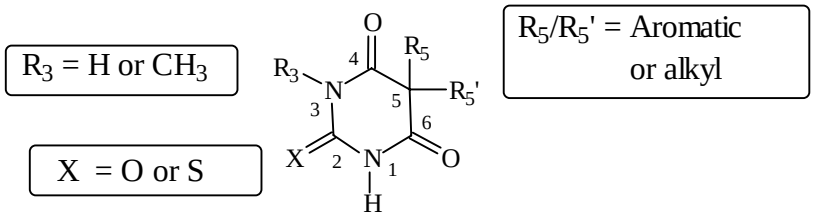
THE BARBITURATES

1. Barbiturate General Structure and Numbering

- Barbiturates contain a "balance" of hydrophilic (2,4,6-pyrimidinetrione ring structure) and lipophilic (5,5'-substituents) functionality. The overall hydrophilic (polar) or lipophilic (non-polar) character of the barbiturates is a function of:

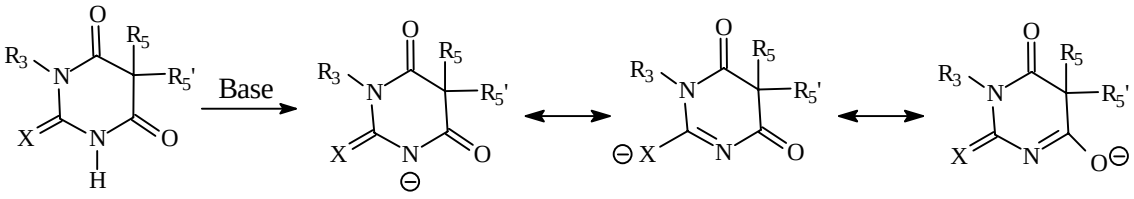
  - The hydrophilicity of the pyrimidinetrione ring which is a function of the number of N-substituents and the pKa of the acidic proton(s), and
  - The overall size and structure of the two substituents at the 5-position



Barbiturate

2. Barbiturate Ionization, Acidity and Salt Formation

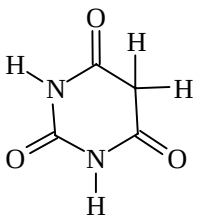
- Barbiturates containing at least one N-H hydrogen atom are acidic. Acidity results from the ability of the N to lose hydrogen and the stabilization of the resulting anionic charge of the conjugate base by resonance delocalization as shown below:



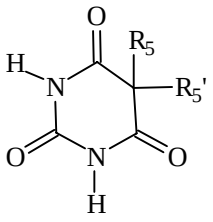
Acid form

Conjugate Base Resonance Forms

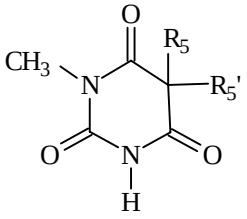
- The relative acidity of different barbiturates is a function of the degree of N-substitution and C-5-substitution as shown below (<u>electron donors decrease acidity</u>!):



Barbituric acid: pKa 4.12



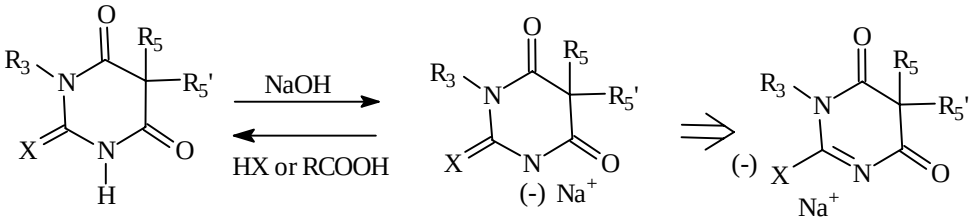
5,5'-Disubstituted barbituric acid: pKa 6.5-8



3,5,5'-Trisubstituted barbituric acid: pKa > 8

- Barbituric acid (N- and C-5-unsubstituted) is the highly acidic (but not active as a CNS depressant): See structures above
- Addition of substituents at the 5-position decrease acidity (raise pKa) due to the electron donating effects (+I) of the 5-alkyl groups: See structures above
- Substitution at one ring nitrogen atom reduces acidity (raise pKa) due to the electron donating effects (+I) of the N-alkyl group: See structures above
- Substitution at BOTH ring nitrogen atoms eliminates both acidic protons (non-acidic)

- Due to the presence of one (or more) acidic protons, barbiturates can be converted to water soluble salt forms by treatment with an appropriate base as shown below. Note that the charge resides primarily on the more electronegative oxygen atom:

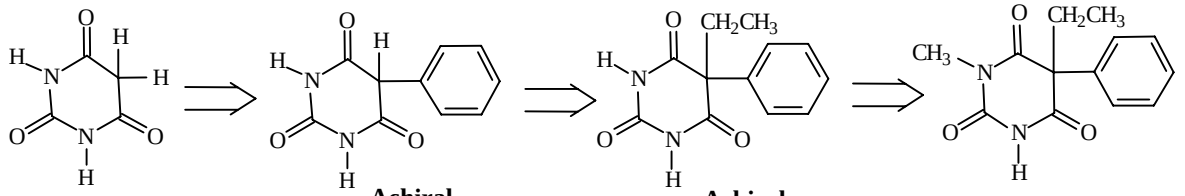


Acid form
Water insoluble

Salt form (conjugate base)
Water soluble

3. Barbiturate Chirality and Stereochemistry

- The barbiturate ring system contains only one sp^2 carbon atom and it is not chiral unless 1) there are two different C-5 substituents AND 2). one ring nitrogen is substituted as shown in the example below:



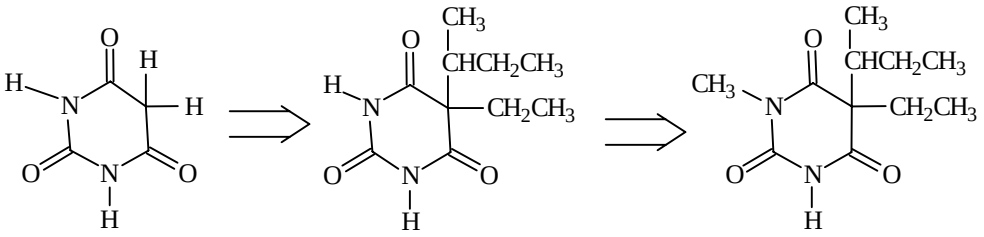
Achiral
(No chiral center)

Achiral
(No chiral center)

Achiral
(No chiral center)

Chiral C-5 carbon
(R&S enantiomers)

- The C-5 substituents may contain chiral (unsymmetrically substituted sp^2 carbon atom(s)) and in such cases the barbiturate is chiral. Some barbiturates have BOTH a chiral C-5 atom AND a chiral side chain as shown in one example below:



Achiral
(No chiral center)

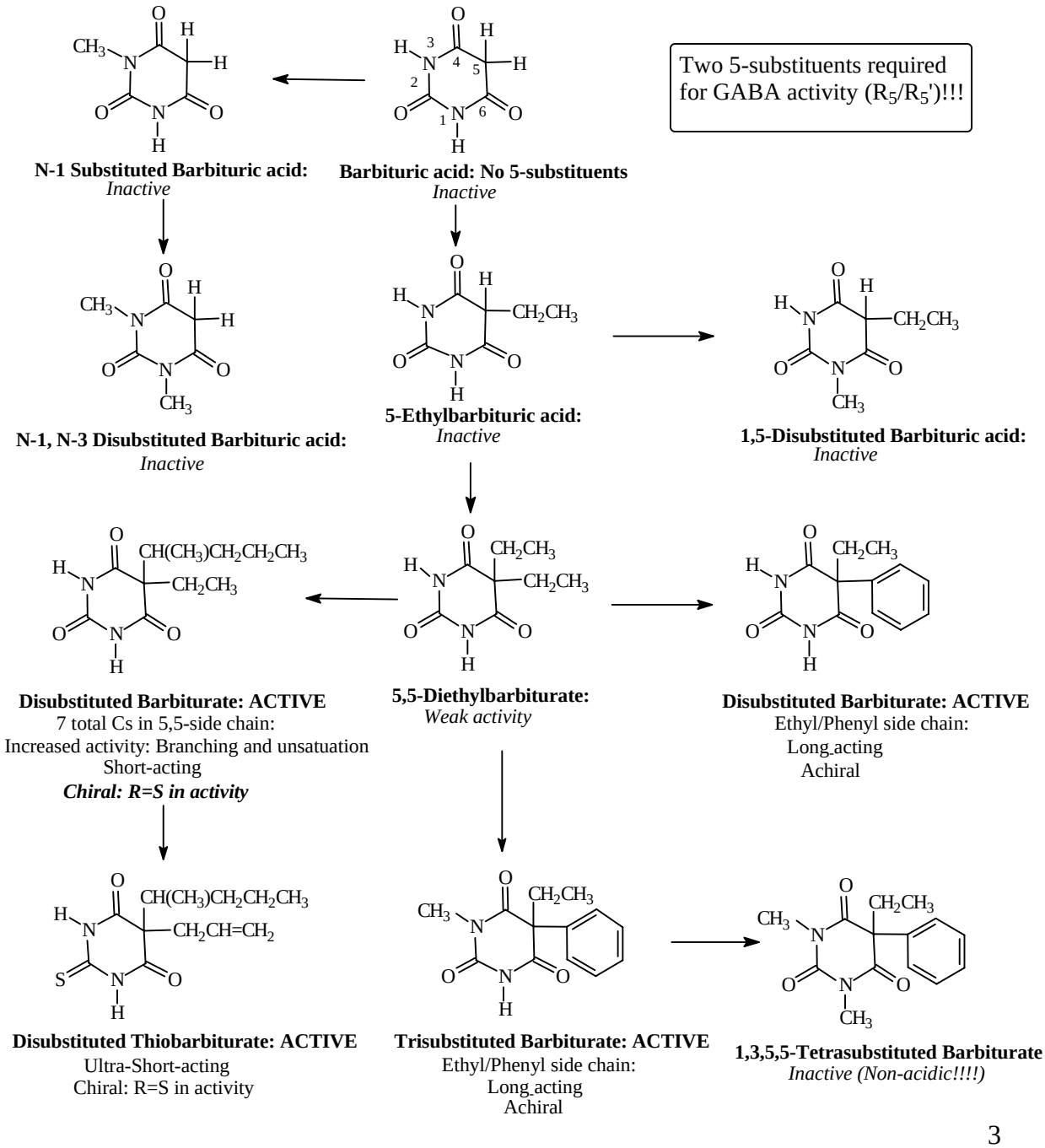
Chiral C-5 substituent
(R&S enantiomers)

Chiral C-5 carbon and
chiral C-5 substituent
(4 enantiomers possible)

- Enantiomers display comparable physicochemical properties, passive membrane permeability, intrinsic pharmacologic activities **but may display differential metabolism**.

4. Barbiturates and Mechanism of Action and Therapeutic Uses

- Barbiturates bind to the $GABA_A$ receptor which ultimately increases GABA-induced Cl^- currents. They bind at a site distinct from the BDZ binding site. Barbiturates also may reduce glutamate-inducde depolization by acting as antagonists at AMPA-type receptors. The actions of the barbiturates are described in more detail in the *Pharmacology Notes.* **The basic structural features required for general CNS depressant activity for the barbiturates are summarized in the following Figure**:



- The following indications apply to most barbiturates:

  ➔ Sedation: Although traditionally used as nonspecific CNS depressants for daytime sedation, the barbiturates have generally been replaced by the benzodiazepines.

  ➔ Hypnotic: Short-term treatment of insomnia, since barbiturates appear to lose their effectiveness in sleep induction and maintenance after 2 weeks. If insomnia persists, seek alternative therapy (including nondrug) for chronic insomnia.

  ➔ Preanesthetic: Used as preanesthetic sedatives as indicated below.

  ➔ Anticonvulsant (mephobarbital, phenobarbital): Treatment of partial and generalized tonic-clonic and cortical focal seizures.

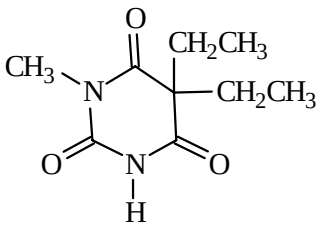
  ➔ Acute convulsive episodes: Emergency control of certain acute convulsive episodes (eg, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus and toxic reactions to strychnine or local anesthetics).

  ➔ Headache products

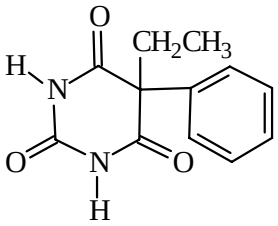
5. Barbiturate Products and Onset and Duration of Action

A. Long-Acting Barbiturates (Typically Anticonvulsants): Relatively slow onset (30-60 minutes) and relatively long duration (10-16 hrs)

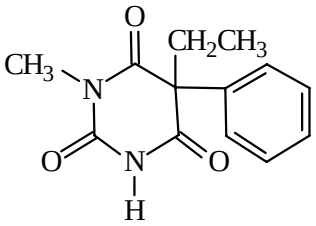
- Structure: N-H or N-Methyl and C-5 side chains consisting of two ethyl groups, or an ethyl and phenyl group. **General Properties**: Relatively low lipophilicity and low plasma protein binding (<40%):



Metharbital



Phenobarbital

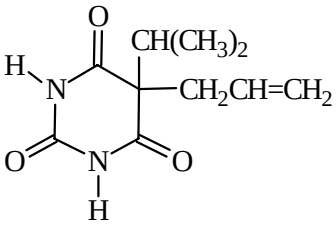


Mephobarbital

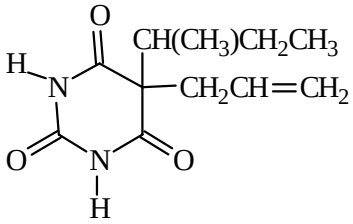
B. Intermediate-Acting Barbiturates (Sedative/Hyponotics): Relatively slow onset (45-60 minutes) and intermediate duration (6-8 hrs)

- Structure: N-H and C-5 side substituents consisting of and ethyl or allyl group and a 3 to 5–carbon atom unit. **General Properties:** Intermediate lipophilicity and intermediate plasma protein binding (50%)

Allyl Substituted!

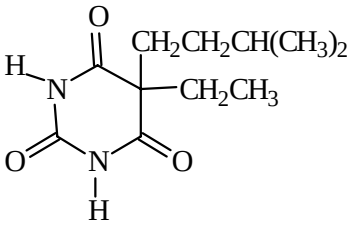


Aprobarbital

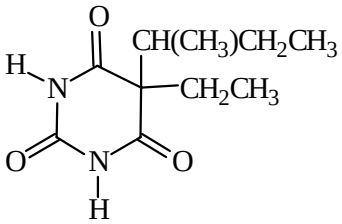


Talbutal

Ethyl Substituted!



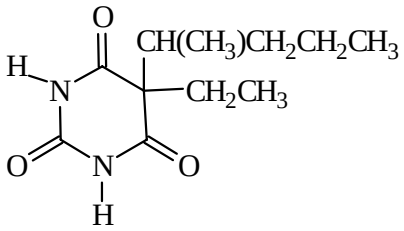
Amobarbital



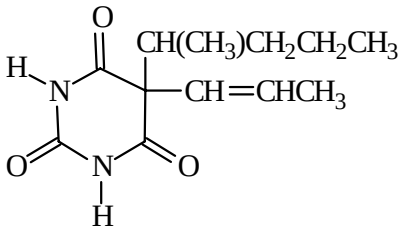
Butabarbital

C. Short-Acting Barbiturates (Typically sedative/hypnotics): Relatively rapid onset (10-15 minutes) and relatively short duration (3-4 hrs)

- Structure: N-H and C-5 side chains consisting of ethyl or allyl and a 5 carbon unit. **General Properties:** High lipophilicity and high plasma protein binding (70%). Rapid distribution and redistribution



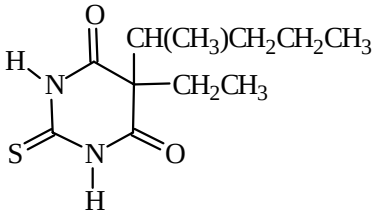
Pentobarbital
(Ethyl Substituted)



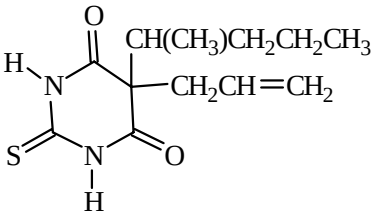
Secobarbital
(Allyl substituted)

D. Ultra-Short-Acting Barbiturates (Induction of Anesthesia): Administered by injection (as salts): immediate onset and very short duration.

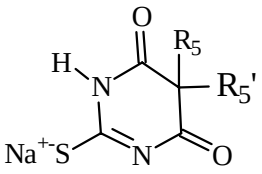
- Structure: N-H with a thiocarbonyl and C-5 side chains consisting of ethyl or allyl with a 5 carbon unit. **General Properties:** Very high lipophilicity and high plasma protein binding (>70%). Rapid distribution and redistribution.



Thiopental
(Ethyl substituted)



Thiamylal
(Allyl Substituted)



Salt forms

6. Barbiturate Disposition

A. Administration and absorption: Oral and parenteral dosage forms are typically formulated as water soluble salts. These compounds are sufficiently lipophilic (C-5 alkyl, and aryl groups) to facilitate absorption from sites of adminstration.

B. Distribution: Plasma protein binding and CNS distribution and redistribution correlates with lipophilicity which, in turn, is determined by the hydrophobic character of the C-5 substituents. This effects onset and duration of action, as well as drug interactions based on competitive plasma protein binding:

Onset of Action: Related to route of administration and barbiturate lipophilicity. More lipophilic barbiturates are distributed more rapidly to the CNS and thus have a more rapid onset. Onset of action for oral or rectal administration varies from 20 to 60 minutes. For IM administration, onset is slightly faster than the oral route. Following IV administration, onset ranges from almost immediate for pentobarbital sodium and secobarbital to 5 minutes for phenobarbital sodium. Maximal CNS depression may not occur for >= 15 minutes after IV administration of phenobarbital sodium.

Plasma Protein Binding: More lipophilic drugs are more highly palsma protein bound. More highly bound drugs generally are eliminated more slowly (not filtered through the glomerulus) and are metabolized more slowly:

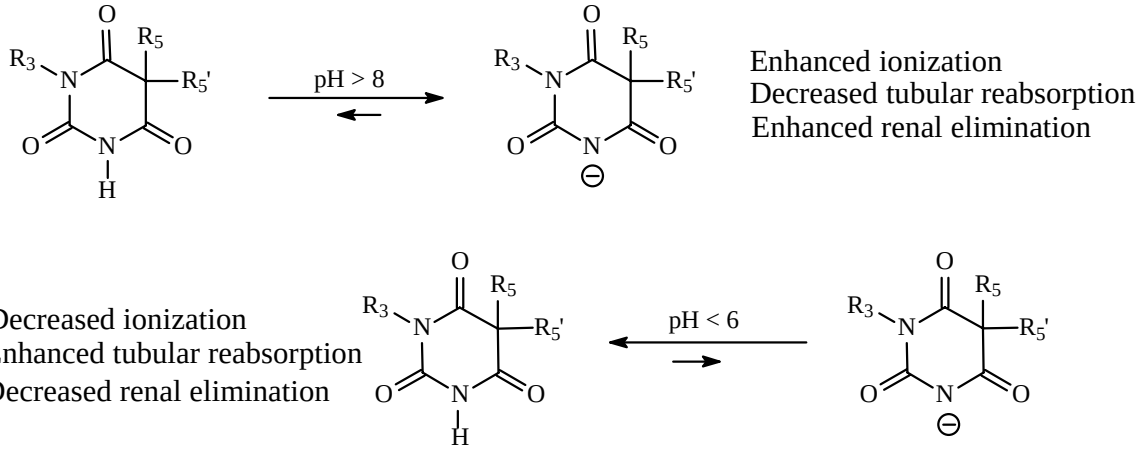
$$\underset{\text{(free)}}{\text{Barb}} + \underset{\text{(bound)}}{\text{Drug-----PB}} \rightleftharpoons \underset{\text{(free)}}{\text{Drug}} + \underset{\text{(bound)}}{\text{Barb-----PB}}$$

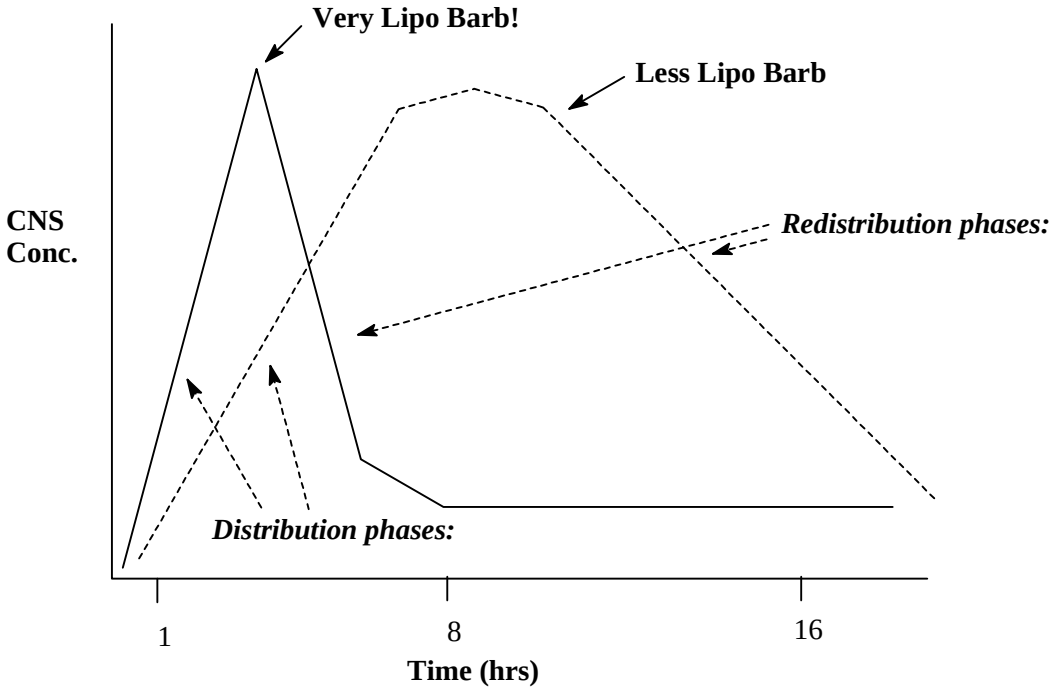
Duration of action (half-life) is largely dependent on redistribution. More lipophilic barbiturates undergo more rapid secondary distribution (redistribution)

to non-target tissues (adipose tissue) and thus their action is terminated more readily. Barbiturates are cleared from plasma by hepatic metabolism and direct renal elimination, and these processes clear drug from the body.

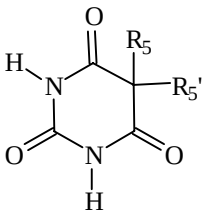
C. Metabolism: Through secondary hepatic metabolic inactivation barbiturates lose their affinity for the GABA receptor complex and thus CNS depressant activity. Oxidative and conjugative reactions also result information of metabolites that are more polar, less protein bound and more readily eliminated renally. (See metabolic reactions).

D. Elimination: Barbiturates and their metabolites are eliminated primarily renally by glomerular filtration. Since the barbiturates are weak acids, the rate of elimination can be altered by fluctuations in urinary pH:



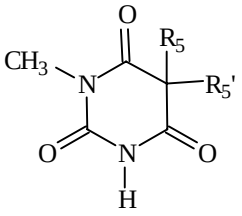


Summary of Barbiturate Structure and Biodispostion



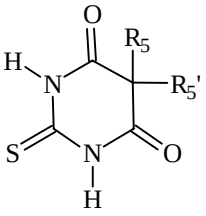
Barbiturates

- Increased lipophilicity with increased Cs at C-5



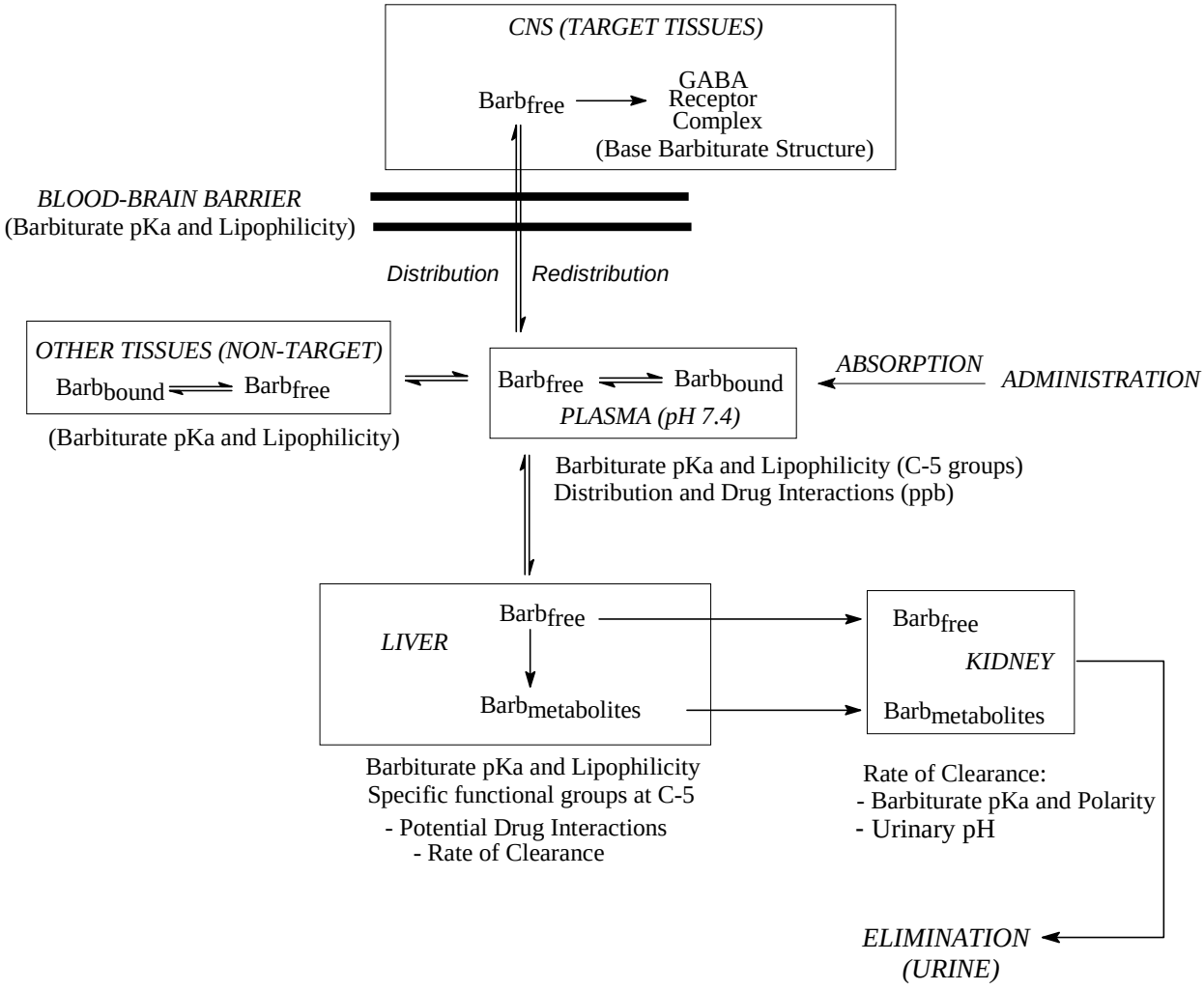
N-MethylBarbs

- Increased lipophilicity
- Decreased acidity



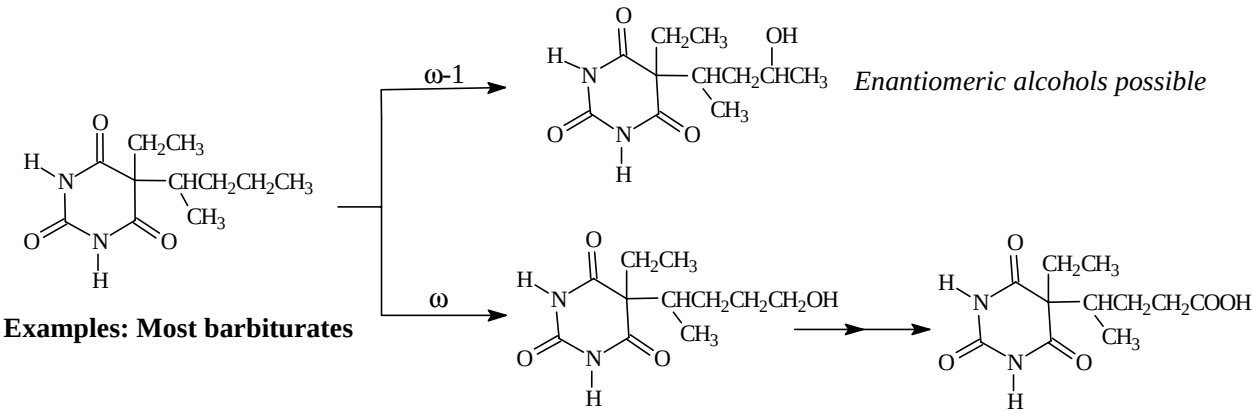
Thiobarbiturates

- Increased lipophilicity
- Increased acidity

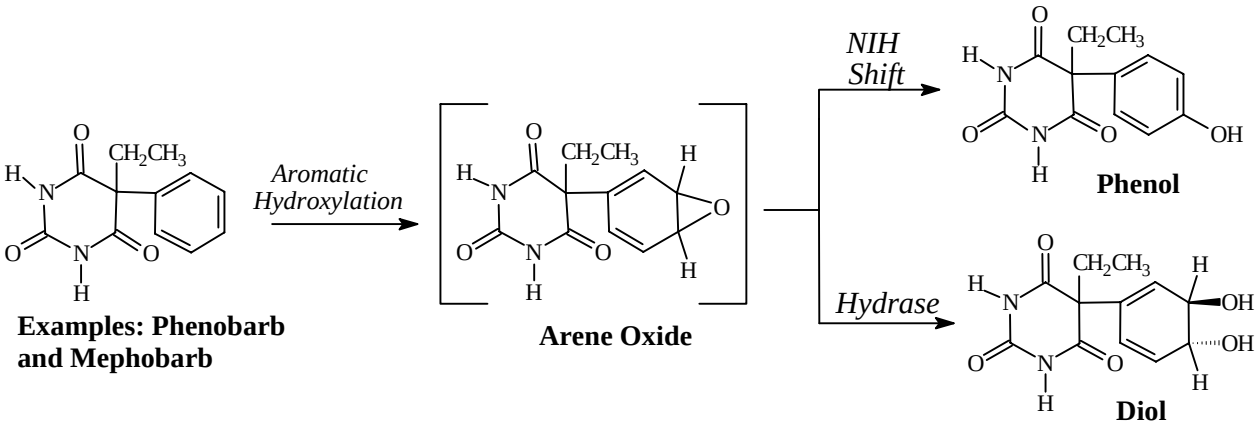


7. Barbiturate Metabolism

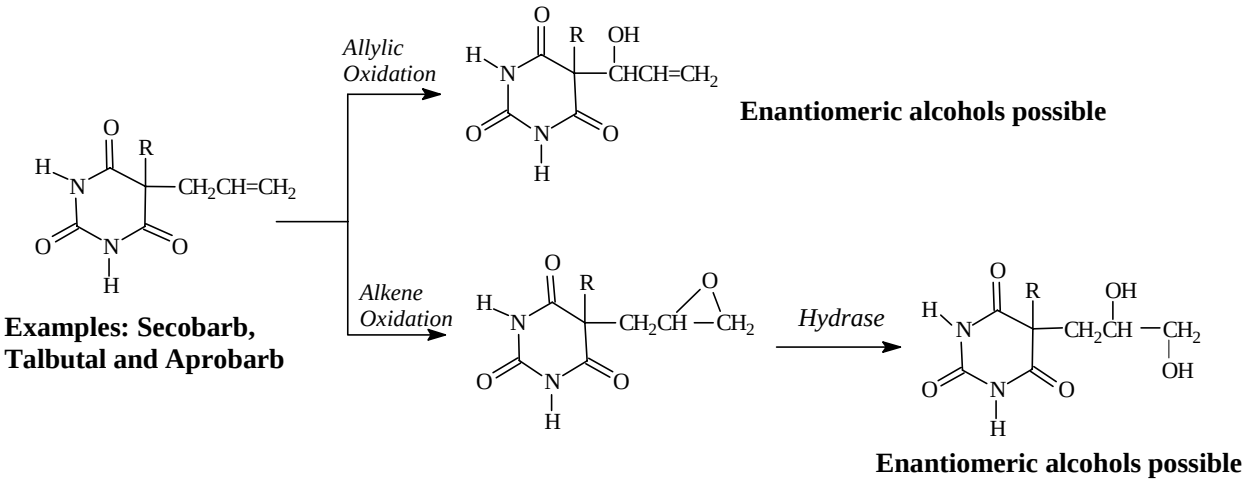
A. Omega and Omega-1 Oxidation



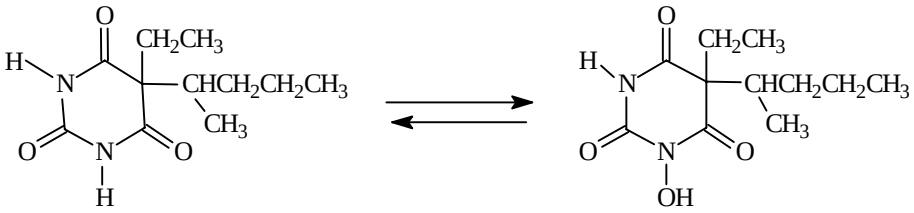
B. Aromatic Hydroxylation



C. Alkene and Allylic Oxidation

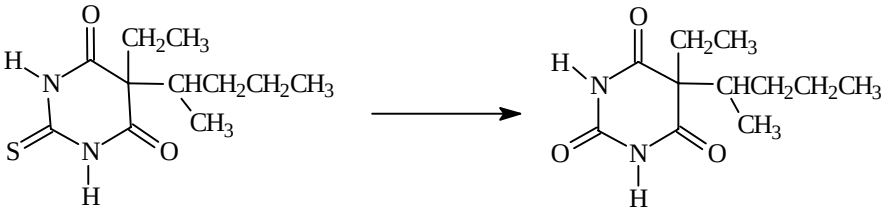


D. N-Oxidation



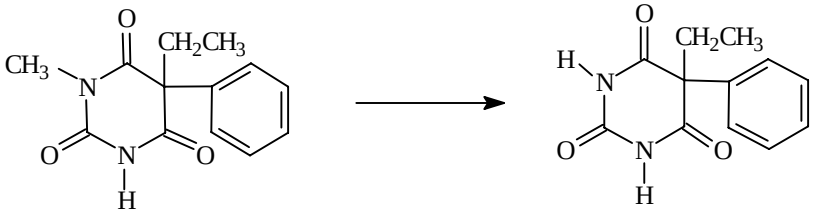
Most Barbs

E. Desulfuration



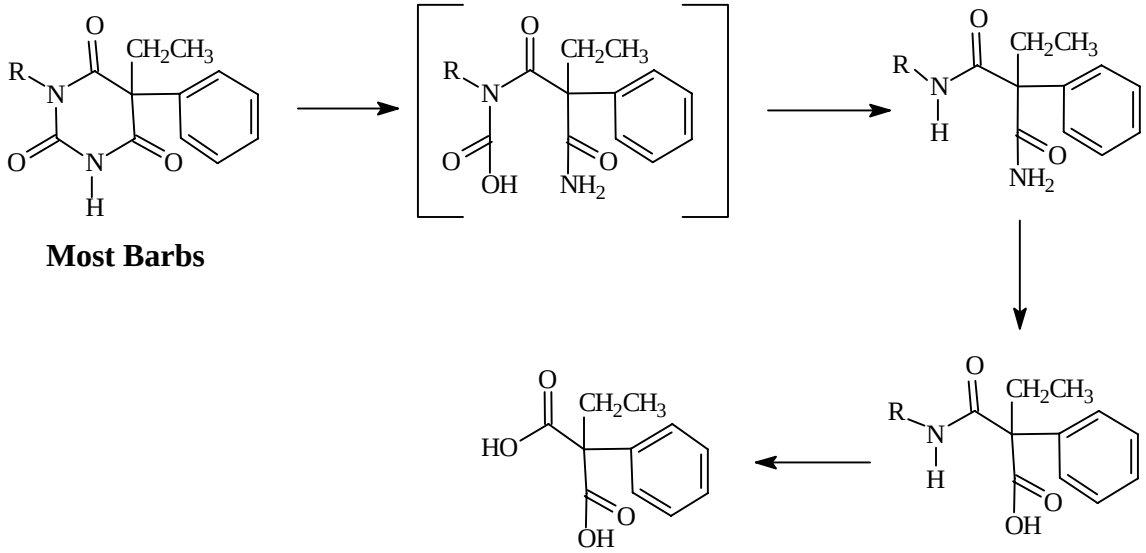
Thiobarbs

F. Oxidation N-Dealkylation



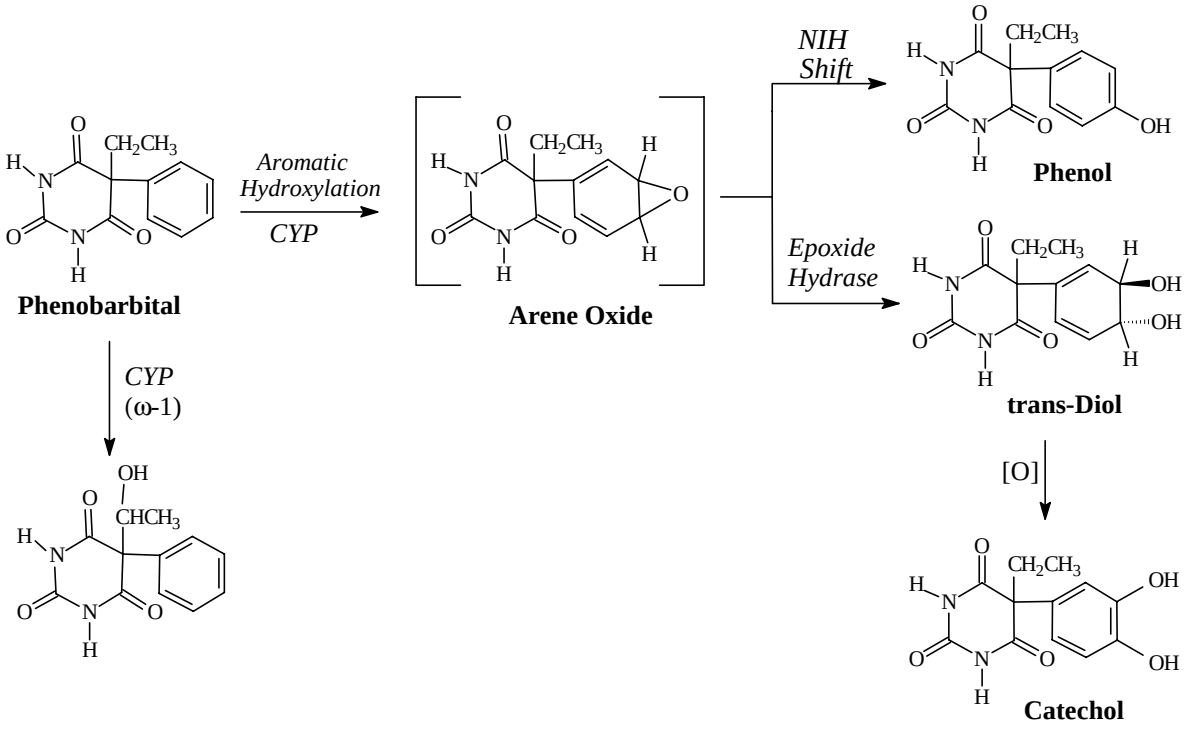
N-Methylbarbs

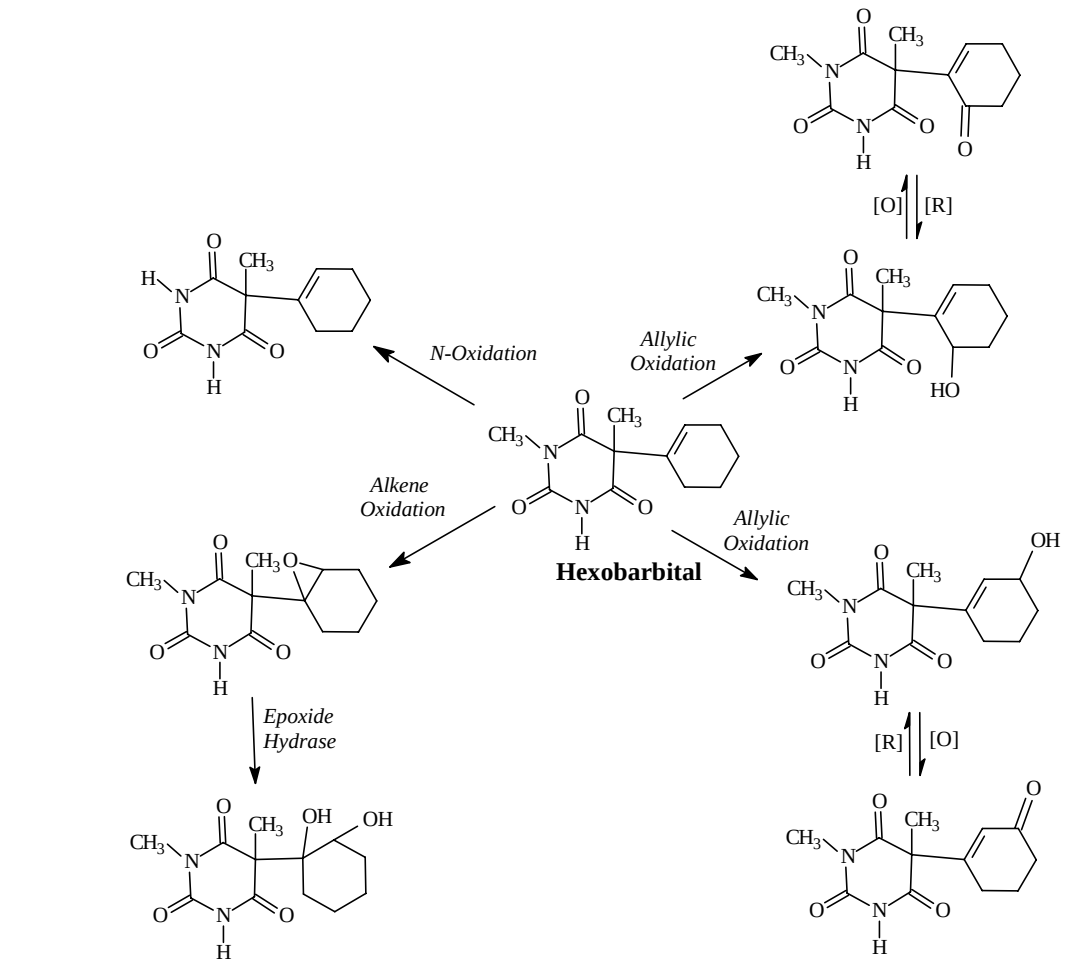
G. Hydrolysis



Most Barbs

H. Examples of Barbiturate Metabolism and Metabolites Formed:





8. Barbiturates: Metabolic and Other Drug Interactions

Chronic administration of barbiturates (as well as phenytoin, carbamazepine, rifampin) results in "enzyme induction", a drug–induced increase in the synthesis of the enzymes of metabolism including MFOs, glucuronyl transferase, aldehyde dehydrogenase and delta-aminolevulinic acid synthetase. Thus barbiturates can induce the metabolism of a variety of drugs, including some beta-blockers, carbamazepine, clonazepam, contraceptive (oral), corticosteroids, digitoxin, doxorubicin, doxycycline, felodipine, fenoprofen, phenylbutazone, quinidine, theophylline, verapamil, etc. Generally then barbiturates may enhance the clearance (and thereby decrease efficacy of these other drugs when used concurrently.

Other drugs can also alter the metabolism of barbiturates. For example, chloramphenicol and valproate can inhibit the metabolism of barbiturates when uswed concurrently. Also rifampin, a potent enzyme inducer, may induce barbiturate metabolism.

There are some reports that barbiturates may interfere with the absorption of other oral drugs (griseofulvin) and that some substances (charcoal) may reduce the absorption of barbiturates.

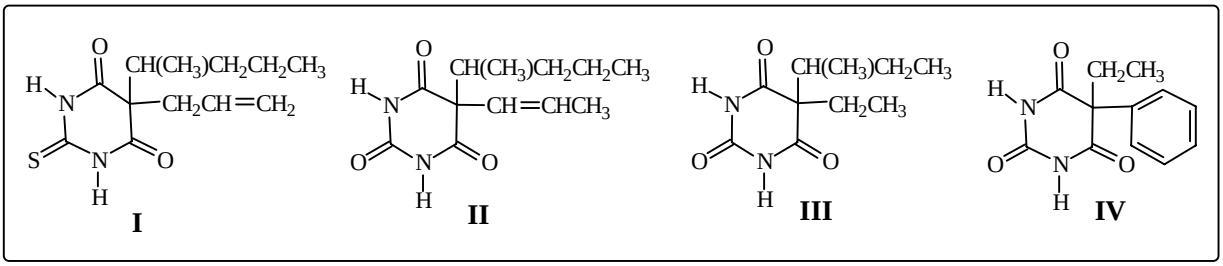
Concomitant use may of barbiturates with alcohol may produce additive CNS effects and death. Methadone actions may be reduced by barbiturates, but the CNS depressant effects of meperidine may be prolonged. MAOIs also are reported to enhance the sedative effects of barbiturates.

9. Barbiturate Adverse Reactions (See Pharmacology notes):

- CNS Actions: Drowsiness, hangover, impaired psychomotor function, irritability, increased pain perception.
- Dependence and Tolerance:
- Respiration: Depressed, laryngospasm (major limitation!)
- Peripheral Nervous System: Depressed ganglionic transmission, decreased excitation at N_N receptors (enhanced NMBA blockade)
- Cardiovascular: Decreased cardiac contractility and cardiac output, increased PVR, decreased cerebral blood flow
- Liver: Enzyme induction
- Renal: Decreased GFR and hypotension decreased urine volume

SAMPLE BARBITURATE QUESTIONS

Answer questions 11-8 below for the following barbiturate derivatives (I-IV):



1. Which barbiturates above (I-IV) would yield water soluble salts if treated with NaOH?

A. Only I
B. Only I and II
C. Only II and III
D. Only II, III and IV
E. All of the barbiturates above (I-IV)

2. Which barbiturates above (I-IV) would be appropriate for oral long-term treatment of seizure disorders?

A. Only I
B. Only IV
C. Only III and IV
D. Only II and IV
E. Only II, III and IV

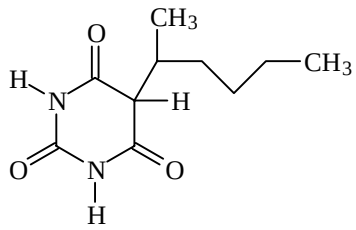
3. Which barbiturate above (I-IV) would have the shortest duration of action

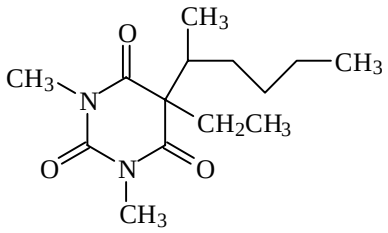
A. I
B. II
C. III
D. IV

4. Which barbiturates above (I-IV) would be capable of forming epoxide metabolites by oxidative metabolism (cytochrome-mediated oxidation)?

A. Only I
B. Only IV
C. Only I and II
D. Only I, II and IV
E. All of the barbiturates above (I-IV)

5. Why are the barbiturates shown below <u>inactive</u> as sedatives, anti-epileptics or anesthetics?





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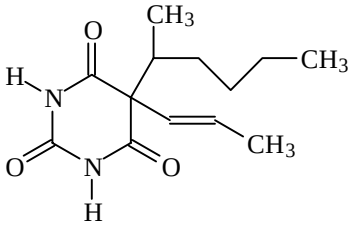
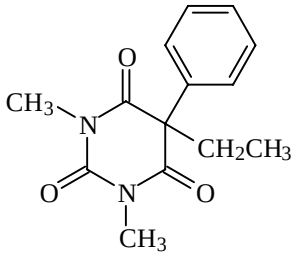
6. Which barbiturate below is more extensively bound by plasma proteins? What is the therapeutic relevance of this? Why don't the highly protein bound have significantly longer durations of ation than those barbiturates less extensively bound?





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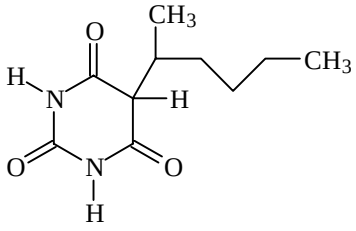
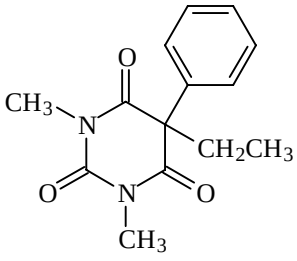
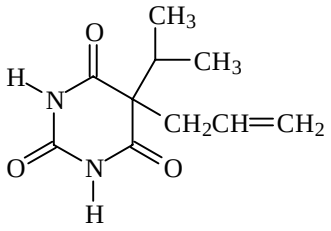
7. Why does alkalinization of the urine enhance the renal excretion of the barbiturates?

8. Which barbiturate below is a long-acting sedative? Rapid-acting sedative? More extensively metabolized? Distributed and accumulated in adipose tissue most extensively? Are these barbiturates primarily ionized or non-ionized at physiological pH?







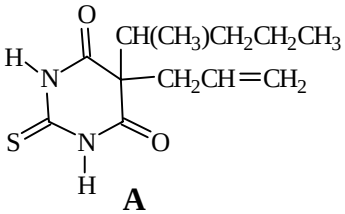
9. Why do the barbiturates decrease patient respons to warfarin? Why do they decrease carbamazepine plasma levels? Why do they increase renal toxicity of methoxyflurane?

10. What effect does N-substitution have on pKa? On lipophilicity?

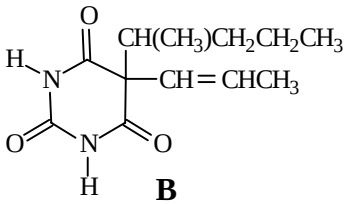
11. Why are there four ω-1 oxidation products formed from racemic pentobarbital? Why do desulfuration reactions limit the duration of action of the thiobarbiturates?

12. How does stereochemistry influence sedative activity? Distribution to the CNS? Route of elimination?

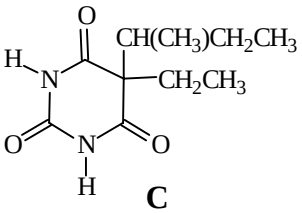
13. For the compounds shown below, circle the appropriate response or responses. There may be more than one correct answer, or no correct answer.



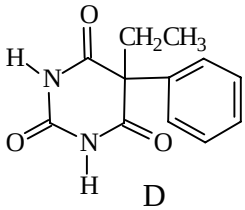
A



B



C



D

a. Which compounds yield a water soluble salt with NaOH?……....A B C D None
b. Which compounds are chiral?……..…..A B C D None
c. Which compounds are active CND depressants?……..…….A B C D None
d. Which compound is longest acting?……..…….A B C D None
e. Which compound is shortest acting?……...A B C D None
f. Which compound displays the lowest plasma protein binding?…..…A B C D None
g. Which compound is more hydrophilic?……..A B C D None
h. Which compounds are eliminated primarily by renal mechanisms?...A B C D None

14. Draw the structure of the primary metabolites formed from D above by cytochrome-mediated aromatic ring oxidation? Are these metabolites as active as the parent drug?

15. Draw the structure of the diol formed from alkene oxidation followed by hydrolysis of compound A above.

16. Draw the omega and omega-1 oxidation products formed from cytochrome-mediated oxidation of compound B above?