Anticonvulsant Drugs

SUBJECT- PHARMACEUTICAL CHEMISTRY-VII (4T2)

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Introduction

- Epilepsies are a group of disorders of central nervous system. Epilepsy may be defined as a paroxysmal self-sustaining and self-limiting cerebral dysrhythmia, characterized by an abnormal and excessive electroencephalogram (EEG) discharge and loss of consciousness with or without characteristic body movement like convulsion, sensory or psychiatric phenomenon.
- EEG discharge originated from gray matter or other part of the brain. These EEG discharge spreads to other part of CNS and resulting convulsions produced.
- The drugs used in the therapy of various types of epilepsies are known as antiepileptic drugs or anticonvulsant drugs.
- The primary use of antiepileptic drugs (AEDs) is in the prevention and control of epileptic seizures.

- Ideal AEDs should not produce sedation and other undesired CNS toxicity.
- It should be well tolerated and highly effective against various types of seizures and be devoid of undesirable side effect on vital organ and their function.

The epileptic seizures have been classified as follows:

Generalised seizures

- Absences
- Tonic-clonic
- Myoclonic
- Atonic

Partial seizures

- Simple partial seizures
- Complex partial seizures

Generalised Seizures

Absences seizures (Minor Epilepsy)

- Prevalent in children, the attack lasts from a few seconds to half a minute.
- Momentary loss of consciousness usually with motor activity varying from eyelid blinking to jerking of entire body.
- The patient apparently freezes.

Tonic-clonic seizures (Major Epilepsy)

- It is commonest type of epilepsy, lasts about 1-2 min.
- Sudden loss of consciousness.
- Tonic spasm of all body muscles.
- Clonic jerking followed by prolonged sleep and depression of all CNS functions.

Myoclonic seizures

- It can be described as brief jerks of the body.
- It can involve any part of the body, but it is mostly seen in limbs or facials muscles.
- The jerks are usually involuntary and can lead to falls.
- Shock like momentary contraction of muscles of a or the whole body.

Atonic seizures

- Unconsciousness with relaxation of all muscle due to excessive inhibitory discharges.
- Atonic seizures is a type of seizure that consists of partial or complete loss of muscle tone.
- These seizures are brief usually less than 15 sec.
- They usually begin in childhood and may persist into adulthood.

Partial Seizures

Simple Partial seizures

- Simple partial seizures are seizures which affect only a small region of the brain, often the temporal lobes or structures found there, such as the hippocampi.
- The attack lasts from a 30 seconds to 1 minute.
- Convulsions are confined to a group of muscles or localized sensory disturbance depending on the are of cortex involved in seizures without loss of consciousness.

Complex partial seizures

- Attacks of bizarre and confused behavior and purposeless movement changes lasting from 1-2 min along with impairment of consciousness.

Mechanism of Action

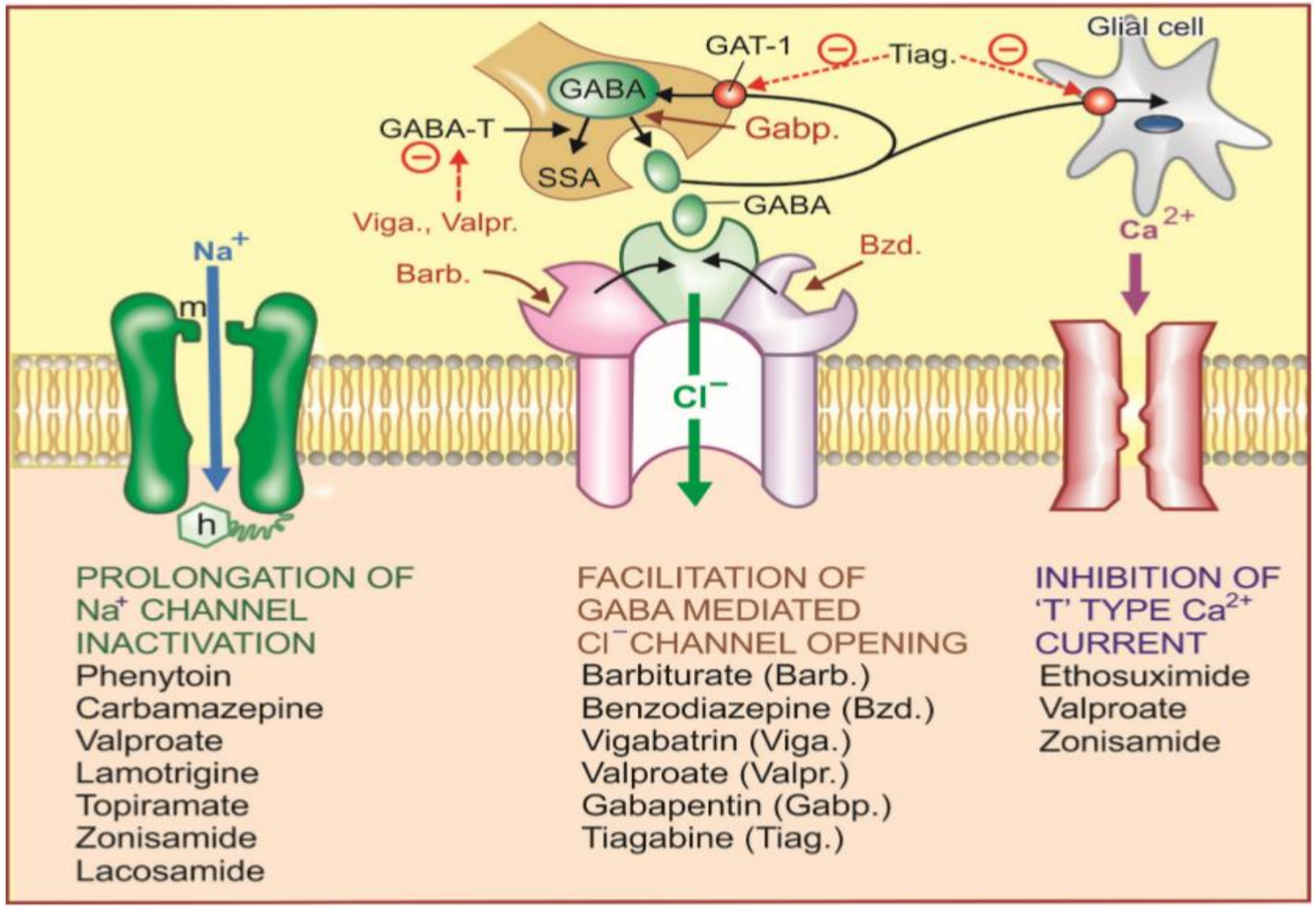


Fig. 30.2: Major mechanisms of anticonvulsant action
m: Activation gate; h: Inactivation gate; GABA-T: GABA transaminase;
SSA: Succinic semialdehyde; GAT-1: GABA transporter

Classification of anticonvulsant Drugs

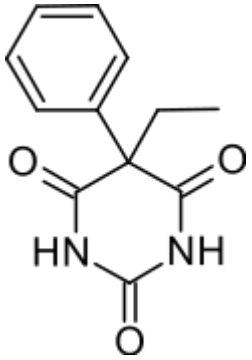
Many of the standard AEDs that contain the ureide structure. Based on their mechanism of action they can be classified as:

1. Enhancement of Na^+ channel inactivation - **Phenytoin**
2. Enhanced GABA synaptic transmission
   a) Agent acting on the GABA/Cl^- complex - **Progabide**
   b) Agent that potentiate GABA - **Vigabatrin, Tiagabine**
   c) Agent that bind to Benzodiazepine receptors - **Diazepam**
   d) Agent that bind to Barbiturate receptors- **Phenobarbitone**
3. Reduction of current through T-type Ca^{2+} channel - **Ethosuximide, Troxidone.**

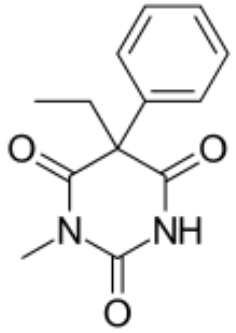
Classification of Anticonvulsant Drugs

1. Barbiturate -

Phenobarbitone

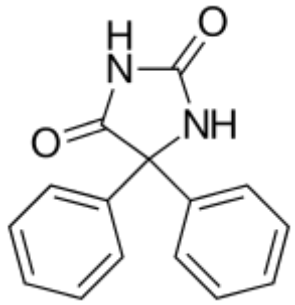


Mephobarbitone

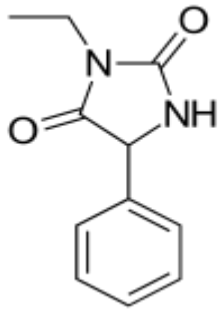


2. Hydantoin –

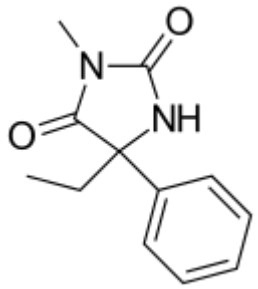
Phenytoin



Ethotoin

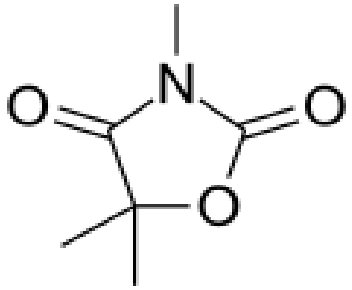


Mephenytoin

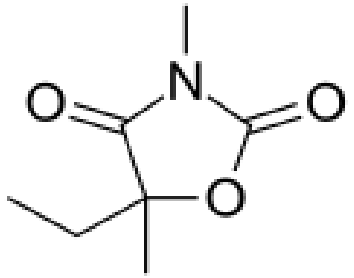


3. Oxazolidinedione-

Troxidone (Trimethadione)

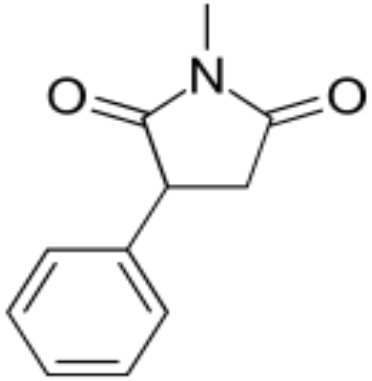


Paramethadione

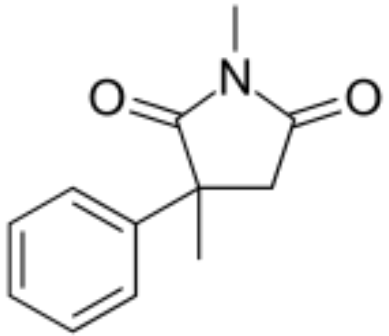


4. Succinimide –

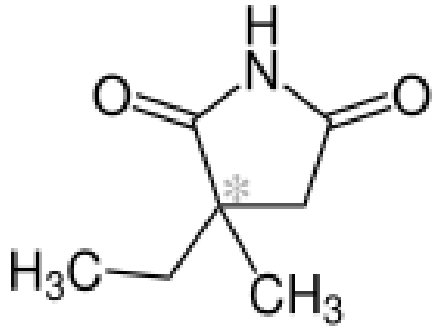
Phensuximide



Methsuximide

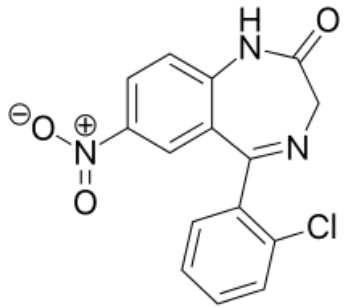


Ethosuximide

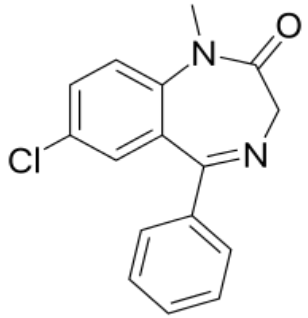


5. Benzodiazepines –

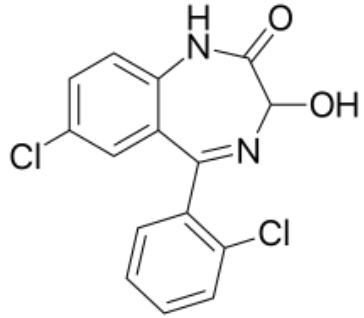
Clonazepam



Diazepam

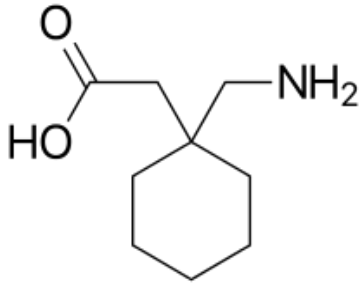


Lorazepam

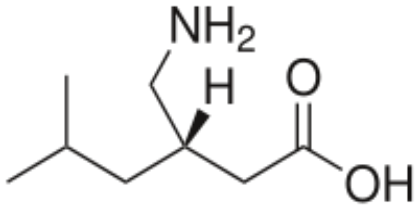


6. GABA analogues –

Gabapentin

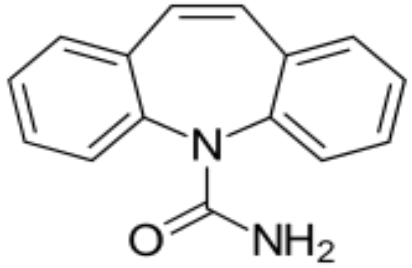


Pregabalin

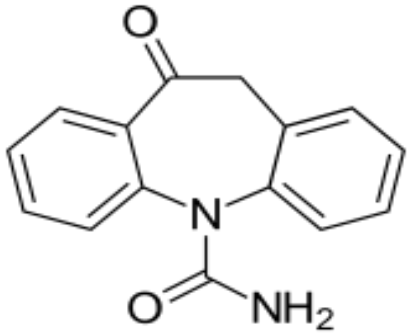


7. Iminostilbene –

Carbamazepine

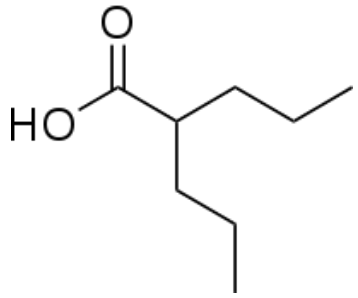


Oxcarbazepine



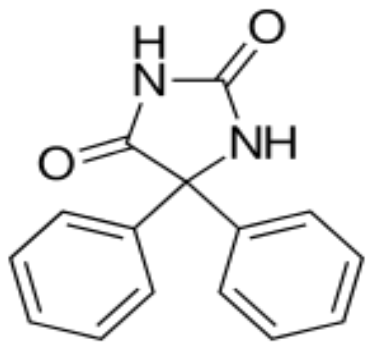
8. Miscellaneous –

Valproic acid



Synthesis of Phenytoin Sodium

Structure-

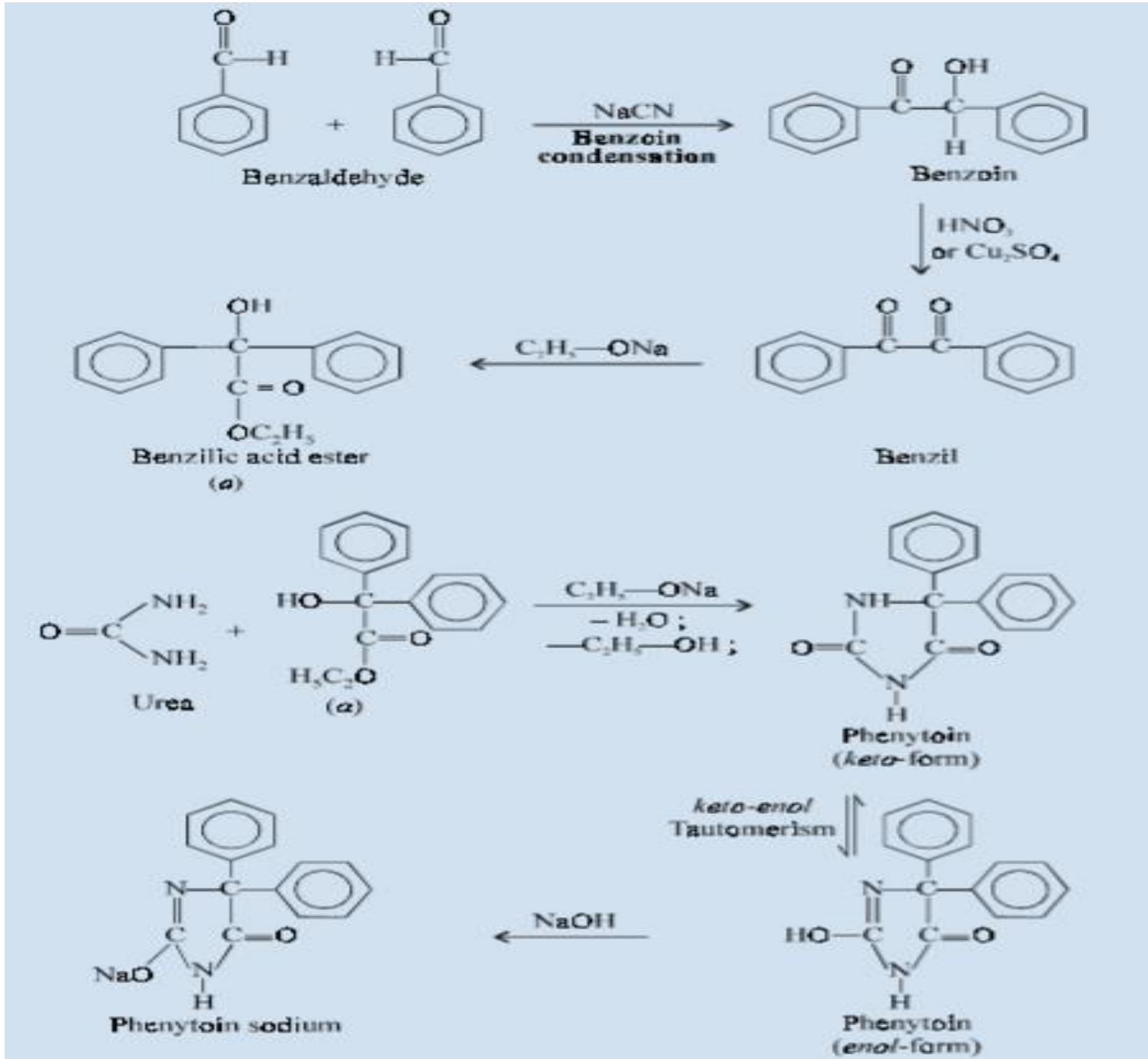


IUPAC Name- 5,5-diphenyl hydantoin. Or

5,5-diphenylimidazolidine-2,4-dione

Synthesis-

Phenytoin Sodium may be prepared by treating benzaldehyde with a solution of sodium cyanide. 2 mol of benzaldehyde are condensed into 1 mol of benzoin which is oxidised to benzil with nitric acid or cupric sulphate. The benzil is then heated with urea and in the presence of sodium ethoxide or isopropoxide forming phenytoin sodium.


Benzaldehyde
NaCN
Benzoin condensation
Benzoin
HNO3 or Cu2SO4
Benzil
C2H5—ONa
Benzilic acid ester (a)
Urea
(a)
C2H5—ONa
– H2O ;
– C2H5—OH ;
Phenytoin (keto-form)
keto-enol Tautomerism
Phenytoin (enol-form)
NaOH
Phenytoin sodium

Properties

- Phenytoin Sodium is a white crystalline powder.
- Slightly hygroscopic in nature, It is soluble in water.
- Solutions are sterilised by filtration.
- Phenytoin Sodium should be kept in airtight container.
- Absorption of Phenytoin Sodium after oral administration is slow, sometimes variable and occasionally incomplete.
- After absorption Phenytoin Sodium is rapidly distributed into all tissues.
- Phenytoin Sodium is extensively metabolised in the liver to 5-(4-hdroxyphenyl)-5-phenyl hydantoin, which is inactive.
- Phenytoin Sodium is excreted initially in the bile and subsequently in the urine, in large part as the glucuronide.
- Phenytoin Sodium is an Anticonvulsant with relatively little hypnotic effect.

Mode of Action

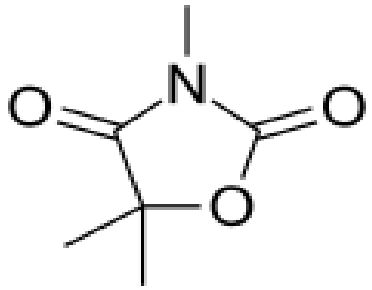
Phenytoin has a stabilizing influence on neuronal membrane- prevents repetitive detonation of normal brain cells during 'depolarization shift' that occurs in epileptic patients and consists of a synchronous and unusually large depolarization over which action potentials are superimposed. This is achieved by prolonging the inactivated state of voltage sensitive neuronal Na^+ channel that governs the refractory period of the neuron. As a result high frequency discharges are inhibited with little effect on normal low frequency discharges which allow Na^+ channels to recover even when their inactivation is prolonged.

Dose- the usual dose of Phenytoin is 50mg daily; increased to 400mg; by i.v. or slow i.v. injection the dose is up to 250mg in accordance with the needs of the patient.

Preparation- Capsule, Tablets and Injection

Synthesis of Troxidone or Trimethadione

Structure-



IUPAC Name- 3,5,5-trimethyl oxazolidine-2,4-dione.

Synthesis-

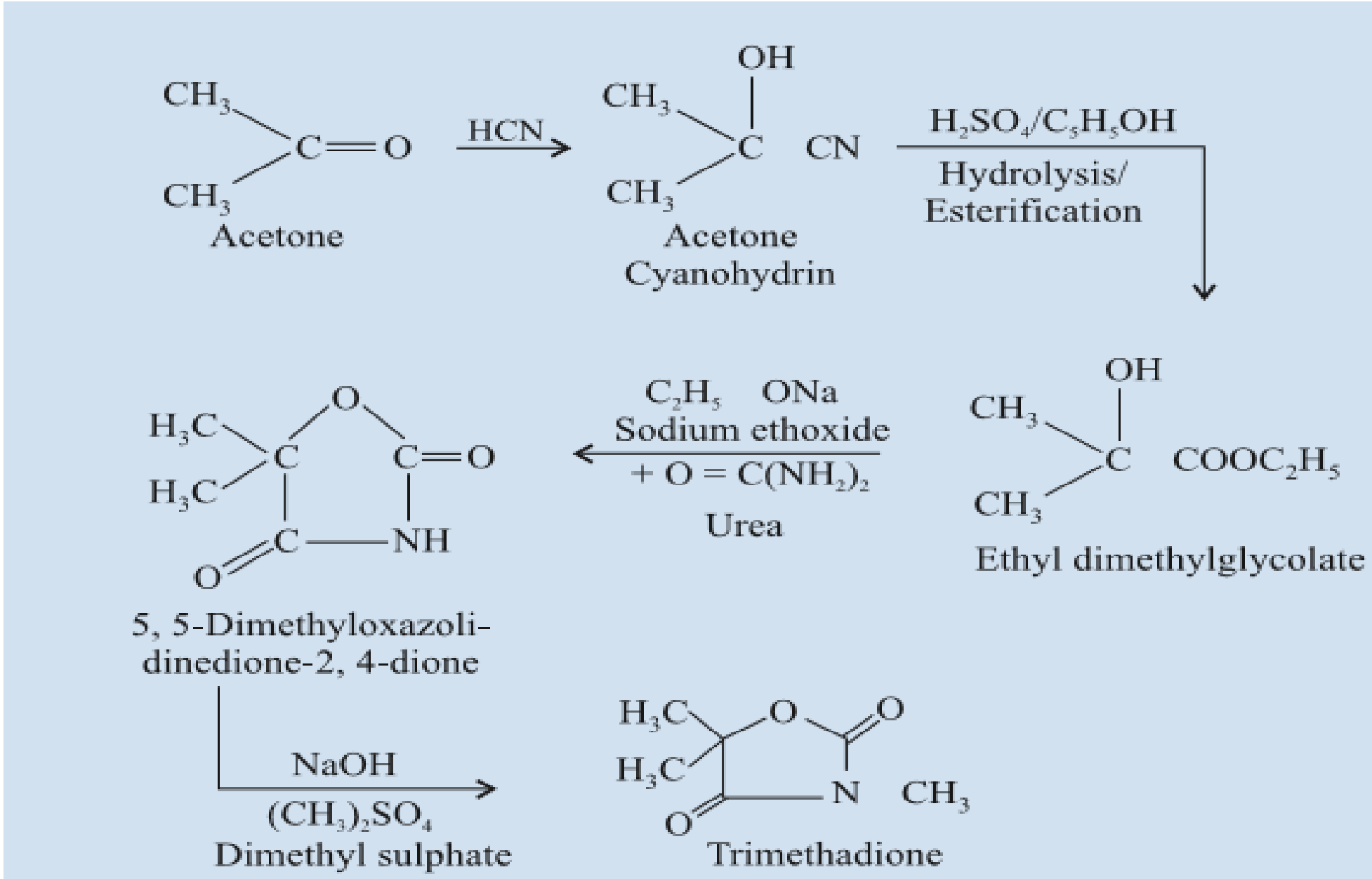
It may be prepared by a series of reaction beginning with acetone and involving the following steps-

Step-1 Conversion of HCN to Acetone cyanohydrin.

Step-2 Hydrolysis and Esterification with alcohol to ethyl dimethyl glycolate.

Step-3 Condensation with urea to 5,5-dimethyl oxazolidine-2,4-dione.

Step-4 Methylation with dimethyl sulphate to Trimethadione or Troxidone.


CH3
C=O
CH3
Acetone
HCN
OH
CH3
C
CN
CH3
Acetone
Cyanohydrin
H2SO4/C2H5OH
Hydrolysis/
Esterification
OH
CH3
C
COOC2H5
CH3
Ethyl dimethylglycolate
C2H5 ONa
Sodium ethoxide
+ O = C(NH2)2
Urea
H3C
H3C
O
C
C=O
C
NH
O
5, 5-Dimethyloxazoli-
dinedione-2, 4-dione
NaOH
(CH3)2SO4
Dimethyl sulphate
H3C
H3C
O
O
N
CH3
O
Trimethadione

Properties

- It is colourless or almost colourless crystal with slightly camphoraceous odour.
- It is soluble in water.
- It should be kept in a well closed container and protected from light.
- Troxidone is readily absorbed from gastrointestinal tract and has a half life is 16 to 24 hrs.
- It is largely demethylated in the liver to dimethadione, which is active.
- Dimethadione is not further metabolised and is excreted unchanged in the urine.

Mode of Action

Trimethadione (Troxidone) is indicated only for control of absence seizures refractory to treatment with other AEDs. It is ineffective against other seizure types. Trimethadione is a prodrug and is metabolized by N-demethylation to dimethadione, which is effective in the pentylenetetrazole test and which acts by decreasing T-type calcium currents.

Dose-

The usual dose for adult is 1 to 2 g daily in divided doses.

For children 0.25 to 0.5 g daily in divided dose.

Preparation- Capsules

Thank you…