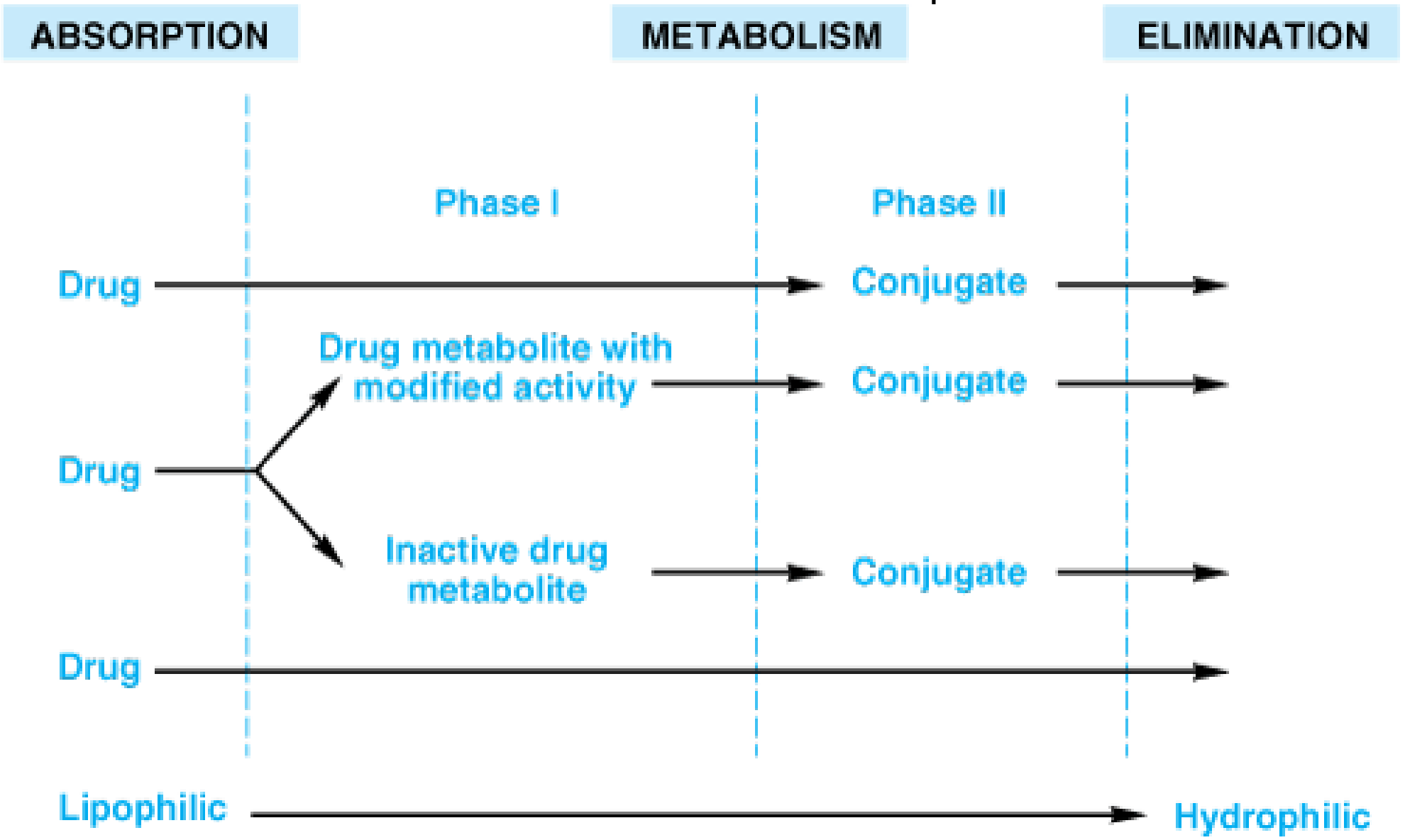
Drug metabolism or biotransformation

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

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

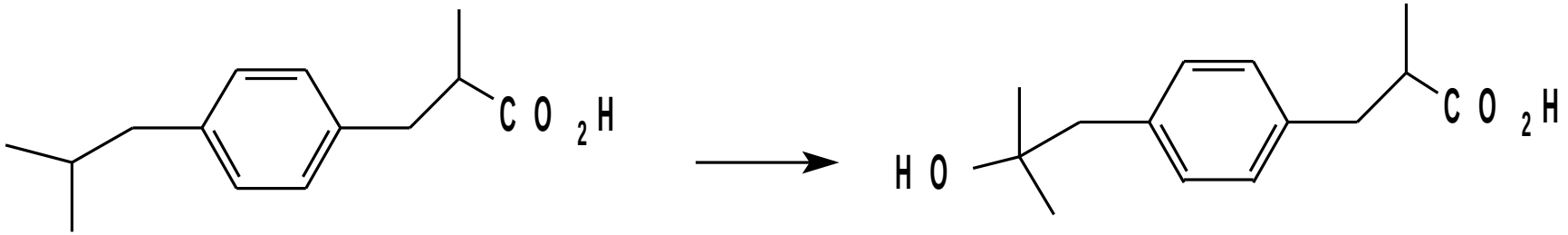
OXIDATIVE REACTIONS: on drugs, such as aromatic hydroxylation, aliphatic hydroxylation, N-dealkylation, O-dealkylation, S-dealkylation, N-oxidation, S-oxidation, desulfuration etc. in most on CYP.

REDUCTIVE REACTIONS: azo, nitrile, carbamyl

HYDROLYTIC REACTIONS: ester hydrolysis, amide hydrolysis.

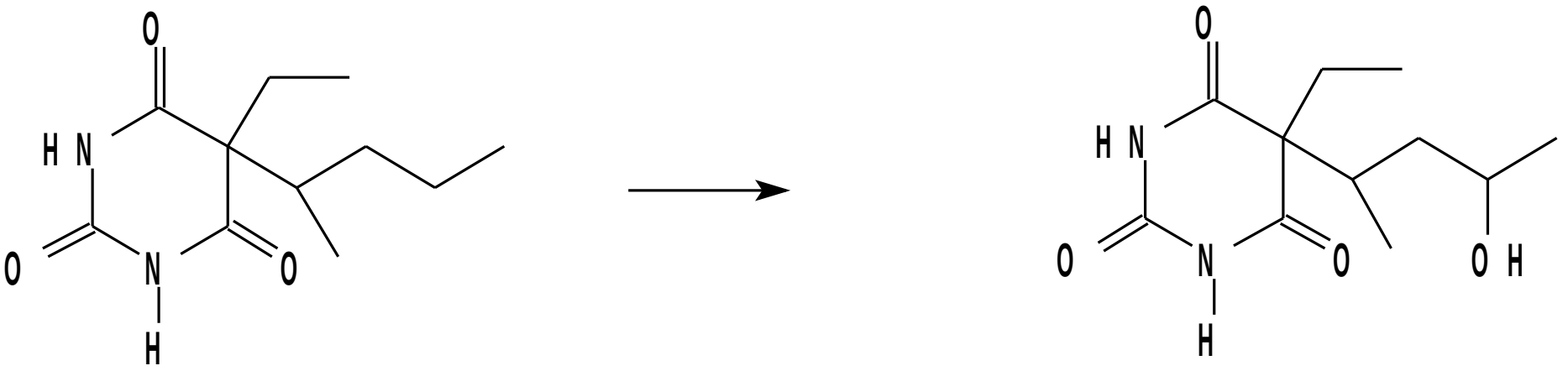
OTHER REACTIONS: decarboxylation

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



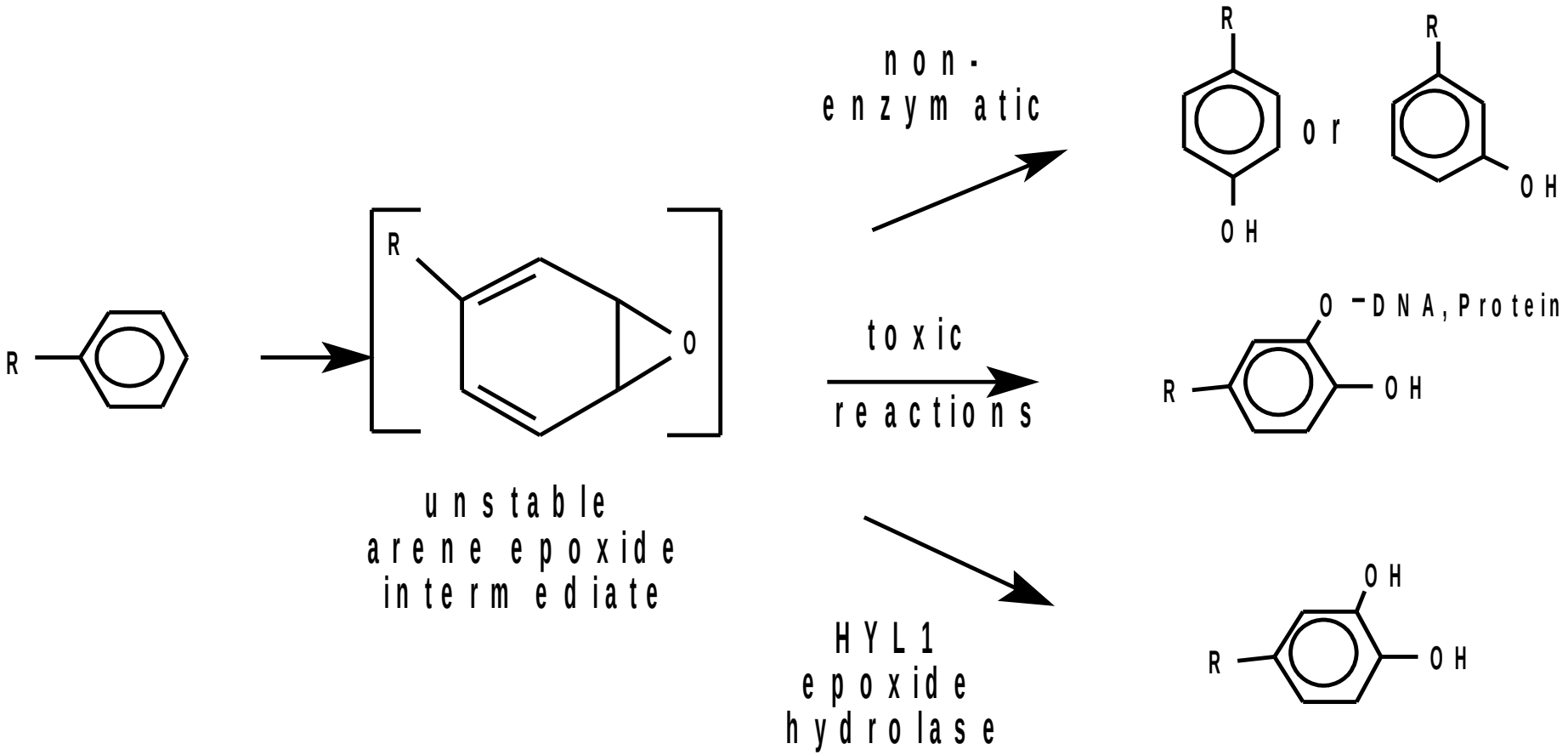
ibuprofen

Aliphatic (ω–1)–hydroxylation: pentobarbital (hypnotic, sedative ...)



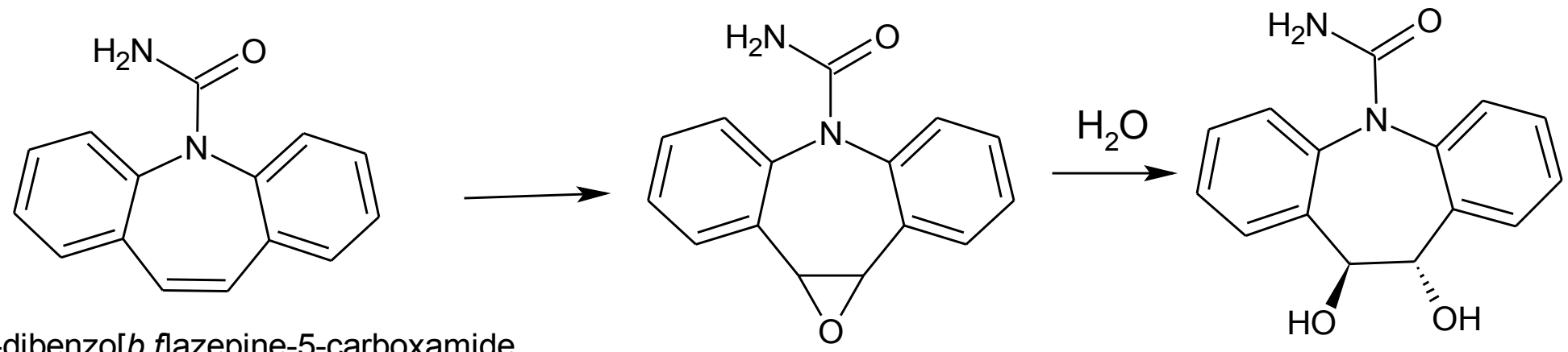
pentobarbital

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



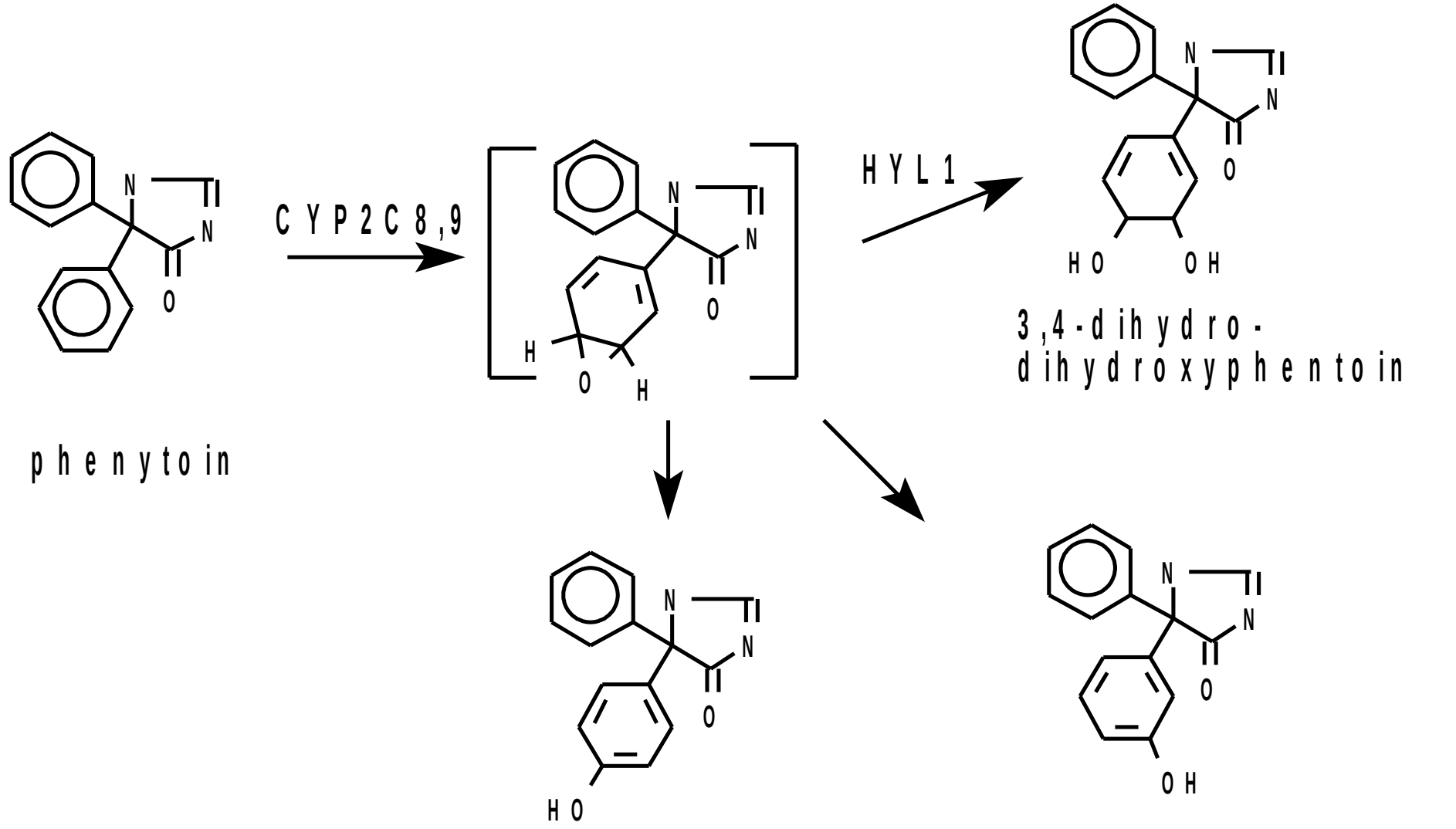
5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide

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

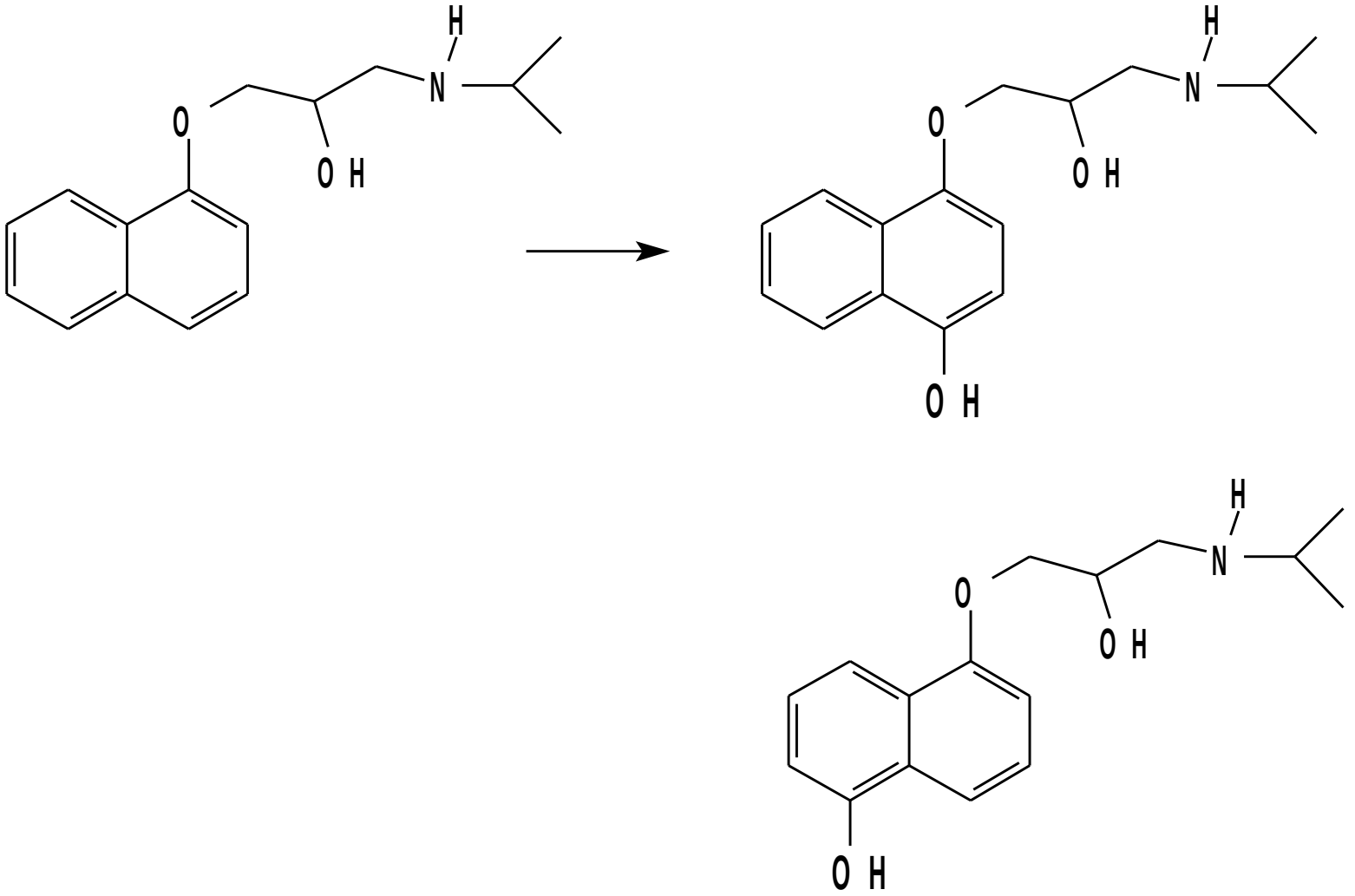
trans-10,11-dihydrocarbamazepine-10,11-diol
•main metabolite excreted by urine

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



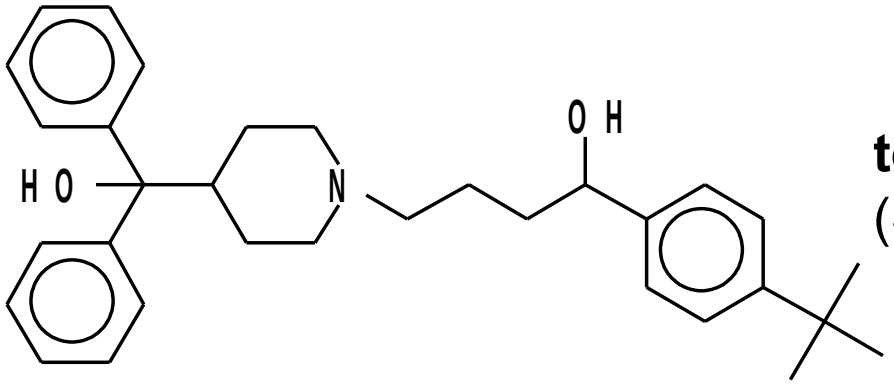
Arene epoxide intermediate produces multiple products

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



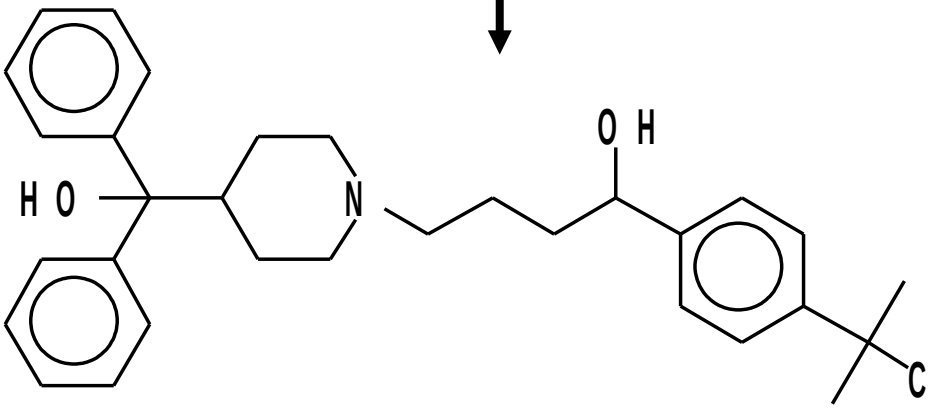
Metabolism of **terfenadine**: oxidation of one of methyls of *tert*-butyl into carboxyl

- H_1-antihistamine if the 2nd generation developed in 1980th
- serious cardiac adverse effects including TdP arrythmias



terfenadine
(Seldane – not authorized in CZ)

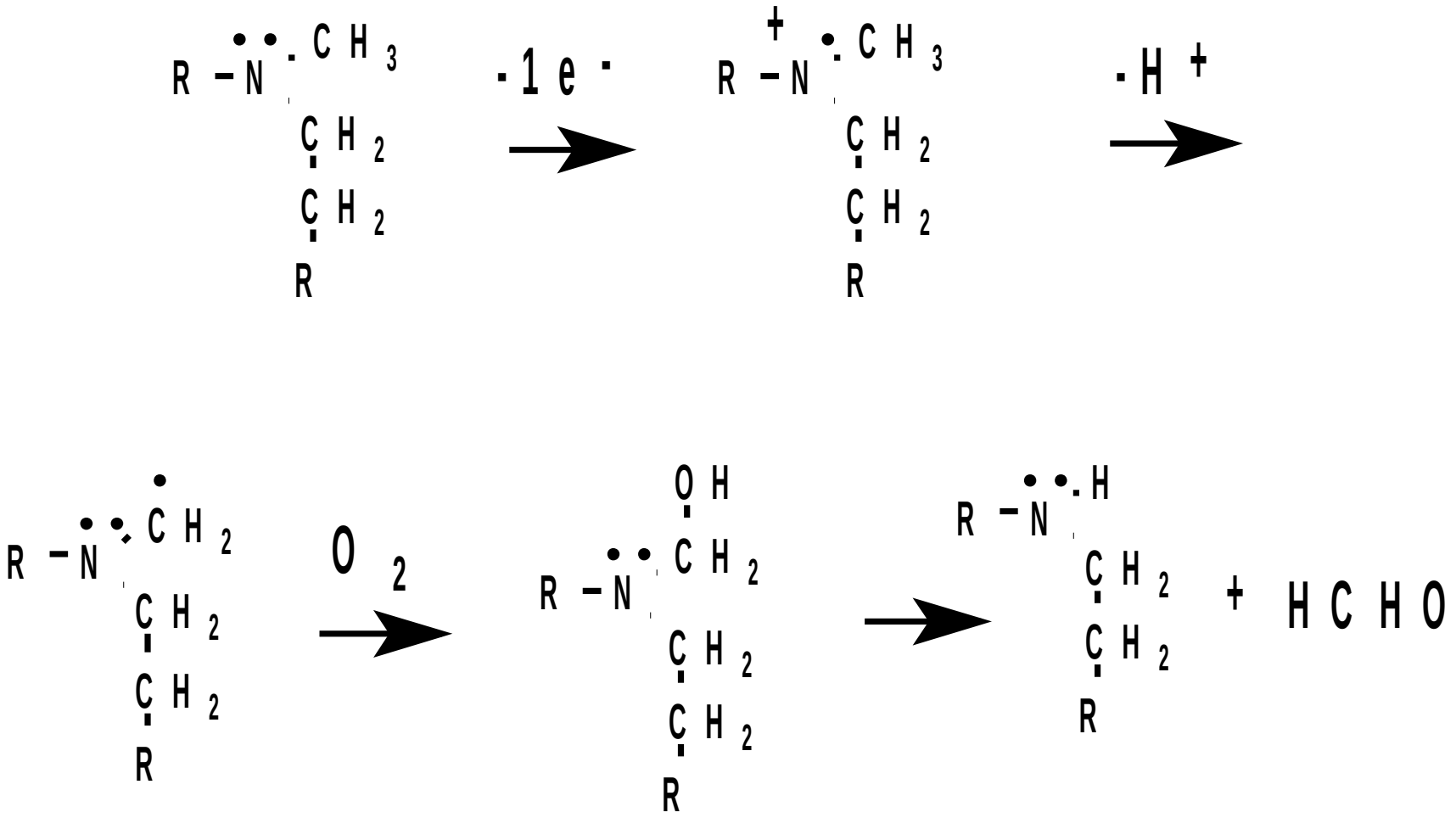
CYP3A4



fexofenadine
(Ewofex ®)

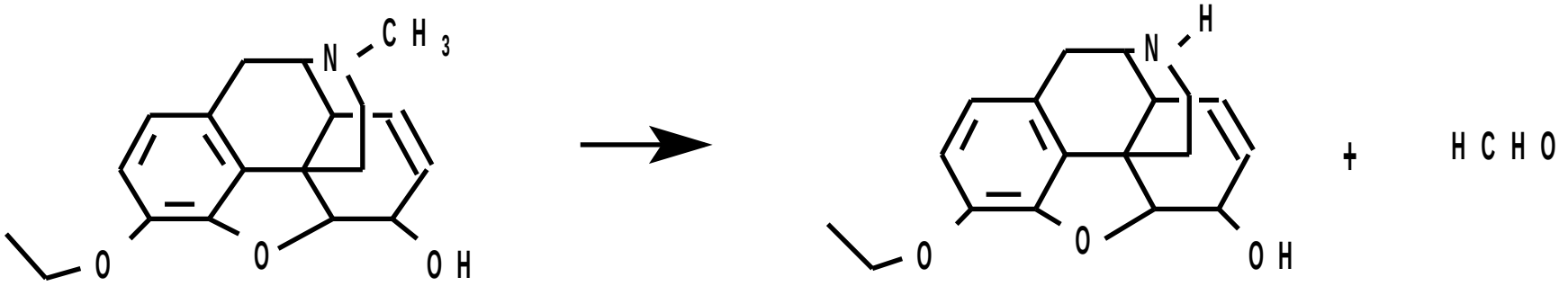
- cardiac adverse effects not present

N (or O, S)-oxidative dealkylation



N-demethylation generates formaldehyde

Oxidative N-demethylation: ethylmorphine (antitussive)

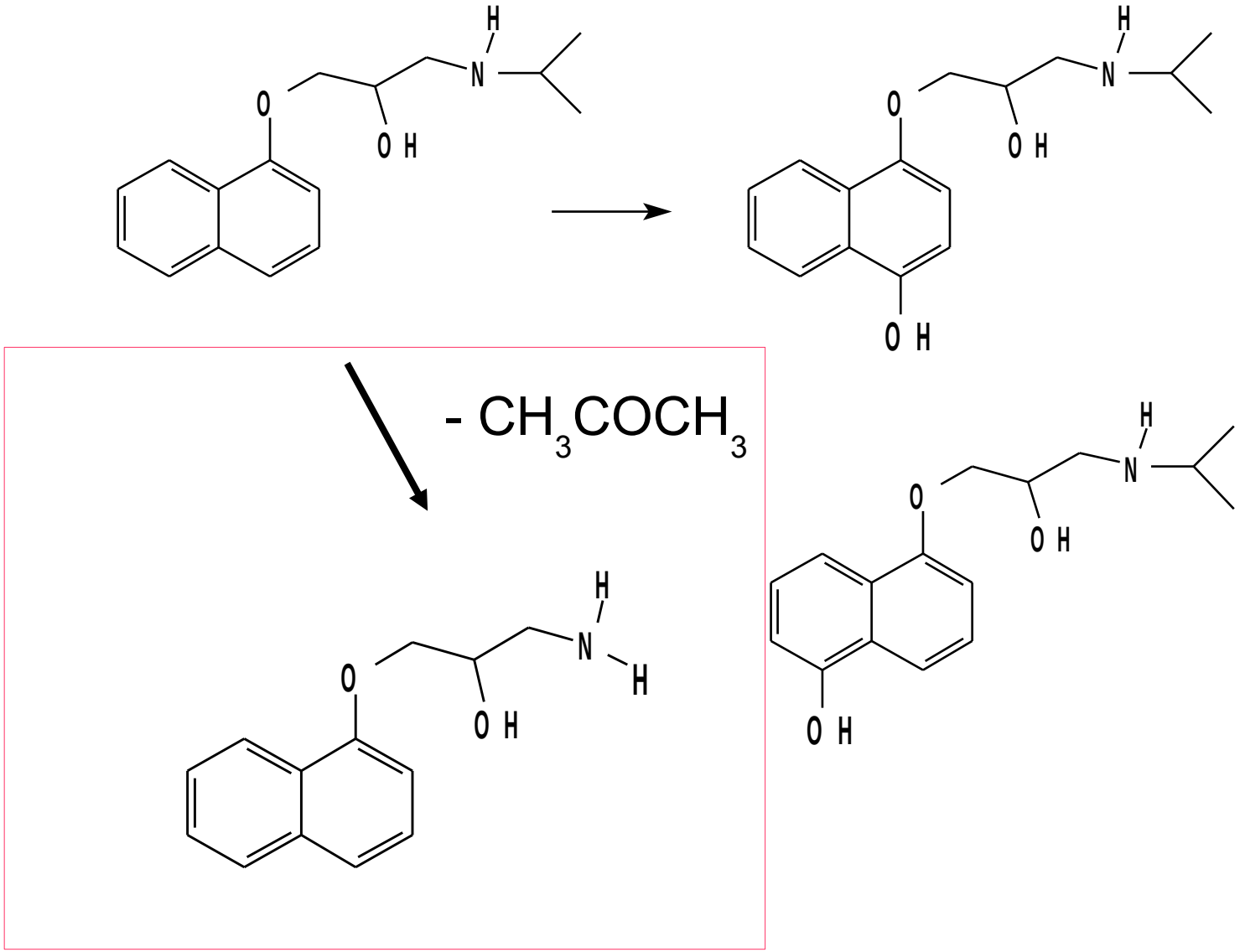


e t h y l m o r p h i n e

d e s m e t h y l - e t h y l m o r p h i n e

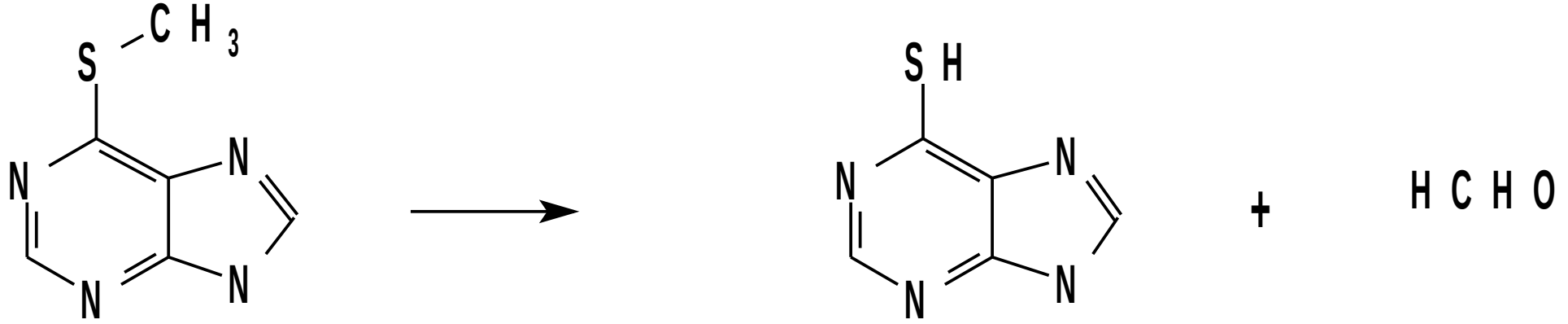
N-demethylation favored over O-deakylation

Oxidative desisopropylation: **propranolol**



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

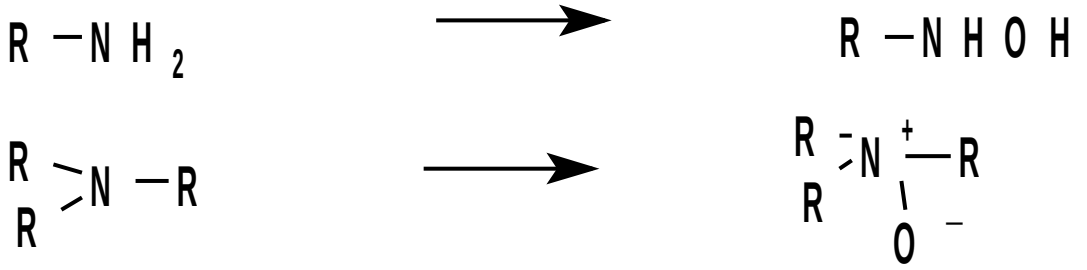
Oxidative S-demethylation: **6-methylthiopurine** = 6-methylsulfanylpurine



6-methythiopurine
•prodrug
•not used

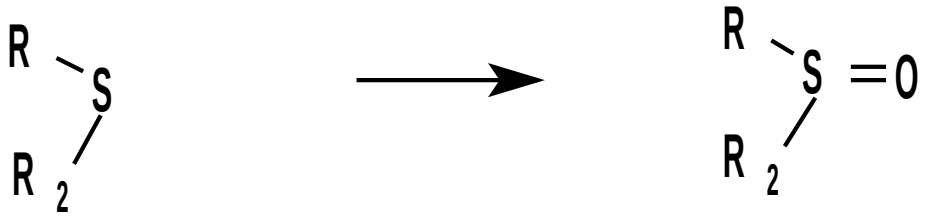
6-mercaptopurine
•active form normaly originated from antineoplastic and antirheumatic azathioprin

N-Oxidation



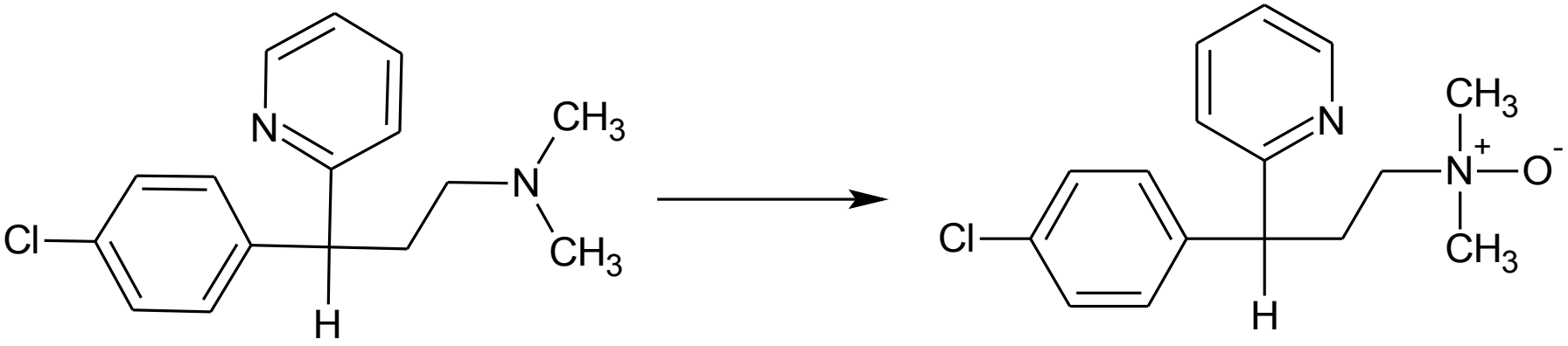
Examples: chlorpheniramine, trimethylamine

S-Oxidation



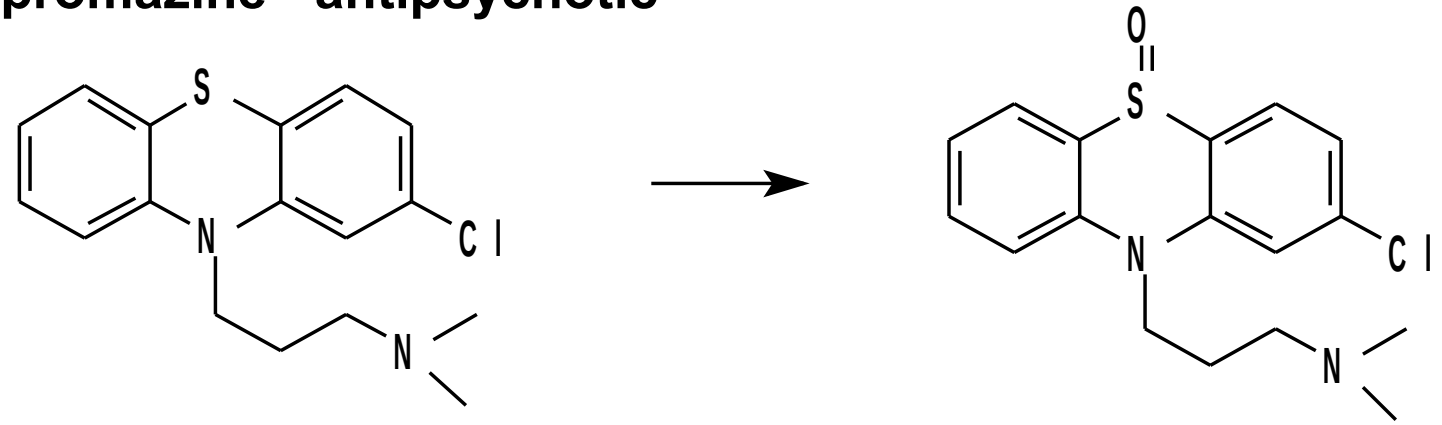
Examples: chlorpromazine, cimetidine

chlorpheniramine - H_1-antihistamine

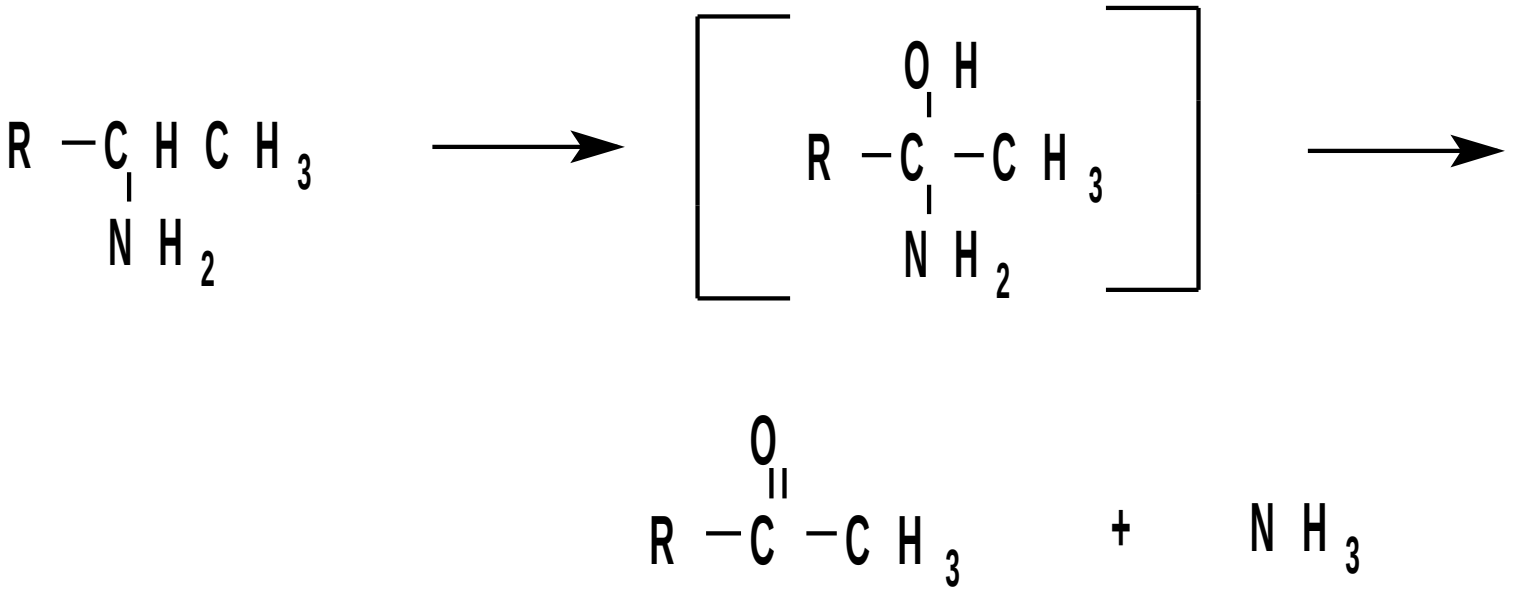


[3-(4-chlorophenyl)-3-(pyridin-2-yl)propyl] dimethylamine oxide

chlorpromazine - antipsychotic

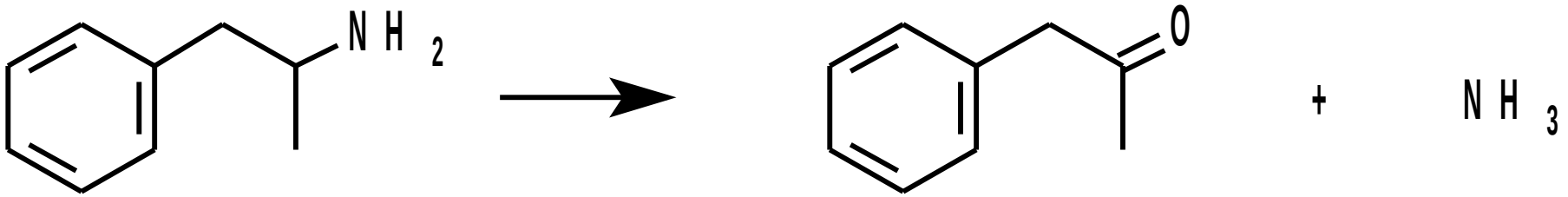


Oxidative deamination of primary amines



Examples: amphetamine, diazepam (after benzodiazepine ring opening)

amphetamine - central stimulant, indirect adrenergic



2-amino-3-phenylpropane
amphetamine

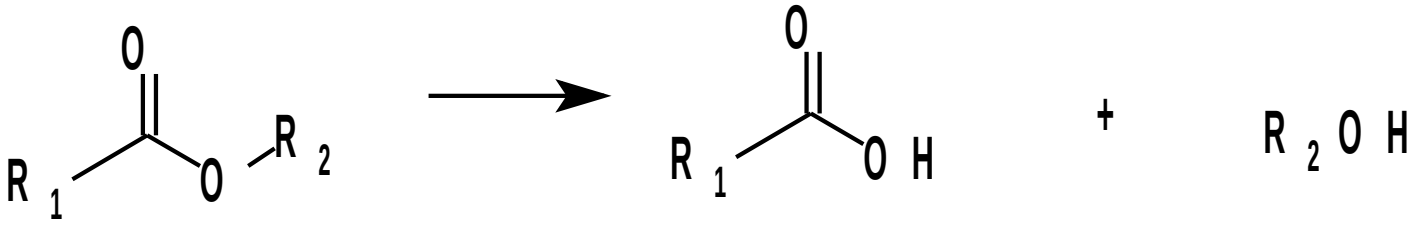
2-phenylpropane-2-on

PHASE I hydrolytic metabolism enzymatic apparatus

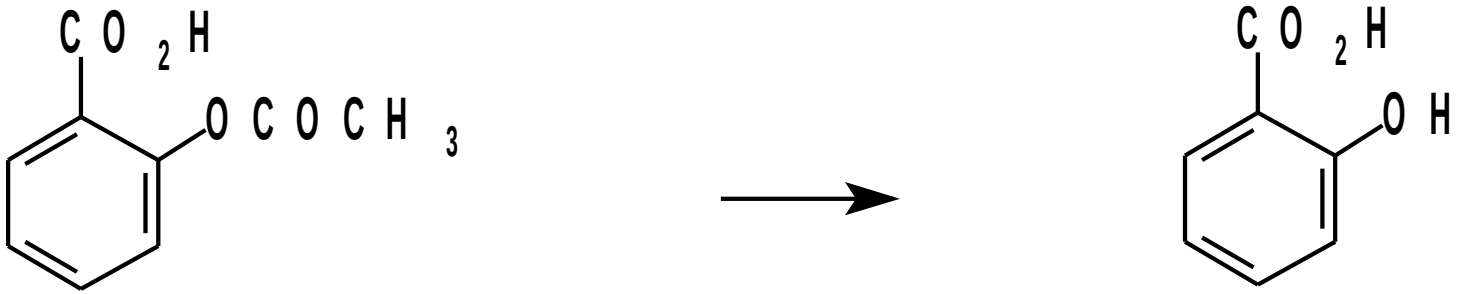
- hydrolases
  - esterases – have also some amidase activity
    - cholinesterases: acetylcholiesterase, butyrylcholinesterase
    - pseudocholinesterase
    - lipases
  - peptidases – naturally cleave the peptidic bond, but are capable to cleave also other amide bonds
    - exopeptidases – cleave peptide 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, naphtylamides etc.

Hydrolysis Reactions

Esters

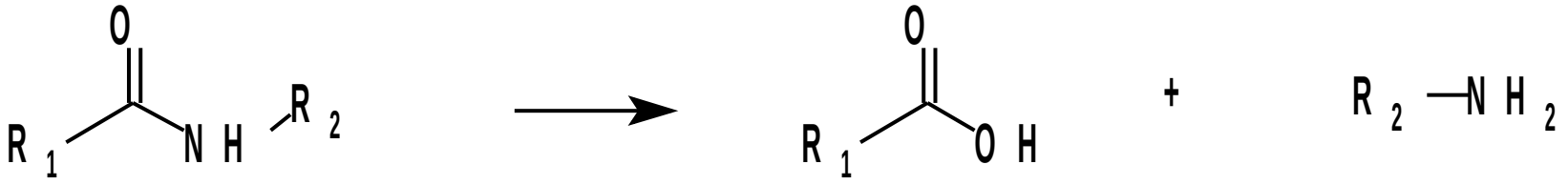


Example: acetylosalicylic acid (others include procaine, clofibrate)

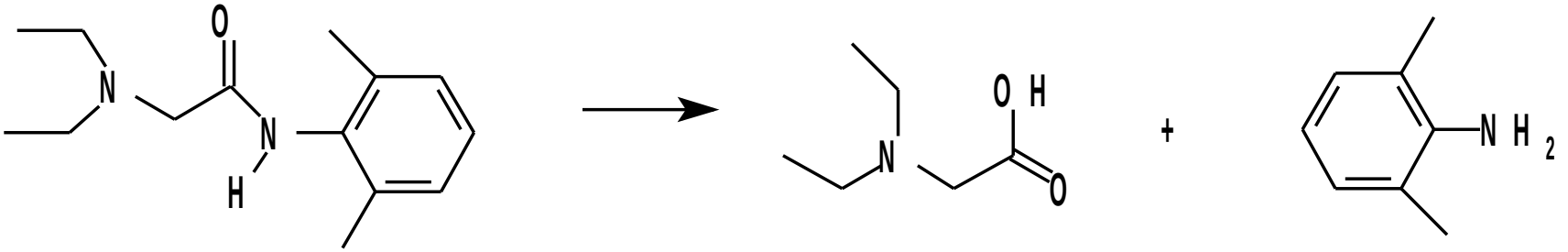


Hydrolysis Reactions

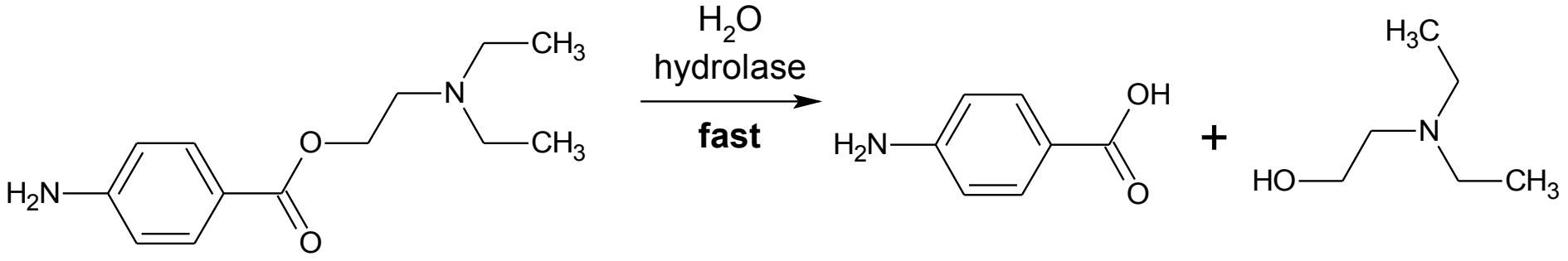
Amides



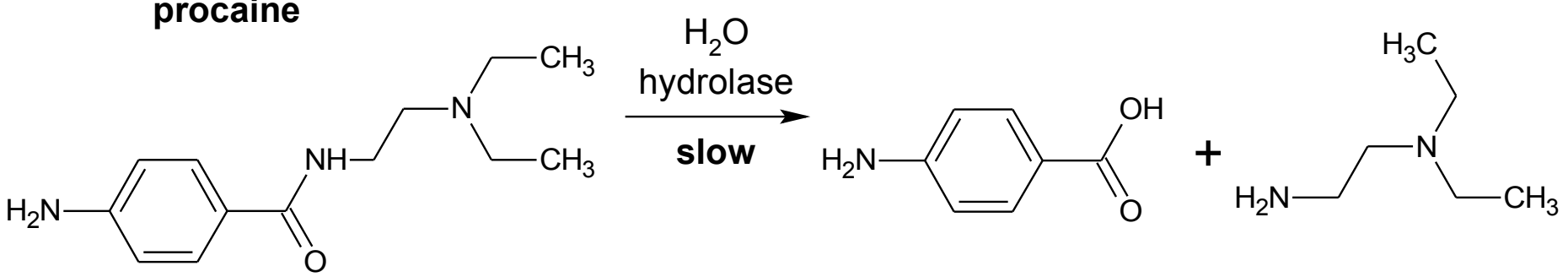
Example: lidocaine; others include peptide drugs



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



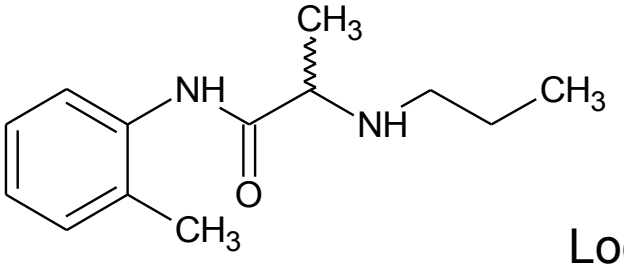
procaine



procainamide

•procaine does not act as an antidysrrhythmic 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



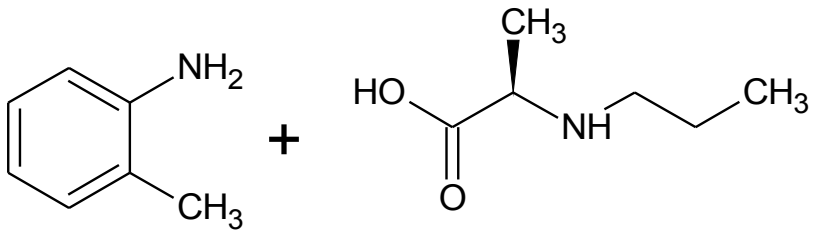
Local anaesthetics of anilide series: **prilocaine**

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

R-(-)

S-(+)

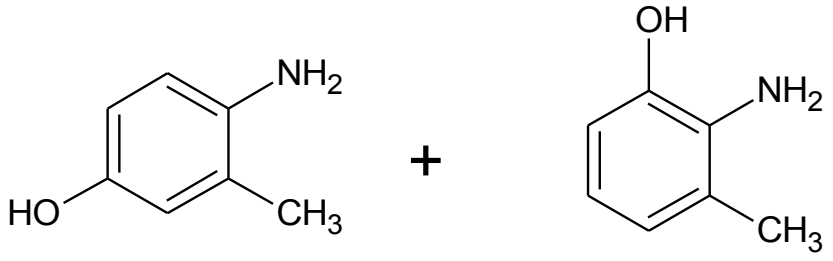
H_2O | hydrolase



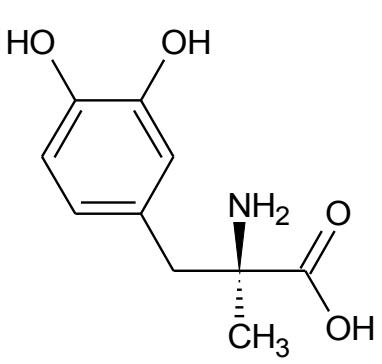
(2*R*)-2-(propylamino)propanoic acid

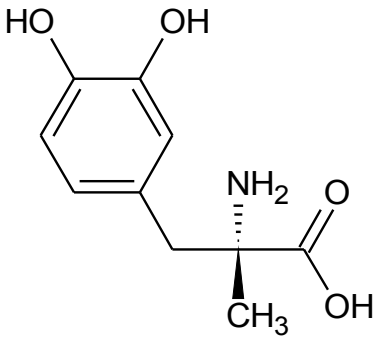
- administration of the pure *S*-(-) enantiomer can eliminate the toxicity

aromatic ring hydroxylation



- toxic metabolites
- methemoglobinemia





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

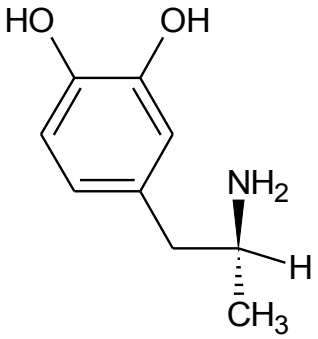
(-)-(*S*) (+)-(*R*) - inactive

Decarboxylation reaction

α-methyldopa – antihypertensive, α-adrenolytic
Dopegyt ® contains (-)-(*S*) sesquihydrate

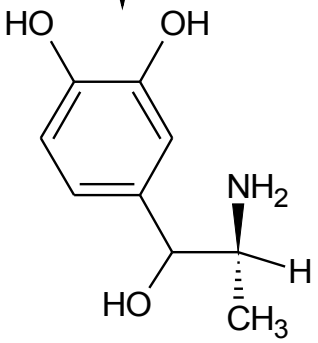
•stereoselectivity of enzyme reaction: (-)-(S)-isomer only undergoes the decarboxylation and thus is active

- CO_2 | decarboxylase



α-methyldopamine

β -hydroxylase

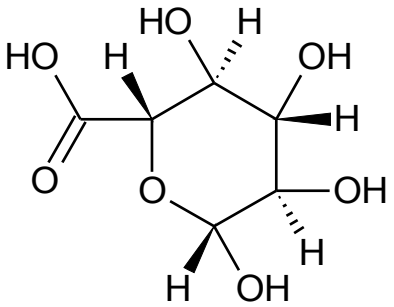


α-methylnoradrenaline – metabolite active as α_1 antagonist

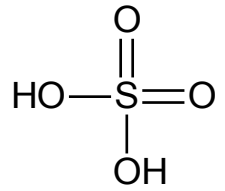
PHASE II metabolic routes: conjugation reactions

- involve the attachement 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 usally 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^+...)

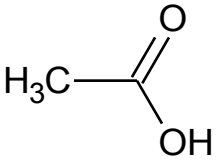
The most common „conjugation partners“



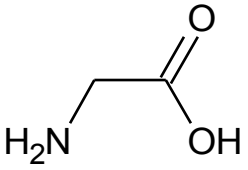
D-glucuronic acid



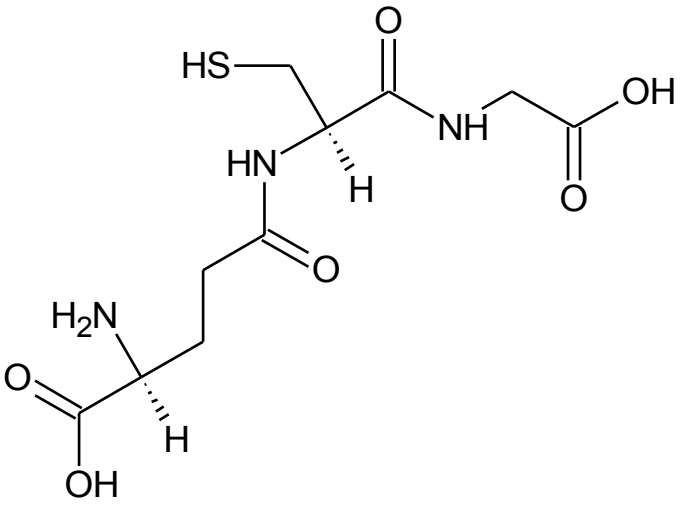
sulfuric acid



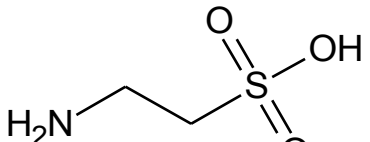
acetic acid



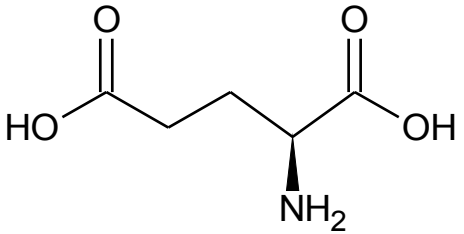
glycine



glutathione

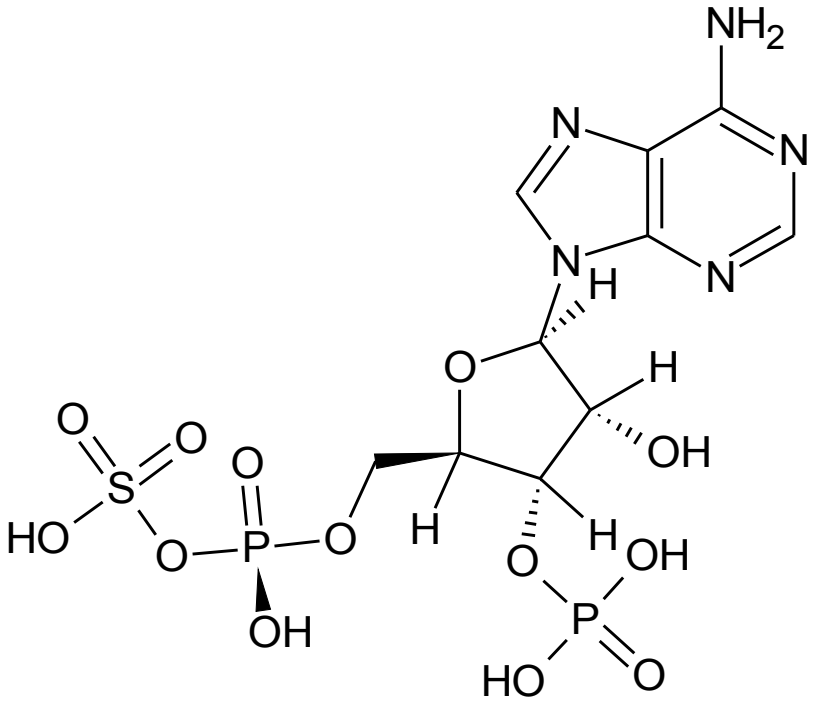


taurine
(2-aminoethanesulfonic acid)



(*S*)-gluatmic 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

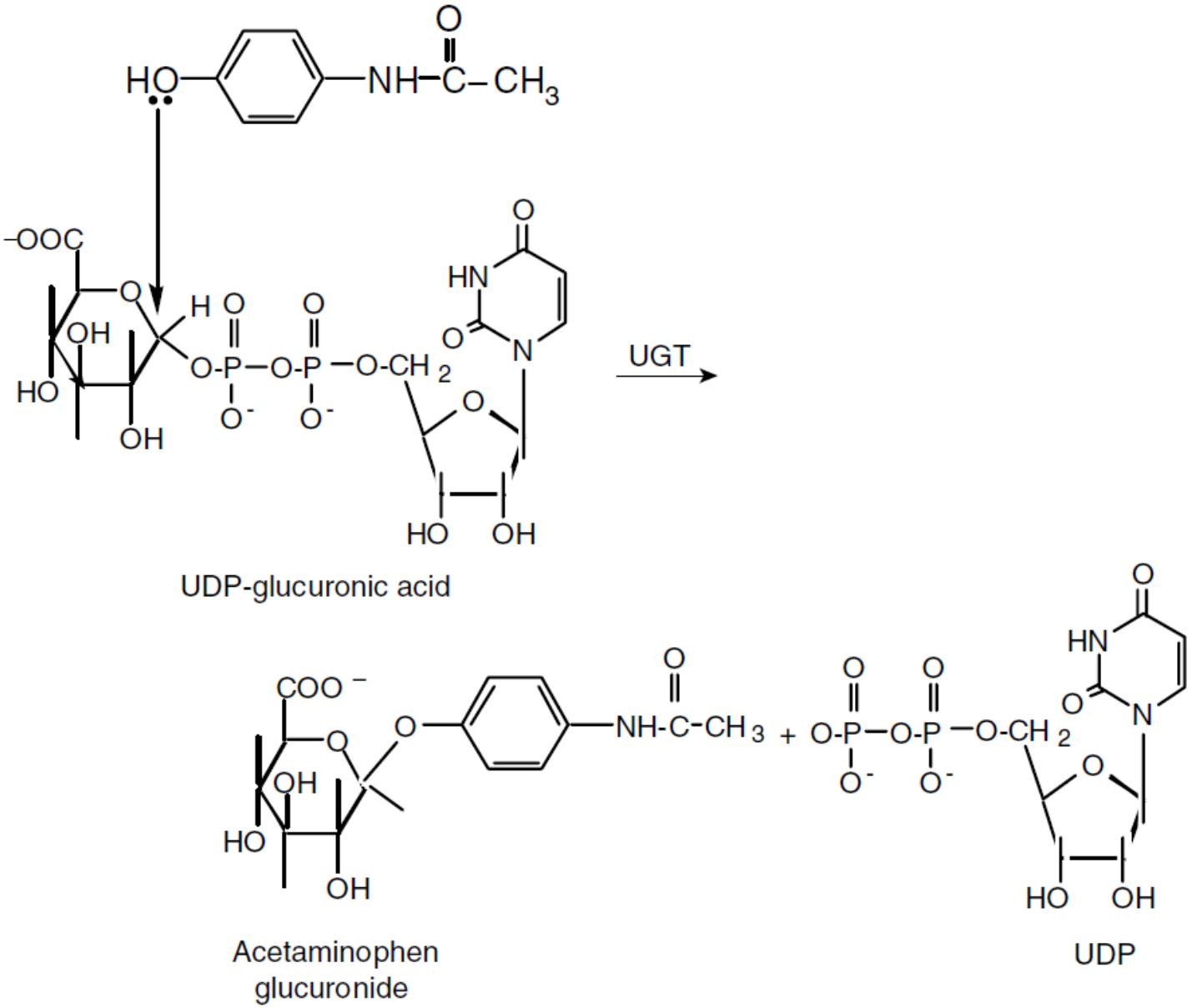
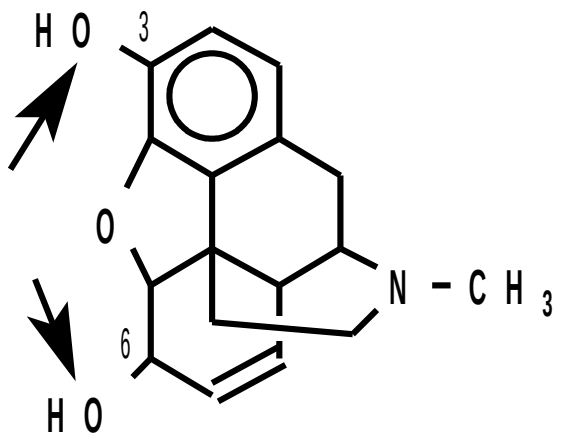
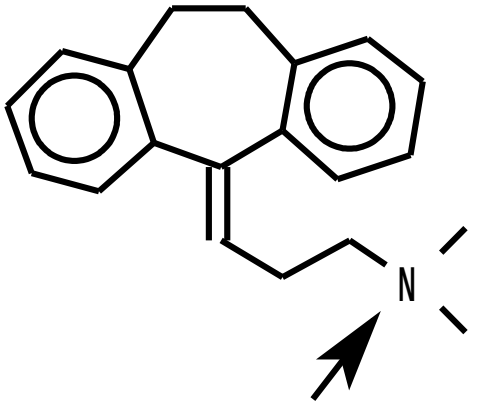


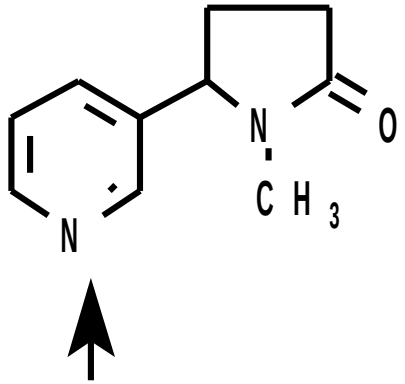
FIGURE 3.1 The glucuronidation reactions. Enzyme: UDP glucuronosyltransferase (UGT or UDPGT); Cosubstrate: uridene diphosphoglucuronic acid (UDPGA)-activated cosubstrate.



Morphine



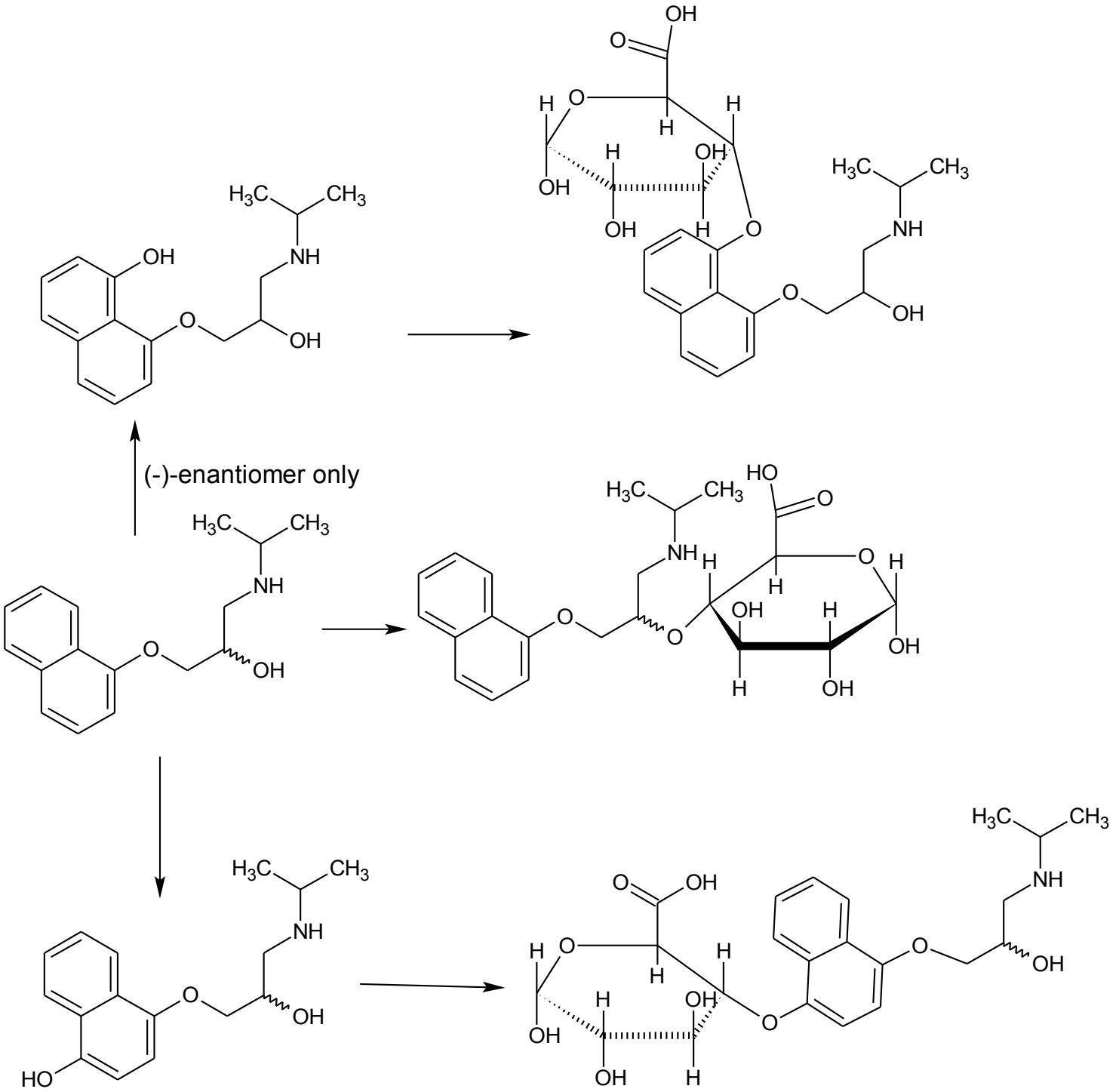
Amitriptyline



Cotinine

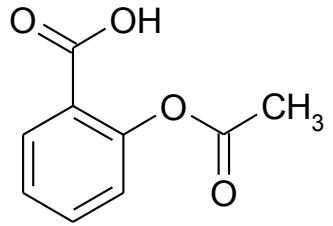
Examples of substrates of glucuronic acid conjugation include alcohols, phenols, 3°-amines, aromatic amines etc.

Glucuronate conjugations of propranolol and some its hydroxylation products



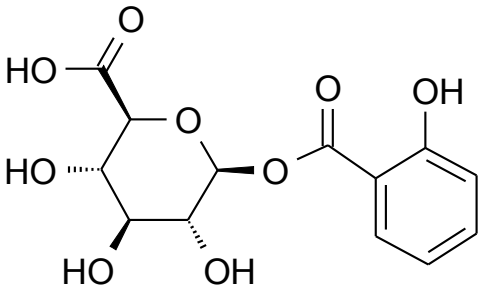
Metabolism of acetylosalicylic acid

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



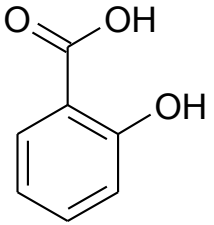
ASA

$t_{1/2}$ = 15 min



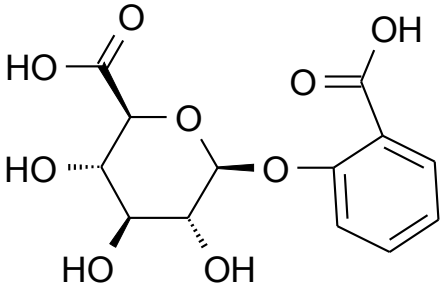
O^1-salicyoylglucuronic acid
5 %

glucuronation



salicylic acid.
10 %

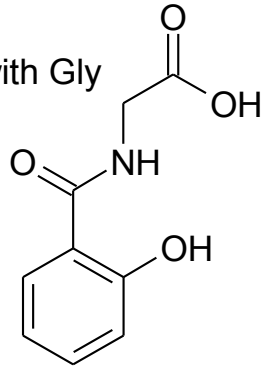
+ CH_3COOH



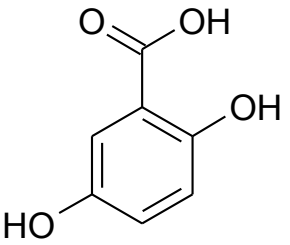
O^1-(2-carboxyphenyl)glucuronic acid
10 %

hydroxylation

conjugation with Gly

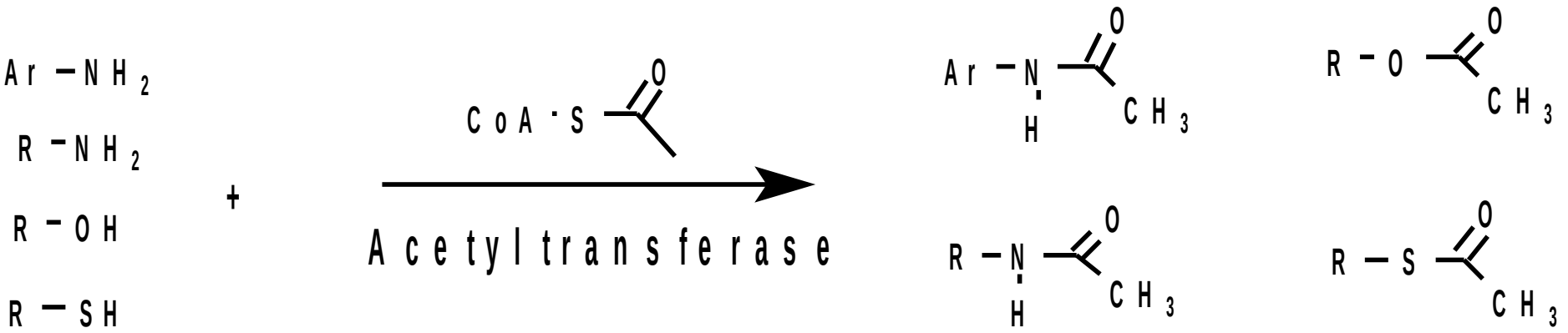


salicyluric acid
(N-salicyoylglycine)
75 %



gentisic acid
< 1 %

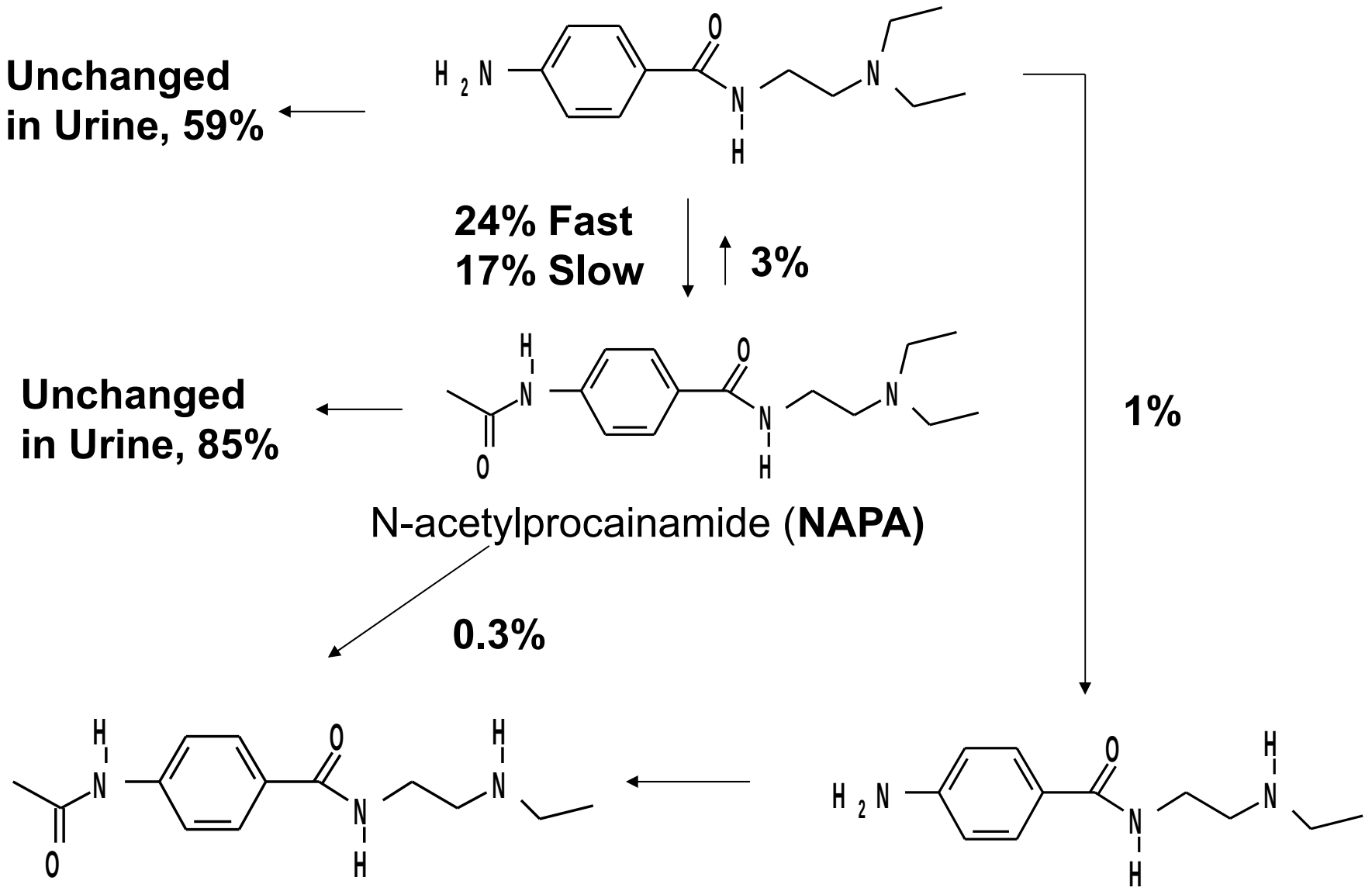
Conjugation Reactions
Acetylation



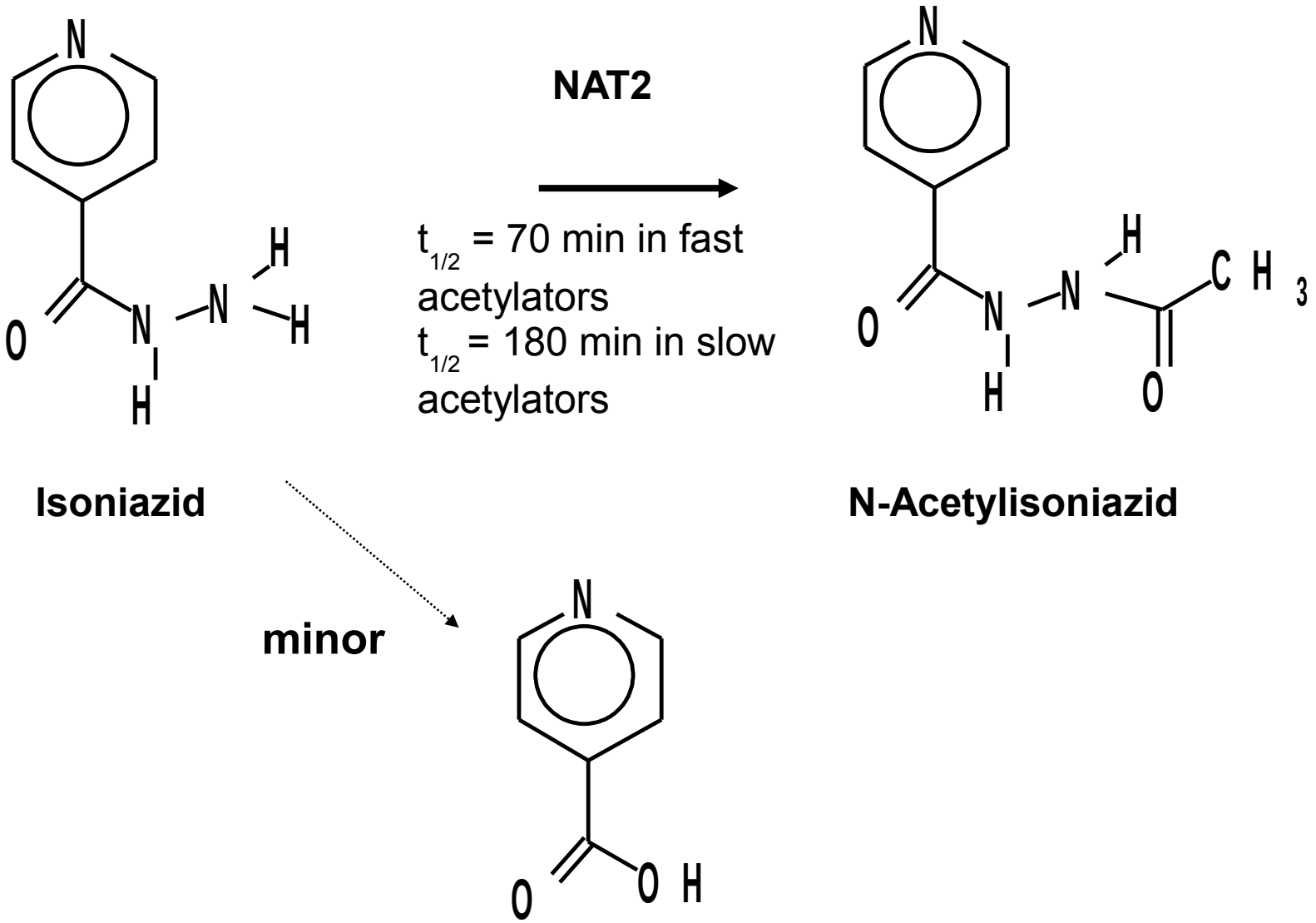
Examples: Procainamide, isoniazid, sulfonamides, histamine

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

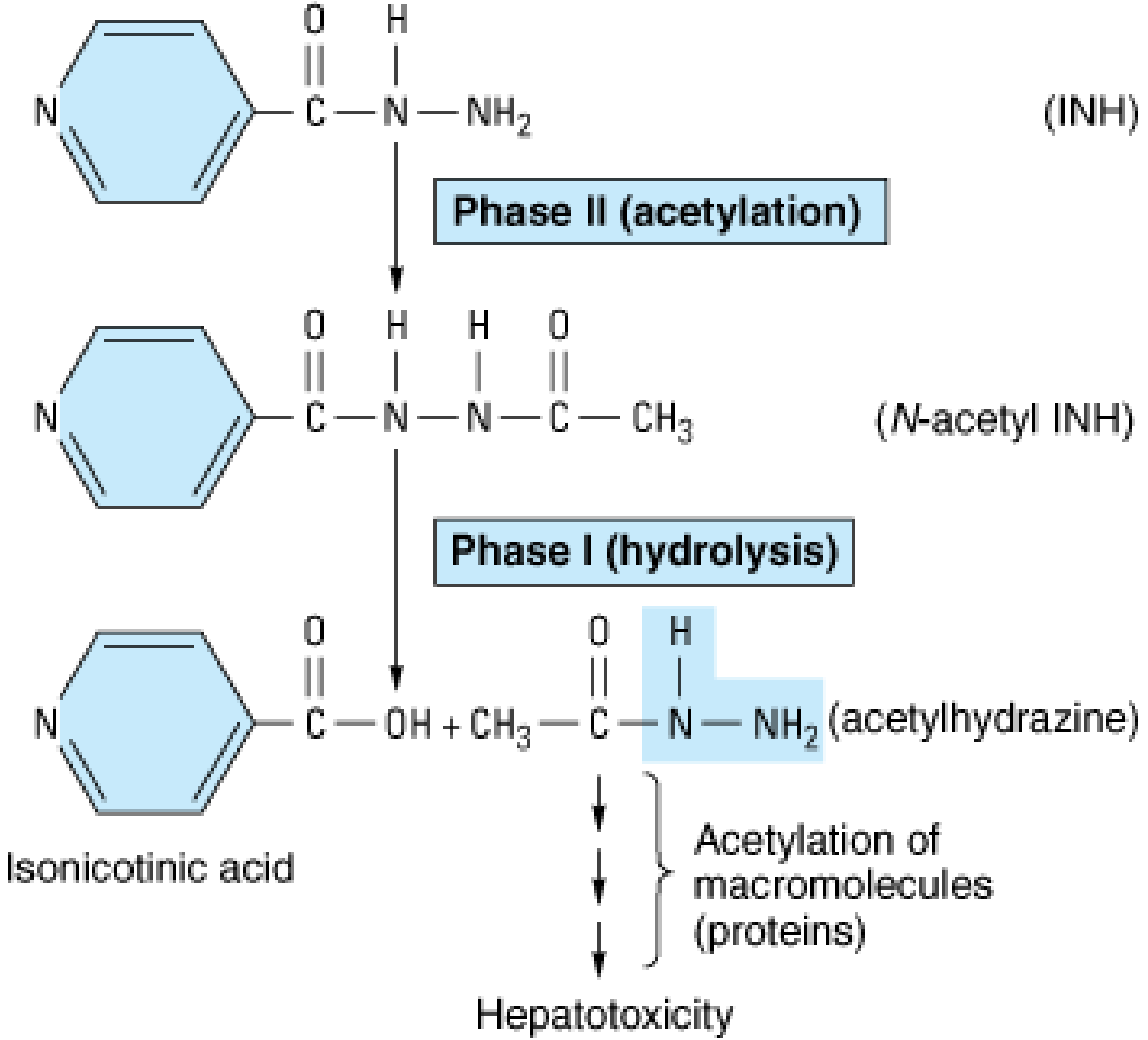


Antituberculotic **isoniazid (INH):** acetylation is an important metabolic step



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

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



Glutathione conjugations on the example of a part of paracetamol metabolism