ANTIEPILEPTIC DRUGS (Anticonvulsants)

PHARMACEUTICAL CHEMISTRY I

PHA385

2017-2018

Epilepsy is a **chronic** neurological disorder characterized by recurrent **seizures**, which are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons.

The antiepileptic drugs can be grouped according to their main **mechanism of action**, although many of them have several actions and others have unknown mechanisms of action. The main groups include sodium channel blockers, calcium current inhibitors, gamma-aminobutyric acid (GABA) enhancers, glutamate blockers, carbonic anhydrase inhibitors, hormones, and drugs with unknown mechanisms of action.

Classification of Antiepileptic Drugs

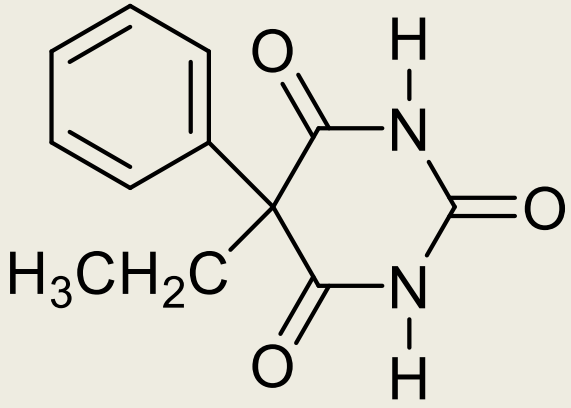
1. Ureide derivatives
2. Benzodiazepines
3. Secondary or tertiary alcohols
4. Dibenzazepine derivatives
5. Valproic acid derivatives
6. GABA analogues
7. Hormons
8. Other drugs

1- Ureide derivatives

BARBITURATES

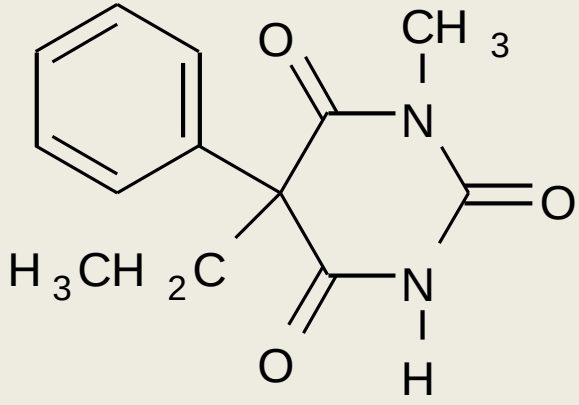
Barbiturates are drugs that act as central nervous system (CNS) depressants, and they are mostly used as **sedative-hypnotic.** The following are also used as anticonvulsants:

PHENOBARBITAL



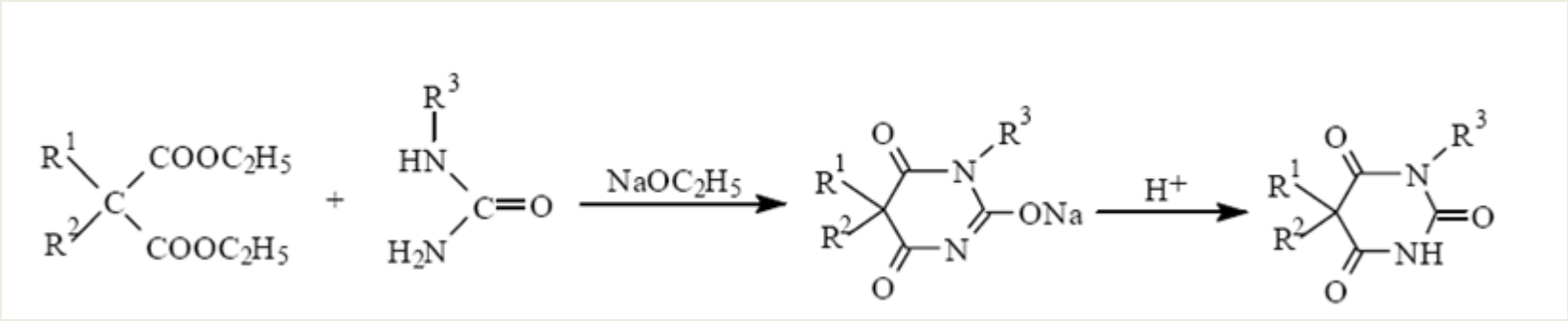
5-ethyl-5-phenyl barbituric acid

MEPHOBARBİTAL



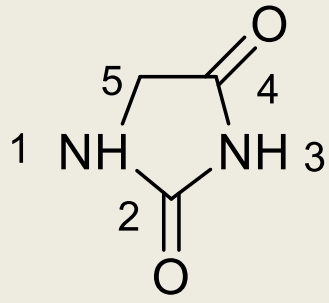
It is converted to phenobarbital via N-dealkylation reaction

General Synthesis of Barbiturates

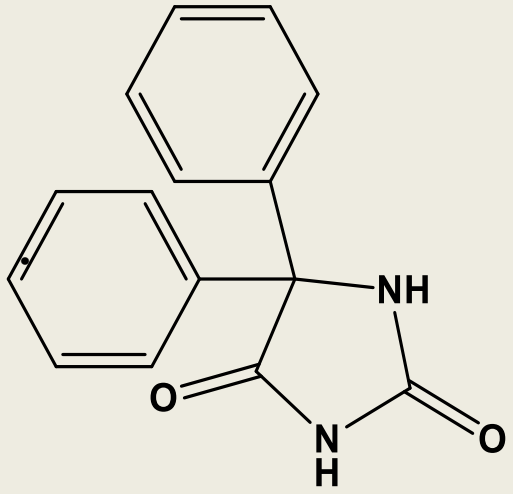


HYDANTOINS

HYDANTOIN (2,4-imidazolidindione)



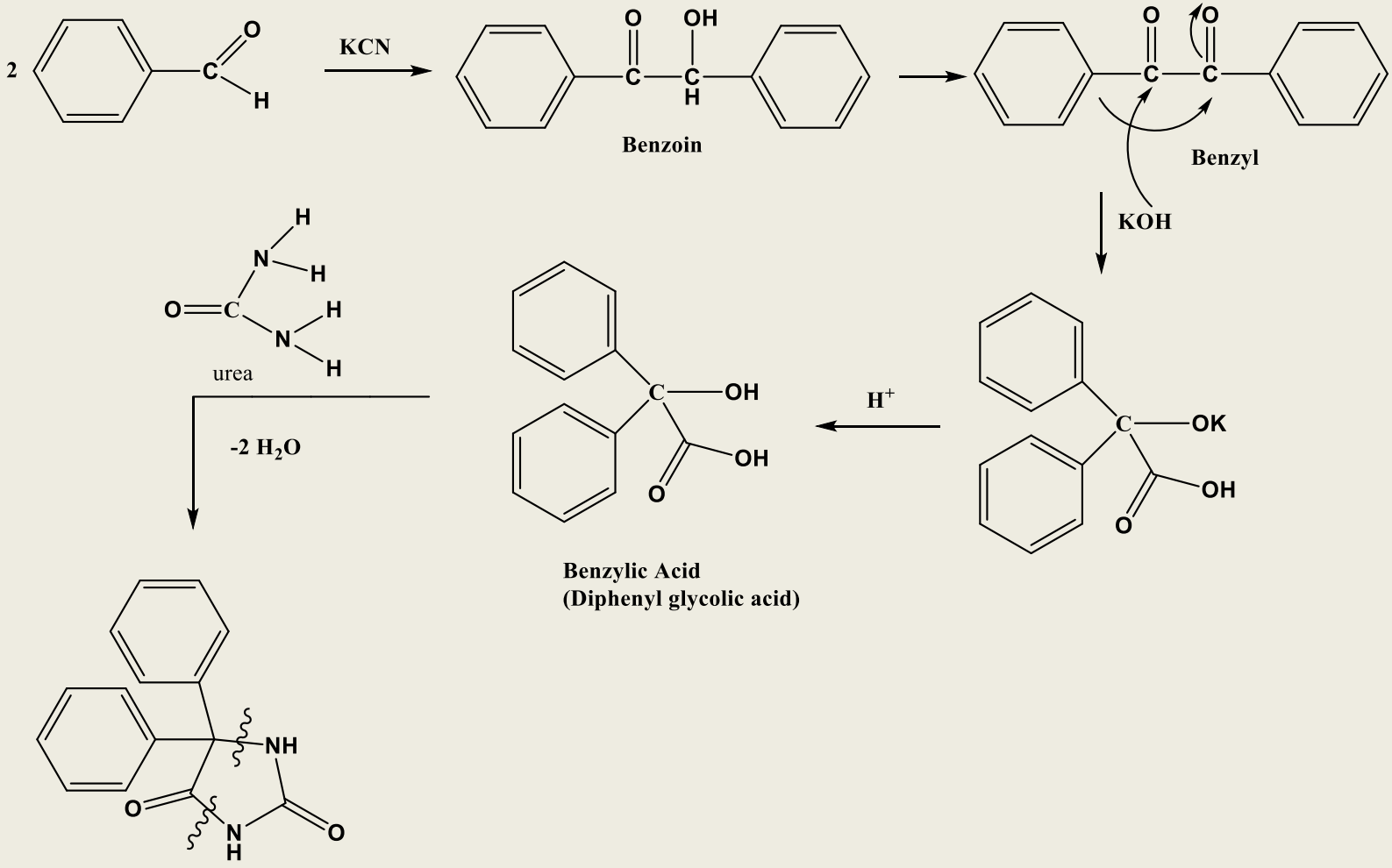
PHENITOIN (Diphenylhydantoin)



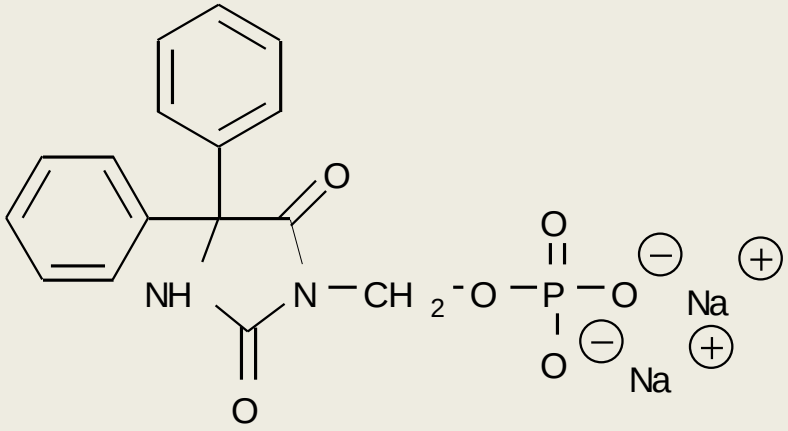
5,5-Diphenyl-2,4-imidazolidindion

(5,5-diphenylhydantoin) ***trivial name***

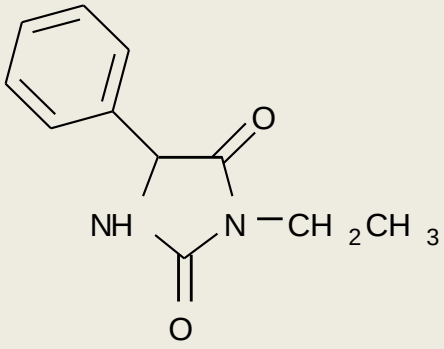
SYNTHESIS OF PHENYTOIN



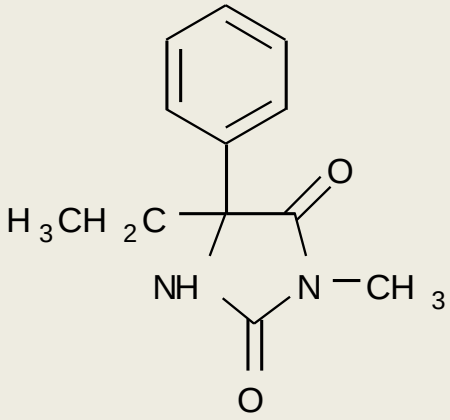
FOSPHENITOIN



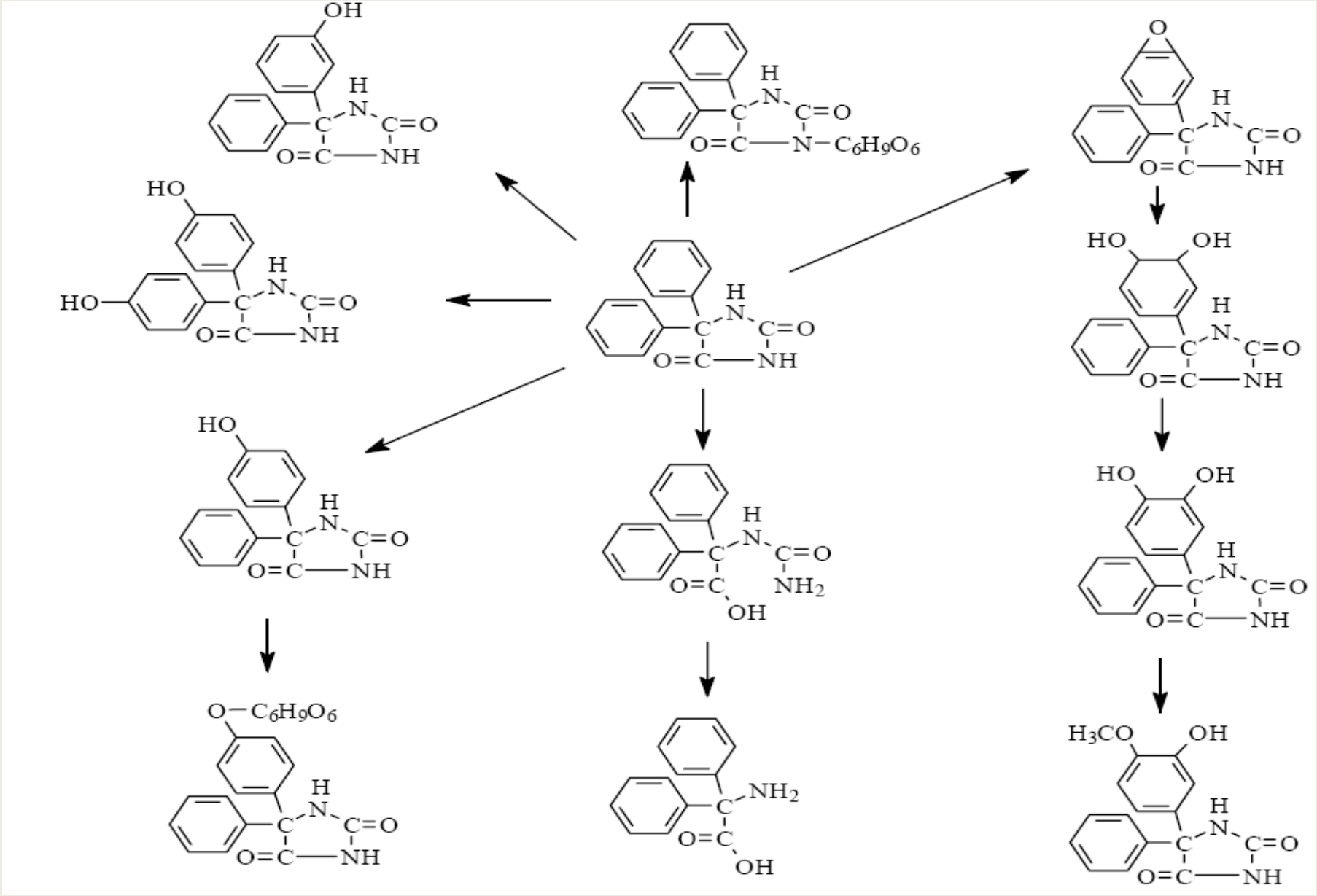
ETHOTOIN



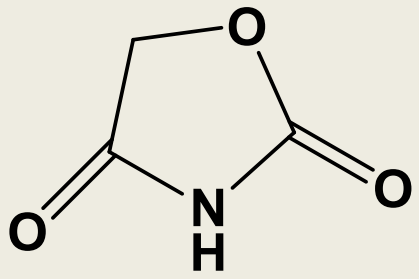
MEPHENITOIN



BIOTRANSFORMATION



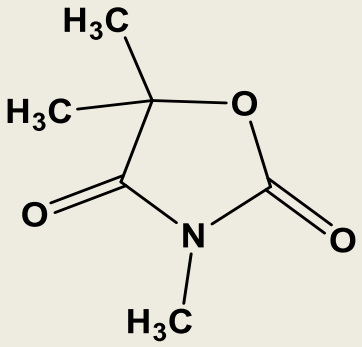
OXAZOLIDINEDIONES



High anticonvulsion activity
Low sedative-hypnotic activity when alkylation of nitrogen at 3. position.

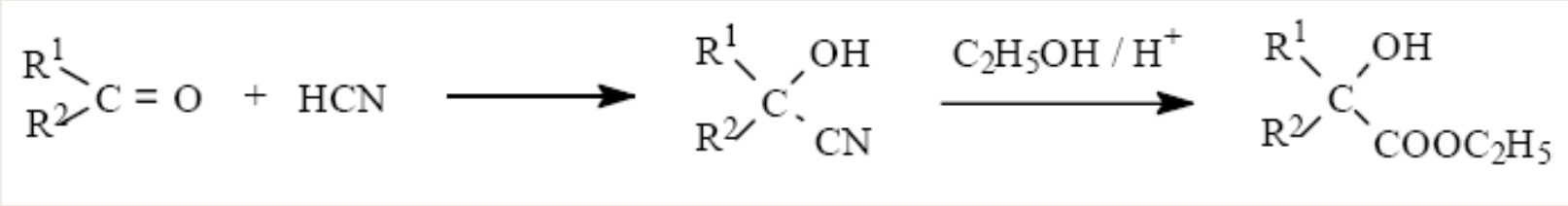
TRIMETHADIONE

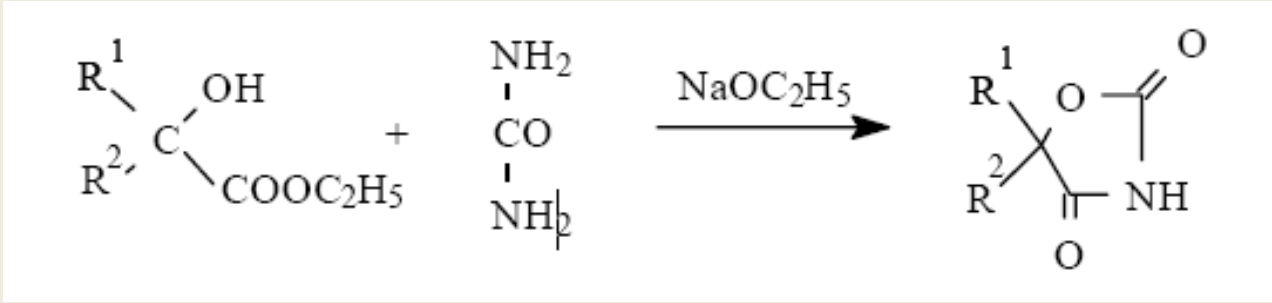
TRIDIONE^{R}



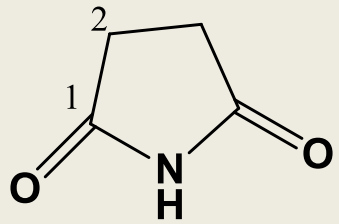
3,5,5-Trimethyl-oxazolidine-2,4-dione

General Synthesis



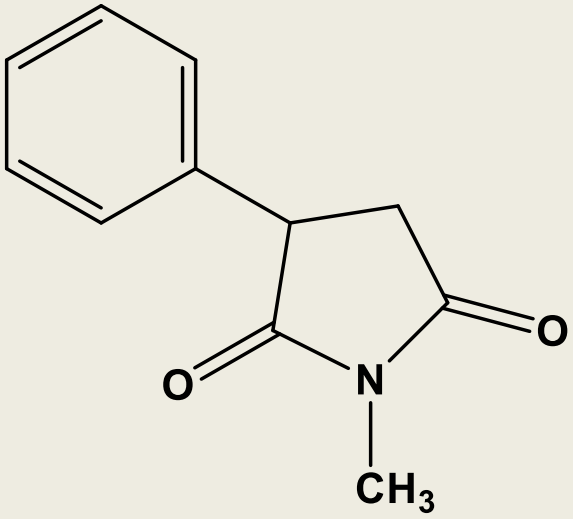


SUCCINIMIDES



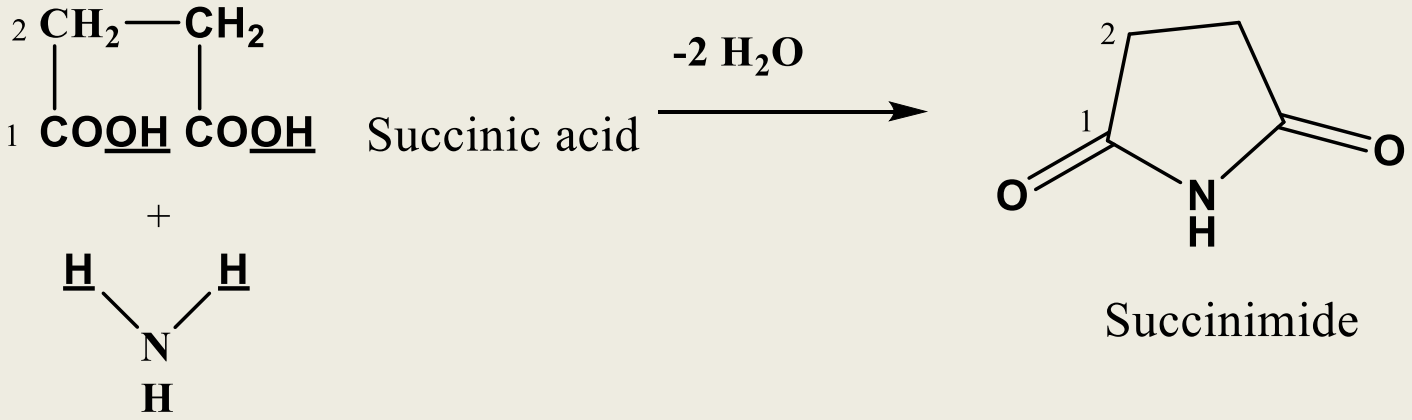
In view of the activity of antiepileptic agents such as the oxazolidine-2,4-dions, succinimides (bioizostere CH_2 replaces O) were a logical choice for synthesis and evaluation. They are more active and less toxic than oxazolidinediones.

PHENSUXIMIDE FENSUKSİM[R] EPİLEPTİN[R]

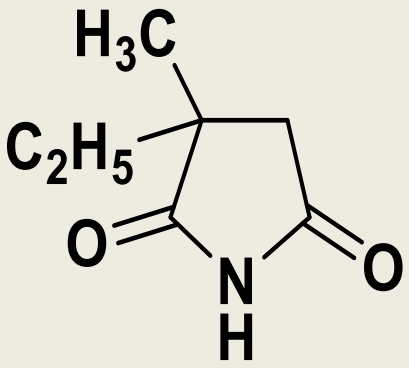


1-Methyl-3-phenylpyrrolidine-2,5-dion

(N-Methyl-2-phenylsuccinimide) ***trivial name***



ETHOSUXIMIDE PETİMİT^{R}



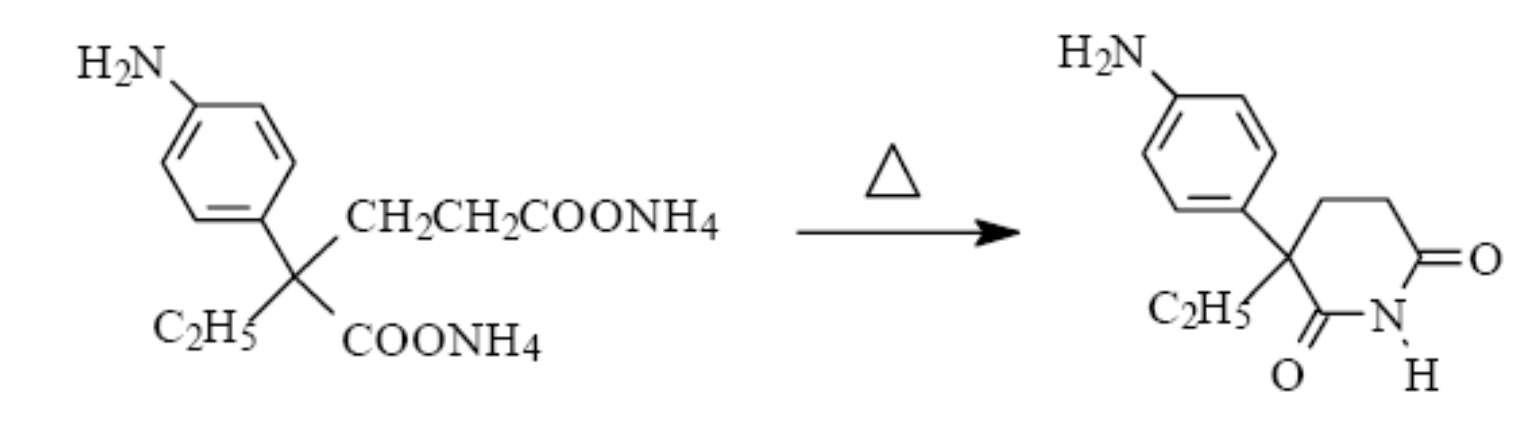
3-ethyl-3-methyl-pyrrolidine-2,5-dion

(2-ethyl-2-methylsuccinimide)

Synthesis ?????

GLUTARIMIDES

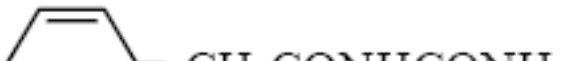
AMINOGLUTETIMID **3-(4-Aminophenyl)-3-ethyl-2,6-piperidinedione**



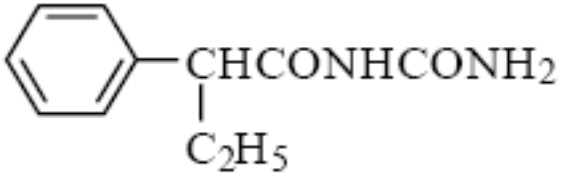
(4-Aminophenyl)-α-ethyl
glutaric acid diamonium salt

ACYLUREAS

Phenacemide
(Phenyl acetyl urea



Ethyl phenacemide
2-phenylbutyryl urea

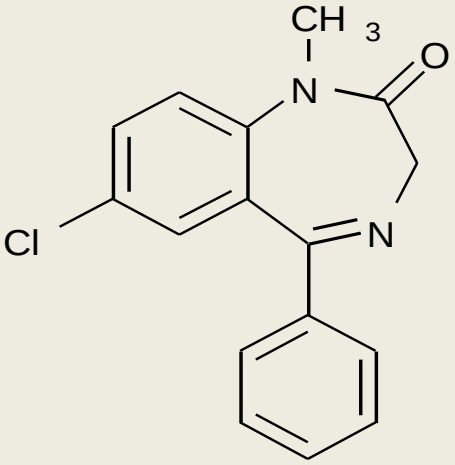


2. BENZODIAZEPINES

- The benzodiazepines are a class of drugs with hypnotic, anxiolytic, **anticonvulsive**, and muscle relaxant properties.
- Benzodiazepines act as a central nervous system depressant.

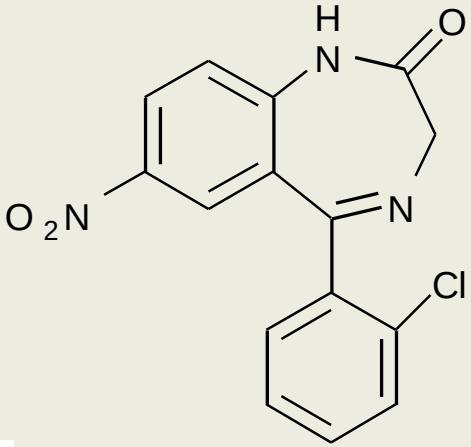
DİAZEPAM

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

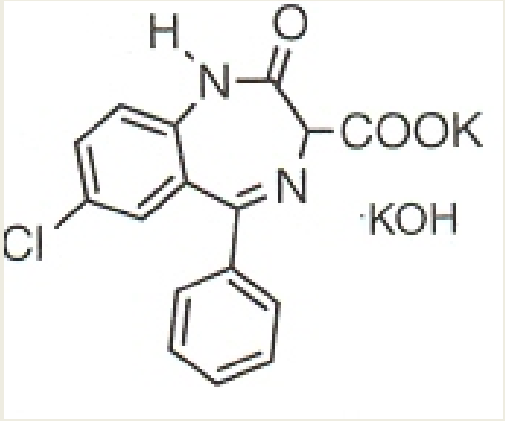


CLONAZEPAM

5-(2-chlorophenyl)-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one



CHLORAZEPATE

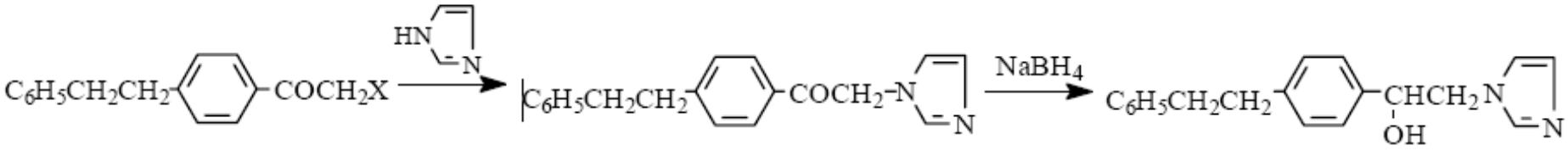


5-Phenyl-7-chloro-1,3-dihidro-2-oxo-2H-1,4-benzodiazepine-3-carboxylic acid dipotassium salt

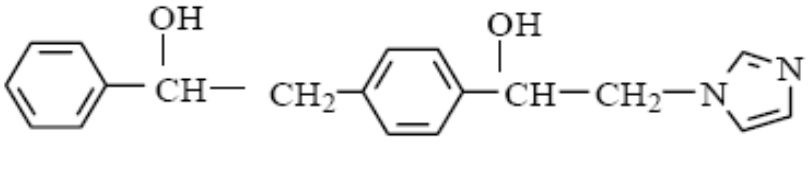
3. SECONDARY VE TERTIARY ALCOHOLS

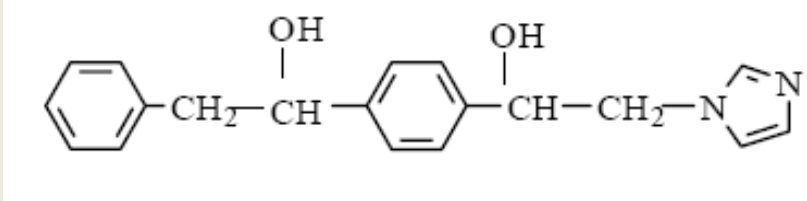
Synthesis of Denzimol

N-[beta-[4-(beta-phenylethyl)phenyl]-beta-hydroxyethyl]imidazole hydrochloride

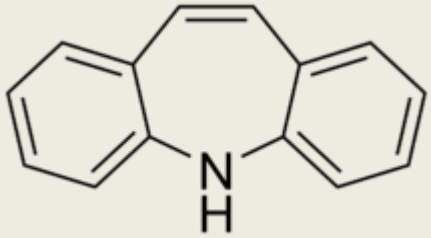


Metabolites of Denzimol



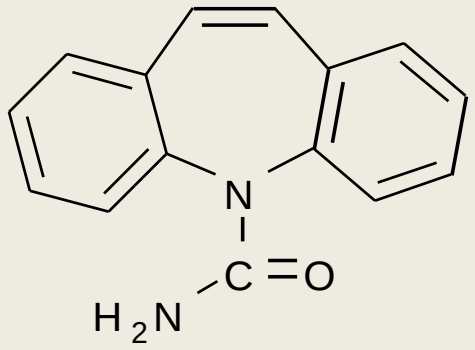


4. DIBENZAZEPINE DERIVATIVES



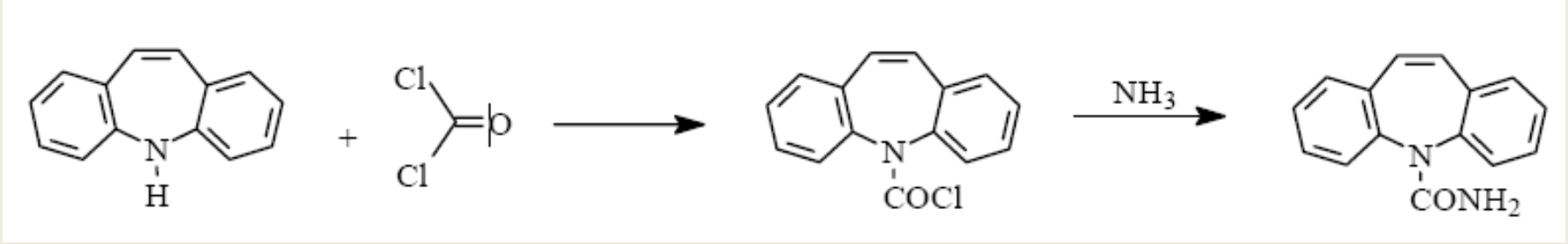
- Although dibenzaepine derivatives are related to the tricyclic antidepressants, they are very often used as anticonvulsants. The different types of anticonvulsants may act on different receptors in the brain and have different modes of action.

CARBAMAZEPINE

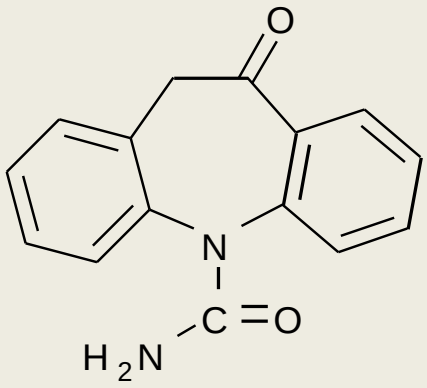


5H-Dibenz[b,f]azepine-5-carboxamide

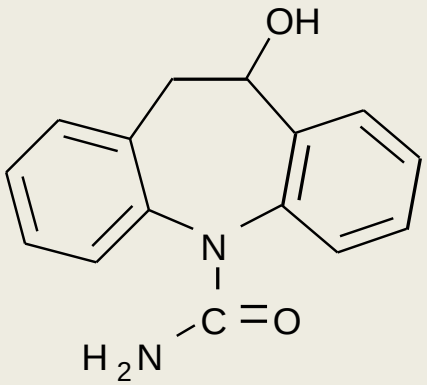
Synthesis of Carbamazepine



OXCARBAZEPINE



10,11-Dihydro-10-oxo-5H-dibenz[b,f] azepine-5-carboxamide



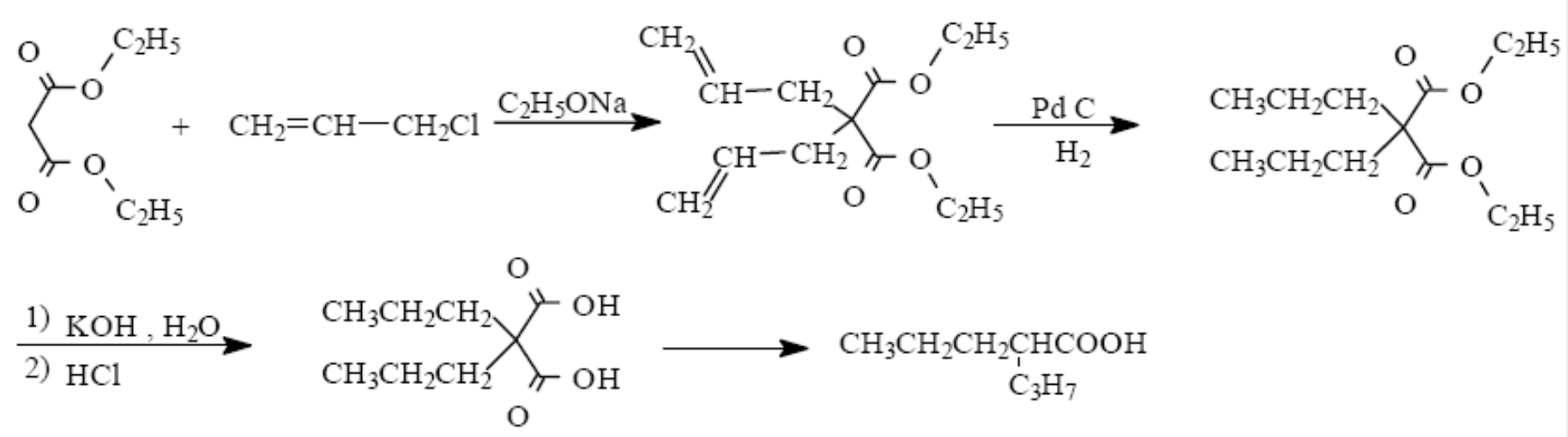
10-hydroxylated metabolite of oxcarbazepine is also active

5. VALPROIC ACID DERIVATIVES

Valproic acid

- Valproic acid, supplied as the sodium salt valproate, is a fatty acid with anticonvulsant properties used in the treatment of epilepsy.

Synthesis of Valproic acid

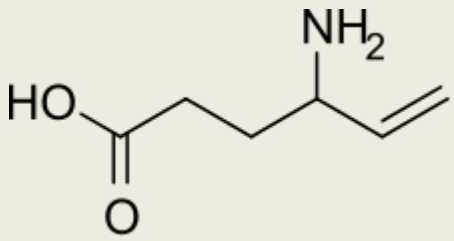


6. GABA ANALOGUES

Many GABA (neurotransmitter gamma-aminobutyric acid) analogues are used as drugs, especially as anticonvulsants, sedatives, and anxiolytics.

VIGABATRIN

- **Vigabatrin** is an antiepileptic drug that inhibits the breakdown of γ-aminobutyric acid (GABA) by acting as a inhibitor of the enzyme GABA transaminase (GABA-T).
- It is also known as **γ-vinyl-GABA**, and is a structural analogue of GABA, but does not bind to GABA receptors.

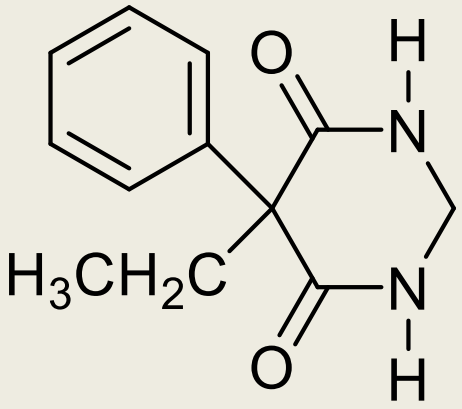


7. HORMONES

Corticotropin and **corticosteroids** are used to treat petit mal epileptic seizures.

8. OTHER DRUGS

PRIMIDONE



5-ethyl-5-phenyldihydropyrimidine-4,6(1*H*,5*H*)-dione