Metabolic Changes of Drugs and Related Organic Compounds

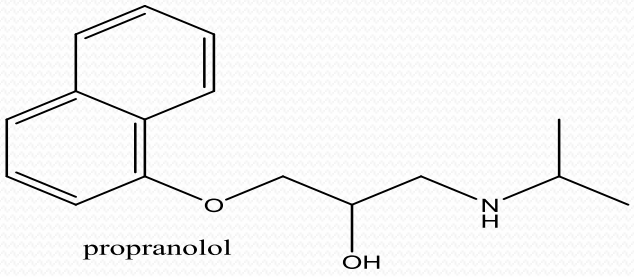
Organic Pharmaceutical Chemistry I

3rd Year Pharmacy

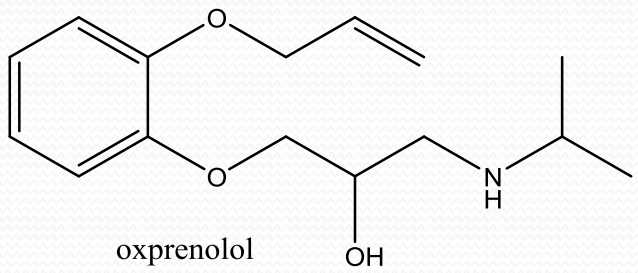
2018-2019

Oxidation of Secondary and Primary Amines

- Secondary amines are susceptible to oxidative N-deakylation, Oxidative N-deamination or N-Oxidation.
- Dealkylation or deamination of secondary amines proceeds via carbinolamine intermediate producing primary amines, e.g. propranolol and oxprenolol undergo N-deisopropylation to the corresponding aldehyde intermediate.



propranolol

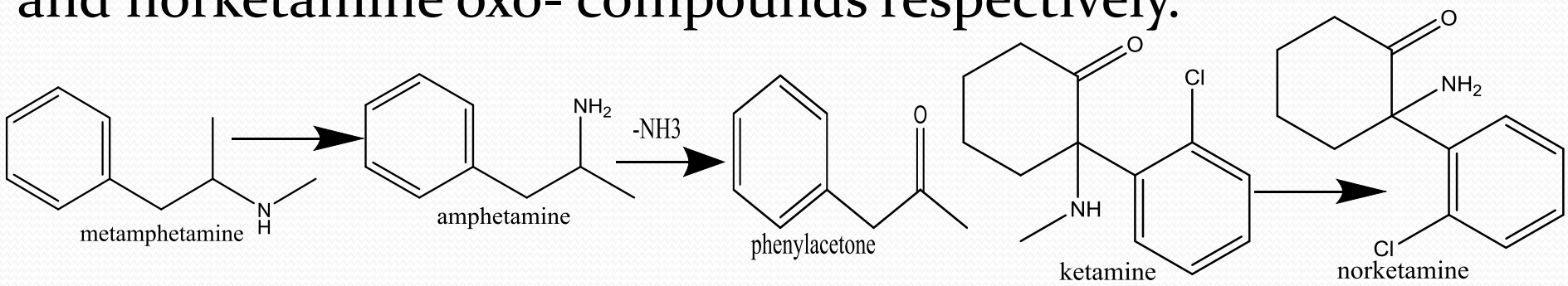


oxprenolol

- **Exc: Demostrate the conversion of a secondary amine to nitrone through the corresponding hydroxylamine intermediate.**

Examples of the Oxidation of Secondary Amines

Examples of secondary amines undergoing dealkylation include metamphetamine and ketamine giving amphetamine and norketamine oxo- compounds respectively.

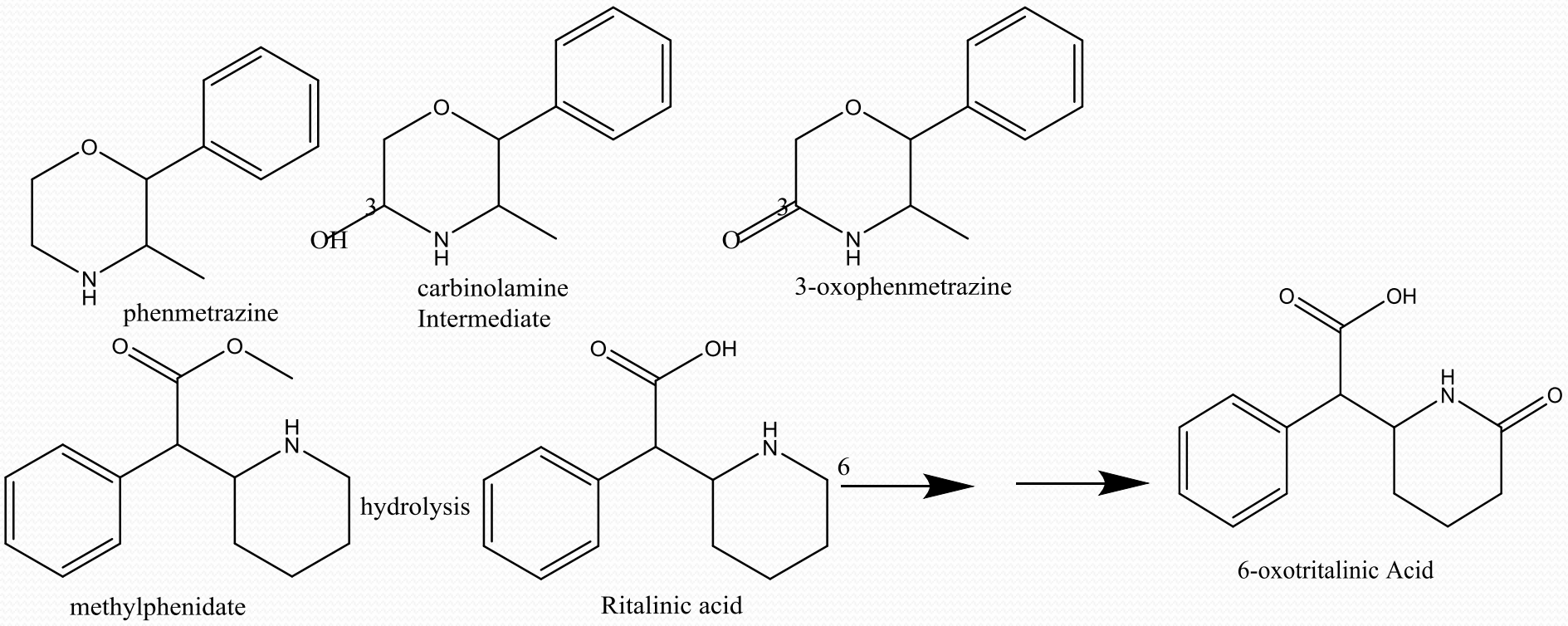


Account for; Norketamine doesn't undergo dealkylation.

Usually, dealkylation of secondary amines takeplace prior to deamination. However, proranolol show direct deamination through carbinol to give the aldehyde and isopropylamine or delkylation to give acetone. Howmuch of the two routes is followed is not clear.

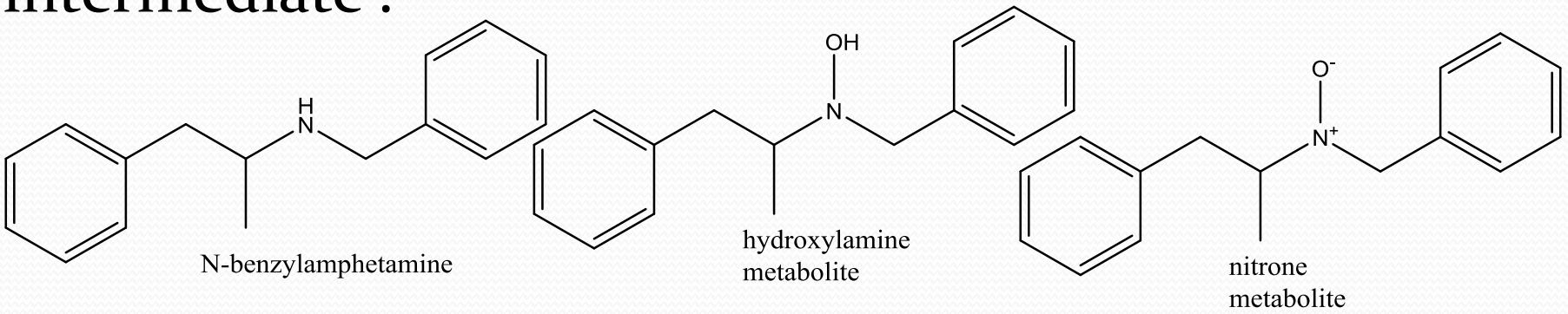
Secondary Alicyclic Amines

Like tertiary amines, secondary amines are metabolised to lactam derivatives. Phenmetrazine and methylphenidate produce 3-oxophenmetrazine and 6-oxorithalnic acid respectively.



N-oxidation of Secondary Amines

Several N-oxygenated products are produced by N-oxidation of secondary amines. The intermediates are hydroxylamine metabolites which are further oxidised to the corresponding nitrone derivatives , e.g. N-benzylamphetamine. In gerneral less N-oxidation occurs than oxidative delkylation and deamination. The nitrone metabolite of phenmetrazine is belived to be formed by further oxidation of the hydroxylamine intermediate .



N-benzylamphetamine

hydroxylamine metabolite

nitrone metabolite

Oxidation of Primary Aliphatic Amines

- Primary aliphatic amines are oxidised by oxidative deamination(through the carbinol intermediate)or N-oxidation.

- **Exc; Demostrate the conversion of a primary amine to nitrone through the corresponding hydroxylamine intermediate.**

Oxidation of Exogenous versus Endogenous Compounds

- The deamination of most exogenous primary amines is carried out by CYP.

- Endogenous primary amines including dopamine, norephidene, tryptamine, and serotonin and xenobiotics based on the structures of these endogenous transmitters are metabolised through oxidative deamination by MAO.

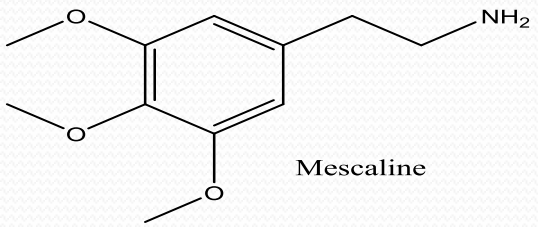
MAO versus CYP

MAO	CYP
▪ It is found in two isozyme forms, MAO-A and MAO-B	It exists in in a wide variety of isozyme forms
▪ It is a flavin (FAD) dependent enzyme.	It is an NADP dependent system
▪ It is widely distributed in in CNS and peripheral organs.	It is found mainly in the liver and intestinal mucosa
▪ MAOs are coded for by two genes, both on the X chromosome and have about 70% amino acid sequence homology.	Different genes for different families
▪ It is located on the outer mitochonderial membrane	It is found on endoplasmic reticulum of the cells cytosol.

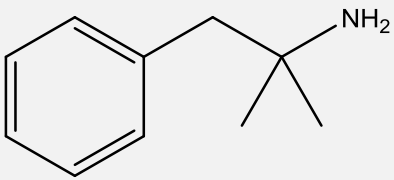
Deamination versus N-oxidation

α-Carbon to N will determine the type of oxidation; deamination or N-oxidation. For example, in phentramine α-hydroxylation cannot occur. Mescaline is expected to undergo deamination.

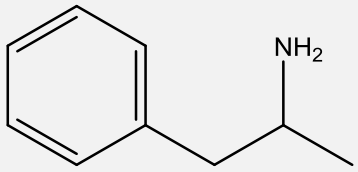
Exc: Compare the oxidation of amphetamine with phentermine.



Mescaline



phentermine

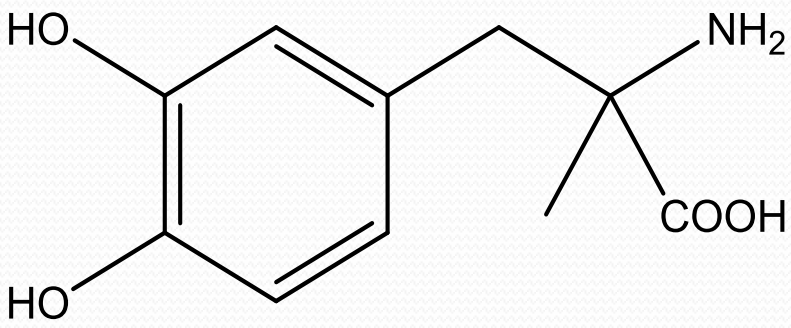


amphetamine

Deamination versus N-oxidation

The metabolite of decarboxylation **of α-methyldopa is oxidised by deamination** to the corresponding ketone after being decabolated.(p69)

Amphetamine undergoes both α-hydroxylation and N-oxidation. Many primary amines undergo N-oxidation because α-hydroxylation is not possible. These include....., ..., ..., and.....(p69)



methyldopa

Aromatic Amines and Hetrocyclic Nitrogen Compounds

The oxidation of aromatic amines is similar to oxidation of the C and N aliphatic amines.

Tertiary aromatic amines are oxidized by N-dealkylation or N-oxide formation e.g. N,N-diethyl aniline. P71

Secodany aromatic amines may undergo N-dealkylation or N-hydroxylation then oxidised to the nitroso pooducts. The latter may be hydrolysed to primary hydroxyl amines.

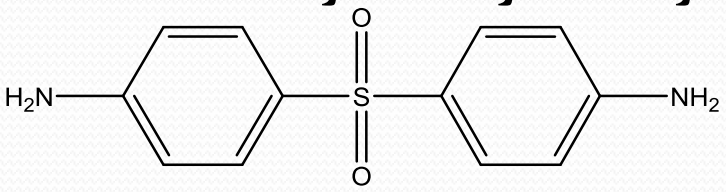
Unlike tertiary and secondary amines, primary amines are found in many medicinal agents.

Primary amines are produced by enzymatic reduction of aromatic nirtro compounds, reductive cleavage of azo compounds, and hydrolysis of aromatic amides.

Aromatic Amines and Hetrocyclic Nitrogen Compounds

Aniline is an example of the N-oxidation of primary aromatic amines to produce the N-hydroxlamines then to the nitroso derivatives.

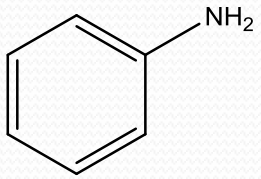
For primary aliphatic amines, N-oxidation forms only a miner route as compared to other paths such as N-acetylation or aromatc hydroxylation. However, dapsone and its acetylated metabolite are metabolized extensively to hydroxylamine products.



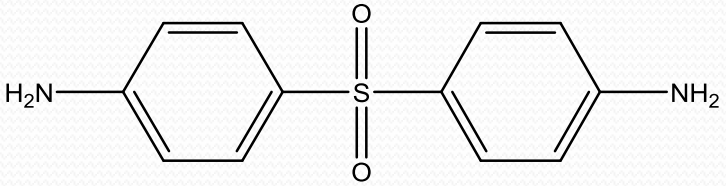
dapsone

Methemoglomebia Toxicity

Several aromatic amines cause methemoglomebia toxicity. Examples are aniline and dapsone and acetyldapsone.



aniline



dapsone

It is caused by the hydroxlation to the N-hydroxylamine derivative which oxidizes ferrous ions of hemoglobin to ferric ions.

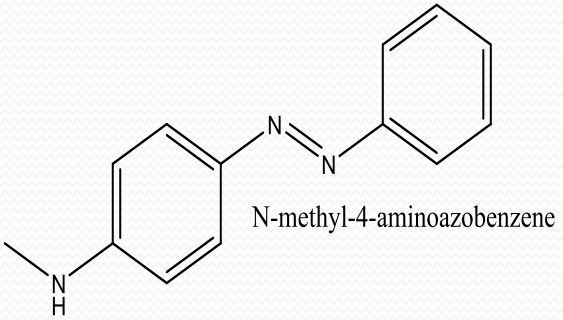
The resulting methemoglobin or ferrihemoglobin cannot act as an oxygen carrier which leads to serious hypoxia or anemia. The latter is a unique type of chemical suffocation.

Carcinogenicity of Azoamino Dyes

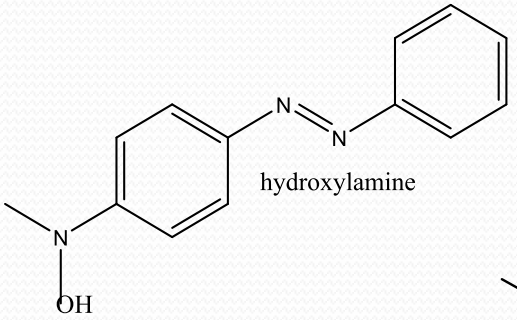
Several aromatic amines especially azoaminodyes are known to be carcenogenic. This is caused by potentially active electrophiles produced by N-oxidation. Nucleophiles in DNA, RNA and proteins form covalent bonds with these electrophiles.

N-methyl-4-aminoazobenzene is an example. The formed hydroxylamine, through sulphate conjugation can form highly reactive nitronium electrophylic species which covalently binds to neucleophiles.

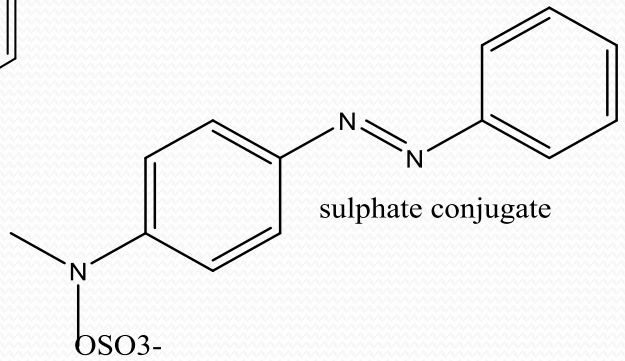
Carcinogenicity of Azoamino Dyes



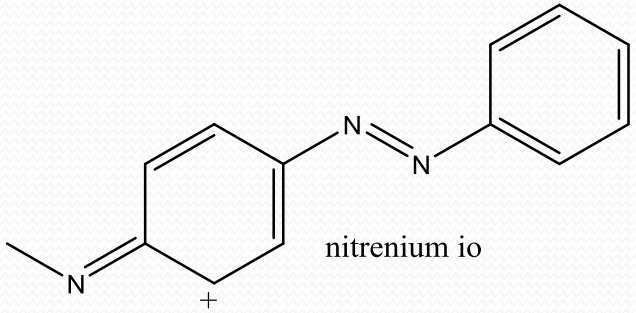
N-methyl-4-aminoazobenzene



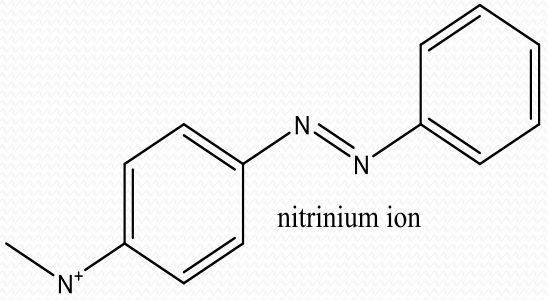
hydroxylamine



sulphate conjugate



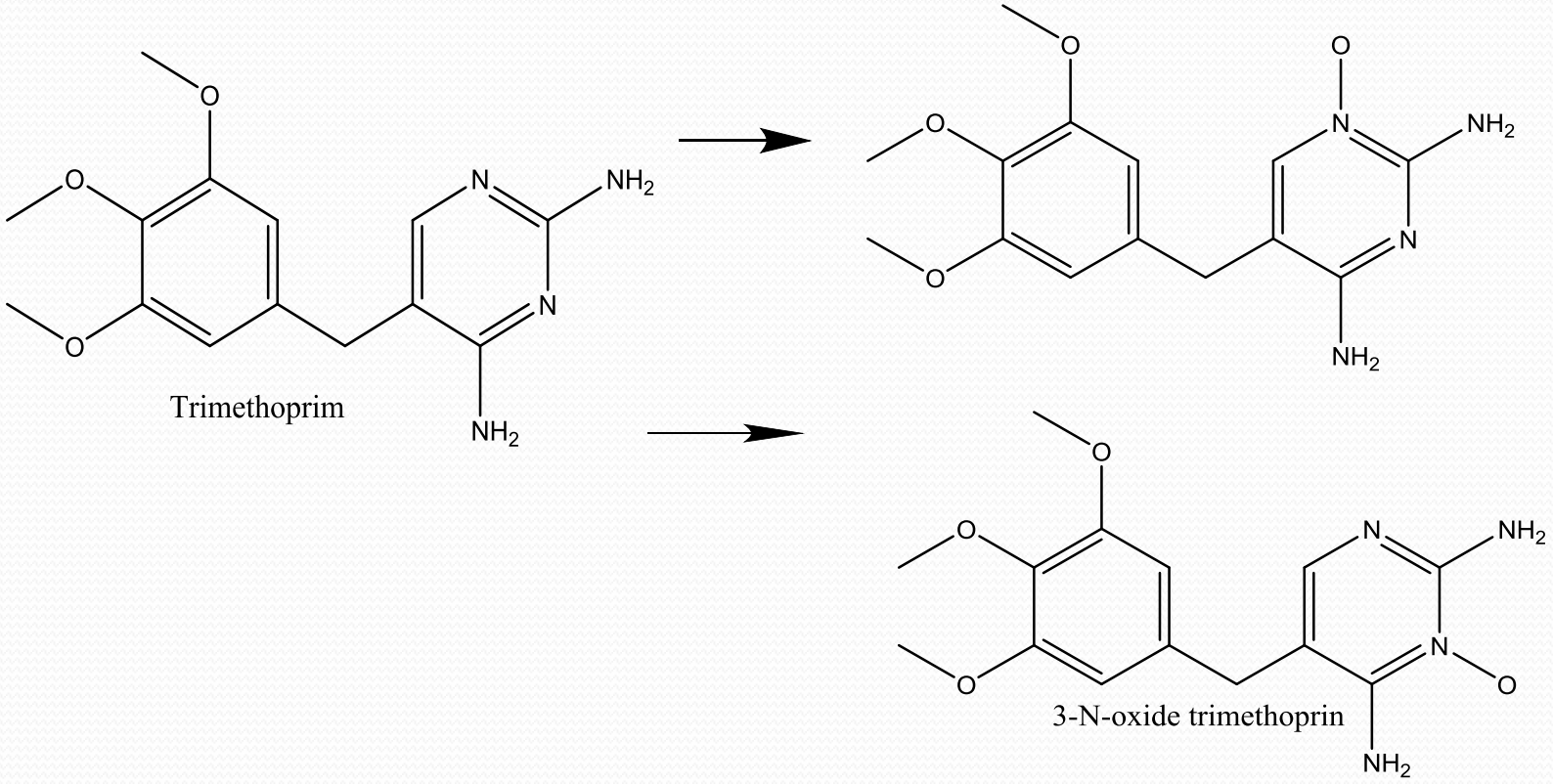
nitrenium io



nitrinium ion

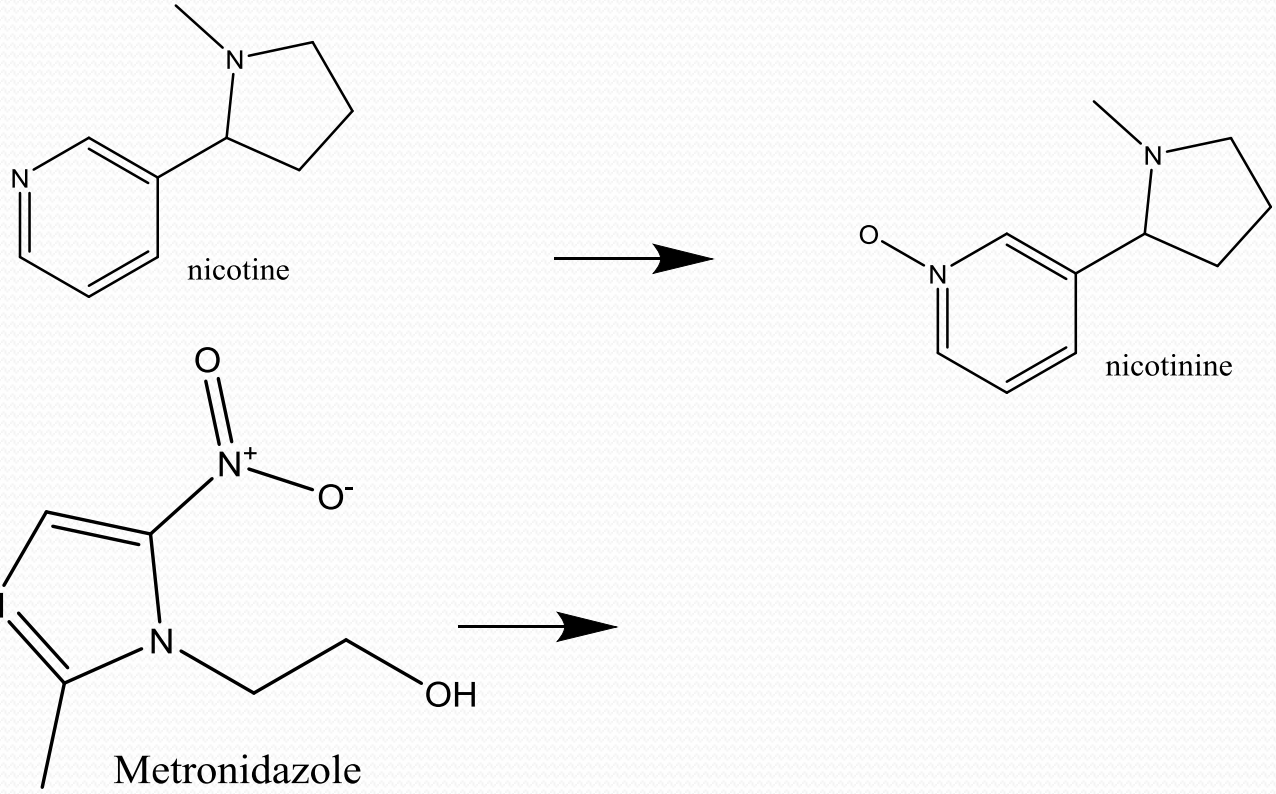
N-Oxidation of Aromatic Heterocyclic Compounds

N-oxidation of nitrogen in aromatic heterocyclic compounds occur to minor extent. Trimethoprim yields equal amounts of 1-N-oxide and 3-N-oxide.



N-Oxidation of Aromatic Heterocyclic Compounds

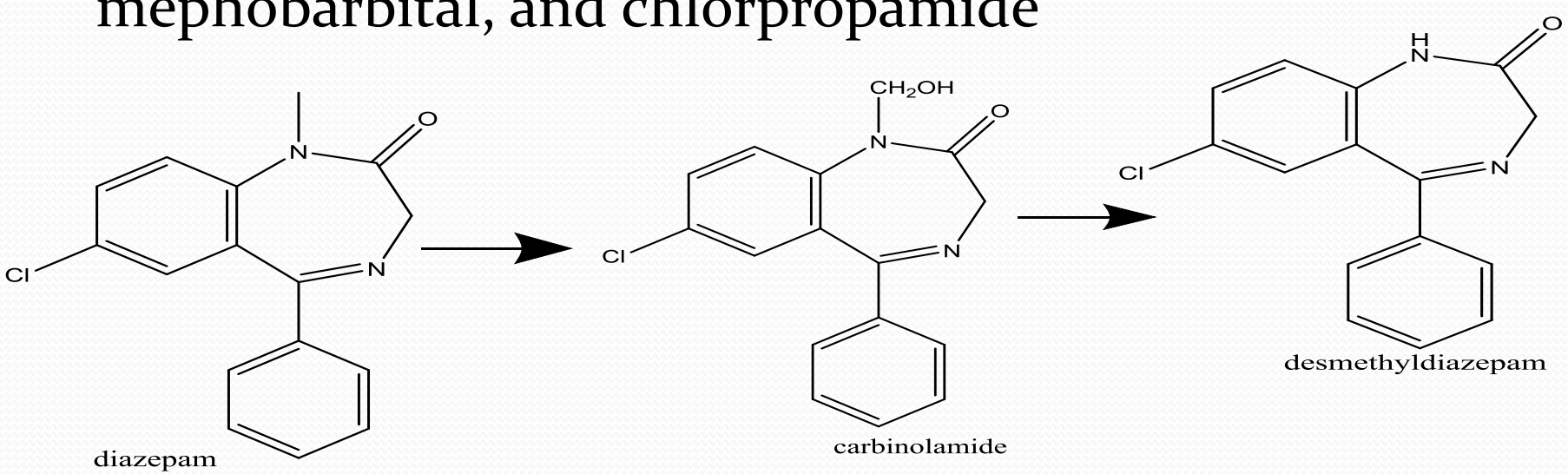
Nicotinine (an oxonicotine-a metabolite of nicotine) undergoes oxidation to the corresponding N-oxide metabolite. Metronidazole also undergoes N-oxidation.



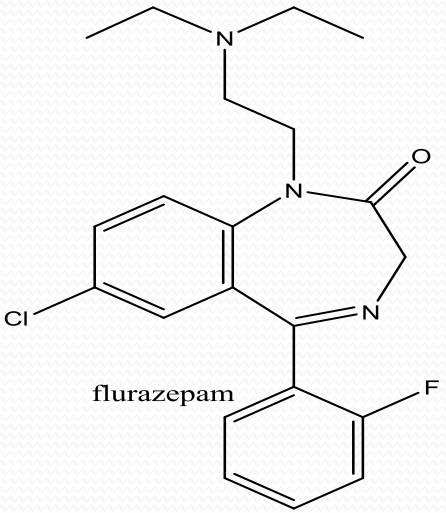
Oxidation of Amides

Two possible oxidation reactions can take place in drugs containing amides;

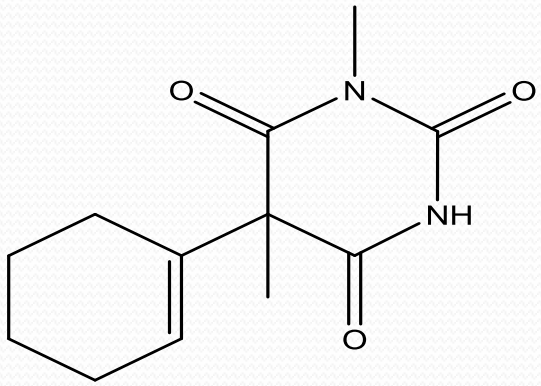
1. Carbon-nitrogen bond cleavage i.e. dealkylation(via carbinolamide) e.g diazepam, flurzepam, mephobarbital, and chlorpropamide



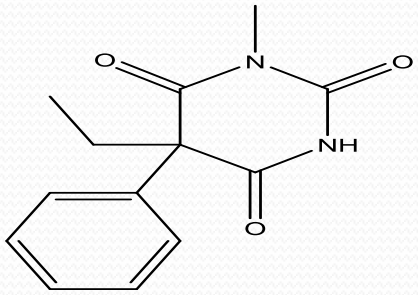
More Examples



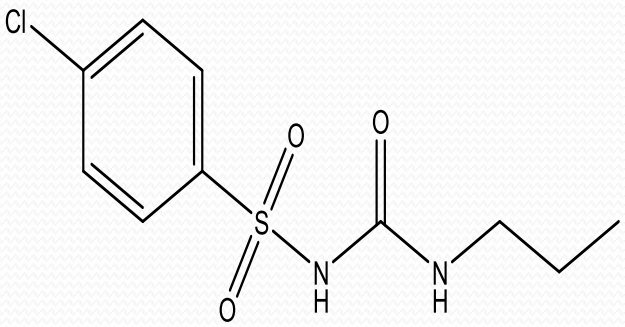
flurazepam



hexobarbital

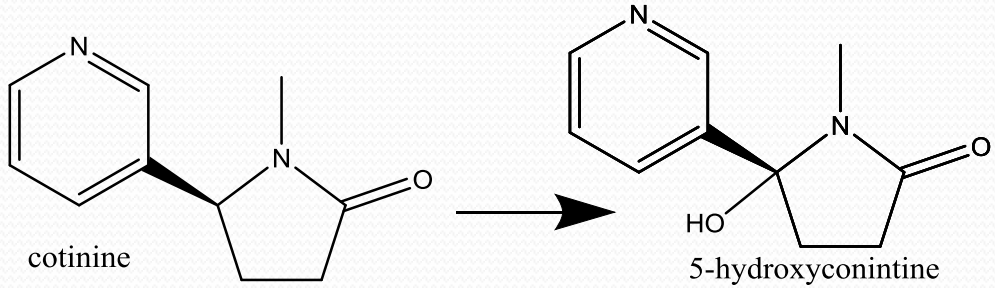


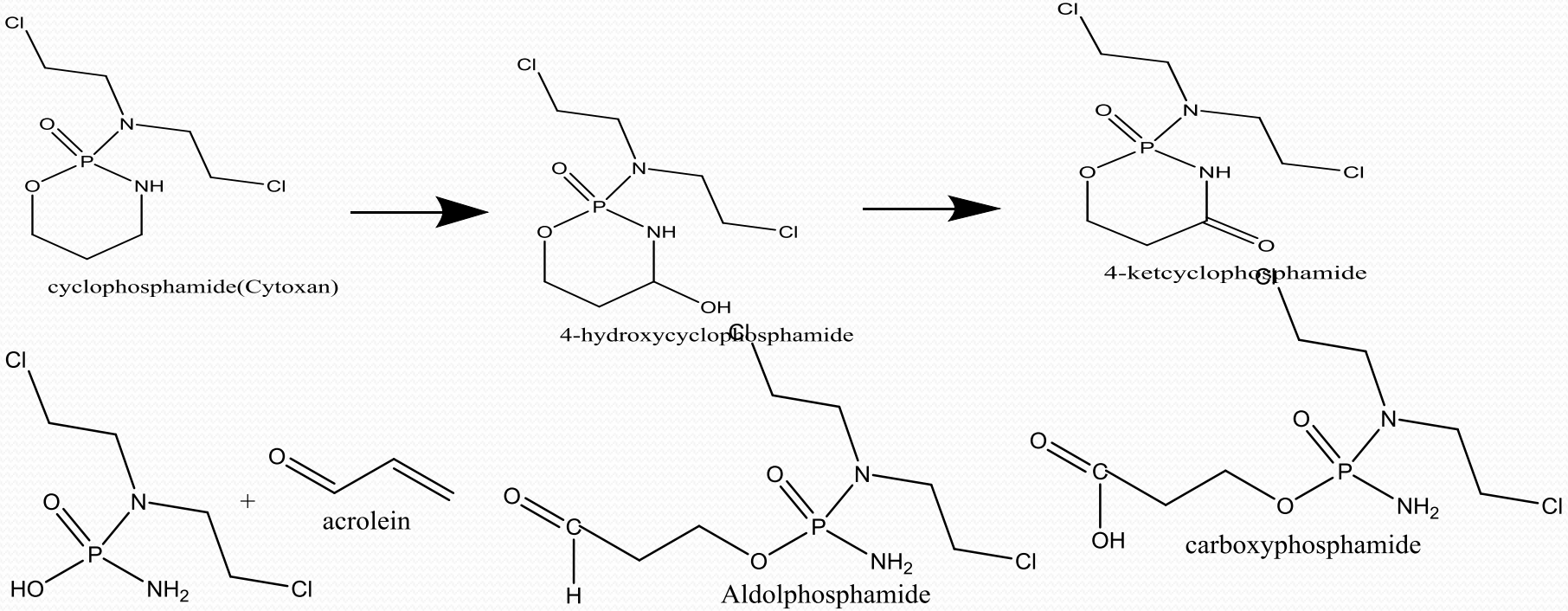
mephobarbital



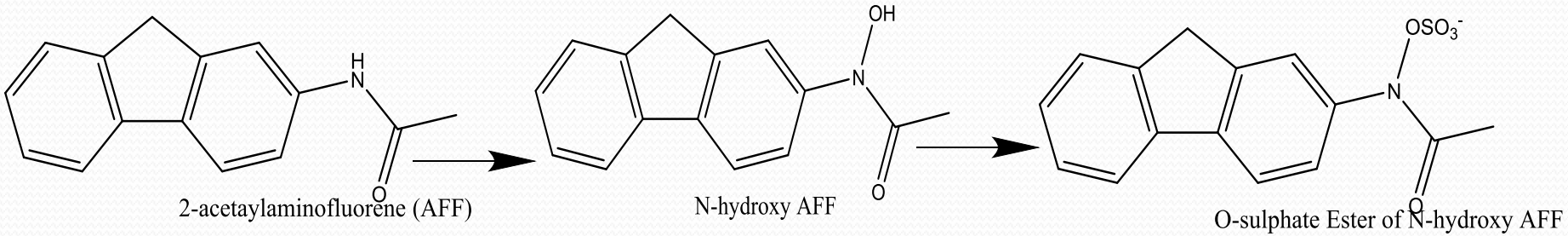
chlorpropamide

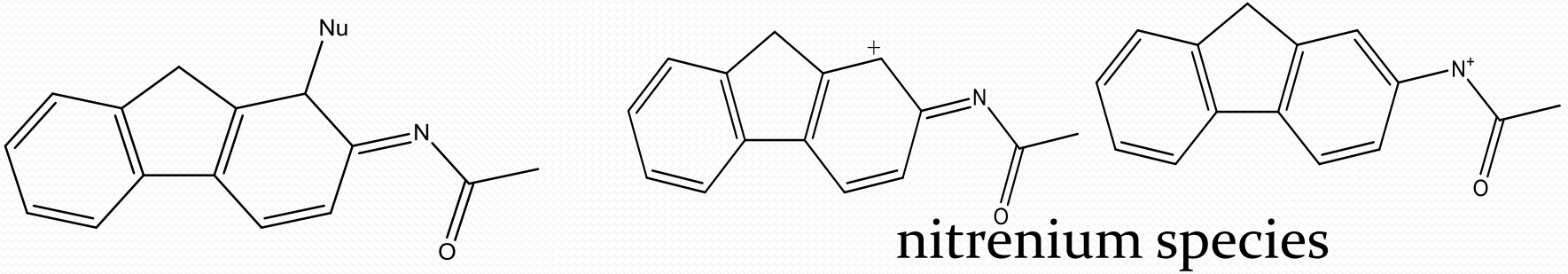
Oxidation of Cyclic Amides, Lactams



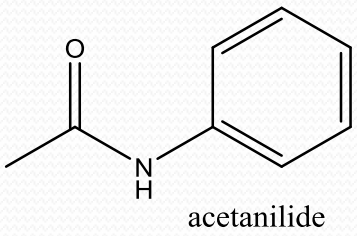


N-Hydroxylation of Aromatic Amides

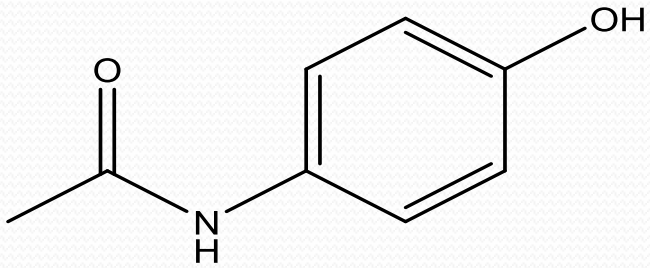




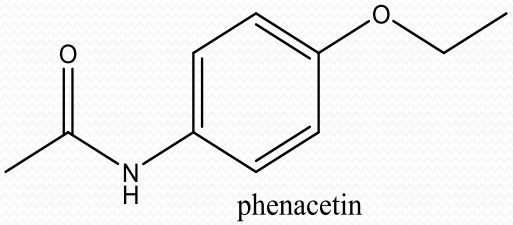
Exc: Oxidation of Acetoaminophen



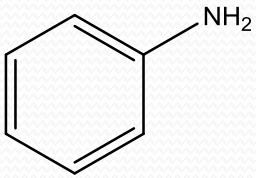
acetanilide



acetoaminophen



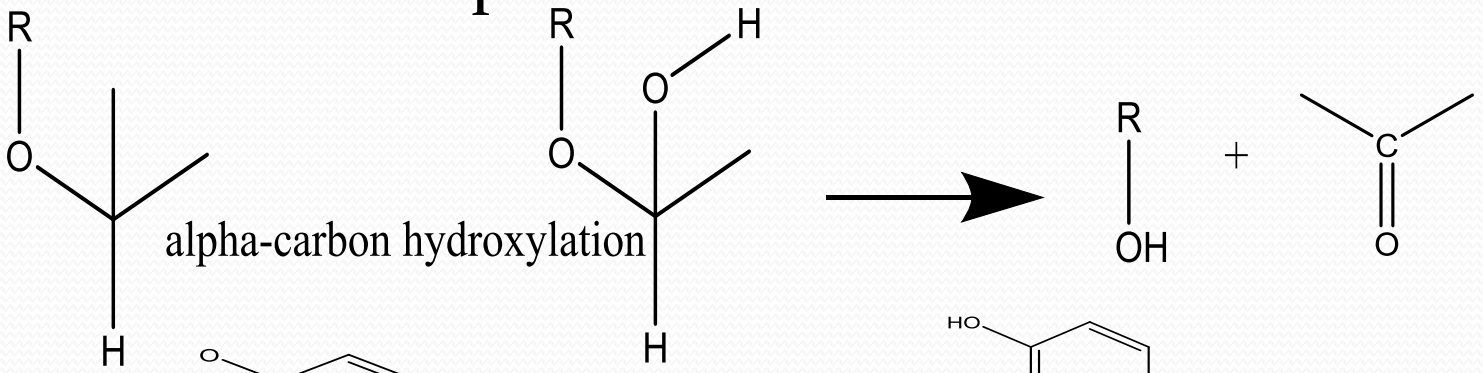
phenacetin

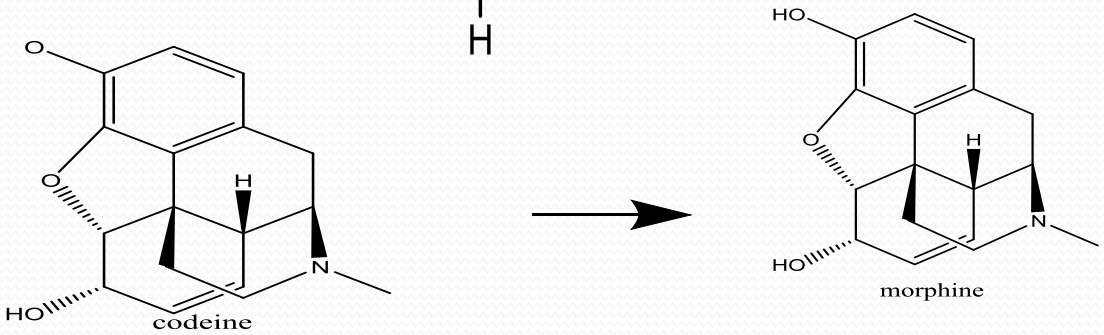


sulphate conj. Glucuronide N-acetylindoquinoline Glutathione conj. Nu adduct

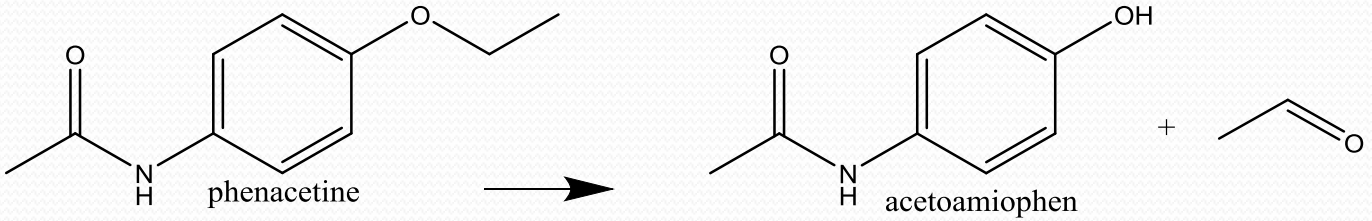
Oxidation involving Carbon-Oxygen Systems

Oxidation of ethers is through α-carbon hydroxylation to form ether hemicetal or hemiketal. This intermediate sponteneously undergoes C-O bond cleavage to the corresponding alcohol or phenol species, e.g. codeine is oxidized to morphine.

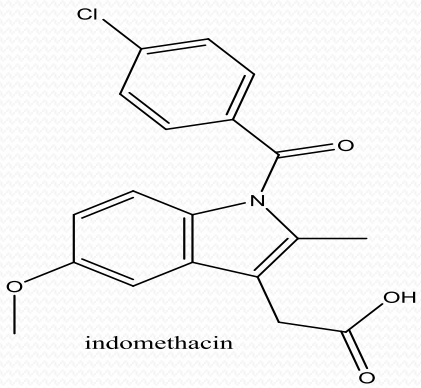


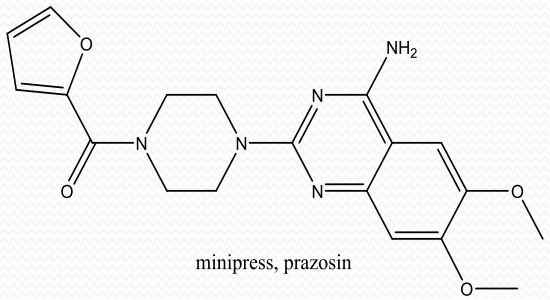


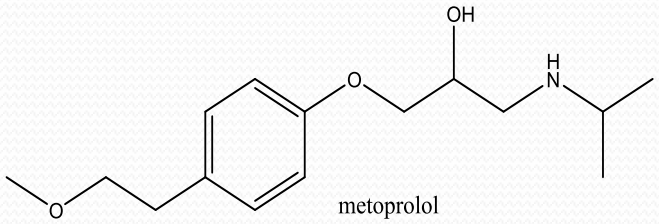
Acetaminophen is produced by the O-deethylation of phenacetin.



Exc: Demonstrate the oxidation of the following:

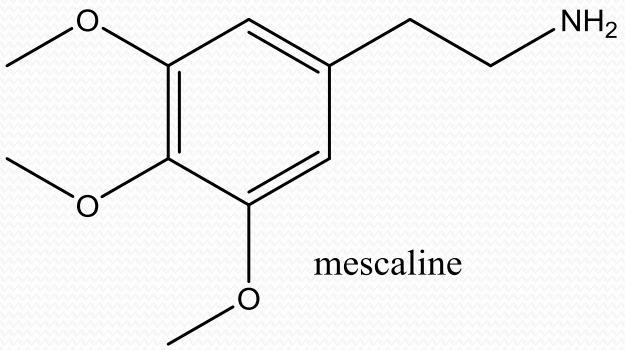




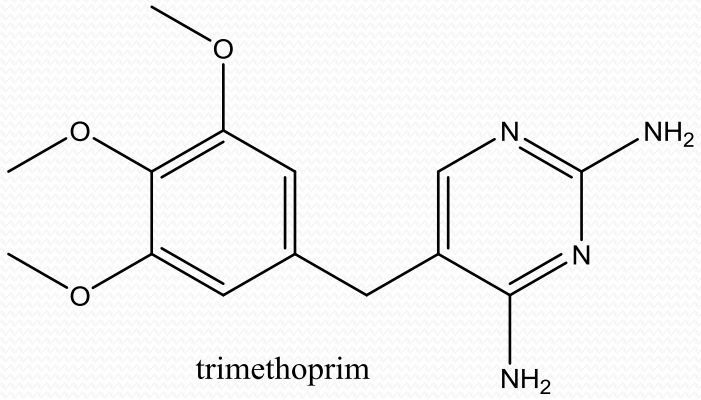


Oxidation of Ethers with many O-R Groups

Selectively or preferentially, one of the O-R groups in drugs containing more than one ether group are oxidised to the corresponding pheolic or alcoholic metabolites.



mescaline

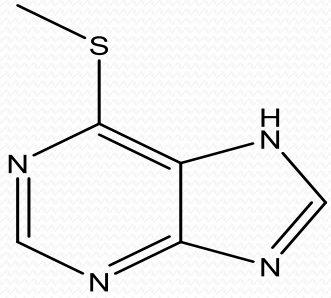


trimethoprim

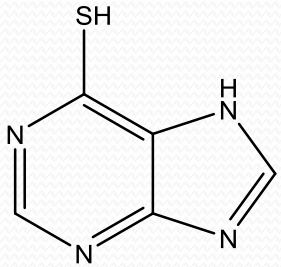
Oxidation of C-S Systems

Sulphur containing druges are metabolised through;

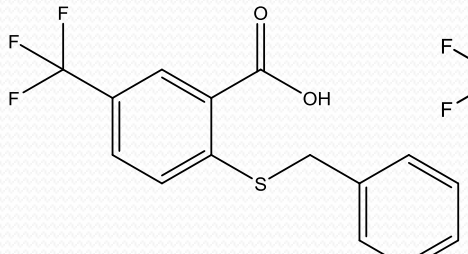
1. S-dealkylation, desulphuration (through α-carbon hydroxlation). Examples are 6-methylthiopurine, methitural, and 2-benzylthio-5-trifluoromethyl benzoic acid. However, only few drugs contain sulphur.

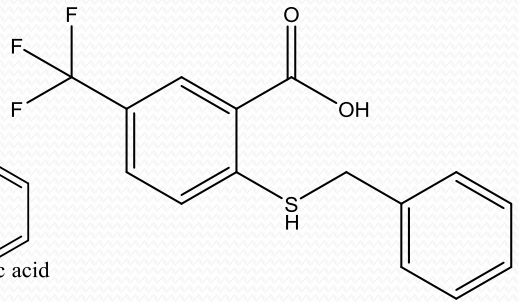


6-methylthiopurine

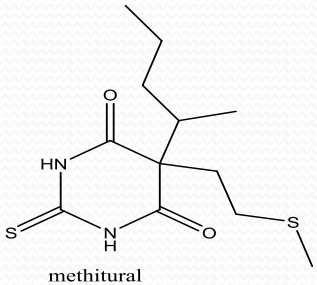


6-mercaptopurine

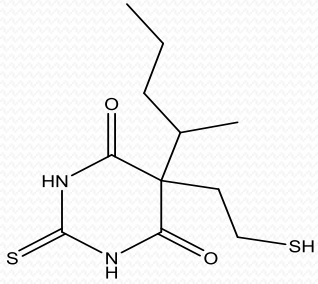




2-benzylthio-5-trifluoromethylbenzoic acid

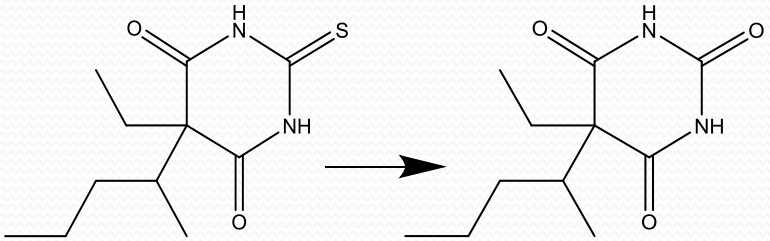


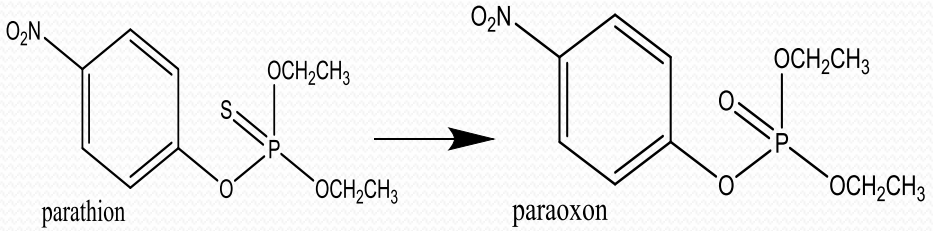
methitural



Oxidation of C-S Systems

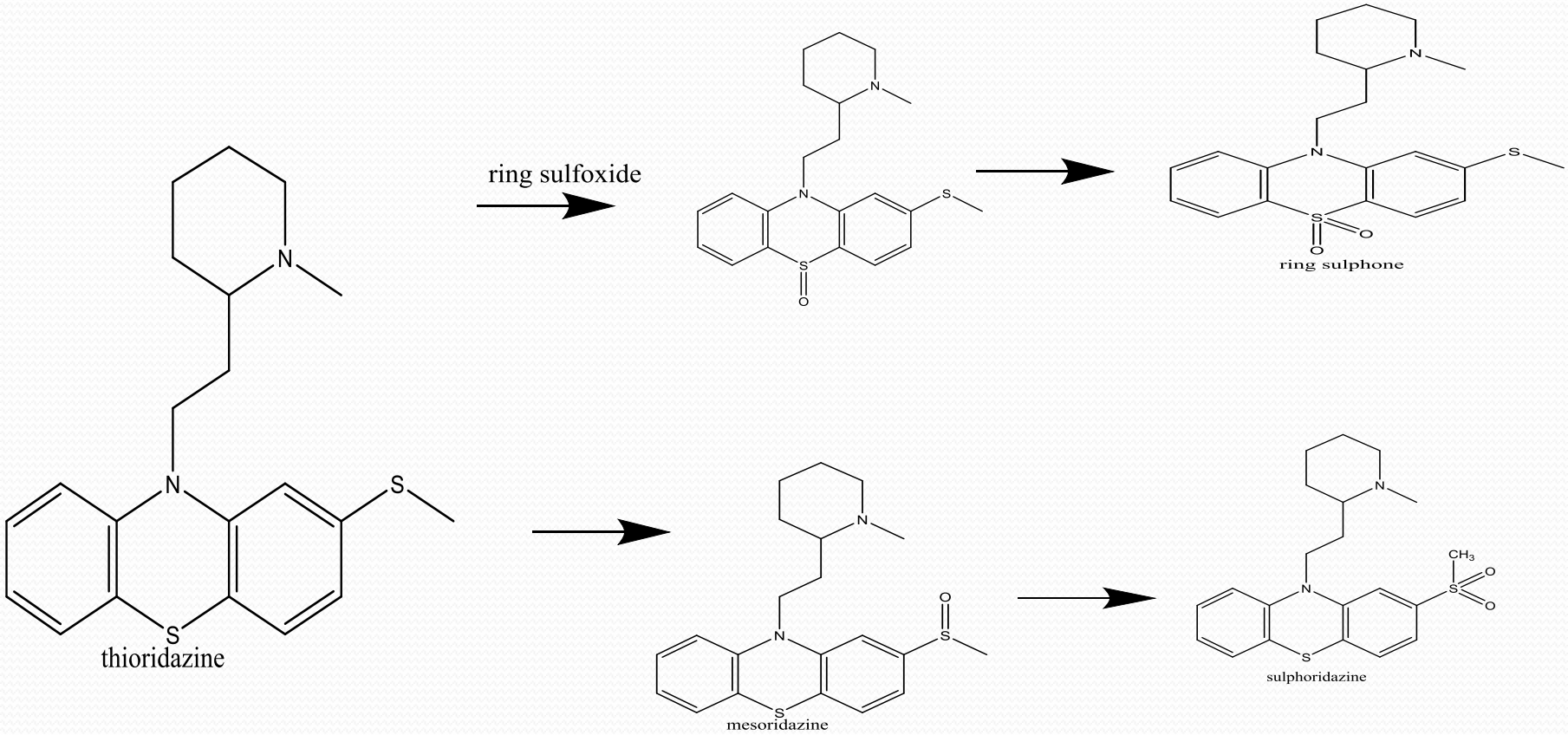
2. Oxidation of the **thiono** bond C=S to C=O is called desulphuration, e.g. thiopental to pentobarbital and parathion to paraoxon.



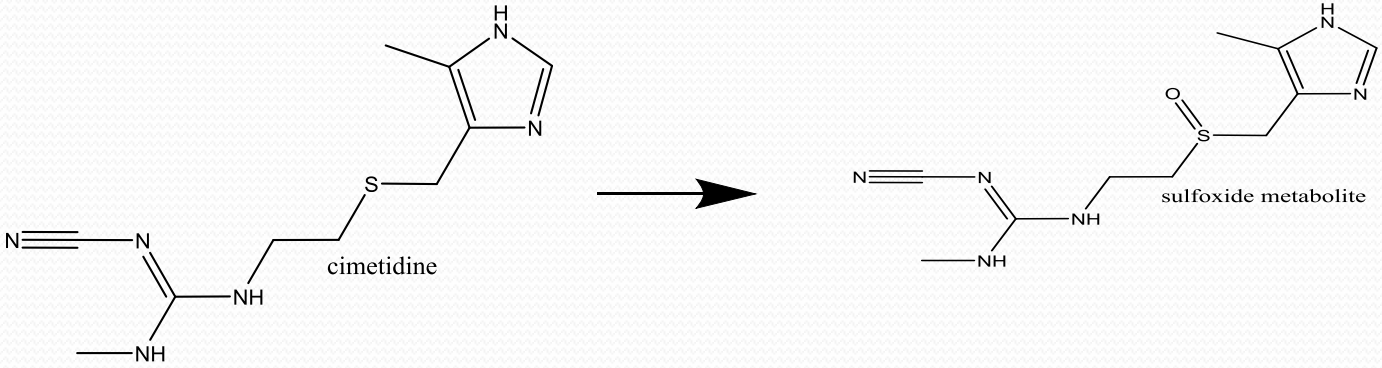


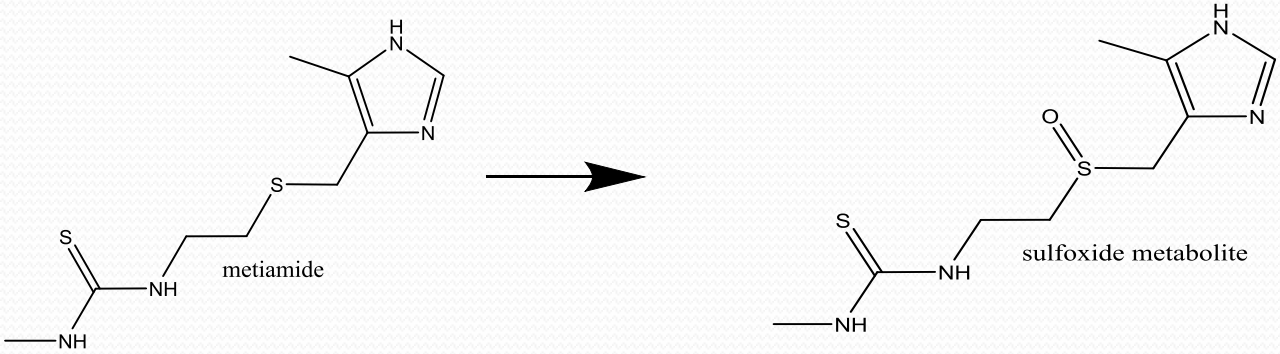
3. S-oxidation reactions (to yield sulphoxide derivatives. For example phenothiazine where both sulphur atoms in thiodidizine are susceptible to S-oxidation i.e. thioridazine to the more active mesoridazine, Also S-Oxidation is noticed in cimetidene and metiamide. Further oxidation of sulphoxide drugs and metabolites to the corresponding sulphone have been noticed e.g. oxisuran. DMSO is oxidized to the its sulphone adduct.

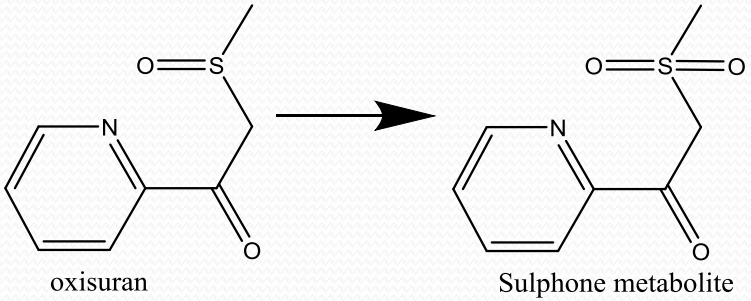
Oxidation of C-S Systems

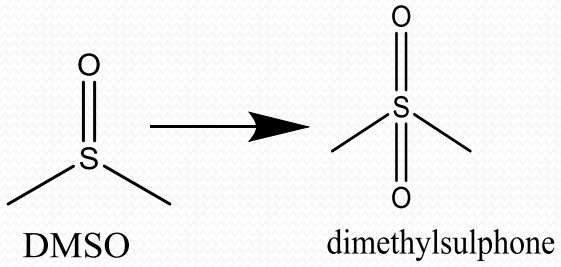


Oxidation of C-S Systems









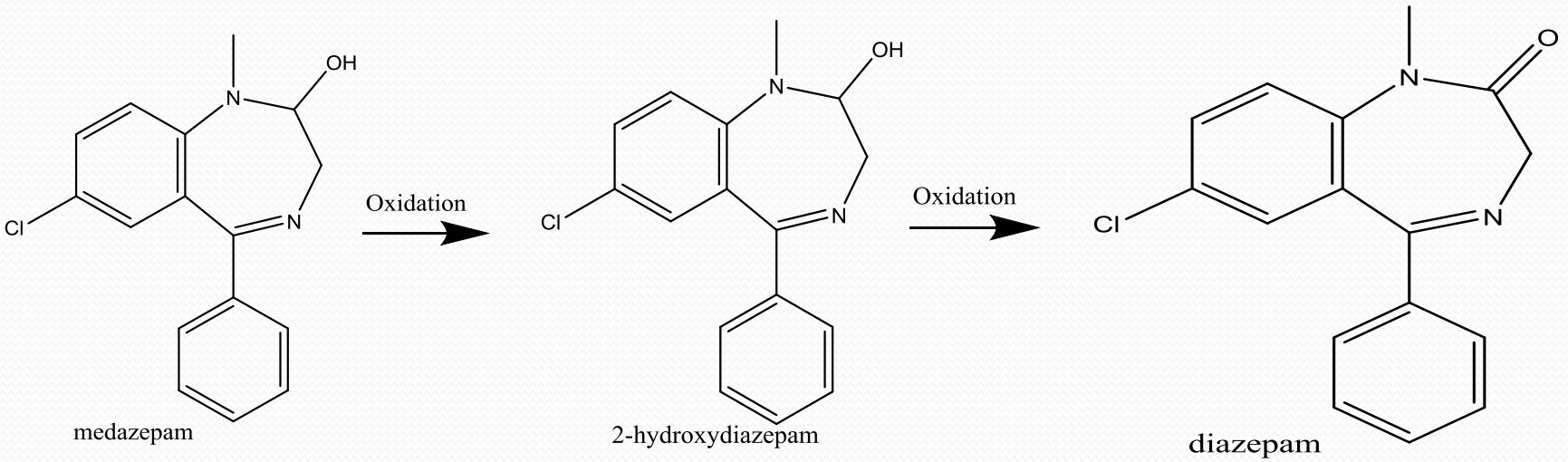
Oxidation of Alcohols and Aldehydes

Alcohols or carbinol metabolites, if not conjugated, are further oxidized to; aldehydes (for primary alcohols)- which are further oxidised to carboxylic acids - or ketones (for secondary alcohols). However, this reaction is reversible i.e. it goes back to secondary amines.

- The oxidation of alcohols is catalysed by alcohol dehydrogenase present in the liverand other tissues and needs NAD^+ and $NADH^+$ are required as coenxzymes.
- Aldehyde dehydrogenases including aldehyde dehydrogenase and xanthine oxidase carry out the oxidation of aldehydes to their corresponding acids.

Oxidation of Alcohols and Aldehydes

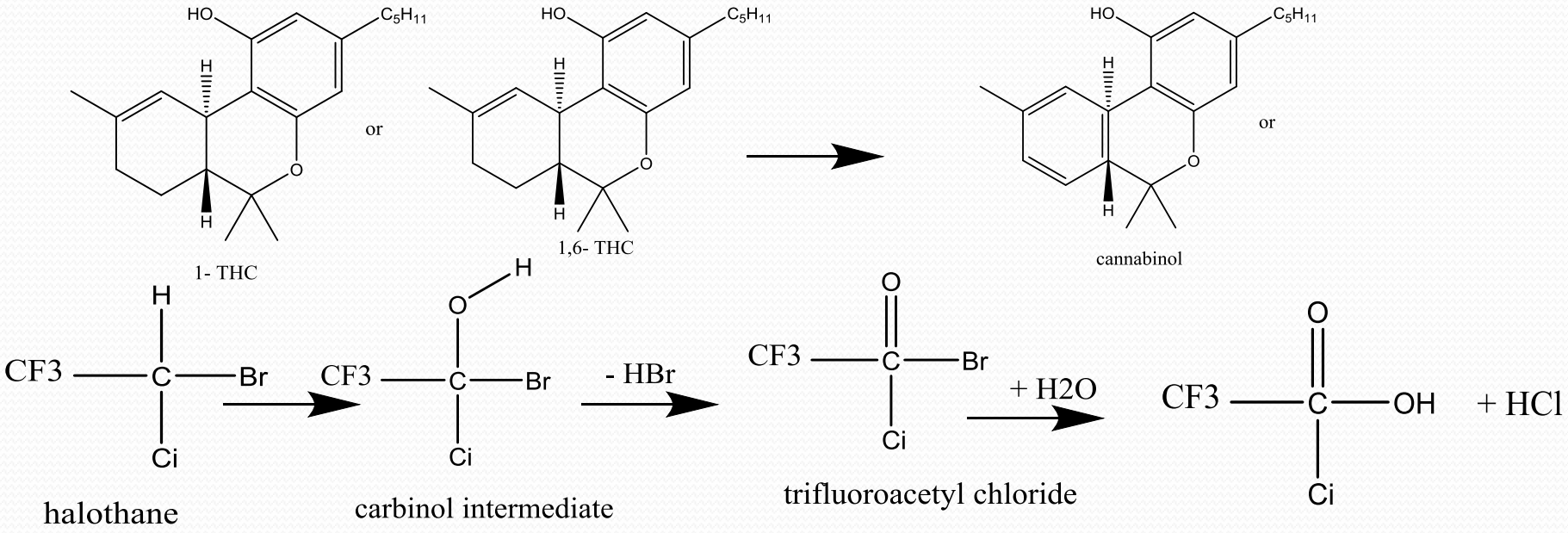
In the metabolism of medazepam to diazepam, the intermediate carbinolamine produces carbonyl adduct. Microsomal dehydrogenase carry out this reaaction.

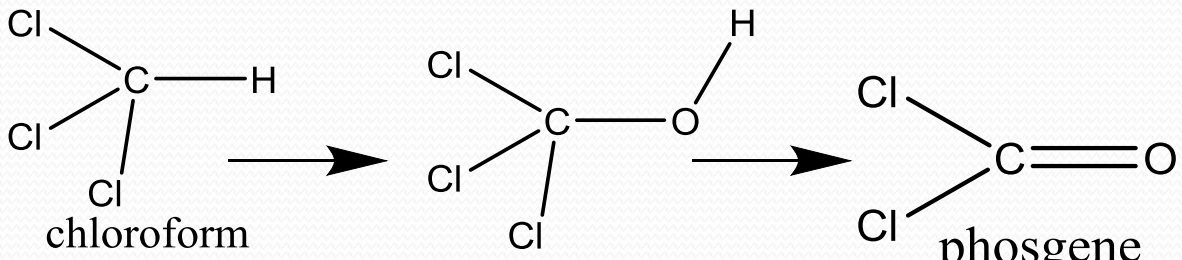


Other oxidative Biotransformation Pathways

In addition to the oxidative pathways discussed earlier, aromatisation or dehydrogenation amy take place. A ring in the steroid norgestrol is oxidised to the corresponding phenolic product as a major metabolite in women.

In mice, the terpene ring of .....is oxidised to cannabinol.

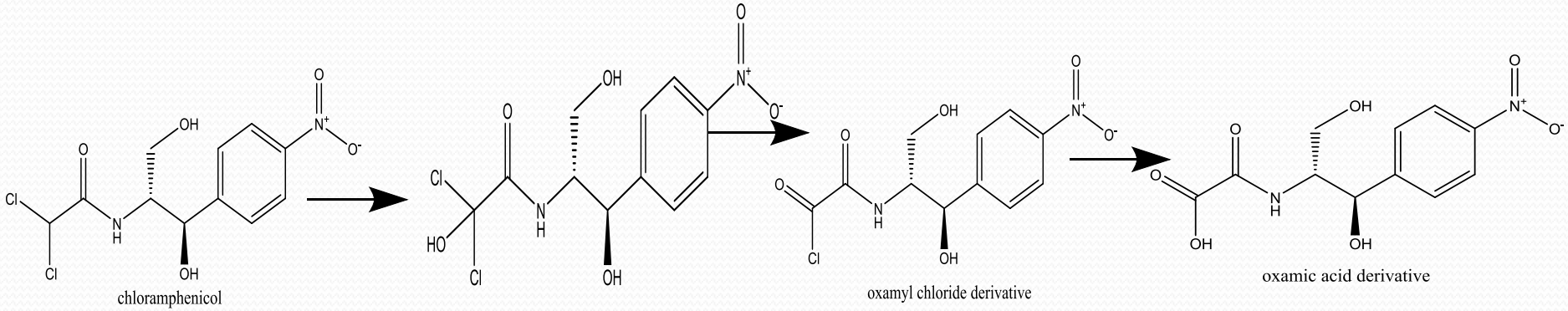




$H_2CO_3 + HCl$

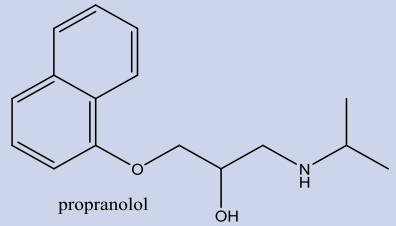
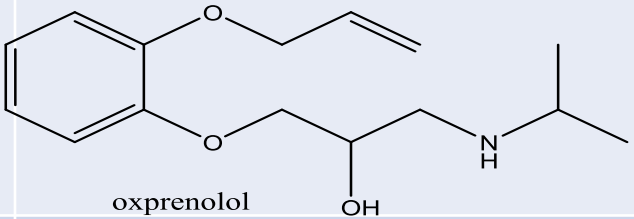
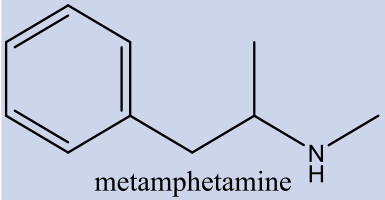
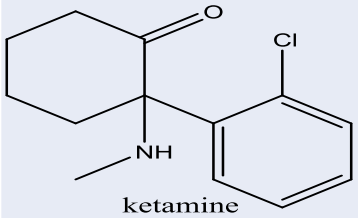
Tissue Nucleophiles

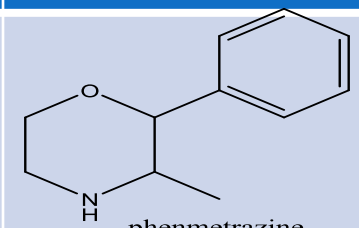
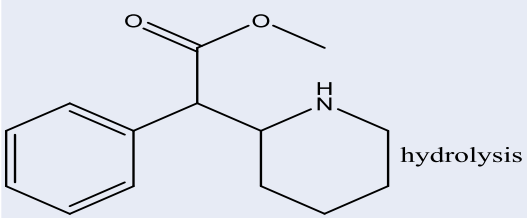
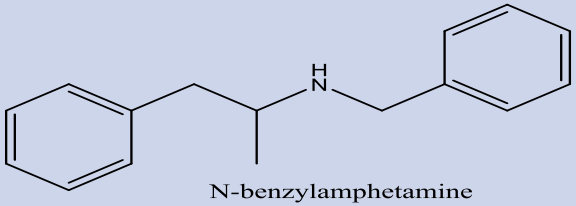
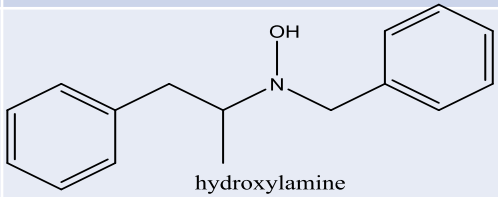
Covalent Bonding

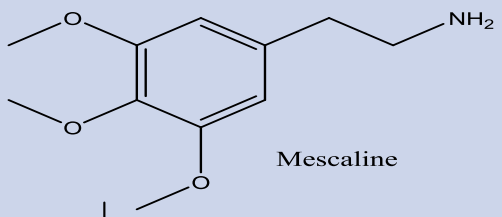
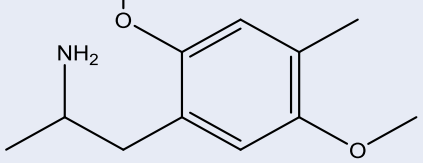
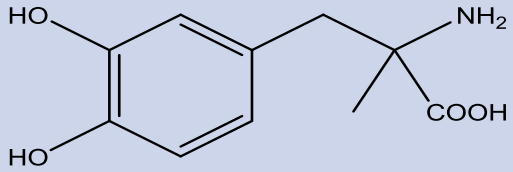
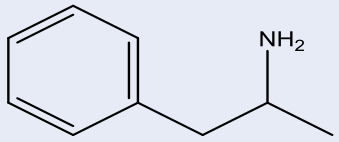
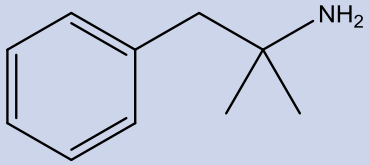


Tissue Nucleophiles

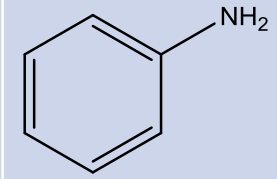
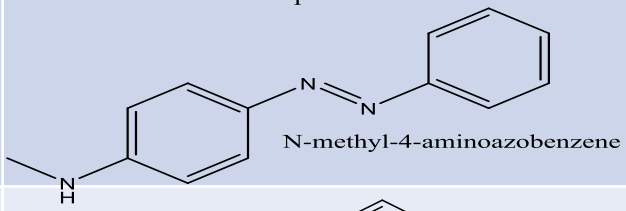
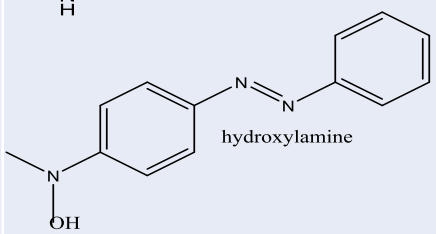
Covalent Bonding

1		Dealkylation and Deamination	
2		Dealkylation and Deamination	
3		Demethylation Benzylhydroxlation para-hydroxylation	
4		Demethylation to primary amine	

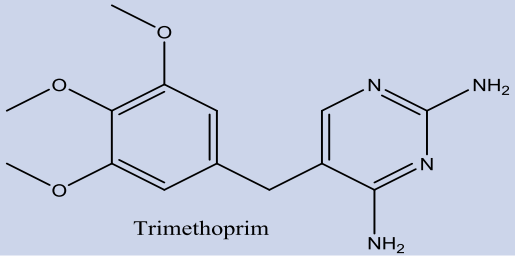
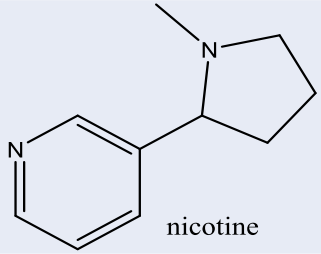
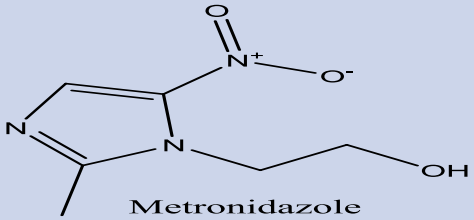
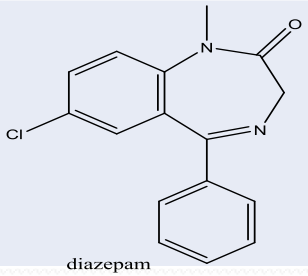
	 phenmetrazine	At position 3 alpha to N gives phenol the oxidised to lactam (ketone) C=O
	 hydrolysis methylphenidate	Hydrolysis of ester to the acid then hydroxlyation at position 6 (alpha to nitrogen) then lactam (C=O)formation
	 N-benzylamphetamine	N-oxidation produces hydroxylamine
	 hydroxylamine metabolite	oxidation of hydroxylamine to the nitrone

	 Mescaline	Alpha to N hydroxylation leads to deamination.	Demethoxylation - hydroxylation alpha to oxygen (heteroatom) Benzylic hydroxlation
	 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane	Alpha to N hydroxylation leads to deamination.	
	 methyldopa	Decarboxylation of the acid to give secondary amine then deaminated	
	 amphetamine	α-carbon hydroxylation then deamination (removal of ammonia)to give phenylacetone.	
	 phentermine	Alpha hydroxlation is not possible	Benzylic and para hydroxlations are possible

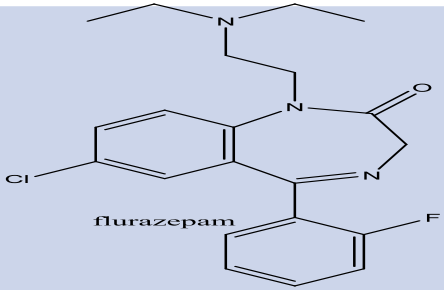
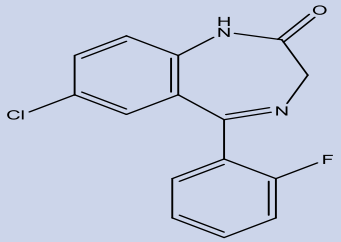
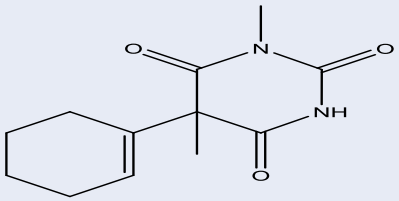
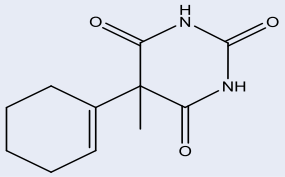
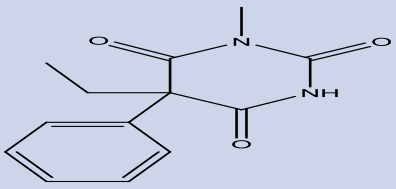
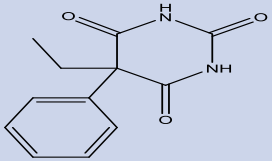
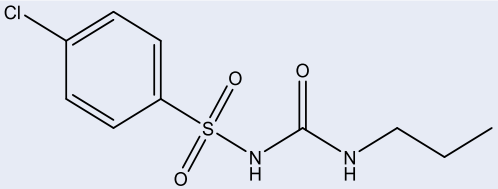
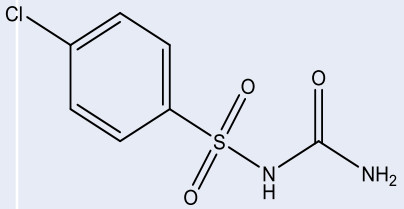
Aromatic Amines and Heterocyclic Nitrogen Compounds

	 aniline	N-oxidation to give hydroxlamine (-NH-OH) which gives the nitroso (-N=O)	
	 dapsone	N-oxidation give N-Hydroxydapsone (similar to aniline)	
	 N-methyl-4-aminoazobenzene	N-oxidation to give N-hydroxylamine	
	 hydroxylamine	Conjugation to sulphate which is a good leaving group giving nitrenium ion	The nitrenium ion stablises itself by resonace leading forming a stable electrophile for Nu attack

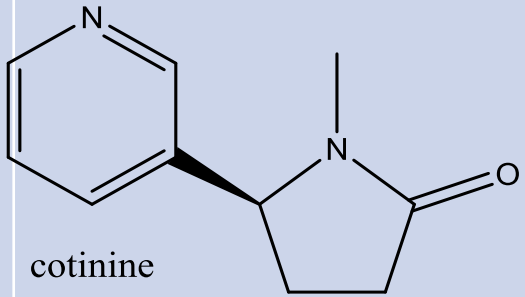
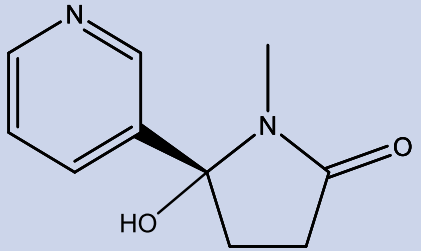
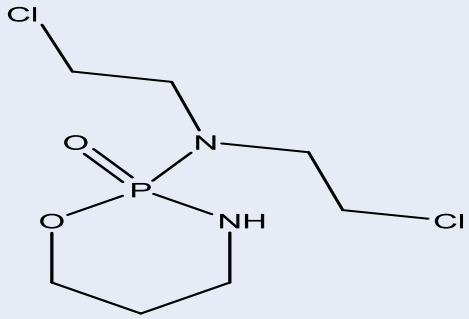
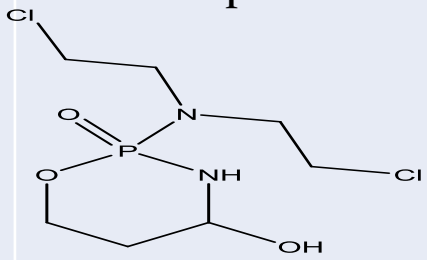
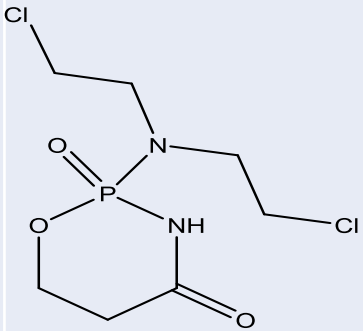
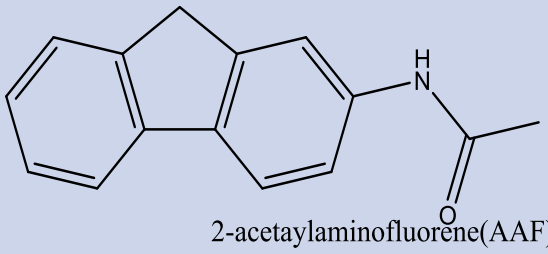
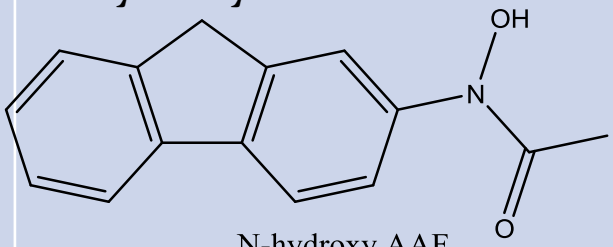
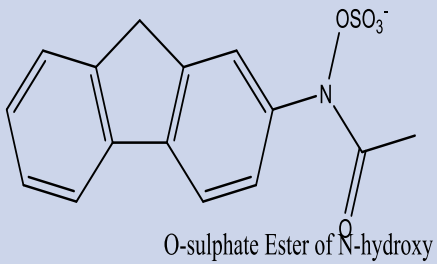
N-oxidation of Aromatic Compounds

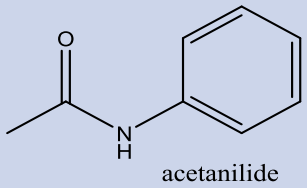
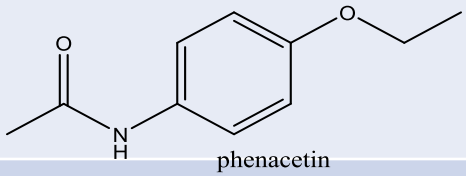
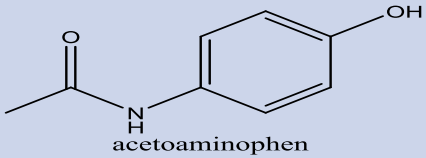
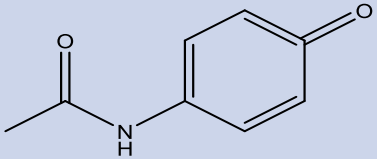
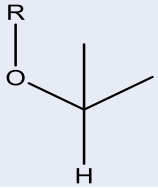
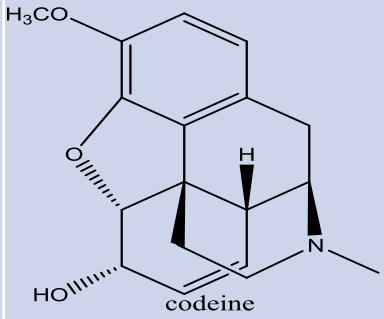
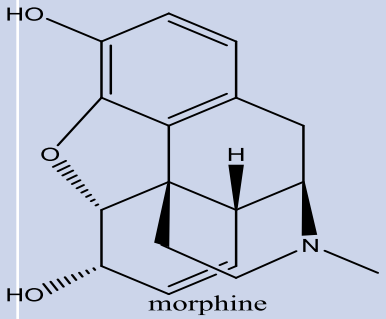
	 Trimethoprim	N-oxidation at positions 1 or 3	
	 nicotine	N-oxidation at N of heterocyclic ring	
	 Metronidazole	N-oxidation at N of heterocyclic ring	
	 diazepam	Hydroxlation at C alpha to N of amide, demethylation	What are the other possible oxidation sites?

Oxidation of Amides

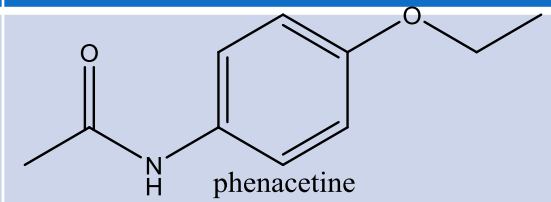
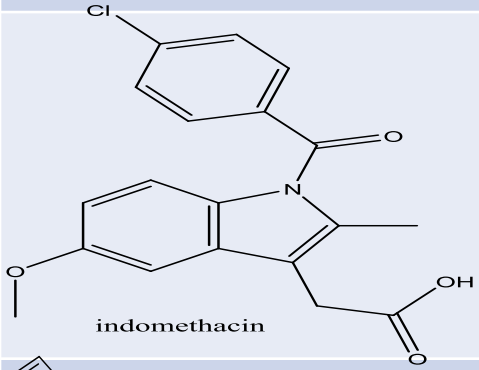
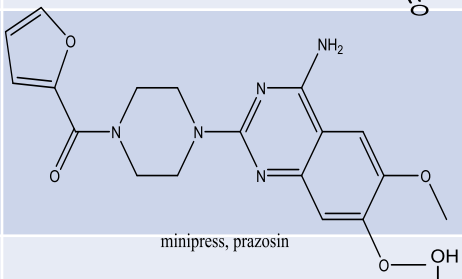
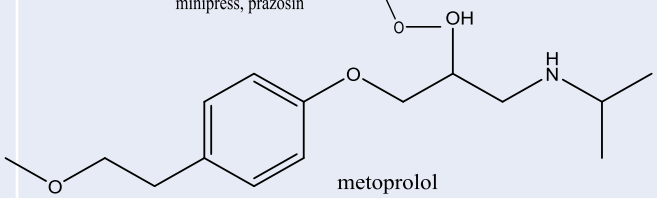
	 flurazepam	Dealkylation 	
	 hexobarbital	Dealkylation 	
	 mephobarbital	Dealkylation 	
	 chlorpropamide	Dealkylation of n-propyl 	

Oxidation of Amides

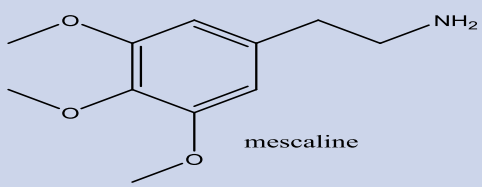
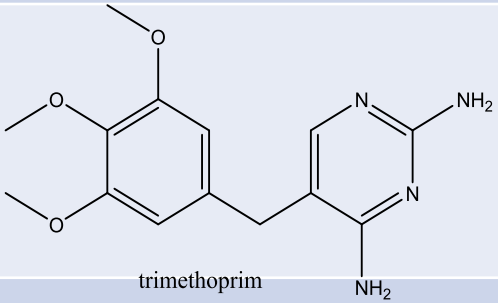
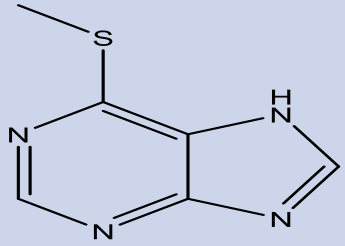
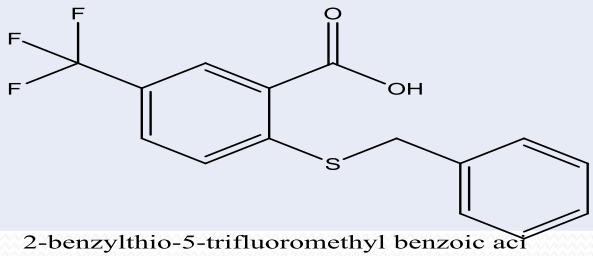
	 cotinine	Hydroxylation at position 5, carbon alpha to N of amide.	 5-hydroxyconintine
	 cyclophosphamide(Cytoxan)	Hydroxylation at position 4, carbon alpha to N of amide.  4-hydroxycyclophosphamide	 4-ketocyclophosphamide
	 2-acetaylaminofluorene(AAF)	N-hydroxylation  N-hydroxy AAF	 O-sulphate Ester of N-hydroxy AFF

	 acetanilide	P-hydroxylation	
	 phenacetin	O-dealkylation	
	 acetoaminophen	Keto adduct  N-acetylaminoquinone	
		Hydroxylation of C Alpha to heteroatom (O) i.e. replacing H by OH to give hemiacetal or hemiketal then to ketone	By demethoxylation
	 codeine	Demethxylation  morphine	

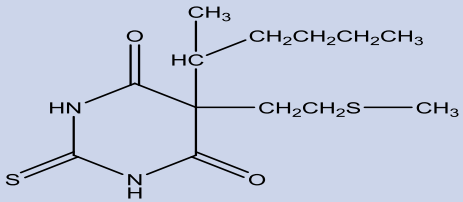
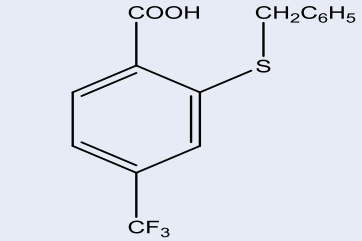
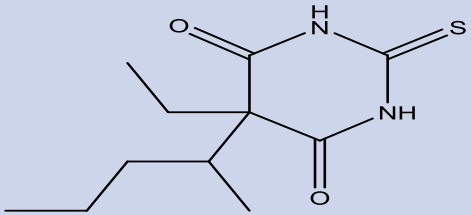
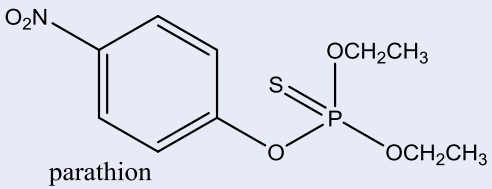
Oxidation Involving O-C Sytems

	 phenacetine	O-deethylation	
	 indomethacin	O-Demethylation	
	 minipress, prazosin	O-demethylation of one CH_3	
	 metoprolol	O-demethylation	

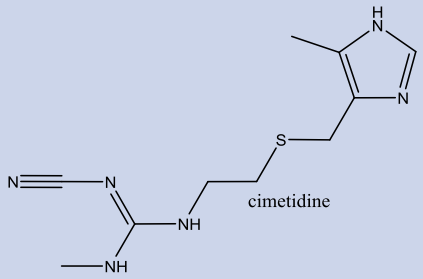
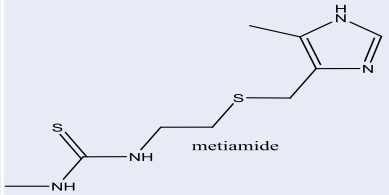
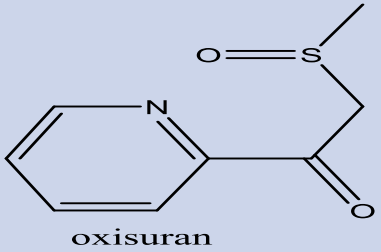
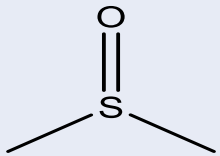
Oxidation Involving O-C and S-S

	 mescaline	O-demethylation of one of OCH_3	
	 trimethoprim	O-demethylation	
	 6-methylthiopurine	S-dealkylation (demethylation)	
	 2-benzylthio-5-trifluoromethyl benzoic acid	S-debenzylation	

Oxidation of C-S Systems

	 methithural	S-demethylation	
	 2-benzylthio-5-trifluoromethyl benzoic acid	Debenzylation	
	 thiopental	Desulphuration(conversion of C=S to C=O bonds	
	 parathion	Desulphuration(conversion of C=S to C=O bonds	

Oxidation of Sulfoxides to sulfones

		Sulphoxide metabolite	
		Sulphoxide metabolite	
		Sulphone metabolite	
		Further oxidation of sulfoxide to sulfone