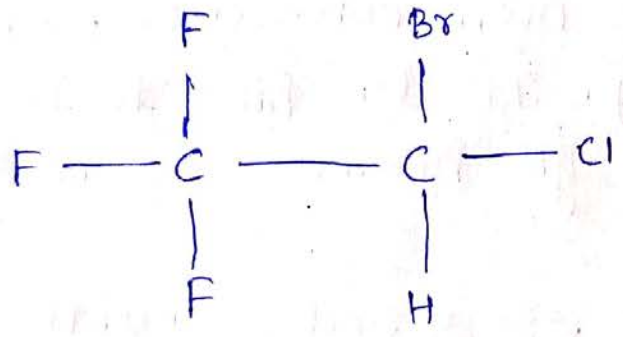
GENERAL ANAESTHETICS

General anesthetics are drugs that act in the CNS, causing reversible loss of consciousness, thereby causing a generalized loss of sensation. Anesthesia means, lack of feeling.

Inhalation Anaesthetics:

Inhalation anesthetics are used for induction and maintenance of general anesthesia as well as sedation. Inhalation anesthetics could be either volatile liquids or gases and they are administered through inhalation process.

A. Halothane (Fluothane)

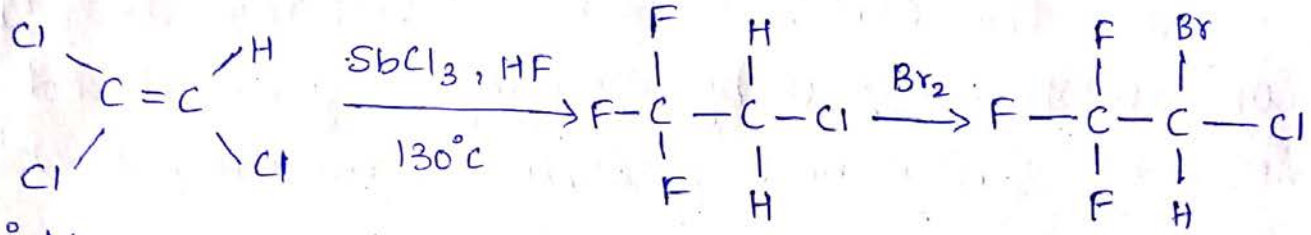


2-Bromo-2-chloro-1,1,1-trifluoro ethane.

Halothane is a volatile, non-flammable fluorinated hydrocarbon. It is the only inhalational anesthetic agent containing a bromine atom.

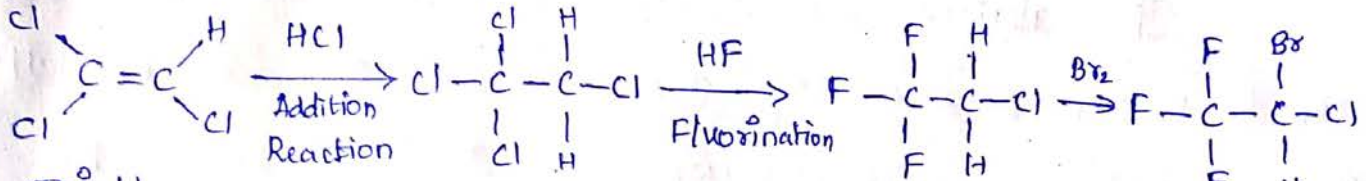
Synthesis:

Method - I



Trichloro ethene — Trifluoro chloro ethane — Halothane

Method - II



Trichloro ethane — Tetrachloro ethane — Trifluoro Chloro ethane — Halothane

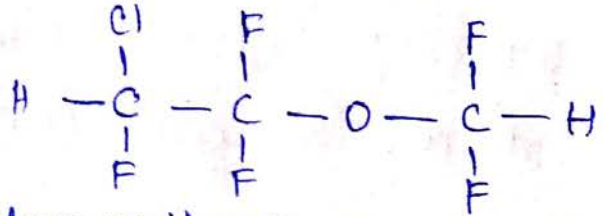
Mechanism of action:-

It act on multiple ion channels, which ultimately depresses nerve conduction, breathing, cardiac contractility. It also binds to potassium channels in cholinergic neurons and also to NMDA.

USES:

It is a potent, safe and frequently employed general inhalation anaesthetic.

B. Euflurane (Erthrane)



1-Difluro methoxy-2-chloro 1,1,2-trifluoro ethane

It is a halogenated ether. It is a structural isomer of Isoflurance. It vaporizes readily but it is liquid at room temperature.

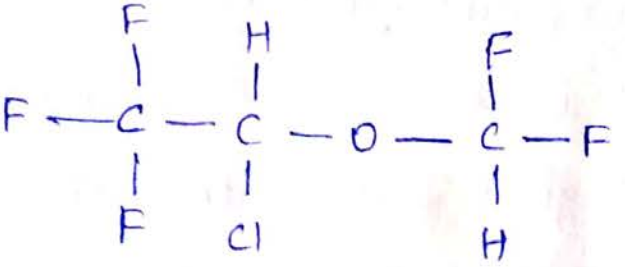
Mechanism of action :-

It activates calcium dependent ATPase in the Sarcoplasmic reticulum by increasing the fluidity of the lipid membrane. It also binds to the GABA receptor potassium channel, the glycine receptor and antagonizes the glutamate receptor.

Use :-

It is used for induction and maintenance of general anesthesia. It is also used to analgesia for vaginal delivery.

C. Isoflurance (Isorane)



1-Difluoro methoxy-1-chloro-2,

2,2-trifluoroethane.

Isoflurane is closely related to Enflurane. It is an isomer of Enflurane, non-inflammable liquid Vapourizes readily.

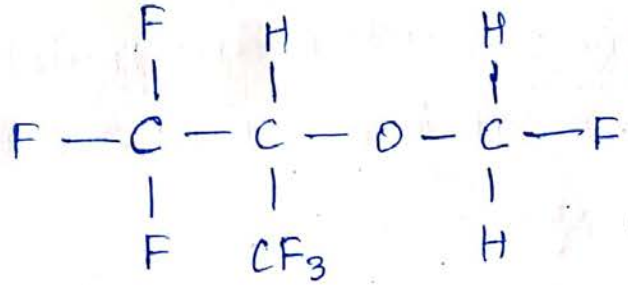
Mechanism of action :-

Same as Enflurane.

Use :-

It is used as inhalation anaesthetics for maintenance of general anesthesia induced by another drug. It is frequently used in Veterinary Practice.

D. Sevoflurance (sevorane)



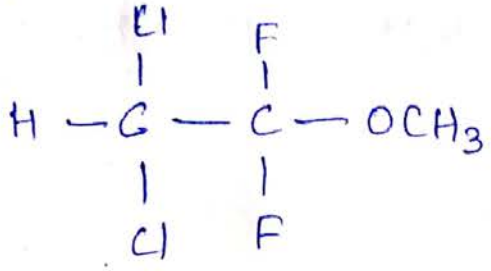
2 - Fluoro methoxy -1,1,1,3,3,3- hexafluoropropane.

Sevoflurane is a sweet smelling, non-flammable highly fluorinated ether, often used inhalation anesthetics nowadays. It can be given by mask because its does not cause irritation.

Mechanism of action :- Same as Enflurance

Use :- It is used as an inhalation anaesthetic.

E. Methoxyflurane (Pentrane)



1-methoxy-2,2-dichloro-1,1-difluoroethane.

Methoxyflurane is freely soluble in lipid, so the partition co-efficient (blood/gas) is large, consequently recovery is slow.

Mechanism of action :-

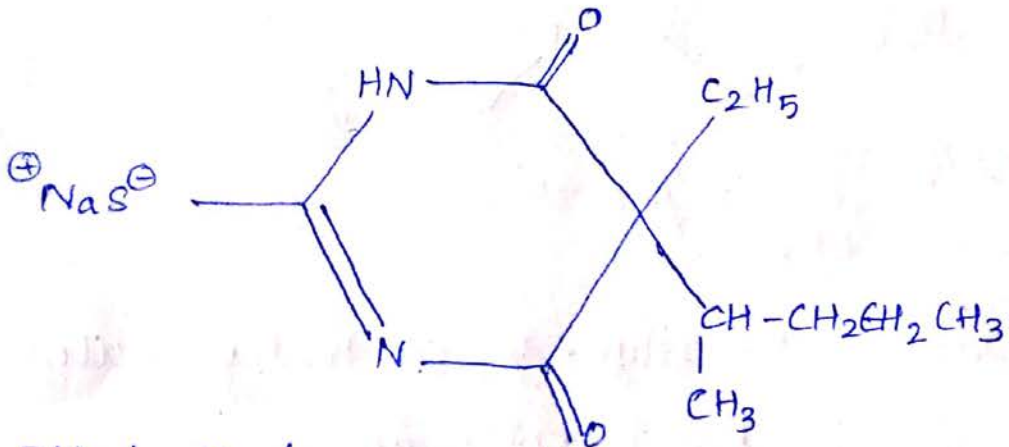
Same as Enflurance

Use :-

It is employed to cause light anaesthesia with deep analgesic and muscle relaxation feature, which make it convenient for surgical operation.

B. ULTRA SHORT ACTING BARBITUTRATES :-

A. Thiopental Sodium (Thiopen)



5-Ethyl-5-(1-methyl butyl)-2-thio barbituric acid.

Thiopental is an ultra-short acting barbiturate. It is used to produce quick anaesthesia and initiate anaesthesia.

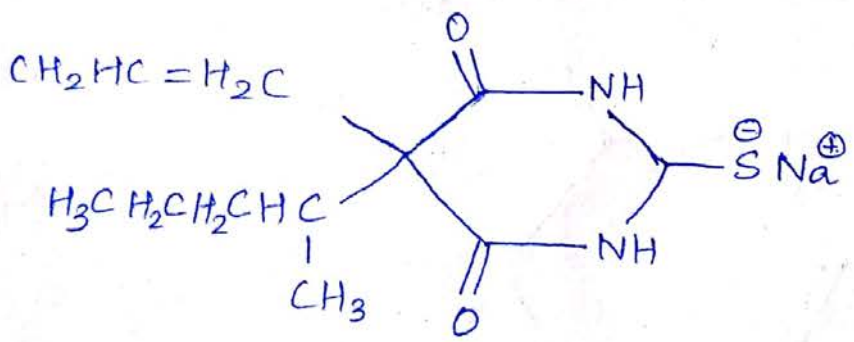
Mechanism of action :-

It depresses the CNS and inhibits ascending transmission of impulses in the reticular formation. Thiopental may enhance or mimic inhibitory action of δ-aminobutyric acid, thereby causing anticonvulsant effect and producing sedation and hypnosis.

Use :-

It belongs to the category of ultra-short acting barbiturates, usually administered intravenously for the production of complete anaesthesia for short duration. It is also used as a basal anaesthesia.

B. Thiamylal Sodium (Citosol)



Sodium-5-allyl-5-(1-methyl butyl)-2-thiobarbiturate.

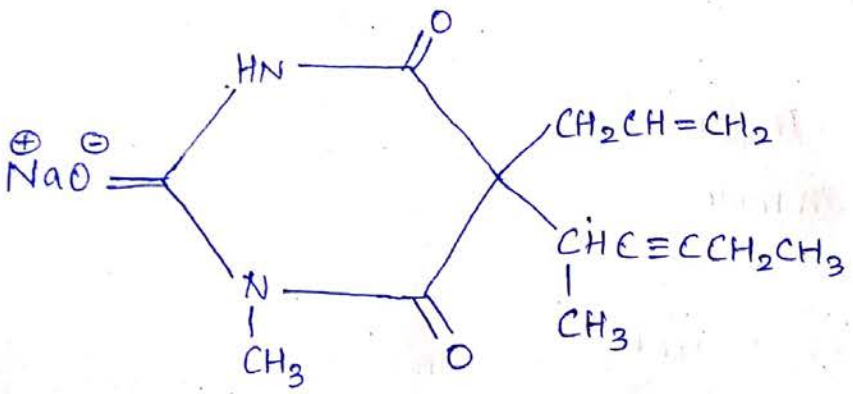
Mechanism of action :-

It binds at a distinct binding site associated with a Cl^- ionopore at the $GABA_A$ receptor, increasing the duration of time for which the Cl^- ionopore is open. The post-synaptic inhibitory effect of GABA in the thalamus is, therefore, prolonged.

Use :-

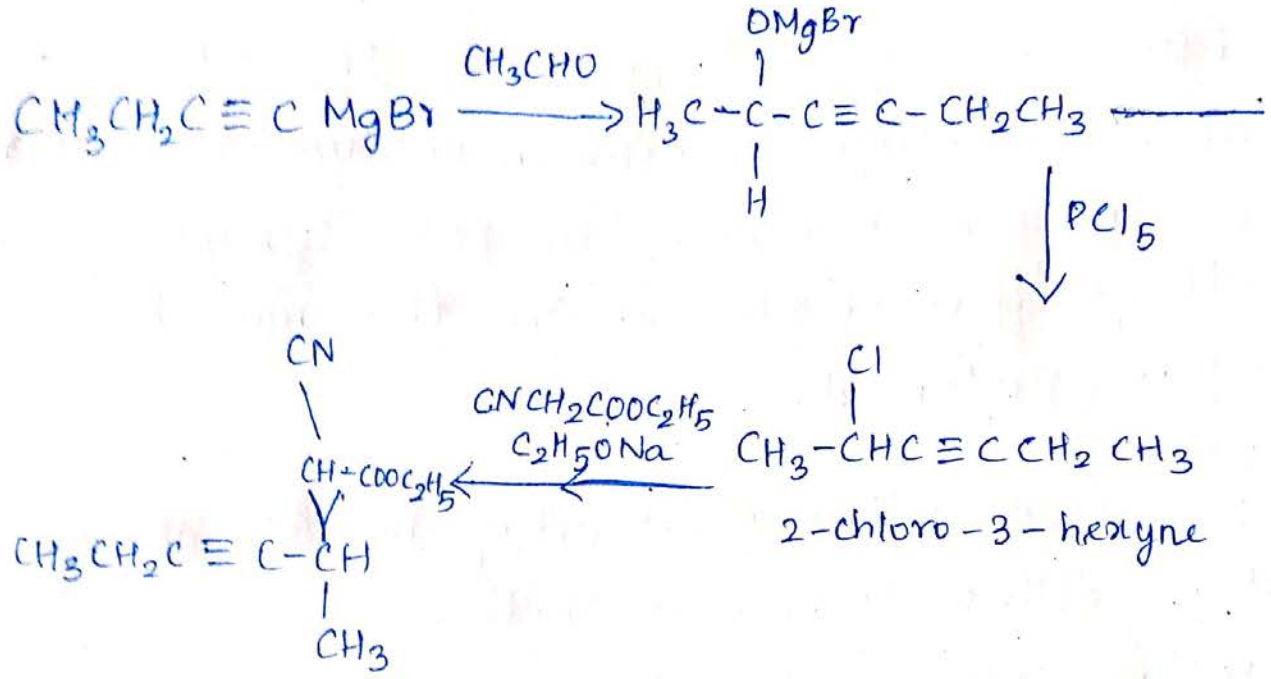
It is an ultra-short acting barbiturate used as intravenous anaesthetic.

C. Methohexital sodium (Brevital)

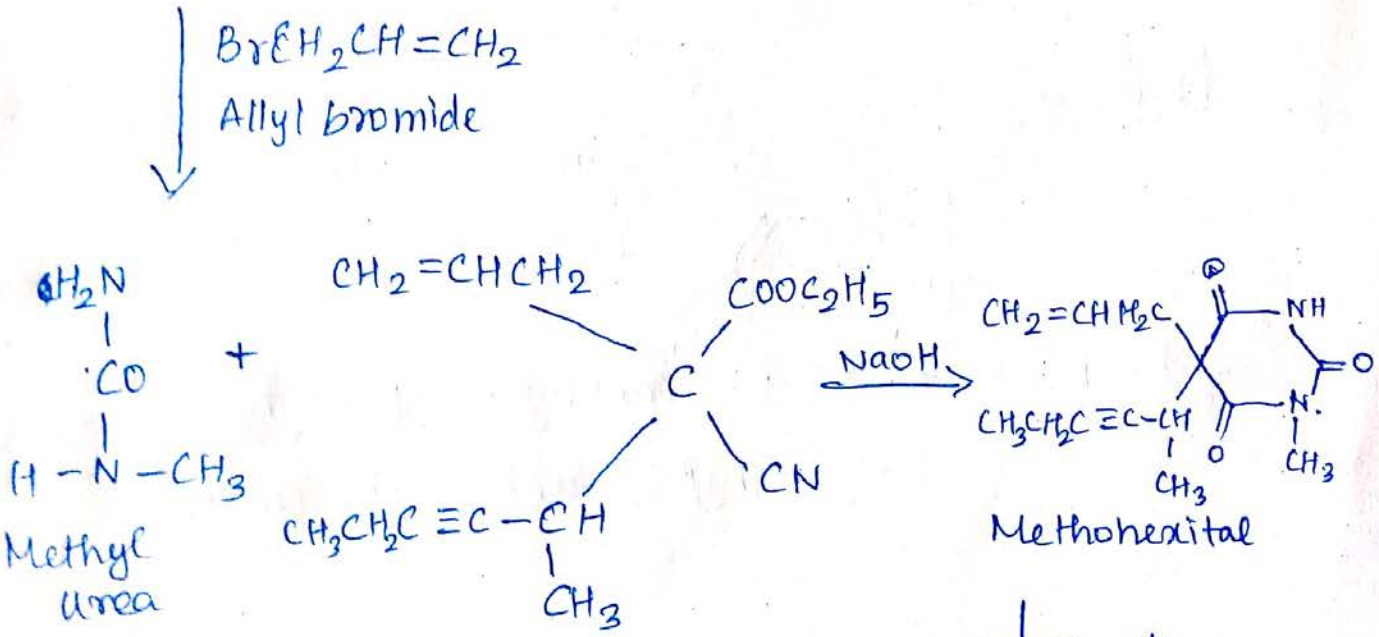


1-Methyl-5-(1-methyl-2-pentynyl)-5-(2-propenyl) barbituric acid.

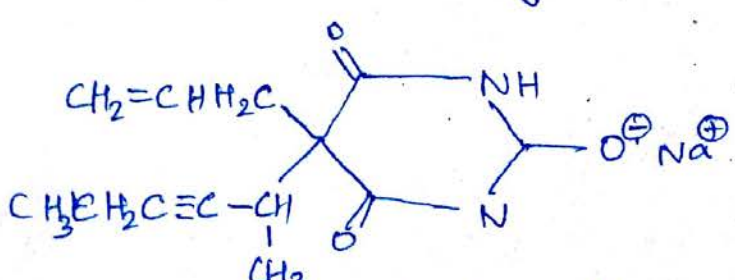
Synthesis :-



Ethyl-(1-methyl-2-Pentynyl) Cyano acetate



Methohexital



Methohexital sodium

Mechanism of action :-

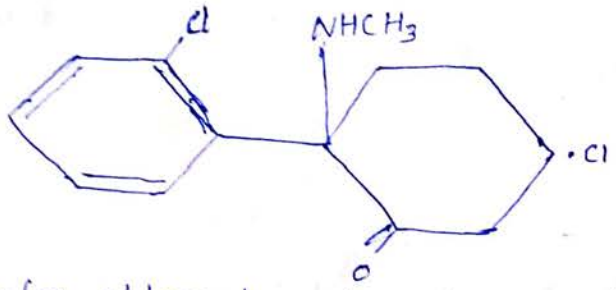
Same as Thiamylal Sodium.

Use :-

It is useful for short surgical operation such as oral surgery, gynecological investigation and electroconvulsive therapy.

PHENCYCLIDINE DERIVATIVE :

A. Ketamine hydrochloride (Aneket)



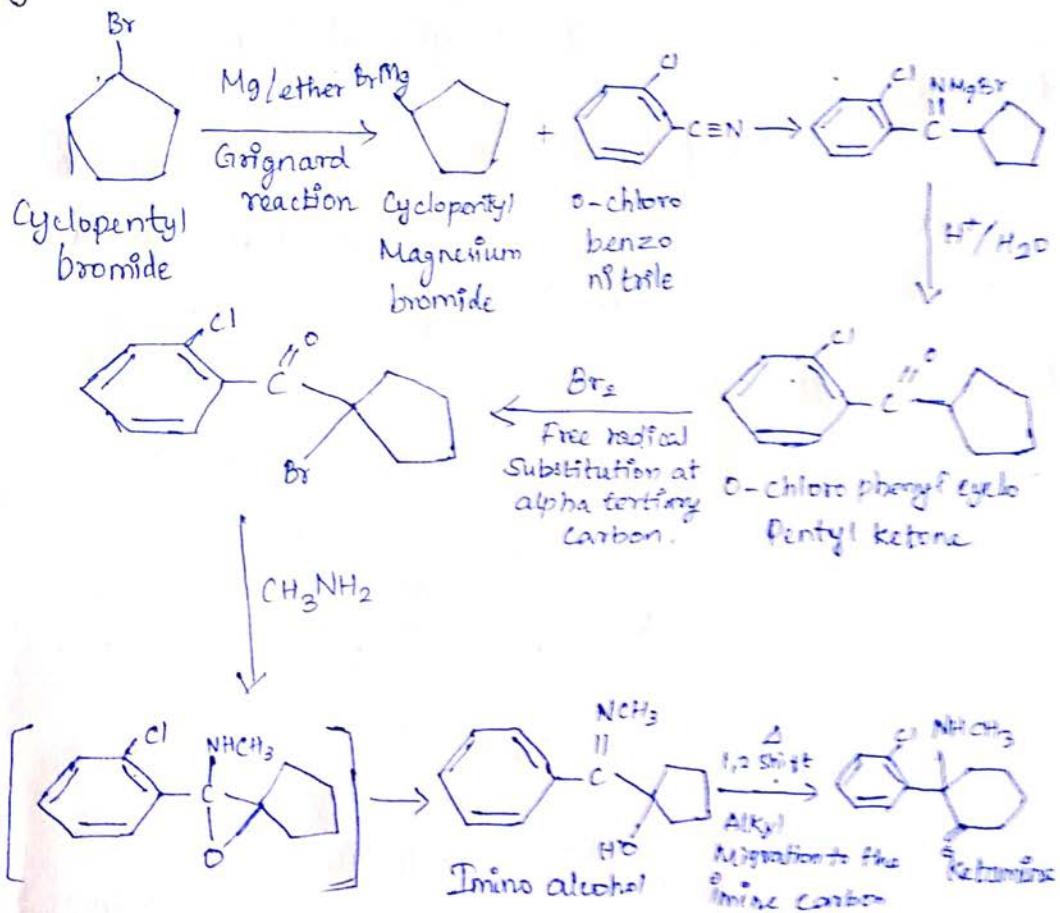
(±)-2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride

It is a dissociative anesthetic. It is a short-acting, non-barbiturate anesthetic, includes a dissociated state in which the patient is unconscious and does not feel pain.

Mechanism of action :-

It inhabits the excitatory neurotransmitter glutamate at NMDA receptors. It functions at the thalamus and the limbic cortex.

Synthesis :-



Use :-

It is an intravenous anaesthetic agent and drug of choice for short surgical operation and mainly used as induction anesthesia in children and elderly people.

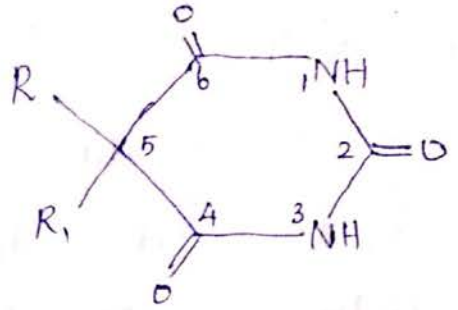
SEDATIVE AND HYPNOTICS

Barbiturates :-

Barbiturates are derived from barbituric acid or 2,4,6-trioxo hexahydro pyrimidine. In general, the barbiturates exert a significant depressant action on the cerebrospinal axis.

Structure Activity Relationship :-

Barbituric acid does not possess any hypnotic activity. Activity is exhibited only when two active hydrogen atoms are substituted in 5th position of barbituric acid.

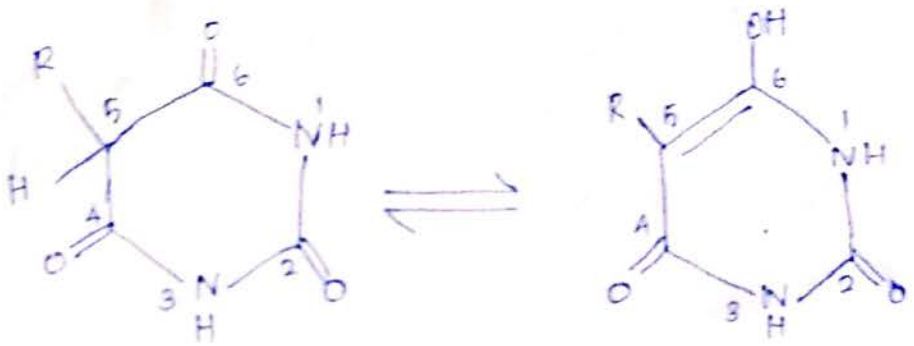


(i) Modification at position C-5 :-

Modification at c-5 positions is important for barbiturates used as sedative and hypnotics.

* Mono substitution at 5th carbon decreases the activity, because of the presence of one available proton at that site increases

the acidity due to tautomerism. The proper acidity ratio of ionized and unionized form is important to cross the blood brain barrier (BBB).



* The 5, 5'-disubstituted barbituric acid contains three lactum group that can undergo lactum - lactim tatomrism. The acidity of babituric acid depends upon the number of Substituent present in the position 5.

* Both the hydrogen at position 5 should be replaced, but the sum of the carbon of both Substituents should be between 6 and 10 for optimal hypnotic activity. This sum is also indexed for duration of action.

* As the sum of alkyl group increases the lipid solubility of the compound also increases, it leads to increased onset of action and decreased duration of action

* Stereo isomers have same potencies

* The presence of halogen in the 5-alkyl group increases the potency.

(ii) Modification of position 1 and 3 :-

Modifications at nitrogen 1 or 3 position are important for barbiturates used as anaesthetics and anticovulsant.

* Alkylation at position C-1 or C-3 may result in shorter onset and duration of action because N-methylation reduces the activity value.

* Attachment of larger alkyl group to the nitrogen imparts anticonvulsant property to barbiturates.

* Attachment in both the nitrogen at N-1 and N-3 render the drug non-acidic making them inactive.

(iii) Modification at position 2, 4 and 6 :-

Modification at oxygen is important for barbiturates used as anaesthetics.

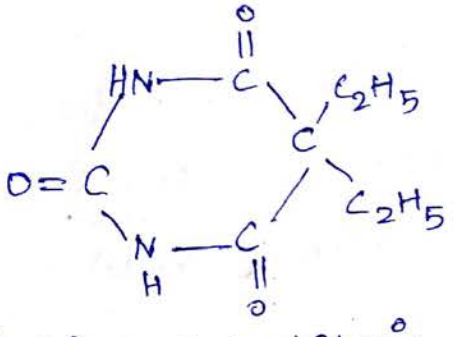
* The replacement of oxygen by sulphur at

C-2 increases the lipid solubility hence shortens the duration and onset of action.

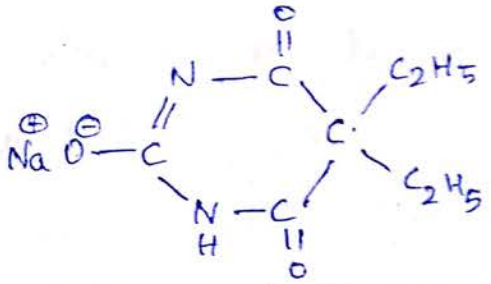
* Introduction of more sulphur at position C-4 and C-6 decreases the hypnotic activity.

* These drugs are used as intravenous anaesthetics Eg: Thiopental.

A. Barbital (or) Barbitone (veronal) :-

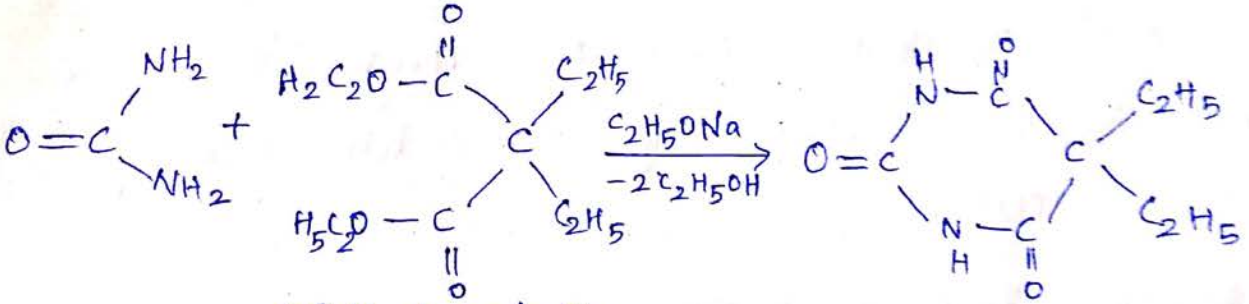


5,5'-Diethyl barbituric acid



Sodium-5,5'-diethyl barbiturate

Synthesis :-



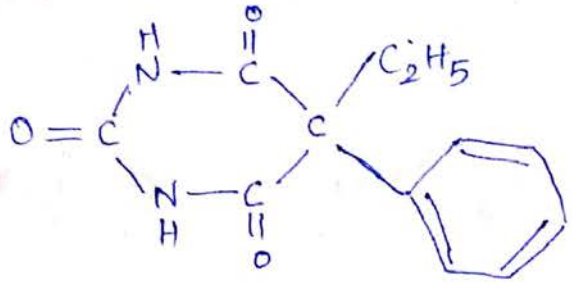
Diethyl malonic ester

Barbital

Use :-

It is a powerful hypnotic drug and generally used in the treatment of seizures.

B. Phenobarbital (or) Phenobarbitone (Mudrane):-

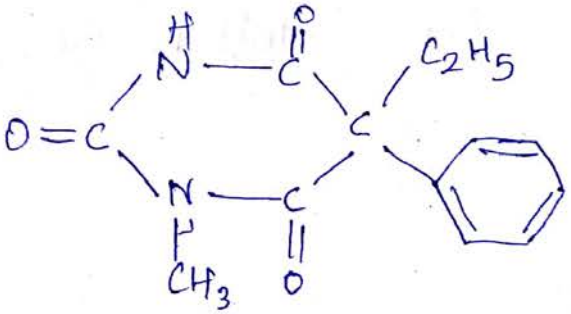


5- Ethyl - 5 - phenyl barbituric acid.

Use :-

It is used as sedative and hypnotic. It is a drug of choice for the treatment of grandmal and petit mal epilepsy.

C. Mephobarbital or Methylphenobarbitone (prominal):-

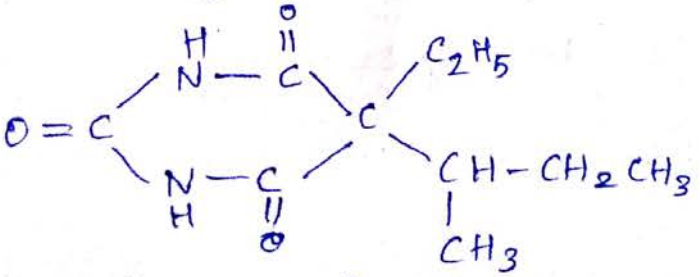


5- Ethyl - 1 - methyl - 5 - phenyl barbituric acid.

Use :-

It is used as anticonvulsant with strong hypnotic activity.

D. Butabarbital (Butisal):-

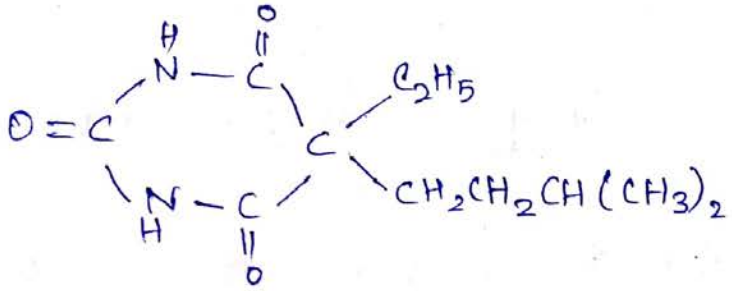


5 - (1- methyl propyl) - 5- ethyl barbituric acid.

Use :-

It is used as sedative and hypnotic at different dose intervals.

E. Amobarbital or Amylobarbitone (Amytal):-

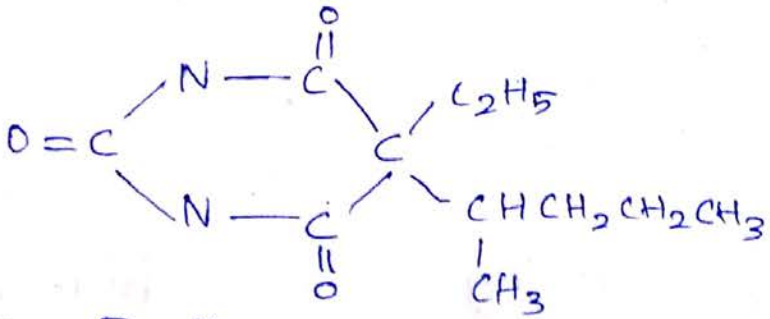


5-Ethyl-5-isopentyl barbituric acid.

Use :-

It is used in the treatment of insomnia and pre-operative medication.

F. Pentobarbital (or) Pentobarbitone (Barbinol) :-

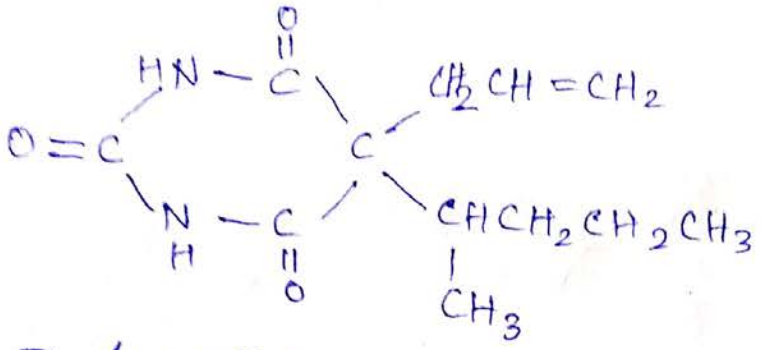


Sodium-5-alkyl-5-(1-methyl butyl*) barbiturate

Use :-

It is used mostly in the treatment of insomnia, as basal anaesthetics and also in strychnine poisoning.

G. Secobarbital (or) Quinalbarbitone (Seconal):-



5-Alkyl-5-(1-methyl butyl) barbituric acid.

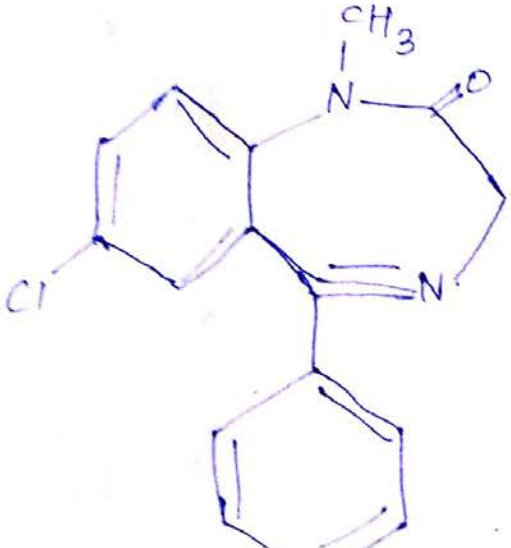
Use:-

It is widely used as Sedative and hypnotics. It is also used in Status epileptics and toxic reactions to Strychnine and local anaesthetics.

BENZODIAZEPINES:-

A. Diazepam (Alzepam):-

Diazepem is the most successful sedative form benzodiazepine group. It is discovered by Strenhack and Hoffmann.

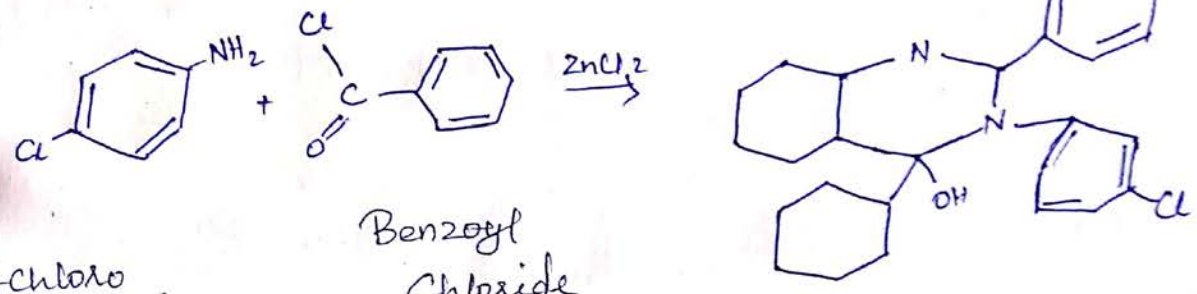


7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

Synthesis :-

Method - 1

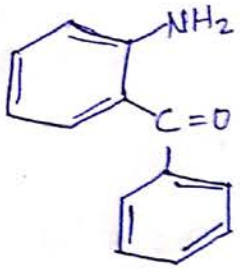
Step 1 :



4-chloro amine

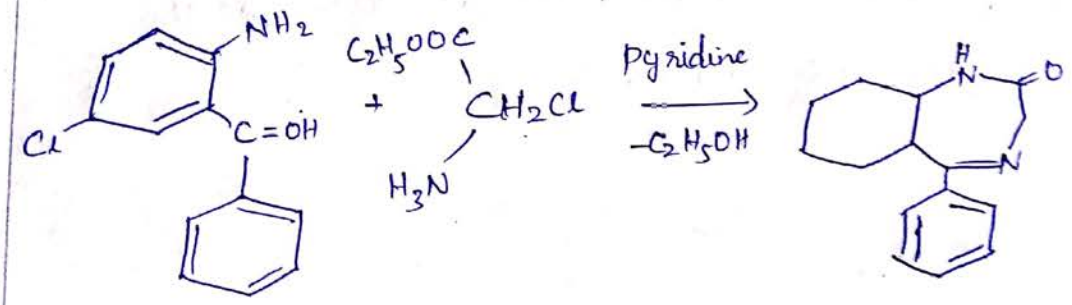
Benzoyl Chloride

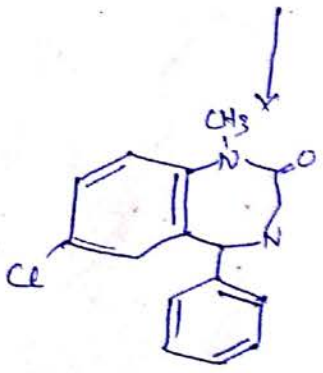
↓ H_2O



2-amino-5-chloro benzophenone

Step 2 :



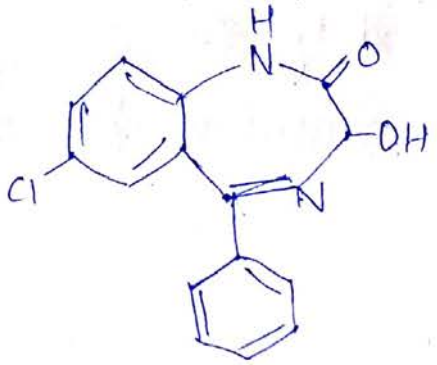


Diazepam

Use :-

It is used as Skeletal muscle relaxant, anticonvulsant and antianxiety agent.

B. Oxazepam (Serepax) :-

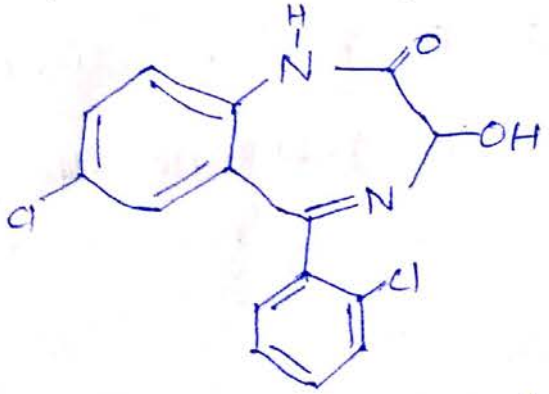


7- chloro - 1, 3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1, 4 - benzodiazepin - 2 - one.

Use :-

It is a mild sedative useful in the management and control of anxiety, tension, agitation, irritability and related symptoms. It is also useful for the control of acute tremulousness inebriation or anxiety associated with alcohol withdrawal.

C. Lorazepam (Lorivan) :-



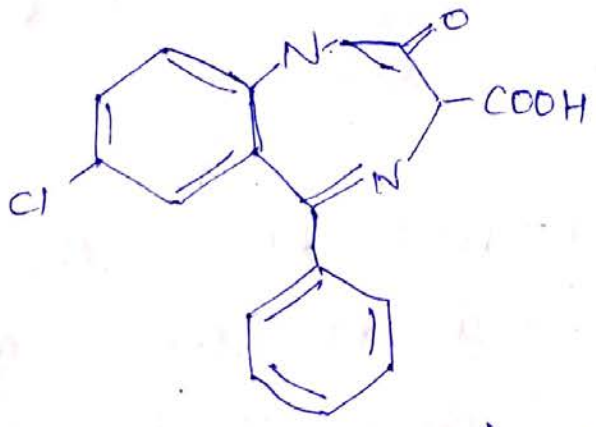
7- chloro - 5 - (2 - chlorophenyl) - 1, 3 - dihydro - 3 - hydroxy - 2H - 1, 4 - benzodiazepin - 2 - one.

Lorazepam is 2'-chloro substituted analogue of Oxazepam. The presence of 2' chloro group increase the activity.

Use :-

It is used to treat anxiety disorders. It is used for the short term treatment of insomni acute seizure and sedation.

D. Chlorazepate (Tranxene) :-



7-chloro-2-oxo-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-3-carboxylic acid.

Use :-

It is used to treat anxiety disorders. It is also used as muscle relaxant and anticonvulsant.