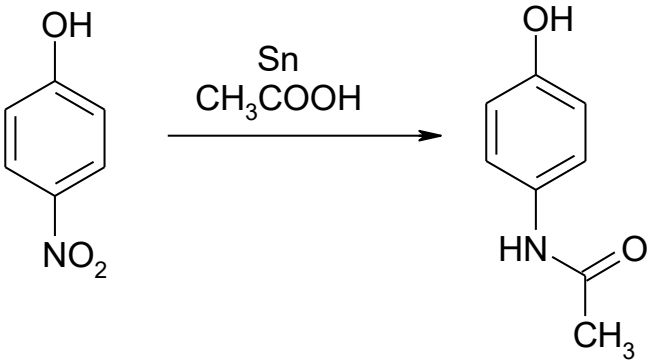
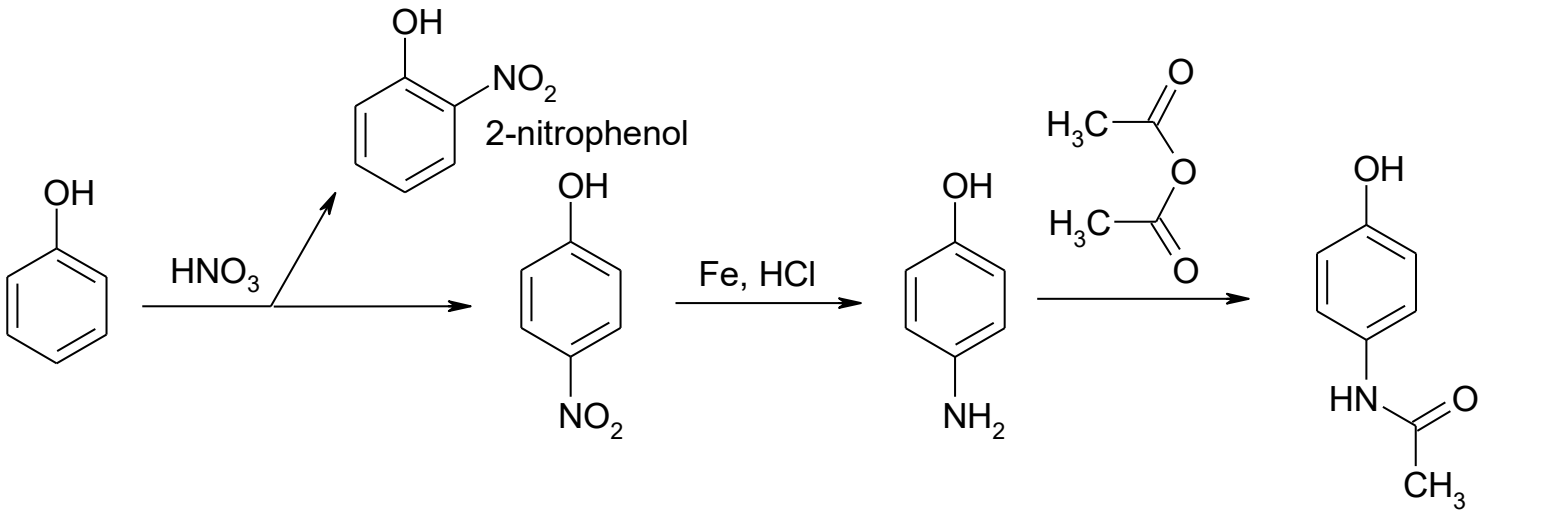
Sytheses & metabolism of selected weak and strong analgesics

Synthesis of paracetamol



Morse, Chem. Ber. **11**, 232 (1878)



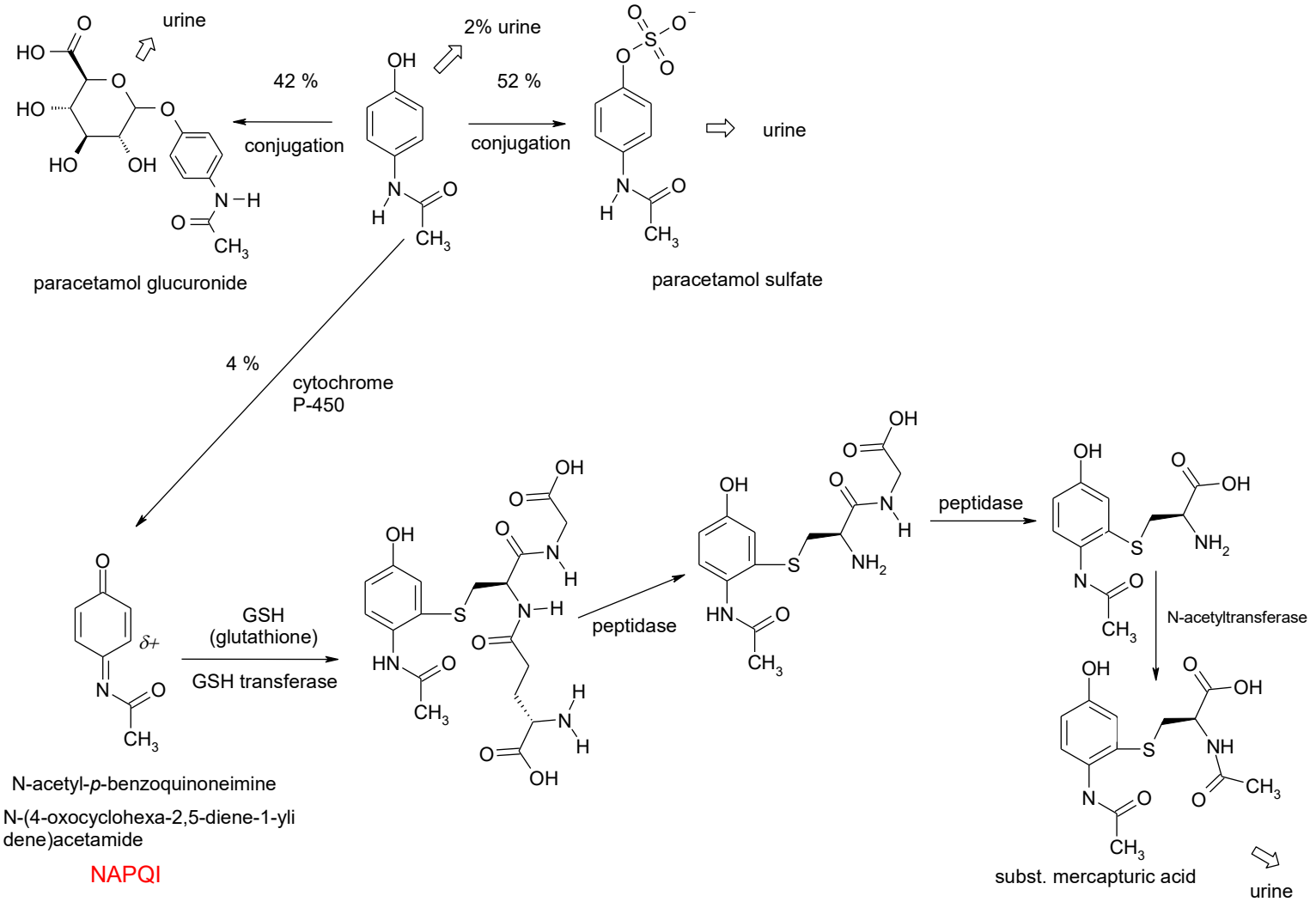
phenol

4-nitrophenol

4-aminophenol

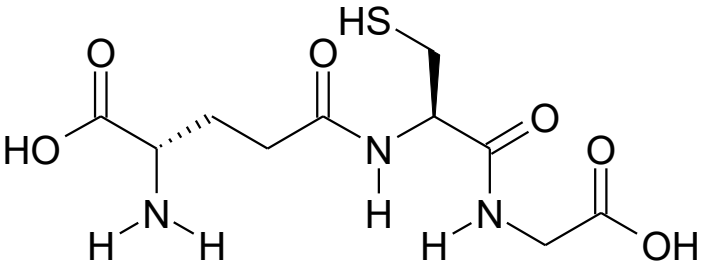
4-(acetylamino)phenol

Metabolism of paracetamol

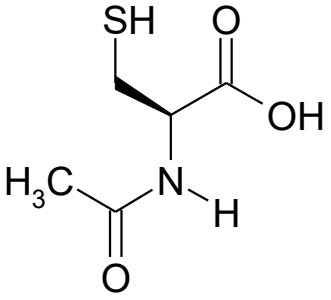


Thiols detoxicating *N*-acetyl-*p*-benzoquinoneimine

γ–Glu-Cys-Gly



glutathione

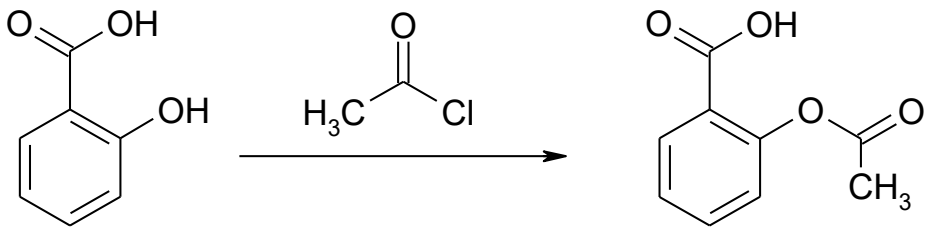


N-acetyl-L-cysteine
syn. mercapturic acid

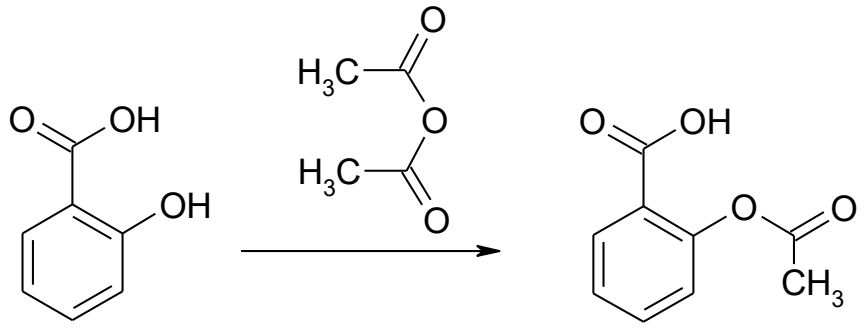
mucolytic

ACC®, Mucobene®

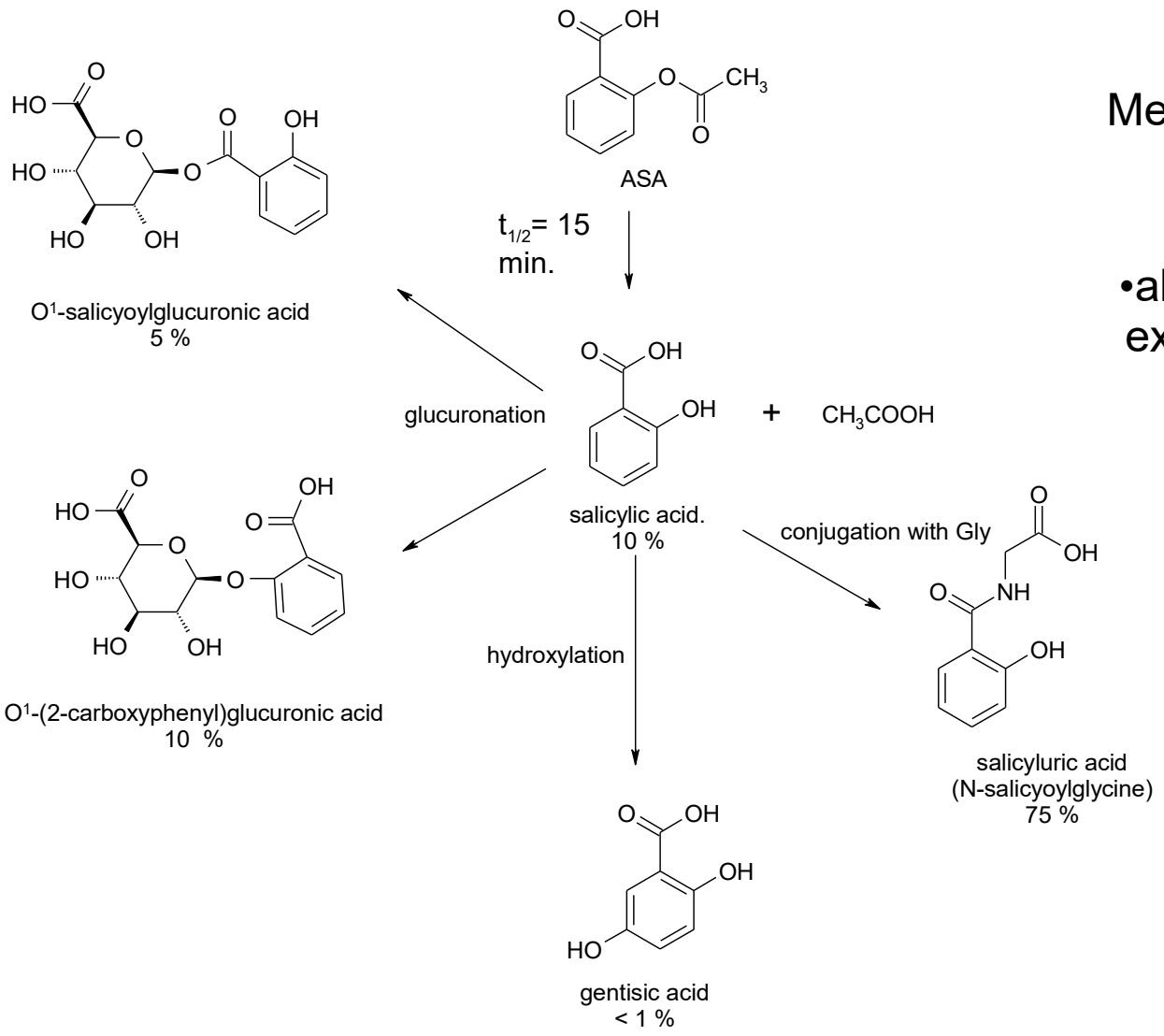
Syntheses of acetylsalicylic acid (ASA)



Gerhardt, Justus Liebigs Ann. Chem. **87**, 164 (1853)
Gilm, Justus Liebigs Ann. Chem. **112,** 181 (1859)
Kraut, Justus Liebigs Ann. Chem. **150**, 10 (1869)



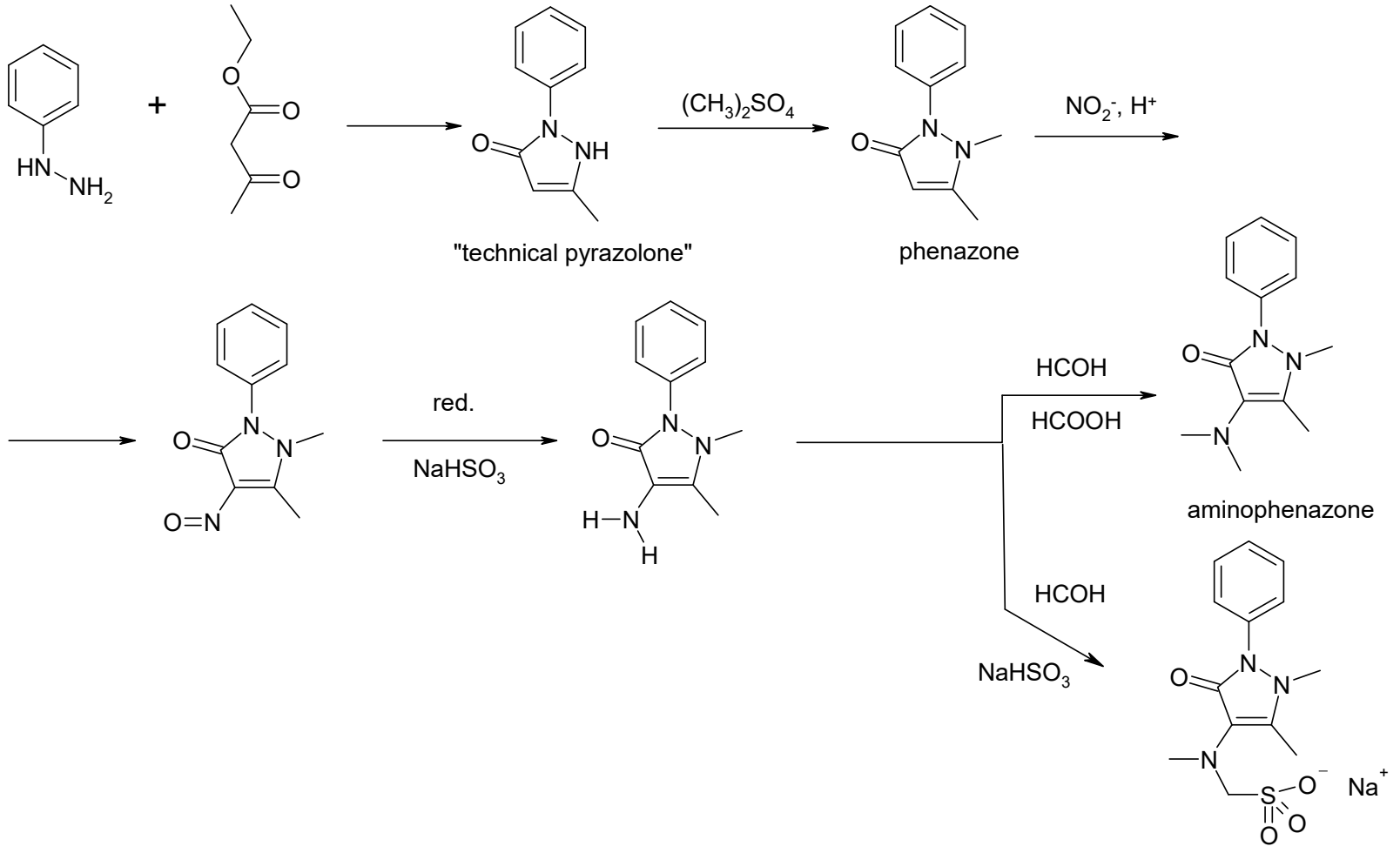
Felix Hoffmann 1897; since 1899 Aspirin ®
Bayer



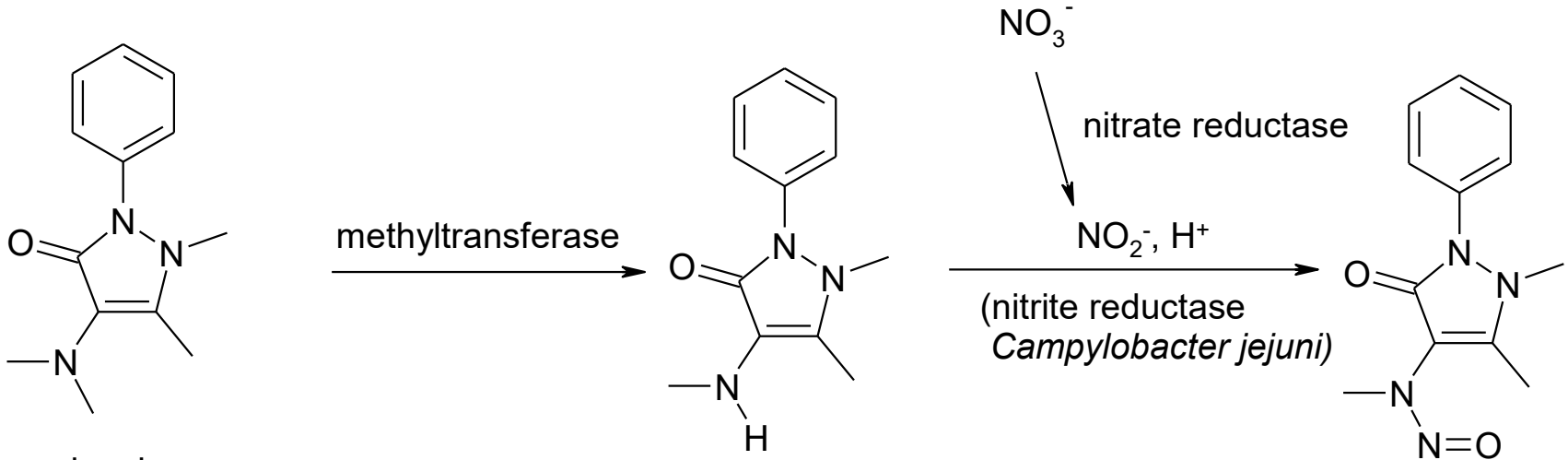
Metabolism of ASA

- runs in liver
- all metabolits are excreted by urine

Synthesis of aminophenazone and metamizole



Aminophenazone cancerogenity



aminophenazone

1,5-dimethyl-4-methylamino-2-phenyl
-1,2-dihydropyrazole-3-one
(desmethylaminophenazone)

1,5-dimethyl-4-methyl(nitroso)amino
-2-phenyl-1,2-dihydropyrazole-3-one

CANCEROGENIC

Main metabolic routes of aminophenazone and metamizole

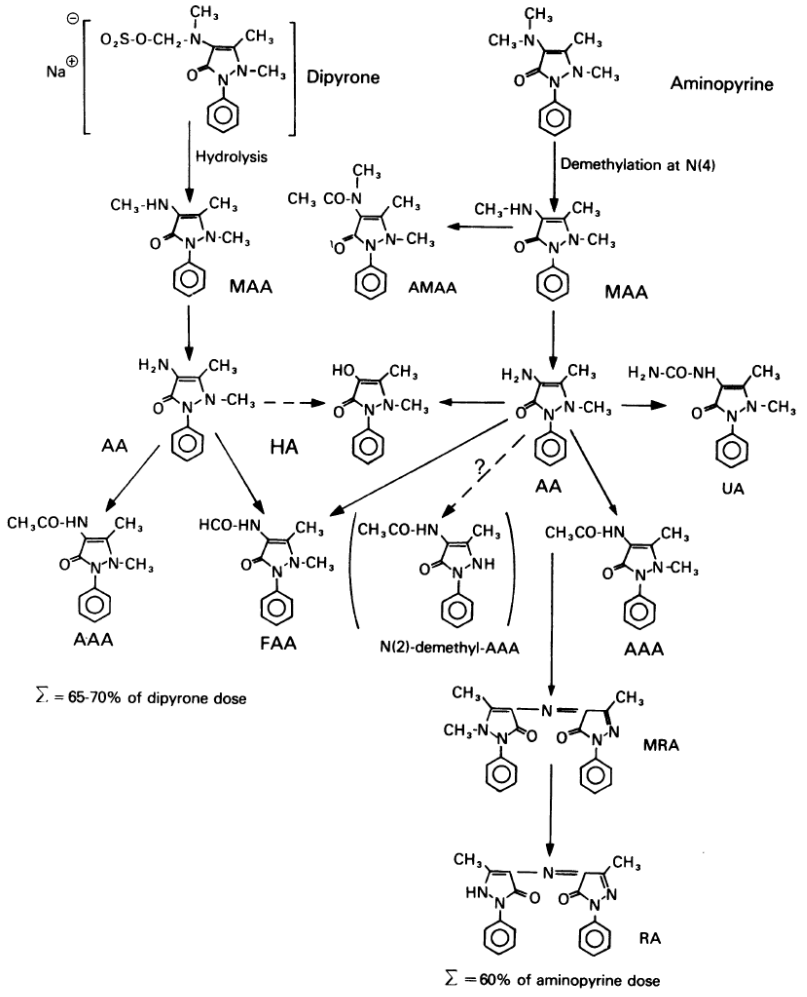
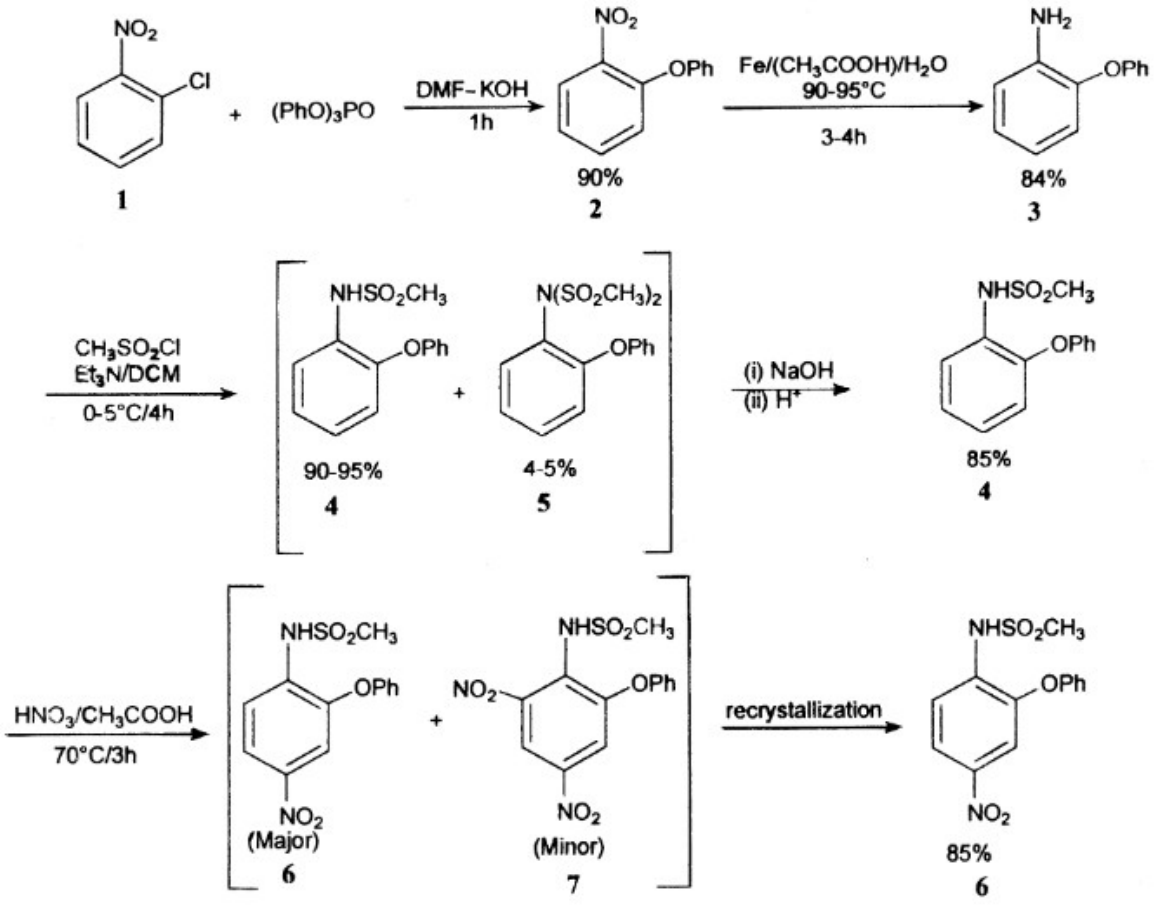
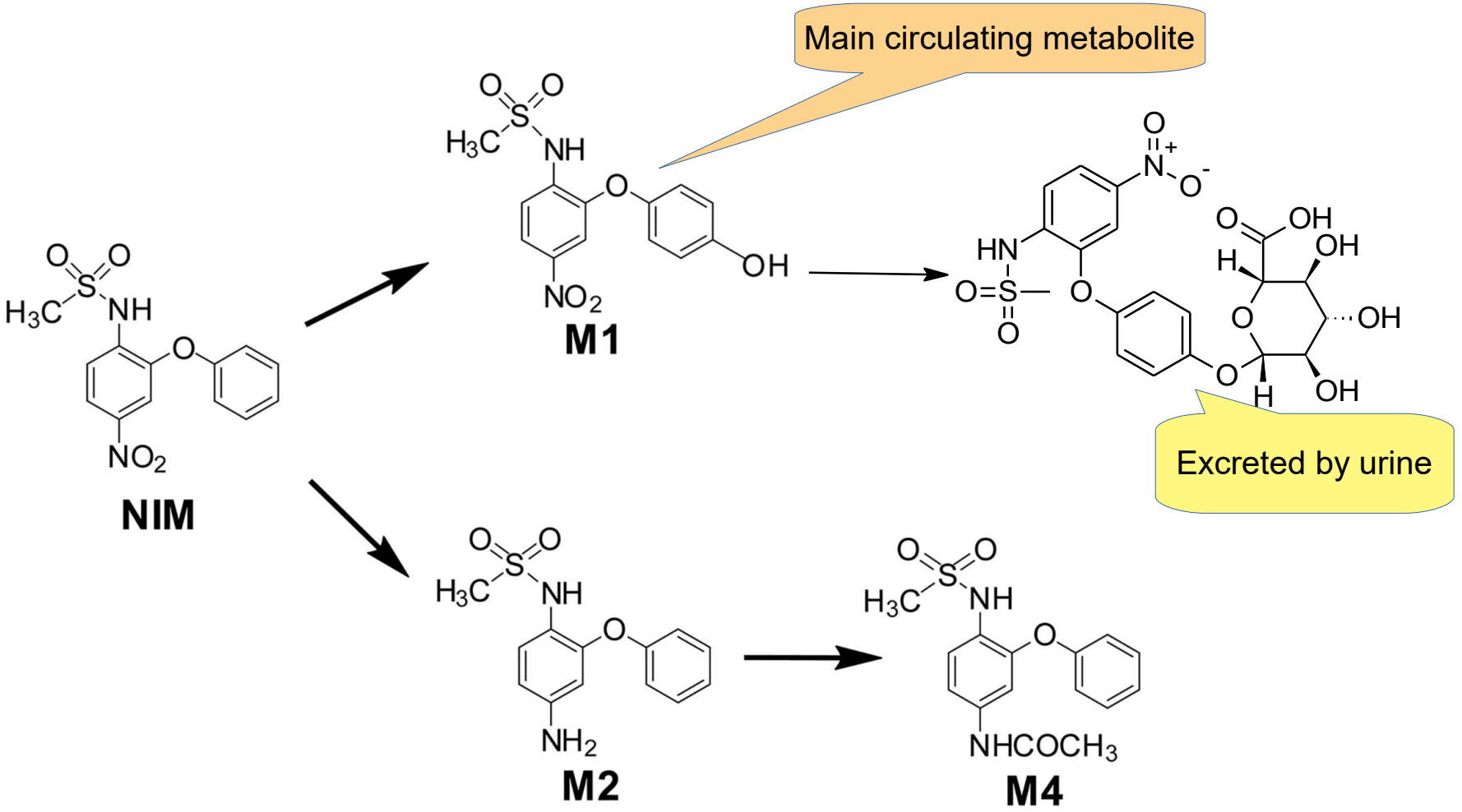


Figure 4 Comparison of the metabolism of dipyrone and aminopyrine in man, based on published and reported studies. MAA, 4-methylaminoantipyrine; AA, 4-aminoantipyrine; AAA, 4-acetylaminoantipyrine; FAA, 4-formylaminoantipyrine; HA, 4-hydroxyantipyrine; AMAA, 4-acetylmethylaminoantipyrine; UA, 4-ureidoantipyrine; MRA, methyl rubazonic acid; RA, rubazonic acid.

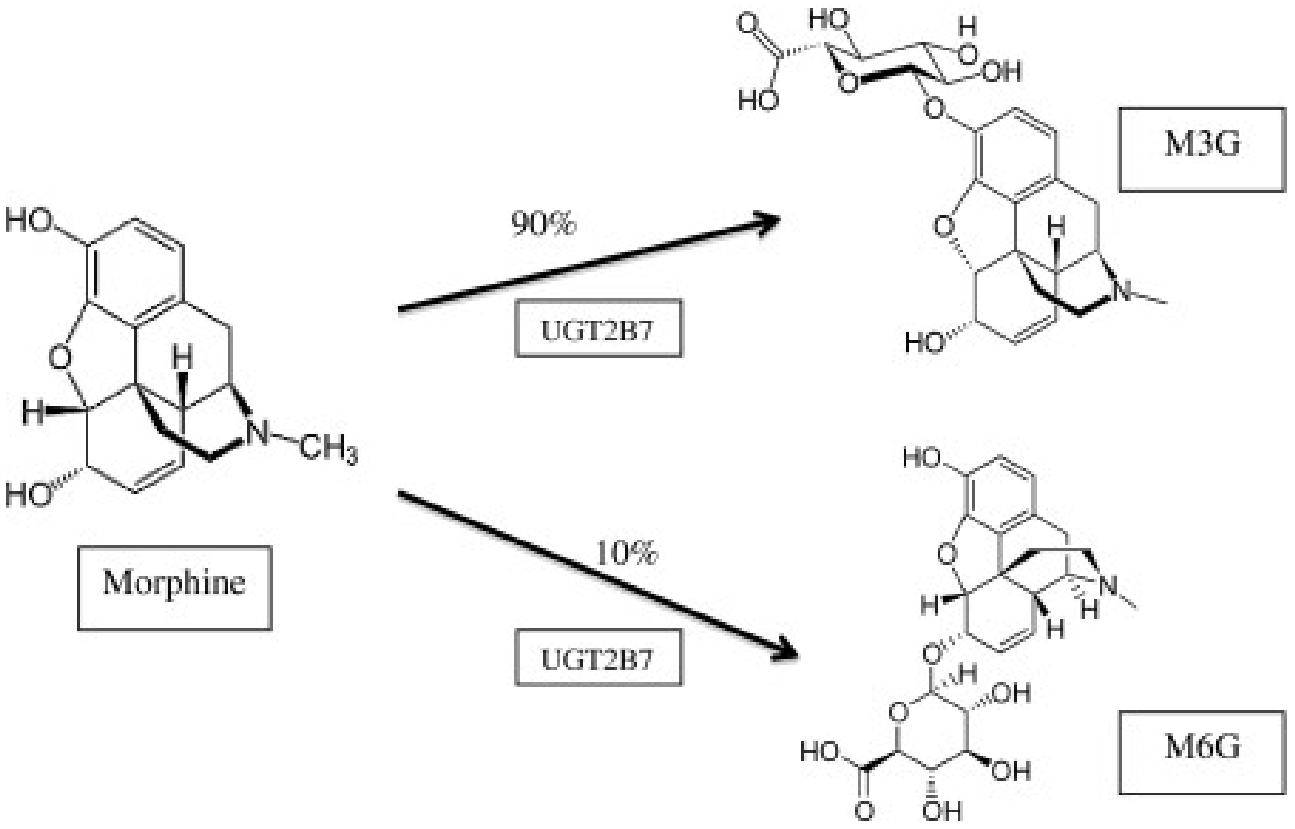
A large scale synthesis of nimesulide



Main metabolites of nimesulide



Morphine metabolism: glucuronidation

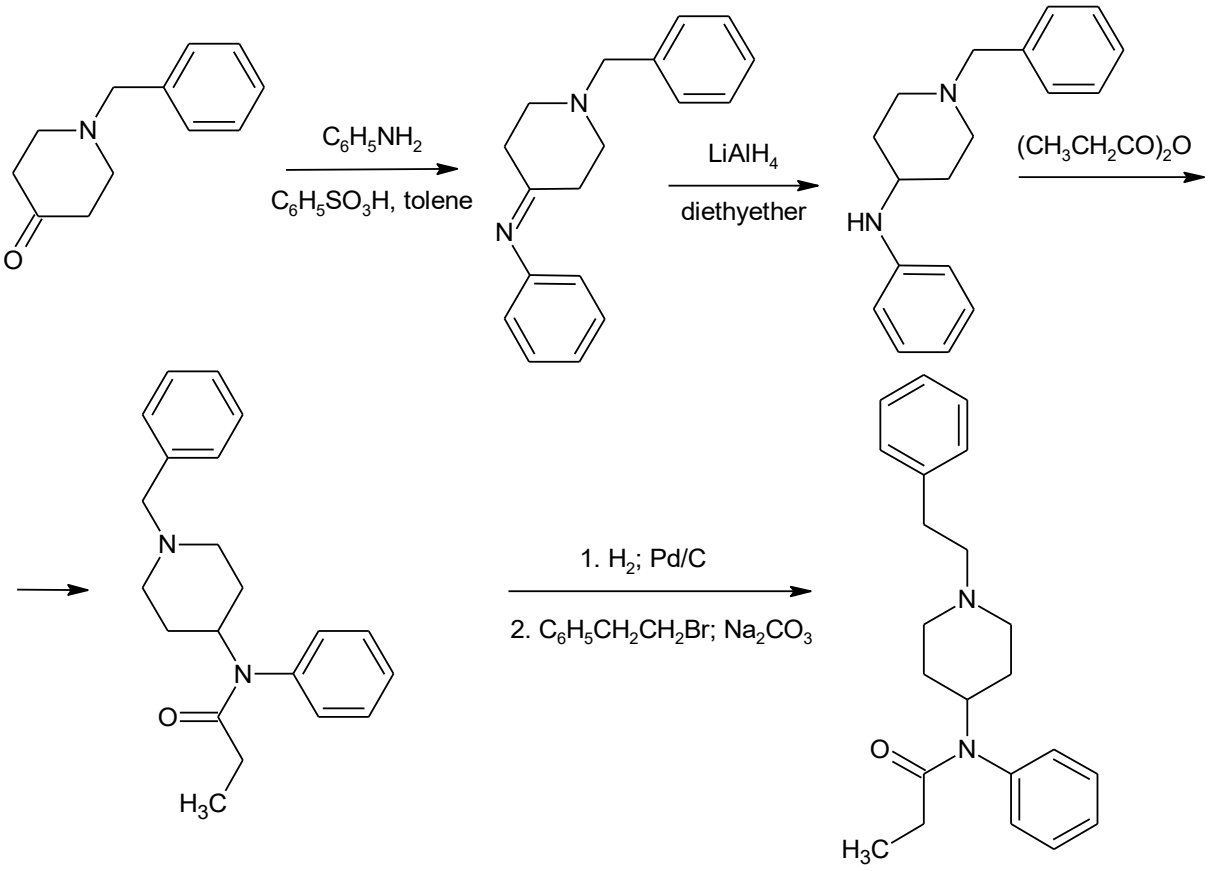


no analgesic activity;
morphine antagonist

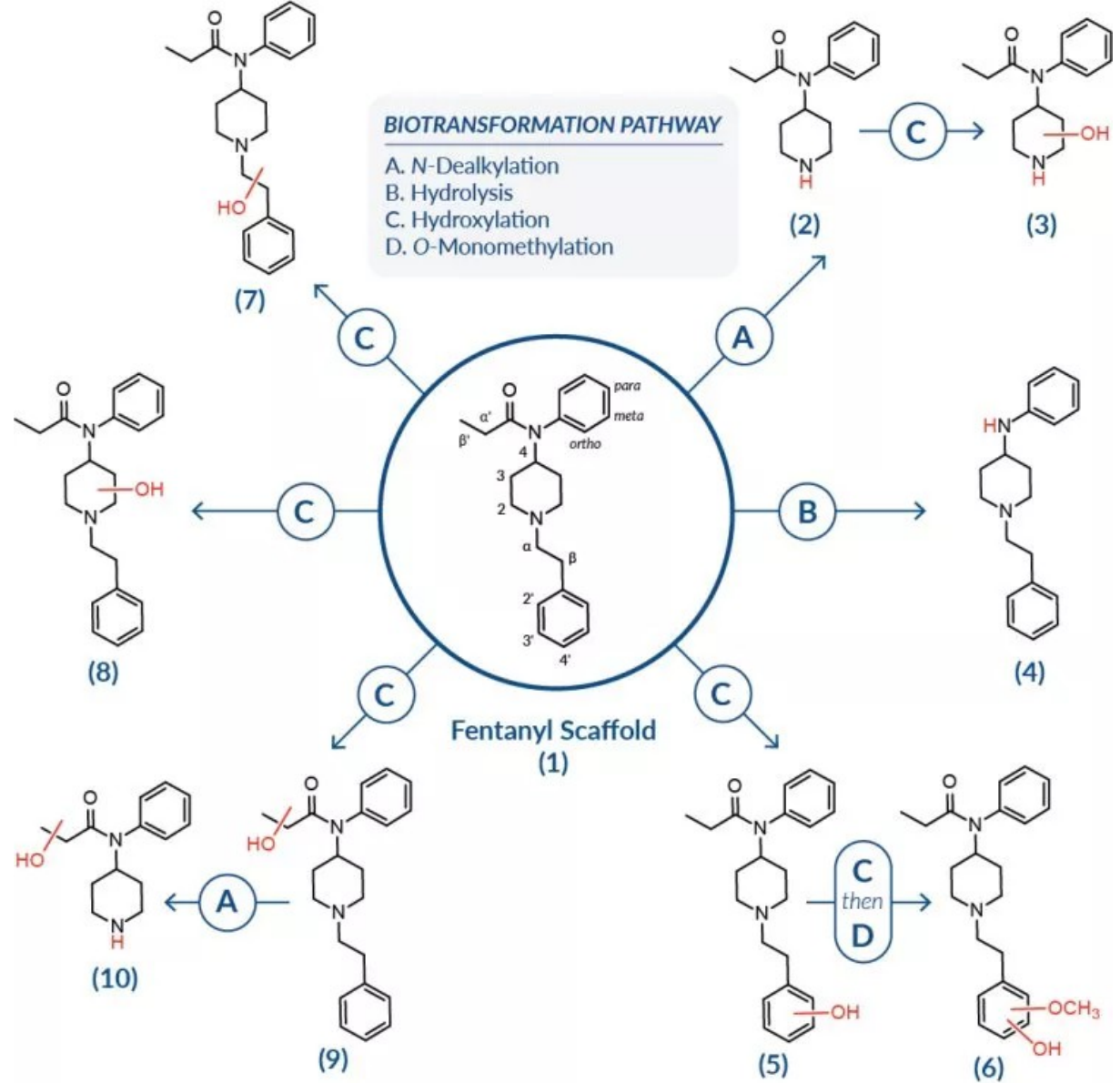
crosses BBB; much more analgesic than morphine

UGT - UDP-glucuronosyltransferases

Synthesis of fentanyl

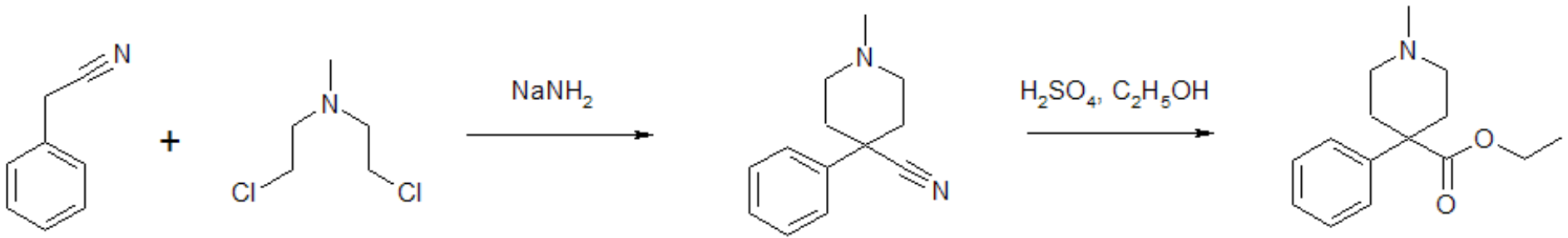


fentanyl



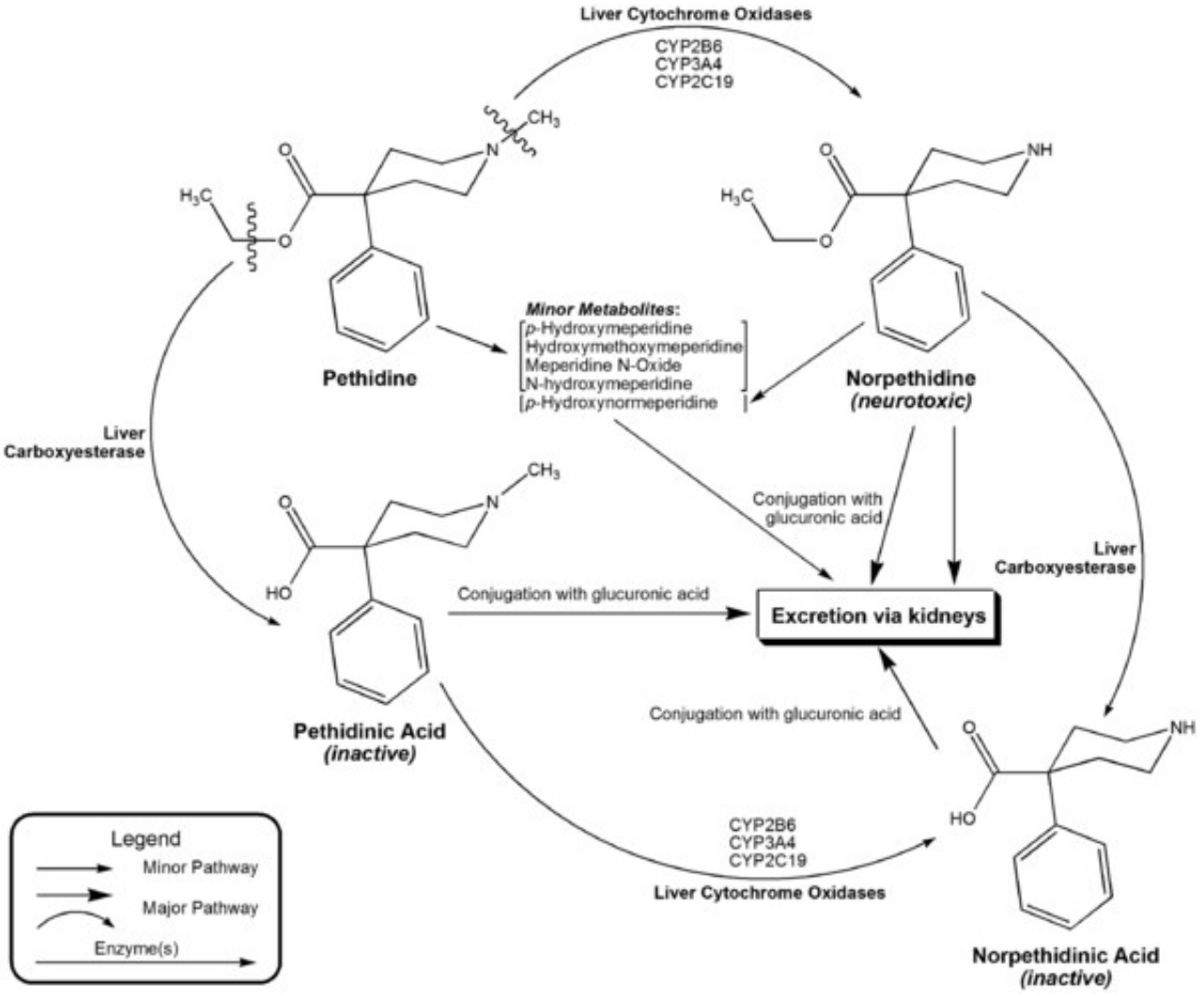
The major route of fentanyl metabolism is via oxidative N-dealkylation to the inactive desphenethyl metabolite norfentanyl (2). Another known (but minor) human metabolite is despropionyl fentanyl (4), which is also known as 4-ANPP. This amide hydrolysis metabolite can coincidentally be formed as a metabolic product of several different fentanyl analogs, so its presence isn't particularly diagnostic. It is also a precursor contaminant found in seized illicit fentanyl and fentanyl analog powders, further adding to the complexity of identifying it in urine analysis. There are numerous hydroxylated compounds that are typically less abundant (3, 5, 7, 8, 9, and 10). It has been reported, for example, that hydroxylation can occur on the ethyl linker of the phenethyl moiety (either at the α or β position), at the 2 or 3 position on the piperidine ring, along the amide alkyl chain, or on the phenyl ring of the phenethyl moiety. Some of these hydroxylated metabolites, such as 4'-hydroxy fentanyl (5), are potentially bioactive, but most are believed to be inactive. Hydroxy fentanyls like 5 can be further biotransformed via a second hydroxylation to afford a catechol that is then *O*-monomethylated to yield metabolite 6. This methylation conjugation reaction is presumably catalyzed by the enzyme catechol-*O*-methyltransferase and is believed to occur at the 3' position. This is technically a phase II metabolic product, but it is detected in both hydrolyzed and non-hydrolyzed urine specimens due to its stability. Norfentanyl (2) is also further oxidized (Figure 1). Keep in mind that most of the metabolites depicted in Figure 1 can potentially undergo further transformations to yield additional metabolites and often the exact positioning of the hydroxyl group is unknown.

Synthesis of pethidine

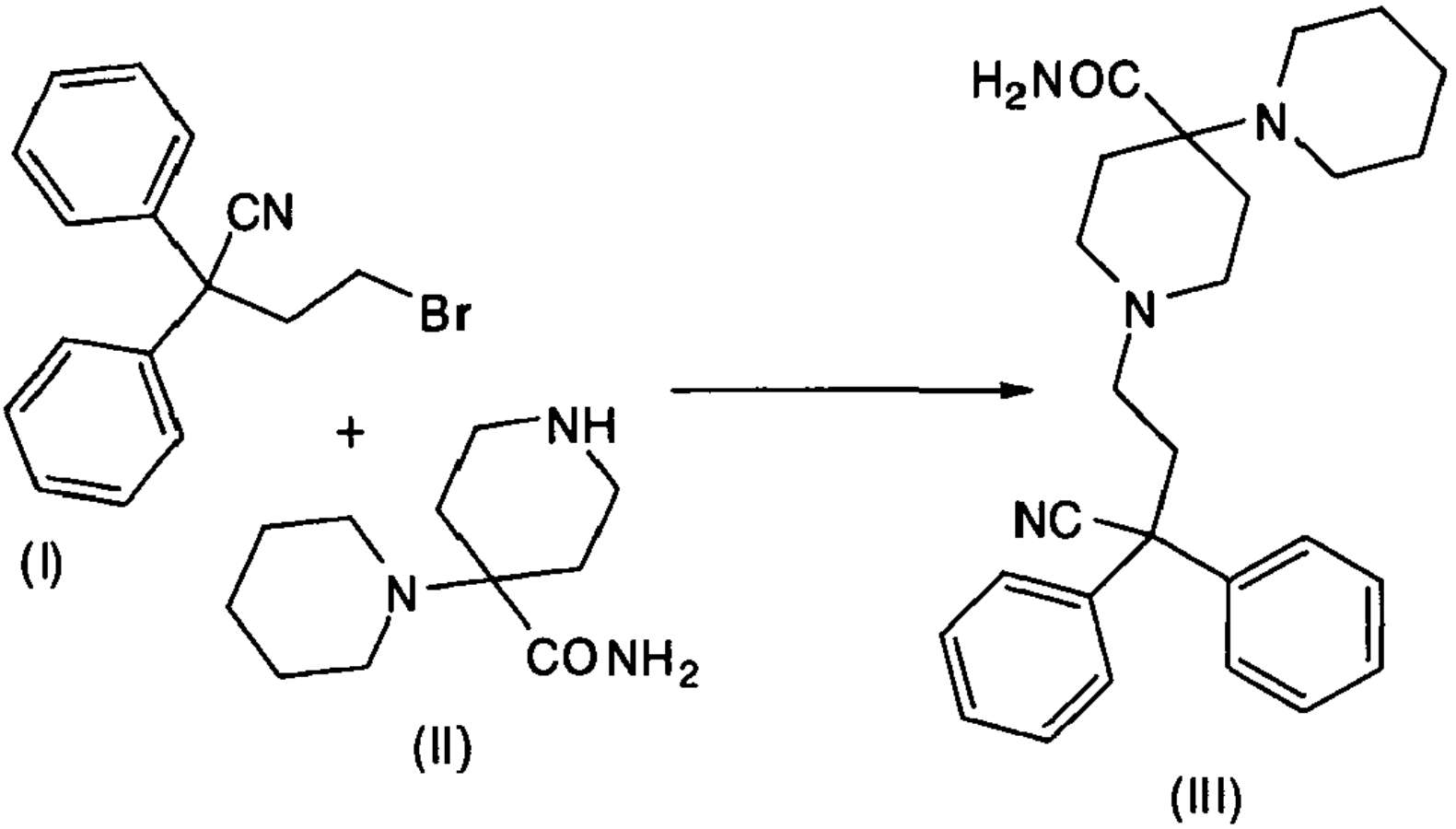


DE 679 281 IG Farben 1937

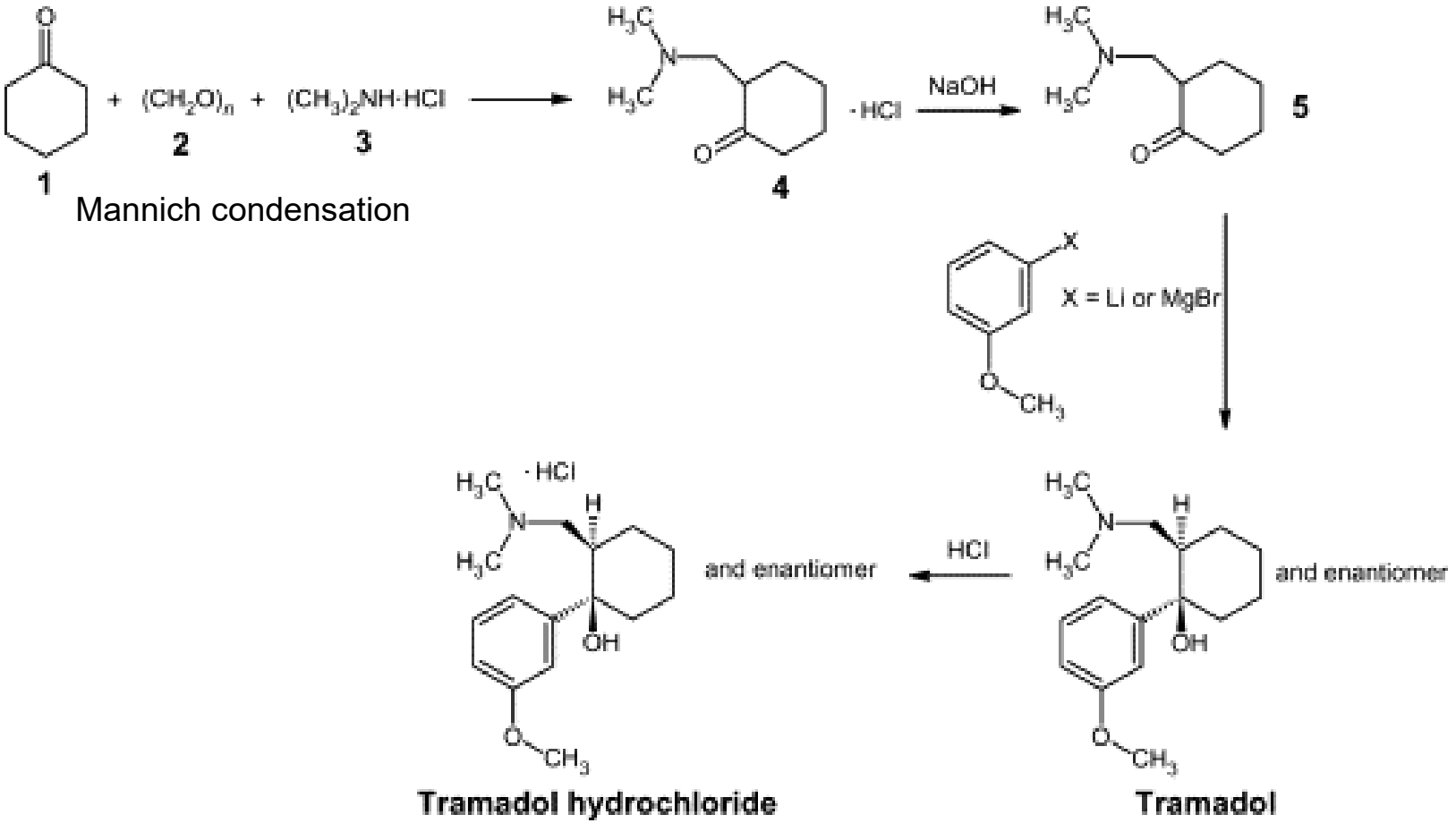
Metabolism of Pethidine



Partial synthesis of piritramide



A synthesis of tramadol



Metabolism of tramadol

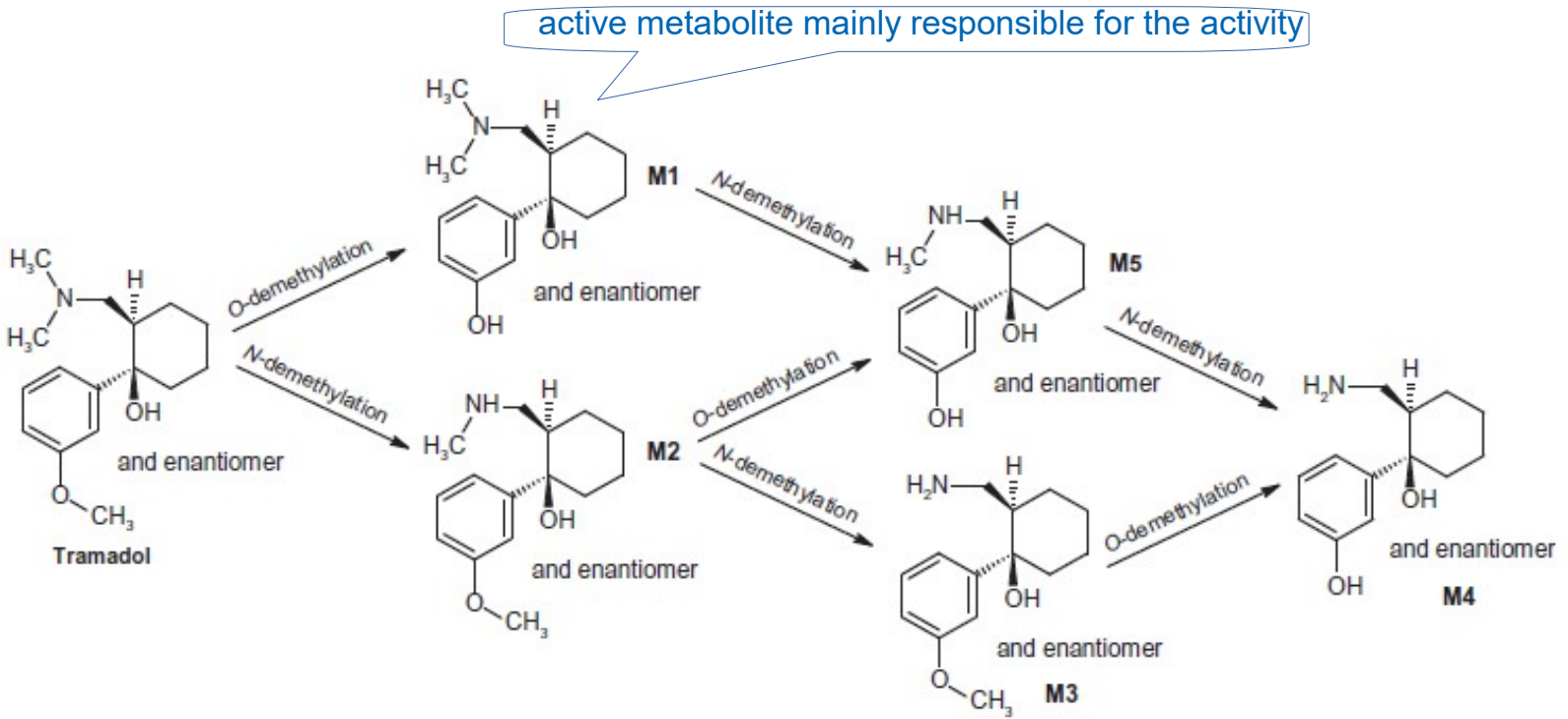


Figure 11.13 Metabolic pathways of tramadol in phase 1 reactions.