evropský sociální fond v ČR
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2007-13
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Farmaceutická chemie I. 2. rok studia

Metabolismus léčiv.

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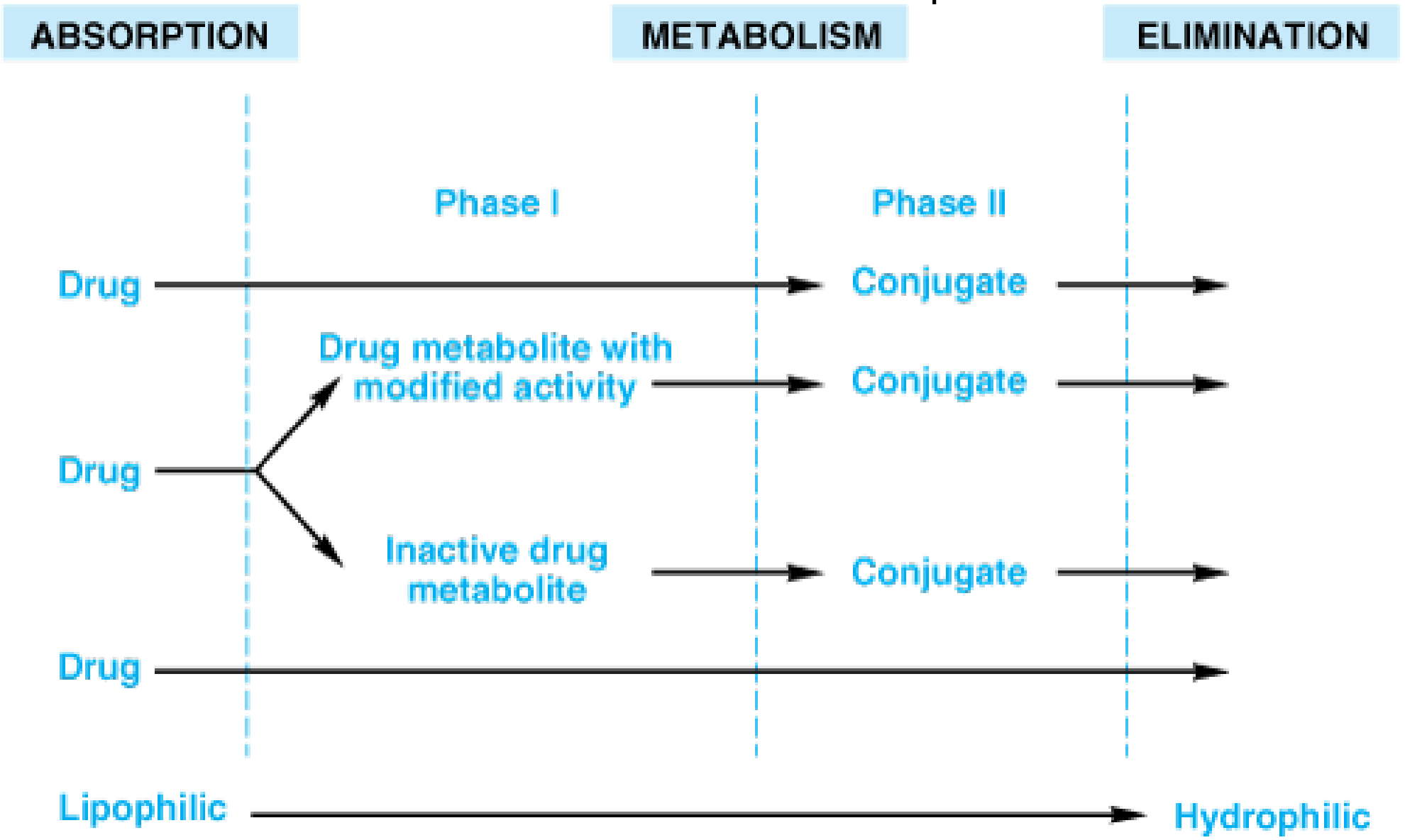
Drug metabolism or biotransformation

- 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

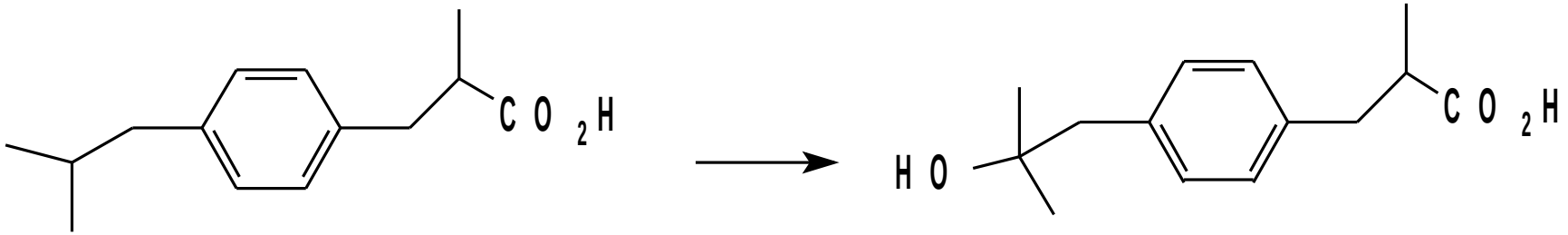
OXIDATIVE REACTIONS: on drugs, such as aromatic hydroxylation, aliphatic hydroxylation, N-dealkylation, O-dealkylation, S-dealkylation, N-oxidation, S-oxidation, desulfuration etc. in most on CYP.

REDUCTIVE REACTIONS: azo, nitrile, carbamyl

HYDROLYTIC REACTIONS: ester hydrolysis, amide hydrolysis.

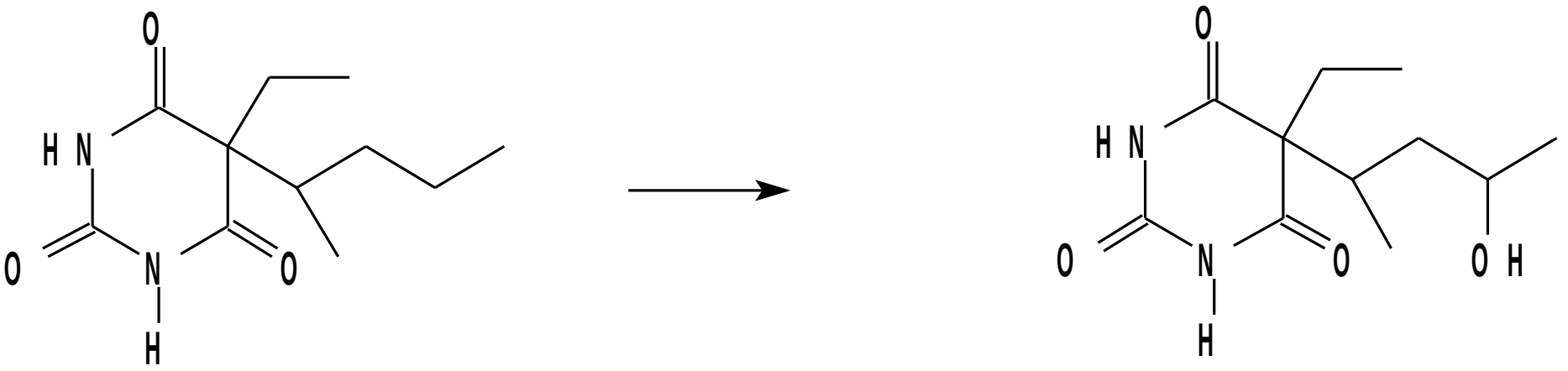
OTHER REACTIONS: decarboxylation

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



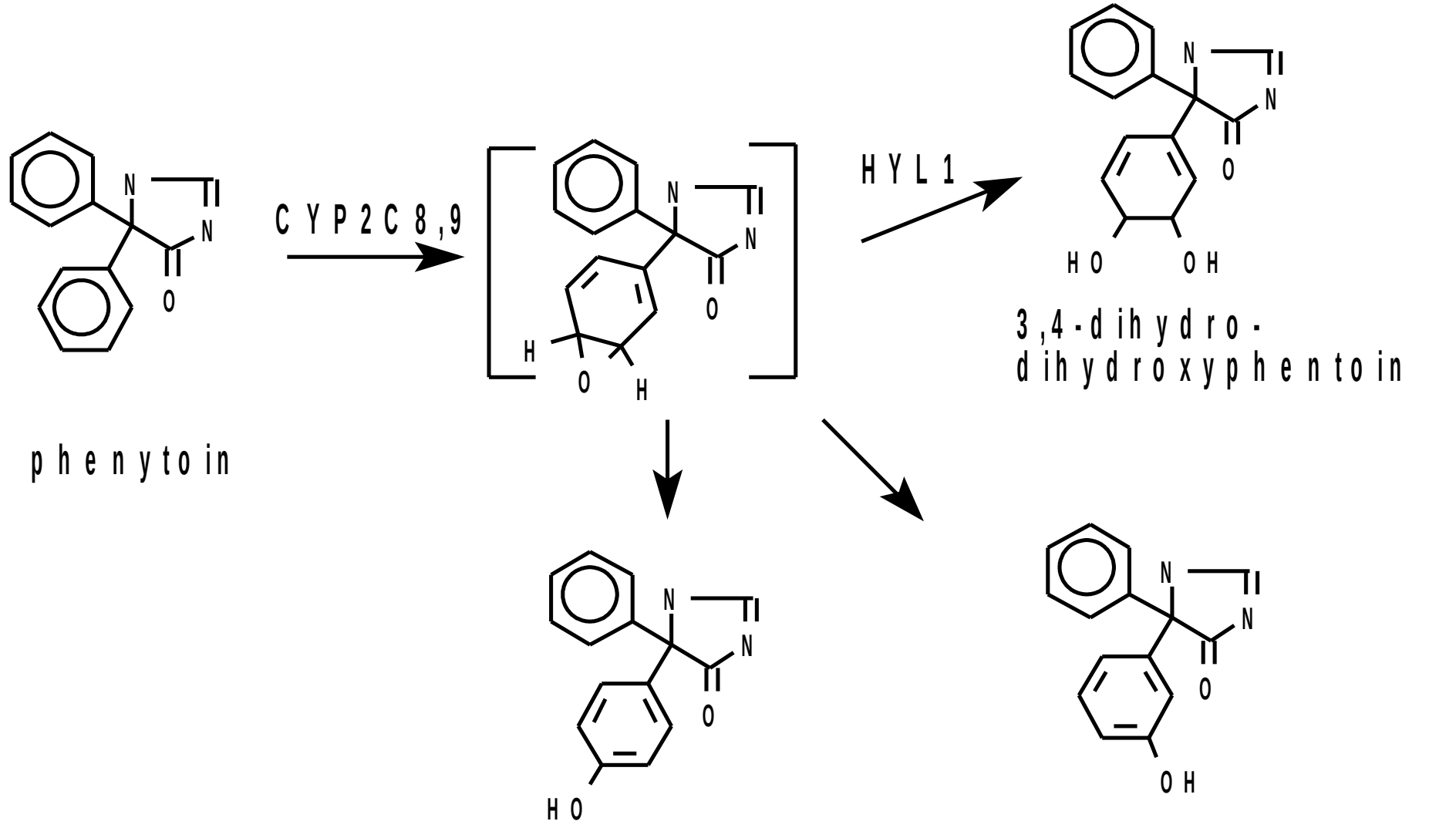
ibuprofen

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



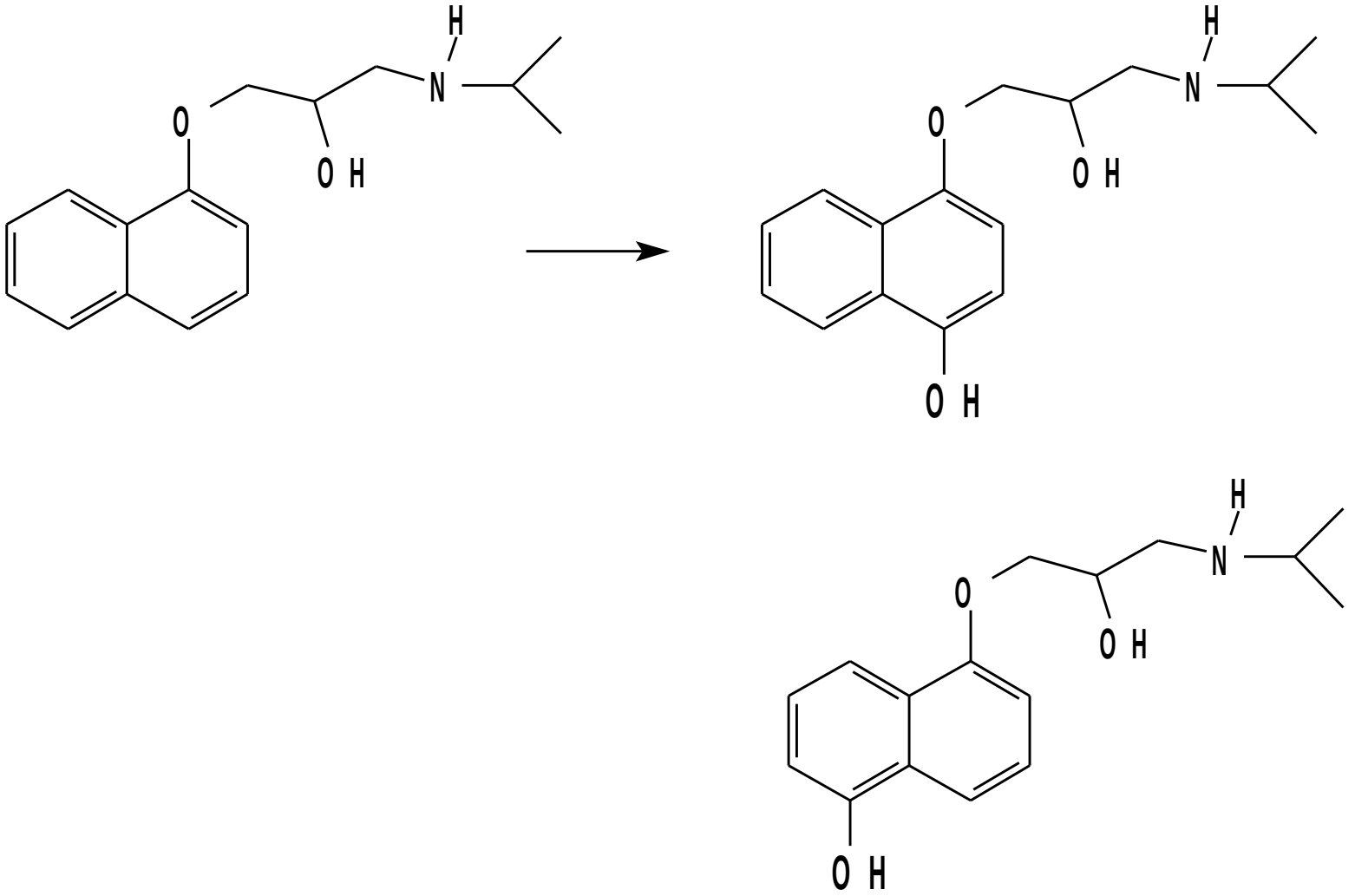
pentobarbital

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



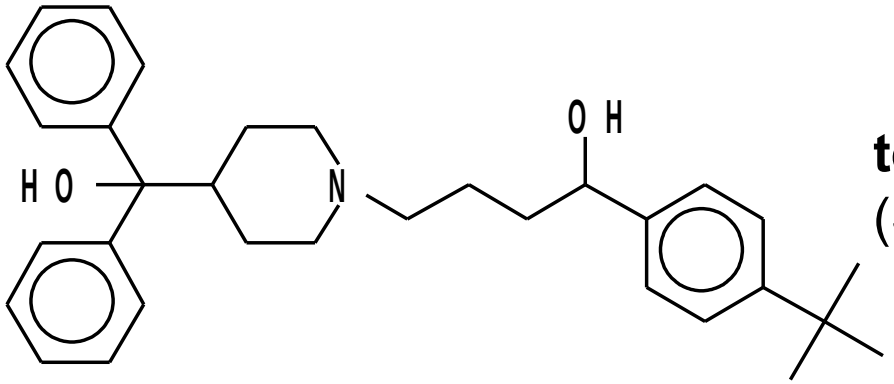
Arene epoxide intermediate produces multiple products

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



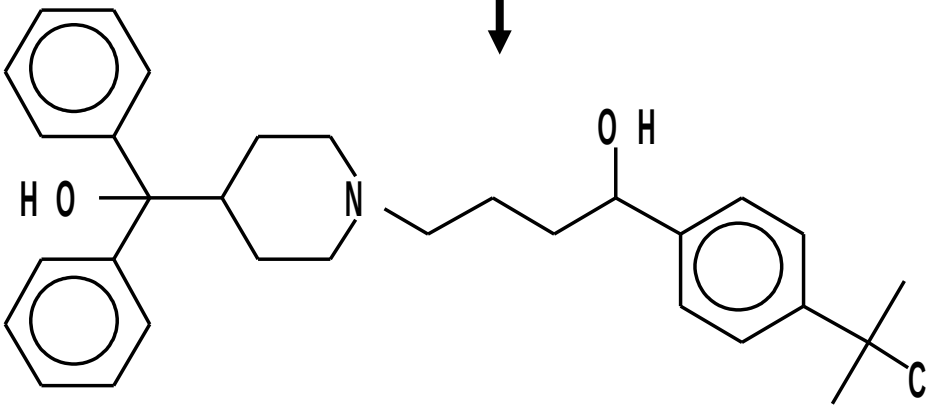
Metabolism of **terfenadine**: oxidation of one of methyls of *tert*-butyl into carboxyl

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



terfenadine
(Seldane – not authorized in CZ)

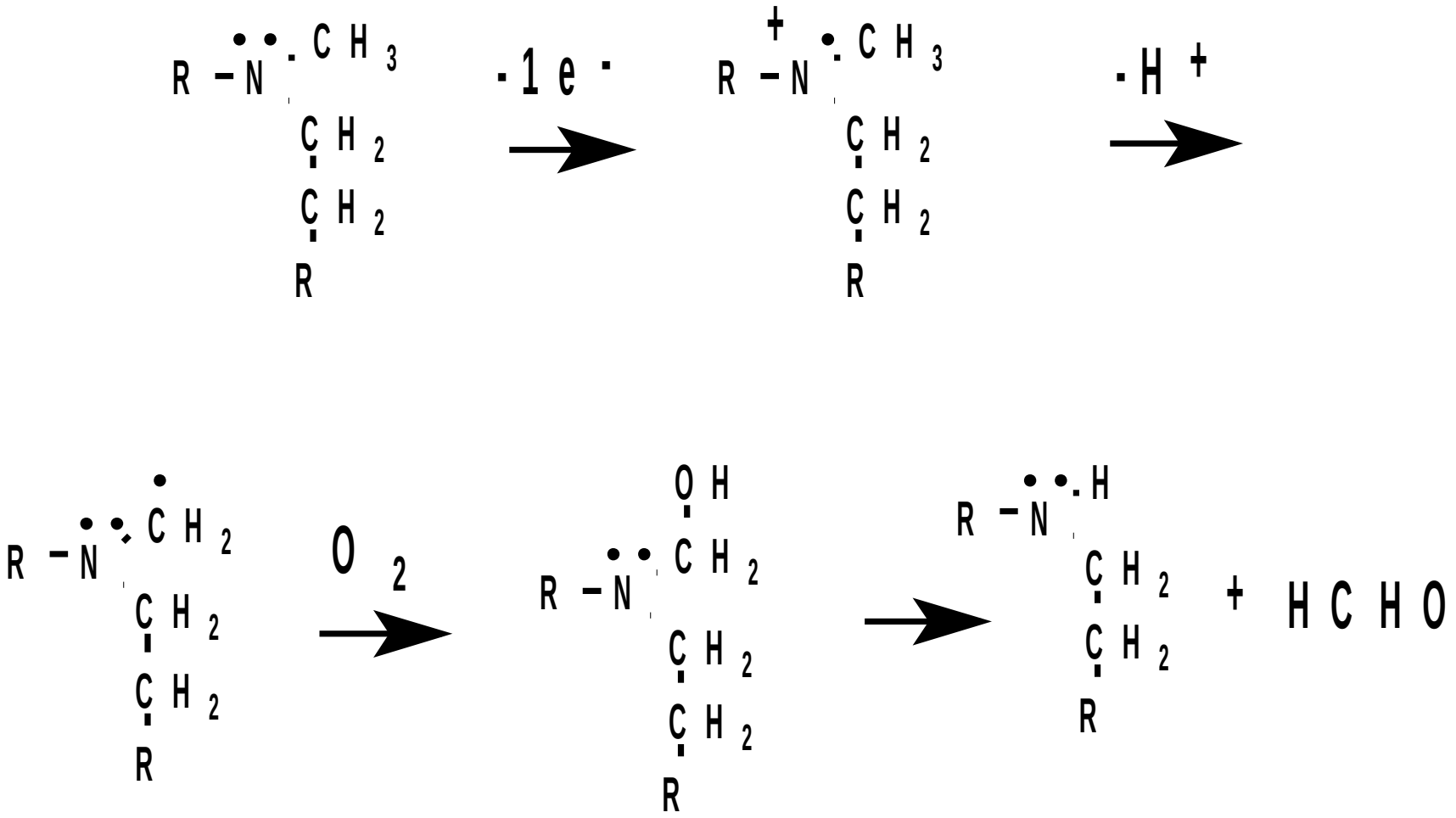
CYP3A4



fexofenadine
(Ewofex ®)

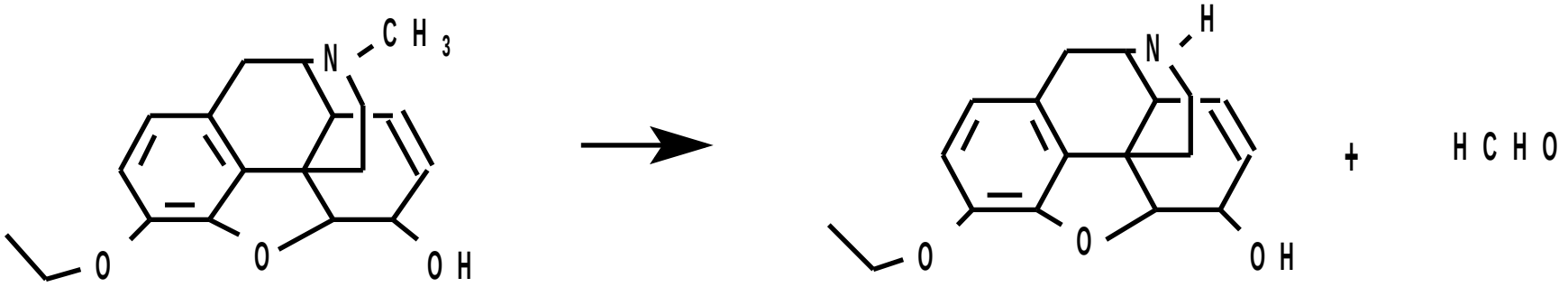
- cardiac adverse effects not present

N (or O, S)-oxidative dealkylation



N-demethylation generates formaldehyde

Oxidative N-demethylation: ethylmorphine (antitussive)

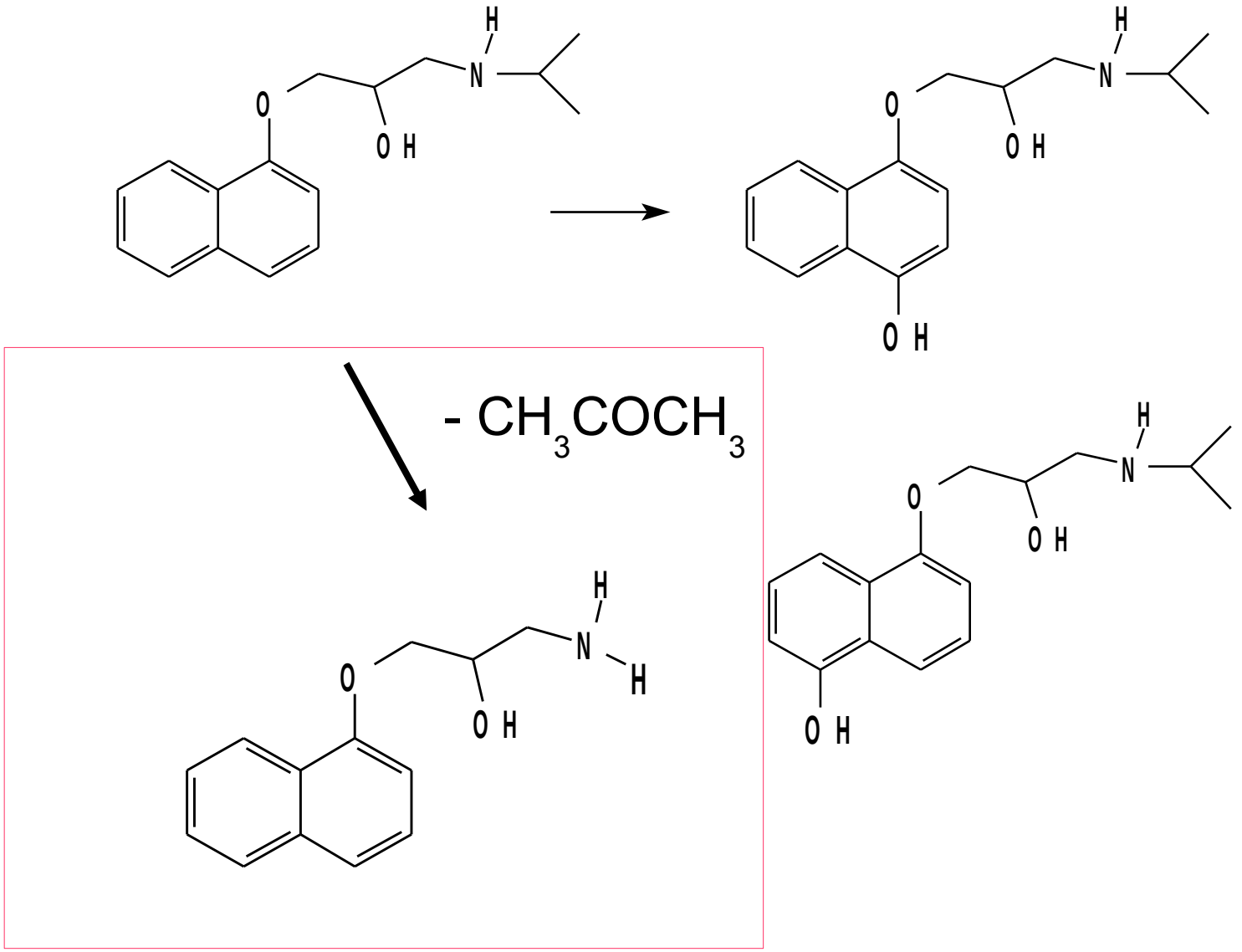


ethylmorphine

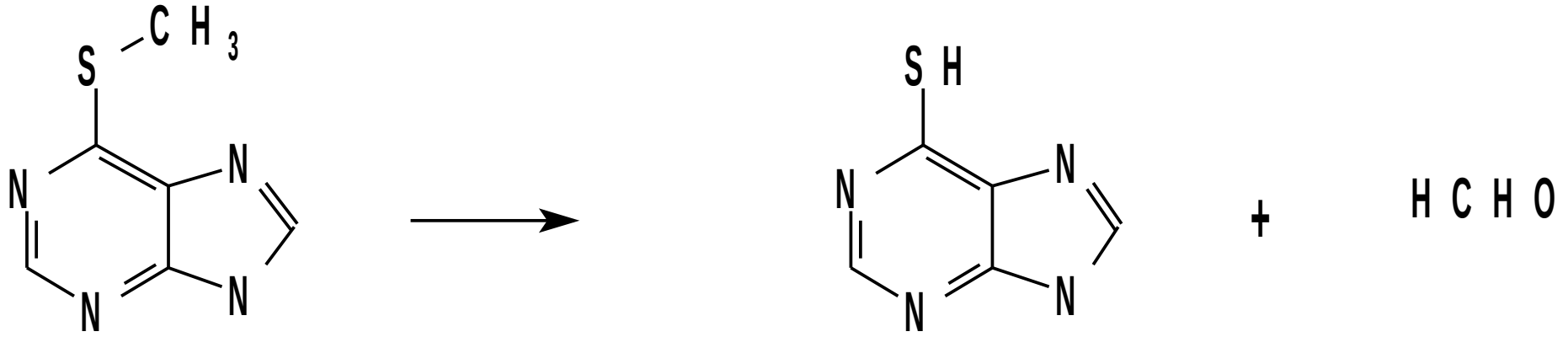
desmethyl-ethylmorphine

N-demethylation favored over O-deakylation

Oxidative desisopropylation: **propranolol**



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



6-methythiopurine
•prodrug
•not used

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

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.