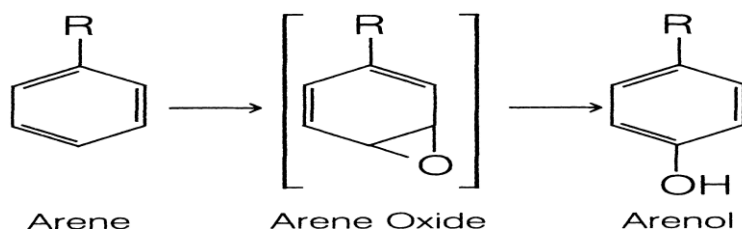


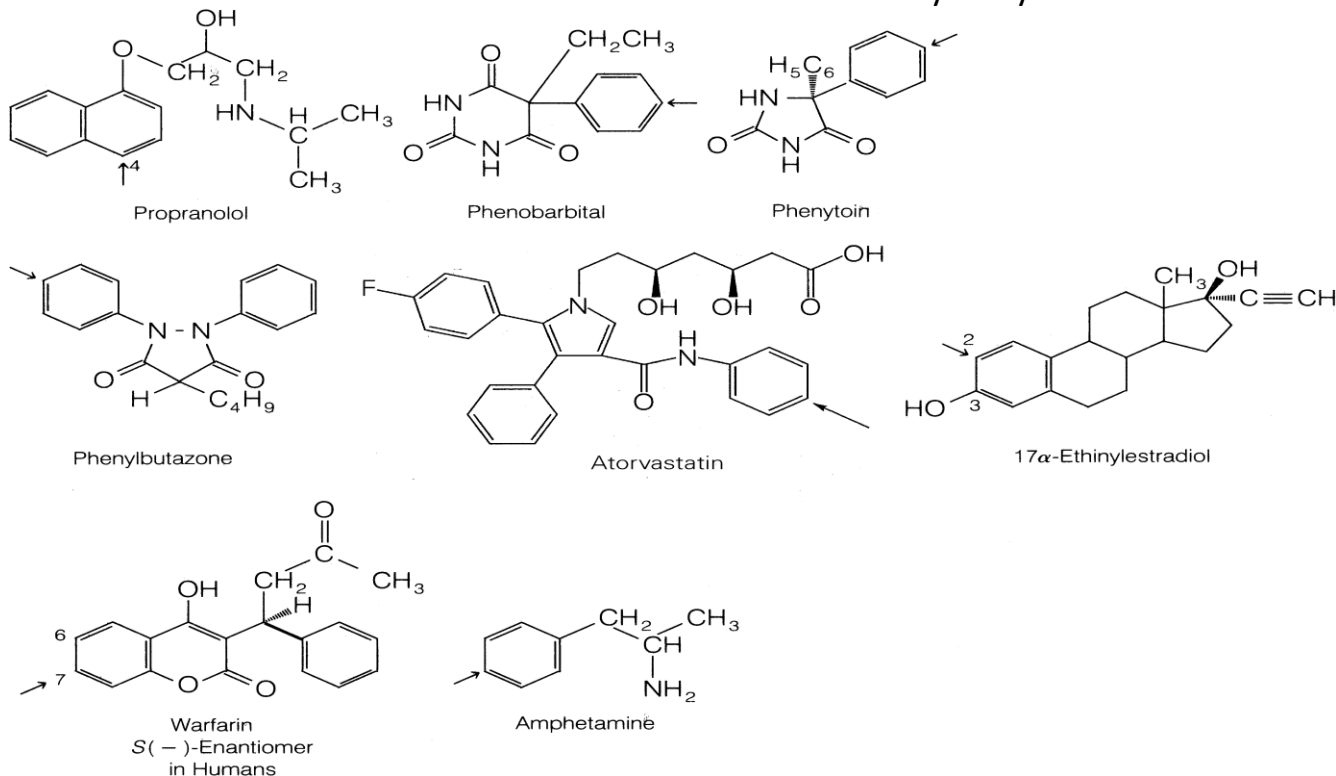
OXIDATIVE REACTIONS

Oxidation of Aromatic Moieties

Aromatic hydroxylation refers to the mixed-function oxidation of aromatic compounds (arenes) to their corresponding phenolic metabolites (arenols). Almost all aromatic hydroxylation reactions are believed to proceed initially through an epoxide intermediate called an "arene oxide," which rearranges rapidly and spontaneously to the arenol product in most instances.

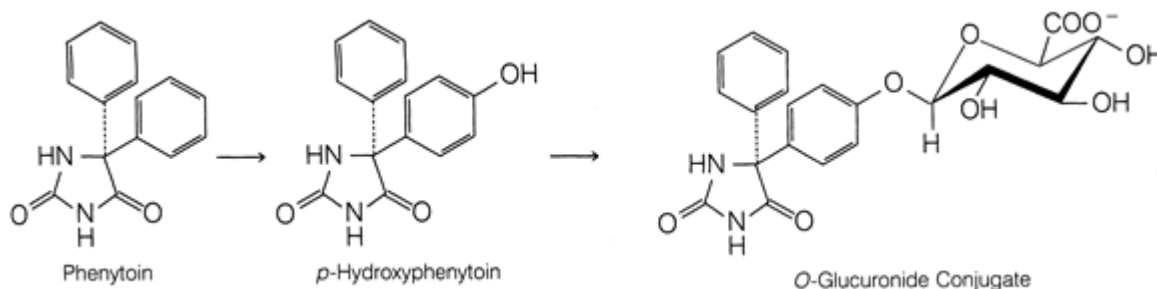


Most foreign compounds containing aromatic moieties are susceptible to aromatic oxidation. In humans, aromatic hydroxylation is a major route of metabolism for many drugs containing phenyl groups. Important therapeutic agents such as propranolol, phenobarbital, phenytoin, phenylbutazone, atorvastatin, 17 α -ethinylestradiol, and (*S*)(-)-warfarin, among others, undergo extensive aromatic oxidation. Examples of drugs and xenobiotics that undergo aromatic hydroxylation in humans are shown below. Arrow indicates site of aromatic hydroxylation.

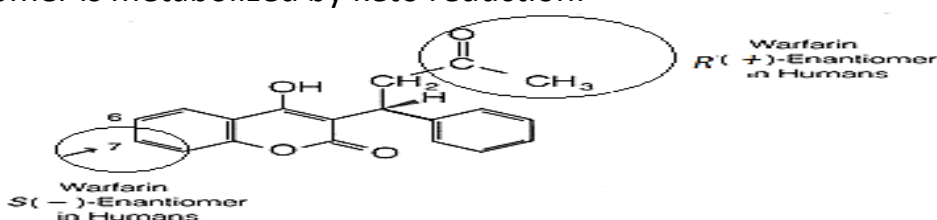


✚ In most of the drugs just mentioned, hydroxylation occurs at the **para position**. Most phenolic metabolites formed from aromatic oxidation undergo further

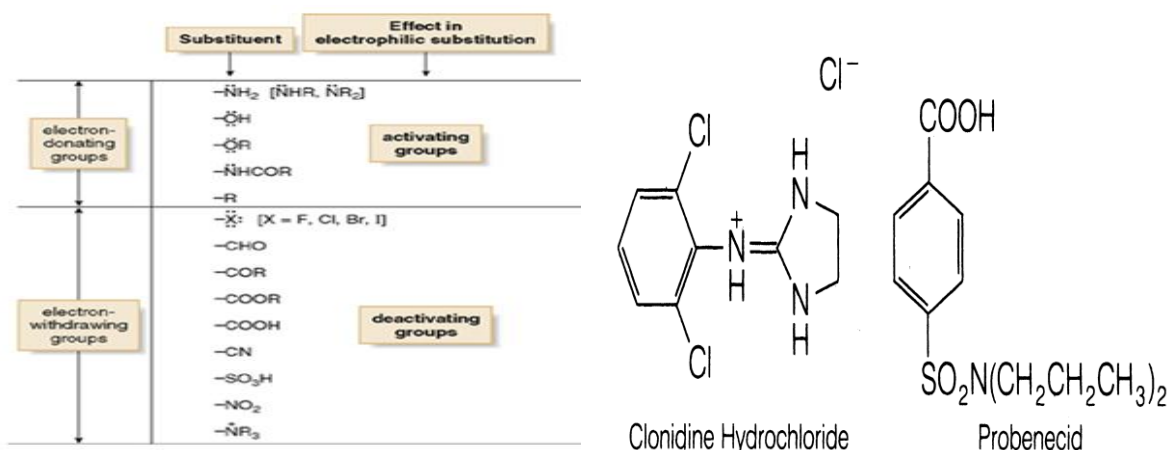
conversion to polar and water- soluble glucuronide or sulfate conjugates, which are readily excreted in the urine. For example, the major urinary metabolite of phenytoin found in humans is the *O*-glucuronide conjugate of *p*-hydroxyphenytoin.



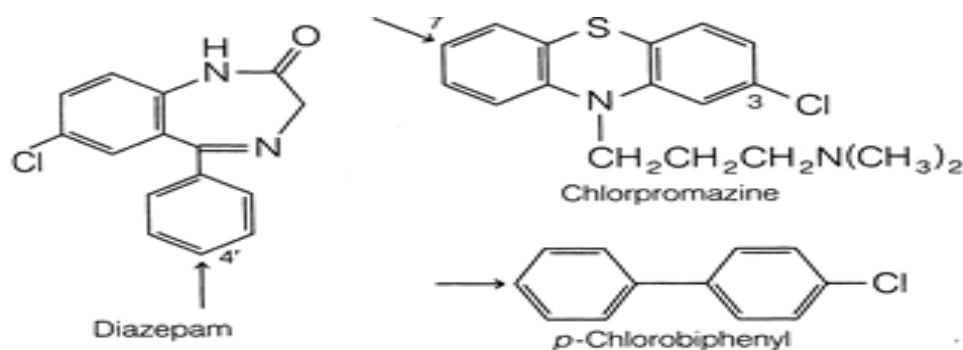
- ✚ The *para*-hydroxylated metabolite of phenylbutazone, oxyphenbutazone, is pharmacologically active and has been marketed itself as an anti-inflammatory agent.
- ✚ Of the two enantiomeric forms of the oral anticoagulant warfarin, only the more active *S*(-) enantiomer has been shown to undergo substantial aromatic hydroxylation to 7-hydroxywarfarin in humans. In contrast, the (*R*)(+) enantiomer is metabolized by keto reduction.



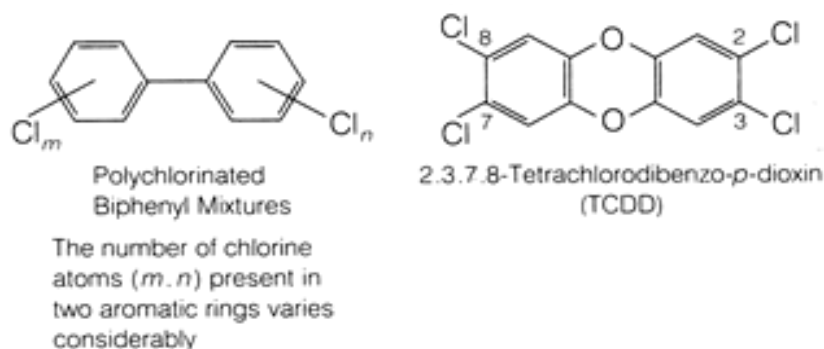
- ✚ Often, the substituents attached to the aromatic ring may influence the ease of hydroxylation. As a general rule, microsomal aromatic hydroxylation reactions appear to proceed most readily in activated (electron-rich) rings, whereas deactivated aromatic rings (e.g., those containing electron-withdrawing groups Cl, -N⁺R₃, COOH, SO₂NHR) are generally slow or resistant to hydroxylation. The deactivating groups (Cl, -N⁺H=C) present in the antihypertensive clonidine may explain why this drug undergoes little aromatic hydroxylation in humans. The uricosuric agent probenecid with its electron-withdrawing carboxy and sulfamido groups, has not been reported to undergo any aromatic hydroxylation.



In compounds with two aromatic rings, hydroxylation occurs preferentially in the more electron-rich ring. For example, aromatic hydroxylation of diazepam occurs primarily in the more activated ring to yield 4-hydroxydiazepam. A similar situation is seen in the 7-hydroxylation of the antipsychotic agent chlorpromazine and in the para-hydroxylation of p-chlorobiphenyl to p-chloro-p-hydroxybiphenyl.



Recent environmental pollutants, such as polychlorinated biphenyls (PCBs) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), have attracted considerable public concern over their toxicity and health hazards. These compounds appear to be resistant to aromatic oxidation because of the numerous electronegative chlorine atoms in their aromatic rings. The metabolic stability coupled to the lipophilicity of these environmental contaminants probably explains their long persistence in the body once absorbed.



Arene oxide intermediates are formed when a double bond in aromatic moieties is epoxidized. Arene oxides are of significant toxicologic concern because these

intermediates are electrophilic and chemically reactive (because of the strained three-membered epoxide ring).

Arene oxides are mainly detoxified by:

1. Spontaneous rearrangement to arenols,
2. Enzymatic hydration to trans-dihydrodiols
3. Enzymatic conjugation with GSH also plays very important roles.

If not effectively detoxified by the first three pathways, arene oxides will bind covalently with nucleophilic groups present on proteins, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA), thereby leading to serious cellular damage. This, in part, helps explain why benzene can be so toxic to mammalian systems

