Al-Azhar University-Gaza

Pharmaceutical Chemistry and Pharmacognosy Department

Sedative and Hypnotics

MedChem-III

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2020-2021

Defination

- A *sedative* drug decreases activity and excitement of the patient and calms 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

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

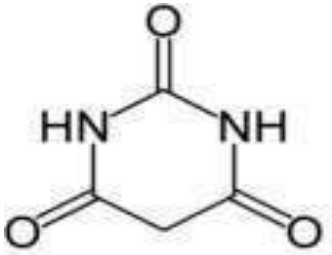
1. Cause a temporary decrease in the level of consciousness for the purpose of falling asleep without any alteration to sleep cycle
2. Must not decrease or arrest respiration, even at high doses
3. Cause no addiction, tolerance or dependence

Drug classification

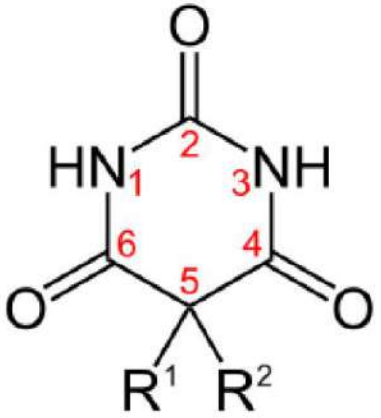
1. Barbiturates :Phenobarbitone
2. Benzodiazepines:

Alprazolam, Diazepam, Nitrazepam, Lorazepam

3. Non-Benzodiazepines: zolpidem, zopiclone
4. Others: paraldehyde, Glutethimide, Chloral Hydrate
5. Herbal sedatives: Ashwagandha, Valerian and passiflora



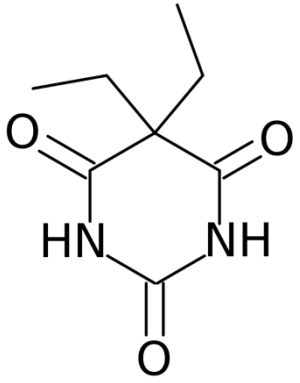
Barbiturates

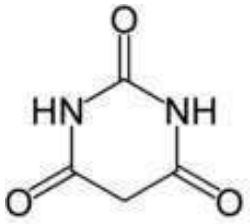


- All derivatives of Barbituric acid
- They are CNS depressants. They are effective as anxiolytics, hypnotics, anticonvulsants and analgesics.
- They have addiction potential, both physical and psychological.
- Thus Benzodiazipines have largely replaced them in term of sedative-hypnotic

Types

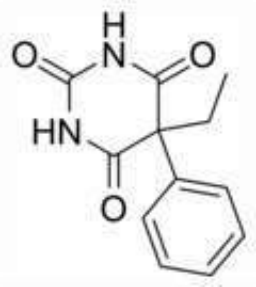
Barbital





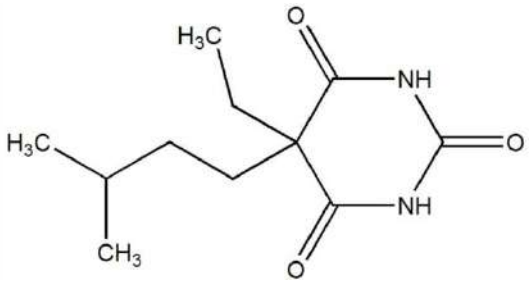
Barbituric Acid

Long-Acting



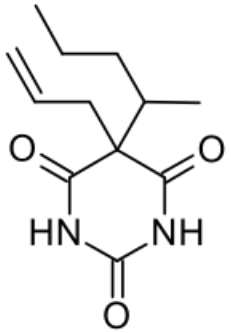
Phenobarbital

Intermediate acting



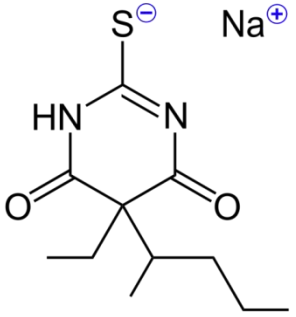
Amobarbital

Short acting

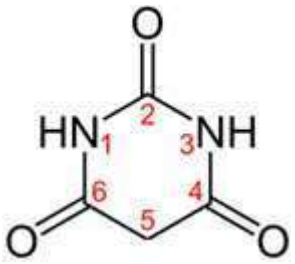


Secobarbital

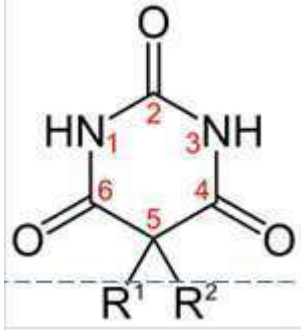
Ultra shortacting



Thiopental sodium



Structure-Activity Relationship



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

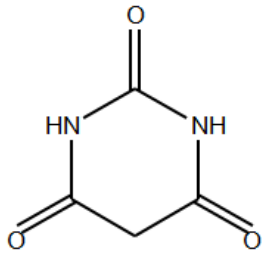
❖To make the drug sufficiently acidic, both or at least one of the two nitrogen must be unsubstituted

❖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

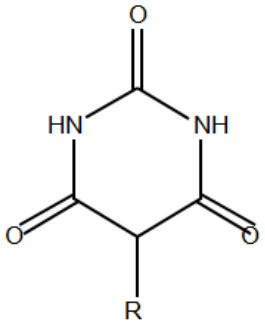
❖Potency

❖Duration of Action.

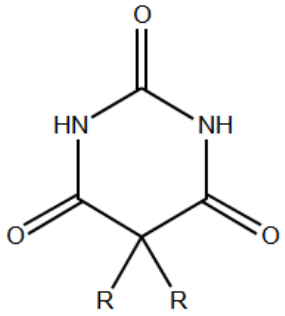


Barbituric acid

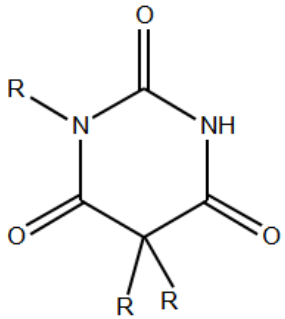
Inactive inactive coz not lipophilic enough



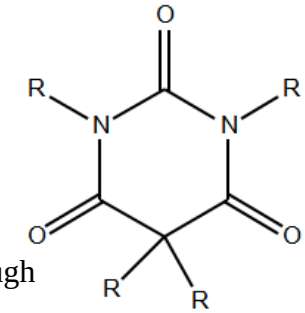
inactive
coz not lipophilic enough



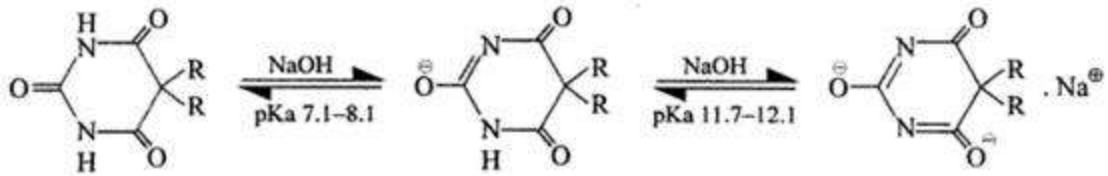
active



active



Inactive coz not acidic enough



SAR of barbiturates

- Both hydrogen atoms at the 5-position of barbituric acid must be replaced.
- Beginning with lower alkyls, there is an increase in onset and a decrease in duration of action with increasing hydrocarbon content up to about 7 to 9 total carbon atoms substituted on the 5-position.
- Increase the lipid/water partition coefficient generally increase the rate of metabolism, except with extremely high partition coefficient.
- N-methylation decreases duration of action by increasing the conc. of lipid-soluble free acid.
- 2-thiobarbiturates have a very short duration of action since they are highly lipophilic which cause depotization.
- Oral absorption is good.
- They are used as hypnotic, sedative, for induction of anesthesia, and as anticonvulsants.

- The total number of carbon atoms present in the two groups at carbon 5 must not be less than 4 and not more than 9 and influences onset of action and duration

Total carbon	Duration of action
7-9	Rapid onset and shorter duration
5-7	Intermediate duration of action
4	Slowest onset and longest duration of action

Classification :

Depending upon the duration of action barbiturates are divided into four classes like

(1) Long acting barbiturates (6 hours or more)

(2) Intermediate acting (3-6 hours)

(3) Short acting (less than 3 hours)

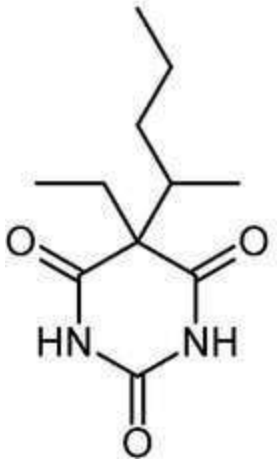
(4) Ultra-short acting (I.V.)

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

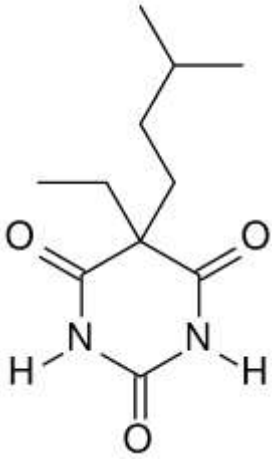
➢**The branched chain isomer exhibits** <u>greater activity</u> but **shorter duration.** The greater the branching, the more potent is the drug (e.g., pentobarbital > amobarbital).

➢This Branched, cyclic or unsaturated alkyl groups reduce duration of action due to increased ease of metabolic inactivation (Double bonds in the alkyl substituent groups produce compounds more readily vulnerable to oxidation)

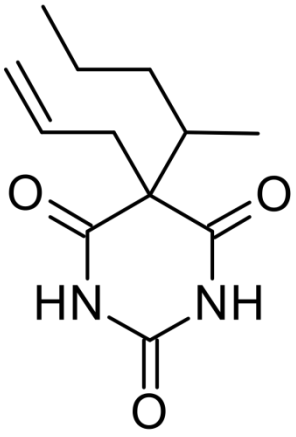
➢Aromatic and alicyclic moieties exert greater potency than the corresponding aliphatic moiety having the same number of carbon atoms.



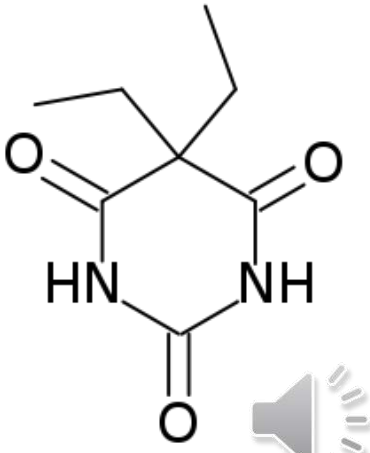
Pentobarbital



Amobarbital



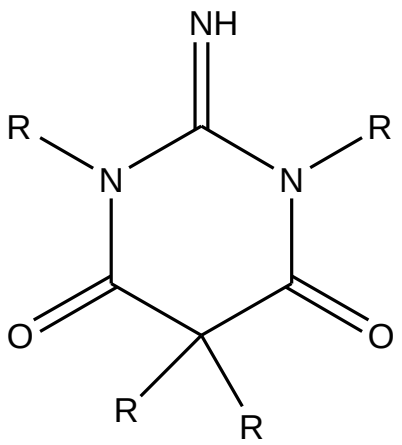
Secobarbital



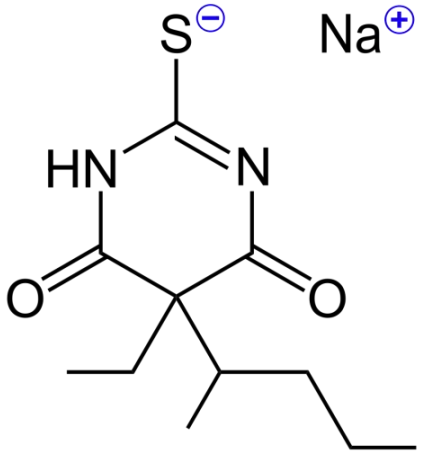
barbital

➢The replacement of O-atom with an S-atom, at C-2 position of the barbiturates significantly enhances the lipid solubility. Exert a rapid onset of action 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.’

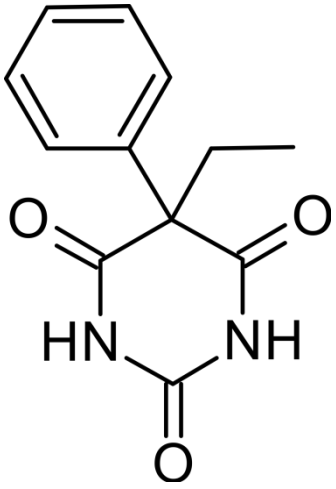
➢Inclusion of more sulphur atoms (at C-2 and C-6) decreases activity. Likewise replacement of Oxygen with Nitrogen abolishes activity



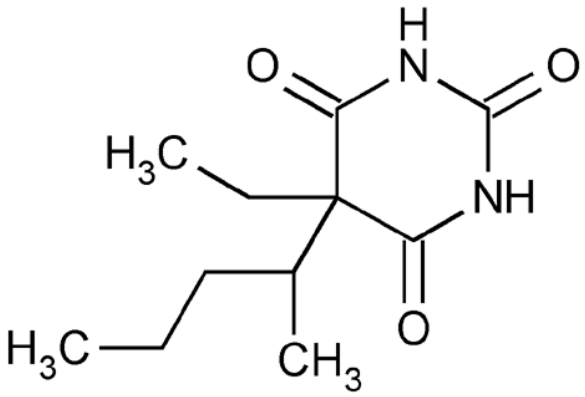
Inactive



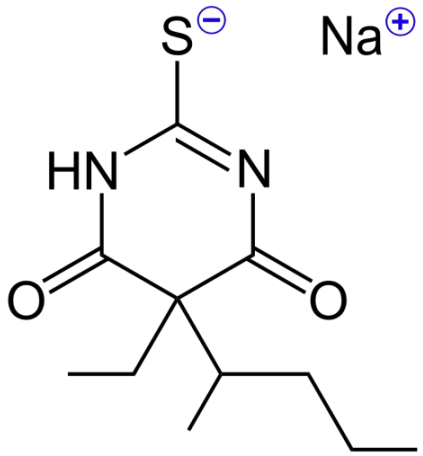
Thiopental sodium



Phenobarbital



Pentobarbital

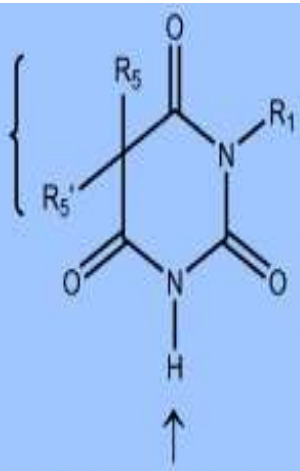


Thiopental

Factors effecting Duration of action as by the SAR	
Phenobarbital	Thiopental Sodium
	Branched R group
Short ethyl chain (Total carbon = 2 not counting aromatic)	Long chain of R group Total C= 7
	Additional improvements to Thiopental Sodium to further decrease duration of action •N methylation (potency also inc) •Unsaturated R group

Summary of barbiturates SAR

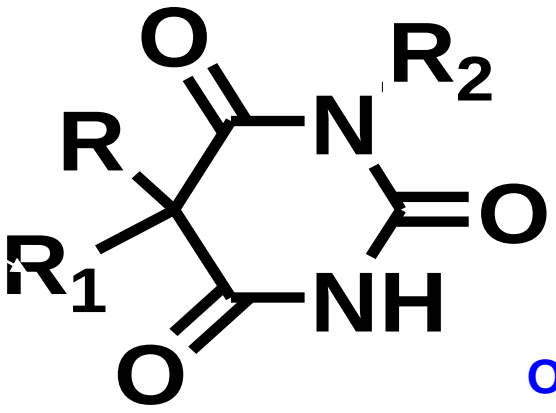
5,5-disubstitutents are important for activity and duration of action



R_1 = alkyl→↑ lipophilicity → quicker onset & shorter duration of action

O →S →↑ lipophilicity → rapid onset

must be a weak acid



R_2: CH_3

fast action

If R (R_1) = H, no activity;

it needs to be 2-5 carbon chains or 1 phenyl group

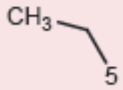
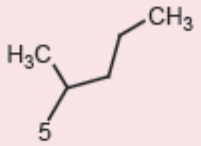
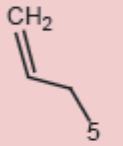
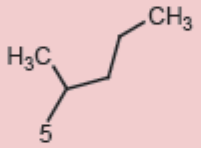
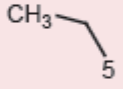
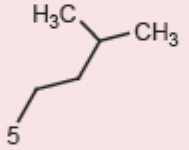
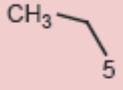
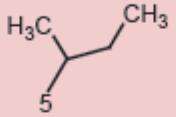
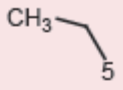
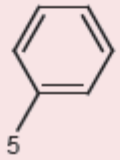
O: replace with S

fast action

The sum of R and R_1 needs to be 4-8

Note the correlation between the lipophilicity (logP) and the onset and duration of action for each drug.

TABLE 15.1 Pharmacokinetic Parameters of Barbiturates Approved for Sedative-Hypnotic Use

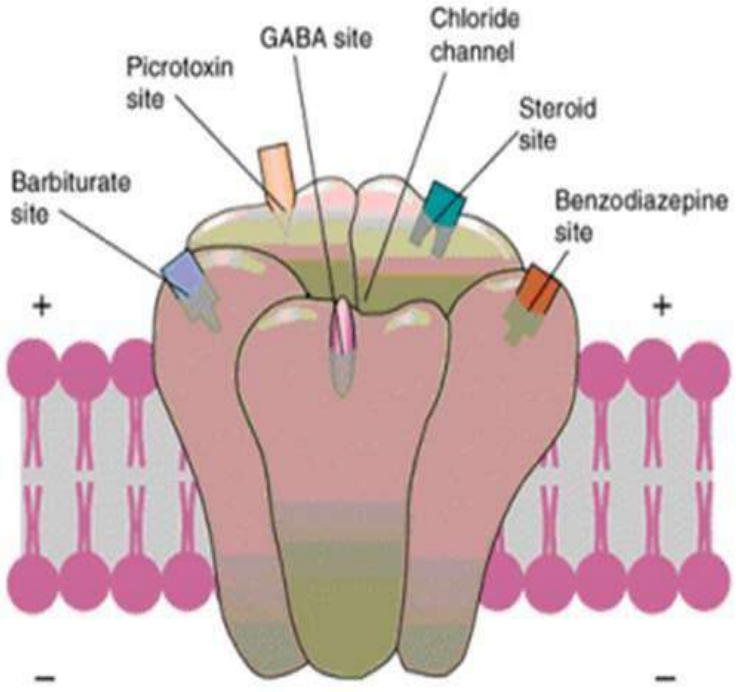
Barbiturate	R1	R2	LogP	Onset Time (min)[d]	Duration of action (hour)	Classification
Pentobarbital			2.10[a]	10–15	3–4	Short-acting
Secobarbital			2.36[b]	10–15	3–4	Short-acting
Amobarbital			2.07[d]	45–60	6–8	Intermediate acting
Butabarbital			1.60[b]	45–60	6–8	Intermediate acting
Phenobarbital			1.46[b]	30–60	10–16	Long-acting

Mode of action of barbiturates

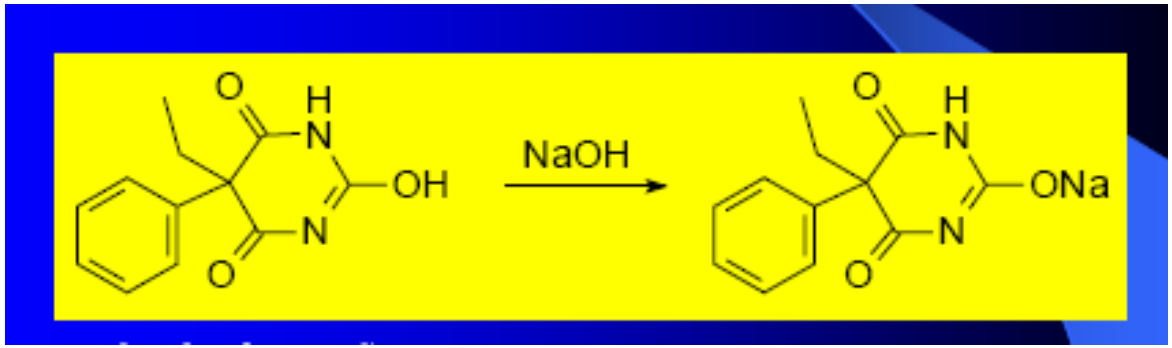
1. They have positive allosteric effect at GABA receptor. They bind at a different site than GABA or Benzodiazepines and stimulate the pharmacologic action of GABA which is the principal inhibitory neurotransmitter in the CNS

2. They inhibit AMPA receptor, which binds **glutamate** which is principal *excitatory* neurotransmitter in the CNS

3. At higher does they inhibit Ca^{+2} dependent release of neurotransmitters

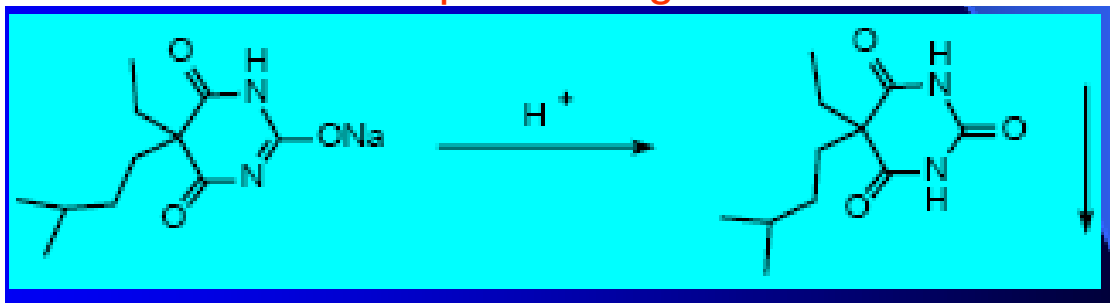


When it dissolves in sodium-containing basic solutions, it becomes sodium salt. Amobarbital sodium is used as injections.



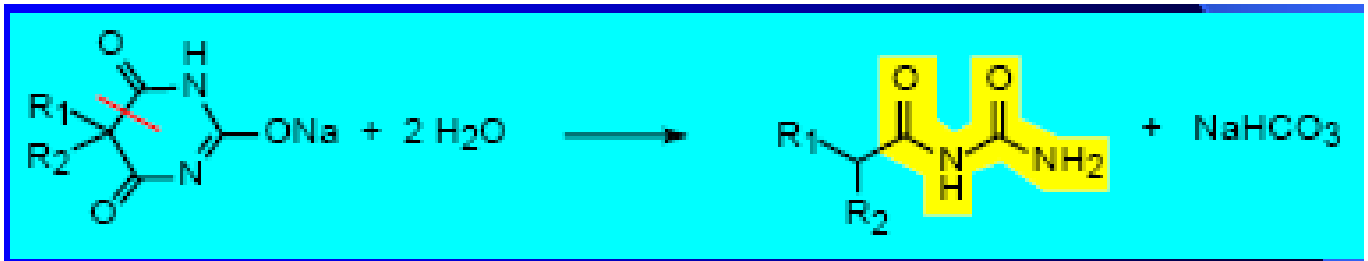
The sodium solution absorbs CO_2 and the free drug precipitates from the solution,

Suggestion: it cannot be exposed long in the air.



The sodium solution absorbs water and decomposes

Suggestion: it cannot be left long in the air.



When 10% sodium solution is placed at 35°C, 22% of the drug decomposes in one month.

If it is stored at 1°C for two month, the drug is basically stable.

Be caution if the injection is used

In order to avoid the invalidation of

the injections, be careful the following

- ★ **Avoid pre-formulation, sterilization by heating**
- ★ **should be made in powder-injection, dissolved before used**

Intravenous Anesthetics

Ultrashort-acting barbiturates:

- Administered IV. In aqueous solutions for the induction of anesthesia

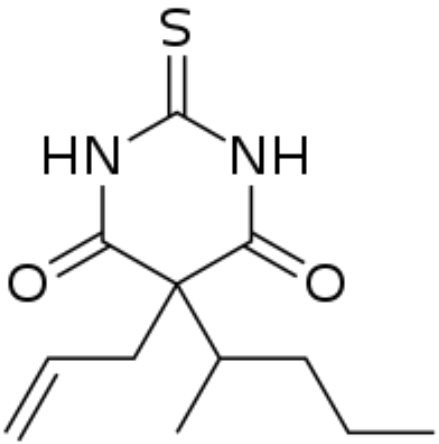
- Respiratory depression is marked at anesthetic doses therefore they are not used to maintain surgical anesthesia

Act within seconds and last for 30 minutes

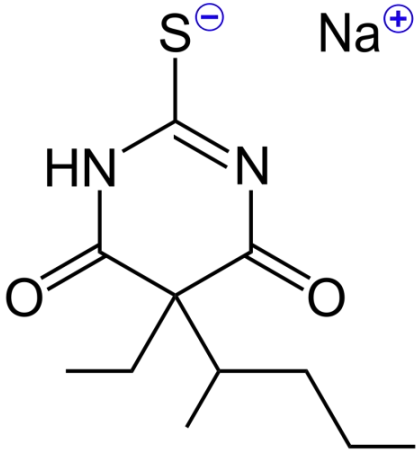
- This is due to high lipid/water partition coefficient, so fast penetration from the blood to the site of action in the brain lead to rapid onset of action.

- The short duration of action due to fast distribution to the well perfused tissues in the peripheral organs and subsequently to fat tissue

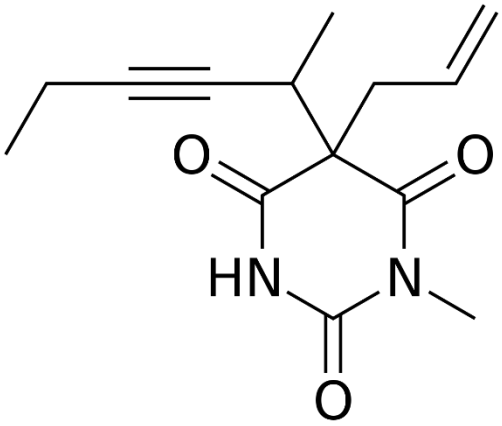
Thiamylal sodium



Thiopental sodium



Methohexital



General scheme for synthesis of Barbiturate :