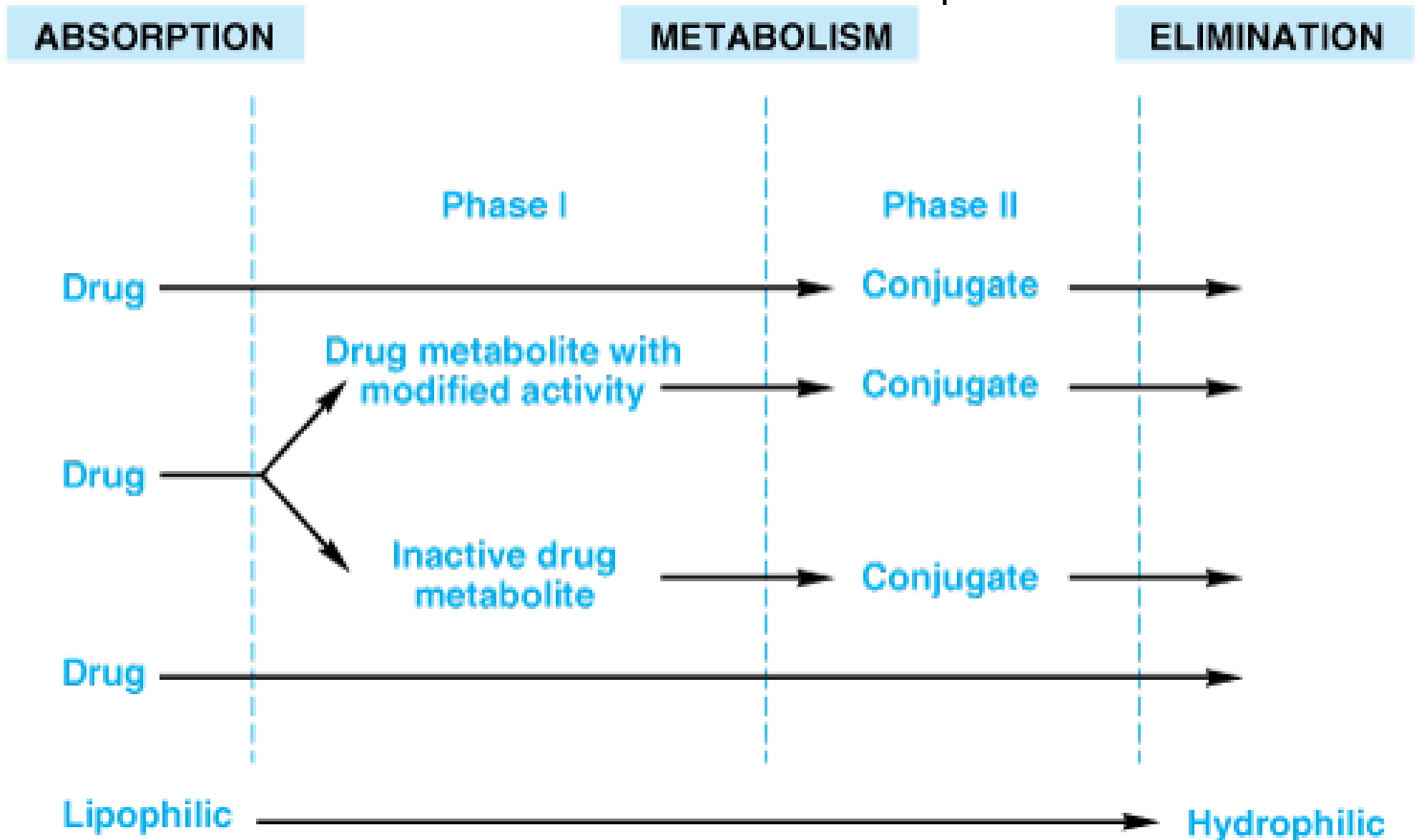


Drug metabolism or biotransformation

Drug metabolism or biotransformation

- reactions that are responsible for the conversion of drugs or other xenobiotics into another products (*metabolites*) within the body before and after they have reached their sites of action
- it usually occurs by more than one route
- their end products are normally pharmacologically inert compounds that are more easily excreted than the original drug
- classified for convenience as *Phase I* reactions which either **introduce** or **unmask** functional groups that are believed to act as a centre for *Phase II* reactions; product of *Phase I* are often more water soluble and so more readily excreted than the parent drug
- *Phase II* reactions produce compounds that are often very water soluble and usually form the bulk of the inactive excreted products of drug metabolism

Schematic of biotransformation phases



Source: Katzung BG: *Basic & Clinical Pharmacology*, 10th Edition:
<http://www.accessmedicine.com>

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Phase I metabolism

- Oxidative metabolism — **mixed function oxidases** (cytochrome P-450), **NAD⁺, FAD**
- Reductive metabolism — **NADPH, cytochrome reductases**
- Hydrolysis (enzymatic)
- Hydration— addition of water

All designed to detoxify chemicals by rendering them more soluble

PHASE I redox metabolism enzymatic apparatus

Mixed-Function Oxidases, formed by **microsomes** made out of smooth endoplasmic reticulum (SER) folded over on itself.

- Cytochrome-P450 Enzyme Complex: Has four required components in order to work.
- **Cytochrome-P450 Enzyme**
- **Cytochrome-P450 Reductase**
- O_2
- **NADPH**: NADPH is the only energy source.

Types of Phase I reactions

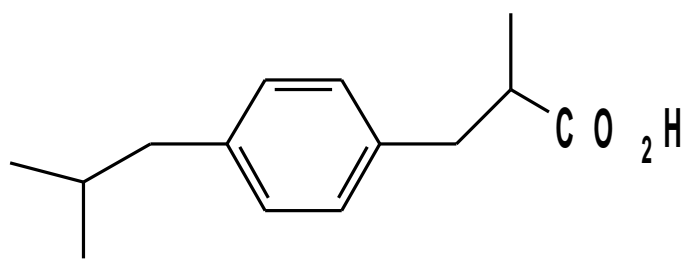
OXIDATIVE REACTIONS: on drugs, such as aromatic hydroxylation, aliphatic hydroxylation, N-dealkylation, O-dealkylation, S-dealkylation, N-oxidation, S-oxidation, desulfuration etc. in most on CYP.

REDUCTIVE REACTIONS: azo, nitrile, carbamyl

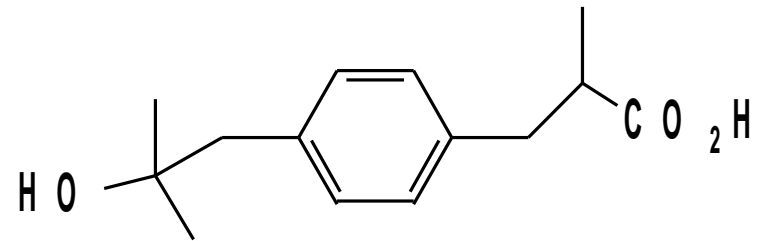
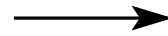
HYDROLYTIC REACTIONS: ester hydrolysis, amide hydrolysis.

OTHER REACTIONS: decarboxylation

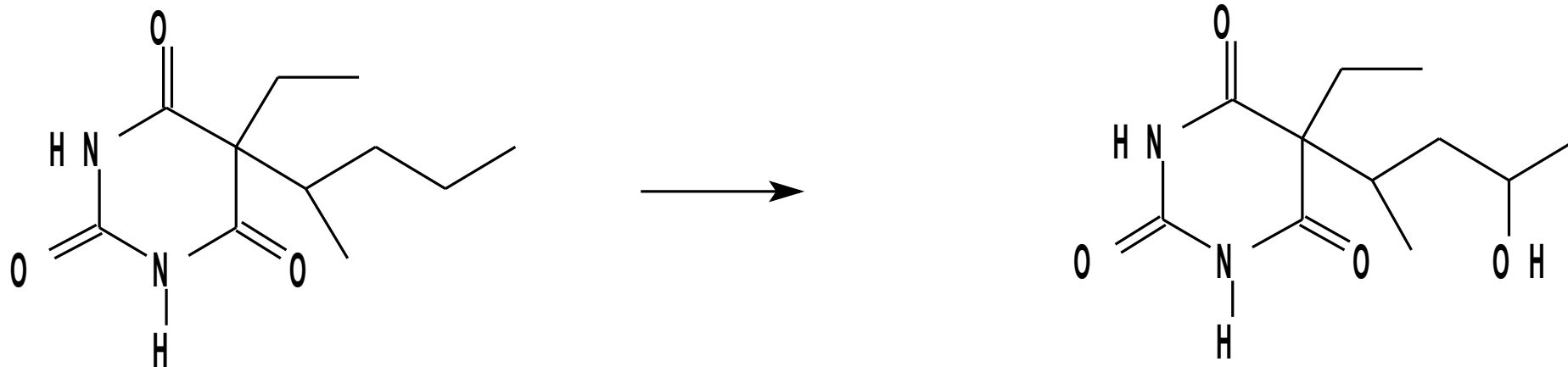
Aliphatic ω -hydroxylation: **ibuprofen** (NSAID)



ibuprofen

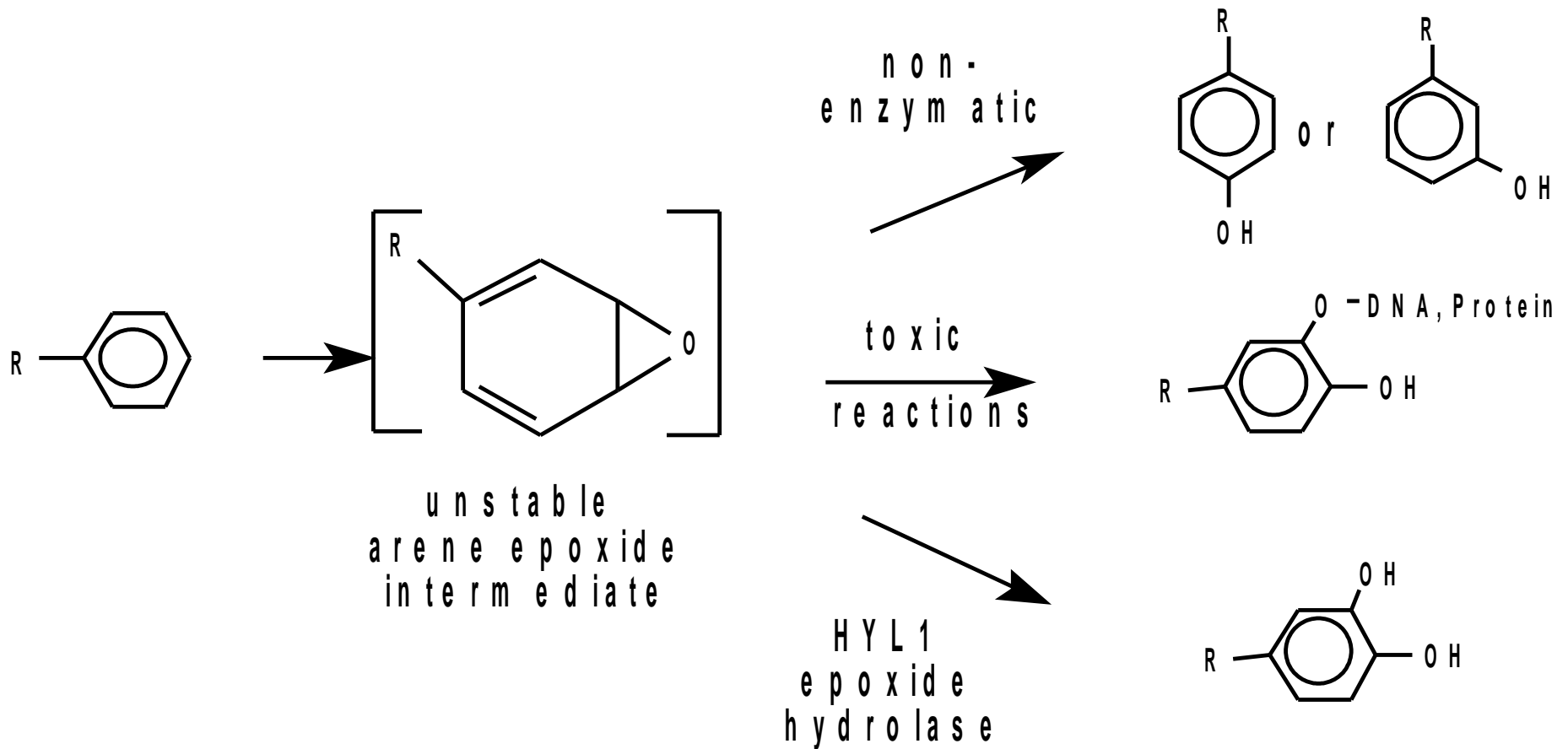


Aliphatic ($\omega-1$)-hydroxylation: pentobarbital (hypnotic, sedative ...)



pentobarbital

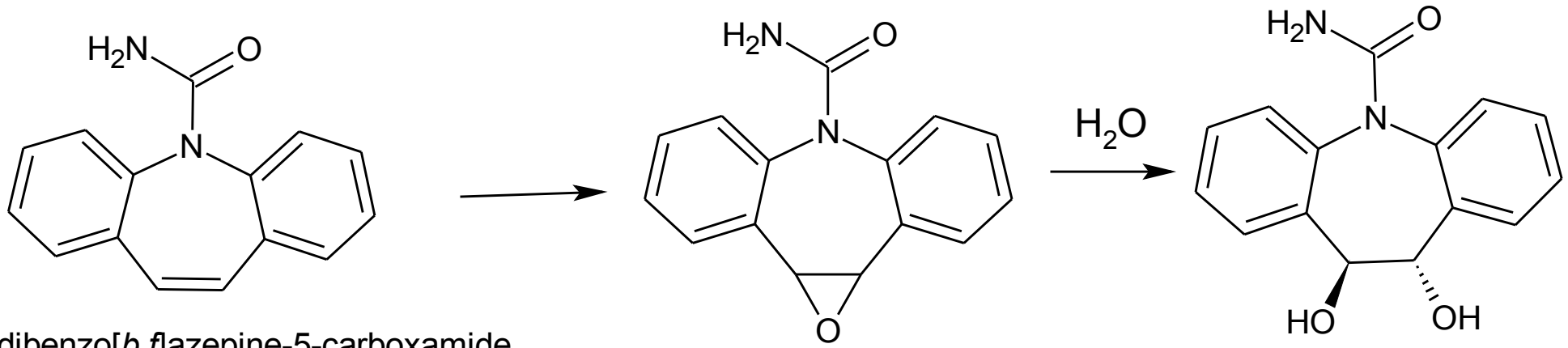
Aromatic hydroxylation



Examples: acetanilide, phenytoin, propranolol

Endogenous substrates: steroid hormones (not aromatic amino acids)

- arene epoxide can be quite stable in some cases: carbamazepine and carbamazepine epoxide



5H-dibenzo[*b,f*]azepine-5-carboxamide

carbamazepine

Carbamazepinum PhEur

Biston[®], Neurotop[®], Tegretol[®] CR ...

- antiepileptic
- blocks voltage gated Na⁺ channels and thus inhibits fast and non-controlled impulse spreading

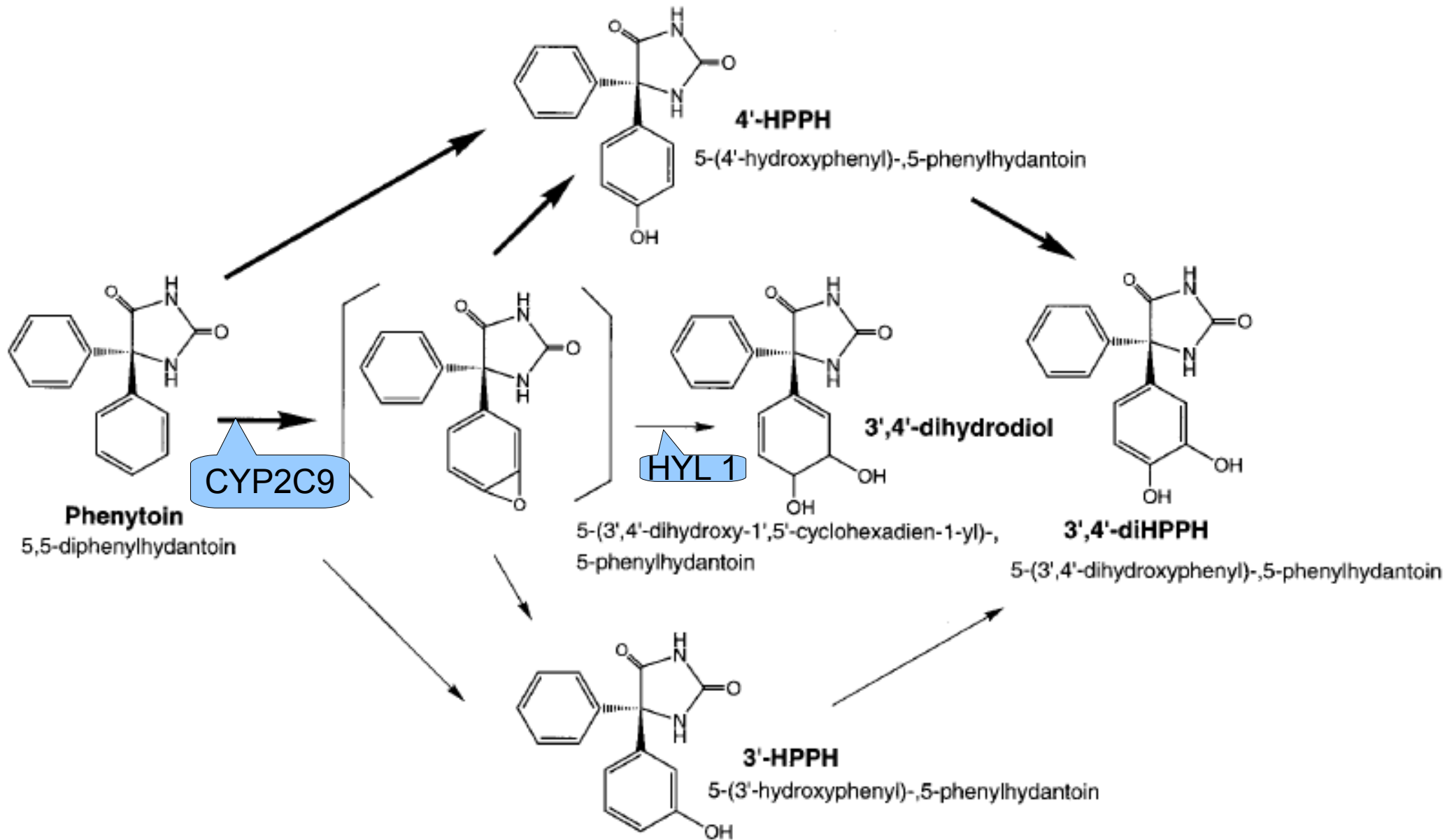
carbamazepine 10,11-epoxide

- active
- stable; found in waste water

trans-10,11-dihydrocarbamazepine-10,11-diol

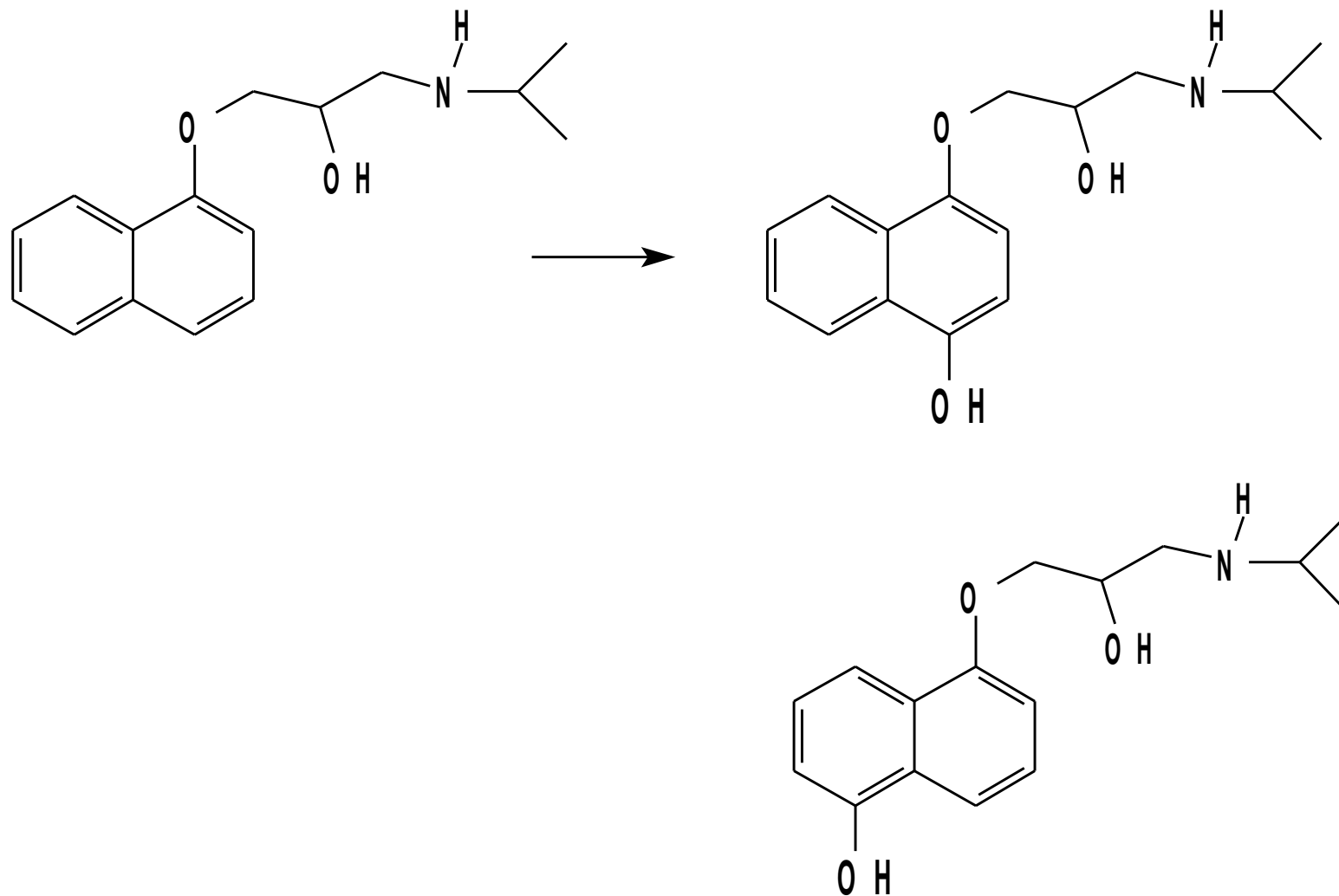
- main metabolite excreted by urine

•antiepileptic **phenytoin**: aromatic hydroxylation and water addition



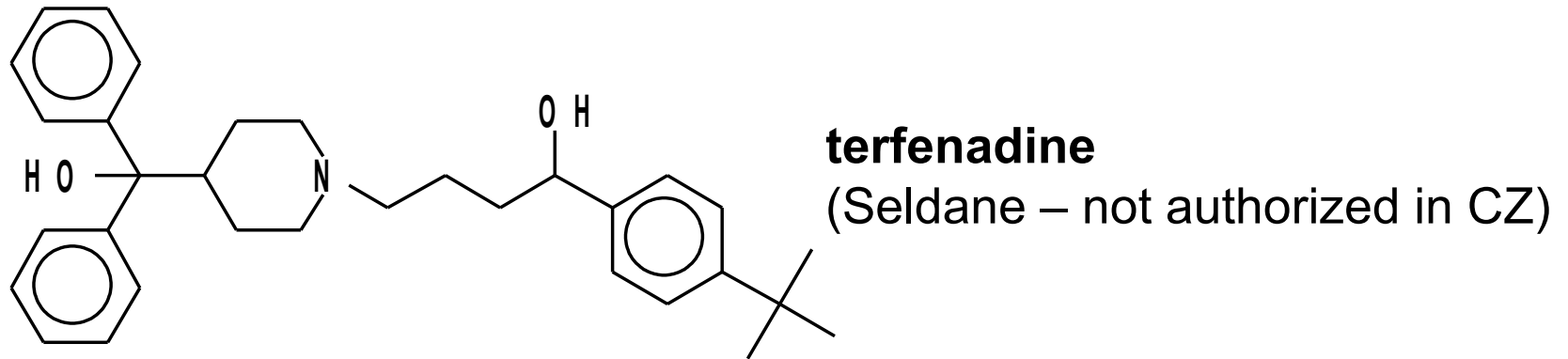
Arene epoxide intermediate produces multiple products

β -adrenolytic – anti-hypertensive **propranolol**: hydroxylation in 2 positions of naphthalene ring

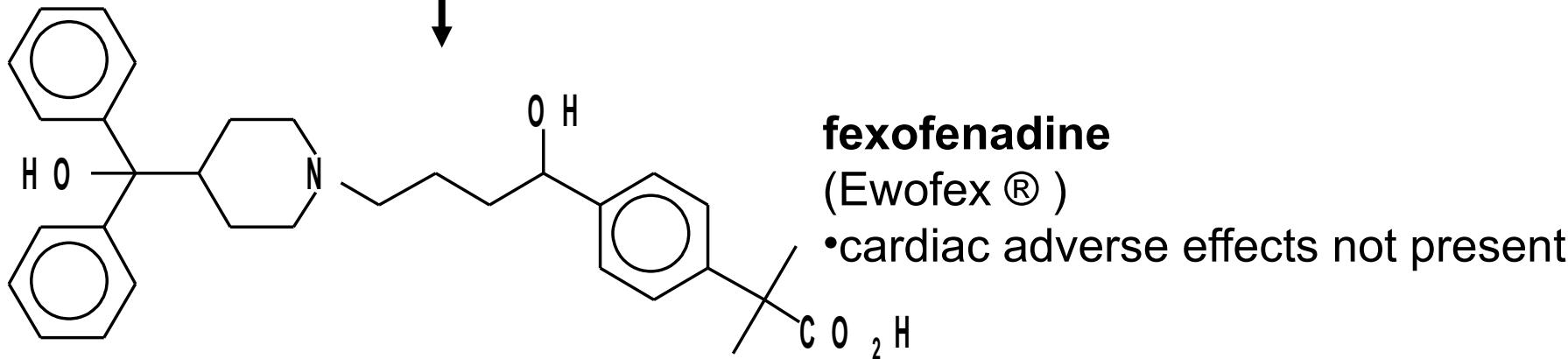


Metabolism of **terfenadine**: oxidation of one of one methyl of *tert*-butyl into carboxyl

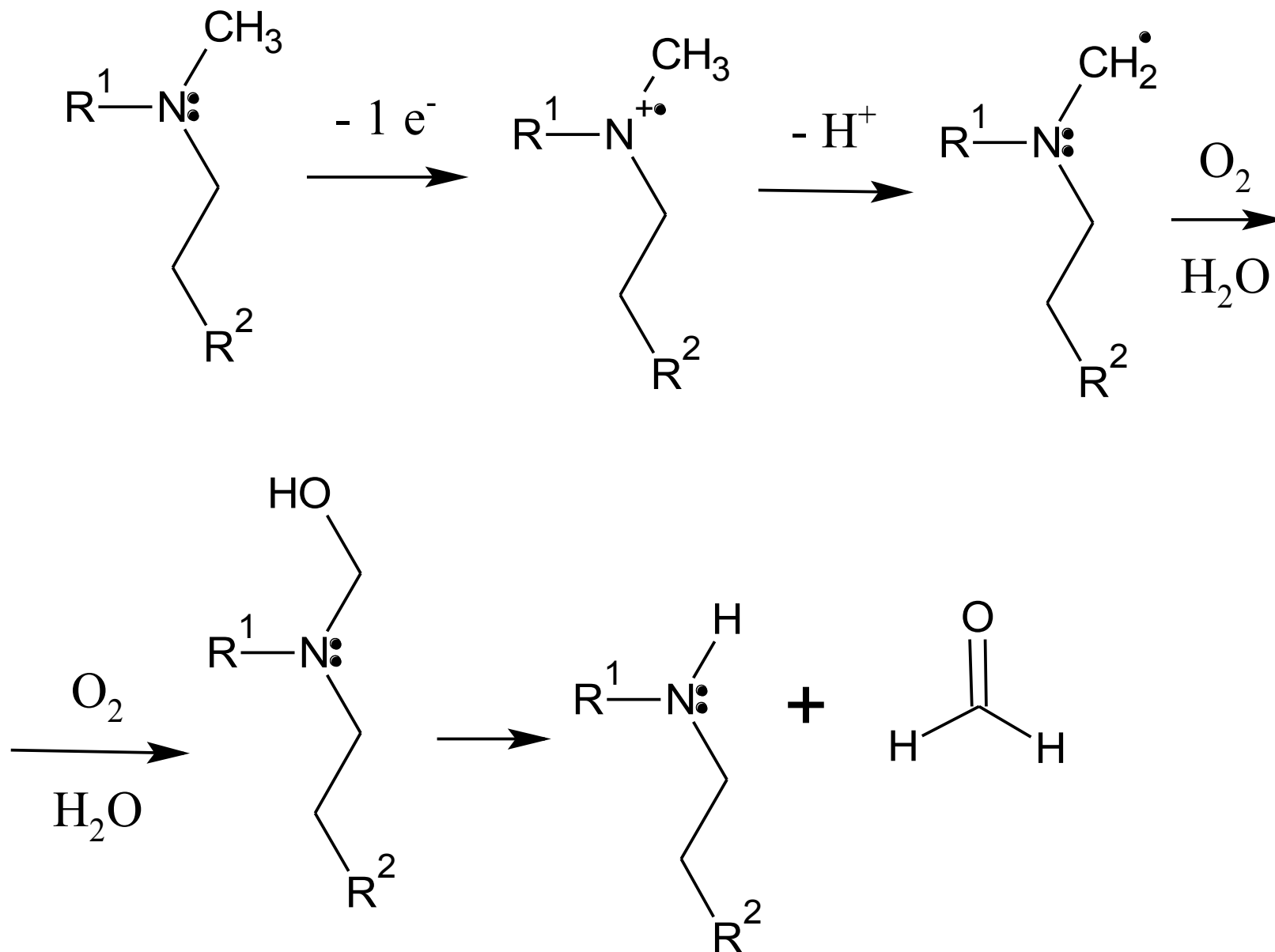
- H₁-antihistamine of the 2nd generation developed in 1980th
- serious cardiac adverse effects including TdP arrhythmias



CYP3A4

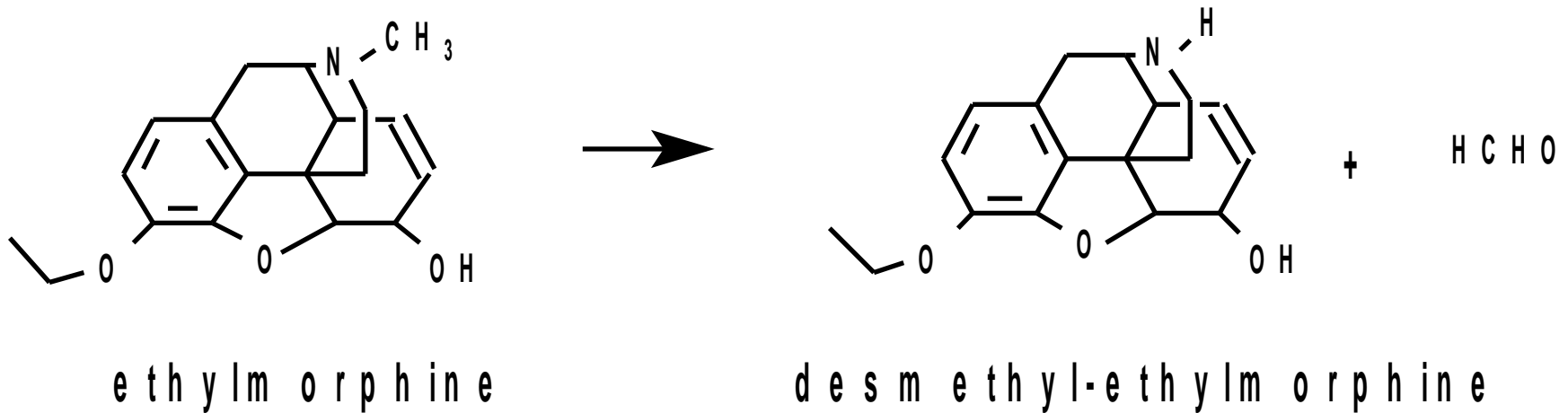


N (or O, S)-oxidative dealkylation



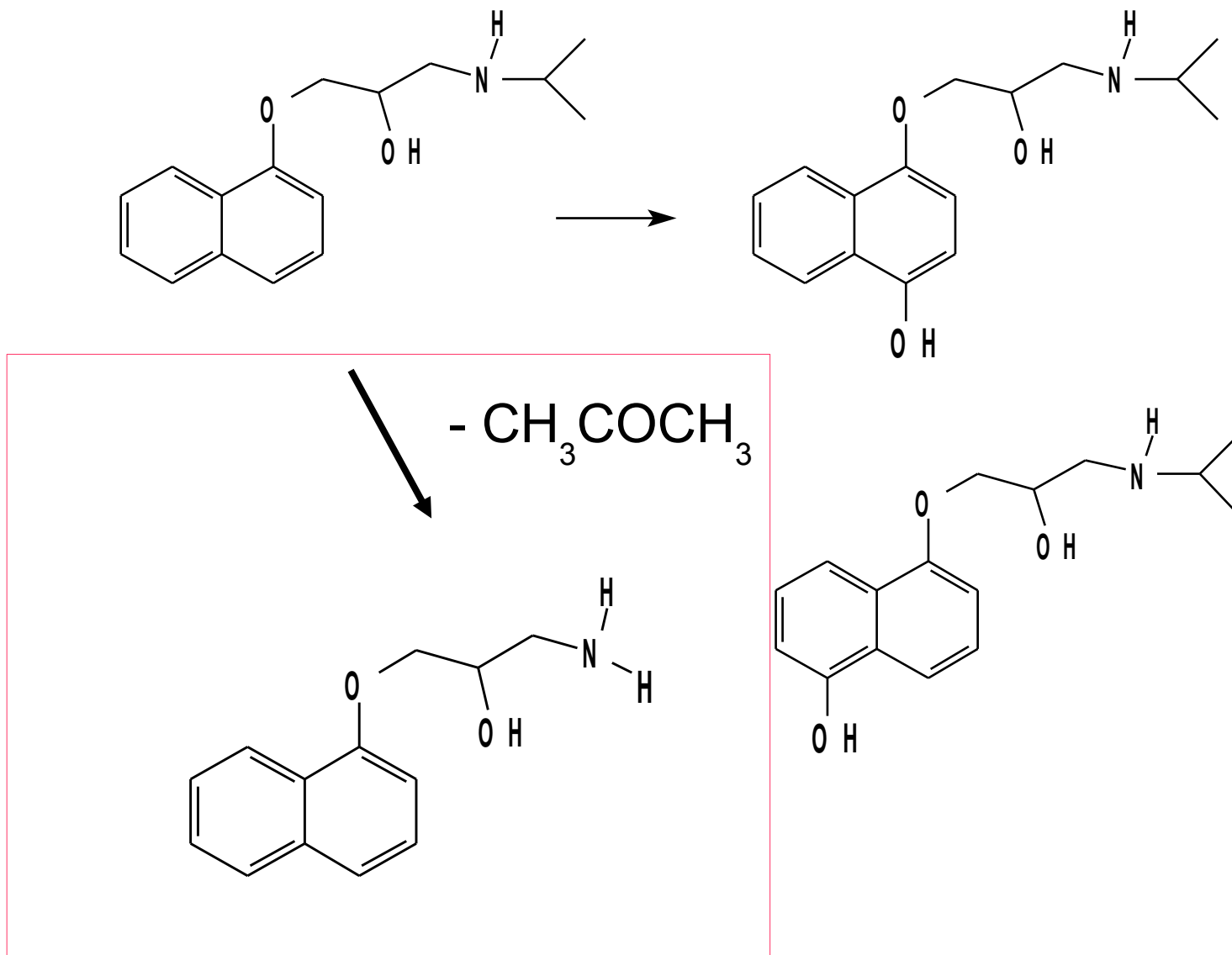
N-demethylation generates formaldehyde

Oxidative N-demethylation: ethylmorphine (antitussive)



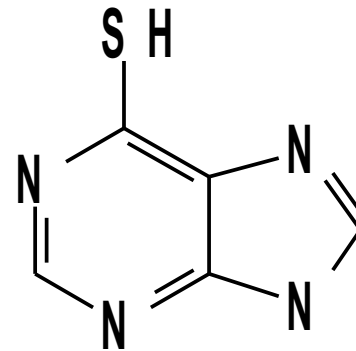
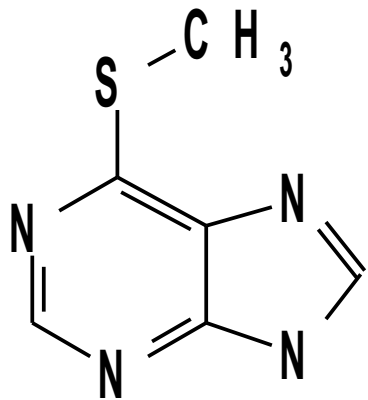
N-demethylation favored over O-dealkylation

Oxidative desisopropylation: **propranolol**



•also 2' and 7' hydroxylated metabolites have been reported

Oxidative S-demethylation: **6-methylthiopurine** = 6-methylsulfanylpurine



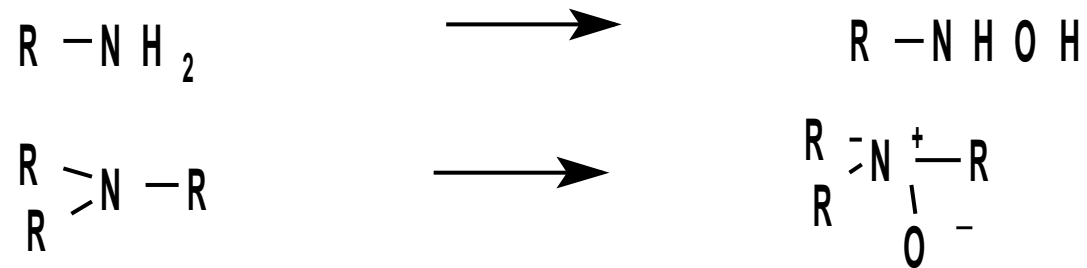
6-methylthiopurine

- prodrug
- not used

6-mercaptapurine

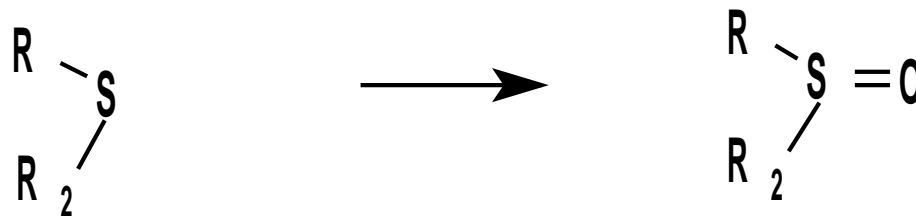
- active form normally originated from antineoplastic and antirheumatic azathioprin

N - O x i d a t i o n



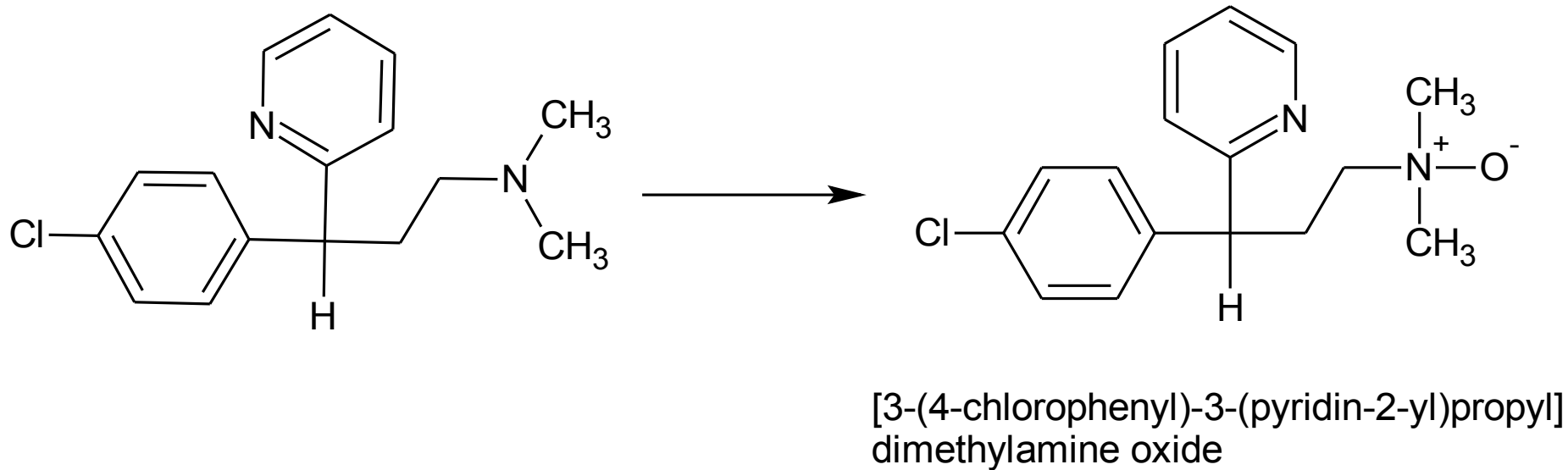
Examples: chlorpheniramine, trimethylamine

S - O x i d a t i o n

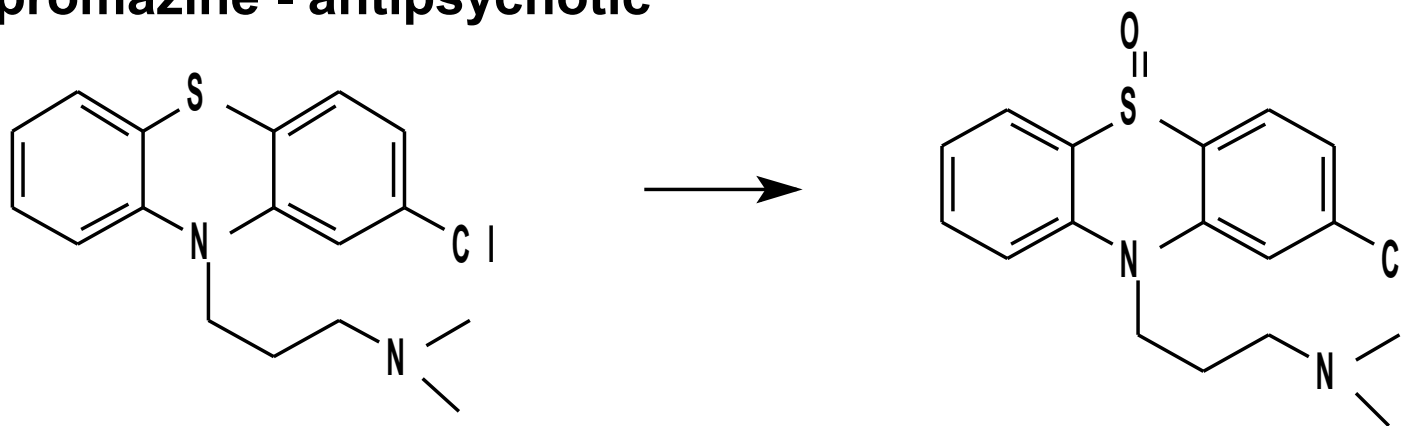


Examples: chlorpromazine, cimetidine

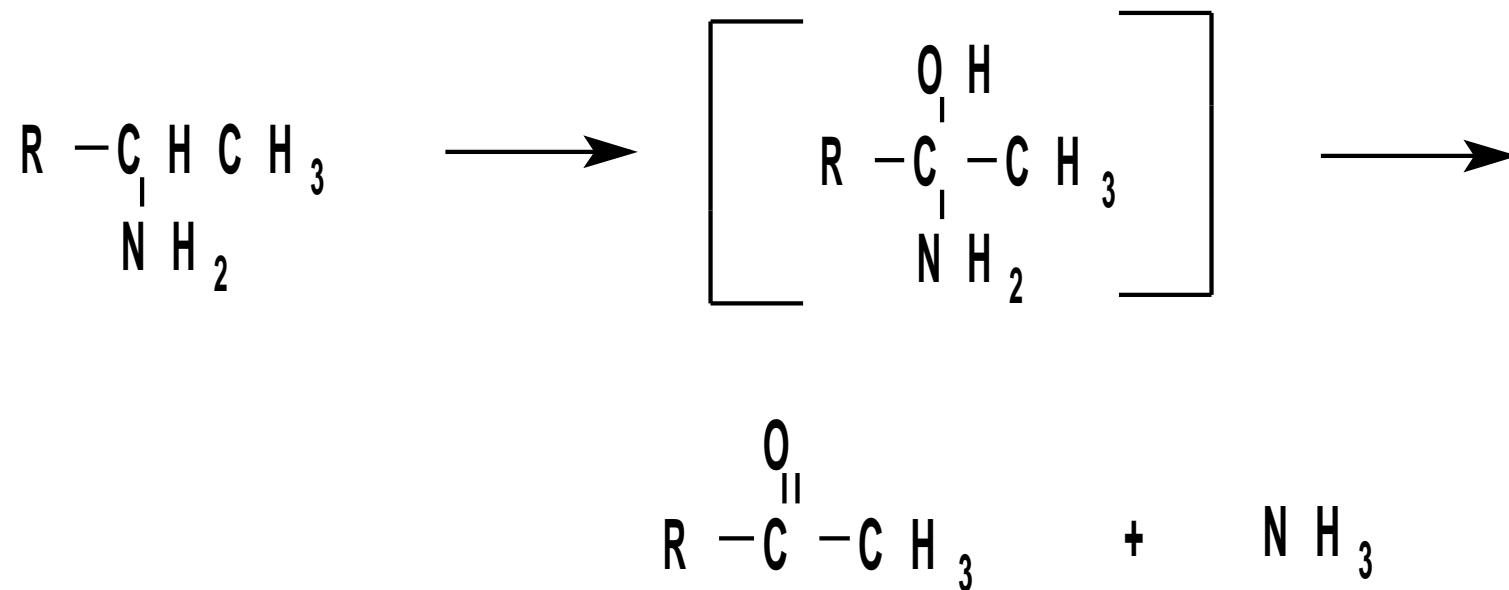
chlorpheniramine - H₁-antihistamine



chlorpromazine - antipsychotic

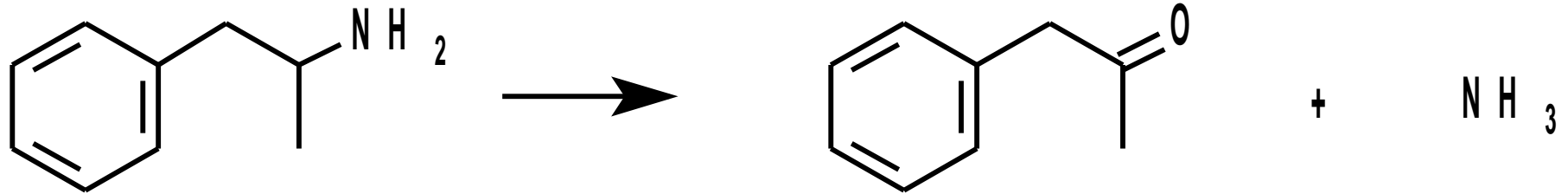


Oxidative deamination of primary amines



Examples: amphetamine, diazepam (after benzodiazepine ring opening)

amphetamine - central stimulant, indirect adrenergic



2-amino-3-phenylpropane
amphetamine

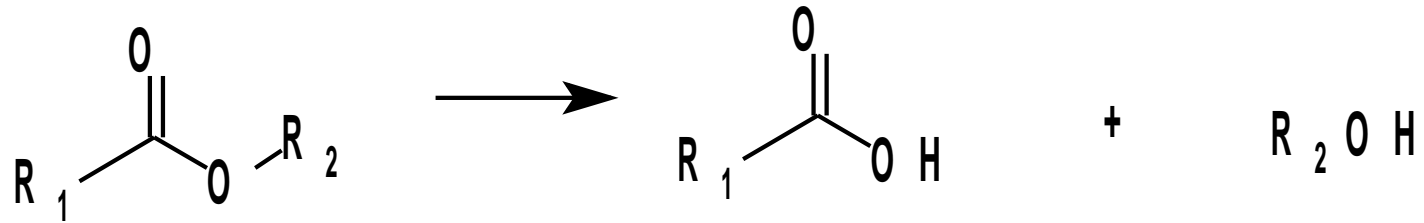
2-phenylpropane-2-on

PHASE I hydrolytic metabolism enzymatic apparatus

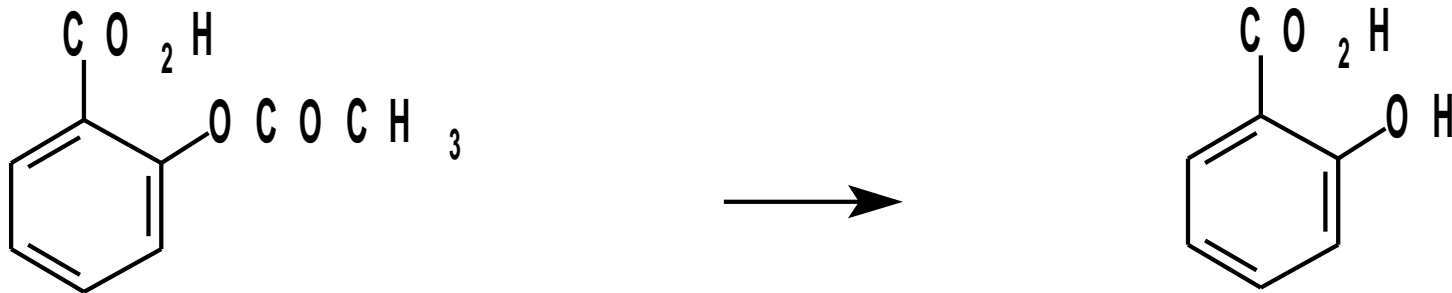
- hydrolases
 - esterases – have also some amidase activity
 - cholinesterases: acetylcholinesterase, butyrylcholinesterase
 - pseudocholinesterase
 - lipases
 - peptidases – naturally cleave the peptidic bond, but are capable to cleave also other amide bonds
 - exopeptidases – cleave peptide bonds of terminal amino acid rests
 - carboxypeptidases – from C-terminal
 - aminopeptidases – from N-terminal
 - endopeptidases – cleave peptide bonds inside peptide chain
 - in general are all the types of peptidases capable to cleave anilides, naphthylamides etc.

Hydrolysis Reactions

Esters

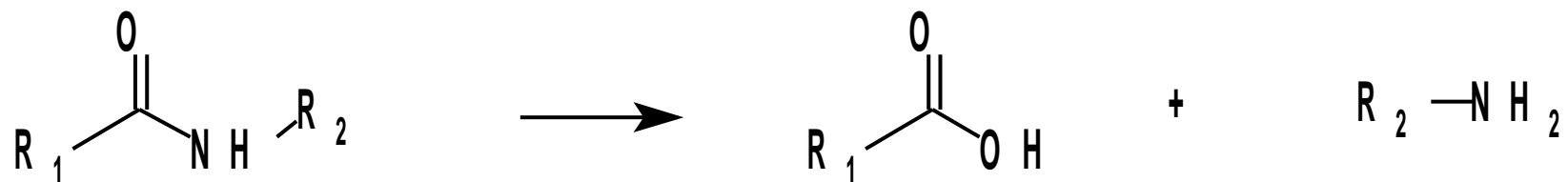


Example: acetylosalicylic acid (others include procaine, clofibrate)

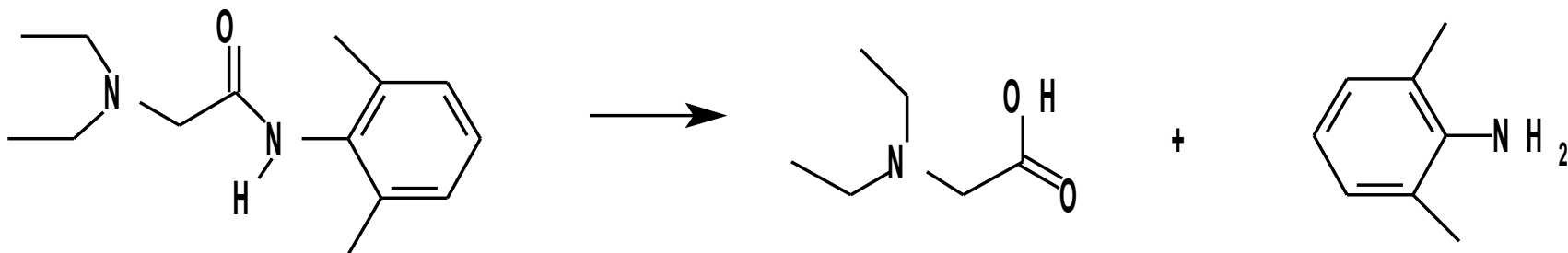


Hydrolysis Reactions

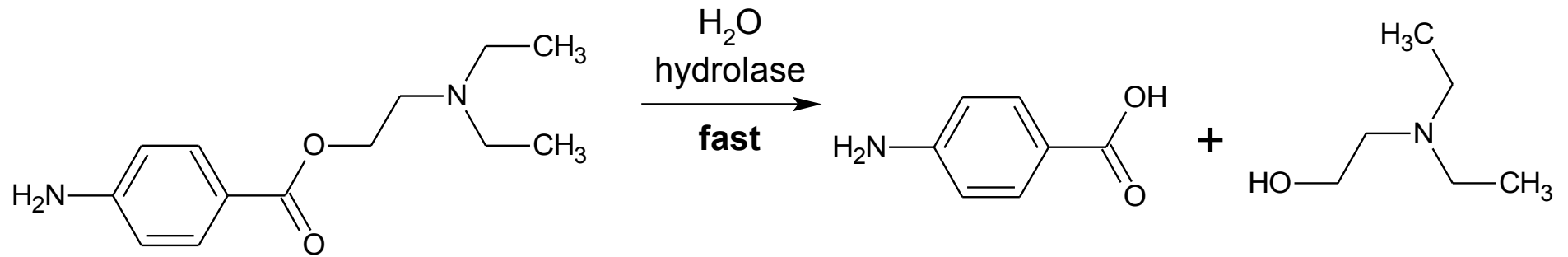
Amides



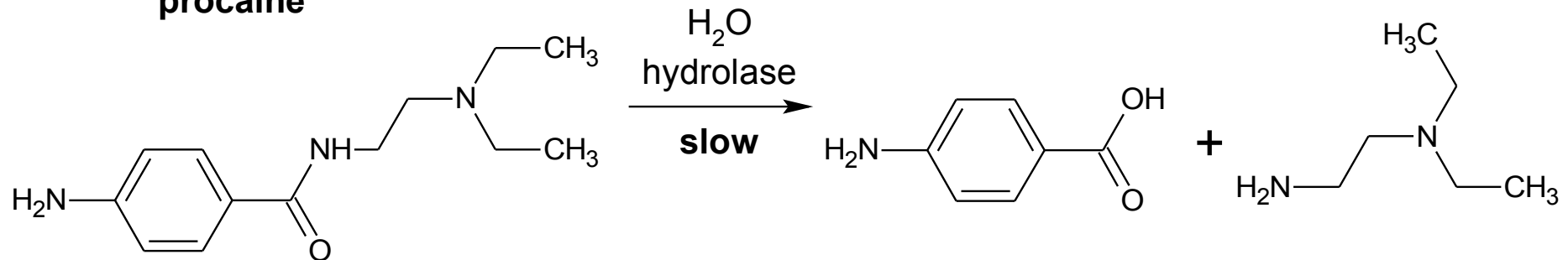
Example: lidocaine; others include peptide drugs



Hydrolysis reactions in local anaesthetics: a difference between esters and amides



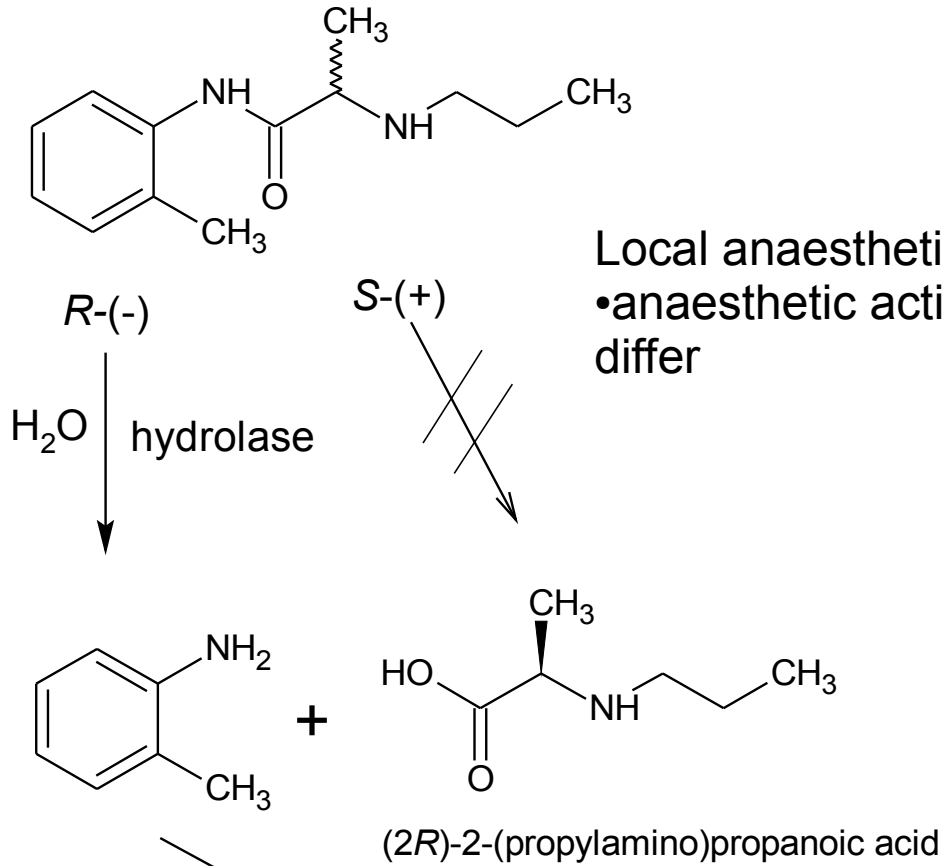
procaine



procainamide

- procaine does not act as an antidysrhythmic after *i.v.* administration because of its fast hydrolysis by esterases in blood it does not reach the myocardium tissue in enough concentration while isosteric procainamide does because the amide bond is hydrolyzed much more slowly due to its higher stability and low activity of esterases in hydrolysis of this bond

Hydrolysis reactions in local anaesthetics: stereoselectivity

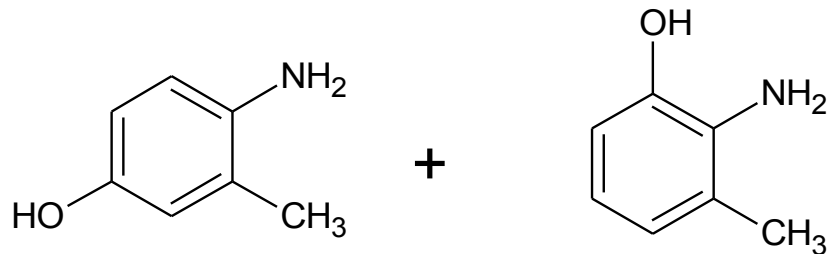


Local anaesthetics of anilide series: **prilocaine**

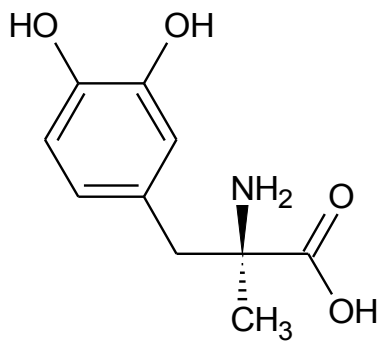
- anaesthetic activity of *R* and *S* enantiomers does not markedly differ

- administration of the pure *S*-(-) enantiomer can eliminate the toxicity

aromatic ring
hydroxylation

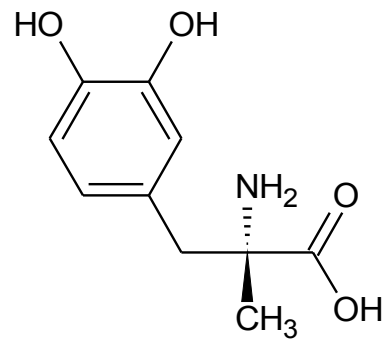


- toxic metabolites
- methemoglobinemia



2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid

(-)-(S)



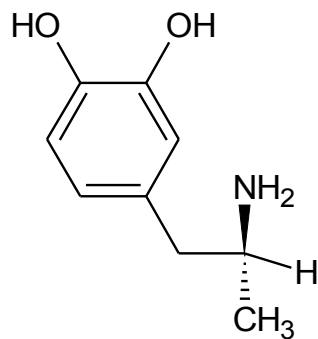
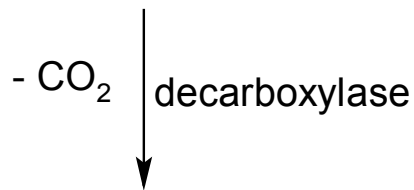
(+)-(R) - inactive

Decarboxylation reaction

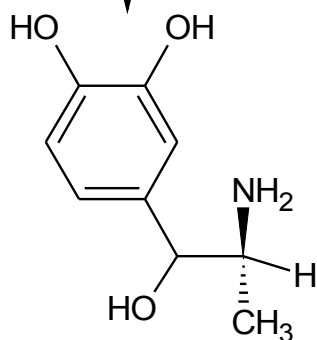
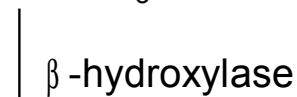
α -methyldopa – antihypertensive, α -adrenolytic

Dopegyt® contains (-)-(S) sesquihydrate

• stereoselectivity of enzyme reaction: (-)-(S)-isomer only undergoes the decarboxylation and thus is active



α -methyldopamine

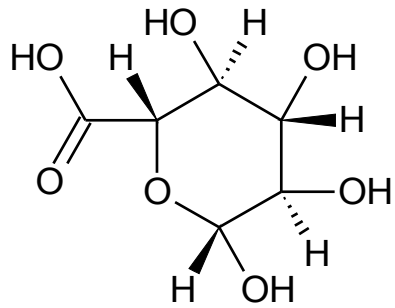


α -methylnoradrenaline – metabolite active as α_1 antagonist

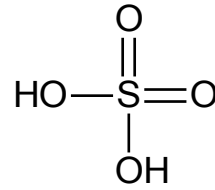
PHASE II metabolic routes: conjugation reactions

- involve the attachment of a group or a molecule to the drug or metabolite
- may occur at any point in the metabolism of a drug or xenobiotic but they are often the final step in the metabolic pathway before excretion
- conjugates are usually inactive with some exceptions
- in most cases markedly more hydrophilic than the parent compound but with frequent exceptions
- excreted from body in most in form of salts (Na^+ ...)

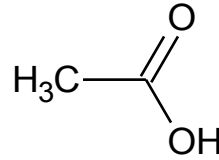
The most common „conjugation partners“



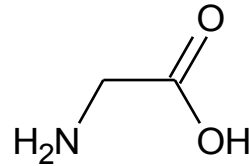
D-glucuronic acid



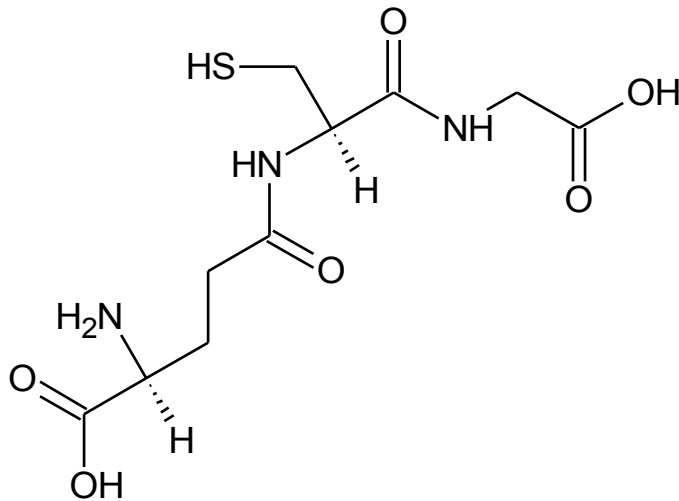
sulfuric acid



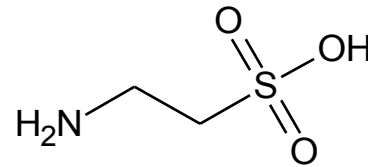
acetic acid



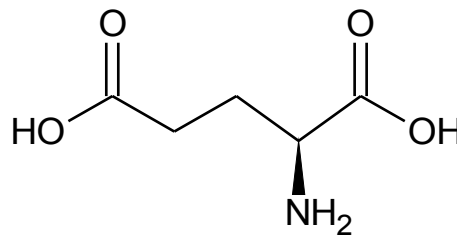
glycine



glutathione

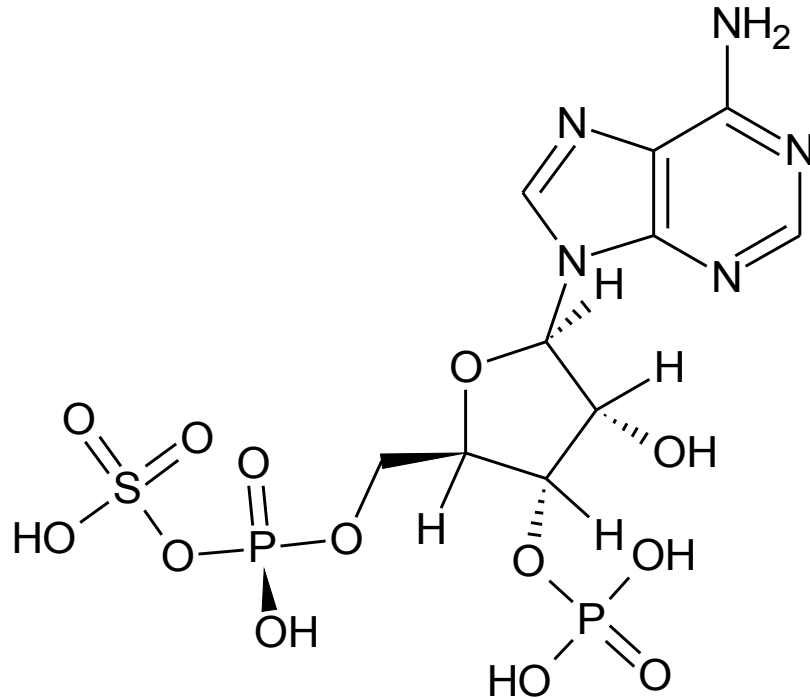


taurine
(2-aminoethanesulfonic acid)



(S)-glutamic acid

PAPS: 3'-Phosphoadenosine-5'-phosphosulfate



- „activated form“ of sulfuric acid used as cosubstrate for sulfate conjugations

„Activated“ glucuronic acid = UDP-glucuronic acid as cosubstrate in conjugation of paracetamol

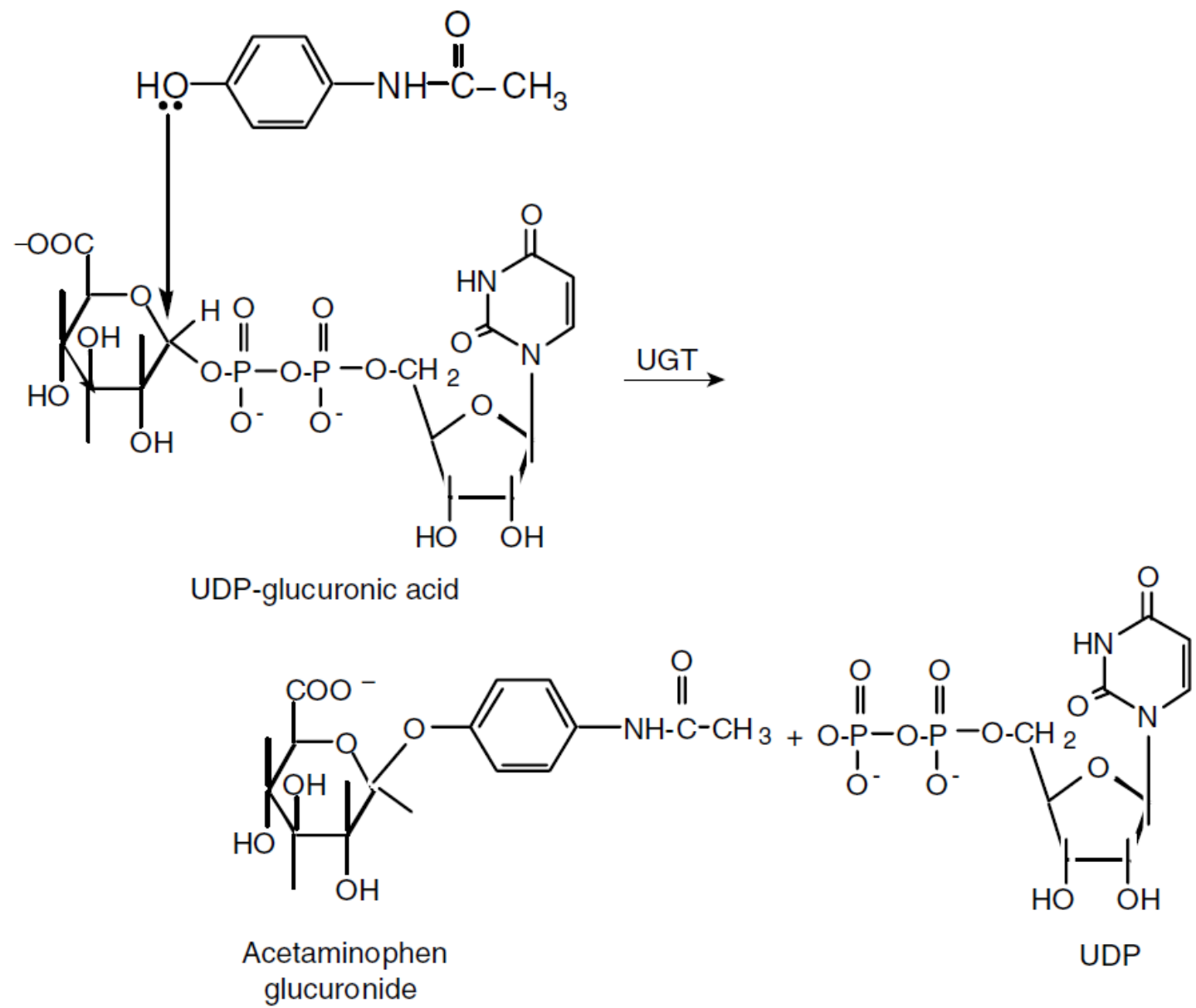
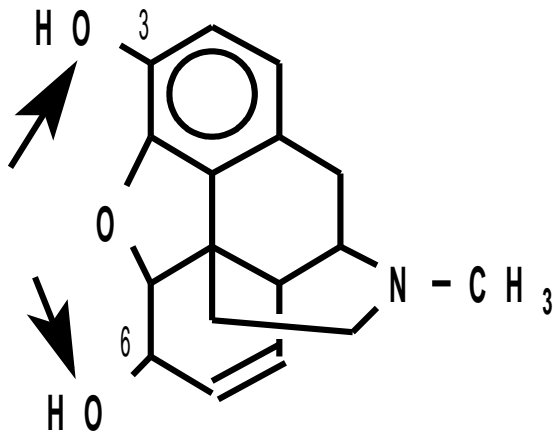
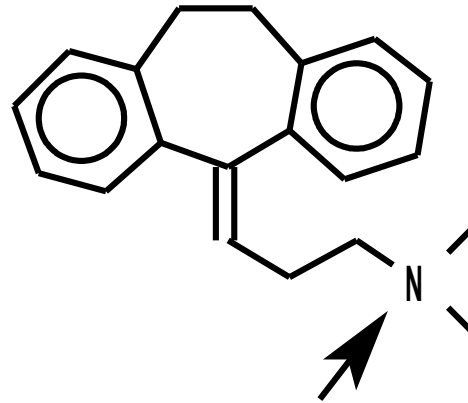


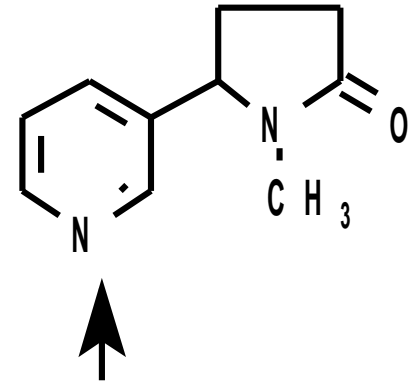
FIGURE 3.1 The glucuronidation reactions. Enzyme: UDP glucuronosyltransferase (UGT or UDPGT); Cosubstrate: uridene diphosphoglucuronic acid (UDPGA)-activated cosubstrate.



M o r p h i n e



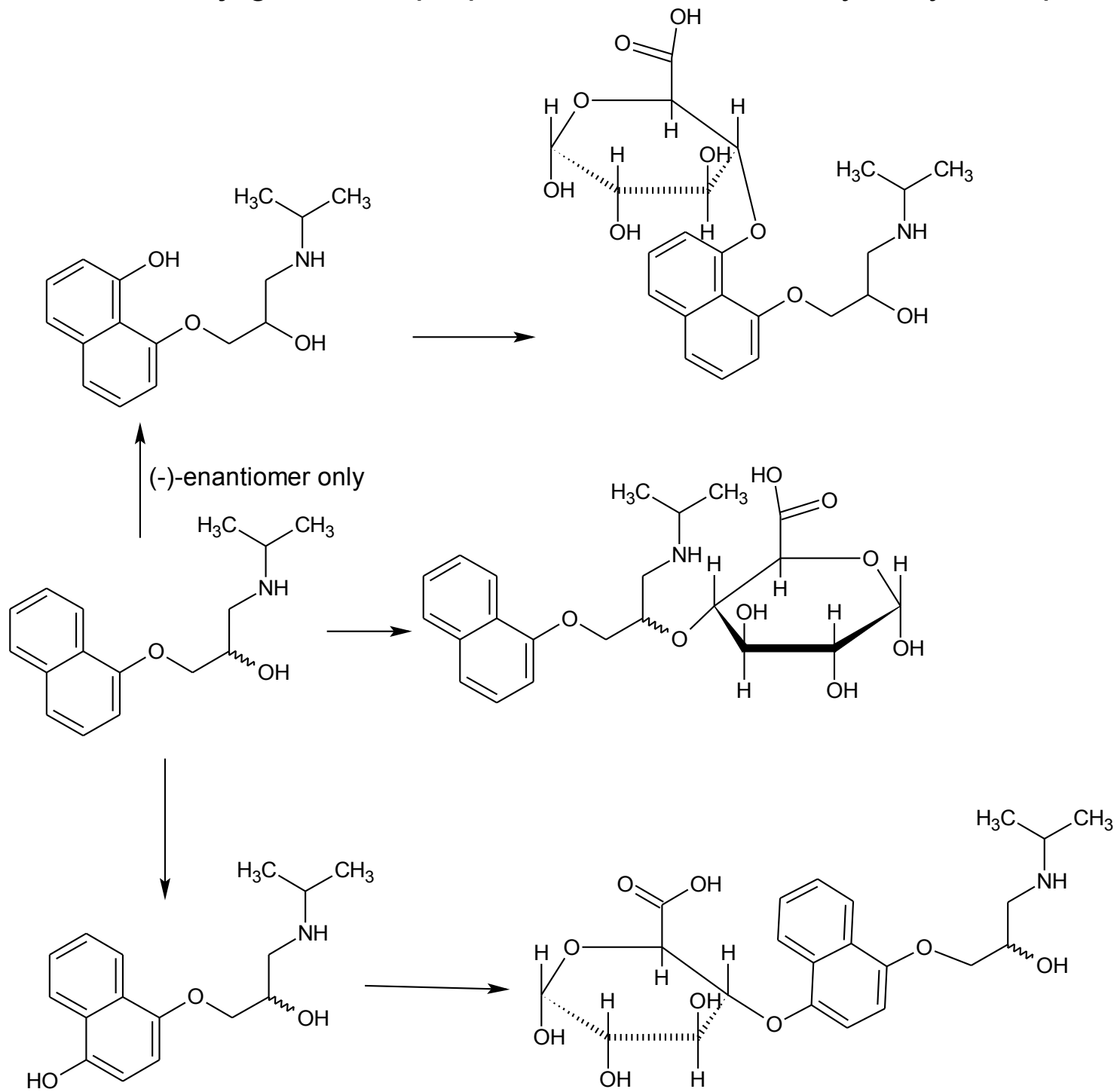
A m i t r i p t y l i n e



C o t i n i n e

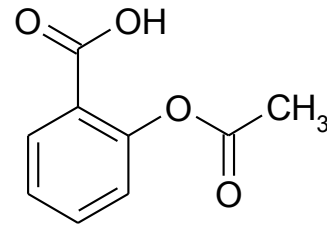
Examples of substrates of glucuronic acid conjugation include alcohols, phenols, 3°-amines, aromatic amines etc.

Glucuronate conjugations of propranolol and some its hydroxylation products



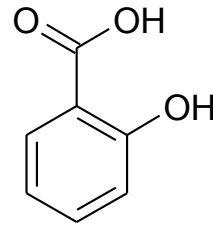
Metabolism of acetylosalicylic acid

- proceeds in most in liver
- conjugations are the most important part of its biotransformation
- all metabolites are excreted by urine



ASA

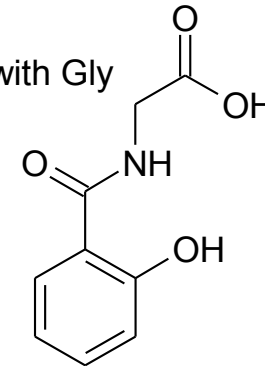
$t_{1/2} = 15 \text{ min}$



salicylic acid.
10 %

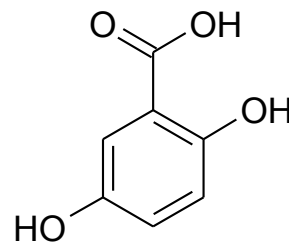
+ CH₃COOH

conjugation with Gly



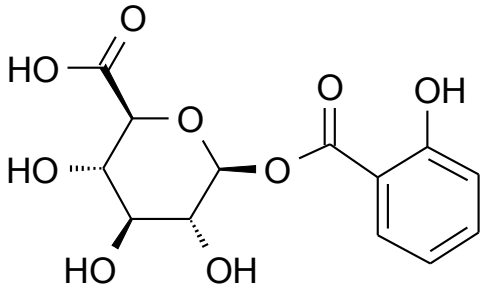
salicyluric acid
(N-salicyoylglycine)
75 %

hydroxylation

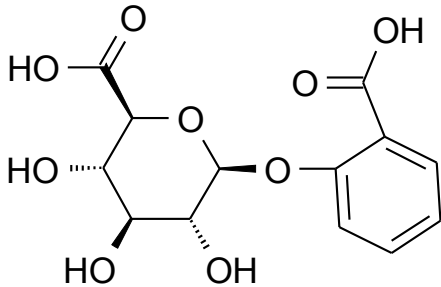


gentisic acid
< 1 %

glucuronation



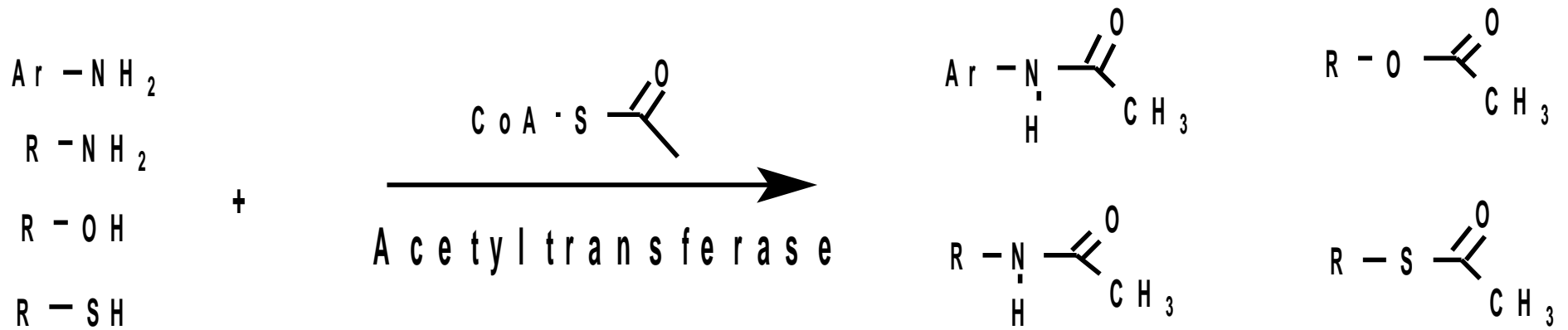
O¹-salicyoylglucuronic acid
5 %



O¹-(2-carboxyphenyl)glucuronic acid
10 %

Conjugation Reactions

Acetylation

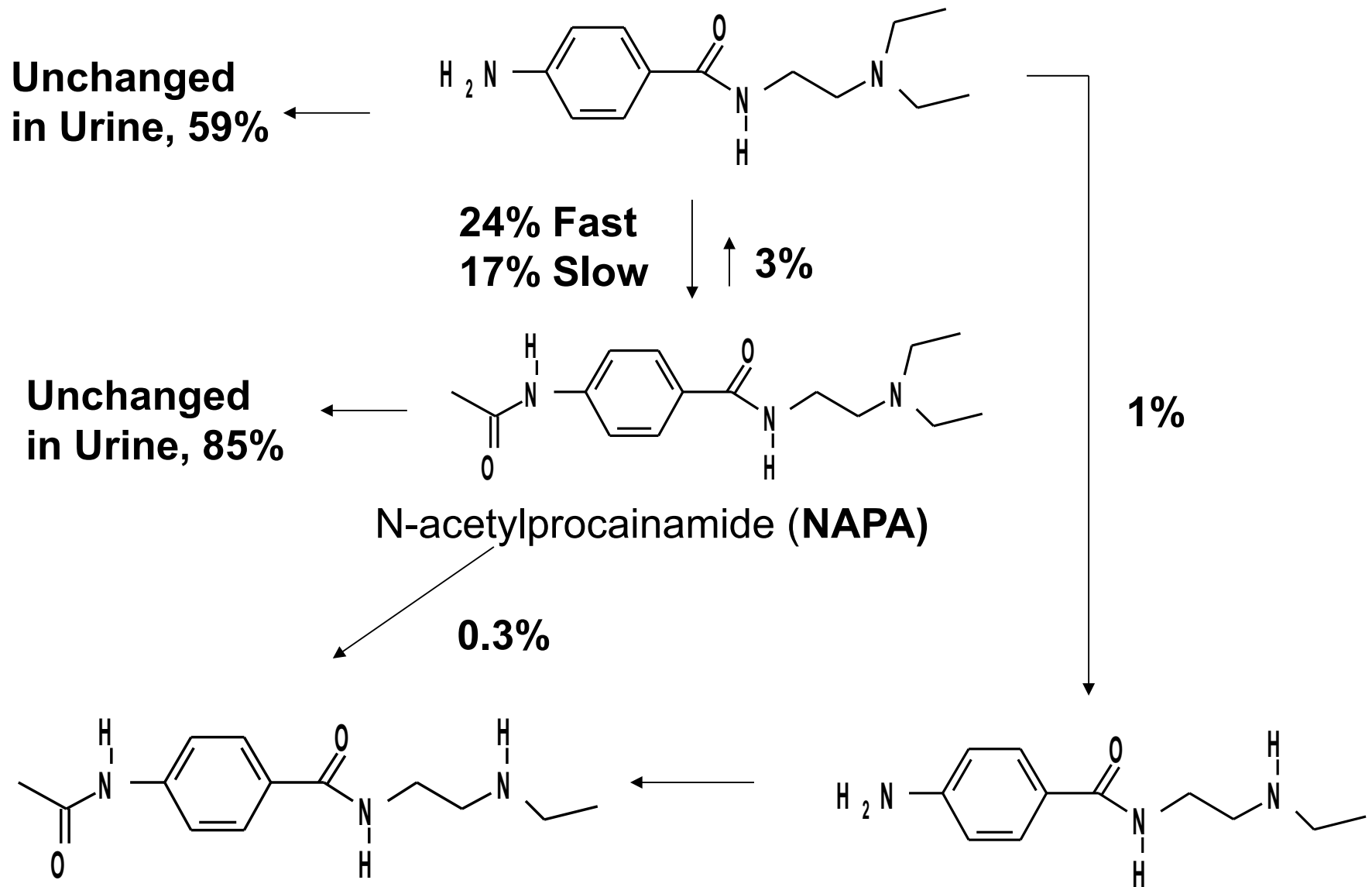


Examples: Procainamide, isoniazid, sulfonamides, histamine

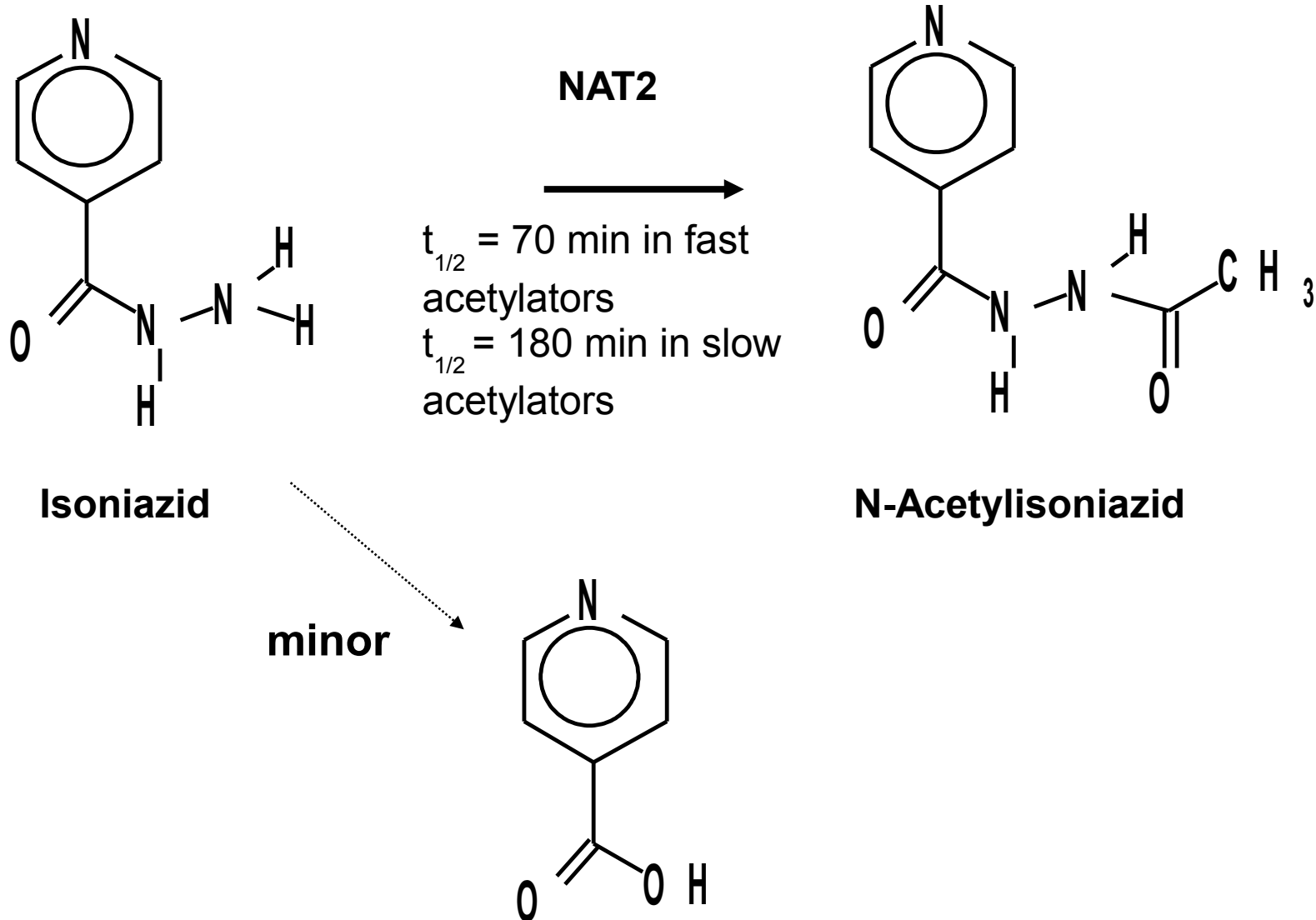
N-acetyl transferase (NAT) enzyme is found in many tissues, including liver
 Acetylation leads in most cases to conjugates which are **more lipophilic** and thus **less soluble in water** than the parent compound

Whole human population is genetically divided into **fast** and **slow** acetylators

Procainamide: participation of acetylation in its metabolism

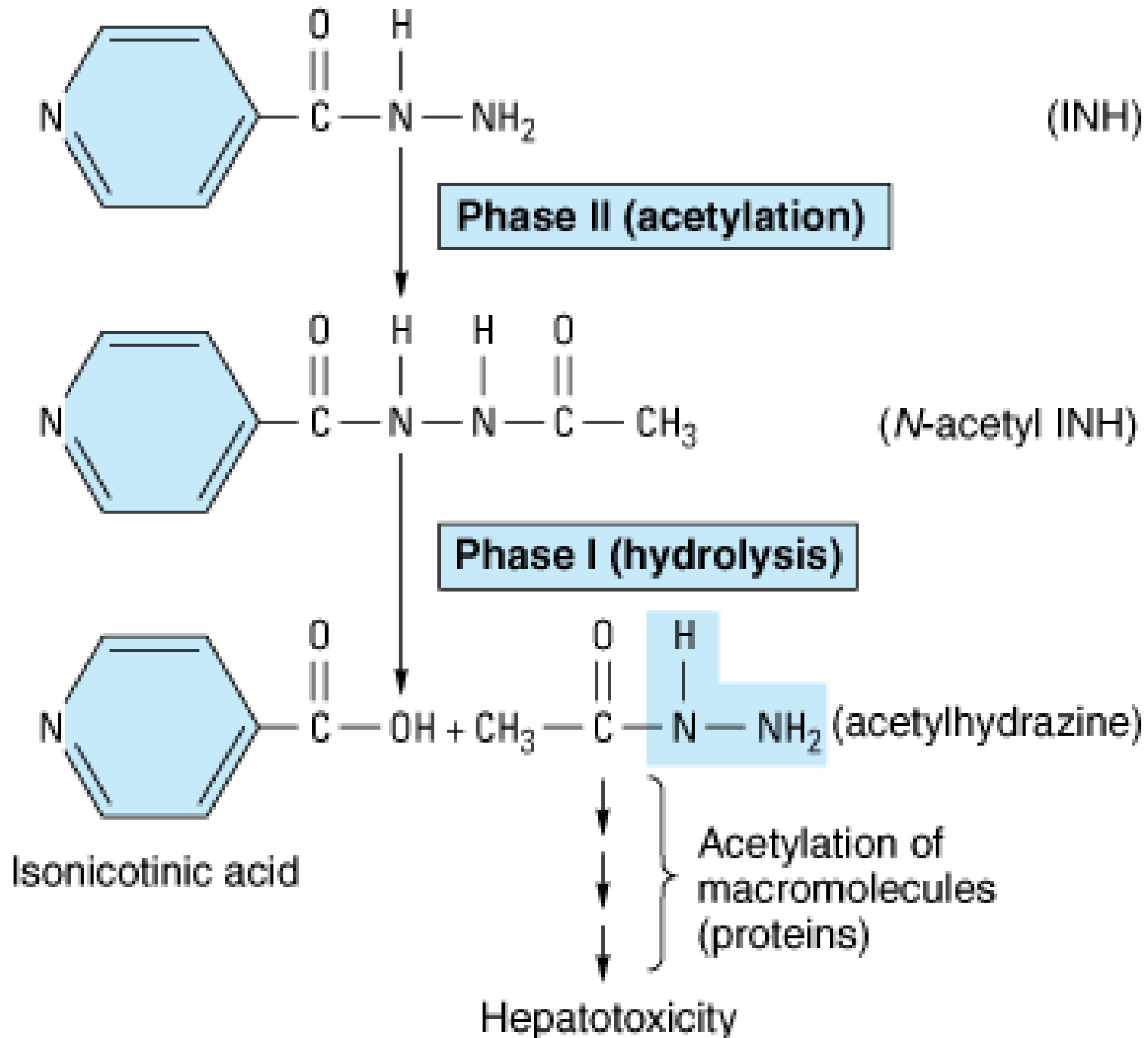


Antituberculous **isoniazid (INH)**: acetylation is an important metabolic step

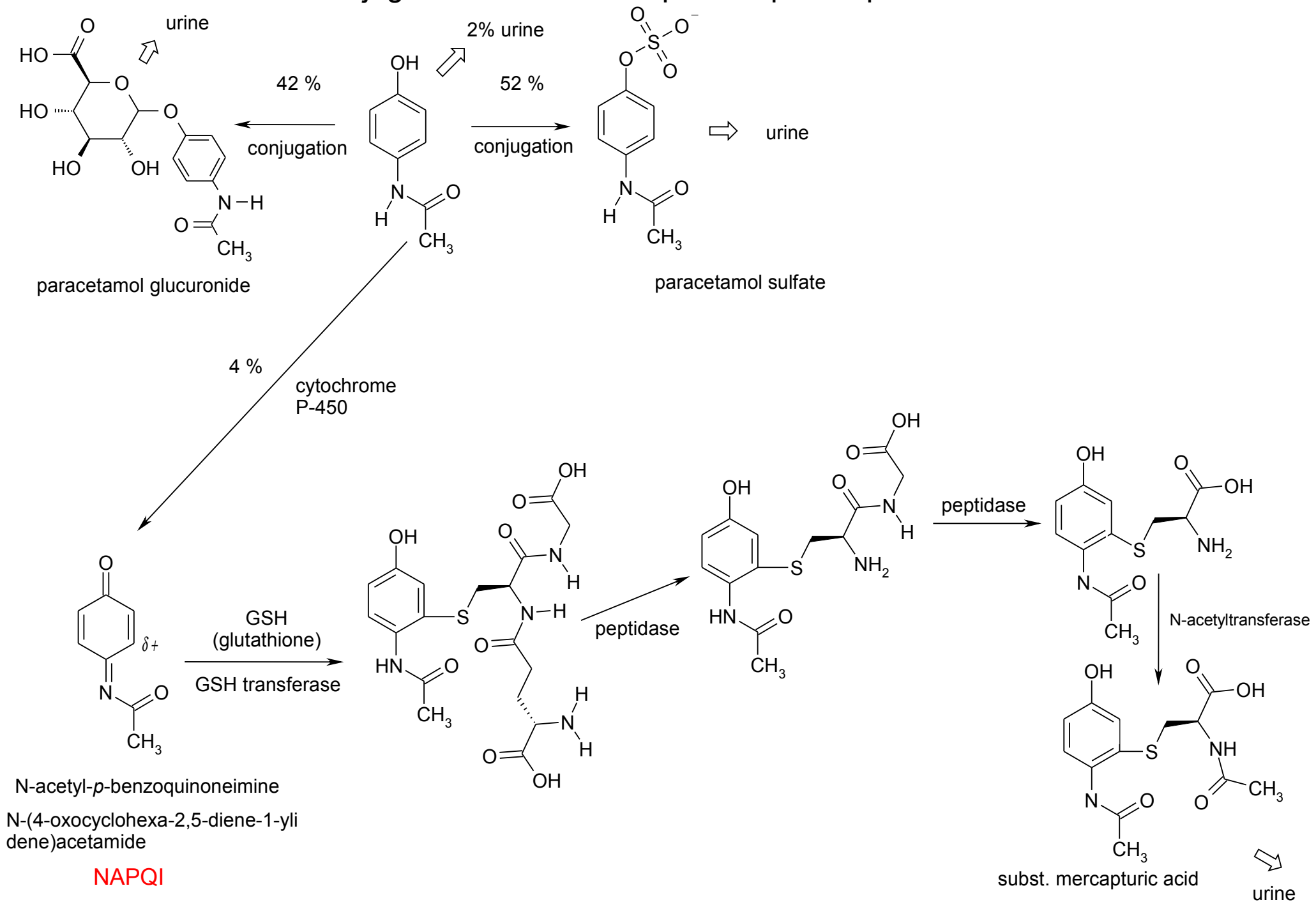


- N-acetyltransferase (NAT2 isoform) is in liver, gut
- the first drug in which slow and fast acetylators were seen
- peripheral neuropathy seen in slow acetylators

Antituberculotic **isoniazid (INH)**: acetylation followed with hydrolysis



Glutathione conjugations on the example of a part of paracetamol metabolism



N-acetyl-*p*-benzoquinoneimine

N-(4-oxocyclohexa-2,5-diene-1-ylidene)acetamide

NAPQI

subst. mercapturic acid

urine

