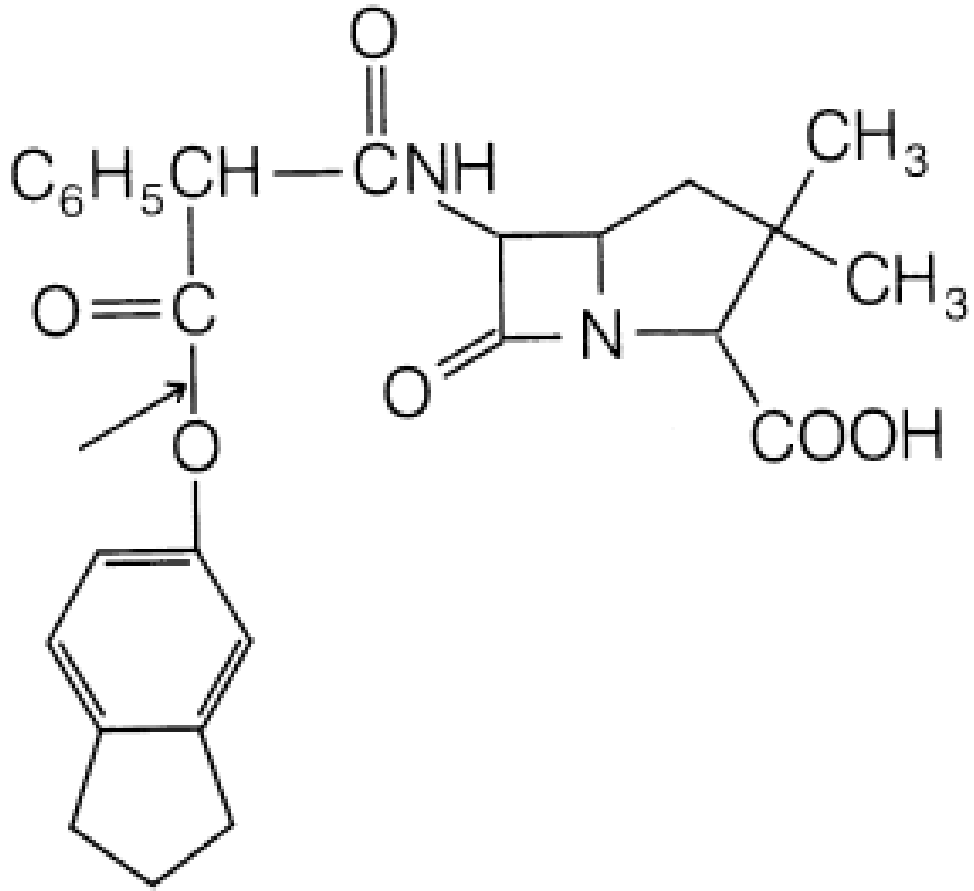
- Accordingly, antibiotics such as chloramphenicol and clindamycin have been derivatized as their palmitate esters to minimize their bitter taste and to improve their palatability in pediatric liquid suspensions. After oral administration, intestinal esterases and lipases hydrolyze the palmitate esters to the free antibiotics.
- To improve the poor oral absorption of carbenicillin, a lipophilic indanyl ester has been formulated. Once orally absorbed, the ester is hydrolyzed rapidly to the parent drug.
- A final example involves derivatization of prednisolone to its C-21 hemisuccinate sodium salt. This water-soluble derivative is extremely useful for parenteral administration and is metabolized to the parent steroid drug by plasma and tissue esterases.



Chloramphenicol
Palmitate



Clindamycin
Palmitate

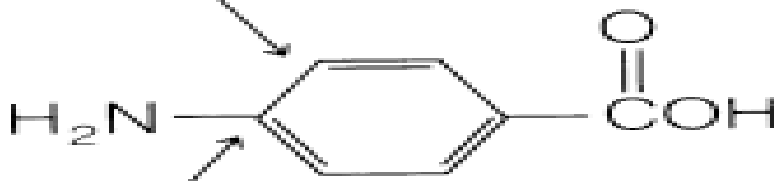


Carbenicillin Indanyl Ester

- Amides are hydrolyzed slowly in comparison to esters. Consequently, hydrolysis of the amide bond of procainamide is relatively slow compared with hydrolysis of the ester linkage in procaine.
- Drugs in which amide cleavage has been reported to occur, to some extent, include lidocaine, carbamazepine, indomethacin and prazosin.

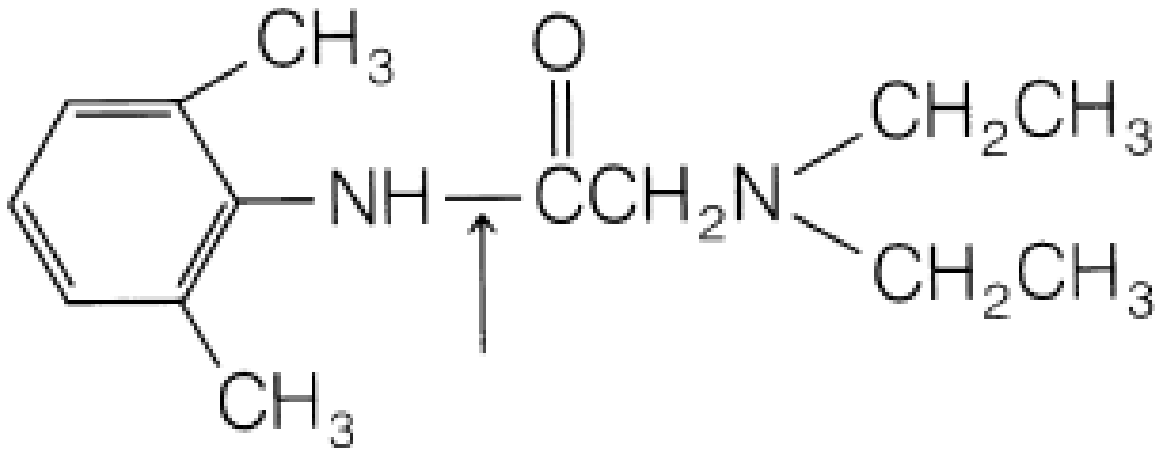
Procainamide

Slow Hydrolysis

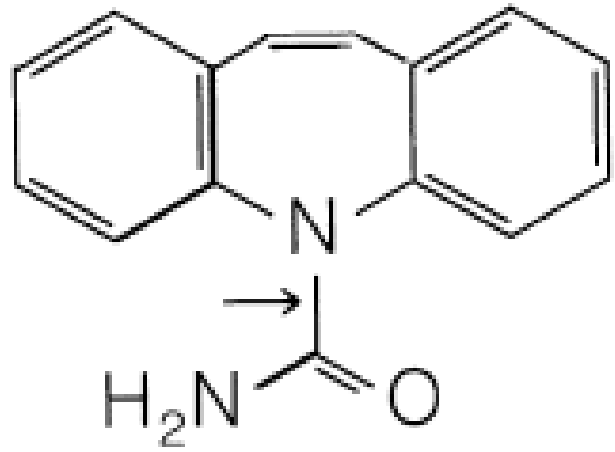


Rapid Hydrolysis

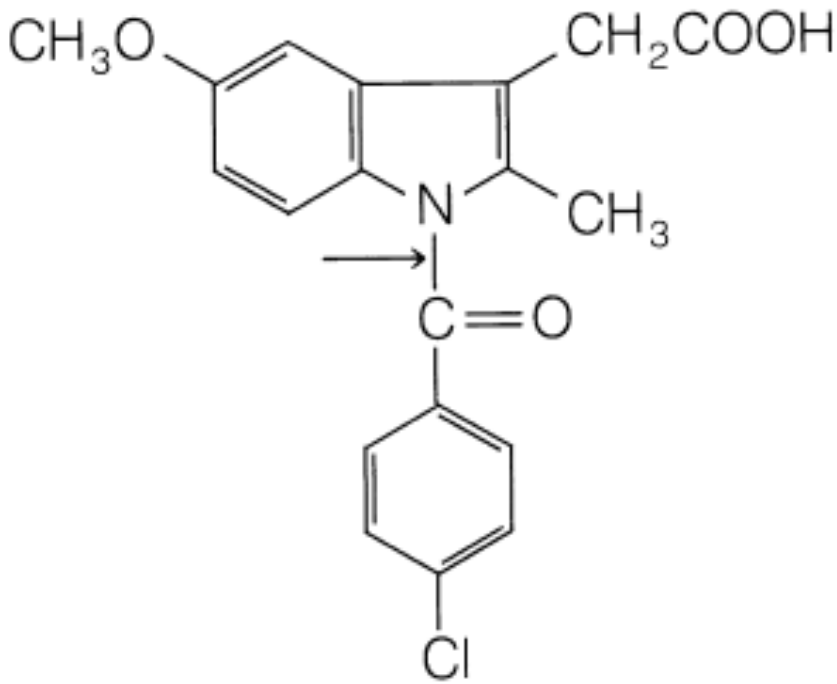
Procaine



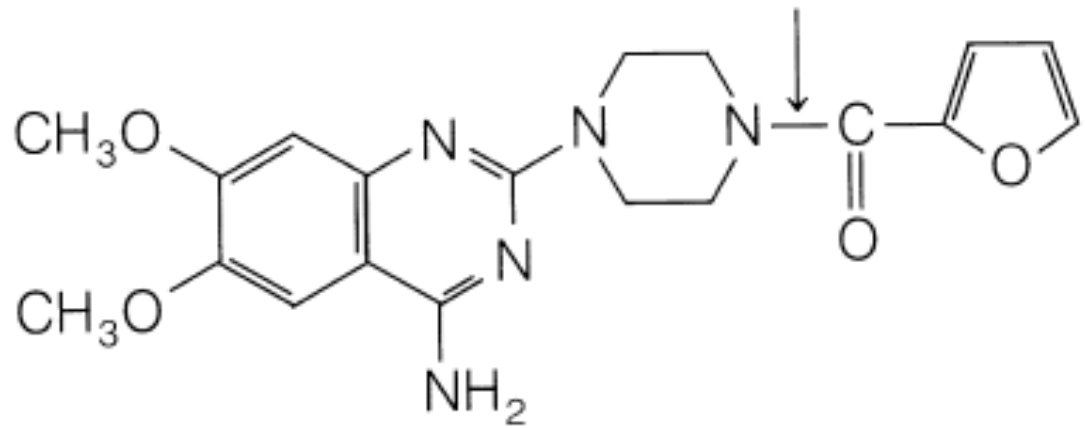
Lidocaine



Carbamazepine



Indomethacin



Prazosin

THANK YOU

- ANY QUESTIONS??

Rest for 15 minutes