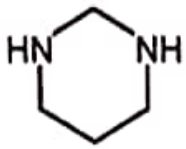
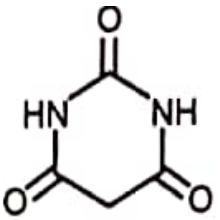
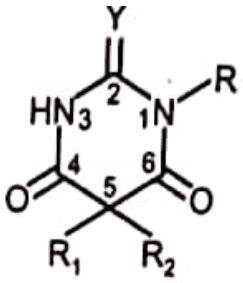


Saturated pyrimidine

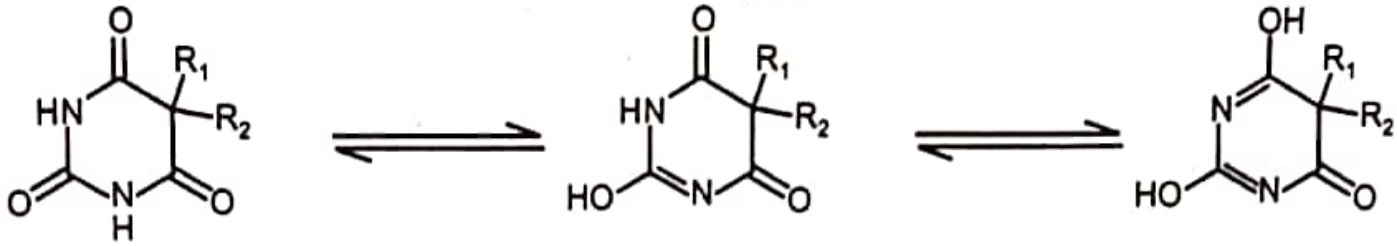


Barbituric acid



Barbiturates

The derivatives of Barbituric acid (2, 4, 6-trioxypyrimidine) are known as Barbiturates.



Lactam form (Tri-oxo form) (Di-oxo form) Lactim form (Mono-oxo form)

In an order to possess the hypnotic activity of Barbiturates has been rationalized on basis of two criteria:

(A) Acidity.

(B) Lipid-water partition coefficient.

A. Acidity

(1) Barbiturate should be a weak acid with pKa value more than 4.1. pKa values 4.1 for Unsubstituted (R_1, R_2 and R_3 = H, Y = O), 6.5-8 for Disubstituted (R_1 and R_2) and greater than 8 for Trisubstituted (R_1, R_2, and R_3).

(2) Barbiturates (R_1, R_2, and R_3 = H) which are comparatively acidic, are not acting as a CNS depressant.

(3) Additions of Alkyl substituents reduce acidity (high pKa) due to the positive inductive effect of these alkyl groups.

B. Lipid-water Partition Coefficient

(1) On branching, sulphurization, etc. lipophilicity increases. Usually, drugs with high lipophilicity are highly plasma protein bound and hereby eliminated more slowly.

(2) High lipophilicity is a requisite to cross blood-brain barrier for rapid onset.

(3) Conventionally Barbiturates are subdivided into four groups:

1. Long-acting Barbiturates :

   Relatively low lipophilicity and low plasma protein binding (<40%) Examples : Phenobarbital, Mephobarbital, and Metharbital.

   Duration of action (06-08 hrs) and Onset of action (30-60 mins).

2. Intermediate-lasting Barbiturates:

   Intermediate lipophilicity and intermediate plasma protein binding (50%) Examples : Butalbital, Amobarbital, and Talbutal.

   Duration of action (04-06 hrs) and Onset of action (45-60 mins).

3. Short-acting Barbiturates :

   High lipophilicity and high plasma protein binding (70%).

   Examples : Secobarbital, and Pentobarbital.

   Duration of action (02-04 hrs) and Onset of action (10-15 mins)

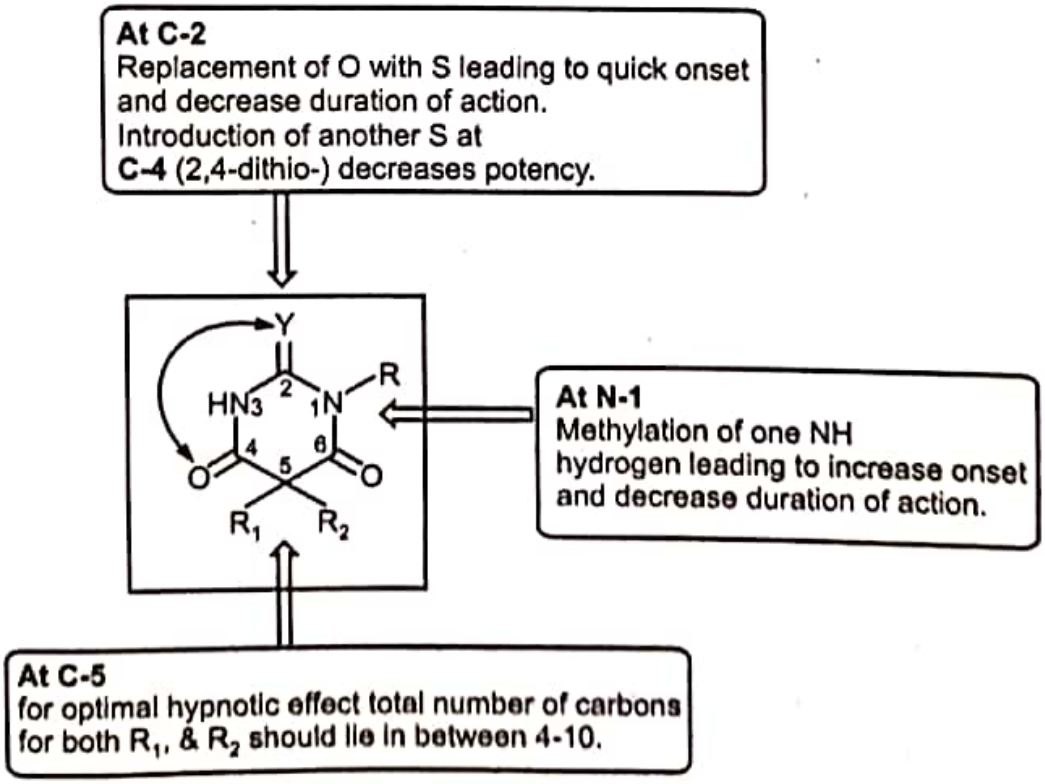
4. Ultrashort-acting Barbiturates :

   Very high lipophilicity and high plasma protein binding (>70%).

   Examples : Thiopental, Methohexital

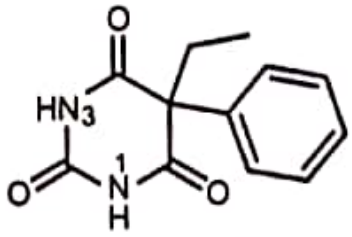
   Duration of action (10-30 mins) and rapid onset.

4.5.1 Structure-activity Relationship of Barbiturates

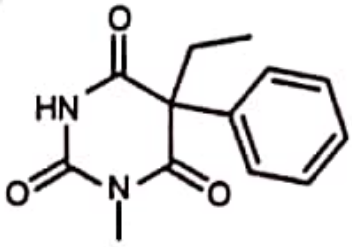


4.5.1.1 At Position 1 & 3

Methylation of a nitrogen atom at N-1, increase onset but decrease the duration of action.



Phenobarbital



Mephobarbital

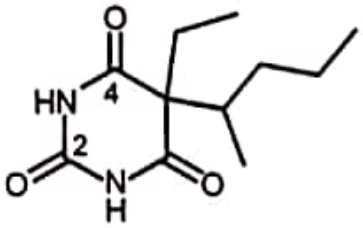
Onset of action	1 hr	30 mins
Duration of action	10-12hrs	06-08 hrs

As the size of alkyl substitution increases from methyl to propyl lipophilicity increases leading to further increase onset but decrease duration of action.

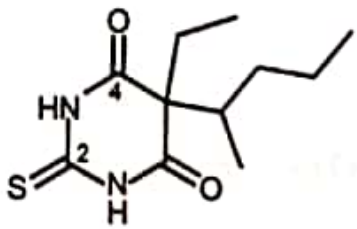
$$N\text{-}CH_3 < N\text{-}C_2H_5 < N\text{-}C_3H_7 \text{ (Increase onset)}$$

4.5.1.2 At Position 2, 4 & 6

Replacement of an oxygen at C-2, by sulfur led fast onset but decrease duration of action. Further replacement from position C-4 diminishes bioactivity.

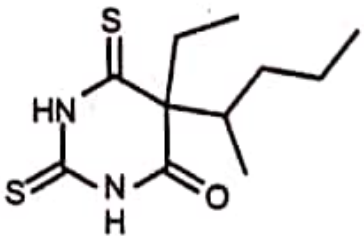


Pentobarbital

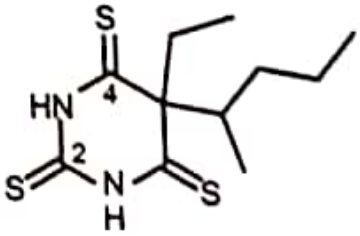


Thiopental

Onset of action	30 mins	2-10 mins (IM)
Duration of action	4-8 hrs	30 mins



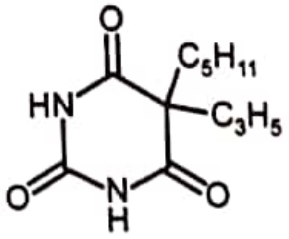
Inactive compounds



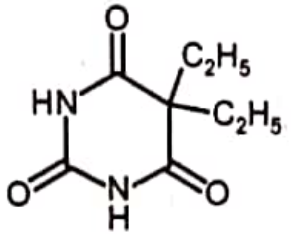
Inactive compounds

4.5.1.3 At Position 5

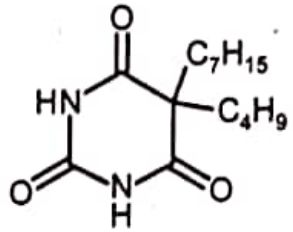
For improved sedative and hypnotic activity, a total number of carbon atom present two groups at the C-5 position should not be less than 4 and not more than 10.



Secobarbital
Total C atoms=8

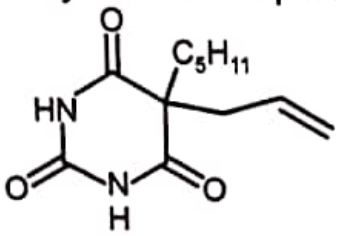


Barbital
Total C atoms=4

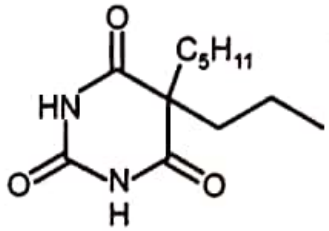


Inactive compounds
Total C atoms=11

With the same numbers of carbon atoms, unsaturated, allyl, alkenyl, cycloalkenyl analogs have increased potency than the aliphatic substituents.



Secobarbital



Less active compounds

With the same numbers of carbon atoms, aliphatic substituents are less potent than Alicyclic or Aromatic substituents at C-5.

The introduction of polar groups such as $-NH_2$, –OH, –C=O, -COOH, –RNH etc. at C-5 in the Aromatic ring, decreases lipid solubility and potency.