ANTIEPILEPTIC DRUGS (ANTICONVULSANT DRUGS)

The term epilepsy, based on the Greek word epilambaein (meaning to seize), has been first mentioned by Hippocrates. It is characterised by abnormal and excessive **electroencephalographic** discharge and a disturbance or loss of consciousness.

Types of epilepsy

There are three principal types of epilepsy are found.

A) **Grandma**l => In which seizures last (continuous) from 2-5 minutes, being characterized by sudden loss of consciousness, tonic and clonic convulsions of all muscles.
B) **Petitmal (Absence seizures**)=> The seizures last from 5 to 30 seconds, being characterised by brief attack of unconsciousness, occurs in children at the age of 4-8 years.
C) **Psychomotor seizures** => Characterised by attacks without convulsions lasting from 2-3 minutes.

The primary use of anticonvulsant drug is in the prevention and control of epileptic seizures. The ideal antiepileptic drug should completely suppress seizures, do not cause sedation or other undesired CNS toxicity.

The epileptic seizures have been classified into two category.

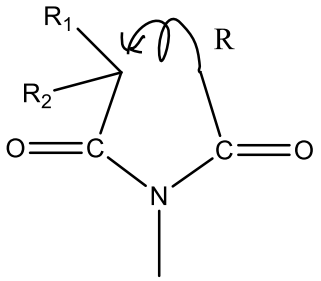
a) Generalised
b) Partial

Mode of Action => Anticonvulsants are drugs which selectively depress the CNS. Anticonvulsant drugs inhibited the neuronal discharge or its spread and do so in one or more of three ways.

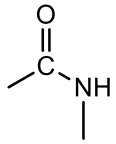
1) Reducing (altering) cell membrane permeability to ions (Na and Ca ions).
2) Enhancing the activity of GABA (Gamma-aminobutyric acid) the principal inhibitory transmitter of the brain the result is increased membrane permeability to Cl^-(ion), which reduces cell excitability.
3) Inhibiting excitatory neurotransmitters (Glutamate).

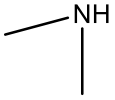
Classification => The different chemical classes of anticonvulsant agents are-

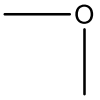
Most of the anticonvulsant drugs contain the ureide structure.

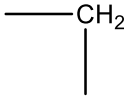


Structure common to anticonvulsant Drugs

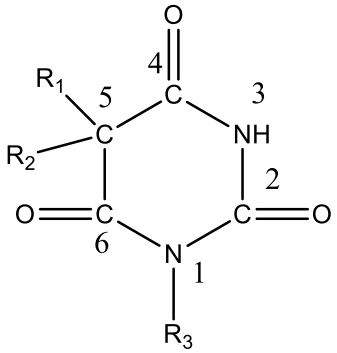
R=  Barbiturates

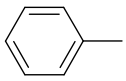
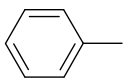
R=  Hydantoin

R=  Oxazolidinediones

R=  Succinimides

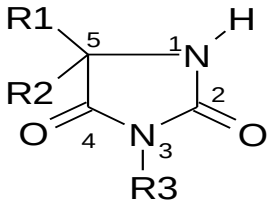
A) **Barbiturates** =>



S.NO.	DRUG	R1	R2	R3
1.	Phenobarbital	C_2H_5		H
2.	Mephobarbital	C_2H_5		CH_3

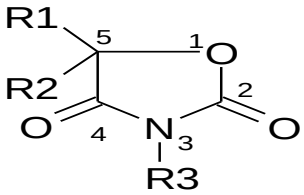
3.	Methbarbital	C_2H_5	C_2H_5	CH_3

B) **Hydantoin** =>



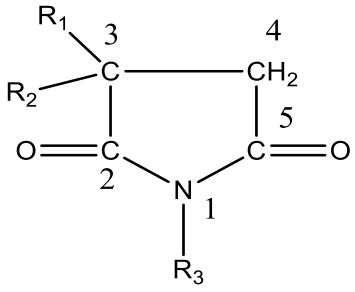
S.NO.	GENERIC NAME	R1	R2	R3
1.	Phenytoin	C_6H_5	C_6H_5	H
2.	Mephenytoin	C_6H_5	CH_3CH_2-	-CH_3
3.	Ethotoin	C_6H_5	H	CH_3CH_2-

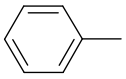
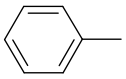
C) **Oxazolidinediones** =>



S.NO.	GENERIC NAME	R1	R2	R3
1.	Trimethadione (Troxidone)	CH_3	CH_3	CH_3
2.	Paramethadione	CH_3	C_2H_5	CH_3

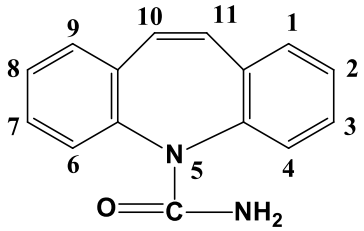
D) **Succinimides** =>



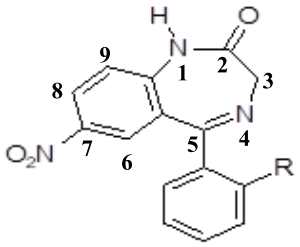
S.NO.	GENERIC NAME	R1	R2	R3
1.	Phensuximide		H	CH_3
2.	Methsuximide		CH_3	CH_3
3.	Ethosuximide	C_2H_5-	CH_3	H

E) **Ureas and monoacylureas** =>

Exa- Carbamazepine

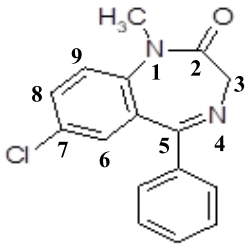


F) Benzodiazepines =>



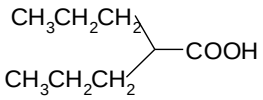
S.NO.	GENRIC NAME	R
1.	Nitrazepam	H
2.	Clonazepam	Cl

- Diazepam

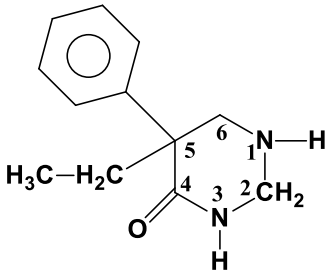


G) Miscellaneous type-

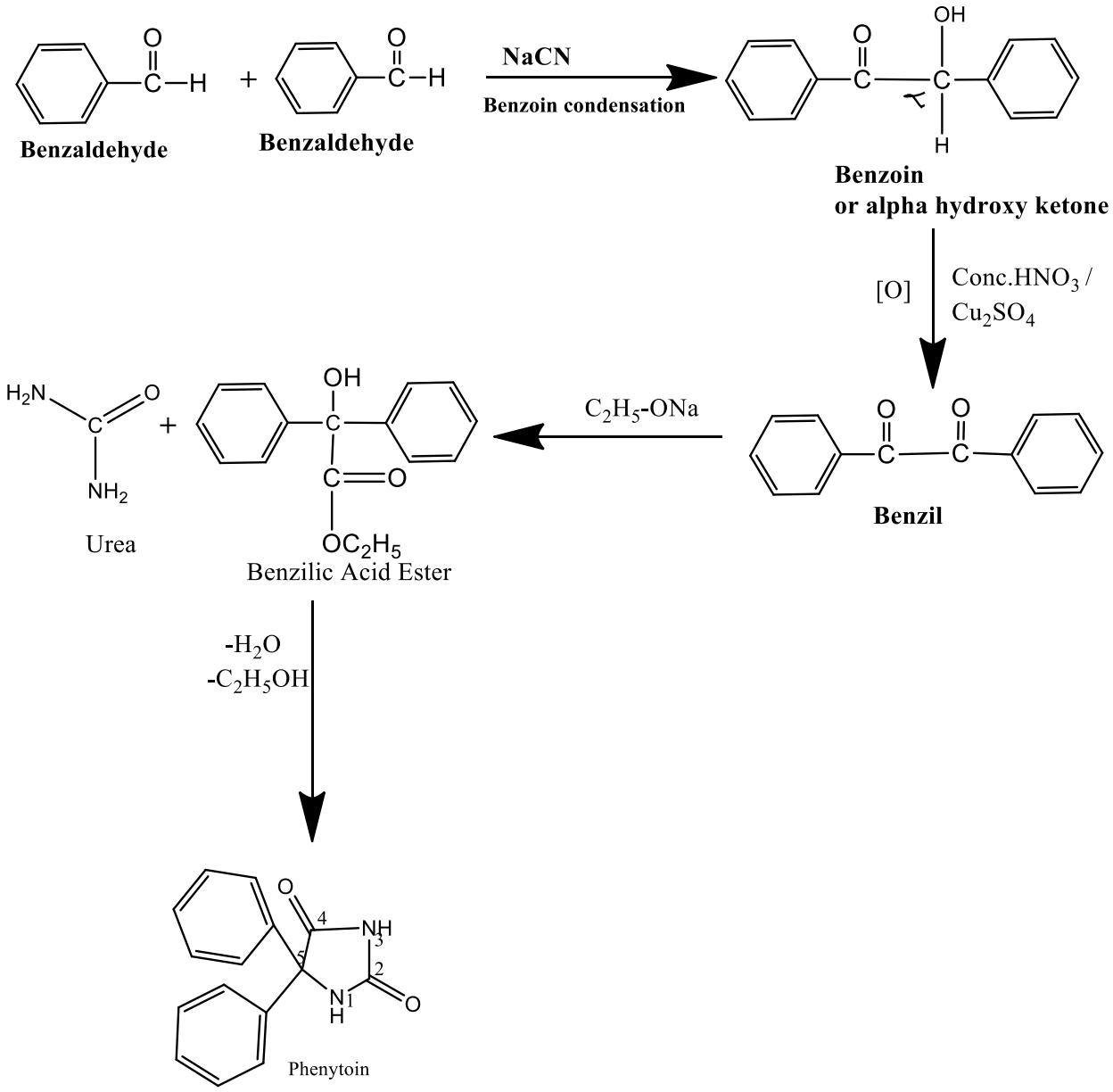
Exa- Valproic acid



Primidone



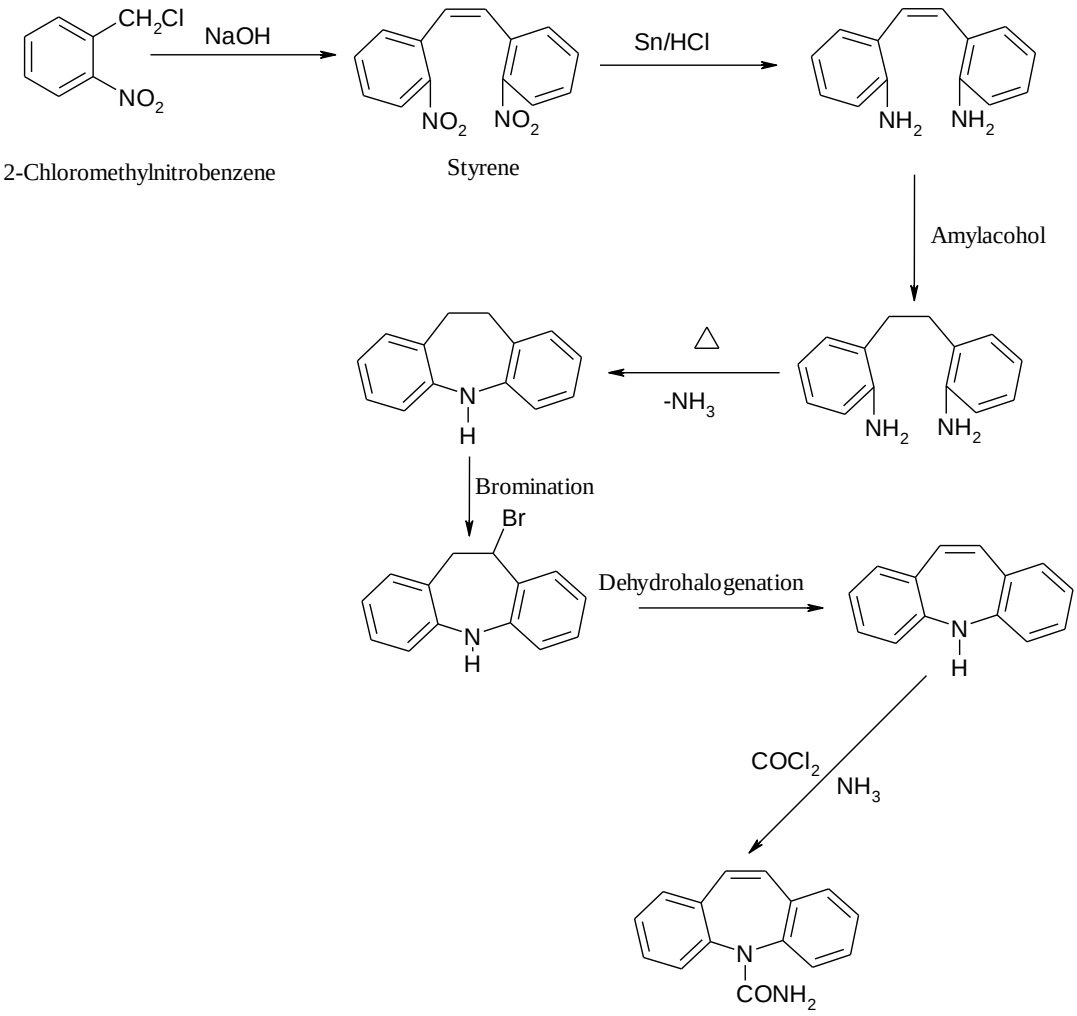
SYNTHESIS OF PHENYTOIN



Note- . Phynytoin (5,5,-diphenylhydantoin) is the first anticonvulsant in which it was clearly demonstrated that anticonvulsant activity could definitely be separated from sedative-hypnotic activity. It is a prime example of an anticonvulsant acting as a sodium channel blocker. One effect of neuronal sodium channel block is to decrease presynaptic glutamic acid release giving anticonvulsant activity. Another, consequence is to reduce glutamate-induced ischemic damage to neurons.

The drug is useful against all seizure types except absence seizure.

SYNTHESIS OF CARBAMAZEPINE



2-Chloromethylnitrobenzene

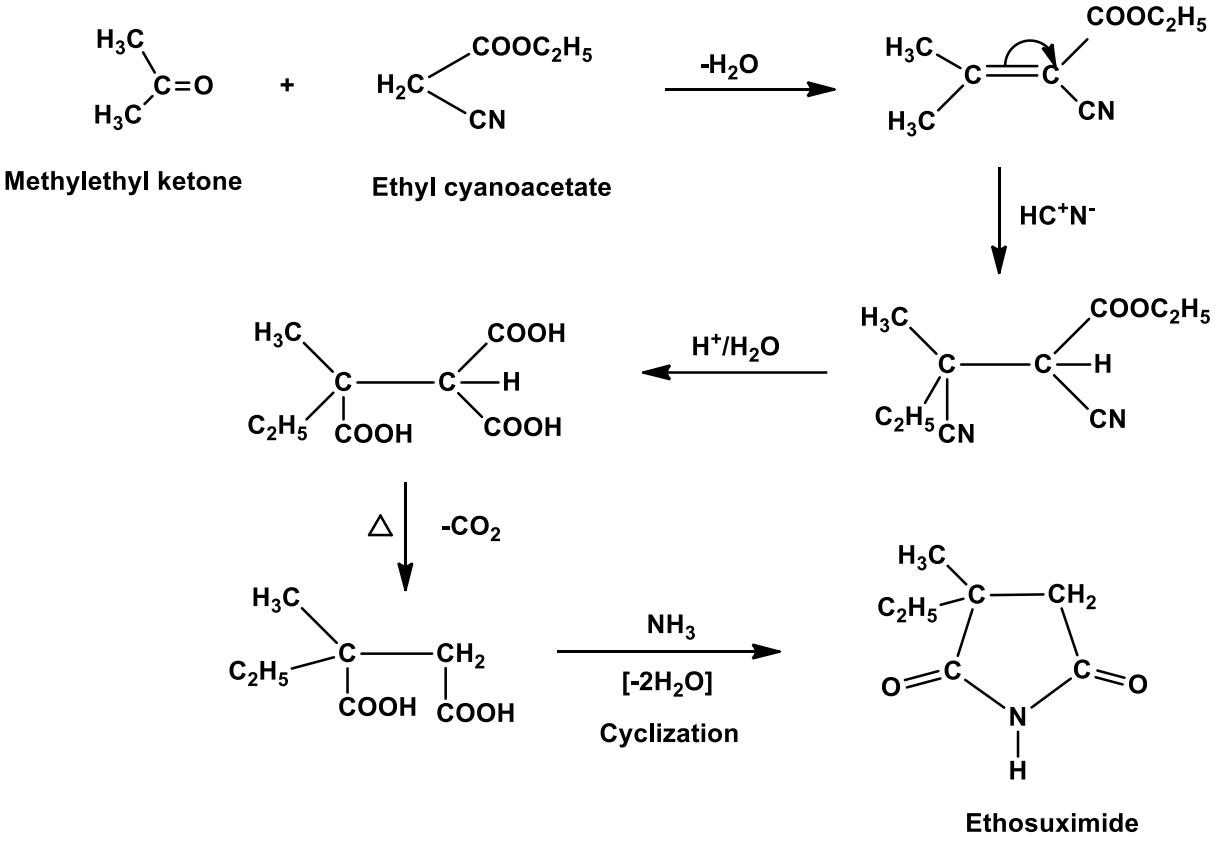
Styrene

Carbamazepine

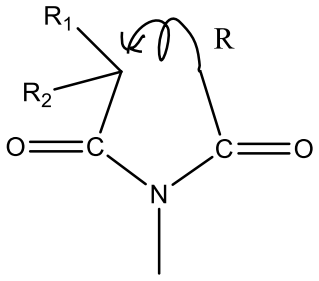
NOTE- Overall shape of the molecule suggests the mode of action, sodium channel blocker.

- It is useful in generalized tonic-clonic and partial seizures.

SYNTHESIS OF ETHOSUXIMIDE



SAR OF ANTICONVULSANT AGENT



Structure common to Anticonvulsant Drugs

- For anticonvulsant activity R_1 and R_2 should be both hydrocarbon radicals.
- If both R_1 and R_2 are lower alkyls, the tendency is to be active against absence seizures (petitmal) and not active against generalized tonic-clonic (grandmal) or partial seizures. Examples- Methbarbital, Trimethadione, Paramethadione, Valproic Acid.

- If one of the hydrocarbon substituents (R_1 or R_2) is an aryl group, activity tends to be directed towards generalized tonic-clonic and partial seizures and not anti-absence activity. Examples- Phenobarbital, Mephobarbital, Phenytoin, Carbamazepine.
- A conformational analysis of the aryl-containing anti-generalized tonic-clonic agents indicates that the conformational arrangement of the hydrophobic groups is important.