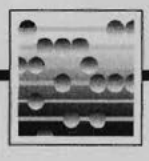

Wilson and Gisvold's Textbook of

ORGANIC MEDICINAL AND PHARMACEUTICAL CHEMISTRY

ELEVENTH EDITION

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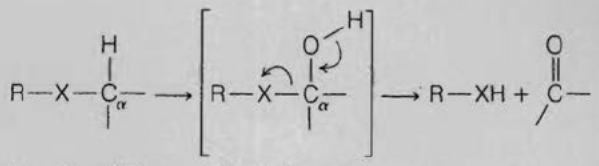
The stereochemistry of the hydroxylated centers in the two metabolites has not been clearly established. Biotransformation of the antihypertensive agent minoxidil (Loniten) yields the 4′-hydroxypiperidyl metabolite. In the dog, this product is a major urinary metabolite (29 to 47%), whereas in humans it is detected in small amounts (~3%).[157, 158]

Oxidation Involving Carbon–Heteroatom Systems

Nitrogen and oxygen functionalities are commonly found in most drugs and foreign compounds; sulfur functionalities occur only occasionally. Metabolic oxidation of carbon–nitrogen, carbon–oxygen, and carbon–sulfur systems principally involves two basic types of biotransformation processes:

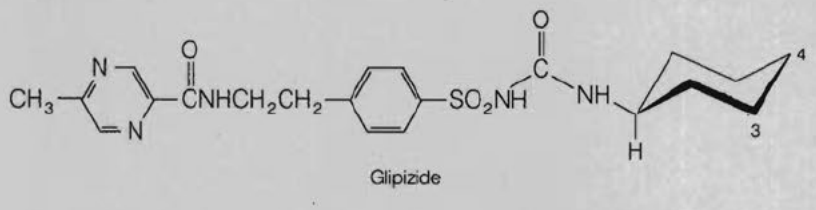
1. Hydroxylation of the α-carbon atom attached directly to the heteroatom (N, O, S). The resulting intermediate is often unstable and decomposes with the cleavage of the carbon–heteroatom bond:

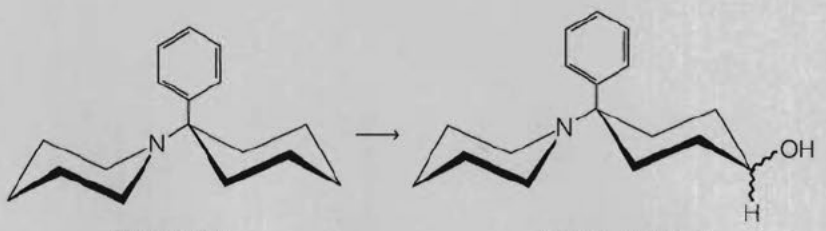


Oxidative N-, O-, and S-dealkylation as well as oxidative deamination reactions fall under this mechanistic pathway.

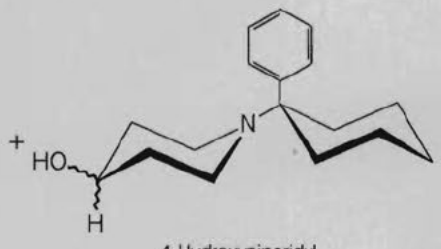
2. Hydroxylation or oxidation of the heteroatom (N, S only, e.g., N-hydroxylation, *N*-oxide formation, sulfoxide, and sulfone formation).

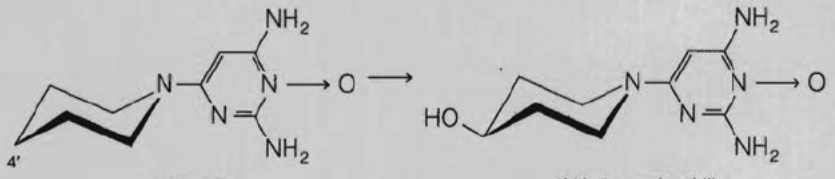
Several structural features frequently determine which pathway will predominate, especially in carbon–nitrogen systems. Metabolism of some nitrogen-containing compounds is complicated by the fact that carbon- or nitrogen-


Glipizide


Phencyclidine

4-Hydroxycyclohexyl Metabolite


4-Hydroxypiperidyl Metabolite


Minoxidil

4′-Hydroxyminoxidil

hydroxylated products may undergo secondary reactions to form other, more complex metabolic products (e.g., oxime, nitrone, nitroso, imino). Other oxidative processes that do not fall under these two basic categories are discussed individually in the appropriate carbon–heteroatom section. The metabolism of carbon–nitrogen systems will be discussed first, followed by the metabolism of carbon–oxygen and carbon–sulfur systems.

OXIDATION INVOLVING CARBON–NITROGEN SYSTEMS

Metabolism of nitrogen functionalities (e.g., amines, amides) is important because such functional groups are found in many natural products (e.g., morphine, cocaine, nicotine) and in numerous important drugs (e.g., phenothiazines, antihistamines, tricyclic antidepressants, β-adrenergic agents, sympathomimetic phenylethylamines, benzodiazepines).[159] The following discussion divides nitrogen-containing compounds into three basic classes:

1. Aliphatic (primary, secondary, and tertiary) and alicyclic (secondary and tertiary) amines
2. Aromatic and heterocyclic nitrogen compounds
3. Amides

The susceptibility of each class of these nitrogen compounds to either α-carbon hydroxylation or N-oxidation and the metabolic products that are formed are discussed.

The hepatic enzymes responsible for carrying out α-carbon hydroxylation reactions are the cytochrome P-450 mixed-function oxidases. The N-hydroxylation or N-oxidation reactions, however, appear to be catalyzed not only by cytochrome P-450 but also by a second class of hepatic mixed-function oxidases called *amine oxidases* (sometimes called *N-oxidases*).[160] These enzymes are NADPH-dependent flavoproteins and do not contain cytochrome P-450.[161, 162] They require NADPH and molecular oxygen to carry out N-oxidation.

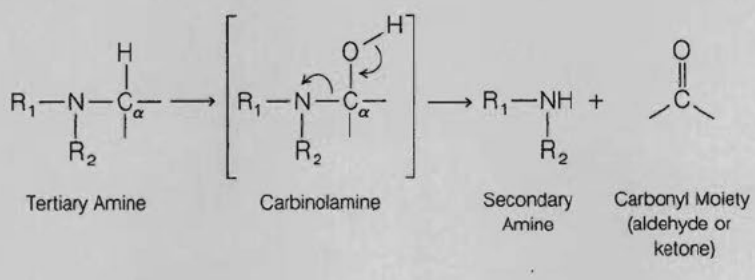
Tertiary Aliphatic and Alicyclic Amines. The oxidative removal of alkyl groups (particularly methyl groups) from tertiary aliphatic and alicyclic amines is carried out by hepatic cytochrome P-450 mixed-function oxidase enzymes. This reaction is commonly referred to as *oxidative N-dealkylation*.[163] The initial step involves α-carbon hydroxylation to form a carbinolamine intermediate, which is unstable and undergoes spontaneous heterolytic cleavage of the C–N bond to give a secondary amine and a carbonyl moiety (aldehyde or ketone).[164, 165] In general, small alkyl groups, such as methyl, ethyl, and isopropyl, are removed rapidly.[163] N-dealkylation of the *t*-butyl group is not possible by the carbinolamine pathway because α-carbon hydroxylation cannot occur. The first alkyl group from a tertiary amine is removed more rapidly than the second alkyl group. In some instances, bisdealkylation of the tertiary aliphatic amine to the corresponding primary aliphatic amine occurs very slowly.[163] For example, the tertiary amine imipramine (Tofranil) is monodemethylated to desmethylimipramine (desipramine).[166, 167] This major plasma metabolite is pharmacologically active in humans and contributes substantially to the antidepressant activity of the parent drug.[168] Very little of the bisdemethylated metabolite of imipramine is detected. In contrast, the local anesthetic and antiarrhythmic agent lidocaine is metabolized extensively by N-deethylation to both monoethylglycylxylidine and glycyl-2,6-xylidine in humans.[169, 170]

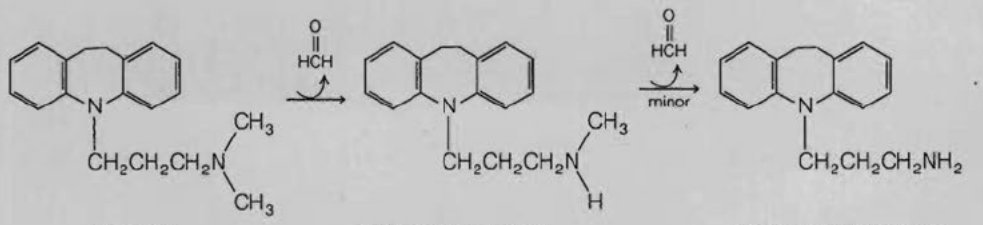
Numerous other tertiary aliphatic amine drugs are metabolized principally by oxidative N-dealkylation. Some of these include the antiarrhythmic disopyramide (Norpace),[171, 172] the antiestrogenic agent tamoxifen (Nolvadex),[173] diphenhydramine (Benadryl),[174, 175] chlorpromazine (Thorazine),[176, 177] and (+)-α-propoxyphene (Darvon).[178] When the tertiary amine contains several different substituents capable of undergoing dealkylation, the smaller alkyl group is removed preferentially and more rapidly. For example, in benzphetamine (Didrex), the methyl group is removed much more rapidly than the benzyl moiety.[179]

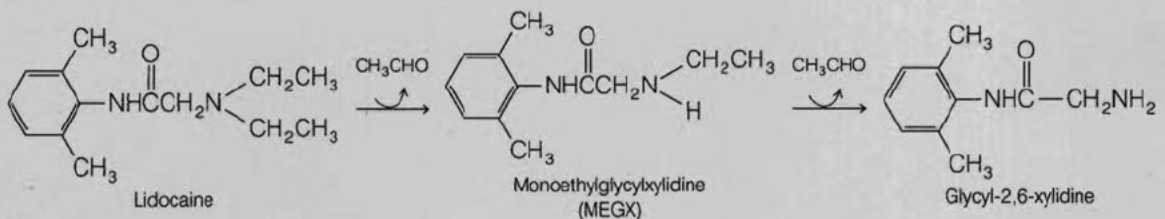
An interesting cyclization reaction occurs with methadone on N-demethylation. The demethylated metabolite normethadone undergoes spontaneous cyclization to form the enamine metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP).[180] Subsequent N-demethylation of EDDP and isomerization of the double bond leads to 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (EMDP).

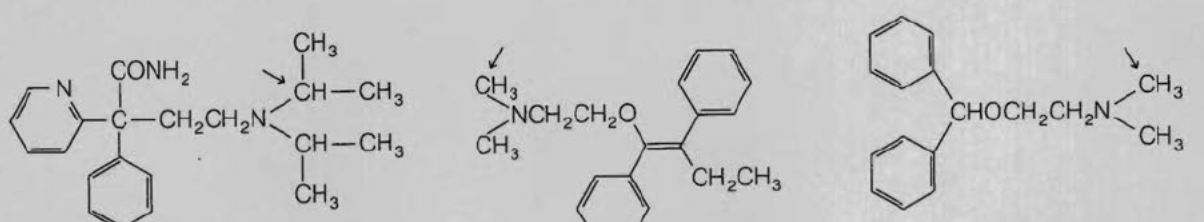
Many times, bisdealkylation of a tertiary amine leads to the corresponding primary aliphatic amine metabolite, which is susceptible to further oxidation. For example, the bisdesmethyl metabolite of the H_1-histamine antagonist brompheniramine (Dimetane) undergoes oxidative deamination and further oxidation to the corresponding propionic acid metabolite.[181] Oxidative deamination is discussed in greater detail when we examine the metabolic reactions of secondary and primary amines.

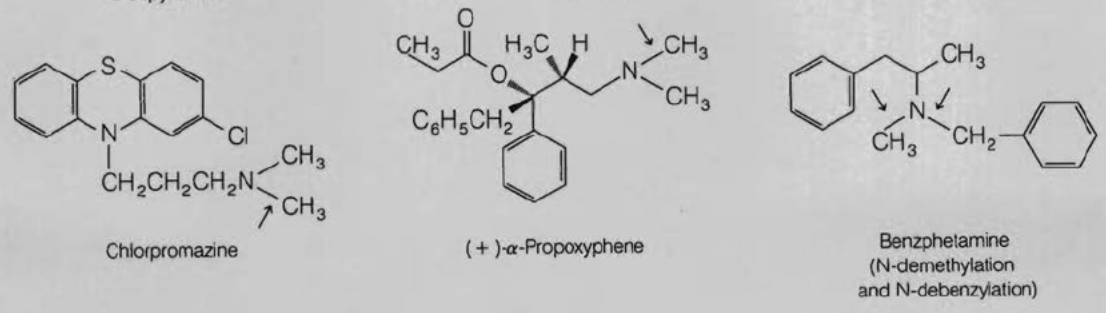
Like their aliphatic counterparts, alicyclic tertiary amines are susceptible to oxidative N-dealkylation reactions. For example, the analgesic meperidine (Demerol) is metabolized





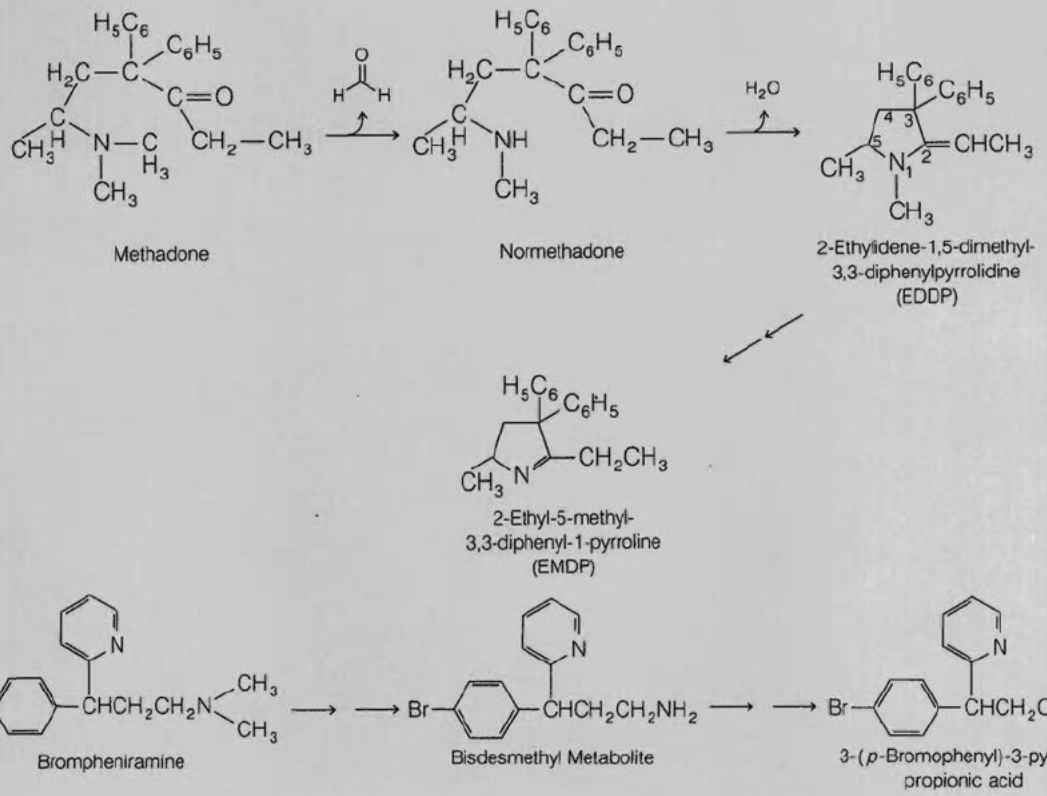




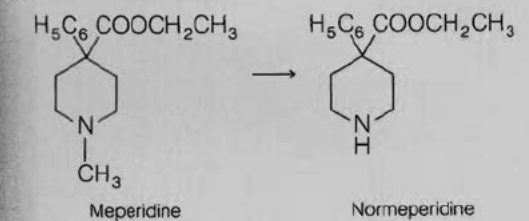


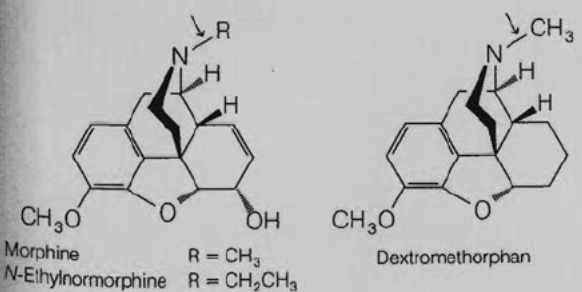
principally by this pathway to yield normeperidine as a major plasma metabolite in humans.[182] Morphine, *N*-ethylnormorphine, and dextromethorphan also undergo some N-dealkylation.[183]

Direct N-dealkylation of *t*-butyl groups, as discussed above, is not possible by the α-carbon hydroxylation pathway. In vitro studies indicate, however, that *N*-*t*-butylnorchlorocyclizine, is, indeed, metabolized to significant amounts of norchlorocyclizine, whereby the *t*-butyl group is lost.[184] Careful studies showed that the *t*-butyl group is removed by initial hydroxylation of one of the methyl groups of the *t*-butyl moiety to the carbinol or alcohol product.[185] Further oxidation generates the corresponding carboxylic acid that, on decarboxylation, forms the *N*-isopropyl deriva-



tive. The *N*-isopropyl intermediate is dealkylated by the normal α-carbon hydroxylation (i.e., carbinolamine) pathway to give norchlorocyclizine and acetone. Whether this is a general method for the loss of *t*-butyl groups from amines is still unclear. Indirect N-dealkylation of *t*-butyl groups is not observed significantly. The *N*-*t*-butyl group present in many β-adrenergic antagonists, such as terbutaline and salbutamol, remains intact and does not appear to undergo any significant metabolism.[186]



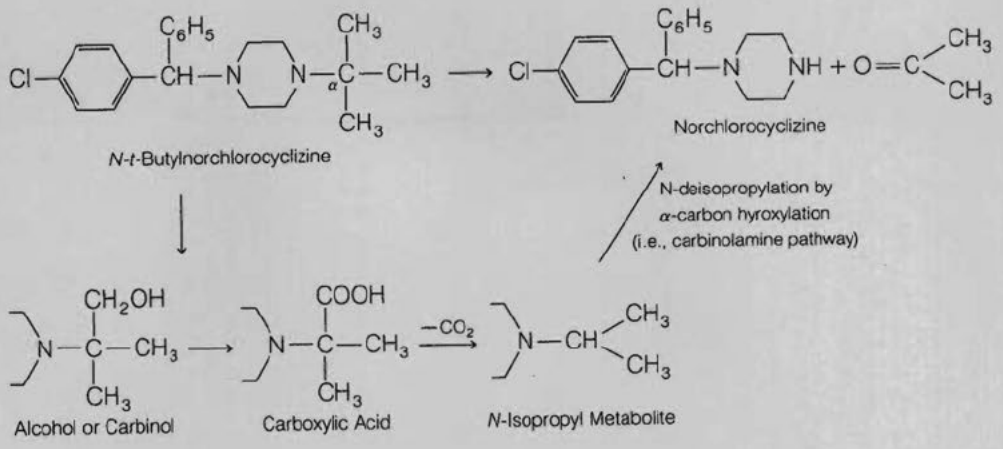


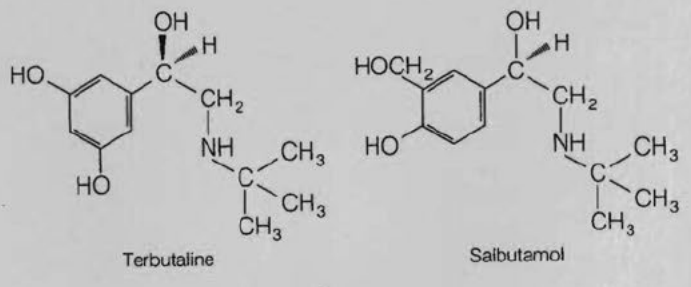
Alicyclic tertiary amines often generate lactam metabolites by α-carbon hydroxylation reactions. For example, the tobacco alkaloid nicotine is hydroxylated initially at the ring carbon atom α to the nitrogen to yield a carbinolamine intermediate. Furthermore, enzymatic oxidation of this cyclic carbinolamine generates the lactam metabolite cotinine.[187, 188]

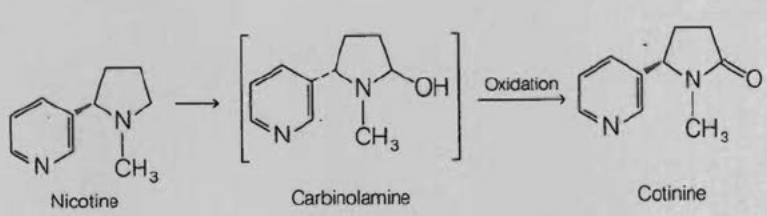
Formation of lactam metabolites also has been reported to occur to a minor extent for the antihistamine cyproheptadine (Periactin)[189, 190] and the antiemetic diphenidol (Vontrol).[191]

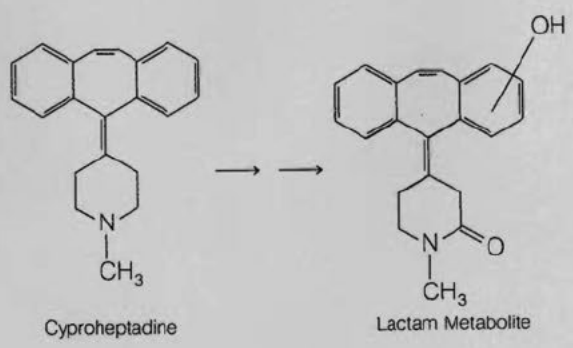
N-oxidation of tertiary amines occurs with several drugs.[192] The true extent of *N*-oxide formation often is complicated by the susceptibility of *N*-oxides to undergo in vivo reduction back to the parent tertiary amine. Tertiary amines such as H_1-histamine antagonists (e.g., orphenadrine, tripelenamine), phenothiazines (e.g., chlorpromazine), tricyclic antidepressants (e.g., imipramine), and narcotic analgesics (e.g., morphine, codeine, and meperidine) reportedly form *N*-oxide products. In some instances, *N*-oxides possess pharmacological activity.[193] A comparison of imipramine *N*-oxide with imipramine indicates that the *N*-oxide itself possesses antidepressant and cardiovascular activity similar to that of the parent drug.[194, 195]

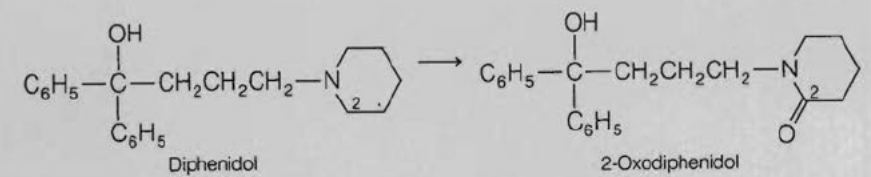
Secondary and Primary Amines. Secondary amines (either parent compounds or metabolites) are susceptible to oxidative N-dealkylation, oxidative deamination, and N-oxidation reactions.[163, 196] As in tertiary amines, N-dealkylation of secondary amines proceeds by the carbinolamine path-


N-t-Butylnorchlorocyclizine
Norchlorocyclizine
N-deisopropylation by
α-carbon hyroxylation
(i.e., carbinolamine pathway)
Alcohol or Carbinol
Carboxylic Acid
N-Isopropyl Metabolite


Terbutaline
Salbutamol


Oxidation
Nicotine
Carbinolamine
Cotinine

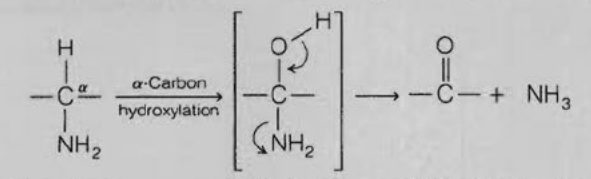

Cyproheptadine
Lactam Metabolite


Diphenidol
2-Oxodiphenidol

way. Dealkylation of secondary amines gives rise to the corresponding primary amine metabolite. For example, the α-adrenergic blockers propranolol[46, 47] and oxprenolol[197] undergo N-deisopropylation to the corresponding primary amines. N-dealkylation appears to be a significant biotransformation pathway for the secondary amine drugs methamphetamine[198, 199] and ketamine,[200, 201] yielding amphetamine and norketamine, respectively.

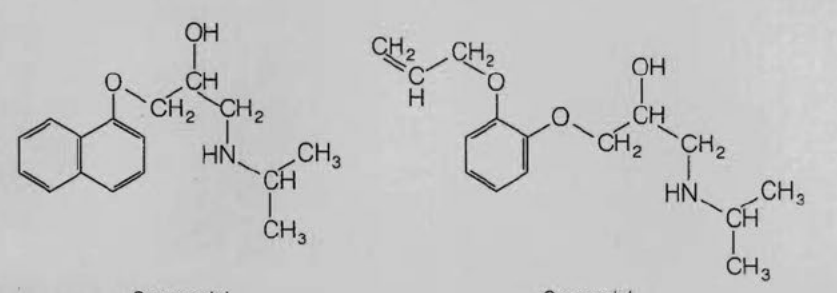
The primary amine metabolites formed from oxidative dealkylation are susceptible to *oxidative deamination*. This process is similar to N-dealkylation, in that it involves an initial α-carbon hydroxylation reaction to form a carbinolamine intermediate, which then undergoes subsequent carbon–nitrogen cleavage to the carbonyl metabolite and ammonia. If α-carbon hydroxylation cannot occur, then oxidative deamination is not possible. For example, deamination does not occur for norketamine because α-carbon hydroxylation cannot take place.[200, 201] With methamphetamine, oxidative deamination of primary amine metabolite amphetamine produces phenylacetone.[198, 199]

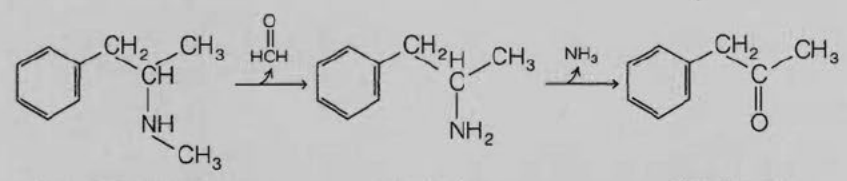
In general, dealkylation of secondary amines is believed to occur before oxidative deamination. Some evidence indicates, however, that this may not always be true. Direct deamination of the secondary amine also has occurred. For example, in addition to undergoing deamination through its desisopropyl primary amine metabolite, propranolol can undergo a direct oxidative deamination reaction (also by α-carbon hydroxylation) to yield the aldehyde metabolite and isopropylamine (Fig. 4-9).[202] How much direct oxidative deamination contributes to the metabolism of secondary amines remains unclear.

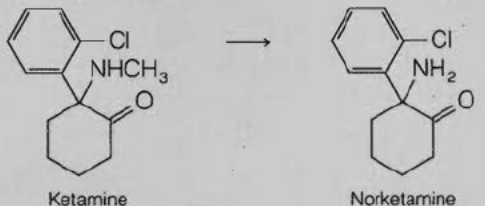


Some secondary alicyclic amines, like their tertiary amine analogues, are metabolized to their corresponding lactam derivatives. For example, the anorectic agent phenmetrazine (Preludin) is metabolized principally to the lactam product 3-oxophenmetrazine.[203] In humans, this lactam metabolite is a major urinary product. Methylphenidate (Ritalin) also reportedly yields a lactam metabolite, 6-oxoritalinic acid, by oxidation of its hydrolyzed metabolite, ritalinic acid, in humans.[204]

Metabolic N-oxidation of secondary aliphatic and alicyclic amines leads to several N-oxygenated products.[196] N-hydroxylation of secondary amines generates the corresponding *N*-hydroxylamine metabolites. Often, these hydroxylamine products are susceptible to further oxidation (either spontaneous or enzymatic) to the corresponding nitrone derivatives. *N*-benzylamphetamine undergoes metabolism to both the corresponding *N*-hydroxylamine and the nitrone metabolites.[205] In humans, the nitrone metabolite of phenmetrazine (Preludin), found in the urine, is believed to be formed by further oxidation of the *N*-hydroxylamine intermediate *N*-hydroxyphenmetrazine.[203] Importantly,







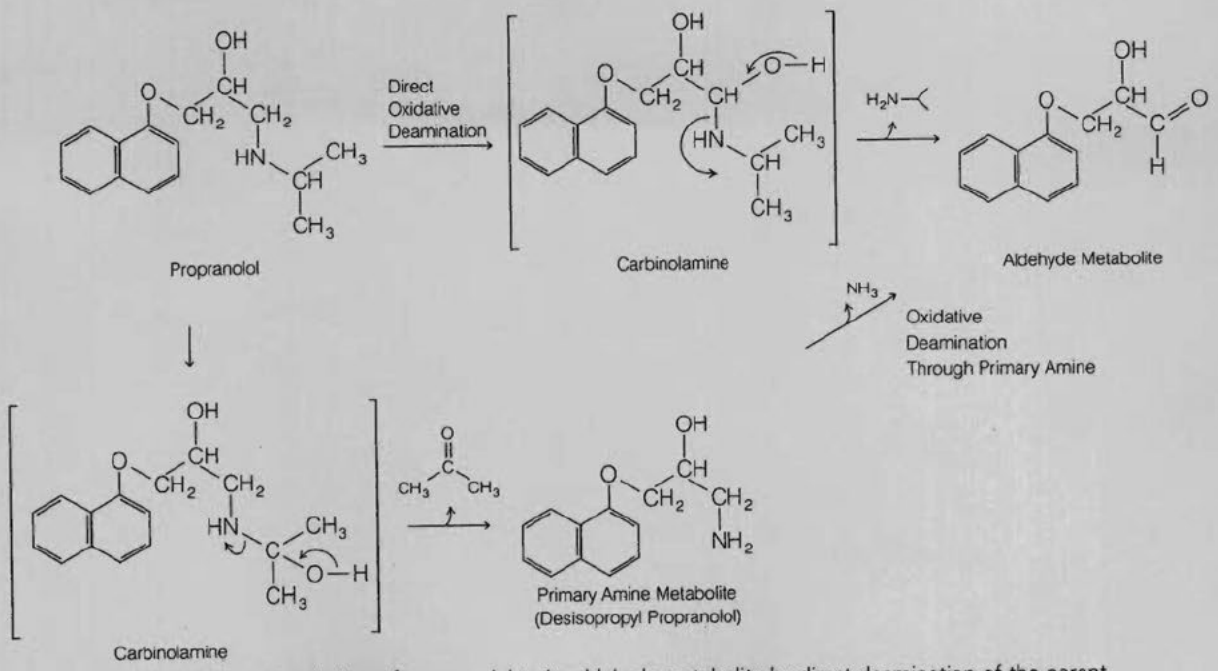
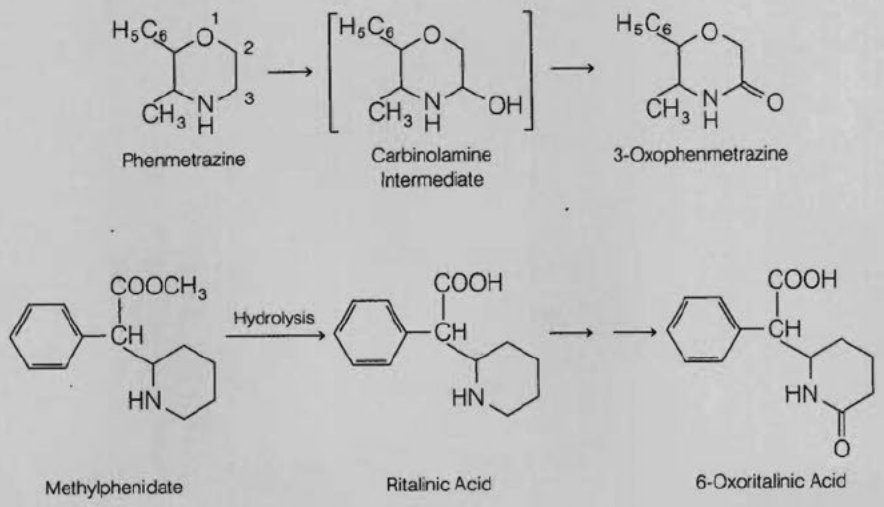
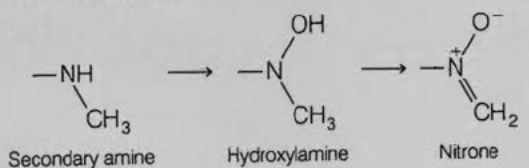


Figure 4–9 ▪ Metabolism of propranolol to its aldehyde metabolite by direct deamination of the parent compound and by deamination of its primary amine metabolite, desisopropyl propranolol.



much less N-oxidation occurs for secondary amines than oxidative dealkylation and deamination.



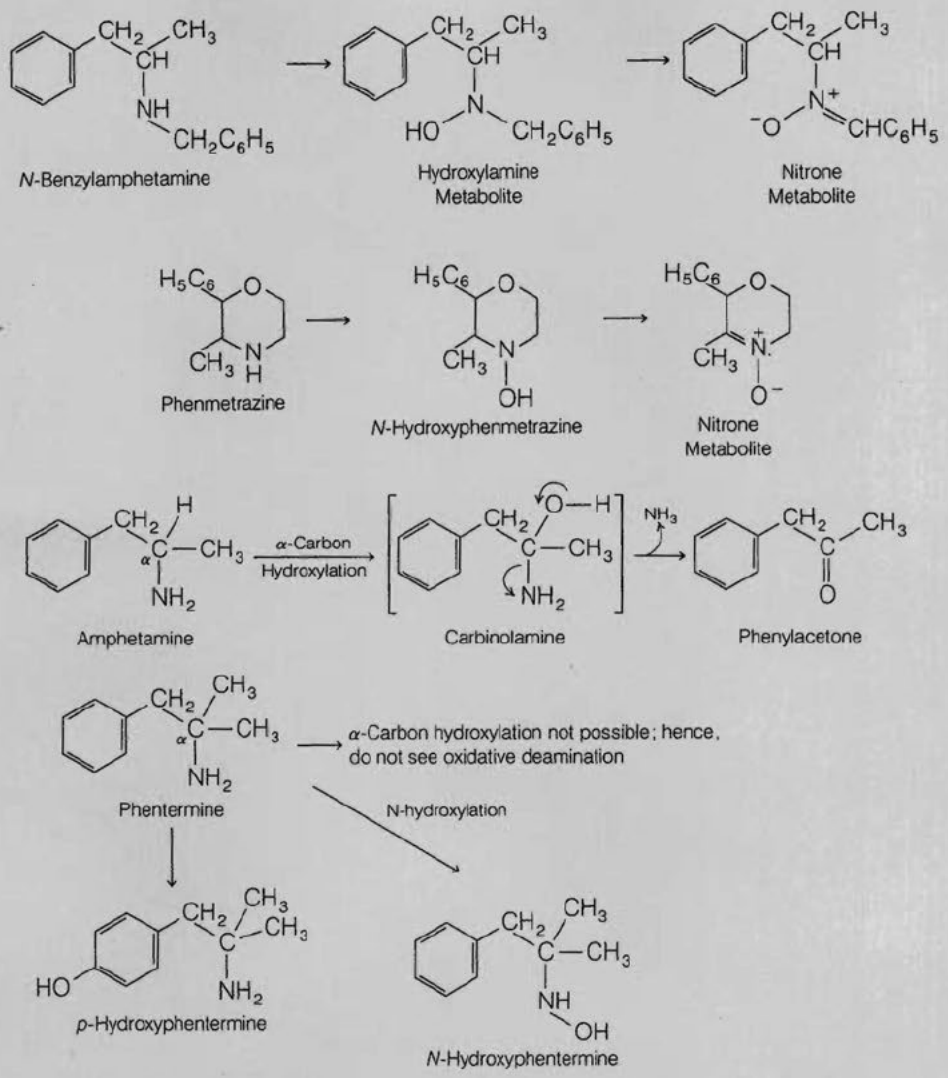
Primary aliphatic amines (whether parent drugs or metabolites) are biotransformed by oxidative deamination (through the carbinolamine pathway) or by N-oxidation. In general, oxidative deamination of most exogenous primary amines is carried out by the mixed-function oxidases discussed above. Endogenous primary amines (e.g., dopamine, norepinephrine, tryptamine, and serotonin) and xenobiotics based on the structures of these endogenous neurotransmitters are metabolized, however, via oxidative deamination by a specialized family of enzymes called *monoamine oxidases* (MAOs).[206]

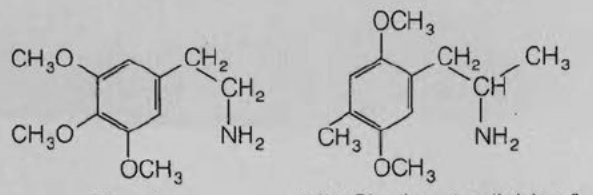
MAO is a flavin (FAD)-dependent enzyme found in two isozyme forms, MAO-A and MAO-B, and widely distributed in both the CNS and peripheral organs. In contrast, cytochrome P-450 exists in a wide variety of isozyme forms and is an NADP-dependent system. Also the greatest variety of CYP isozymes, at least the ones associated with the metabolism of xenobiotics, are found mostly in the liver and intestinal mucosa. MAO-A and MAO-B are coded by two genes, both on the X-chromosome and have about 70% amino acid sequence homology. Another difference between the CYP and MAO families is cellular location. CYP enzymes are found on the endoplasmic reticulum of the cell's cytosol, whereas the MAO enzymes are on the outer mitochondrial membrane. In addition to the xenobiotics illustrated in the reaction schemes, other drugs metabolized by the MAO system include phenylephrine, propranolol, timolol and other β-adrenergic agonists and antagonists and a variety of phenylethylamines.[206]

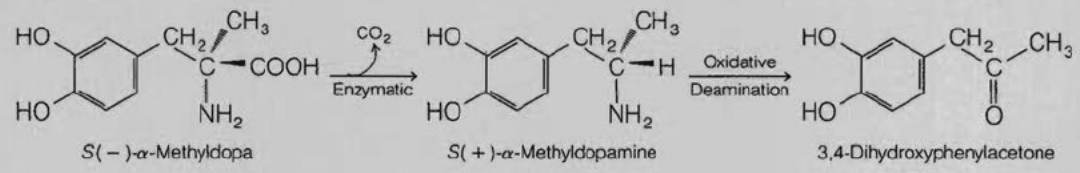
Structural features, especially the α substituents of the primary amine, often determine whether carbon or nitrogen oxidation will occur. For example, compare amphetamine with its α-methyl homologue phentermine. In amphetamine, α-carbon hydroxylation can occur to form the carbinolamine intermediate, which is converted to the oxidatively deaminated product phenylacetone.[67] With phentermine, α-carbon hydroxylation is not possible and precludes oxidative deamination for this drug. Consequently, phentermine would be expected to undergo N-oxidation readily. In humans, *p*-hydroxylation and N-oxidation are the main pathways for biotransformation of phentermine.[207]

Indeed, *N*-hydroxyphentermine is an important (5%) urinary metabolite in humans.[207] As discussed below, *N*-hydroxylamine metabolites are susceptible to further oxidation to yield other N-oxygenated products.

Xenobiotics, such as the hallucinogenic agents mescaline[208, 209] and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM or "STP"),[210, 211] are oxidatively deaminated. Primary amine metabolites arising from N-



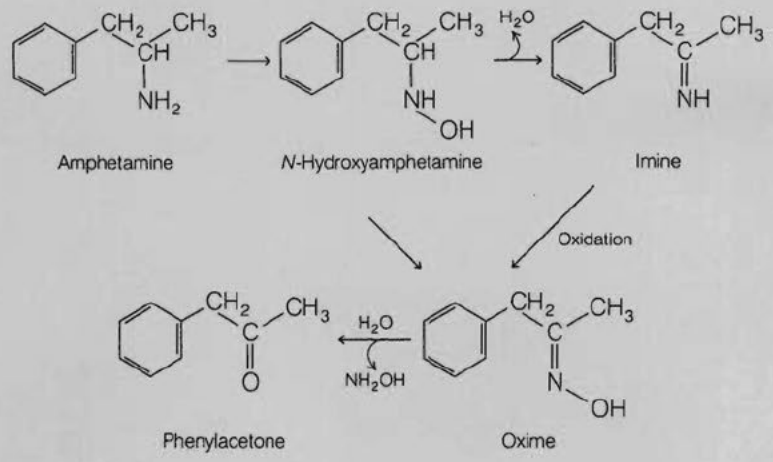




dealkylation or decarboxylation reactions also undergo deamination. The example of the bisdesmethyl primary amine metabolite derived from bromopheniramine is discussed above (see section on tertiary aliphatic and alicyclic amines).[181] In addition, many tertiary aliphatic amines (e.g., antihistamines) and secondary aliphatic amines (e.g., propranolol) are dealkylated to their corresponding primary amine metabolites, which are amenable to oxidative deamination. (*S*)(+)-α-Methyldopamine resulting from decarboxylation of the antihypertensive agent (*S*)(−)-α-methyldopa (Aldomet) is deaminated to the corresponding ketone metabolite 3,4-dihydroxyphenylacetone.[212] In humans, this ketone is a major urinary metabolite.

The N-hydroxylation reaction is not restricted to α-substituted primary amines such as phentermine. Amphetamine has been observed to undergo some N-hydroxylation in vitro to *N*-hydroxyamphetamine.[213, 214] *N*-Hydroxyamphetamine is, however, susceptible to further conversion to the imine or oxidation to the oxime intermediate. Note that the oxime intermediate arising from this N-oxidation pathway can undergo hydrolytic cleavage to yield phenylacetone, the same product obtained by the α-carbon hydroxylation (carbinolamine) pathway.[215, 216] Thus, amphetamine may be converted to phenylacetone through either the α-carbon hydroxylation or the N-oxidation pathway. The debate concerning the relative importance of the two pathways is ongoing.[217–219] The consensus, however, is that both metabolic pathways (carbon and nitrogen oxidation) are probably operative. Whether α-carbon or nitrogen oxidation predominates in the metabolism of amphetamine appears to be species dependent.

In primary aliphatic amines, such as phentermine,[207] chlorphentermine (*p*-chlorphentermine),[219] and amantadine,[220] N-oxidation appears to be the major biotransformation pathway because α-carbon hydroxylation cannot occur. In humans, chlorphentermine is N-hydroxylated extensively. About 30% of a dose of chlorphentermine is found in the urine (48 hours) as *N*-hydroxychlorphentermine (free and conjugated) and an additional 18% as other products of N-oxidation (presumably the nitroso and nitro metabolites).[219] In general, *N*-hydroxylamines are chemically unstable and susceptible to spontaneous or enzymatic oxidation to the nitroso and nitro derivatives. For example, the *N*-hydroxylamine metabolite of phentermine undergoes further oxida-



tion to the nitroso and nitro products.[207] The antiviral and antiparkinsonian agent amantadine (Symmetrel) reportedly undergoes N-oxidation to yield the corresponding *N*-hydroxy and nitroso metabolites in vitro.[220]

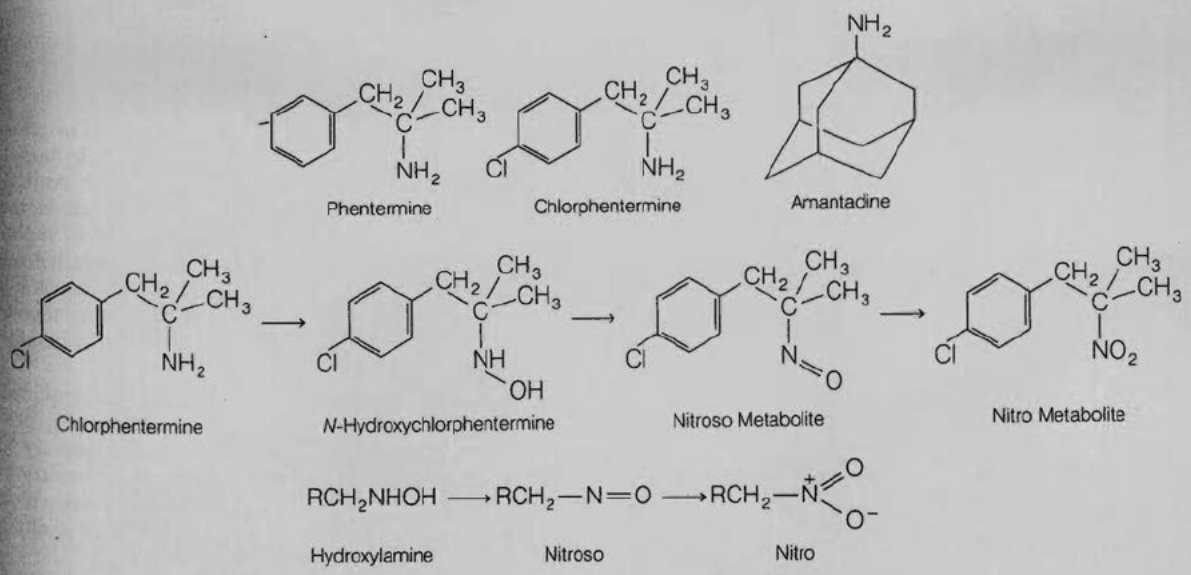
Aromatic Amines and Heterocyclic Nitrogen Compounds. The biotransformation of aromatic amines parallels the carbon and nitrogen oxidation reactions seen for aliphatic amines.[221–223] For tertiary aromatic amines, such as *N,N*-dimethylaniline, oxidative N-dealkylation as well as *N*-oxide formation take place.[224] Secondary aromatic amines may undergo N-dealkylation or N-hydroxylation to give the corresponding *N*-hydroxylamines. Further oxidation of the *N*-hydroxylamine leads to nitrone products, which in turn may be hydrolyzed to primary hydroxylamines.[225] Tertiary and secondary aromatic amines are encountered rarely in medicinal agents. In contrast, primary aromatic amines are found in many drugs and are often generated from enzymatic reduction of aromatic nitro compounds, reductive cleavage of azo compounds, and hydrolysis of aromatic amides.

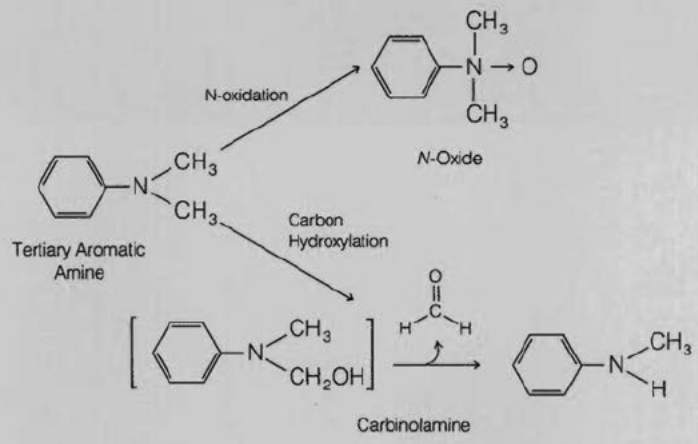
N-oxidation of primary aromatic amines generates the *N*-hydroxylamine metabolite. One such case is aniline, which is metabolized to the corresponding *N*-hydroxy product.[223] Oxidation of the hydroxylamine derivative to the nitroso derivative also can occur. When one considers primary aromatic amine drugs or metabolites, N-oxidation constitutes only a minor pathway in comparison with other biotransformation pathways, such as N-acetylation and aromatic hydroxylation, in humans. Some N-oxygenated metabolites have been reported, however. For example, the antileprotic agent dapsone and its N-acetylated metabolite are metabolized significantly to their corresponding *N*-hydroxylamine derivatives.[226] The *N*-hydroxy metabolites are further conjugated with glucuronic acid.

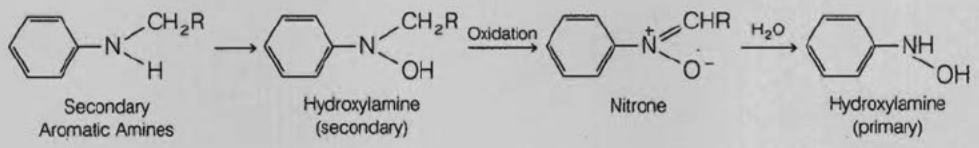
Methemoglobinemia toxicity is caused by several aromatic amines, including aniline and dapsone, and is a result of the bioconversion of the aromatic amine to its *N*-hydroxy derivative. Apparently, the *N*-hydroxylamine oxidizes the Fe^{2+} form of hemoglobin to its Fe^{3+} form. This oxidized (Fe^{3+}) state of hemoglobin (called *methemoglobin* or *ferrihemoglobin*) can no longer transport oxygen, which leads to serious hypoxia or anemia, a unique type of chemical suffocation.[227]

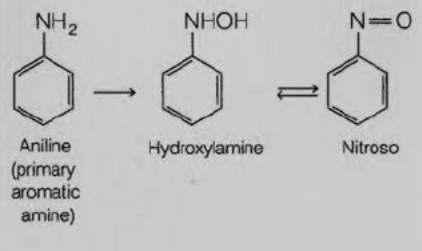
Diverse aromatic amines (especially azoamino dyes) are known to be carcinogenic. N-oxidation plays an important role in bioactivating these aromatic amines to potentially reactive electrophilic species that covalently bind to cellular protein, DNA, or RNA. A well-studied example is the carcinogenic agent *N*-methyl-4-aminoazobenzene.[228, 229] N-oxidation of this compound leads to the corresponding hydroxylamine, which undergoes sulfate conjugation. Because of the good leaving-group ability of the sulfate (SO_4^{2-}) anion, this conjugate can ionize spontaneously to form a highly reactive, resonance-stabilized nitrenium species. Covalent adducts between this species and DNA, RNA, and proteins have been characterized.[230, 231] The sulfate ester is believed to be the ultimate carcinogenic species. Thus, the example indicates that certain aromatic amines can be bioactivated to reactive intermediates by N-hydroxylation and *O*-sulfate conjugation. Whether primary hydroxylamines can be bioactivated similarly is unclear. In addition, it is not known if this biotoxification pathway plays any substantial role in the toxicity of aromatic amine drugs.

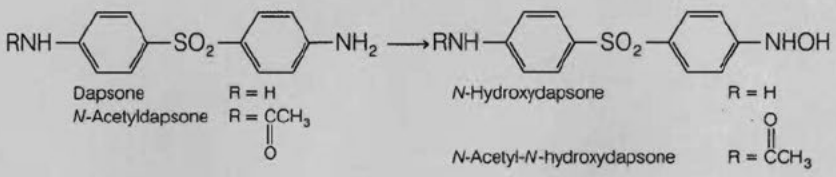
N-oxidation of the nitrogen atoms present in aromatic heterocyclic moieties of many drugs occurs to a minor extent. Clearly, in humans, N-oxidation of the folic acid antagonist trimethoprim (Proloprim, Trimpex) has yielded approximately equal amounts of the isomeric 1-*N*-oxide and 3-*N*-oxide as minor metabolites.[232] The pyridinyl nitrogen atom present in nicotinine (the major metabolite of nicotine) undergoes oxidation to yield the corresponding *N*-oxide metabolite.[233] Another therapeutic agent that has been observed to undergo formation of an *N*-oxide metabolite is metronidazole.[234]

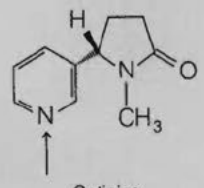


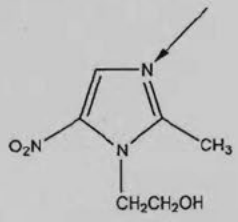








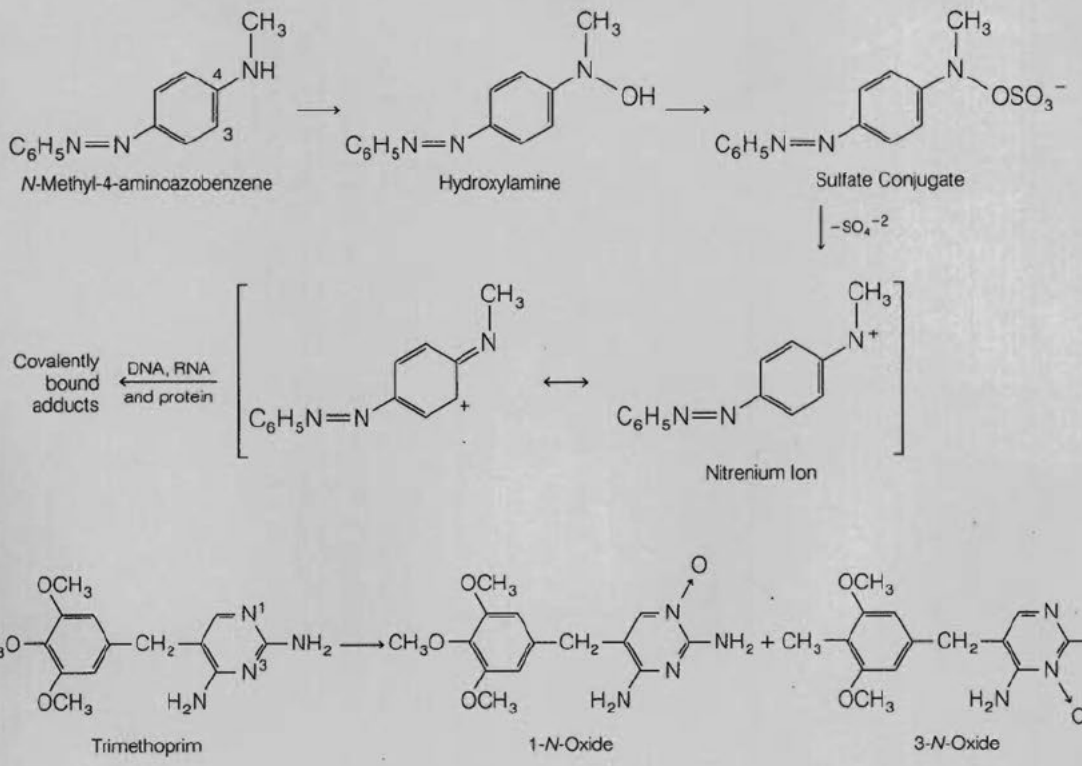

Cotinine


Metronidazole
2-(2-Methyl-5-nitro-imidazol-1-yl)-ethanol

Amides. Amide functionalities are susceptible to oxidative carbon–nitrogen bond cleavage (via α-carbon hydroxylation) and N-hydroxylation reactions. Oxidative dealkylation of many N-substituted amide drugs and xenobiotics has been reported. Mechanistically, oxidative dealkylation proceeds via an initially formed carbinolamide, which is unstable and fragments to form the N-dealkylated product. For example, diazepam undergoes extensive N-demethylation to the pharmacologically active metabolite desmethyldiazepam.[235]

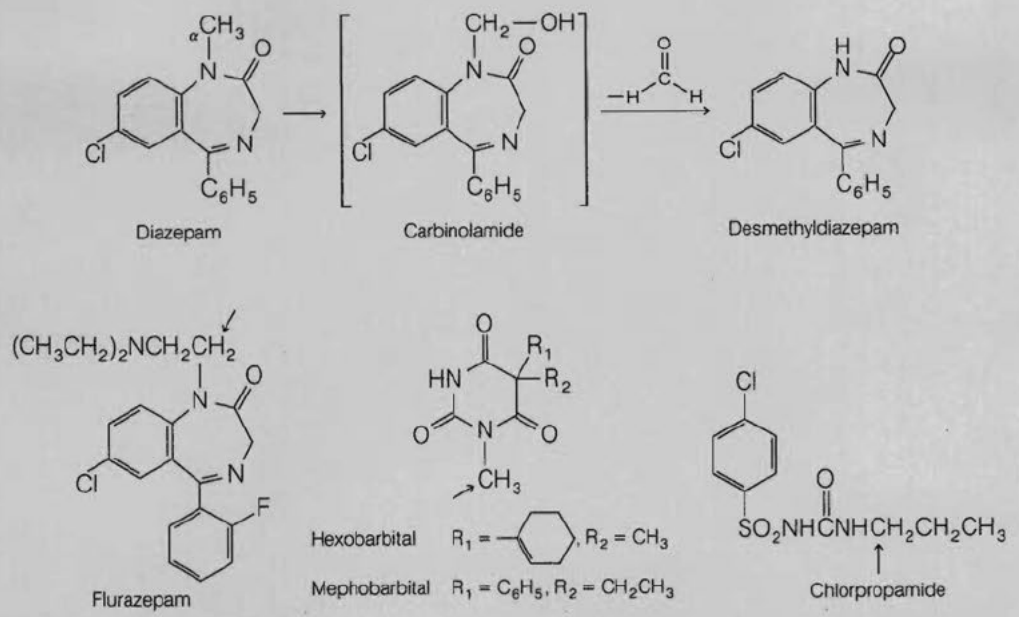
Various other *N*-alkyl substituents present in benzodiazepines (e.g., flurazepam)[136–138] and in barbiturates (e.g., hexobarbital and mephobarbital)[128] are similarly oxidatively N-dealkylated. Alkyl groups attached to the amide moiety of some sulfonylureas, such as the oral hypoglycemic chlorpropamide,[236] also are subject to dealkylation to a minor extent.

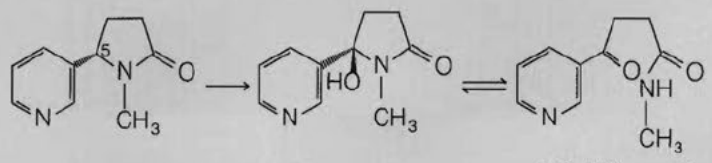
In the cyclic amides or lactams, hydroxylation of the alicy-



clic carbon α to the nitrogen atom also leads to carbinolamides. An example of this pathway is the conversion of cotinine to 5-hydroxycotinine. Interestingly, the latter carbinolamide intermediate is in tautomeric equilibrium with the ring-opened metabolite γ-(3-pyridyl)-γ-oxo-*N*-methylbutyramide.[237]

Metabolism of the important cancer chemotherapeutic agent cyclophosphamide (Cytoxan) follows a hydroxylation pathway similar to that just described for cyclic amides. This drug is a cyclic phosphoramide derivative and, for the most part, is the phosphorous counterpart of a cyclic amide. Because cyclophosphamide itself is pharmacologically inac-

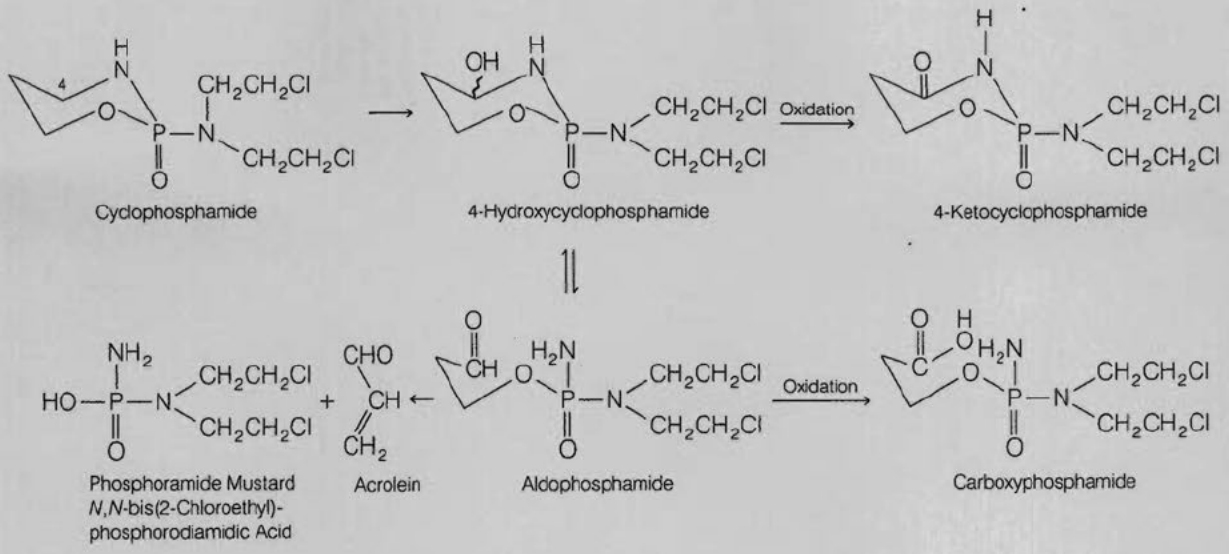


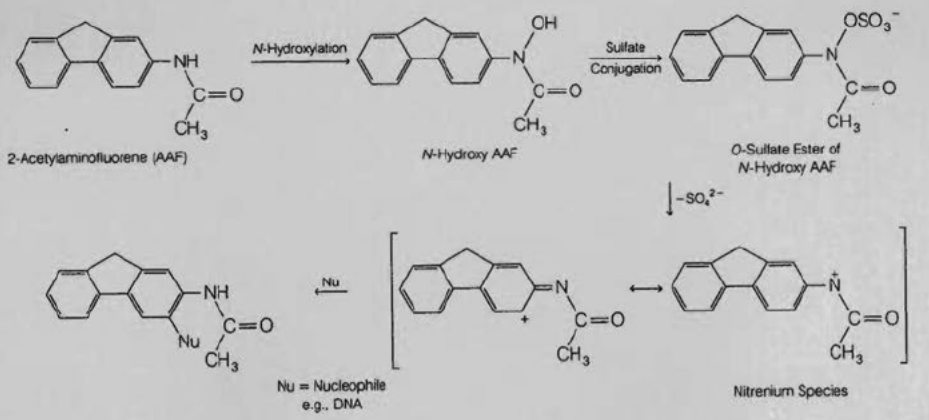


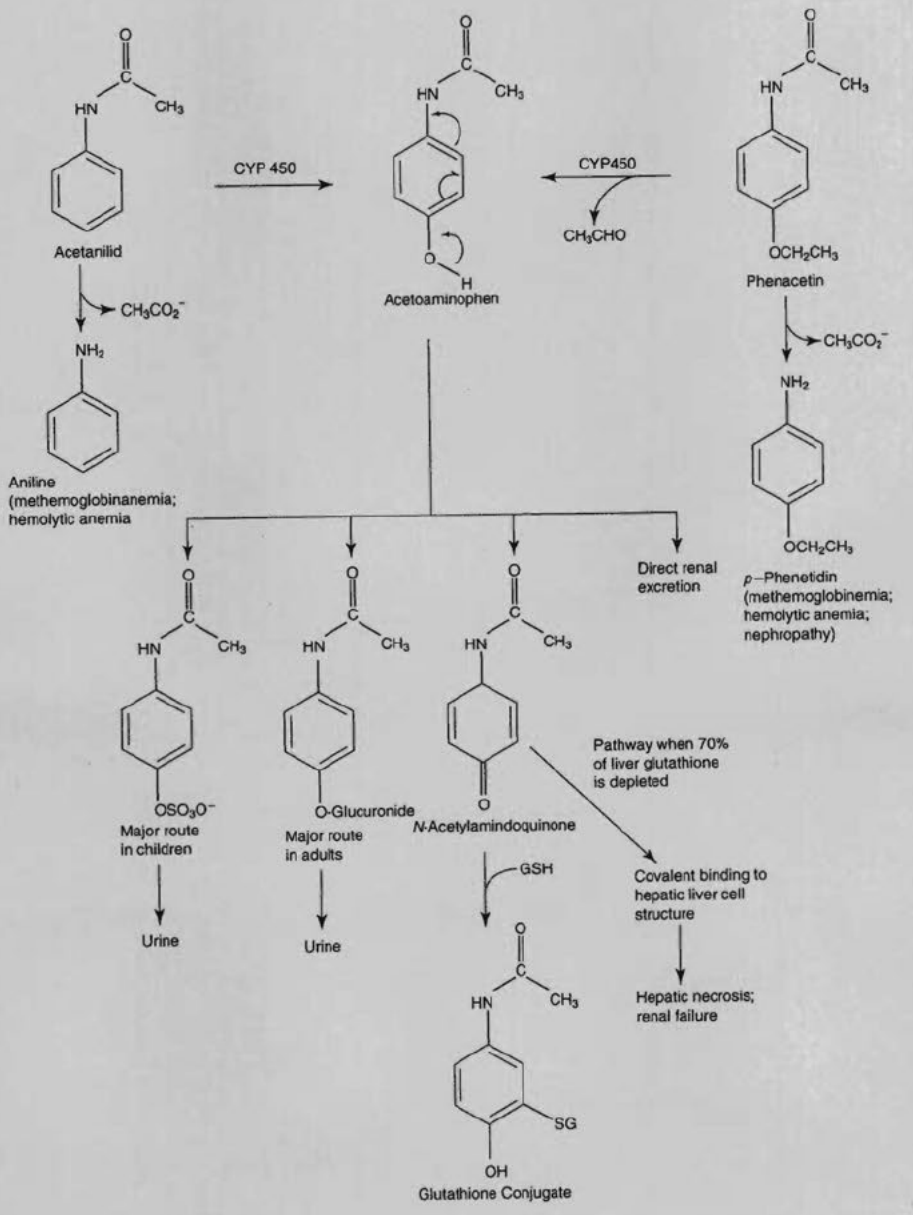
tive,[238] metabolic bioactivation is required for the drug to mediate its antitumorigenic or cytotoxic effects. The key biotransformation pathway leading to the active metabolite involves an initial carbon hydroxylation reaction at C-4 to form the carbinolamide 4-hydroxycyclophosphamide.[239, 240] 4-Hydroxycyclophosphamide is in equilibrium with the ring-opened dealkylated metabolite aldophosphamide. Although it has potent cytotoxic properties, aldophosphamide undergoes a further elimination reaction (reverse Michael reaction) to generate acrolein and the phosphoramide mustard *N,N*-bis(2-chloro-ethyl)phosphorodiamidic acid. The latter is the principal species responsible for cyclophosphamide's antitumorigenic properties and chemotherapeutic effect. Enzymatic oxidation of 4-hydroxycyclophosphamide and aldophosphamide leads to the relatively nontoxic metabolites 4-ketocyclophosphamide and carboxycyclophosphamide, respectively.

N-hydroxylation of aromatic amides, which occurs to a minor extent, is of some toxicological interest, since this biotransformation pathway may lead to the formation of chemically reactive intermediates. Several examples of cytotoxicity or carcinogenicity associated with metabolic N-hydroxylation of the parent aromatic amide have been reported. For example, the well-known hepatocarcinogenic 2-acetylaminofluorene (AAF) undergoes an N-hydroxylation reaction catalyzed by cytochrome P-450 to form the corresponding N-hydroxy metabolite (also called a hydroxamic acid).[241] Further conjugation of this hydroxamic acid produces the corresponding *O*-sulfate ester, which ionizes to generate the electrophilic nitrenium species. Covalent binding of this reactive intermediate to DNA is known to occur and is likely to be the initial event that ultimately leads to malignant tumor formation.[242] Sulfate conjugation plays an important role in this biotoxification pathway (see "Sulfate Conjugation," for further discussion).

Acetaminophen is a relatively safe and nontoxic analgesic agent if used at therapeutic doses. Its metabolism illustrates the fact that a xenobiotic commonly produces more than one metabolite. Its metabolism also illustrates the effect of age, since infants and young children carry out sulfation rather than glucuronidation (see discussion at the end of this chapter). New pharmacists must realize that at one time acetanilide and phenacetin were more widely used than acetaminophen, even though both are considered more toxic because they produce aniline derivatives. Besides producing toxic aniline and *p*-phenetidin, these two analgesics also produce acetaminophen. When large doses of the latter drug are ingested, extensive liver necrosis is produced in humans and animals.[243, 244] Considerable evidence argues that this hepatotoxicity depends on the formation of a metabolically generated reactive intermediate.[245] Until recently,[246, 247] the accepted bioactivation pathway was believed to involve an initial N-hydroxylation reaction to form *N*-hydroxyacetaminophen.[248] Spontaneous dehydration of this *N*-hydrox-




N-Hydroxylation
Sulfate Conjugation
2-Acetylaminofluorene (AAF)
N-Hydroxy AAF
O-Sulfate Ester of N-Hydroxy AAF
Nu
Nu = Nucleophile e.g., DNA
Nitrenium Species


CYP 450
CYP450
Acetanilid
Acetoaminophen
Phenacetin
Aniline (methemoglobinanemia; hemolytic anemia
Direct renal excretion
p-Phenetidin (methemoglobinemia; hemolytic anemia; nephropathy)
Major route in children
Major route in adults
O-Glucuronide
N-Acetylamindoquinone
Pathway when 70% of liver glutathione is depleted
Urine
Urine
GSH
Covalent binding to hepatic liver cell structure
Hepatic necrosis; renal failure
Glutathione Conjugate

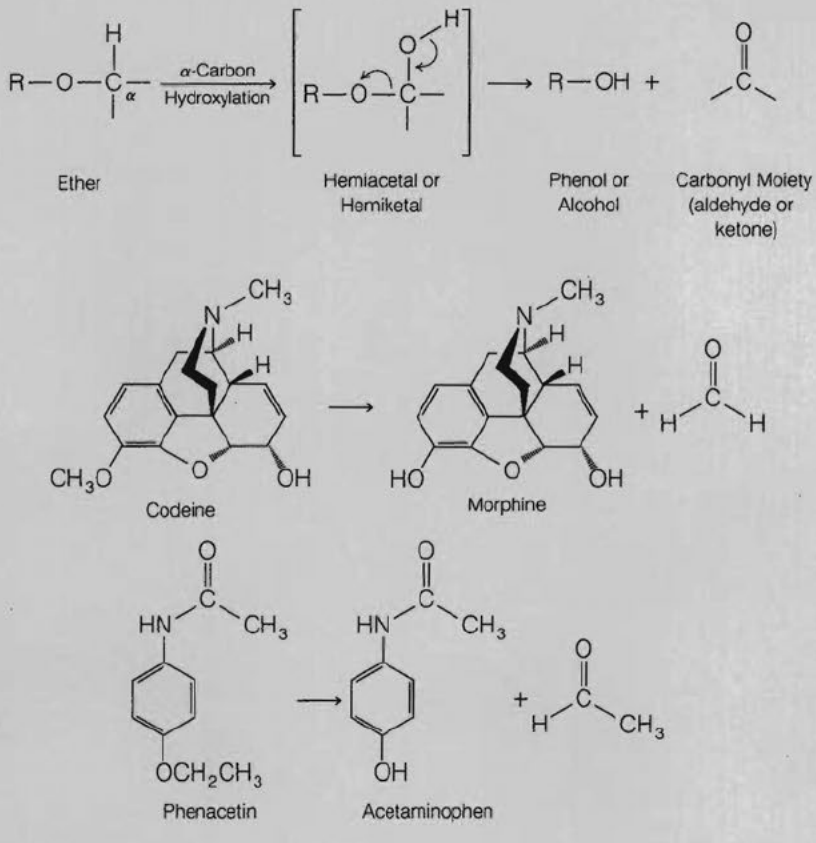
yamide produces *N*-acetylimidoquinone, the proposed reactive metabolite. Usually, the GSH present in the liver combines with this reactive metabolite to form the corresponding GSH conjugate. If GSH levels are sufficiently depleted by large doses of acetaminophen, covalent binding of the reactive intermediate occurs with macromolecules present in the liver, thereby leading to cellular necrosis. Studies indicate, however, that the reactive *N*-acetylimidoquinone intermediate is not formed from *N*-hydroxyacetaminophen.[245–247] It probably arises through some other oxidative process. Therefore, the mechanistic formation of the reactive metabolite of acetaminophen remains unclear.

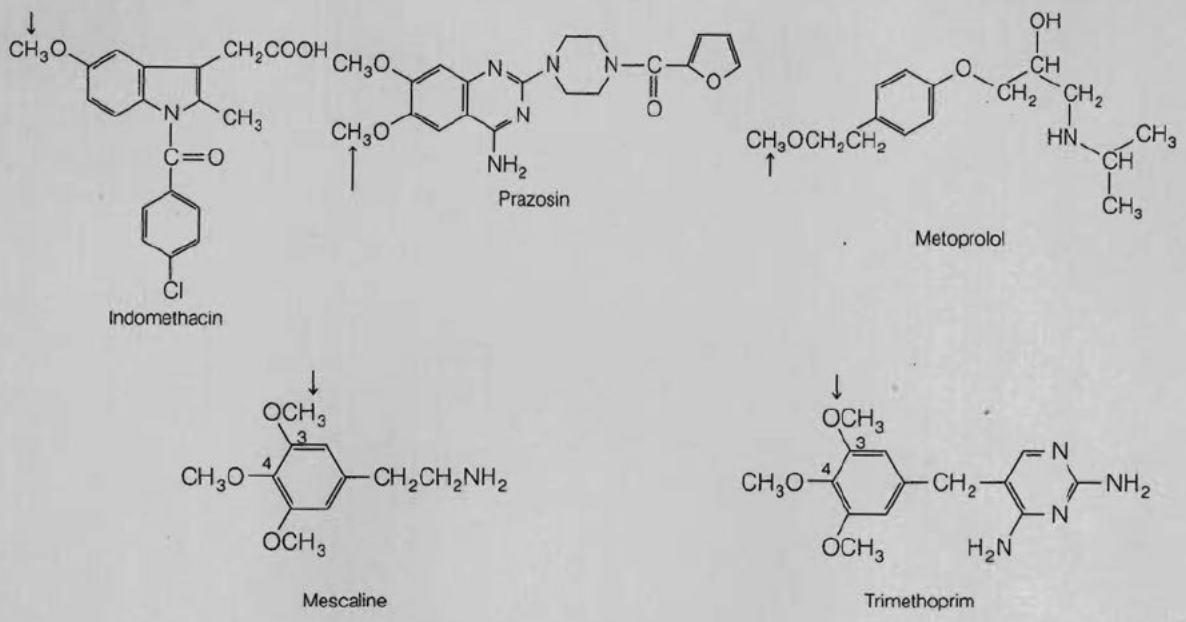
OXIDATION INVOLVING CARBON–OXYGEN SYSTEMS

Oxidative O-dealkylation of carbon–oxygen systems (principally ethers) is catalyzed by microsomal mixed function oxidases.[163] Mechanistically, the biotransformation involves an initial α-carbon hydroxylation to form either a hemiacetal or a hemiketal, which undergoes spontaneous carbon–oxygen bond cleavage to yield the dealkylated oxygen species (phenol or alcohol) and a carbon moiety (aldehyde or ketone). Small alkyl groups (e.g., methyl or ethyl) attached to oxygen are O-dealkylated rapidly. For example, morphine is the metabolic product of O-demethylation of codeine.[249] The antipyretic and analgesic activities of phenacetin (see drawing of acetaminophen metabolism) in humans appear to be a consequence of O-deethylation to the active metabolite acetaminophen.[250] Several other drugs containing ether groups, such as indomethacin (Indocin),[251, 252] prazosin (Minipress),[253, 254] and metoprolol (Lopressor),[122, 123] have reportedly undergone significant O-demethylation to their corresponding phenolic or alcoholic metabolites, which are further conjugated. In many drugs that have several nonequivalent methoxy groups, one particular methoxy group often appears to be O-demethylated selectively or preferentially. For example, the 3,4,5-trimethoxyphenyl moiety in both mescaline[255] and trimethoprim[232] undergoes O-demethylation to yield predominantly the corresponding 3-O-demethylated metabolites. 4-O-demethylation also occurs to a minor extent for both drugs. The phenolic and alcoholic metabolites formed from oxidative O-demethylation are susceptible to conjugation, particularly glucuronidation.

OXIDATION INVOLVING CARBON–SULFUR SYSTEMS

Carbon–sulfur functional groups are susceptible to metabolic S-dealkylation, desulfuration, and S-oxidation reactions. The first two processes involve oxidative carbon–sulfur bond cleavage. S-dealkylation is analogous to O- and N-dealkylation mechanistically (i.e., it involves α-carbon hydroxylation) and has been observed for various sulfur xenobiotics.[163, 256] For example, 6-(methylthio)purine is demethylated oxidatively in rats to 6-mercaptopurine.[257, 258] S-demethylation of methitural[259] and S-debenzylation of 2-benzylthio-5-trifluoromethylbenzoic acid also have been reported. In contrast to O- and N-dealkylation, examples of drugs undergoing S-dealkylation in humans are





limited because of the small number of sulfur-containing medicinals and the competing metabolic S-oxidation processes (see diagram).

Oxidative conversion of carbon–sulfur double bonds (C=S) (thiono) to the corresponding carbon–oxygen double bond (C=O) is called *desulfuration*. A well-known drug example of this metabolic process is the biotransformation of thiopental to its corresponding oxygen analogue pentobarbital.[260, 261] An analogous desulfuration reaction also occurs with the P=S moiety present in a number of organophosphate insecticides, such as parathion.[262, 263] Desulfuration of parathion leads to the formation of paraoxon, which is the active metabolite responsible for the anticholinesterase activity of the parent drug. The mechanistic details of desulfuration are poorly understood, but it appears to involve microsomal oxidation of the C=S or P=S double bond.[264]

Organosulfur xenobiotics commonly undergo S-oxidation to yield sulfoxide derivatives. Several phenothiazine derivatives are metabolized by this pathway. For example, both sulfur atoms present in thioridazine (Mellaril)[265, 266] are susceptible to S-oxidation. Oxidation of the 2-methylthio group yields the active sulfoxide metabolite mesoridazine. Interestingly, mesoridazine is twice as potent an antipsychotic agent as thioridazine in humans and has been introduced into clinical use as Serentil.[267]

S-oxidation constitutes an important pathway in the metabolism of the H_2-histamine antagonists cimetidine (Tagamet)[268] and metiamide.[269] The corresponding sulfoxide derivatives are the major human urinary metabolites.

Sulfoxide drugs and metabolites may be further oxidized to sulfones ($-SO_2-$). The sulfoxide group present in the immunosuppressive agent oxisuran is metabolized to a sulfone moiety.[270] In humans, dimethylsulfoxide (DMSO) is found primarily in the urine as the oxidized product dimethylsulfone. Sulfoxide metabolites, such as those of thioridazine, reportedly undergo further oxidation to their sulfone $-SO_2-$ derivatives.[265, 266]

Oxidation of Alcohols and Aldehydes

Many oxidative processes (e.g., benzylic, allylic, alicyclic, or aliphatic hydroxylation) generate alcohol or carbinol metabolites as intermediate products. If not conjugated, these alcohol products are further oxidized to aldehydes (if primary alcohols) or to ketones (if secondary alcohols). Aldehyde metabolites resulting from oxidation of primary alcohols or from oxidative deamination of primary aliphatic amines often undergo facile oxidation to generate polar carboxylic acid derivatives.[116] As a general rule, primary alcoholic groups and aldehyde functionalities are quite vulnera-