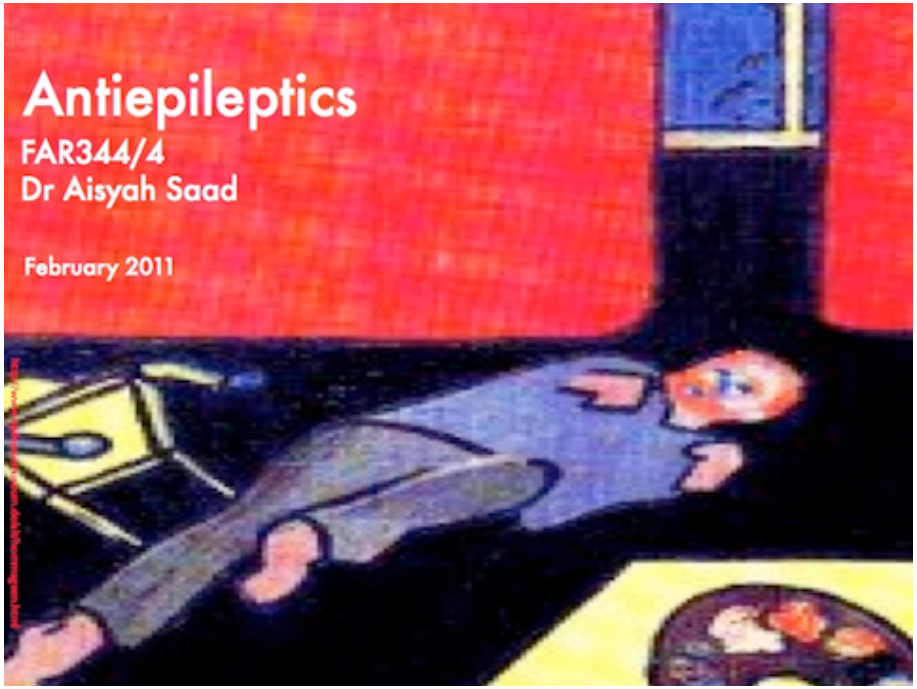
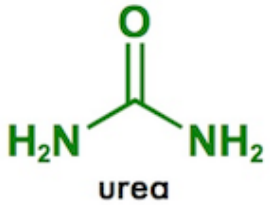
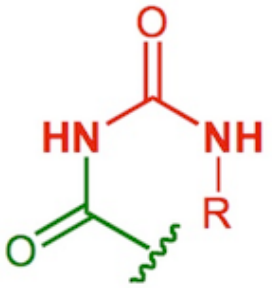


The framework of anticonvulsants are generally made up of :
a UREIDE structure
(a ring-opened acyl derivative of urea)



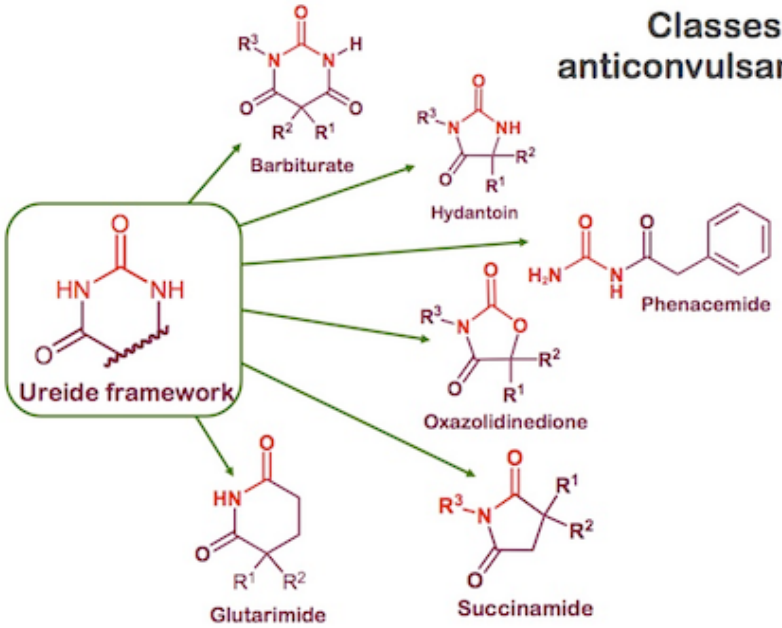
urea



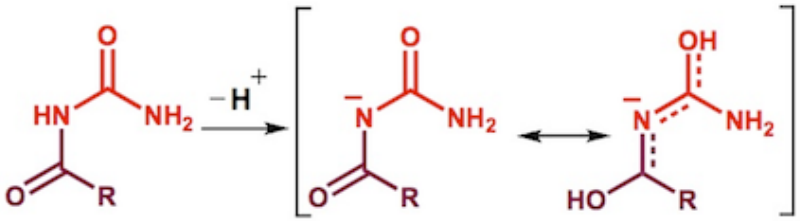
ureide

URE-IDE = urea + -ide (suffix)
OXIDE = oxygen + -ide

Classes of anticonvulsants



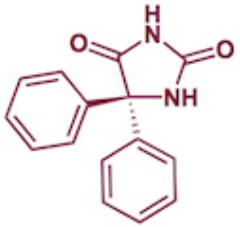
Acidic properties of a ureide



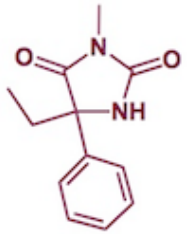
Ureide

Acidity : Barbiturate >> hydantoin
d/t greater mesomeric potential

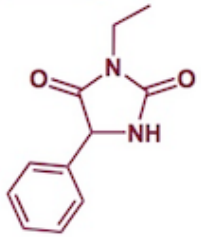
Hydantoin



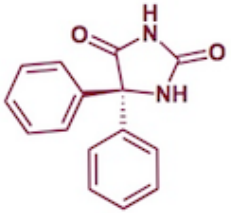
Phenytoin



Mephenytoin



Ethotoin



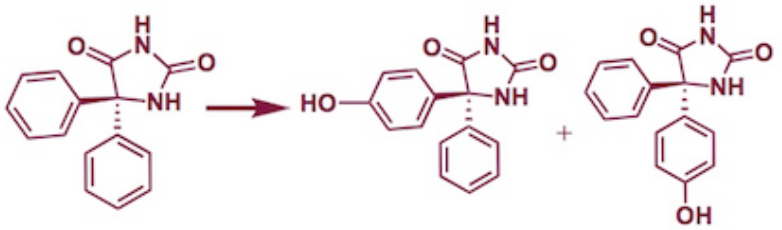
Phenytoin (1908)

ACD of choice for partial seizures
& generalised tonic-clonic seizures

Chemical name :
Diphenylhydantoin
5,5-diphenyl-2,4-imidazolidinedione

dissolves in dilute alkali (pKa = 8.33)

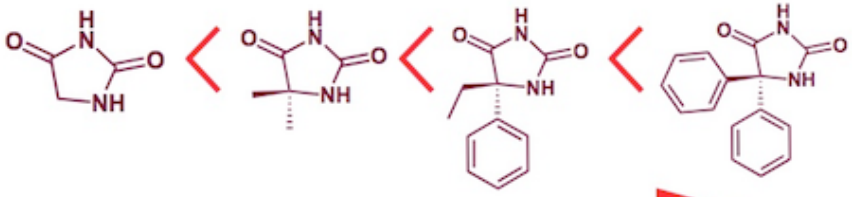
Metabolism



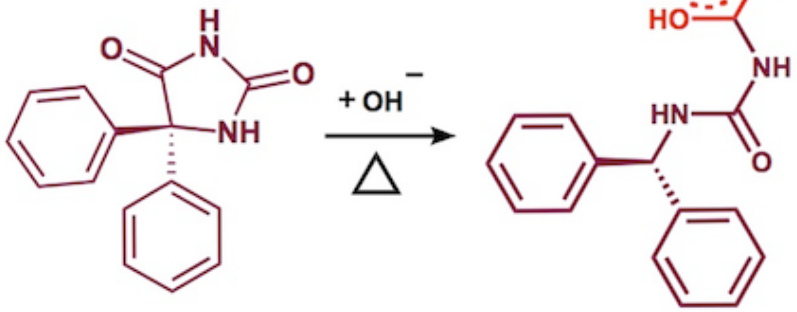
Acidity of hydantoins

Phenytoin is the most acidic; d/t -I effect of Ph

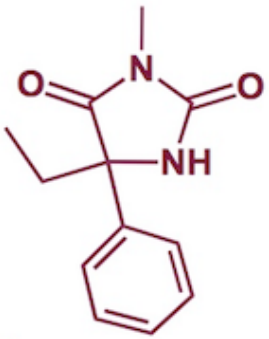
pKa 9.12 9.19 8.5 8.33



In hot alkali, the hydantoin ring opens :



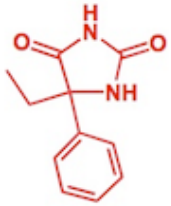
Remember NOT to dissolve and heat the solution of phenytoin in an alkali



Mephenytoin

Chemical name :
3-methyl-5-ethyl-5-phenylhydantoin

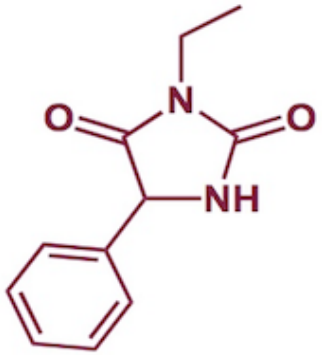
Similar anticonvulsant activities to phenytoin



Toxic Mephenytoin metabolite

Biotransformation via N-demethylation to give a metabolite:

5-ethyl-5-phenylhydantoin (Nirvanol)
elicits more potent anticonvulsant effects
but, due its toxicity its use in clinical setting is limited

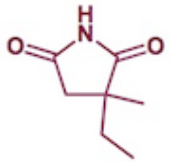


Ethotoin

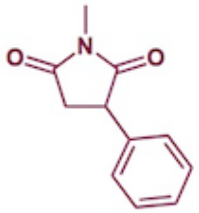
Chemical name :
3-ethyl-5-phenylhydantoin

Minus point : weaker than phenytoin

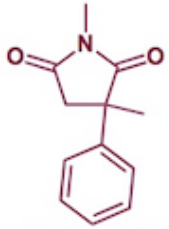
Succinimides



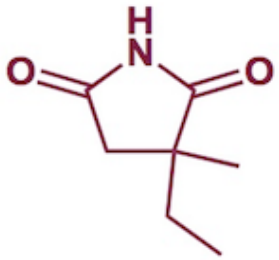
Ethosuximide



Phensuximide



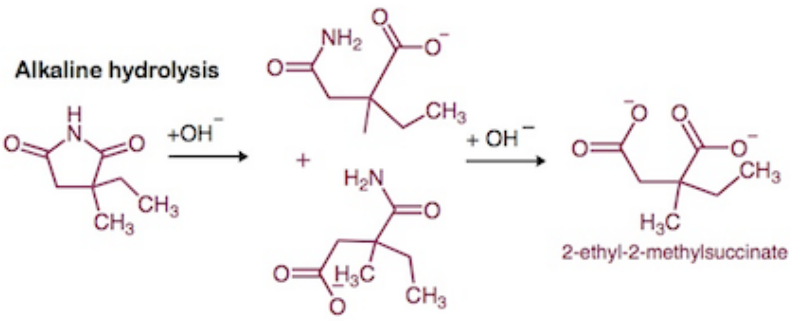
Methsuximide

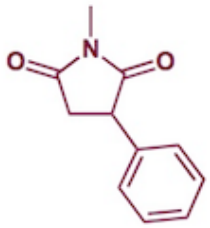


Ethosuximide

Chemical name :
(*R*,*S*)-3-ethyl-3-methylpyrrolidine-2,5-dione

Its urinary metabolite :

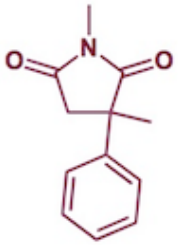




Phensuximide

Chemical name :

1-methyl-3-phenylpyrrolidine-2,5-dione

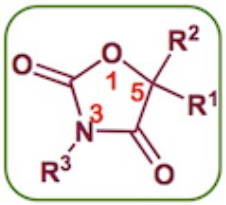


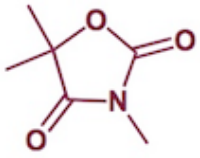
Methsuximide

Chemical name :

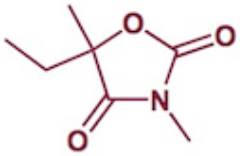
1-methyl-3-methyl-3-phenylpyrrolidine-2,5-dione

Oxazolidinedione

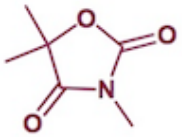




Trimethadione

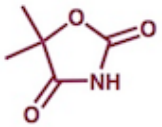


Paramethadione



Trimethadione

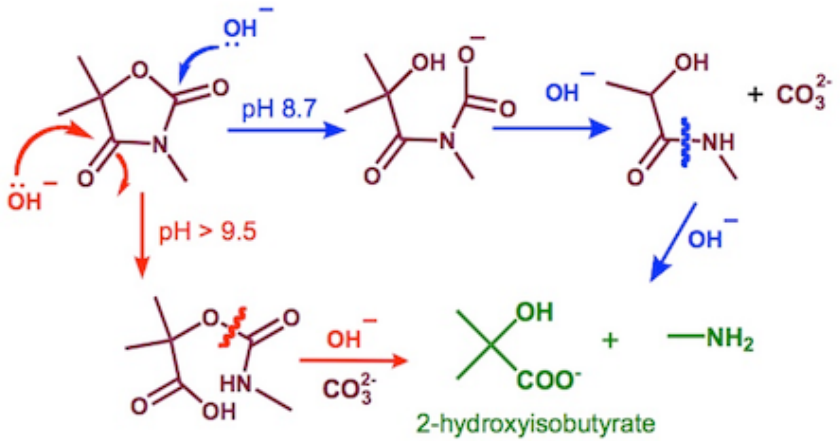
Chemical name :
3,5,5-trimethyloxazolidine-2,4-dione

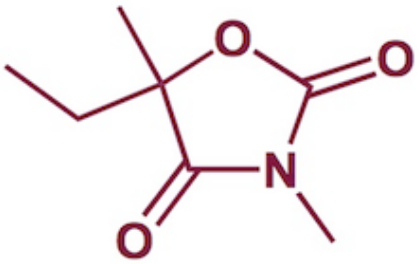


5,5-trimethyl oxazolidine-2,4-dione

contains partial structures of :
lactone
cyclic urethane
N-susbtituted lactam
these are hydrolysis-prone structures

Hydrolysis of Trimethadione





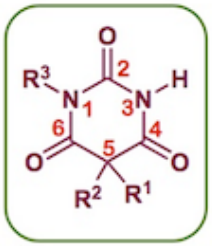
Paramethadione

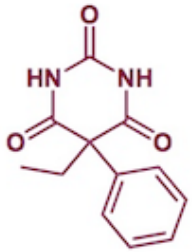
Chemical name :
5-ethyl-3,5-dimethyloxazolidine-2,4-dione

Active metabolite : Unknown

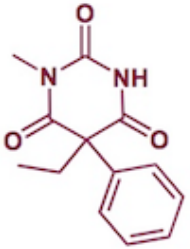
Barbiturates

These are long-acting and sedative ACDs
Phenobarbital (1912)

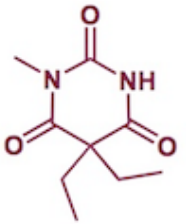




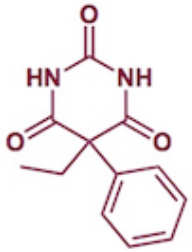
Phenobarbital



Mephobarbital



Methabarbital

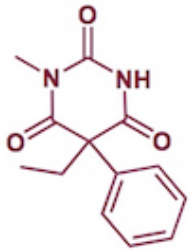


Phenobarbital

Chemical name :
5-ethyl-5-phenylpyrimidine-2,4,6(1H,3H,5H)-trione

Inactive metabolite :
5-ethyl-5-(4-hydroxyphenyl)pyrimidine-2,4,6 (1H,3H,5H)-trione

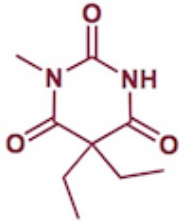
Physicochemical properties :
Polymorphism – seen in other barbiturates; up to 13 crystal modifications
the commercial preparations are usually made up largely of thermally stable modification II (174°C)



Mephobarbital

Chemical name :
5-ethyl-1-methyl-5-phenylpyrimidine-2,4,6 (1H,3H,5H)-trione
(N-methylphenobarbital)

Active metabolite :
forms Phenobarbital via N-dealkylation

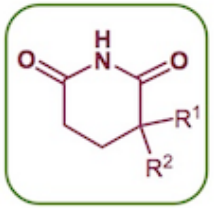


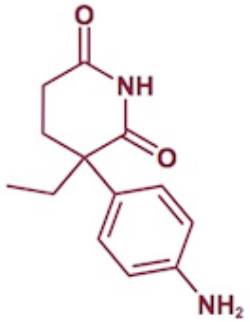
Metharbarbital

Chemical name :
5,5-diethyl-1-methylpyrimidine-2,4,6 (1H,3H,5H)-trione

Obsolete/Rare-used ACDs

Glutarimide





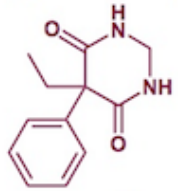
Aminoglutethimide

Chemical name :
3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione

Obsolete?
Useful as antineoplastic agent

Primidone

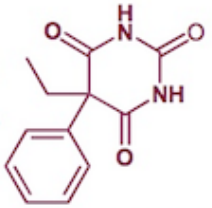
5-ethyl-5-phenyl-dihydropyrimidine-4,6(1H,5H)-dione



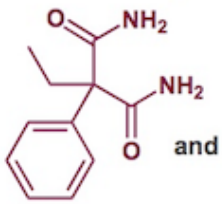
Oxidation w/ dichromate

with H_2SO_4

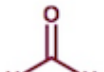
Hydrolysis Products / Metabolites



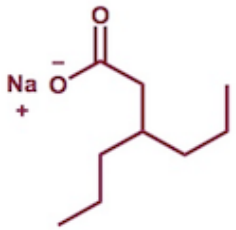
Phenobarbital



and



2-ethyl-2-phenylmalonamide



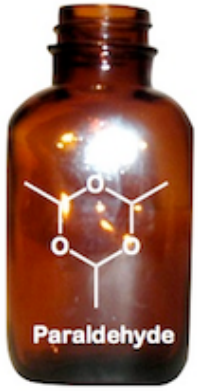
Sodium valproate

Sodium 2-propylpentanoate

quite stable : storage 15 - 30 °C
a fatty acid derivative - penetrates blood-brain barrier even placenta

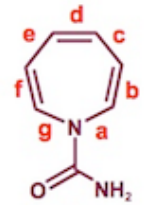
2,4,6-Trimethyl-1,3,5-trioxan (1882)

Unstable in dilute acid to form acetaldehyde
addition of antioxidants to reduce this under unsuitable conditions (↑light/heat), acetaldehyde + acetic acid + peroxides are formed
storage : 50 ml or smaller volume brown bottle & not more than 3 months after opening



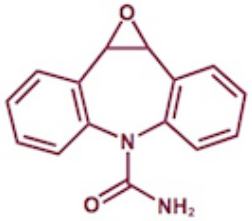
Carbamazepine

5H-dibenz[b,f]azepine-carboxamide
consists of the core - iminostilbene ring

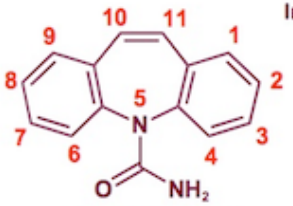


Facets of Iminostilbene

Its equally active metabolite :



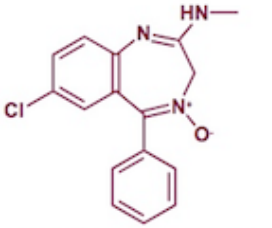
Carbamazepine-10,11-epoxide



Carbamazepine

In 1968, first introduced for the relief of trigeminal neuralgia pain

Benzodiazepines



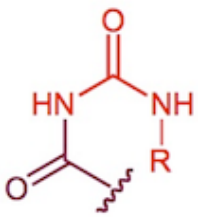
Chlordiazepoxide (Librium)

7-chloro-2-(methylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide

Diazepam (Valium)

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

A few conclusions…



1. The ureide framework is prone to hydrolysis in basic or strong acid conditions
2. The presence of two NH groups imparts some acidity to compounds sporting ureide structure
3. Some metabolites have similar anticonvulsant activities to their parents