Medicinal Chemistry

Chapter 12

SEDATIVE AND HYPNOTIC

Contents

DEFINITION

- A **sedative drug** decreases activity and excitement of the patient and clams anxiety by producing mild depression of CNS without causing drowsiness or sleep
- A **hypnotic drug** produces drowsiness, forcing the patient to sleep by depressing the CNS, particularly the reticular activity which influences wakefulness

DOSE DEPENDENT ACTIVITY

- All sedative, hypnotic and GA depress the CNS

➢ The observed effect depends on the dose given to patient

- Small dose cause sedation (calmness)
- Medium dose cause hypnosis (sleepy)
- Larger dose causes surgical anesthesia

DIFFERENT

Sedative

- A drug that reduces excitement, calms the patient (without inducing sleep)
- Sedatives in therapeutic doses are anxiolytic agents
- Most sedatives in larger doses produce hypnosis (trans like state in which subject becomes passive and highly suggestible)
- Site of action is on the limbic system which regulates thought and mental function

Hypnotic

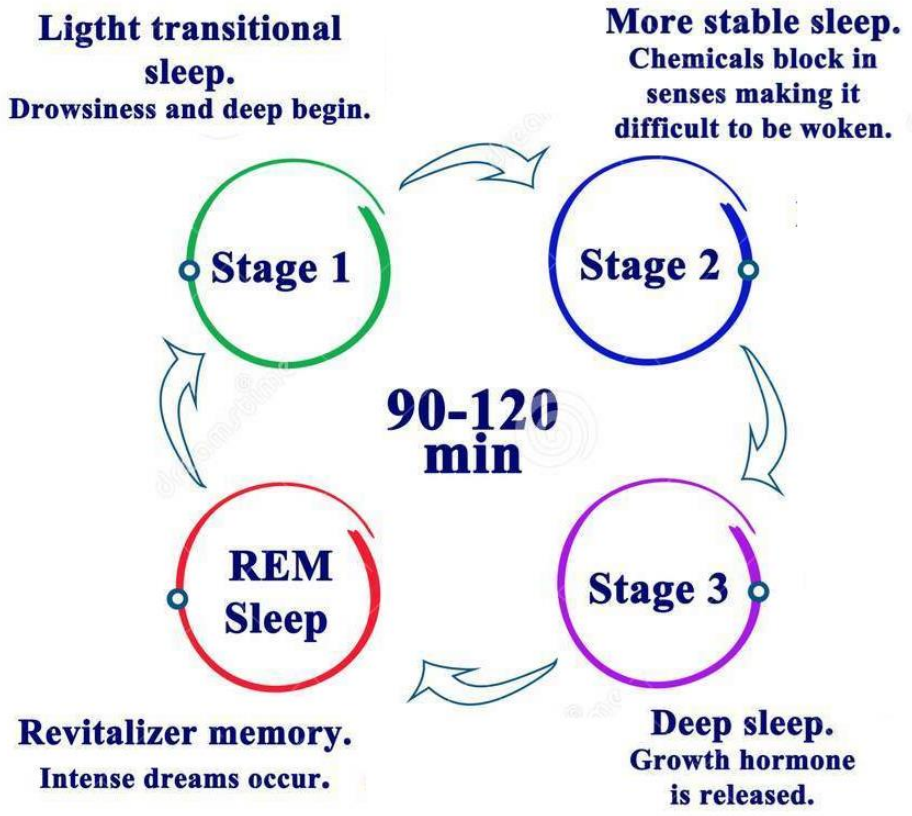
- A drug which produces sleep resembling natural sleep
- They are used for initiation and / or maintenance of sleep.
- Hypnotics in higher doses produce General anaesthesia.
- Site of action is on the midbrain

Utility

Sedatives counter various types of anxiety such as

- Obsessive-compulsive disorder (OCD)
- Post-traumatic stress disorder (PTSD)
- Social anxiety disorder
- Specific phobias

Hypnotics is for insomnia. Insomnia is a condition where person is not able to fall sleep



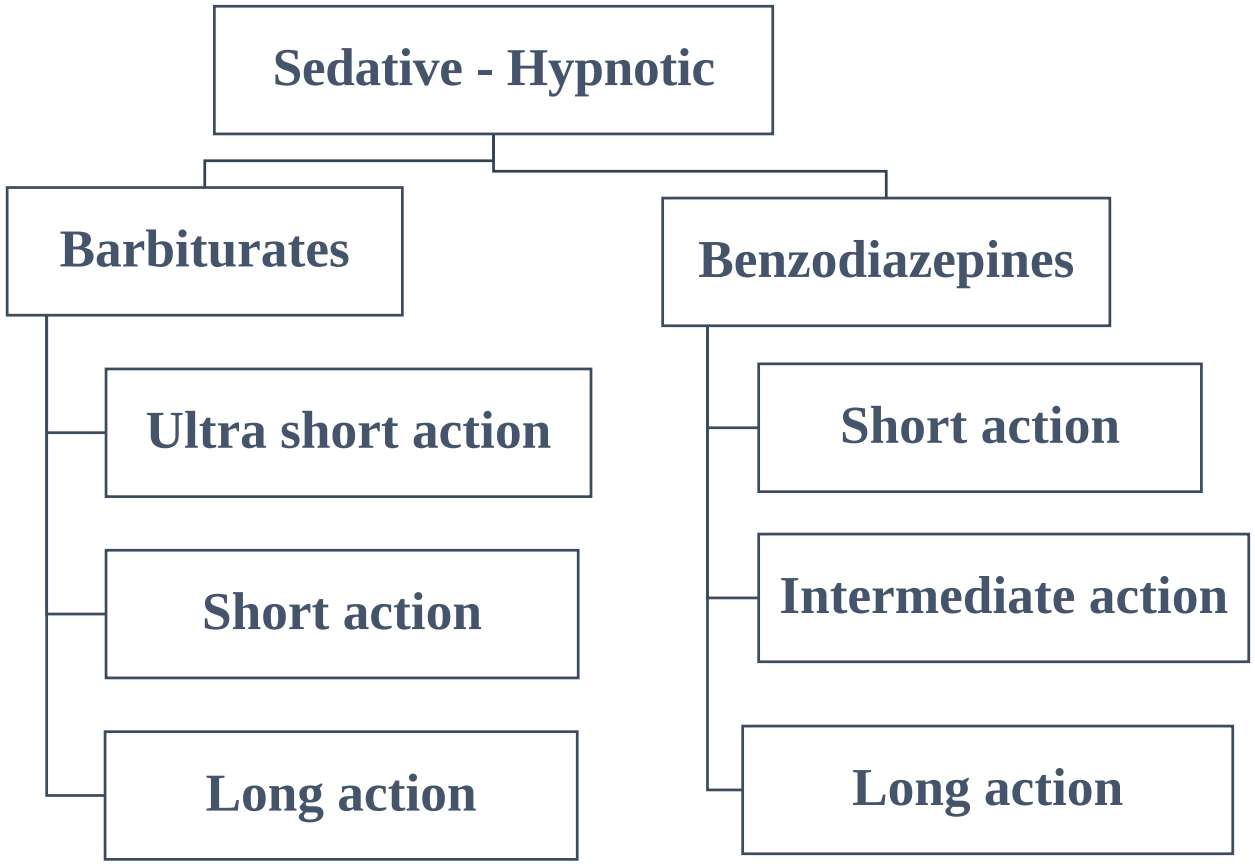
Ideal properties of hypnotics

1. Cause a temporary decrease in the level of consciousness for the purpose of falling asleep without any alteration to sleep cycle
2. Must not decrease or arrest respiration, even at high doses
3. Cause no addiction, tolerance or dependence

Drug classification

1. Barbiturates: Phenobarbitone*
2. Benzodiazepines: Alprazolam, Diazepam, Nitrazepam, Lorazepam
3. Non-Benzodiazepines: zolpidem, Zalephon
4. Others: paraldehyde, Glutethimide, Chloral Hydrate
5. Herbal sedatives: Ashwagandha, Valerian and passiflora

Acting duration classification

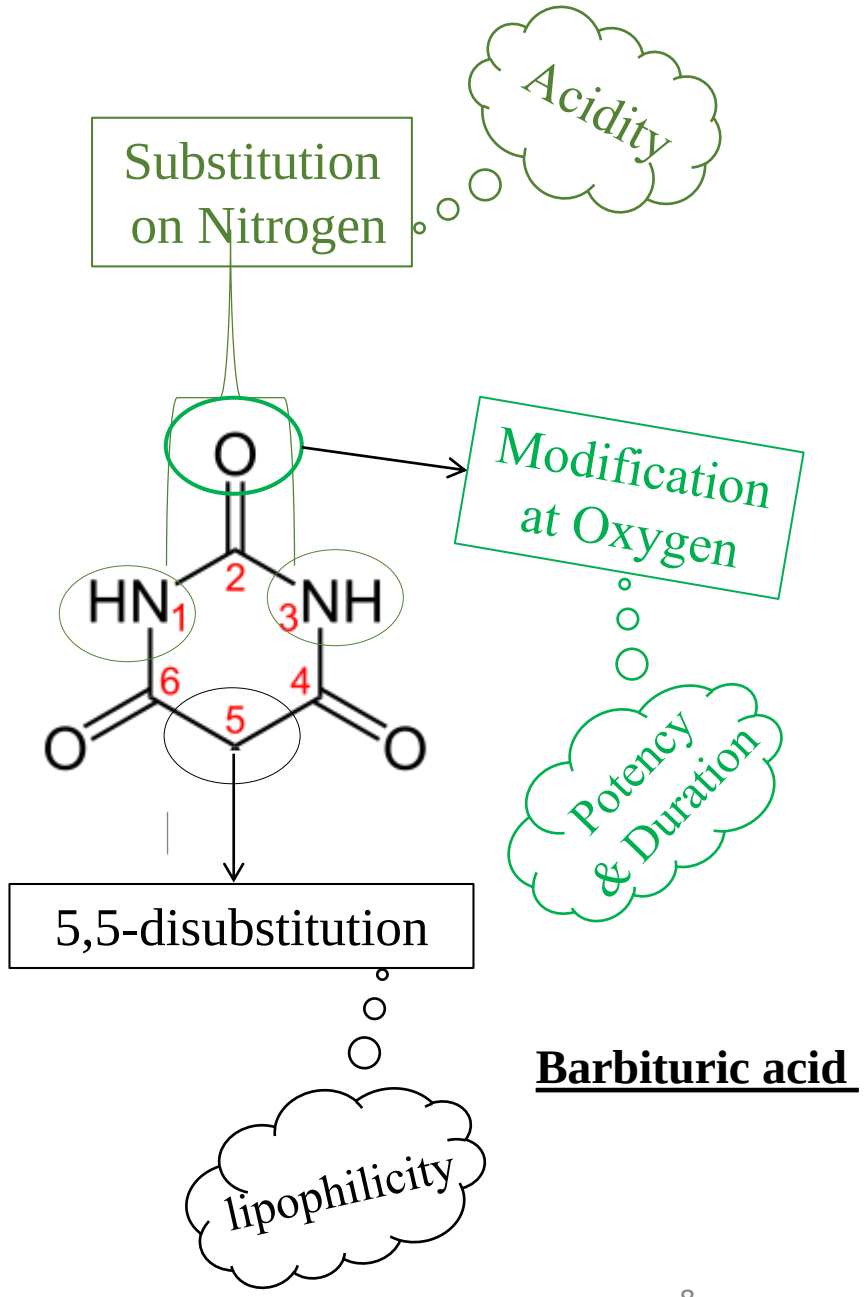


HISTORY

- Barbituric acid was first created in 1864 by a German scientist named **Adolf von Baeyer**. It was a combination of urea from animals and malonic acid from apples.
- Its first derivative utilized as medicine was used to put dogs to sleep but was soon produced by **Bayer** as a sleep aid in 1903 called **Veronal**
- Phenobarbital was soon discovered and marketed as well as many other barbituric acid derivatives
- Prescribed as sedatives, anesthetics, anxiolytics, and anti- consulsants
- Also popular to abuse because of their alcohol like effects

Barbiturates

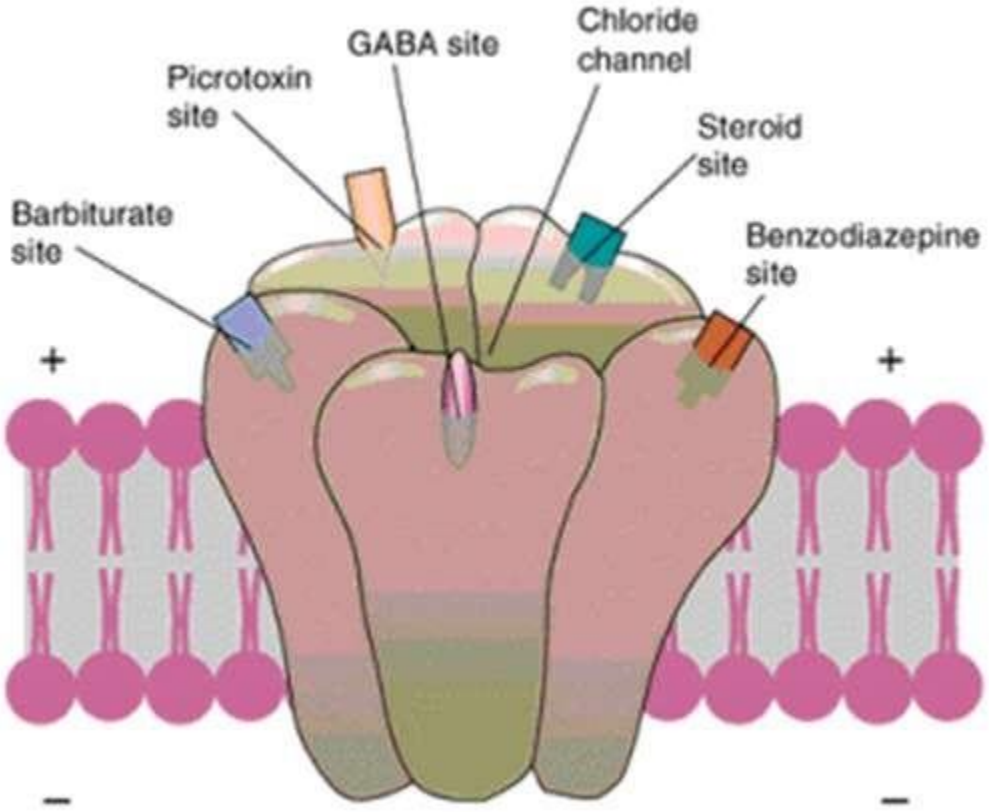
- All derivatives of Barbituric acid
- They are CNS depressants. They are effective as anxiolytics, hypnotics, anticonvulsants and analgesics.
- They have addiction potential, both physical and psychological.
- Thus Benzodiazipines have largely replaced them in term of sedative-hypnotic
- Barbituric acid itself does not possess any hypnotic properties.
- Activity requires a balance of acidic and lipophilic properties
- Three potential sites are available for the structure modification
  - ❑5,5-disubstitution
  - ❑Substitution on Nitrogen
  - ❑Modification at Oxygen



Barbituric acid

Mode of action of barbiturates

1. Barbiturates primarily act on GABA: benzodiazepin receptor Cl^- channel complex and potentiate GABA ergic inhibitory action by increasing the lifetime of Cl^- channel opening induced by GABA.
2. Barbiturates do not bind to benzodiazepine receptor promptly, but it binds to another site on the same macromolecular complex to exert the GABAergic facilitator actions. The barbiturate site appears to be located on α and ß subunit. At high concentrations, barbiturates directly increases Cl^- conductance and inhibit Ca^{2+} dependent release of neurotransmitters and they also depress glutamate-induced neuronal depolarization.



Structure-Activity Relationship

- Barbituric acid itself does not possess any hypnotic properties.
- Activity requires a balance of acidic and lipophilic properties.

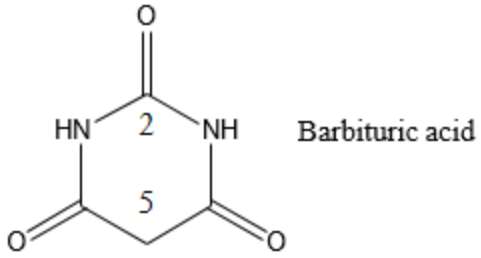
❖To make the drug sufficiently acidic, both or at least one of the two nitrogen must be unsubstituted

❖To make drug sufficiently lipophilic, the two hydrogen atoms at position 5 : 5 must have the appropriate substituent (*e.g.*, *alkyl or aryl groups)*

The type of substituent's control 2 aspects of the drug

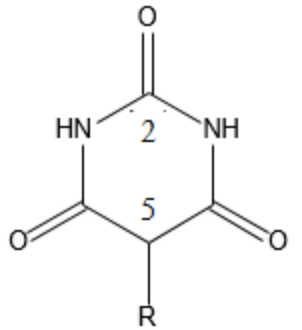
❖ Potency

❖ Duration of Action.

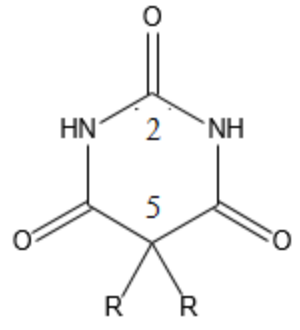


Barbituric acid

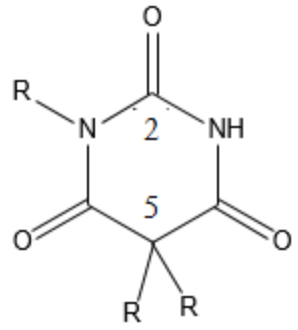
Inactive inactive coz not lipophilic enough



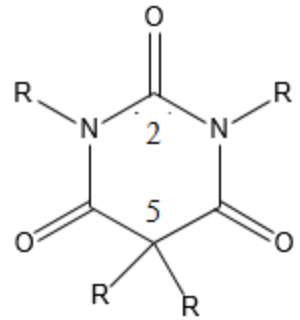
inactive
coz not lipophilic enough



active



active

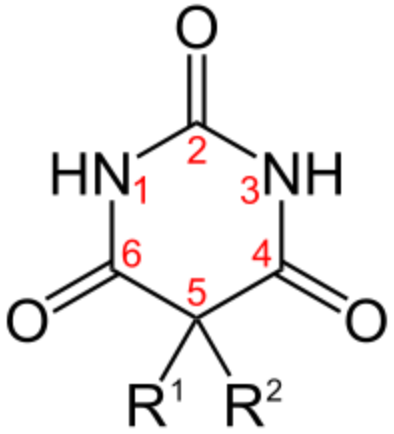


Inactive coz not acidic enough

- 5,5-disubstitution

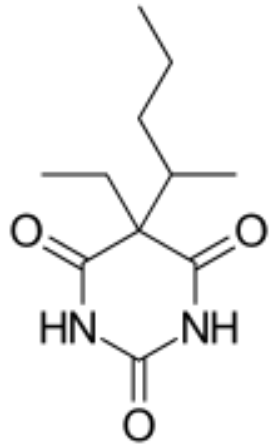
1. The total number of carbon atoms present in the two groups at carbon 5 must not be less than 4 and more than 10 and influences onset of action and duration

C	**Duration of action**
7-9	Rapid onset & shorter duration
5-7	Intermediate duration of action
4	Slowest onset & longest duration of action

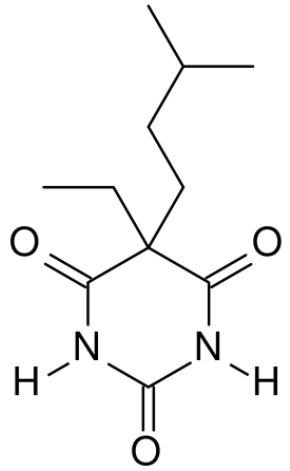


2. The branched chain isomer exhibits greater activity but shorter duration. The greater the branching, the more potent is the drug (e.g., pentobarbital > amobarbital).

This Branched, cyclic or unsaturated alkyl groups reduce duration of action due to increased ease of metabolic inactivation

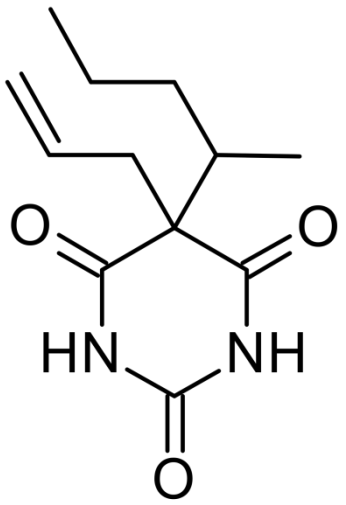


Pentobarbital



Amobarbital

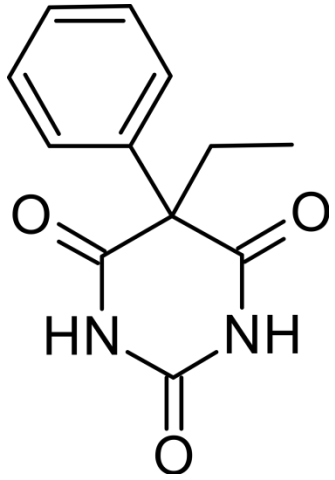
3. Double bonds in the alkyl substituent groups produce compounds more readily vulnerable to tissue oxidation; hence, they are short-acting.



Secobarbital

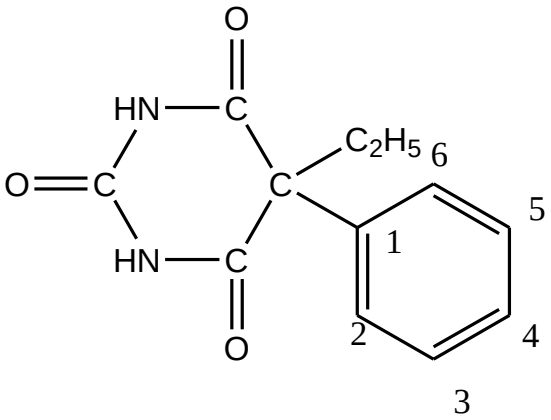
4. Inclusion of polar groups (e.g., OH, CO, COOH, NH_2, RNH, and SO_3H) in the 5-alkyl moiety reduces potency considerably.

5. Only one of the substituent groups at position 5 may be a cyclic group.

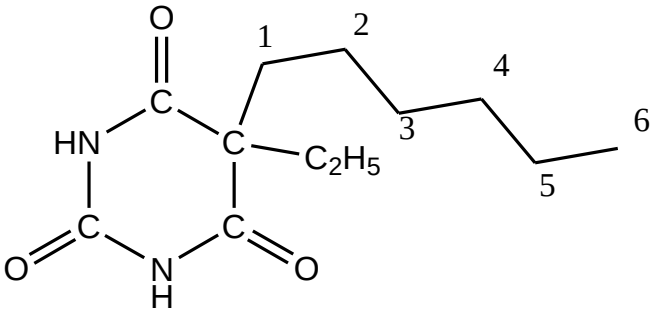


Phenobarbital

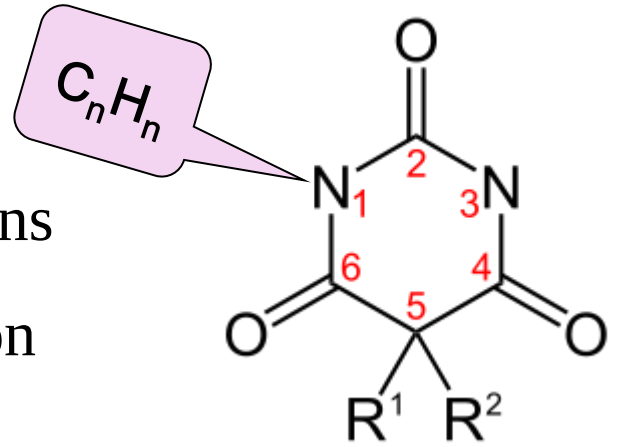
6. Aromatic and alicyclic moieties exert greater potency than the corresponding aliphatic moiety having the same number of carbon atoms.



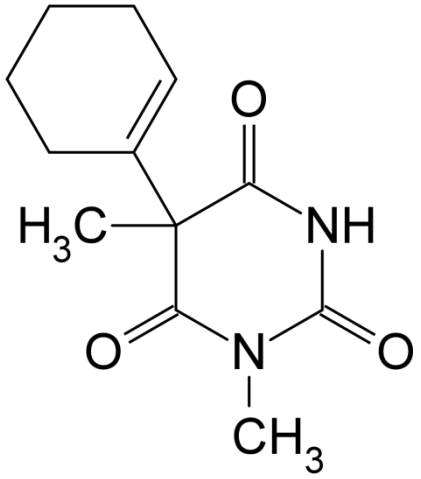
more potent than



➢ Substitution on Nitrogen

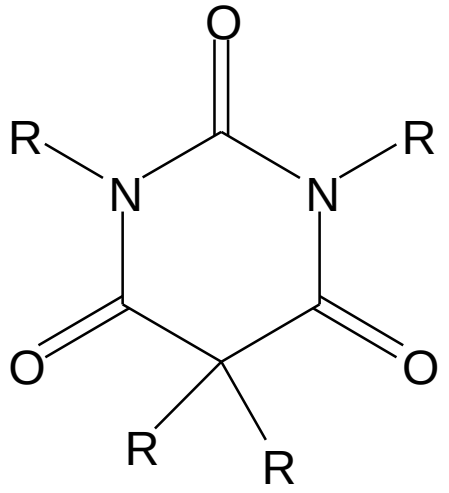


1. Methylation of one of the imide hydrogens enhances onset and reduces duration of action



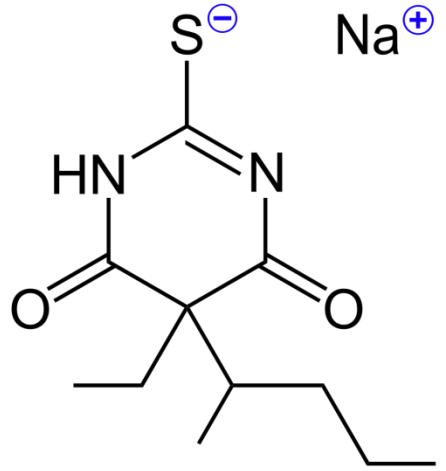
Hexobarbital

2. Attachment of alkyl groups to both nitrogen produce an inactive compound.



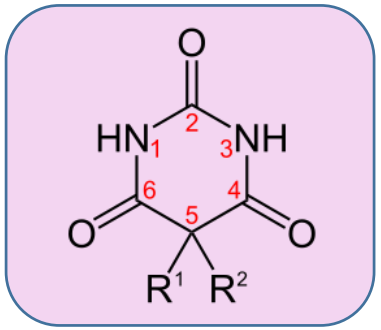
- Modification of Oxygen

1. The replacement of O-atom with an S-atom, at C- 2 position of the barbiturates significantly enhances the lipid solubility. The resulting modified versions of the barbiturates thus obtained exert a rapid onset of activity by virtue of the fact that they attain maximal thiobarbiturate-brain levels. Therefore, such drugs as 'thiopental sodium' find their profuse and abundant application as 'intravenous anaesthetics'.

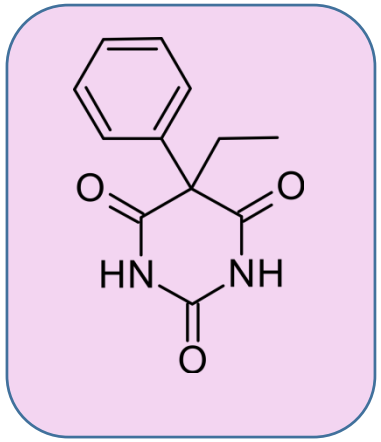


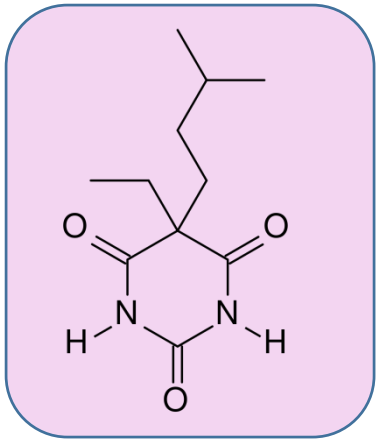
2. Attachment of more oxygen atom with Sulphur like 2,4-dithio or 2,4,6-trithio produce an inactive compound.

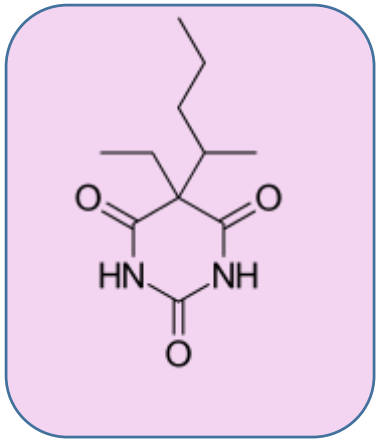
➢ Classifications

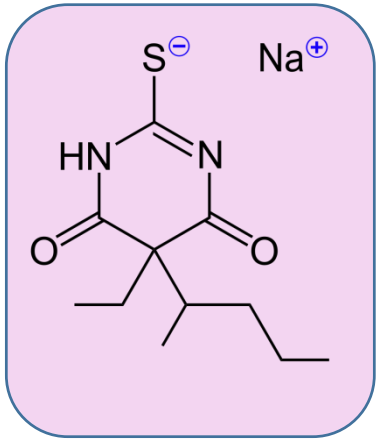


Long acting	Intermediate acting	Short acting	Ultra shortacting
Phenobarbital	*Amobarbital*	*Pentobarbital*	*Thiopental sodium*



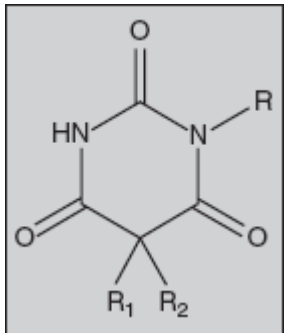




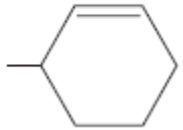


(i) Long duration of action (six or more hours)

	R	R_1	R_2
Phenobarbital	H	C_2H_5—	C_6H_5—
Mephobarbital	CH_3—	C_2H_5—	C_6H_5—
Metharbital	CH_3—	C_2H_5—	C_2H_5—



(ii) Intermediate duration of action (3–6 hours)

	R	R_1	R_2
Butabarbital	H	C_2H_5—	$CH_3CH_2CH(CH_3)$—
Amobarbital	H	C_2H_5—	$(CH_3)_2CHCH_2CH_2$—
Aprobarbital	H	CH_2═CH—CH_2—	$(CH_3)_2CH$—
Talbutal	H	CH_2═CH-CH_2—	$CH_3CH_2CH(CH_3)$—
Butalbital	H	CH_2═CH—CH_2—	$(CH_3)_2CHCH_2$—
Hexobarbital	CH_3—	CH_3—	

(iii) Short duration of action (less than three hours)

	R	R_1	R_2
Pentobarbital	H	C_2H_5—	$CH_3CH_2CH_2CH(CH_3)$—
Secobarbital	H	CH_2═CH-CH_2—	$CH_3CH_2CH_2CH(CH_3)$—

(iv) Ultra short-acting barbiturates (15 min)

Name	R^1	R^5	$R^{5'}$
Thiopentone	–H	$-C_2H_5$	—$CH(CH_2)_2CH_3$ CH_3

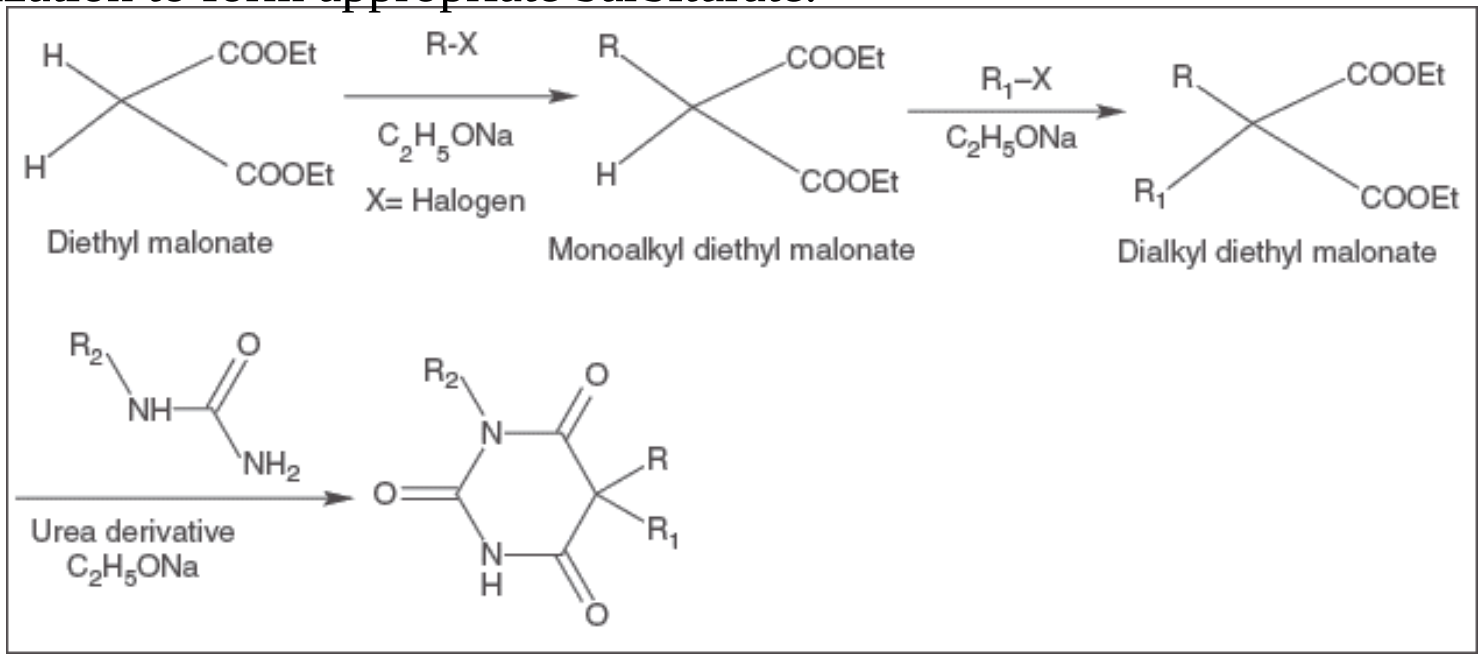
(At C – 2 = S instead of = O)

❖ General method of preparation of 5,5-dialkyl barbiturates:

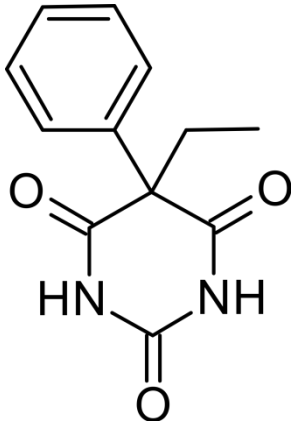
This method is applicable for the synthesis of all barbiturates except **phenobarbital and hexobarbital**.

Diethyl malonate reacts with sodium ethoxide to form mono sodium salt of diethyl malonate, which in turn reacts with first alkyl halide to form mono alkyl diethyl malonate. This further reacts with second alkyl halide in presence of sodium ethoxide and gives dialkyl diethyl malonate. Dialkyl diethyl malonate on condensation with urea undergoes cyclization to form appropriate barbiturate.

Generally Barbiturate drugs are obtained via condensation reactions between a derivative of diethyl malonate and urea in the presence of a strong base.



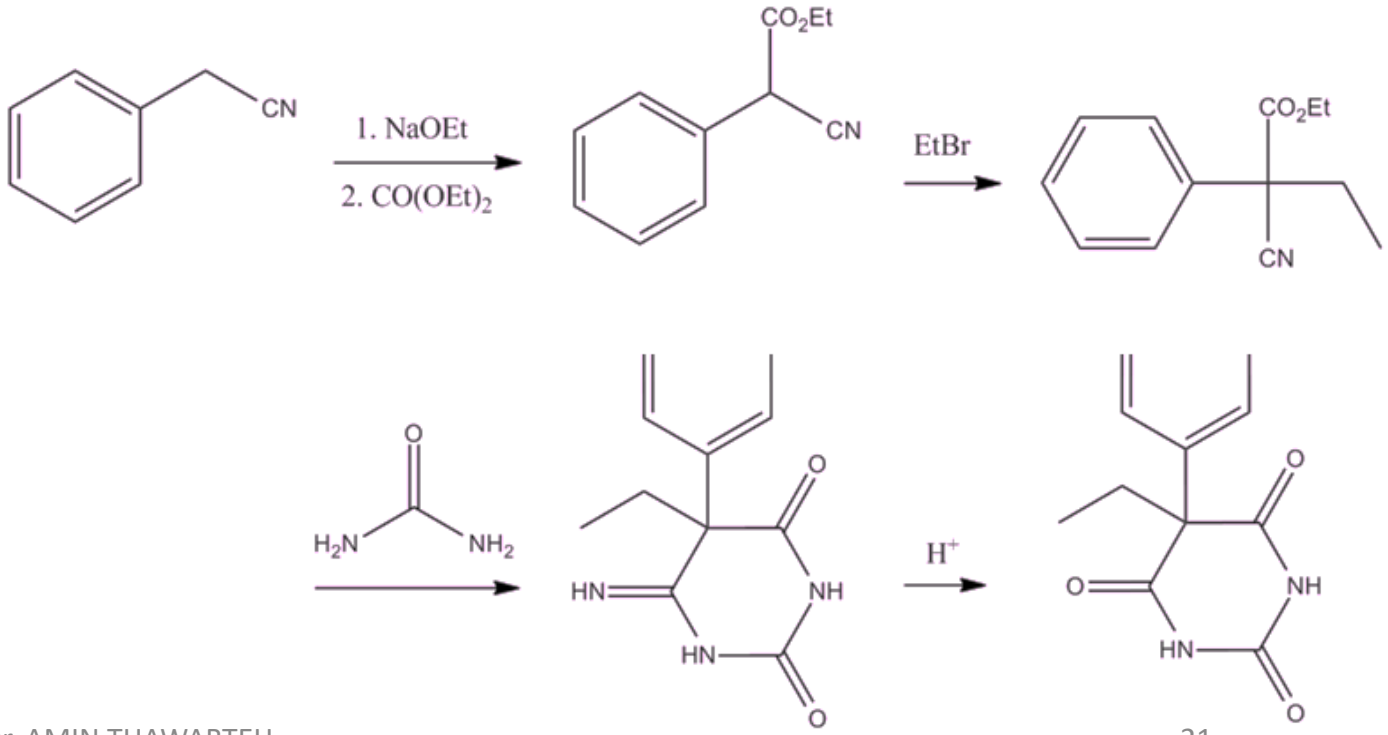
❖ Phenobarbital (Luminal))



- Phenobarbital or phenobarbitone is a barbiturate which is most widely used anticonvulsant worldwide and the oldest still commonly used.
- It is one of the **longest-acting barbiturates available** – it remains in the body for a very long time (half-life of 2 to 7 days) and has very low protein binding
- Phenobarbital is metabolized by the liver, mainly through hydroxylation and glucuronidation
- It is excreted primarily by the kidneys
- Dosage forms: Phenobarbital **sodium tablets**, Phenobarbital **sodium injection**, Phenobarbitone **tablets**, Phenobarbital **injection**, Paediatric phenobarbital **oral solution.**

➢ Synthesis of phenobarbitone

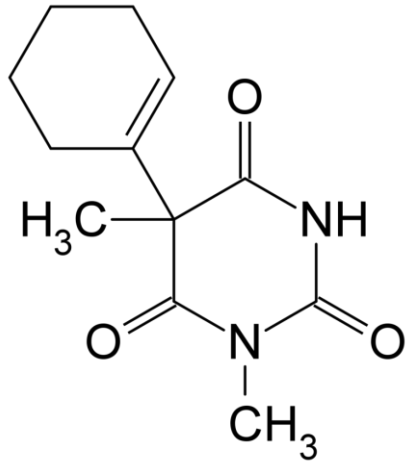
For phenobarbital synthesis utilizes diethyl carbonate in the presence of a strong base to give α-phenylcyanoacetic ester from benzyl cyanide. Alkylation of this ester using ethyl bromide proceeds via a nitrile anion intermediate to give the α-phenyl-α-ethylcyanoacetic ester. This product is then further converted into the 4-iminoderivative upon condensation with urea. Finally acidic hydrolysis of the resulting product gives phenobarbital.



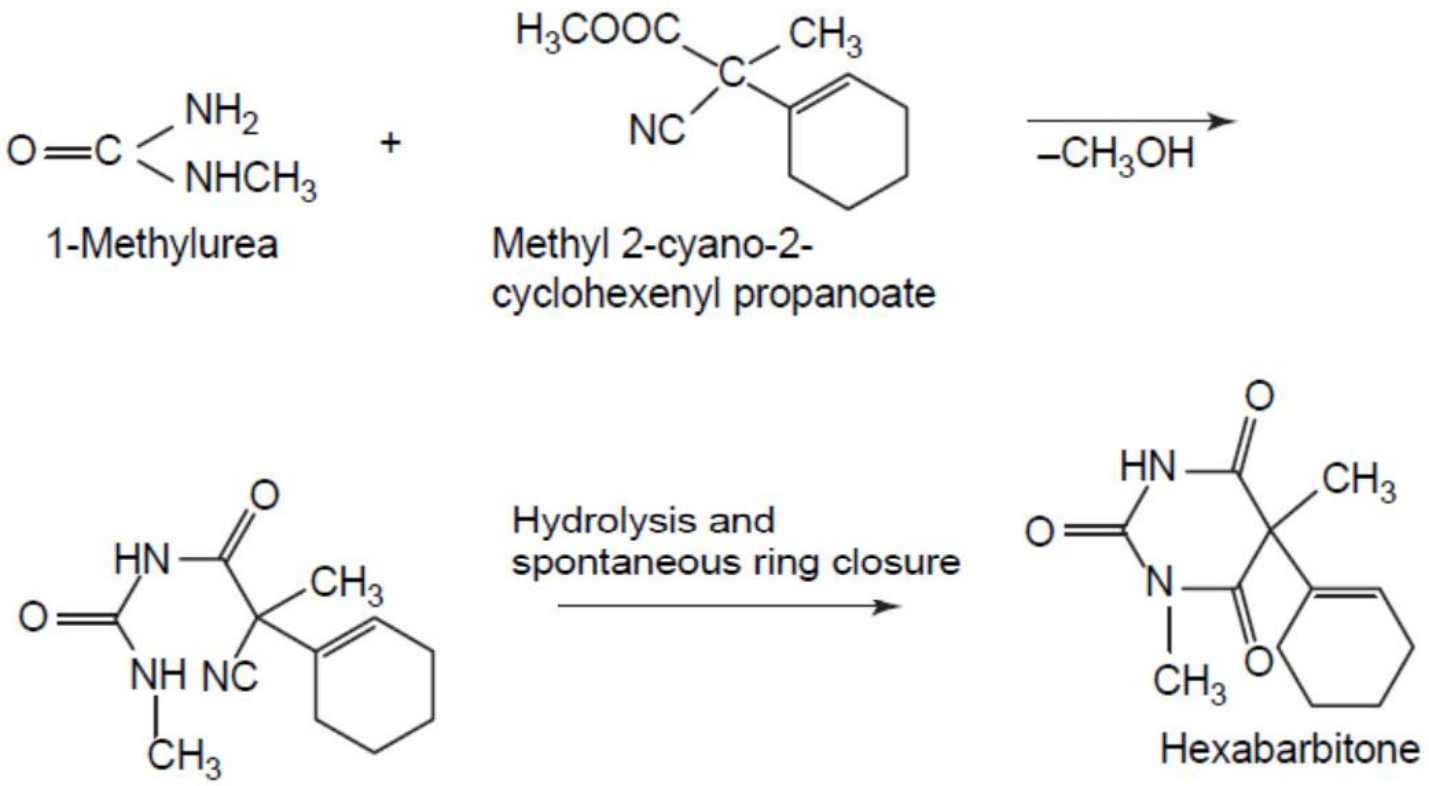
Obtained via alkylation of the ester formed from reactions between a derivative of diethyl carbonate and benzyl cyanide in the presence of a strong base.

❖ Hexabarbitone (Hexobarbital, Evipal, Sombulex)

- Hexobarbital is a barbiturate derivative having hypnotic and sedative effects. It was subsequently used in the 1940s and 1950s as an anesthetic for surgery.
- Rapid-acting, short-lasting hypnotic for general use, and has a relatively fast onset of effects and short duration of action.
- Difficult to control the depth of anesthesia with hexobarbital which makes it quite dangerous, and it has now been replaced by safer drugs in human medicine, usually thiopental would be the barbiturate of choice for this application these days.

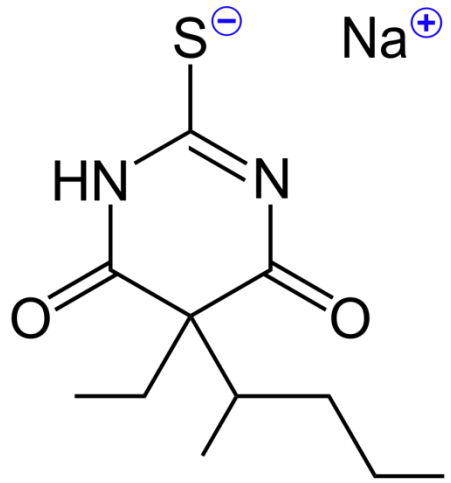


➢ Synthesis of Hexabarbitone

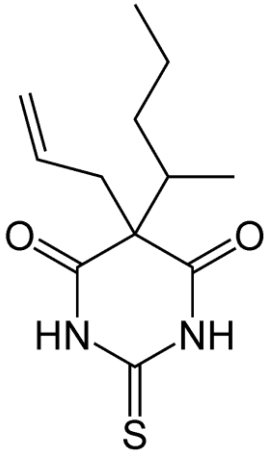


❖ Thiopental sodium

- Ultra short acting barbiturate (5-10 min)
- Rapid action (10 -15 sec) and rapid recovery
- Used mainly as inducing anesthetic
- has no analgesic properties
- it is a poor muscle relaxant
- It is stored as a solid white salt and needs to be prepared in sterile water to inject the patient
- Rapid recovery not due to rapid metabolism

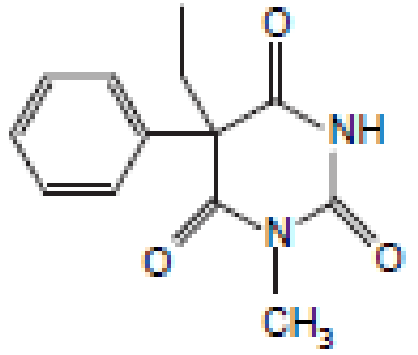


- **Thiamylal:** Ultra short acting barbiturate, rapid action but not rapid recovery due to high lipophilicity and subsequent drug accumulation in the fatty tissues, used mainly as inducing anesthetic in lab animals

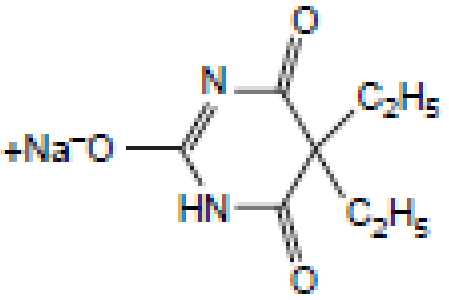


- **Use limited to *Veterinary* field.** Only its sodium salt is used in humans

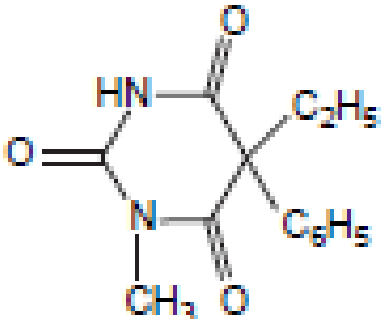
- **Mephobarbitol:** used as sedative, hypnotic and anticonvulsant. Administered through the intravenous (IV) route for inducing anaesthesia.



- **Barbitone sodium:** It is a powerful hypnotic drug and generally used in the treatment of epileptic seizures.

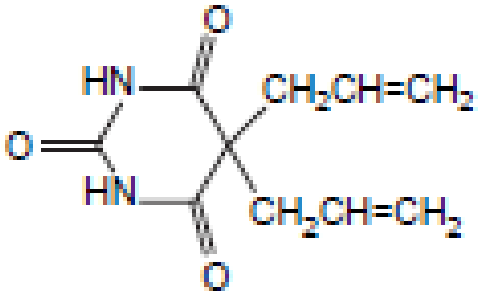


- **Methyl phenobarbitone (Mephobarbital):** Strong sedative with anticonvulsant action, but a relatively mild hypnotic. Hence, it is used for the relief of anxiety, tension, and apprehension, and is an antiepileptic in the management of generalized tonic-clonic and absence seizures.



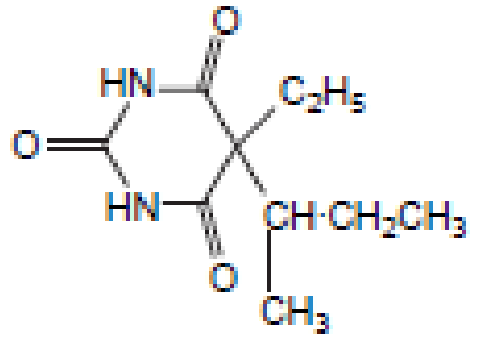
Dose: As a sedative 30–100 mg 3–4 times/day; as an anticonvulsant 400–600 mg daily.

- **Allobarbitone:** It can be used both as sedative and hypnotic at different dose intervals.



Dose: As a sedative 30 mg 3–4 times a day; as a hypnotic 100–200 mg at night..

- **Butabarbitone (Neonal):** It is used as a sedative and hypnotic, especially used for the short-term treatment of insomnia. Because of tolerance, barbiturates lose efifcacy after tw weeks of use.



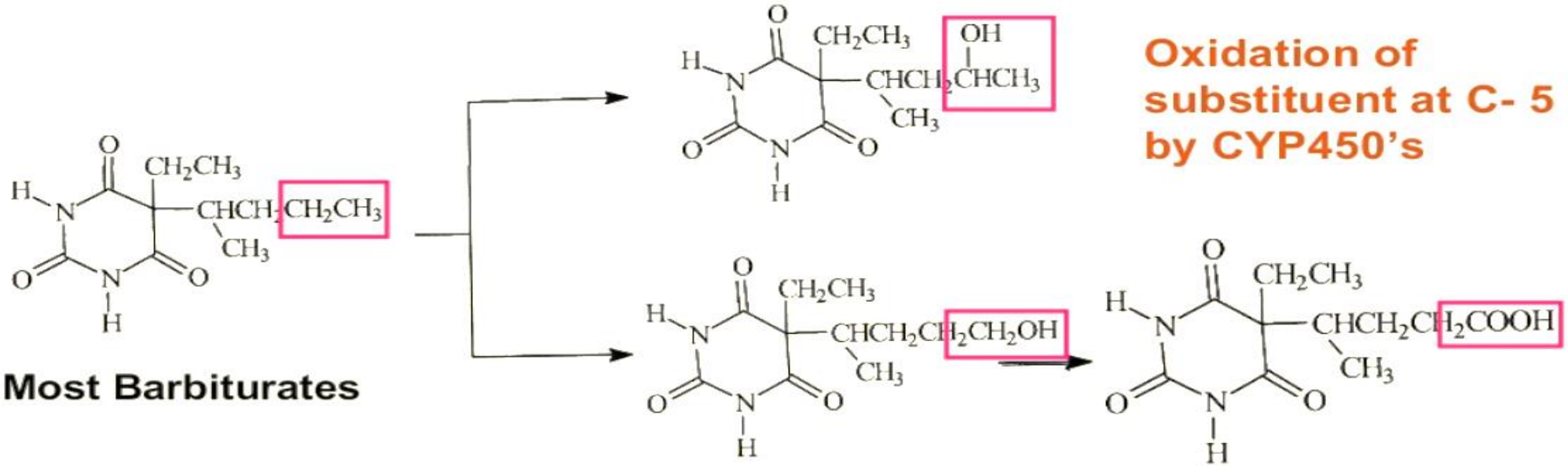
- Dose: 30 mg as a sedative and 100–200 mg at night as a hypnotic.

Metabolism of barbiturates

These drugs are metabolized in the liver and forms less lipophilic compounds. These are mediated through glucuronide or sulphate conjugation.

1. Oxidation of a substituent at C-5 forms alcohols or phenols, and these undergo further oxidation to form ketones or carboxylic acids. The barbiturates containing a propene at the fifth position inactivates CYP450 by alkylation of the porphyrin ring of CYP450.
2. The conjugation of heterocyclic nitrogen with glucuronic acid is due to the oxidative metabolism in the biotransformation of 5,5-disubstituted barbiturates (phenobarbital and amobarbital).
3. It undergoes oxidative N-dealkylation at nitrogen.
4. Oxidative desulphation of 2-thio barbiturates yields more hydrophilic barbiturates, which is excreted through urine.

An ultimate (ω) or penultimate (ω-1) oxidation of C-5 substituents

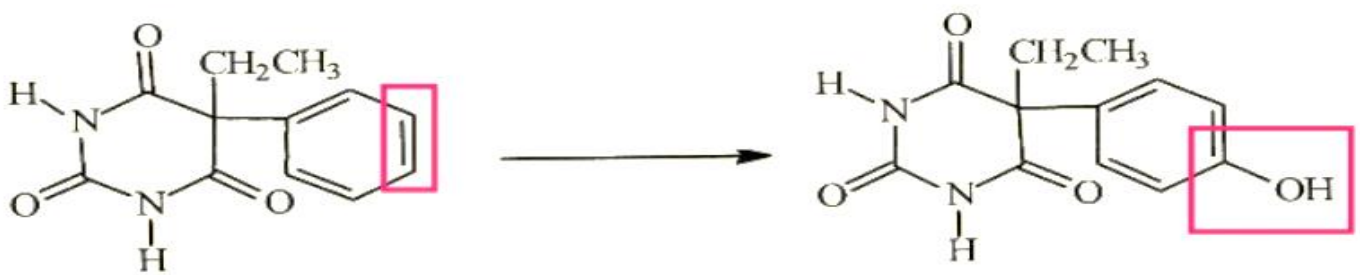


Most Barbiturates

Oxidation of substituent at C- 5 by CYP450's

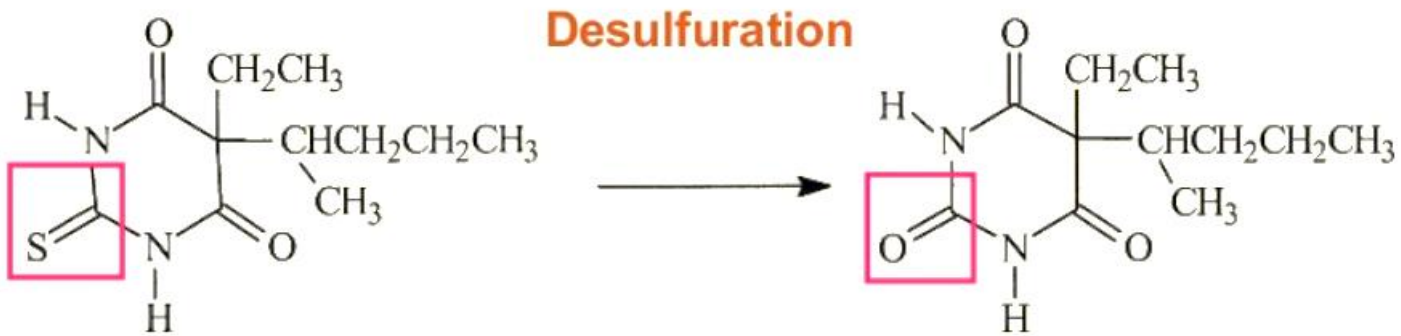
Aromatic Hydroxylation

Phenobarbital
Mephobarbital

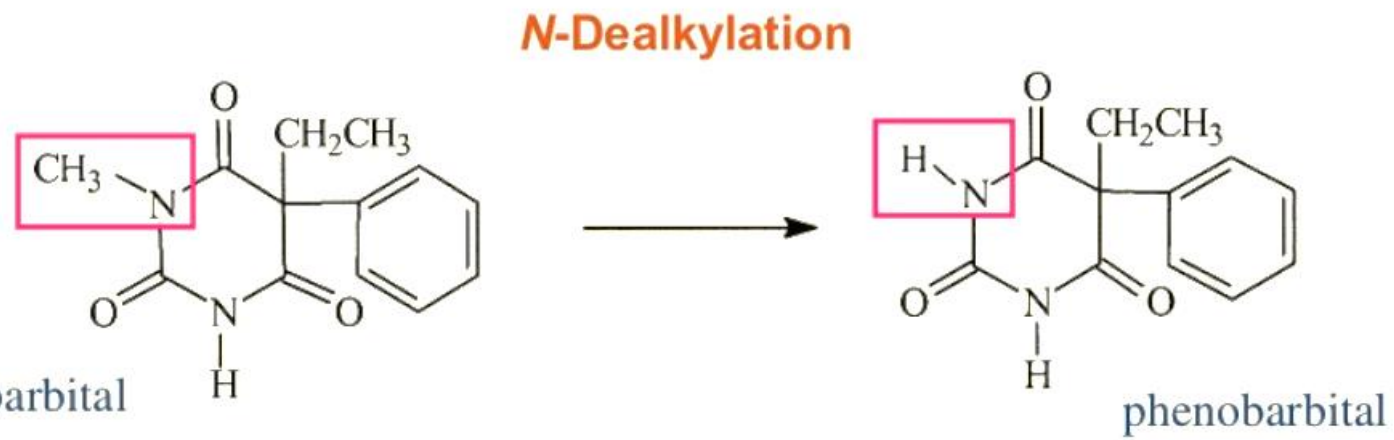


Glucuronide and sulfate conjugates

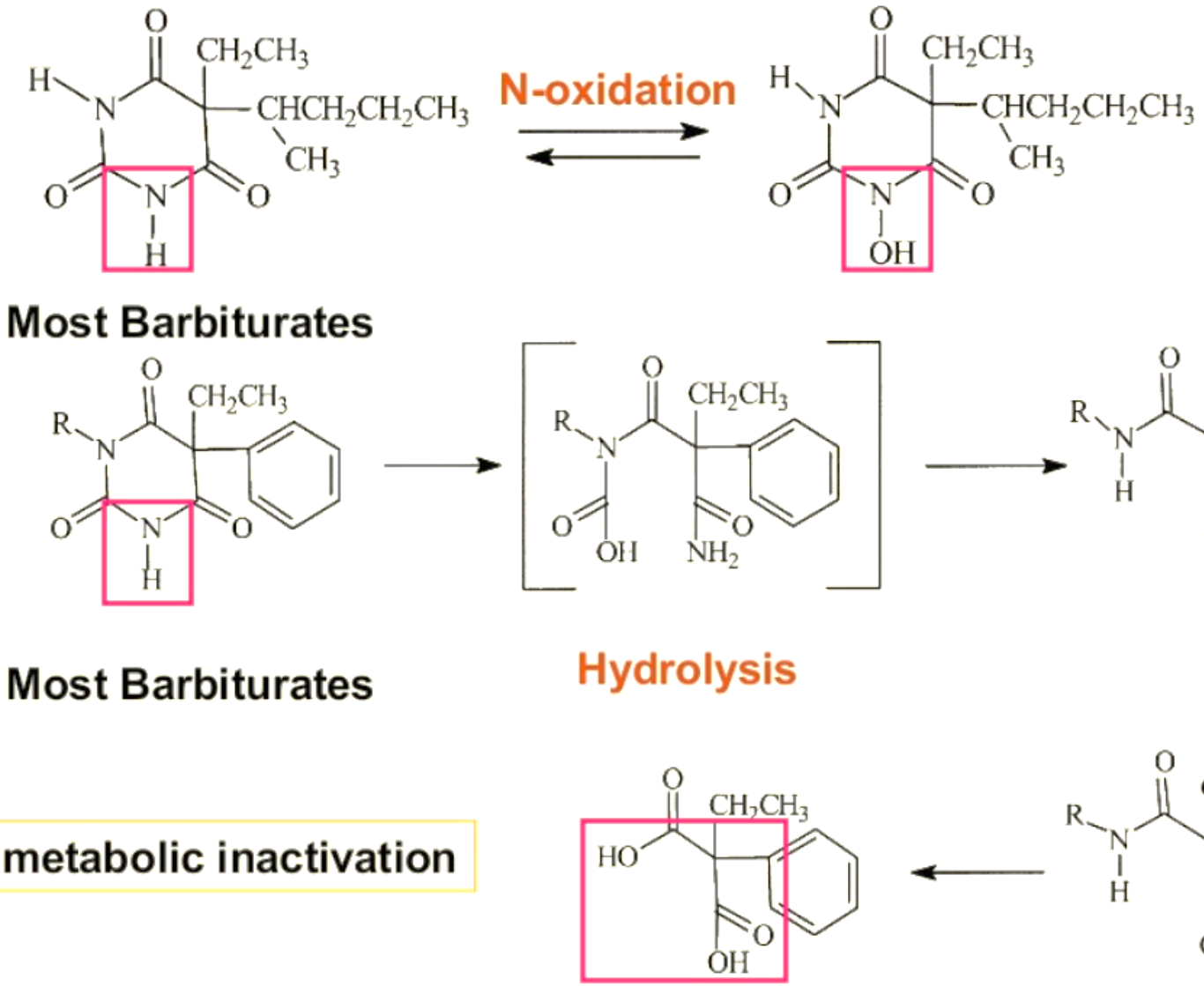
Desulfuration of 2-thiobarbiturates to yield more hydrophilic barbiturates



Thiobarbiturates



***N*-Methylbarbiturates**


N-oxidation
Most Barbiturates
Most Barbiturates
Hydrolysis
hepatic metabolic inactivation