Wilson and Gisvold's Textbook of

ORGANIC MEDICINAL AND PHARMACEUTICAL CHEMISTRY

ELEVENTH EDITION

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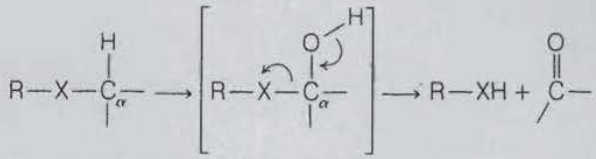
The stereochemistry of the hydroxylated centers in the two metabolites has not been clearly established. Biotransformation of the antihypertensive agent minoxidil (Loniten) yields the 4′-hydroxypiperidyl metabolite. In the dog, this product is a major urinary metabolite (29 to 47%), whereas in humans 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:

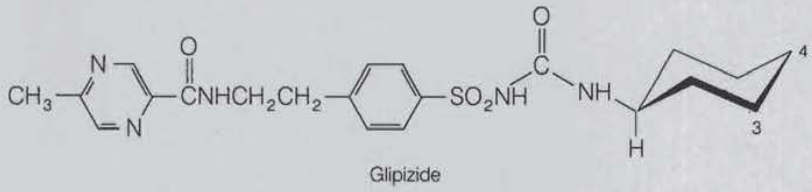


Where X = N,O,S Usually Unstable

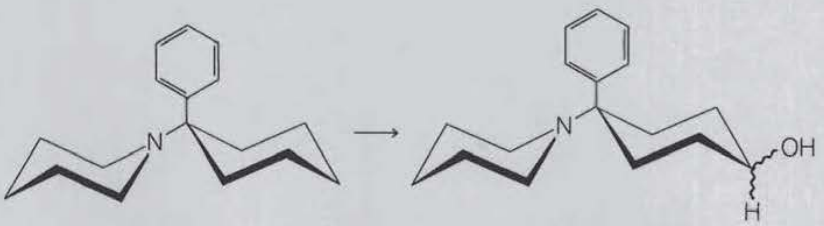
Oxidative N-, O-, and S-dealkylation as well as oxidative deamination reactions fall under this mechanistic pathway.

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

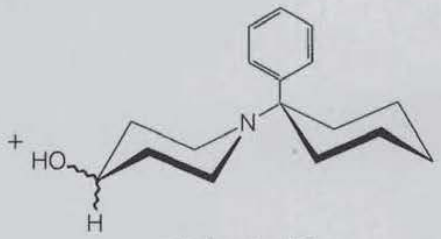
Several structural features frequently determine which pathway will predominate, especially in carbon–nitrogen systems. Metabolism of some nitrogen-containing compounds is complicated by the fact that carbon- or nitrogen-



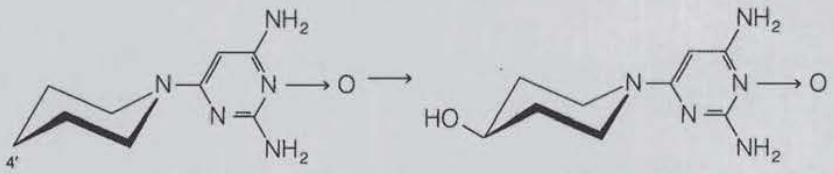
Glipizide



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.

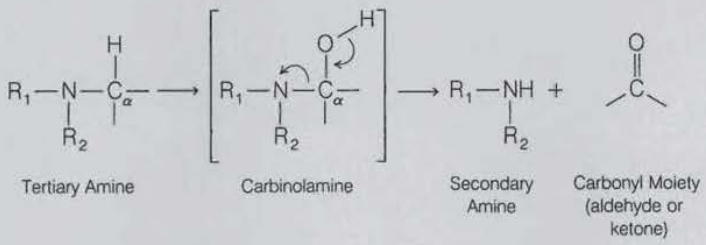
Tertiary Aliphatic and Alicyclic Amines. The oxidative removal of alkyl groups (particularly methyl groups) from tertiary aliphatic and alicyclic amines is carried out by hepatic cytochrome P-450 mixed-function oxidase enzymes. This reaction is commonly referred to as *oxidative N-dealkylation*.[163] 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]

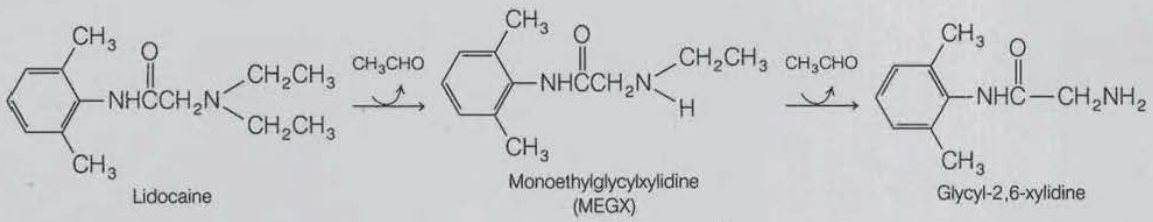
An interesting cyclization reaction occurs with methadone on N-demethylation. The demethylated metabolite normethadone undergoes spontaneous cyclization to form the enamine metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP).[180] Subsequent N-demethylation of EDDP and isomerization of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

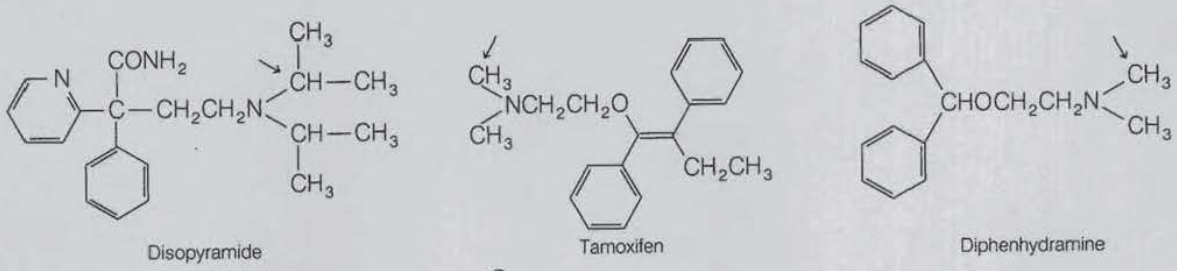
Like their aliphatic counterparts, alicyclic tertiary amines are susceptible to oxidative N-dealkylation reactions. For example, the analgesic meperidine (Demerol) is metabolized



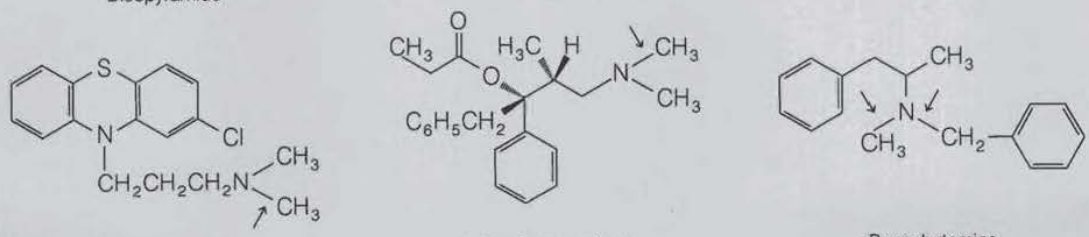
Imipramine | Desmethylimipramine (desipramine) | Bisdesmethylimipramine



Lidocaine | Monoethylglycylxylidine (MEGX) | Glycyl-2,6-xylidine



Disopyramide | Tamoxifen | Diphenhydramine



Chlorpromazine | (+)-α-Propoxyphene | Benzphetamine (N-demethylation and N-debenzylation)

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-

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