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DRUG METABOLISM: REVIEW OF PRINCIPLES AND THE FATE OF ONE-RING PSYCHOTOMIMETICS

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Interest in the metabolic fate of compounds foreign to the body (xenobiotics) has intensified dramatically during the past decade. Research efforts are derived today from a variety of disciplines and any attempt to review the entire field is likely to require a "team of experts." Fortunately, a number of books that cover various aspects of drug metabolism have appeared recently. The most chemically oriented is the Testa and Jenner monograph (1976), which provides an excellent description of biotransformation processes with much fine molecular detail. The Chemical Society, London, publishes a good review series entitled "Foreign Compound Metabolism in Mammals" (Hathway, 1975). A bibliographic survey, "The Fate of Drugs in the Organism" (Hirtz, 1976), has recorded 9000 references (through about 1972) dealing with various aspects of drug metabolism. Two textbook-type publications (Goldstein *et al.*, 1974; La Du *et al.*, 1971) are mainly concerned with the fate and mechanism of action of small molecules. The more traditional textbooks in medicinal chemistry contain good chapters on drug metabolism (McMahon, 1970; Daniels and Jorgensen, 1977). Biologically oriented material will be found in the series "Concepts in Biochemical Pharmacology," particularly Part 2 (Brodie and Gillette, 1971) and Part 3 (Gillette and Mitchell, 1975). The publications of the proceedings of a number of symposia provide first-rate discussions of specific topics. Two symposium publications focus on *in vitro* aspects of microsomal oxidations (Estabrook *et al.*, 1973*a*; Gillette *et al.*, 1969). Applications of mass spectrometry techniques to problems in drug metabolism are compiled in two volumes (Frigerio and Castagnoli, 1974, 1976). Biological aspects of drug hydroxylation (Shugar, 1969), the metabo-

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lism of organic molecules containing nitrogen (Bridges *et al.*, 1972), and drug metabolism in man (Vessell, 1971) are additional topics of recent symposia.

Research publications and review articles on drug metabolism will be found in numerous journals. In recent years the following new journals in this area have appeared: *Drug Metabolism and Disposition, Chemico-Biological Interactions, Xenobiotica, European Journal of Drug Metabolism and Pharmacokinetics, Drug Metabolism Reviews,* and *Journal of Pharmacokinetics and Biopharmaceutics.* These journals join an already impressive list where drug metabolism articles appear. Some of the journals where drug metabolism articles are frequently published include the following: *Biochemical Pharmacology, Journal of Biological Chemistry, Science, Nature, Biochemistry Journal, Journal of Pharmacology and Experimental Therapeutics, Journal of Medicinal Chemistry, Molecular Pharmacology, Journal of Pharmaceutical Sciences, Journal of Pharmacy and Pharmacology, Life Sciences, European Journal of Pharmacology, Biochimica-Biophysica Acta, Pharmacology Reviews, Proceedings of the National Academy of Science, British Journal of Pharmacology, Experientia, Pharmacology, Annual Review of Pharmacology, Annals of the New York Academy of Sciences, Arzneimittel-Forschung.*

An important development in the area of foreign compound metabolism has been the recognition that the biotransformations of small molecules do not necessarily lead to metabolites that are less active than the parent compound. Hydroxylated metabolites, for example, of THC (Gill *et al.*, 1973), glutethimide (Aboul-Enein *et al.*, 1975), and diazepam (Schwartz and Postma, 1968), contribute to the pharmacological effects of the parent drugs. The anticancer agent cyclophosphamide must be metabolically activated by carbon hydroxylation before it can exert its therapeutic effects (Takamizawa *et al.*, 1975; Colvin *et al.*, 1973). The subject of active metabolites was recently reviewed by Garattini *et al.* (1975). In addition to the formation of pharmacologically active metabolites, many compounds are biotransformed to highly chemically reactive species that covalently bond to macromolecules, causing toxic reactions (Mitchell *et al.*, 1975; Gillette *et al.*, 1974; Gillette, 1974) including malignant transformations (Weisburger and Weisburger, 1973; Miller, 1970; Miller and Miller, 1966).

Thus the traditional view that biotransformation processes result in the "detoxification" of foreign substances must be modified to take into account the large body of knowledge relating to the formation of toxic metabolites. The present chapter, which is concerned with the metabolic fate of the one-ring psychotomimetics, will attempt to evaluate the significance of biotransformation processes with regard to the mechanisms of action of these compounds. Particular attention is given to the possible formation of chemically reactive metabolites that may contribute to the neurotoxicity of the parent drug. In order to facilitate this discussion, a brief description of the basic principles of biotransformation processes is presented, which is followed by a detailed discussion of the metabolism of amphetamine,

mescaline, and aryl-substituted 1-phenyl-2-aminopropanes. Chapter 9 provides a detailed description of the psychopharmacological properties of these compounds.

1. PRINCIPLES OF DRUG METABOLISM

Unlike many enzyme-catalyzed reactions, the enzyme systems responsible for the majority of foreign compound transformations are relatively nonspecific. In general, one of the basic requirements for good substrate properties is lipophilicity. Within a series of structurally related molecules, the more lipophilic molecules will tend to be more extensively metabolized (Hansch, 1972).

The relationship of lipophilicity to metabolic susceptibility is due at least in part to the lipoidal characteristics of the membranes that house the responsible enzyme systems. Although extrahepatic sites of drug metabolism are well documented (Dajani *et al.*, 1975; Estabrook *et al.*, 1973*b*; Testa and Jenner, 1976, pp. 419–454), the liver is the major organ of metabolism. Primarily through the elegant early structural work of Claude (1969) and later by Fouts (1971) among others and the pioneering metabolic studies by the NIH group (Brodie *et al.*, 1955, 1958), it was learned that the drug metabolizing lipoidal microsomal fraction isolated from liver homogenates in the 100,000*g* pellet was derived from the endoplasmic reticulum of the intact hepatocyte. In order to undergo metabolism by the enzymes embedded in the endoplasmic reticulum (or in the microsomes), a drug must partition from the aqueous cytosol (or incubation medium) into the lipoidal environment of the endoplasmic reticulum (microsomes). Although there are a number of important soluble enzymes that act on foreign compounds [e.g., carbonyl oxido-reductases (Bachur, 1976; Hutson, 1975*a*; McMahon, 1971; Gillette, 1971; Leibman, 1971) and hydrolytic enzymes (Testa and Jenner, 1976; Hutson, 1975*b*; La Du and Shady, 1971)], the majority of metabolic conversions is effected by the complex of membrane-bound enzyme systems located in the endoplasmic reticulum.

Extensive chemical, biochemical, and pharmacological investigations have focused on the characterization of the foreign compound metabolizing enzyme systems of the liver. Efforts to solubilize and purify these enzymes have been partially successful (Sato *et al.*, 1973; Cooper *et al.*, 1973; Fujita and Mannering, 1973; Bleecker *et al.*, 1973; Comai and Gaylor, 1973; Lu *et al.*, 1973) and one can anticipate that the next few years will see significant advances in the characterization of the enzymes and the molecular mechanisms involved in drug metabolism. In most of the *in vitro* studies reviewed below relatively crude liver preparations have been employed. Even so, a large body of information has accumulated. The discussion that follows focuses on those principles of drug metabolism that will help the reader to

better appreciate the events associated with the metabolism of highly lipid soluble drugs, which include all of the psychotomimetic agents to be considered in Section 2.

In general, biotransformation reactions may be considered under three headings: (1) oxidation–reduction reactions, (2) hydrolytic reactions, and (3) conjugation reactions. In terms of structural alterations that may be associated with the biological properties of psychotomimetics, the oxidative transformations reviewed below are of special interest.

Metabolic oxidations of foreign compounds are catalyzed primarily by the so-called mixed-function oxidase (or mono-oxygenase) enzyme complex of the liver endoplasmic reticulum (Coon *et al.*, 1973; Estabrook *et al.*, 1973*c*). Fundamentally, the oxidations follow the stoichiometry given by Eq. (1)

$$\text{R—H} + \text{NADPH} + \text{O}_2 + \text{H}^+ = \text{ROH} + \text{NADP}^+ + \text{H}_2\text{O} \qquad (1)$$

where R—H is the substrate and NADPH is the reduced form of nicotinamide adenine dinucleotide phosphate. The substrate undergoes a two-electron oxidation, while molecular oxygen suffers a four-electron reduction. Studies with $^{18}O_2$ (Mason, 1957) established that one atom of O_2 becomes attached to the substrate while the second atom is found in the water formed in the reaction—hence the name "mixed-function" oxidase. The mechanistic details whereby molecular oxygen becomes "activated" remain incompletely understood. The key macromolecule associated with the activated oxygen is a protoporphyrin IX iron-containing protein (similar to the oxygen-carrying blood pigment hemoglobin) known as cytochrome P_{450} (Omura and Sato, 1964).

A simplified depiction of the sequence of events thought to be associated with the cytochrome P_{450} electron transport system is given in Fig. 1. The

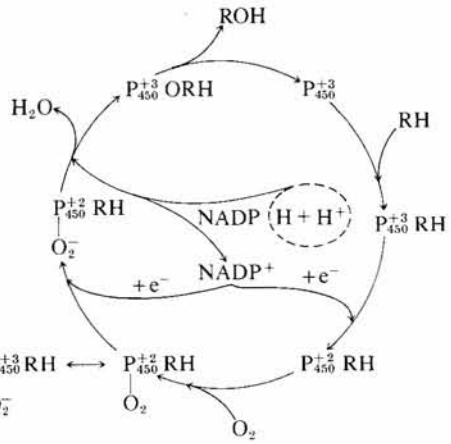


FIG. 1. Simplified depiction of the electron transport system associated with the cytochrome-P_{450}-catalyzed oxidation of foreign compounds.

sequence of events is initiated by the binding of drug, RH, to the oxidized (+3) form of P_{450} to give $P^{+3}_{450}RH$. A NADPH-dependent flavoprotein, NADPH-cytochrome P^{+3}_{450} reductase, transfers an electron to form $P^{+2}_{450}RH$, which then may bind a mole of O_2 to form a species that is depicted as $O_2^- P^{+3}_{450}RH$. A second electron, perhaps derived from the second reducing equivalent of NADPH, then leads to the formation of the oxidized drug ROH and a mole of water. As the details of this cycle become better defined it will be possible to predict more rationally the metabolic fate of foreign compounds and to appreciate more fully the consequences of the interactions of substrates (and metabolites) with the mixed-function oxidase system. These interactions can lead to enhanced enzyme activity (Estabrook *et al.*, 1973*d*; Gram *et al.*, 1967; Gelboin, 1971; Vesell *et al.*, 1976; Michalopoulos *et al.*, 1976; Gielen and Nebert, 1971), inhibition of enzyme activity (Estabrook *et al.*, 1973*e*; Mannering, 1971; Bobik *et al.*, 1975; Cooper *et al.*, 1954; Fouts and Brodie, 1955, 1956), and even destruction of the P_{450} system (De Matteis, 1973; Levin *et al.*, 1973; Rentsch and Johnston, 1976).

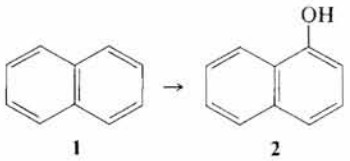
Particularly important with regard to understanding the mechanisms of drug metabolism is the molecular nature of the P_{450}-activated oxygen. A variety of chemical studies have attempted to model mixed-function oxidase reactions but with only marginal success (Ullrich and Staudinger, 1969, 1971; Hamilton, 1964; Brodie *et al.*, 1954; Groves and Van der Puy, 1974; Chang and Dolphin, 1976). Various oxidation states of oxygen including the hydroxyl radical $H\dot{O}$: (Locke and Mayer, 1974), a potential hydroxonium ion $H\dot{O}:^+$ (Jerina *et al.*, 1971), oxene $:\ddot{O}$ (Daly *et al.*, 1972), and superoxide radical anion $O_2^{\cdot -}$ (Moro-oka and Foote, 1976) have been proposed as species that may approximate P_{450}-activated oxygen. Since the P_{450} -bound oxygen is almost certainly ligated to the iron of the porphyrin molecule (Lipscomb and Gunsalus, 1973), model oxidations that are not dependent on an iron–oxygen complex must be viewed with caution.

Whatever the nature of the P_{450}-activated oxygen system, it is capable of carrying out a wide variety of oxidations on an essentially infinite number of lipid-soluble substrates. The compilation of reaction types that follows will provide the reader with some appreciation of the broad scope of biotransformations attributed to the cytochrome P_{450} mixed-function oxidase system.

1.1. Aromatic Hydroxylation

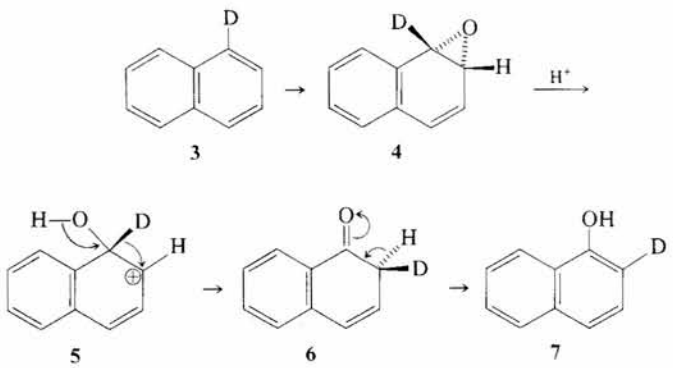
In a formal sense, this reaction leads to the substitution of an aromatic hydrogen atom with a hydroxyl group as illustrated in reaction (2) with the conversion of naphthalene (**1**) to α-naphthol (**2**). Perhaps more is known about the mechanism of this conversion than any other mixed-function oxidase-catalyzed reaction. Two important aspects of aromatic hydroxylation reactions are that molecular oxygen (O_2) is the source of the newly introduced phenolic oxygen atom (Mason, 1957) and that the reaction in most instances

proceeds with a migration to an adjacent carbon atom of the proton located at the carbon atom bearing the hydroxy group—the so-called NIH shift (Jerina and Daly, 1974; Boyd *et al.*, 1972; Kasperek and Bruice, 1972). The reaction pathway is depicted in reaction (3) with the deuterium(D)-labeled substrate naphthalene-1-*d*(**3**).



1 2 (2)

The first step in the overall conversion is the oxidation of **3** to the arene oxide **4** (Jerina *et al.*, 1970), which presumably *via* the protonated ring-opened species **5** undergoes the hydride (deuteride in the case of **5**) shift to the eneone **6**. The direction of ring opening in general will be determined by the stability of the resultant carbonium ion. Due to the greater C–D vs C–H bond energy (Wiberg, 1955), intermediate **6** preferentially loses a proton instead of a deuteron to yield the final product **7**.

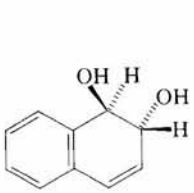


3 4 5 6 7 (3)

An appreciation of this pathway has had far-reaching significance in leading to an understanding of the molecular basis of polycyclic aromatic hydrocarbon toxicity and carcinogenicity (Daly *et al.*, 1972), which very likely are associated with covalent bonding of the chemically reactive (Harvey *et al.*, 1975; Keller and Heidelberger, 1976; Beland and Harvey, 1976) arene oxide (illustrated by **4**) to nucleic acids (Alexanderov *et al.*, 1976; Weinstein *et al.*, 1976; Grover and Sims, 1973). Arene oxide metabolites of benzo(a)pyrene (Grover *et al.*, 1972; Kinoshita *et al.*, 1973) and related carcinogenic aromatic hydrocarbons (Sims *et al.*, 1973; Grover *et al.*, 1971, 1974; Grover, 1974; Selkirk *et al.*, 1971) have been detected. The evidence supports the concept that these electron-deficient, highly chemically reactive species (sometimes classified as proximate carcinogens) react with nucleophilic functionalities of macromolecules to cause structural perturbations that are responsible for the

malignant transformations and cytotoxicity associated with the parent hydrocarbons (Miller and Miller, 1966; Heidelberger and Iype, 1967).

In addition to undergoing spontaneous rearrangement to phenolic products and reactions with macromolecules, arene oxides may be attacked by water, a reaction catalyzed by a microsomal epoxide hydrase (Oesch, 1973; Oesch *et al.*, 1974; Jerina *et al.*, 1970) to form a dihydrodiol. The *trans*-1,2-dihydrodiol **8**, for example, has been characterized as a metabolite of naphthalene (Oesch *et al.*, 1971; Holtzman *et al.*, 1967). A third reaction pathway available to arene oxides is conjugation with glutathione (Hutson, 1975*c*), which after dehydration and modification of the side chain leads to the mercapturic acid **9** (Jerina *et al.*, 1970; Boyland, 1962).



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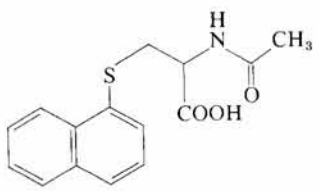

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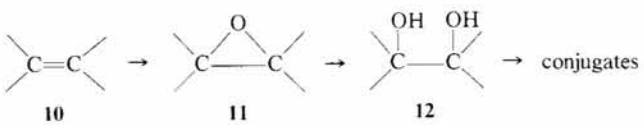
A wide variety of aromatic-containing drugs also has been shown to follow the arene oxide pathway (Horning *et al.*, 1976). The metabolic formation of such chemically reactive intermediates should prove of great interest in terms of the toxicology and pharmacology of clinically useful drugs.

1.2. Aliphatic Epoxidations

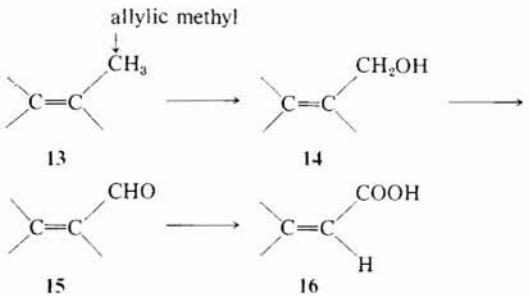
Somewhat related to arene oxide formation is the formation of epoxides (**11**) from olefins (**10**). This oxidation, which is illustrated in reaction (4), is responsible for an important step in the biosynthesis of cholesterol, namely, the conversion of squalene to squalene-1,2-epoxide. Although not a P_{450}-catalyzed reaction, this is a typical mixed-function oxidase system, which requires molecular oxygen and NADPH (Ono and Bloch, 1975). Epoxidations of drugs include carbamazepine (Frigerio *et al.*, 1972), protriptyline (Sisenwine *et al.*, 1970; Hucker *et al.*, 1974), cyproheptadine (Frigerio *et al.*, 1976), cyclobenzaprine (Belvedere *et al.*, 1975), tetrahydrocannabinol (Mechoulam *et al.*, 1972) and diethylstilbesterol (Metzler, 1976). Epoxides are often converted to 1,2-glycols **12** (Maynert *et al.*, 1970).



10 **11** **12** (4)

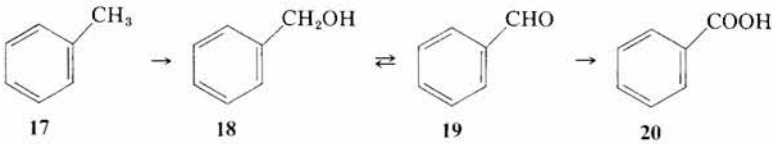
1.3. Allylic and Related Oxidations

A number of centrally active compounds contain allylic groups **13** that are susceptible to mixed-function oxidation to the corresponding allylic alcohols **14**. Pentazocine (Pittman, 1970; Pittman *et al.*, 1969), Δ^1-tetrahydrocannabinol (Mechoulam *et al.*, 1976), and hexobarbital (Bush and Weller, 1972; Kupfer and Rosenfeld, 1973) are examples of CNS-active drugs that undergo allylic oxidation. Reaction (5) illustrates the oxidation of an allylic methyl group together with the possible subsequent oxidations of the carbinol **14** to the corresponding aldehyde **15** and carboxylic acid **16**. Although microsomal preparations can oxidize some alcohols (Orme-Johnson and Ziegler, 1965) it is generally believed that *in vivo* oxidations of alcohols are achieved mainly by the soluble enzyme alcohol dehydrogenase (Theorell, 1967). Similarly, aldehydes are converted to the polar (ionizable) carboxylic acids by a soluble aldehyde oxidase (Rajagopalan *et al.*, 1962) or aldehyde dehydrogenase (Racker, 1949).

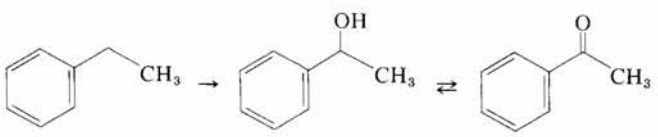


13 14 15 16 (5)

In an analogous fashion [reaction (6)], methyl groups attached to an aromatic moiety, e.g., **17**, may undergo a sequence of three two-electron oxidations to form the corresponding alcohols **18,** aldehydes **19**, and carboxylic acids **20** (Parke, 1968). The process is often referred to as benzylic oxidation. In the event that the benzylic carbon atom is substituted, such as in ethylbenzene (**21**), the compound undergoes a four-electron oxidation [reaction (7)] *via* the carbinol **22** to the ketone **23** (McMahon *et al.*, 1969*b*; El



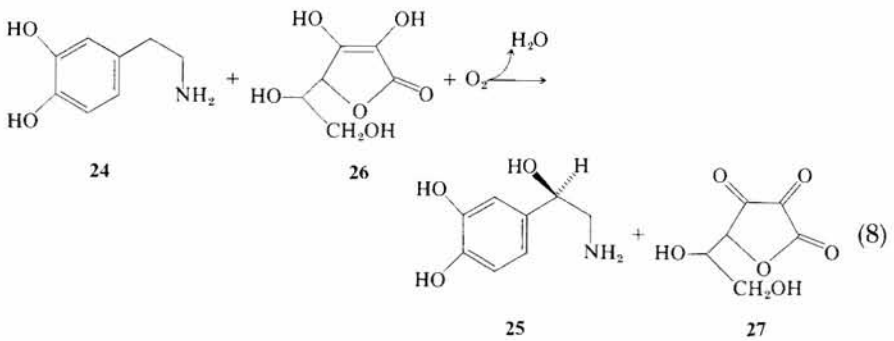
17 18 19 20 (6)



21 22 23 (7)

Masry *et al.*, 1956; Smith *et al.*, 1954). Further oxidation of the carbonyl group of **23** would involve a high-energy process leading to carbon–carbon bond cleavage, a conversion that apparently occurs infrequently as a mixed-function oxidase process (see the section on amphetamine metabolism for an important exception to this generalization).

A special case of benzylic hydroxylation is the conversion of dopamine (**24**) to norepinephrine (**25**) by the membrane-bound enzyme dopamine-β-hydroxylase (Kaufman and Friedman, 1965). This conversion is not a P_{450}-catalyzed reaction but belongs to the general category of mixed-function oxidations. In this case ascorbic acid (**26**) serves as the cofactor that provides the additional two electrons for the overall four-electron reduction of oxygen. The net reaction is shown in (8) with ascorbic acid undergoing conversion to dehydroascorbic acid (**27**) in a fashion analogous to the conversion of NADPH to $NADP^+$ in the P_{450}-catalyzed reactions. One of the potentially important metabolic pathways of amphetamine involves its oxidation first to *p*-hydroxyamphetamine and then, *via* dopamine-β-hydroxylase, to *p*-hydroxynorephedrine (see Section 2).

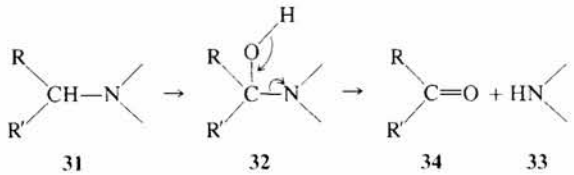


A final example of hydroxylation of carbon attached to an sp^2 hybridized carbon is the conversion of amides (Kiese and Lenk, 1973) and cyclic amides (lactams) such as glutethimide (Keberle *et al.*, 1962, 1963) and diazepam (Sadèe *et al.*, 1971) to carbinolamides. In some instances, cyclic amines are converted to lactams, which subsequently undergo α-hydroxylation. For example, nicotine (**28**) is first oxidized to the pyrrolidinone derivative cotinine (**29**), which is then hydroxylated to the carbinolamide *trans*-3-hydroxycotinine (Dagne and Castagnoli, 1972).

1.4. Oxidations of Carbon Attached to Heteroatoms

Cytochrome P_{450}-catalyzed oxidations at carbon atoms attached to nitrogen and oxygen include the important oxidative N- and O-dealkylations. The generally accepted pathway for N-dealkylation is illustrated in reaction (9),

which shows the initial oxidation product of amine **31** to be the carbinolamine **32**. Except in rare instances (Gorrod, 1976; Sadèe *et al.*, 1971) the HO–C–N moiety is unstable and spontaneously fragments to give the products, the dealkylated amine **33** and an aldehyde or ketone **34**. A continuing mechanistic controversy concerns the initial site of attack by the P_{450}-activated oxygen (McMahon *et al.*, 1969*a*; Faulkner and Smith, 1972; Bickel, 1969) with some authors debating the role of an N–O intermediate (Willi and Bickel, 1973; Beckett and Belanger, 1975*a*; Gorrod *et al.*, 1975; Beckett, 1976).



31 32 34 33 (9)

When **31** is a primary amine, then the conversion is described as oxidative deamination. Monoamine oxidase (MAO) catalyzes the oxidative deamination of a variety of monoamines including the biogenic amines (Tipton *et al.*, 1976). This important enzyme is associated with the mitochondria and not the endoplasmic reticulum.

The oxidation of cyclic amines such as the conversion of nicotine (**28**) to cotinine (**29**) shown in Fig. 2 probably proceeds by an analogous pathway *via* the intermediate carbinolamine **35**, which is then further oxidized by a soluble oxidase to the lactam cotinine (McKennis *et al.*, 1964). Details concerning the actual species undergoing the second two-electron oxidation, i.e., the carbinolamine **35** or its tautomeric ring open aminoaldehyde **36**, are not known. Recent studies have revealed that compound **35** is in equilibrium with the iminium ion **37**, which can be trapped with cyanide ion to form the α-cyanoamine **38** (Murphy, 1973). Similarly, microsomal N-demethylation [a specific example of the conversion shown in reaction (9)] of nicotine to nornicotine (**42**) in the presence of cyanide ion has been shown to lead to *N*-cyanomethylnornicotine (**41**) via the methyleniminium intermediate **40**. Compound **40** presumably is formed by ionization of the metabolically formed carbinolamine **39** (Nguyen *et al.*, 1976). Evidence for oxidative metabolic attack at C-5 of cotinine to form 5-hydroxycotinine (**43**), which is in equilibrium with the ketoamide **44**, has also been reported (McKennis *et al.*, 1962). Finally, norcotinine (**45**) has been identified as a nicotine and cotinine metabolite (Turner, 1969). Reactions summarized in Fig. 2 describe the important carbon oxidative pathways of nicotine and have been reviewed to illustrate the scope of metabolic transformations involving carbon–nitrogen bonds. The significance of these pathways with regard to the pharmacological and toxicological properties of nicotine is not known. The formation of electron-deficient, chemically reactive species such as the iminium ions **37** and **40** opens the possibility of covalent interactions with macromolecules.

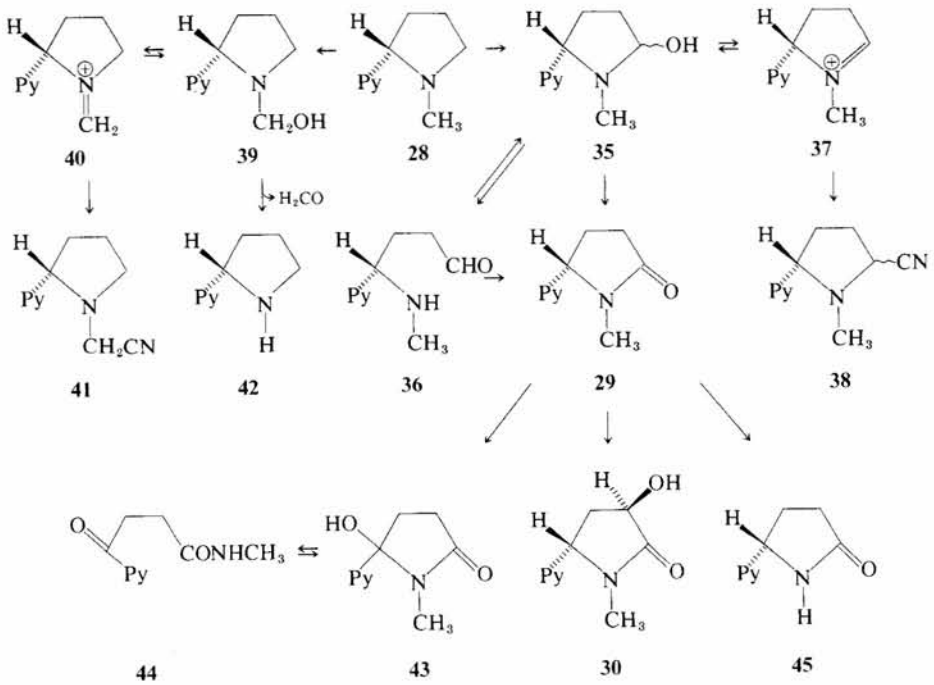


FIG. 2. Oxidative metabolism of nicotine (**28**) illustrating various types of oxidative attack on carbon attached to nitrogen (**28** → **39**, **28** → **35**, and **29** → **43**), the formation and trapping of iminium species (**37** and **40**), and oxidation of carbon α to a lactam carbonyl (**29** → **30**).

Further studies will be required to evaluate the biological significance of transient intermediates involved in aliphatic amine metabolism.

Oxidative O- and S-dealkylation are additional mixed-function oxidase transformations involving attack at carbon followed by cleavage of the heteroatom–carbon bond. The process is illustrated by oxidative O-demethylation of an aryl methyl ether (**46**) in reaction (10). The conversion presumably proceeds via the hemiacetal **47**, which analogous to the carbinolamine **32** spontaneously fragments to yield the phenol **48** and formaldehyde.

$$\underset{\mathbf{46}}{ArOCH_3} \rightarrow \underset{\mathbf{47}}{ArO{-}CH_2{-}O{-}H} \rightarrow \underset{\mathbf{48}}{ArOH} + H{-}\overset{\overset{O}{\|}}{C}{-}H \qquad (10)$$

O-Demethylation of foreign compounds is not the reverse of the catecholamine-*O*-methyltransferase (COMT) catalyzed transmethylation pathway (Kopin, 1972). A limited number of mechanistic investigations concerning structure–activity relationships (Schmidt *et al.*, 1973; Beckett and Morton, 1966; McMahon, 1966) and isotope effects (Foster *et al.*, 1974; Mitoma *et al.*, 1967) have been published for O-demethylation. This conversion is particu-

larly important in the metabolism of psychotomimetic amines since many known psychotogens bear aryl O-methyl groups. Some of the potential pharmacological consequences of oxidative O-demethylation will be considered in Section 2.

1.5. Oxidations and Reductions of Nitrogen-Containing Moieties

Extensive studies on the metabolic oxidations of aromatic amines and amides and a variety of other nitrogen functionalities bonded to an unsaturated group link these transformations to the cytotoxic and carcinogenic properties of the parent compounds (Weisburger and Weisburger, 1973; Miller and Miller, 1969; Bridges *et al.*, 1972; Shugar, 1969). For example, carcinogens such as 2-aminonaphthalene (Radomski and Brill, 1970), related aromatic amines (Radomski and Brill, 1971), and 2-acetylaminofluorene (Miller *et al.*, 1964; Thorgeirsson *et al.*, 1973) and related polycylic N-arylacetamides (Fries *et al.*, 1973) appear to cause malignant transformations *via* their metabolically formed N-oxidation products. The hepatotoxicity (Jollow *et al.*, 1974*a*; Mitchell *et al.*, 1973*a*,*b*) and nephrotoxicity (Calder *et al.*, 1973) of substituted acetanilides similarly are associated with metabolic N-oxidation. The covalent binding of these toxic substances to macromolecules has been shown to depend on metabolic activation (Davis *et al.*, 1976; Jollow *et al.*, 1973; Potter *et al.*, 1973, 1974). Although the exact details of the molecular interactions of metabolically formed aromatic N-hydroxylamines remain obscure, it seems reasonable to invoke the formation of an ArN–OR species in which OR is a good leaving group such as an O-sulfate or O-acetyl derivative (Miller, 1970; Bartsch *et al.*, 1972, Lhoëst *et al.*, 1976; King and Phillips, 1972). Nucleophilic moieties present on macromolecules may then form covalent bonds by displacement of the OR group of the activated hydroxylamine causing structural alterations and cellular dysfunction. Figure 3 summarizes this postulated pathway with the secondary aromatic amine **49**.

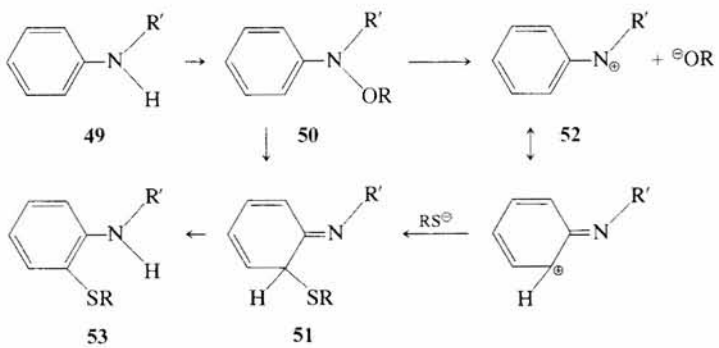
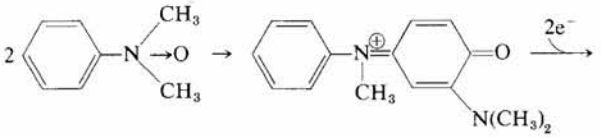


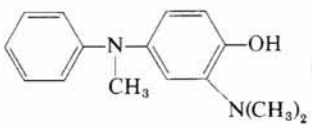
FIG. 3. Metabolic N-oxidation of aromatic amines leading to reactive intermediates that have been postulated to be responsible for cytotoxicity and carcinogenicity.

N-Oxidation followed by esterification generates the reactive intermediate **50**, which then either via heterolytic ionization to the nitrenium ion **52** followed by nucleophilic attack by RSH or by a concerted nucleophilic attack on **50** forms intermediate **51**. Intermediate **51** will then rearrange to the stable adduct **53**.

Methemoglobinemia caused by aromatic amines is also thought to result from an N-oxidation pathway (Kiese, 1966; Vehleke, 1973; Eyer *et al.*, 1974). Again, precise molecular details are incomplete although the responsible metabolic events may be quite complex. For example, Kisese and co-worker (Kiese and Renna, 1976) have examined the pathway involved in methemoglobin formation by *N,N*-dimethylaniline-*N*-oxide (**54**). Apparently compound **54** is converted to a purple dye, compound **55**, which oxidizes hemoglobin by accepting two electrons to form the leuko compound **56** as shown in reaction (11).

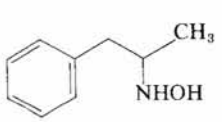


54 **55**



56 (11)

More recently, the potential pharmacological and toxicological significance of aliphatic amine N-oxidation has received attention (Bickel and Gigon, 1971; Gorrod, 1973*a*; Gorrod and Jenner, 1975; Fuller *et al.*, 1974). While aliphatic amine metabolic N-oxidation is well established (Beckett and Gibson, 1975; Caldwell *et al.*, 1975; Beckett and Shenoy, 1973; Beckett *et al.*, 1973*a*; Beckett and Belanger, 1974*b,c*, 1975*b*; Israili *et al.*, 1973) the subsequent fate of the chemically unstable hydroxylamines and the importance of these compounds in metabolic oxidative N-dealkylation and deamination are not thoroughly understood (Tyler *et al.*, 1973; Beckett, 1974; Beckett and Belanger, 1974*a,b*, 1976; Beckett *et al.*, 1973*a,b*). Of particular interest is the recently published evidence that N-hydroxy compounds such as *N*-hydroxyamphetamine (**57**) form strong complexes with cytochrome P_{450}



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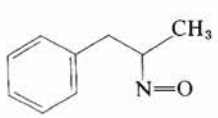

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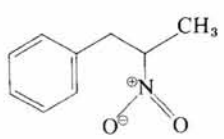


58a

(Franklin, 1974*a,b,c*; James and Franklin, 1975). The "difference" electronic spectrum of cytochrome-P_{450}–*N*-hydroxyamphetamine is shown in Fig. 4a. This difference or binding spectrum is obtained by plotting the difference in absorptivities of the reference cell containing all components of the P_{450} system against the sample cell, which contains the "substrate" as well. When NADPH (the required cofactor for the mixed-function oxidase system) is added to both reference cell and sample cell, a new chromophor absorbing at 455 nm (Fig. 4b) is generated, which is due to the interaction of the presumably oxidized N-hydroxy compound and cytochrome P_{450}. The fact that mixed-function oxidase capability is lost with the formation of the 455-nm complex suggests a chemical modification of one of the essential P_{450} ligands (James and Franklin, 1975). The details of this complexation remain unclear, although one author has speculated that the hydroxylamine may be converted to a nitroso species **58**, which theoretically could react with a sulfhydryl group present at the P_{450} active site (Mansuy *et al.*, 1976). Covalent modification of P_{450} could account for the observed spectral properties and loss of enzymatic activity. The 455-nm complex also forms with the parent primary amine although the relative rates of formation suggest that the N-hydroxy compound is an obligatory intermediate. Further characterization of the 455-nm absorbing complex should provide interesting structural and mechanistic information on the role of metabolic oxidations of hydroxylamines.

Amine oxidative metabolism also may involve non-P_{450} enzymes. Ziegler and co-workers (Gold and Ziegler, 1973; Ziegler *et al.*, 1973; Ziegler and Mitchell, 1972) have demonstrated aromatic N-hydroxylase activity from preparations isolated from liver microsomal fractions. Although it does not utilize cytochrome P_{450}, this microsomal N-oxidase system appears to be a typical mixed-function oxidase process requiring molecular oxygen and NADPH as the second two-electron donor.

One of the exciting possibilities concerning the involvement of a non-P_{450} metabolizing system is that tissues with low P_{450} content may be capable of transforming xenobiotics. Metabolic activation of parent amines by enzymes present in the brain conceivably could utilize non-P_{450} enzymes such as the *N*-oxidase system characterized by Ziegler in the liver.

A final comment on the metabolism of nitrogen-containing compounds concerns the reductive transformations of systems such as the nitroso, azo, and nitro groups (Testa and Jenner, 1976, pp. 123–131; Gillette, 1971). A number of toxic nitroaryl compounds are known to undergo metabolic reduction, again by enzymes systems mainly localized in the endoplasmic reticulum of the liver. Several reports document that reduction of these systems is responsible for the formation of carcinogenic metabolites (Wang *et al.*, 1975; Poirier and Weisburger, 1974). It is quite likely that the same species can be formed metabolically either by oxidation of the amine or by reduction of the corresponding nitro compound. A particularly well-documented example of the metabolic reduction of a carcinogenic agent is that of

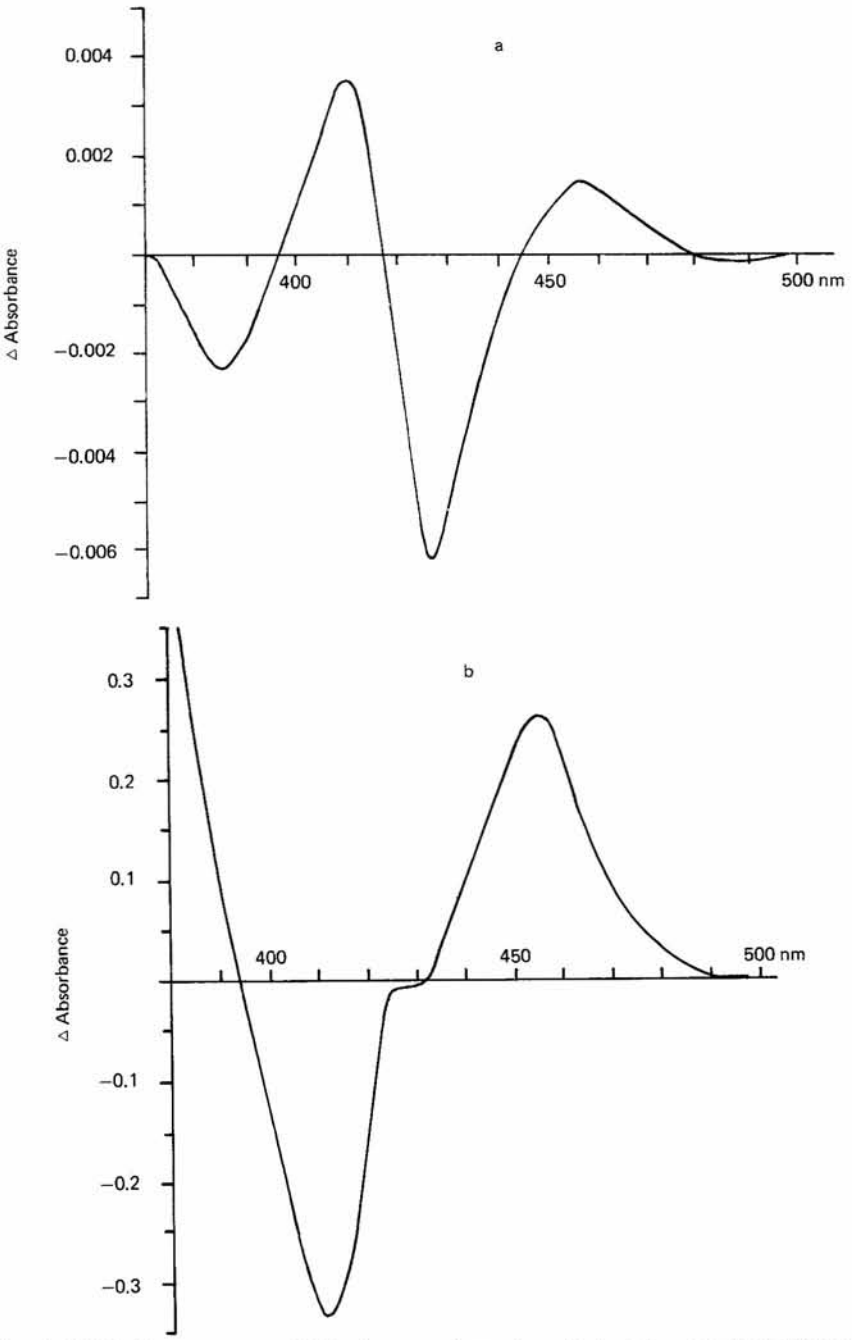
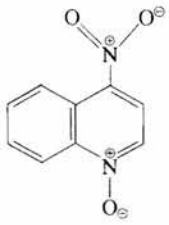


FIG. 4. (a) Binding spectrum of *N*-hydroxyamphetamine obtained by recording differences in absorptivity of a sample cell containing microsomal preparation and *N*-hydroxyamphetamine, while reference cell contains microsomal preparation only. (b) Same as (a) only NADPH has been added to both sample cell and reference cell.

4-nitroquinoline-*N*-oxide (**59**). Apparently the 4-nitro group is reduced in the liver to the 4-hydroxyamino compound **60**, which after loss of $OH^{\ominus}$ then serves as an electron-deficient species that may undergo nucleophilic attack by DNA and other biopolymers, eventually leading to malignant transformations (Sugimura *et al.*, 1966).



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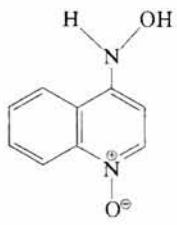
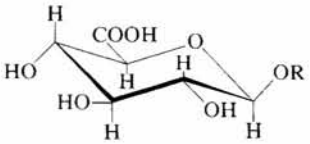


60

In many of the above discussions, attention has been focused on the "metabolic activation" of foreign compounds. Obviously, a majority of the metabolic transformations achieved by the body are designed to "detoxify" foreign substances. A major route by which the body eliminates foreign compounds is via excretion in the urine. The kidney in general can readily eliminate polar compounds, but many of the substances that enter the body are relatively nonpolar. Hence, mixed-function oxidase enzymes functionalize these substances by introducing in one way or another polar groups. Particularly important in terms of detoxification pathways is the so-called second phase of drug metabolism, namely, conjugation reactions (Testa and Jenner, 1976, pp. 312–328; Dutton, 1971; Roy, 1971; Weber, 1971; Axelrod, 1971; Hutson, 1975*c*). Once a nonpolar molecule becomes "functionalized" by the various oxidative, reductive, or hydrolytic transformations, then these polar groups, such as hydroxy, amino, or carboxy, undergo conjugation reactions to form products that are in general highly polar and readily eliminated by the kidney. The major conjugates formed in mammalian systems are glucuronides, sulfates, and various peptides; these are illustrated by the general formulas **61**, **62**, and **63**, respectively. In general conjugates are considerably more polar than the parent metabolites and consequently are more readily excreted. The role of glutathione (**64**) in detoxification pathways may be particularly important. Chemically reactive species including carcinogenic arene oxides may be "trapped" by glutathione to form highly polar molecules, such as compound **65**. As discussed earlier, the glutathione adducts undergo further transformations and eventually are excreted as "mercapturic acids," such as **66** (Boyland, 1971). Recent studies (Mitchell *et al.*, 1975) have shown that depletion of liver glutathione increases the susceptibility of animals to the toxicity of compounds such as bromobenzene (Jollow *et al.*, 1974*b*) and acetaminophen (Mitchell *et al.*, 1973*b*) emphasizing the importance of conjugation reactions in the detoxification of foreign and perhaps endogenous toxins.



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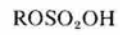

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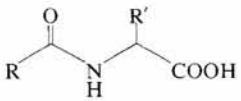

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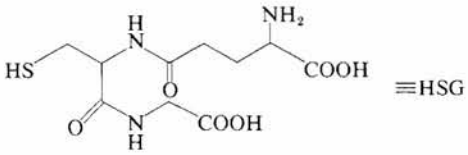

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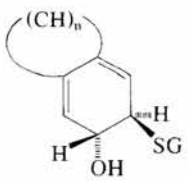

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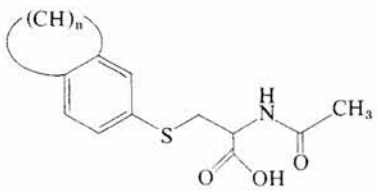

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2. METABOLISM OF ONE-RING PSYCHOTOMIMETICS

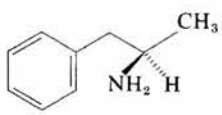
This section will attempt to review the relevant literature concerning the metabolic fate of amphetamine, mescaline, and certain ring-substituted 1-phenyl-2-aminopropanes. Particular attention will be given to primary oxidative metabolic events (as opposed to conjugative pathways) since oxidative biotransformations are more likely to reveal information of value with regard to the mode of action of these drugs. Little or no consideration is given to the clinical, pharmacological, toxicological, and pharmacokinetic aspects of psychotomimetics, these areas being beyond the scope of this chapter. The discussion is limited to the one-ring psychotomimetics. The following citations may prove useful to readers interested in other well-known psychotomimetic drugs. An excellent review on the chemistry and biochemistry (including metabolism) of cannabis recently appeared (Mechoulam *et al.*, 1976). A recent monograph on lysergic acid diethylamide (LSD) contains a brief chapter on its metabolism (Sankar, 1975). In addition to the fairly well-established aromatic oxidation pathway (Freter *et al.*, 1957), metabolic N-dealkylation of LSD has also been reported (Niwaguchi *et al.*, 1974*a,b*). *N,N*-Dimethyltryptamine is reported to undergo metabolic hydroxylation and N-

demethylation (Szara and Axelrod, 1959). Finally, although not itself a psychotomimetic, tryptamine may be metabolized in the brain to N-methylated compounds with psychotomimetic activity (Saavedra and Axelrod, 1972). The somewhat outdated but still interesting article by Giarman and Freedman (1965) on the biochemical aspects of psychotomimetic drugs also should be consulted.

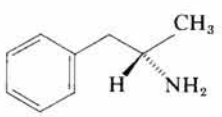
2.1. Amphetamine (Benzeneethaneamine, α-Methyl)*

Of the several drugs to be considered in this section, the metabolic fate of amphetamine has been the most extensively investigated. This drug differs from the other compounds to be discussed in this section since its pharmacological properties are more those of a CNS stimulant than a psychotomimetic (Haefely *et al.*, 1976; Innes and Nickerson, 1975; Knoll, 1970). Nevertheless, long-term abuse of amphetamine leads to a syndrome that at times is difficult to distinguish clinically from psychotic disorders (Connell, 1958; Ellinwood, 1971; Griffith *et al.*, 1970; Jonsson and Gunne, 1970; Davis and Janowsky, 1973). A summary of the current views regarding amphetamine metabolism will prove instructive in terms of evaluating the significance of metabolite formation with regard to the pharmacological actions of this drug and also in terms of contrasting the extensive body of knowledge available on amphetamine with the information available on the metabolic fate of the less well-studied but structurally related psychotomimetic agents.

Structurally amphetamine (**67**) is a relatively simple organic molecule, which bears a single chiral (asymmetric) center. The absolute configuration has been established as R(−) and S(+), structures **67a** and **67b**, respectively.



67a



67b

The pharmacological properties of amphetamine are sensitive to the configuration about the asymmetric side chain with the (S)-enantiomer in general possessing the greater CNS stimulant activity (Alles, 1939; Segal, 1975; Taylor and Snyder, 1970; Holmes and Rutledge, 1976). Some evidence has been published that suggests that the (R)-enantiomer may possess psychotomimetic properties (Angrist and Gershon, 1971; Angrist *et al.*, 1971). This issue is of some interest since the (R)-enantiomers of a number of related psychotomimetic compounds have been shown to be more active than their

* The currently used *Chemical Abstracts* nomenclature for key compounds in this section will be included to aid readers in literature searches.

(S)-antipodes (Shulgin, 1973; Benington *et al.*, 1973). It should be noted that the absolute configuration of LSD-25 at the chiral center corresponding to that of amphetamine is also R (Leemann and Fabbri, 1959).

According to the various oxidative pathways discussed in Section 1, one might predict *a priori* that amphetamine would undergo aromatic hydroxylation to *p*-hydroxyamphetamine (**68**), benzylic hydroxylation to norephedrine (**69**), oxidative deamination to phenyl-2-propanone (**70**), and N-oxidation to *N*-hydroxyamphetamine (**57**). All of these pathways are well documented. In addition to these metabolites, *p*-hydroxynorephedrine (**71**), phenyl-2-propanone oxime (**72**), 1-phenyl-2-propanol (**73**), benzoic acid (**74**), and perhaps 1-phenyl-2-nitropropane (**75**) as well as conjugates of some of these compounds have been well characterized as *in vivo* and/or *in vitro* metabolites of amphetamine. These pathways, which have been discussed at length in a number of articles (Smith and Dring, 1970; Dring and Caldwell, 1973; Dring *et al.*, 1966, 1970; Gorrod, 1973*a*,*b*; Williams *et al.*, 1973), are summarized in Fig. 5. The discussion that follows will review some of the more important findings concerning these pathways with particular regard to stereochemical parameters, species variations, and mechanistic considerations. Readers interested in methods of analysis (Keller and Ellenbogen, 1952; Beckett and Rowland, 1964, 1965; Beckett and Tucker, 1966), drug interactions (Lewander and Jonssan, 1973; Lal *et al.*, 1970; Consolo *et al.*, 1967; Creaven *et al.*, 1970), distribution (Jori and Caccia, 1974; Fuller and Hines, 1967; Cho *et al.*, 1975*a*) and the pharmacokinetics of amphetamine and metabolites (Groppetti and Costa, 1969; Beckett *et al.*, 1969; Beckett and Rowland, 1965; Vree *et al.*, 1972; Rowland and Beckett, 1966) should consult the cited references.

In one of the classical studies on drug metabolism Axelrod (1955)

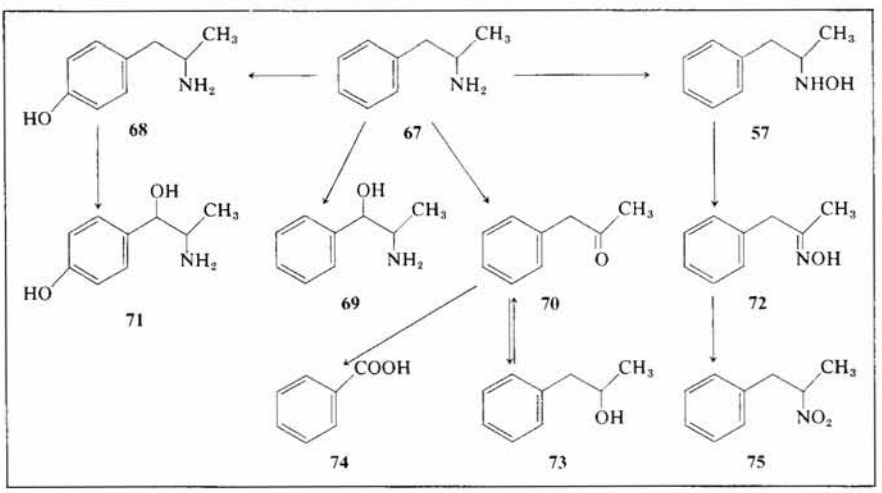


FIG. 5. Metabolic pathways of amphetamine (**67**) exclusive of conjugate formation.

examined the metabolic fate of amphetamine in liver preparations of the rabbit. In a series of elegant experiments, he was able to establish that rabbit liver microsomes in the presence of NADPH, O_2, and a NADPH-generating system convert (R)-amphetamine (**67a**) to phenyl-2-propanone (**70**). In an attempt to rationalize the absence of deaminating activity of rat microsomal preparations, Axelrod coincubated rat and rabbit microsomes with amphetamine and observed a marked inhibition of enzyme activity. When the rat microsomes were preheated (2 min, 100°) an *increase* in enzyme activity was observed. Apparently heat-labile inhibiting and heat-stable stimulating factors were influencing the course of the deamination of (R)-amphetamine. A comparison of the rates of deamination of (R)- vs (S)-amphetamine showed a marked stereoselectivity for the (R)-enantiomer. More recently Hewick and Fouts (1970) reported an analogous stereoselective preference of the rabbit microsomal system (obtained from phenobarbital pretreated animals). Of interest in this regard was the higher affinity of (S)-amphetamine for microsomal P_{450} (as measured by the magnitude of the binding spectra of the two enantiomers).

Studies on the *in vitro* metabolism of amphetamine by rabbit liver preparations have been concerned with possible intermediates formed in the deamination reaction. The classical view held for this biotransformation (Brodie *et al.*, 1958) involves α-carbon hydroxylation to the carbinolamine **76** (analogous to the general structure **32**, p. 344), which spontaneously cleaves to phenyl-2-propanone (**70**) and ammonia. Since mixed-function oxidation reactions in general are known to proceed with the incorporation of molecular oxygen (McMahon *et al.*, 1969*a*,*b*; Mason *et al.*, 1955; Holtzman *et al.*, 1967; Kaufman *et al.*, 1967; Sadèe *et al.*, 1971), the carbinolamine oxygen and therefore the phenyl-2-propanone oxygen should be enriched with ^{18}O if $^{18}O_2$ were employed in the incubation (Fig. 6).

This pathway was challenged by the report (Hucker *et al.*, 1973) that rabbit liver microsomes convert amphetamine to phenyl-2-propanone oxime (**72**). The oxime could result from oxidation of the hydroxylamine or from dehydration of the carbinolamine **76** to the imine **77** followed by oxidation to **72**. Should the hydrolysis of phenyl-2-propanone oxime be an obligatory step in the overall oxidative deamination of amphetamine, then the oxygen atom of phenyl-2-propanone would be derived from water (Fig. 6). Parli *et al.* (1971, 1973) investigated this question by means of $^{18}O_2$ and were able to demonstrate that the ketone **70** isolated was enriched to the extent of 25–31% of the theoretical ^{18}O, thus precluding a hydrolytic pathway as the exclusive route to phenyl-2-propanone. Beckett and Al-Sarraj (1972) have stated that *N*-hydroxyamphetamine is not metabolized by microsomal enzymes. Incubation of oxime **72** with rat liver preparations leads to 1-phenyl-2-nitropropane (**75**) as the major metabolite (36.9%) although phenyl-2-propanone (9.4%) was also identified (Coutts *et al.*, 1976*a*). The situation is complicated by the instability of *N*-hydroxyamphetamine (**57**), which will undergo spontaneous oxidation to the oxime (Beckett and Al-Sarraj, 1973).

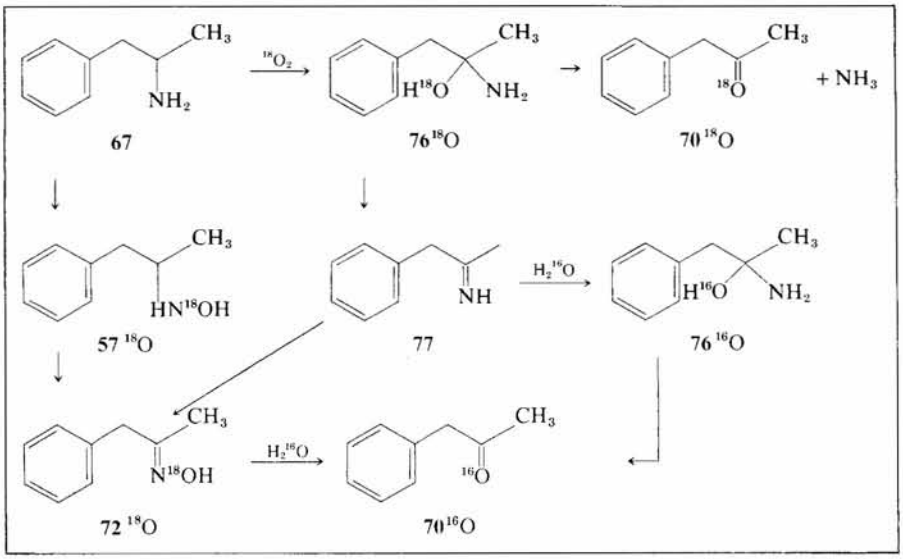
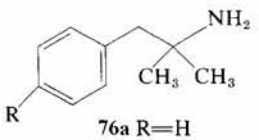


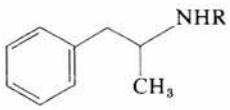
FIG. 6. Postulated intermediates and oxygen-labeling patterns in the deamination of amphetamine in the presence of $^{18}O_2$ and $H_2{}^{16}O$.

In an attempt to characterize the stereochemical parameters of amphetamine metabolism, Gal *et al.* (1976) working under carefully controlled conditions showed that rabbit liver preparations converted racemic amphetamine and the individual enantiomers to *N*-hydroxyamphetamine (**57**), phenyl-2-propanone (**70**), and 1-phenyl-2-propanol (**73**) in varying amounts depending on the stereochemical makeup of the amphetamine substrate. Oxime formation from (R)-amphetamine was reported to be significant only after one hour. In view of these results a likely explanation for the incorporation of the ^{16}O derived from water in phenyl-2-propanone is via hydrolysis of the imine **77** that could form by dehydration of the carbinolamine **76** or from some reactive N-oxidation species (Beckett and Belanger, 1975*a*). Whatever the final outcome of this controversy, the importance of metabolic N-oxidation of l-phenyl-2-aminopropanes is now well established. Examples in addition to amphetamine include phentermine (**76a**) (Cho *et al.*, 1972; Beckett and Belanger, 1974*a,b,c*), chlorphentermine (**76b**) (Caldwell *et al.*, 1975), 1-phenyl-2-alkylaminopropanes (**77**, R = methyl, ethyl, propyl, etc.) (Beckett *et al.*, 1974*a*; Coutts *et al.*, 1976*b*), norephedrine (**69**) (Beckett *et al.*, 1974*b*), and β,β-difluoroamphetamine (**78**) (Fuller *et al.*, 1973). In all cases, N-oxidation proved to be a singificant *in vitro* metabolic pathway leading to a variety of N-oxidation products (hydroxylamines, nitrones, oximes, amine-N-oxides). Thus, although N-oxidation may not be involved in the formation of oxidative deamination products in this series, it is clear that this is an important pathway for aliphatic as well as aromatic nitrogen functionalities.

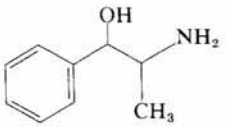
The possible significance of the 455-nm-absorbing complex formed between substrate and cytochrome P_{450} (see Section 1) and amphetamine



76a R=H
76b R=Cl



77 R=CH_3, CH_2CH_3, $CH(CH_3)_2$



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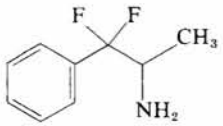


78

metabolism should be considered at this time. The rat normally does not extensively deaminate amphetamine (Axelrod, 1955; Dring *et al.*, 1970; Ellison *et al.*, 1966; Alleva, 1963). Liver microsomes obtained from phenobarbital pretreated rats, however, will deaminate amphetamine (Parli and McMahon, 1973; Fuller *et al.*, 1973) and significant levels of the 455 nm absorbing complex are observed (James and Franklin, 1975). On the other hand, with the metabolically susceptible (R)-enantiomer, significant 455-nm-complex formation and oxidative deamination occur even with microsomes derived from untreated rabbits (James and Franklin, 1975). It is possible therefore that oxidative deamination and the potential for forming the 455 nm complex are related.

The *in vivo* metabolic fate of amphetamine has been shown to be species dependent (Smith and Dring, 1970; Debackere and Massart-Leen, 1965; Ellison *et al.*, 1966; Williams, 1974; Williams *et al.*, 1973). Basically, either *p*-hydroxylation dominates, as in the rat, or side chain degradation takes place, as in the rabbit and man. The extent to which the side chain is modified varies with the species—the rabbit, for example, excretes relatively large amounts of an acid-labile precursor to phenyl-2-propanone for which the enol sulfate structure **78** (Dring *et al.*, 1968) has been proposed. One of the major urinary metabolites found in man (Dring *et al.*, 1970) is benzoic acid **74** or its glycyl conjugate hippuric acid (**79**). It is generally assumed that benzoic acid formation results from the oxidation of phenyl-2-propanone (Caldwell *et al.*, 1972*b*). Williams *et al.* (1973; Williams, 1974) have reported the *in vivo* conversion of phenyl-2-propanone to benzoic acid in the rabbit. This pathway is potentially important since at one stage or another hydroxylation of the benzylic carbon atom is likely to be involved. Should benzylic hydroxylation precede the deamination step, then substances related to norephedrine (**69**) would be formed. Amphetamine and *p*-hydroxyamphetamine undergo β-hydroxylation in several species (Dring *et al.*, 1970; Sever *et al.*, 1973*a*,*b*, 1976; Sjoerdsma and Von Studnitz, 1963; Carlsson and Lindquist, 1962) including man, although these compounds represent minor urinary metabolites compared to benzoic acid and hippuric acid (Caldwell *et*

al., 1972*b*). The conversion presumably occurs in noradrenergic neurons (Costa and Groppetti, 1970) and has been shown to be stereospecific both in terms of substrate requirement [only the (S)-enantiomers are oxidizied] and in terms of product formation [the absolute configuration of *p*-hydroxynorephedrine (**71**) and presumably norephedrine (**69**) possessing the (1R,2S)-*erythro* configurations] (Goldstein *et al.*, 1964; Goldstein and Anagnoste, 1965). The stereospecific formation of **71** has been suggested to be a key factor in the development of tolerance to (S)-amphetamine (Brodie *et al.*, 1970) and could be responsible for the behavioral differences observed with the two enantiomers (Taylor and Snyder, 1970). Beckett *et al.* (1974*a,b*) have reported that rabbit liver homogenates convert norephedrine to the N-oxidation products **80** and **81** and the oxidative deamination products **82** and **83**. The authors did not examine the incubation mixture for benzoic acid. Benzyl alcohol (**84**) was observed as an *in vitro* metabolite of phenyl-2-propanone oxime (Coutts *et al.*, 1976*a*). Therefore, α,β-carbon–carbon bond cleavage of an N-oxidation product of amphetamine metabolism has been established. Chemically feasible reaction sequences leading eventually to benzoic acid via an intermediate possessing a good leaving group on nitrogen, such as the oxime sulfate ester **85** or hydroxylamine sulfate ester **86**, are outlined in Fig. 7 together with some of the known conversions related to these postulated transformations. Should benzaldehyde (**87**) be formed *in vivo*, as proposed in Fig. 7, it would be expected to undergo rapid oxidation to benzoic acid or reduction to benzyl alcohol. The participation of such pathways in the metabolism of amphetamine would imply a quantitatively more significant role of phenylpropanolamines such as norephedrine than indicated by the low levels of norephedrine and *p*-hydroxynorephedrine detected in human urine.

The second quantitatively most important *in vivo* metabolic pathway of amphetamine is *p*-hydroxylation. Urinary aromatic hydroxylation metabolites of amphetamine have been detected in a number of species (Dring *et al.*, 1970; Ellison *et al.*, 1966; Caldwell *et al.*, 1972*b*) and are the major pathway in the rat with 60, 48, and 63% of the administered dose (110 mg) of (R,S)-, (S)-, and (R)-amphetamine, respectively, appearing as *p*-hydroxyamphetamine or a hydrolyzable conjugate of *p*-hydroxyamphetamine (Dring *et al.*, 1970). In view of this extensive *in vivo* hydroxylation of amphetamine, it was very surprising that microsomal preparations from the rat displayed only weak aromatic hydroxylating capability with amphetamine as substrate (Dingell and Bass, 1969; Daly *et al.*, 1967). Recently, this question has been reinvestigated and the microsomal hydroxylation of amphetamine to *p*-hydroxyamphetamine clearly documented (Rommelspacher *et al.*, 1974; Cho *et al.*, 1975*b*). Kinetic studies revealed that the reaction proceeds only at low (nm) substrate concentrations with substrate inhibition occurring at μm concentrations. Jonsson (1974) established the Michaelis–Menton kinetic constants as $K_m = 2.4 \times 10^{-5}\,M$, $V_{max} = 3.7$ nmole $\times$ mg protein$^{-1} \times 10$ min^{-1} for (R)-amphetamine and $K_m = 1.1 \times 10^{-6}\,M$, $V_{max} = 2.8$ nmole $\times$

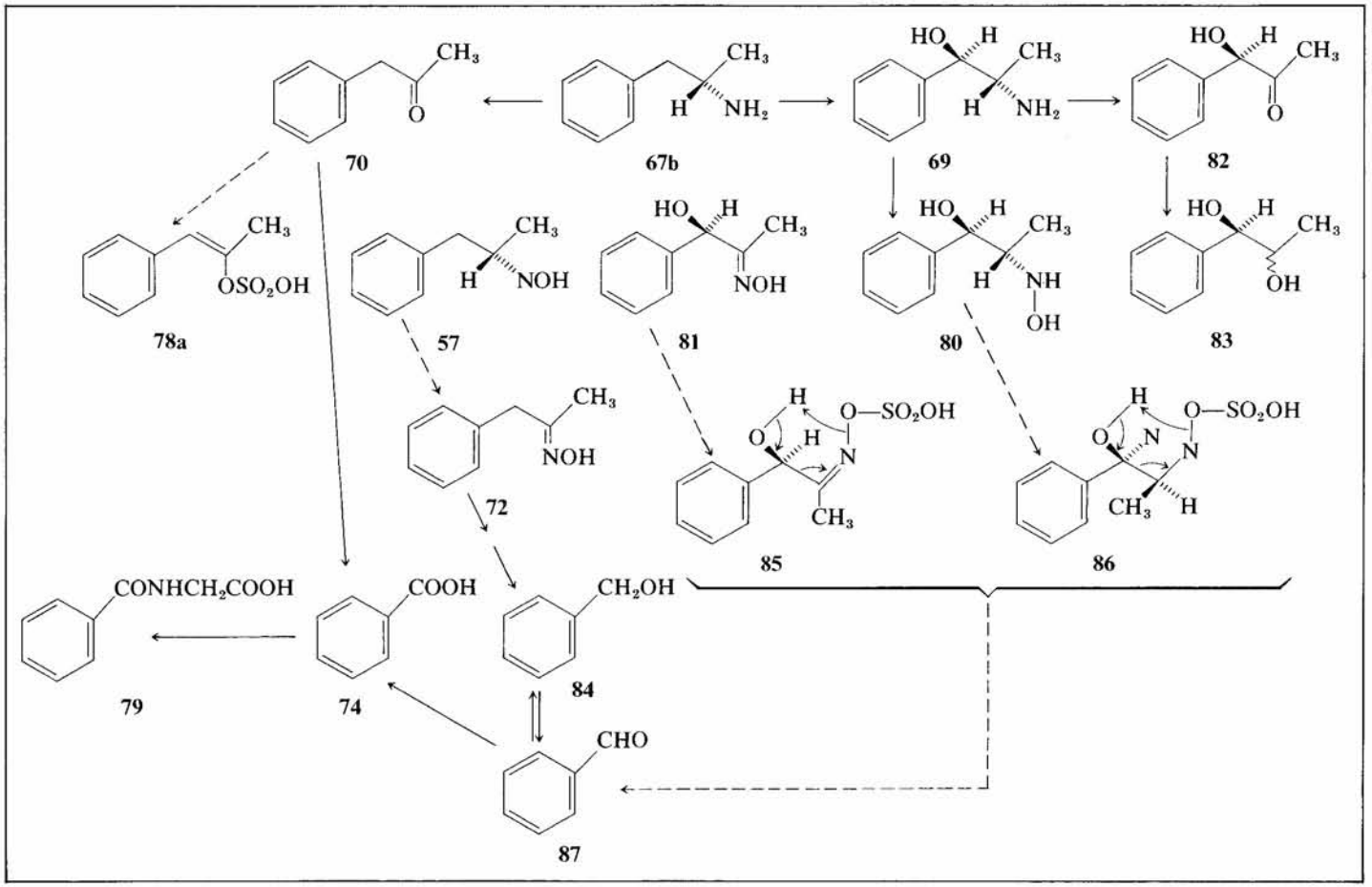


FIG. 7. Metabolic pathways of (S)-amphetamine (**67b**) involving the oxidation of the benzylic carbon atoms and eventually leading to benzoic acid, a major urinary metabolite of amphetamine in man. Solid lines represent established conversions; dashed arrows are speculative conversions.

mg protein^{-1} × 10 min^{-1} for (S)-amphetamine. The larger V_{max} for (R)-amphetamine vs (S)-amphetamine determined *in vitro* is consistent with the *in vivo* results, which show that 63% of an administered dose of (R)-amphetamine is excreted as the *p*-hydroxylated metabolite vs only 48% for (S)-amphetamine. A similar result was obtained by Gunne and Galland (1967) with (R,S)-amphetamine, that is the R/S ratio of urinary *p*-hydroxyamphetamine was found to be greater than 1 (1.22 in the 0–4 hr urine and 1.09 in the 0–24 hr urine). These authors suggest that the enantiomeric difference resulted from the stereospecific metabolism by β-hydroxylation of (S)-*p*-hydroxyamphetamine.

The above discussion has attempted to focus on those aspects of amphetamine metabolism that may contribute to an understanding of its pharmacological properties. The liver has been the major organ for *in vitro* investigations, and one may presume that with the exception of neuronal β-hydroxylation the liver is primarily responsible for the *in vivo* biotransformations of this drug. Published results (Mitra and Guha, 1973) describing the "dehydrogenation" of amphetamine by brain tissues have been seriously questioned because of the nonspecificity of the assay (Marckel and Harrison, 1974). Attempts to identify "proximate psychotogens" such as *p*-methoxyamphetamine (**88**) in patients suffering from "amphetamine psychosis" have, for the most part, been unsuccessful (Friedhoff and Schweitzer, 1971; Angrist *et al.*, 1971; Andreoli *et al.*, 1973). Variations in human metabolism by naive individuals vs amphetamine users have been observed (Sever *et al.*, 1973*b*; Gunne and Anggard, 1973).

It may be concluded that in the nearly 50 years that have passed since the first description of the human pharmacological properties of amphetamine (Alles, 1933) much has been learned about this drug's metabolic fate in mammals. The importance of biotransformation processes in determining the biological properties of amphetamine, however, remain controversial.

2.2. Metabolism of Mescaline (Benzeneethaneamine, 3,4,5-Trimethoxy)

Mescaline (**89**) is the only known naturally occurring one-ring psychotomimetic. From an historical standpoint, this compound is the most important of the "phenylalkylamine" psychotomimetics (see Chapter 6) even though it has proved to be one of the less potent. Unlike amphetamine, which causes psychotic behavior in man usually only after long-term abuse, the ingestion of 300–500 mg (~20–30 μmole/kg) of mescaline causes profound behavioral alterations which usually begin within a few hours.

In part because of the relatively high doses required and the apparent lack of a correlation between the time of onset and duration of effect with the time of maximum levels of drug in the brain of animals, some workers have suggested that a metabolite of mescaline may be responsible for the

psychotomimetic effects of the parent drug (Harley-Mason *et al.*, 1958; Mokrasch and Stevenson, 1962; Smythies, 1963; Friedhoff and Goldstein, 1962). To date, no definitive evidence has been presented to confirm or rule out the formation of a proximate psychotogen derived metabolically from mescaline.

Figure 8 summarizes those metabolic conversions of mescaline that are reasonably well established. Other than mescaline itself, the most commonly encountered metabolite is 3,4,5-trimethoxyphenylacetic acid (**91**), which has been observed in man (Charalampous *et al.*, 1964, 1966; Friedhoff and Hollister, 1966), rat (Musacchio and Goldstein, 1967), monkeys (Taska and Schoolar, 1972), rabbits (Slotta and Muller, 1936), and cats (Neff *et al.*, 1964). Brain homogenates also have been reported to convert mescaline to **91** (Demisch and Seilar, 1975). This compound possesses no mescaline-like properties in man (Slotta and Muller, 1936; Charalampous *et al.*, 1966). Amine oxidases that will act on mescaline have been observed in several tissues including plasma (Tabor *et al.*, 1954; Blaschko *et al.*, 1958). This enzyme presumably catalyzes the conversion of mescaline to 3,4,5-trimethoxyphenylacetaldehyde (**90**), an unstable intermediate that is either further oxidized to the acid **91** or reduced to 2-(3,4,5-trimethoxyphenyl)ethanol (**92**). Based on evidence first reported by Bernheim and Bernheim (1938), mescaline oxidase appears to be similar to but not identical with "diamine oxidase" (Zeller *et al.*, 1958; Huszti and Borsy, 1966) and is distinct from

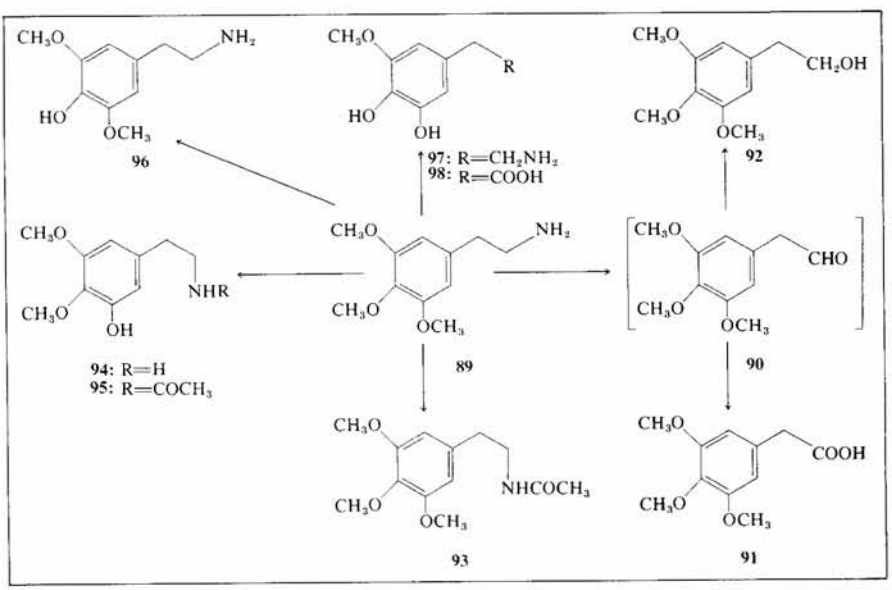
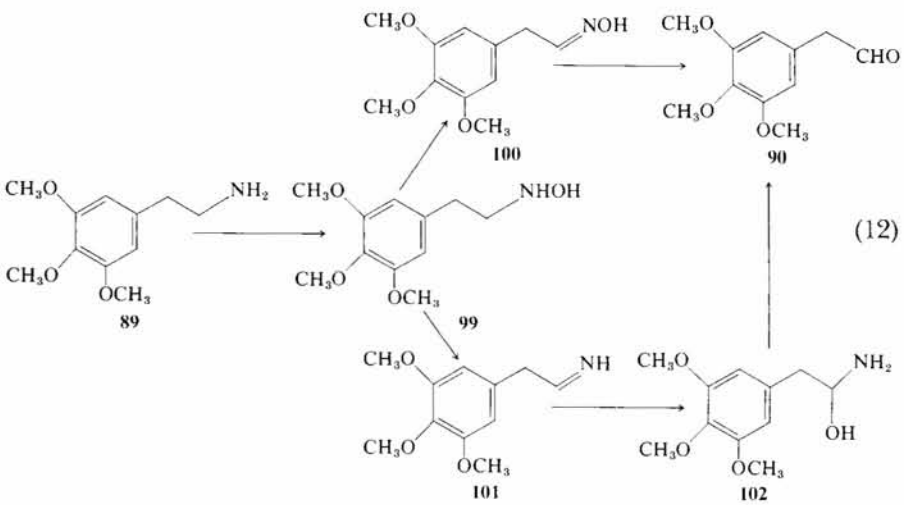


FIG. 8. Summary of metabolic pathways for mescaline (**89**).

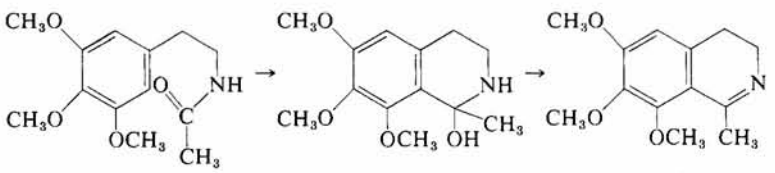
monoamine oxidase. Recent evidence based on inhibition studies with aminoacetonitrile suggests that the rabbit oxidatively deaminates mescaline by a Cu^{+2}-containing "pyridoxal" amine oxidase and not the flavin-containing monoamine oxidase found in the mitochondria (Riceberg *et al.*, 1975). It should be noted that no consideration has been given to the possibility that N-oxidation of mescaline is involved in its deamination. Considering the evidence that amphetamine and a variety of related aliphatic amines undergo metabolic N-oxidation (see above), it would not be surprising if mescaline were to be a substrate for the mammalian N-oxidase enzyme systems. As shown in reaction (12), the hydroxylamine **99** could be further oxidized to the oxime **100** followed by hydrolysis to the aldehyde **90**. A second possible N-oxidation sequence to the aldehyde **90** would involve dehydration of **99** to the imine **101** followed by rehydration to the carbinolamine **102** and loss of ammonia. These reaction pathways are analogous to those already discussed under amphetamine metabolism and in Section 1.



(12)

Some consideration has been given by Friedhoff and Goldstein (1962) to the potential importance of the trimethoxyphenylacetaldehyde **90** as a proximate psychotogen. These workers monitored gross behavioral changes caused by mescaline and 2-(3,4,5-trimethoxyphenyl)ethanol (**92**) in rats pretreated with either an amine oxidase inhibitor, which was found to have no potentiating effect, or an aldehyde oxidase inhibitor, which was found to potentiate the activities of both mescaline and its carbinol metabolite **92**. Such effects are reminiscent of the increased toxicity observed following ethanol ingestion after treatment with disulfuram (Hald and Jacobsen, 1948). Studies by Browne and Ho (1975) suggest, however, that the parent amine is responsible for mescaline's CNS activity since several mescaline metabolites failed to mimic mescaline in an operant discrimination test.

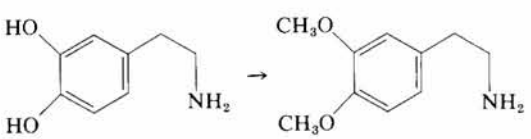
The acetylation of mescaline to form the N-acetyl compound **93** also has been reported in a number of animal species (Charalampous *et al.*, 1966; Taska and Schoolar, 1972; Musacchio and Goldstein, 1967). This metabolite has been found in the brain of mice (Shah and Himmich, 1971) and rats (Ho *et al.*, 1973). Related ring-substituted 2-phenylethylamines have been shown to undergo N-acetylation by the melatonin-forming enzyme located in the pineal gland of the brain (Hartley and Smith, 1973). Since the aromatic nucleus of mescaline is electron rich, cyclization of *N*-acetylmescaline to the dihydroisoquinoline **104** *via* the intermediate carbinolamine **104a** could



93 104a 104 (13)

occur (reaction 13). Analogous processes leading to tetrahydroisoquinolines have been reported in plants (Kapadia *et al.*, 1970) although the conversion in mammalian systems has not been demonstrated. It should be pointed out that a number of tetrahydroisoquinolines derived from catecholamines (Davis and Walsh, 1970; Cohen and Collins, 1970; Sandler *et al.*, 1973; Walsh *et al.*, 1970; Greenberg and Cohen, 1973) and pyridoindoles derived from indolealkylamines (Wyatt *et al.*, 1975; Mandel *et al.*, 1974) have been reported to be formed in mammals. It is not clear, however, if these compounds are metabolically derived or artifacts due to the chemical reactivity of the precursor molecules.

The one-ring psychotomimetics all possess alkoxy (methoxy, methylenedioxy) functionalities. Considerable interest has focused on metabolic pathways involving oxidative cleavage of these groups to form the corresponding phenolic compounds. Also of interest has been the possible *in vivo* methylation of phenolic groups present, for example, on dopamine (**105**) to form aberrant metabolites such as 3,4-dimethoxyphenylethylamine (**106**), which could function as endogenous psychotogens (Friedhoff and Van Winkle, 1962).



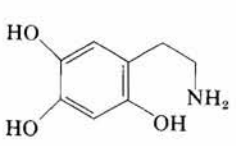
105 106

In the case of mescaline, five O-demethylated metabolites have been characterized, namely, compounds **94–98** shown in Fig. 8 (Daly *et al.*, 1962). Of special interest is the *bis*-O-demethylation of mescaline to form the *o*-

hydroquinone (catechol) derivatives **97** and **98**. As will be discussed in more detail below, hydroquinones are relatively unstable molecules that tend to auto-oxidize to chemically reactive, electron-deficient quinones. These reactive substances may then form covalent bonds with nucleophiles present on macromolecules. In an early study by Block (1953, 1958) on the metabolism of ^{14}C-labeled mescaline, incorporation of the ^{14}C label into liver proteins was observed. Details regarding the pathway leading to this incorporation are lacking. One possible pathway is analogous to that reported for the incorporation into protein of the potent sympatholytic agent 6-hydroxydopamine (**107**), which most likely involves quinone intermediates (Saner and Thoenen, 1971).

Another important consequence of the susceptibility of catechols to undergo oxidation to quinones is the possible formation of cyclic species such as adrenochrome (**108**) from epinephrine (**109**) (Axelrod, 1964). Adrenochrome has been associated with the psychotomimetic activity of LSD (Hoffer *et al.*, 1959) and related molecules have been examined as potential endogenous psychotogens. As with almost all attempts to derive psychopharmacological correlates from metabolic events, this area remains unresolved (Blaschko, 1972). During the past several years however, extensive studies on the neurodegenerative effects of 6-hydroxydopamine (Kostrzewa and Jacobowitz, 1974; Malmfors and Thoenen, 1971), which may be formed *in vivo* from dopamine (Senoh *et al.*, 1959), have led to a renewed interest in the oxidative pathways of catecholamines as being possibly linked to CNS disorders (Stein and Wise, 1971).

Mescaline is oxidized by enzymes present in a number of tissues (Blaschko *et al.*, 1958; Riceberg *et al.*, 1975) including brain (Ho *et al.*, 1973). With regard to the possible participation of drug metabolic processes in the psychotomimetic effects of this drug, the recent series of papers by Seiler and Demisch (1974*a*,*b*) describing the *in vivo* and *in vitro* metabolism of mescaline by mouse brain are of some interest. These workers present evidence (based on $^{14}CO_2$ production *in vivo* and gas chromatographic–mass spectrometric data) for the metabolic formation of 3,4,5-trimethoxybenzoic acid (**110**) from



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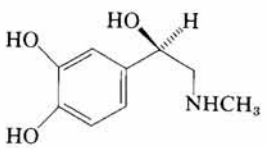

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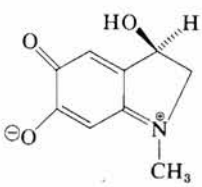

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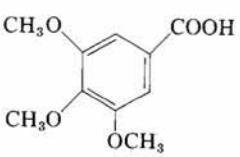

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mescaline by an enzyme system in the mouse brain. As was pointed out when discussing the metabolism of amphetamine, side chain cleavage to benzoic acid is likely to involve benzylic oxidation to β-hydroxylation products that could be pharmacologically active. Further study in this area would seem appropriate.

2.3. The Metabolism of Ring-Substituted 1-Phenyl-2-aminopropane Psychotomimetics

Shulgin *et al.* (1969) in an effort to evaluate the pharmacological consequences of combining the dominant structural features of mescaline, the trimethoxyphenyl moiety, with the dominant structural feature of amphetamine, the phenylisopropylamino unit, have synthesized a variety of 1-phenyl-2-aminopropanes. Although variations in the side chain substituents have been examined, the major focus of Shulgin's work has concerned aryl-substituted derivatives (see Chapter 6 for a review). The 2,4,5-trioxysubstitution pattern led to maximal potency; furthermore it was found that the 4-position could be an alkyl, alkoxy, or halo group without sacrificing activity. The alkoxy groups at the 2 and 5 positions, however, appear to be essential for high potency in this series. The 4-methyl compound **111** (Matin *et al.*, 1974) and 4-bromo compound **112**, (Nichols *et al.*, 1973) are two of the most potent one-ring psychotomimetics known. As with amphetamine, these molecules bear a chiral center. The R-enantiomers **111a** and **112a** are the more potent isomers (Aldous *et al.*, 1974; Shulgin, 1973; Benington *et al.*, 1973). These compounds display activities approximately 100–400 times that of mescaline.

The metabolism of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (benzeneethaneamine,α,4-dimethyl-2,5-dimethoxy, DOM, **111**) has been examined in some detail. Idänpään-Heikkila and McIssac (1970) have determined the tissue distribution of tritium-labeled **111** in mice and Ho *et al.* (1971) in rats and monkeys. Additionally, Ho *et al.* (1971) and Matin *et al.* (1974) have characterized a number of urinary metabolites of **111** (Fig. 9).

Both *in vitro* (McGraw *et al.*, 1977) and *in vivo* (Matin *et al.*, 1974) studies on **111** have shown that the S(+)-enantiomer (**111a**) is metabolized more rapidly than the R(−)-enantiomer when racemic drug is administered. The individual isomers, however, are metabolized by rabbit liver microsomes at approximately the same rate, suggesting an enantiomeric interaction in which the (S)-isomer inhibits the metabolism of the (R)-isomer. Similar results have recently been described for amphetamine (Gal *et al.*, 1976). This stereochemical selectivity is reflected in the enantiomeric composition of the metabolites formed *in vitro* from racemic **111** (Weinkam *et al.*, 1976). In all cases except one, the S/R ratio of the metabolites of racemic **111** is greater than 1. The single exception involves the microsomal N-oxidation of **111** to **117**. Gas chromatographic–mass spectrometric analysis of this metabolite

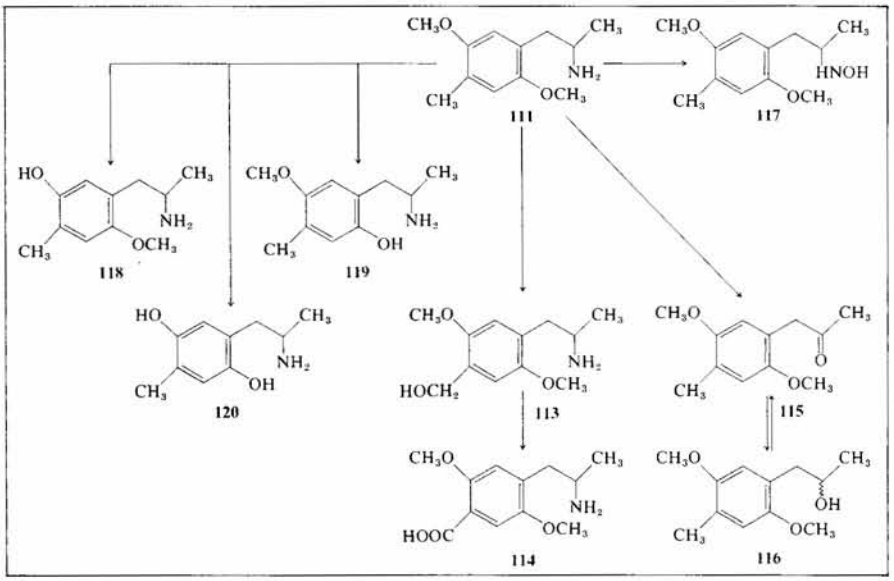


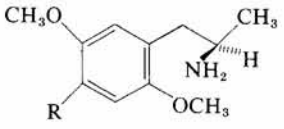
FIG. 9. Metabolic pathways for amine **111** (DOM).

employing selected ion recording established that the R/S ratio ranged between 2.4 and 6.3 under conditions when 6–8% of **111** incubated was isolated in the postincubate as **117** (Gal *et al.*, 1976).

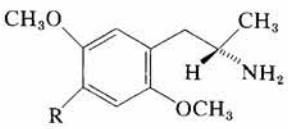
The quantitatively most important metabolic pathway of **111** involves oxidation of the C-4 methyl substituent. The amino acid **114** that has been identified in the urine of rabbits and rats represents about half the dose of **111** administered. The hydroxymethyl compound **113** is the major rabbit liver microsomal metabolite (Weinkam *et al.*, 1976) and has been detected in the brains of monkeys although in very low amounts (Idänpään-Heikkila and McIssac, 1970).

Oxidative deamination of **111** to form the 2-propanone metabolite **115** appears to be a minor metabolic pathway in all species studied. Particularly interesting in this regard is the very low yields of **115** observed in rabbit liver preparations (Weinkam *et al.*, 1976) since this is a major pathway for amphetamine (Axelrod, 1955). This ketone or its carbinol reduction product **116** has been detected as rat and rabbit urinary metabolites, but again in small amounts. No evidence could be obtained in rabbits for side chain cleavage of **111** to 2,5-dimethoxy-4-methylbenzoic acid (**121**), its glycyl conjugate **122**, or its aldehyde precursor **123** or the diacid **124** (Matin *et al.*, 1974).

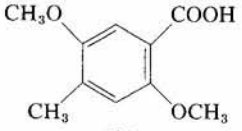
Attempts to characterize the β-hydroxy and N-acetyl compounds **125** and **126**, respectively, in rat urine were unsuccessful (Ho *et al.*, 1971*b*). As



111a: R=CH_3
112a: R=Br



111b: R=CH_3
112b: R=Br



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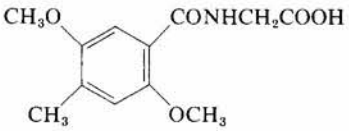

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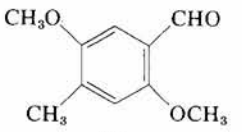

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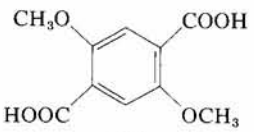

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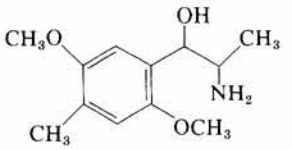
already mentioned, N-oxidation of **111** to the hydroxylamine **117** has been observed in rabbit liver microsomal preparations. Although the air oxidation of **117** to the oxime **127** was found to proceed rapidly in pH 7.4 buffer, no evidence could be obtained for its presence in the incubation mixture. Furthermore, denatured (boiled) microsomes protected the hydroxylamine against this air oxidation, suggesting the presence of an inhibitory substance. An analogous inhibition of the oxidation of 1-hydroxyaminonaphthalene (**128**) has been reported by Ziegler *et al.* (1973).



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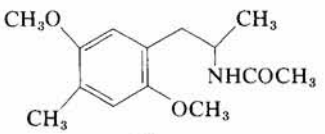

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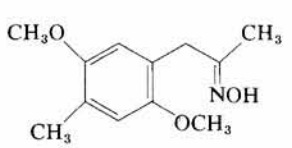

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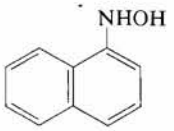

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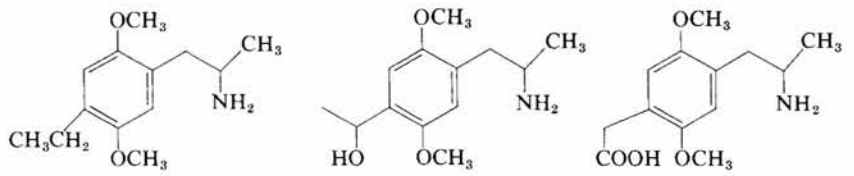
The third general metabolic pathway for **111** is oxidative O-demethylation of the methyl phenyl ether groups. All three possible O-demethylated metabolites, compounds **118–120**, have been characterized in rabbit liver

homogenates (Zweig and Castagnoli, 1975, 1977). The *p*-hydroquinone **120** is an analog of the sympatholytic agent 6-hydroxydopamine (**107**) and has been shown to possess some of the neurodegenerative properties of 6-hydroxydopamine (Butcher, 1975). Similar to 6-hydroxydopamine (Blank *et al.*, 1972), hydroquinone **120** undergoes facile oxidation to form the quinone **129** (Fig. 10), which cyclizes to the iminoquinone **130** (Zweig and Castagnoli, 1974). In the absence of nucleophiles, **130** is relatively stable at pH 7.4. As the pH is raised, however, proton rearrangements take place, eventually leading to the indole **132** via the indolinine **131**.

In view of the ease with which the hydroquinone **120** undergoes oxidation at pH 7.4, it is somewhat surprising that this compound survives the one hour pH 7.4 incubation. This stabilization may be analogous to the inhibition by liver constituents of hydroxylamine auto-oxidation. It should prove of interest to determine the nature and significance of the protection of these substances from air oxidation.

Reports on the metabolism of a number of other ring-substituted psychotomimetic 1-phenyl-2-aminopropanes have appeared. The 4-ethyl analog **133** of DOM is reported to undergo metabolic oxidation to the carbinol **134** and the phenylacetic acid **135** in the rat (Tansey *et al.*, 1975). The slower rate of metabolism of **133** compared to **111** is consistent with the greater potency of the ethyl analog (Snyder *et al.*, 1968).



In an attempt to determine if metabolic factors are associated with differences in psychotomimetic potency, Mitoma (1970) examined the tissue distribution (rats) and *in vitro* O-demethylation (rats and rabbits) of the three

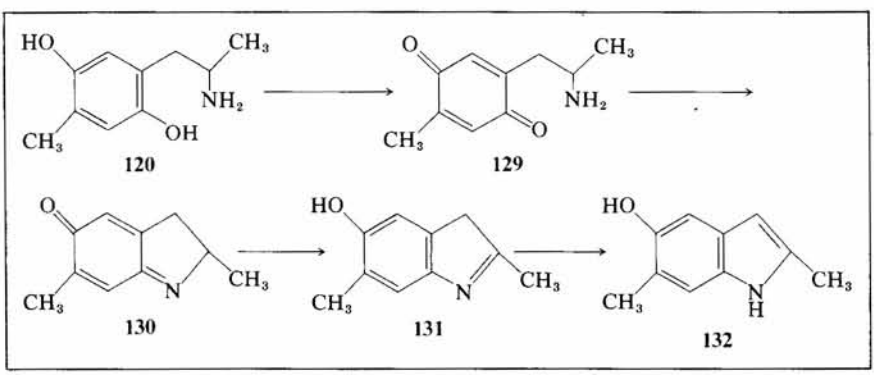
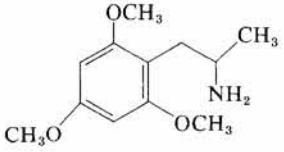


FIG. 10. Oxidative cyclization of *p*-hydroquinone metabolite derived from DOM.

possible 1-(trimethoxyphenyl)-2-aminopropanes, **136–138**. The 2,3,4-trimethoxy isomer **138** is reported to be inactive in man (Shulgin, 1964) and animals (Uyeno *et al.*, 1968) as a psychotogen. No dramatic differences were observed in brain levels or in the extent of *in vitro* O-demethylation as measured by formaldehyde production. A more detailed analysis of the *in vivo* (rat) O-demethylation of 1-(2,4,5-trimethoxyphenyl)-2-aminopropane (**137**), the most potent of the three isomers, was recently described (Sargent *et al.*, 1976). The methyl carbon atom of each of the three methoxy groups was independently labeled with ^{14}C and the rates of $^{14}CO_2$ formation measured. According to these data, the C-4 methoxy group is more extensively cleaved (21.3%) than the C-2 (8.1%) or the C-5 (13.7%) groups. Characterization of the phenolic metabolites resulting from these O-demethylation transformations was not reported.

Beckett and Midha (1974) have examined the metabolism of 1-(4-methoxyphenyl)-2-aminopropane (**139**) by liver preparations of rabbit, guinea pig, and rat. Four side-chain oxidation products, the N-hydroxy derivative **140**, oxime **141**, phenyl-2-propanone **142**, and phenyl-2-propanol **143** were characterized. The chemical lability of the N-hydroxy compound **140** was discussed and the authors suggest that the oxime **141** may not be a true metabolite but rather an artifact resulting from the air oxidation of **140**. No comment was made on the possible formation of phenolic metabolites although it is likely that the isolation procedures followed would not have revealed such compounds.

In addition to methoxy substituents, substitution of the phenyl ring of amphetamine with a methylenedioxy group leads to psychotomimetic activity (Naranjo *et al.*, 1967). The *in vitro* metabolic fate of 1-(3,4-methylenedioxy-



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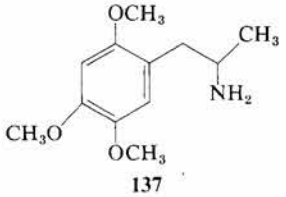

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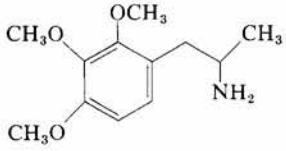

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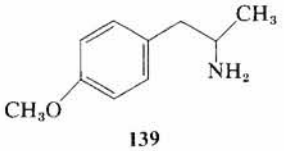

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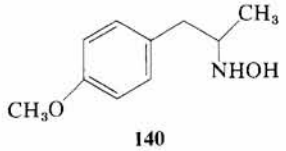

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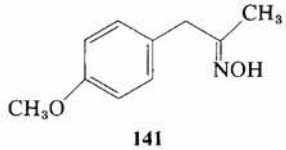

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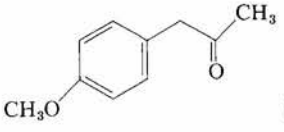

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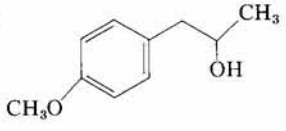

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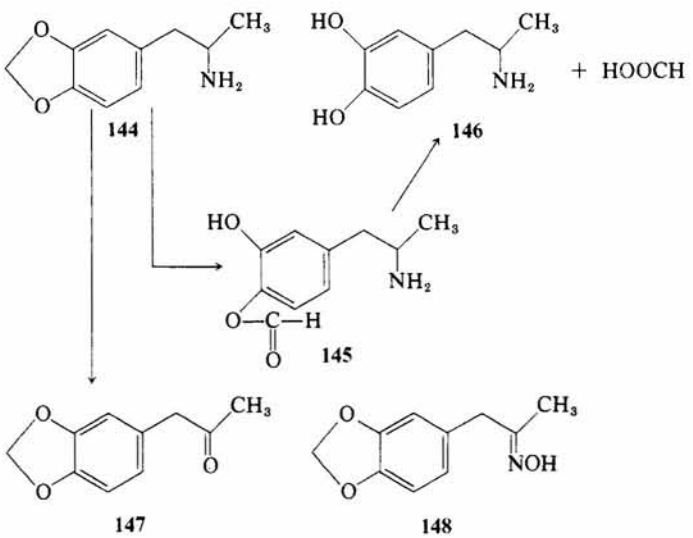
phenyl)-2-aminopropane (**144**) has been examined by two laboratories. Oxidative O-dealkylation of **144** by the microsomal mixed-function oxidase derived from rats has been shown (Marquardt and DiStefano, 1974) to yield the putative false neurotransmitter (Muscholl, 1972) α-methyldopamine (**146**). In terms of the general principles discussed in Section 1, oxidative attack on **144** would lead to the unstable formate ester **145**, which would rapidly hydrolyze to α-methyldopamine and formic acid. In a separate study, Midha (1974) examined by gas-chromatography–mass-spectrometry the neutral and basic extracts of guinea pig and rabbit liver homogenate incubations of the methylenedioxy compound **144**. He was able to characterize the phenyl-2-propanone **147** and its oxime **148** as major metabolic products.



Thus, both side chain oxidation and oxidative O-dealkylation have been demonstrated for **144** although in different species.

3. CONCLUSION

Psychotomimetic drugs deserve careful study since an understanding of their mechanisms of action must eventually contribute to the deciphering of the complex events associated with mental disorders. In a more strictly academic sense, the dramatic alterations in potencies of these substances, which are associated with seemingly minor structural variations, pose an interesting challenge to investigators working in this area. The possibility that metabolic transformations of the parent drugs may be responsible for these differences in biological activity is worthy of study. It is clear that metabolites

are not necessarily "detoxification" products. Often, chemically reactive species are generated and these may covalently interact with biologically important molecules, leading to altered structures and functions. Psychotomimetic amines undergo analogous metabolic conversions to those identified with xenobiotic toxicities—aromatic oxidation, N-oxidation, hydroquinone formation. In reviewing the metabolic fate of the one-ring psychotomimetic amines, particular emphasis has been given to pathways that may lead to biologically and chemically active molecules. It must be stated, however, that efforts on the part of various researchers to link the pharmacological properties of these molecules to structural changes they suffer *in vivo* have not yielded definitive results. On the other hand, with the possible exception of amphetamine, relatively little detailed information on the metabolic fate of psychotomimetics is available and one can anticipate that the molecular events associated with their modes of action are complex. Technological advances will continue to provide increasingly sophisticated avenues to better explore small molecule–macromolecule interactions. Well coordinated, interdisciplinary research programs will continue to cross-fertilize new approaches to the study of these drugs. Hopefully these efforts will lead to a clearer understanding of the pharmacological significance that metabolic transformations can play in psychotomimetic activity and toxicity.

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