

*Wilson and
Gisvold's Textbook of*

ORGANIC MEDICINAL AND PHARMACEUTICAL CHEMISTRY

E L E V E N T H E D I T I O N

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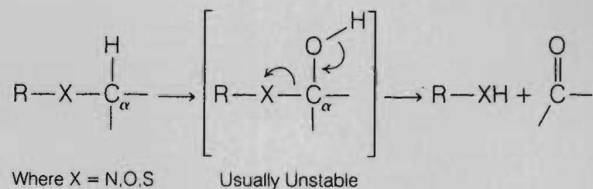
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The stereochemistry of the hydroxylated centers in the two metabolites has not been clearly established. Biotransformation of the antihypertensive agent minoxidil (Loniten) yields the 4'-hydroxypiperidyl metabolite. In the dog, this product is a major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

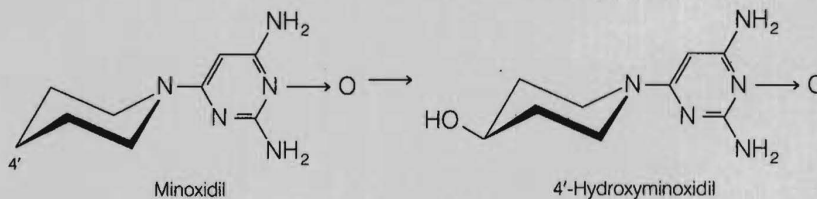
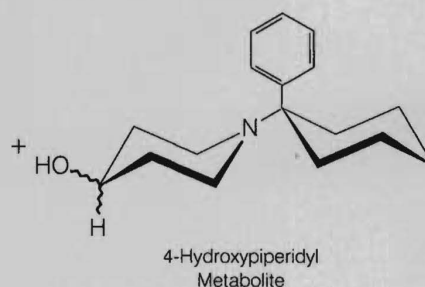
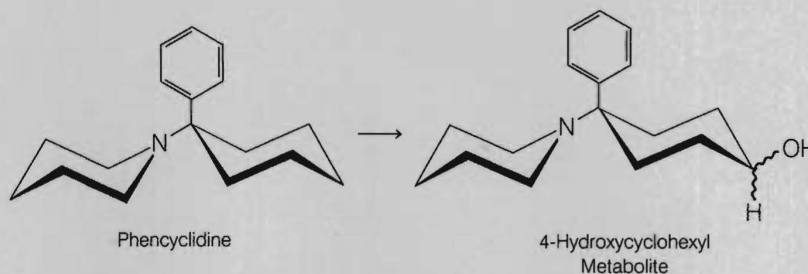
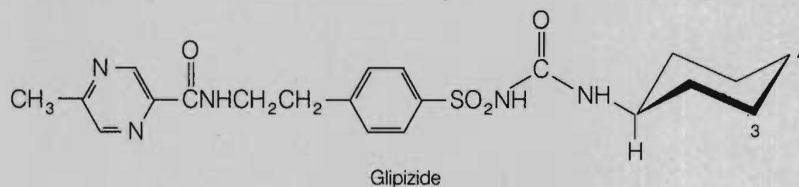
1. Hydroxylation of the α -carbon atom attached directly to the heteroatom (N, O, S). The resulting intermediate is often unstable and decomposes with the cleavage of the carbon-heteroatom bond:

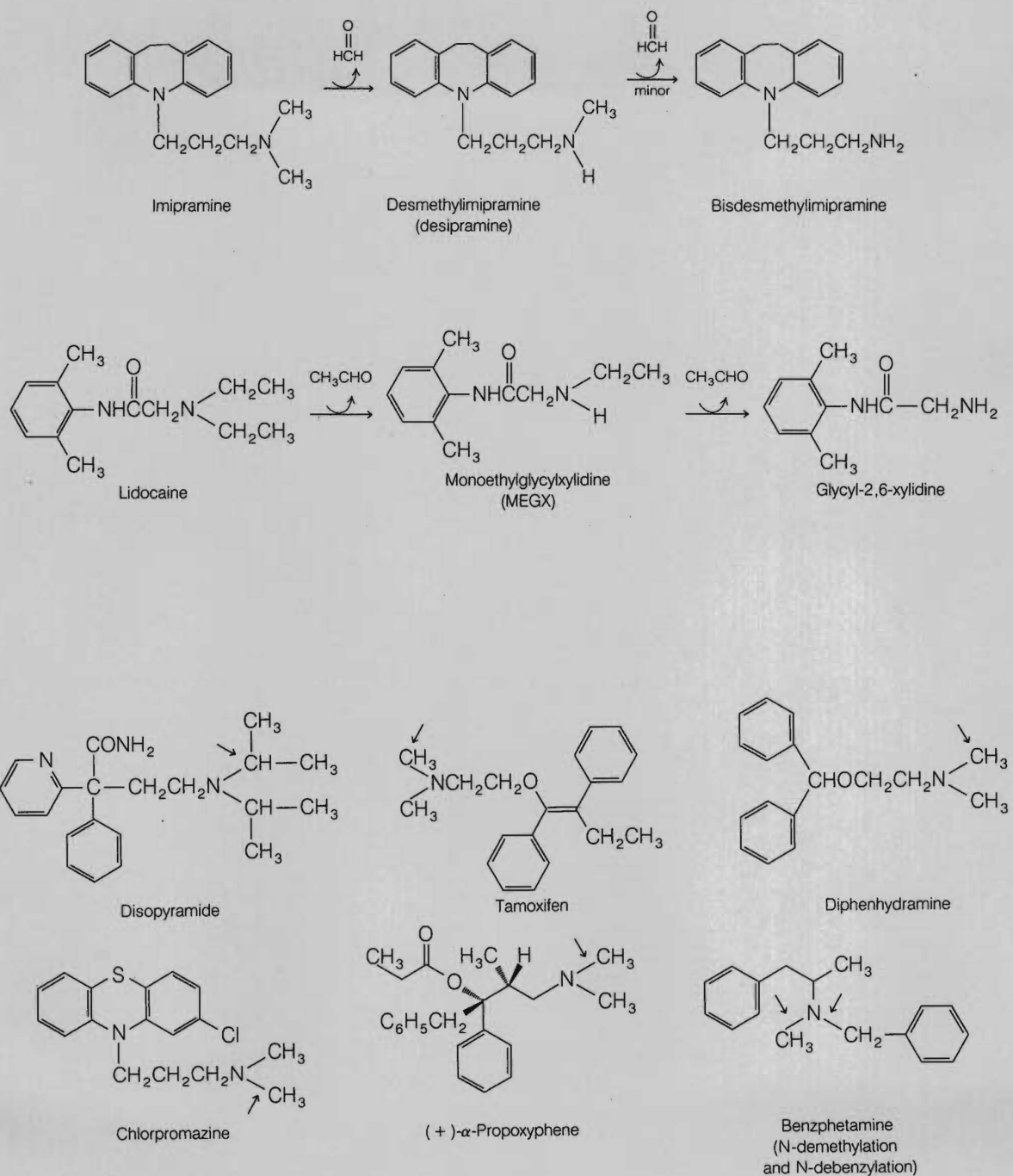


Oxidative N-, O-, and S-dealkylation as well as oxidative deamination reactions fall under this mechanistic pathway.

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-





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*-butylnor-

chlorocyclizine, 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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