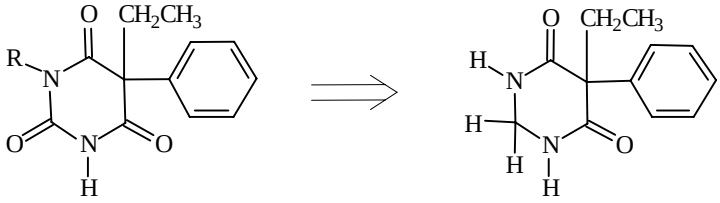
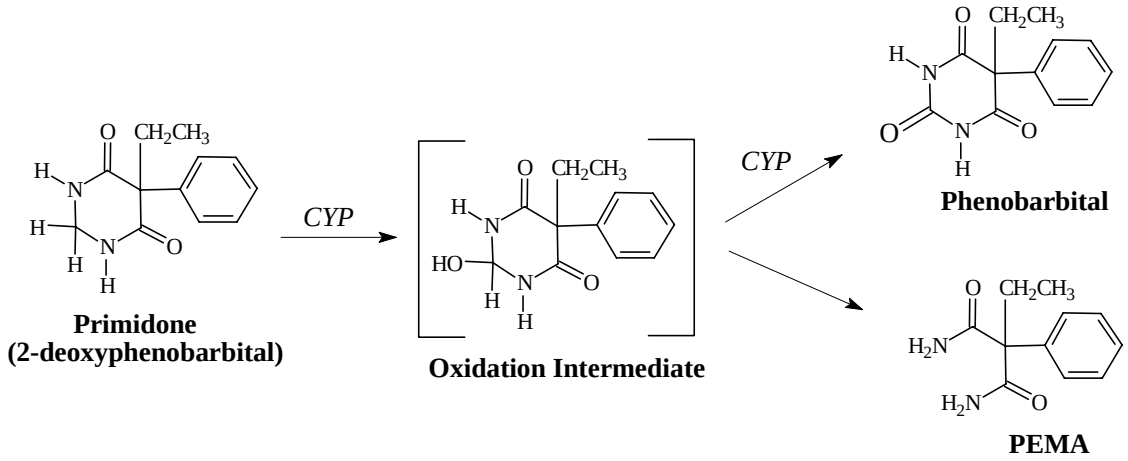
BARBITURATE ANALOGUES AND OTHER SEDATIVE-HYPNOTICS

I. Primidone (Mysoline®)



Phenobarbital **Primidone ("2-deoxyphenobarbital")**

Structure, Chemistry and Actions: The 2-deoxy analogue of phenobarbital. Primidone is similar to phenobarbital in its chemical properties, except that it is not acidic (not an imide!). It is metabolized by oxidation to phenobarbital and phenylethylmalonamide (PEMA), both of which have anticonvulsant activity (tonic/clonic and partial seizures) and may express their actions by a mechanism similar to the barbiturates (GABA actions). Thus primidone could be considered to be a prodrug:

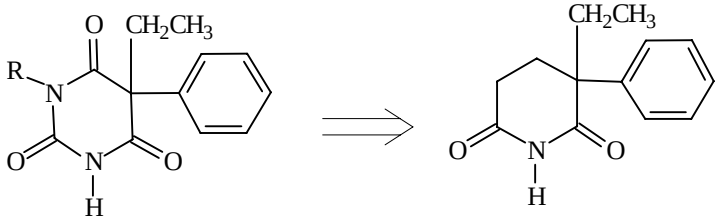


Primidone (2-deoxyphenobarbital) **Oxidation Intermediate** **Phenobarbital** **PEMA**

Absorption/Distribution: Primidone is readily absorbed from the GI tract yielding peak serum concentrations occur in 3 hours. Peak serum concentrations of PEMA occur after 7 to 8 hours. Phenobarbital appears in plasma after several days of continuous therapy. Protein binding of primidone and PEMA is negligible; phenobarbital is about 50% protein bound. Monitoring of primidone therapy should include plasma level determinations of primidone and phenobarbital.

Metabolism/Execretion: PEMA is the major metabolite and is less active than primidone. Phenobarbital formation ranges from 15% to 25%. The plasma half-life of primidone is 5-15 hours. PEMA and phenobarbital have longer half-lives (10-18 hours and 53-140 hours, respectively) and accumulate with chronic use. About 40% of primidone is excreted unchanged in the urine. The remainder of the drug is excreted as unconjugated PEMA and as phenobarbital and its metabolites.

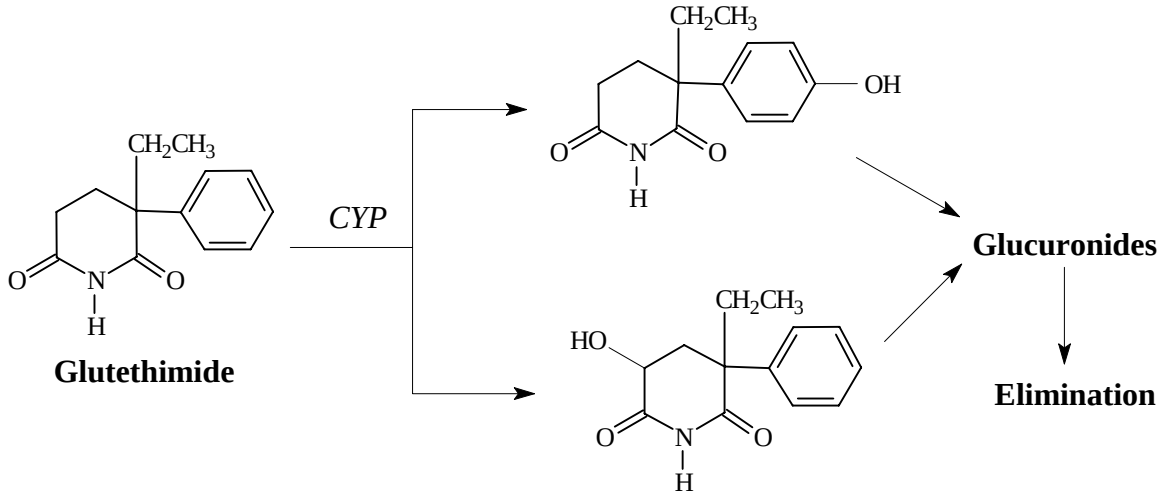
II. Glutethimide (Doriden®)



Barbiturate **Glutethimide (Piperidine-2,6-dione)**

Structure, Chemistry and Actions: A barbiturate analogue lacking one of the "amide components" of the typical barbiturate ring system. Glutethimide is similar to the barbiturates including the presence of an acidic imide group (pKa 9.2). It produces CNS depression similar to the barbiturates. Glutethimide exhibits pronounced anticholinergic activity, which is manifested by mydriasis, inhibition of salivary secretions and decreased intestinal motility. It suppresses REM sleep and is associated with REM rebound. It has generally been replaced by safer and more effective agents.

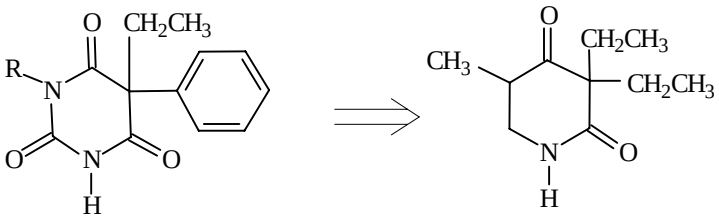
Absorption/Distribution: It is erraticallly absorbed from the GI tract giving peak plasma concentration within 1-6 hours after administration. The average plasma half-life is 10 to 12 hours. About 50% of the drug is bound to plasma proteins; protein binding results in part from modest acidity (imide) Glutethimide stimulates hepatic microsomal enzymes.



Glutethimide

Metabolism/Execretion: Glutethimide is a racemate; both isomers are hydroxylated and both hydroxylated metabolites are reported to be active as sedative. These metabolites are conjugated with glucuronic acid. The glucuronides pass into the enterohepatic circulation and are excreted in the urine (< 2% unchanged).

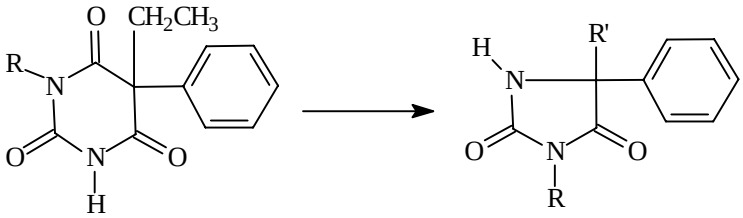
III. Methyprylon (Noludar®)



Barbiturate **Methyprylon (Piperidine-2,4-dione)**

Structure, Chemistry and Actions: An analogue of the barbiturates where one of the "amide goups" have been removed. This compound is generally similar to the barbiturates in its chemical properties, but is only very weakly acidic (pKa 12) due to lack of an imide group (this compound is an amide!). It is similar to glutethimide and the barbiturates in its mechanism of action and use profile. This agent has been replaced by safer drugs.

IV. Phenytoin (Dilantin®) and the Hydantoins



Barbiturate **Hydantoins**

Phenytoin: R = H, R' = 

Mephenytoin: R = CH_3, R' = CH_2CH_3

Ethotoin: R = CH_2CH_3, R' = H

Structure, Chemistry and Actions: Phenytoin and the other hydantoins are "ring-contracted" analogues of the barbiturates (one carbonyl removed). These compounds have physicochemical properties similar to the barbiturates, including acidity when R = H as in phenytoin (an acidic imide with pKa 8.3). Mephenytoin and Ethotoin are not acidic! The hydantoins appear to produce their anti-epileptic effects by depression of the sodium action potential, "filtering out" sustained high frequency neuronal discharges and synaptic activity. This may be related to a voltage dependent blockade of membrane sodium channels responsible for the action potential, resulting in obstruction of the positive feedback underlying the development of maximal seizure activity. Phenytoin is also a weak antiarrhythmic and these actions are also mediated through effects on sodium channels, in this case, in Purkinje fibers.

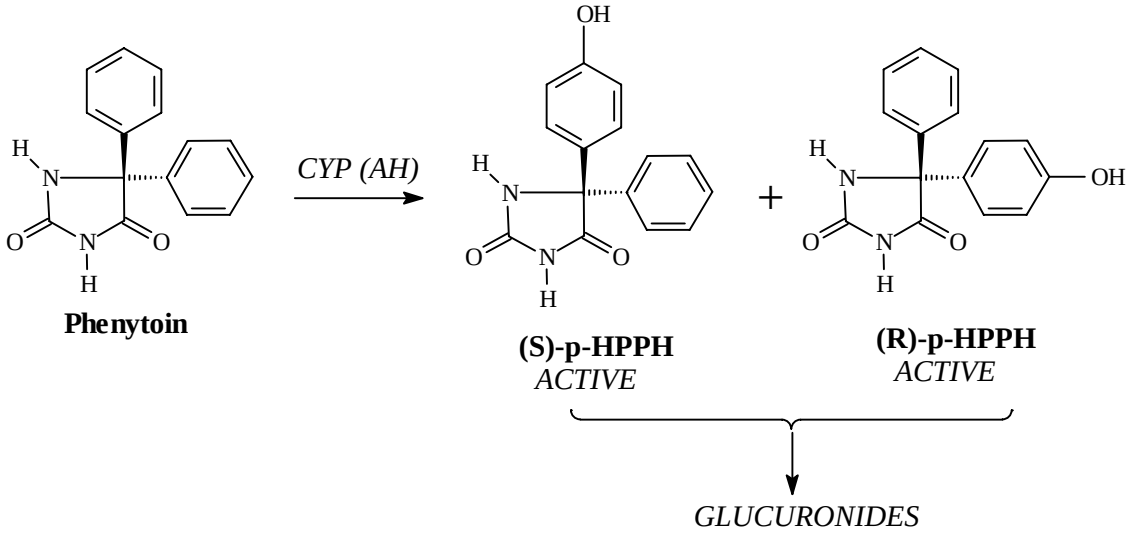
Products: Phenytoin is available as the free acid phenytoin acid (chewable tablets, suspension) and sodium salt forms or phenytoin sodium (capsules, injection).

Oral Absorption: Phenytoin is slowly and erratically absorbed from the small intestine, depending on the formulation. Also, bioavailability may differ among products of different manufacturers. Oral phenytoin sodium extended reaches peak plasma levels in 12 hours; phenytoin sodium prompt peaks within 1.5 to 3 hours.

IM Administration: Results in precipitation of phenytoin at the injection site, resulting in slow and erratic absorption, which may continue for up to 5 days or more; 50% to 75% of an IM dose is absorbed within 24 hours. Plasma levels vary and are significantly lower than those achieved with an equal oral dose.

Distribution: Due to it's acidity, phenytoin plasma protein binding is high (87-93%) and is lower in uremic patients and neonates. Volume of distribution averages 0.6 L/kg.

Metabolism: Phenytoin (a prochiral compound) is metabolized in the liver mainly to inactive enantiomeric phenols similar to aromatic barbiturates. The oxidative metabolism of phenytoin is capacity-limited and shows saturability. These metabolites may be conjugated as glucurionides and excreted in the urine by tubular secretion.

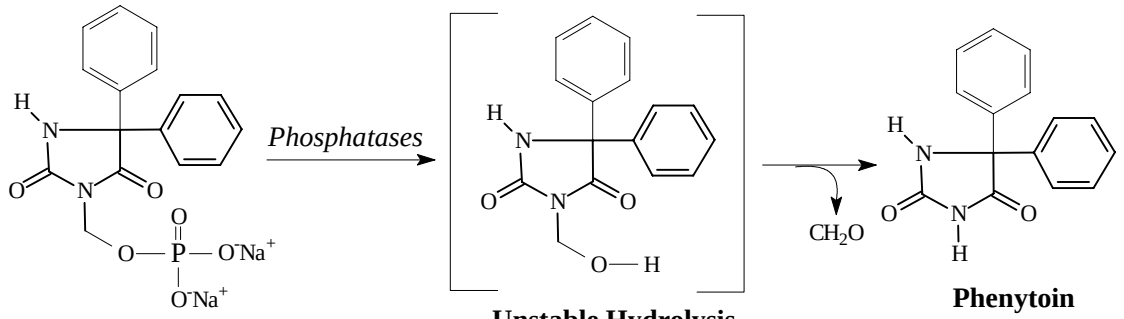


Excretion: 1% to 5% is excreted unchanged. Because the elimination of p–HPPH glucuronide is rate-limited by its formation from phenytoin, measurement of the metabolite in urine can be used to assess the rate of phenytoin metabolism, patient compliance or bioavailability. Elimination is exponential (first-order) at plasma concentrations < 10 mcg/ml, and plasma half-life ranges from 6 to 24 hours. Dose-dependent elimination is apparent at higher concentrations, and half-life increases; values of 20 to 60 hours may be found at therapeutic levels. A genetically determined limitation in ability to metabolize phenytoin has occurred.

Ethotoin: Ethotoin is fairly rapidly absorbed. This drug also exhibits saturable hepatic metabolism with respect to the formation of the major metabolites, N–deethyl and p–hydroxyl-ethotoin. When plasma concentrations are below about 8 mcg/ml, the

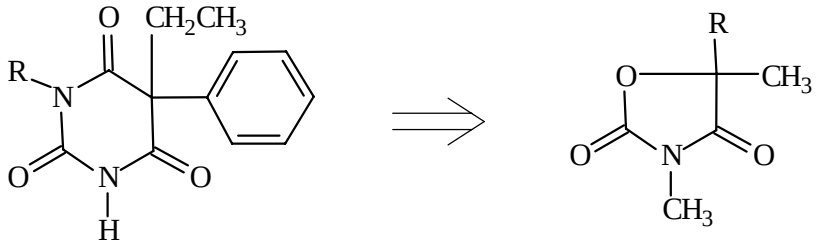
elimination half-life of ethotoin is in the range of 3 to 9 hours. Experience suggests that therapeutic plasma concentrations fall in the range of 15 to 50 mcg/ml.

Fosphenytoin: A disodium phosphate ester of 3-hydroxymethyl-5,5-diphenylhydantoin. It is a water-soluble prodrug of phenytoin, being rapidly converted to the latter by phosphatases in blood and tissues following parenteral administration



Fosphenytoin **Unstable Hydrolysis Intermediate** **Phenytoin**

V. Trimethadione (Tridione®) and the Oxazolidinediones

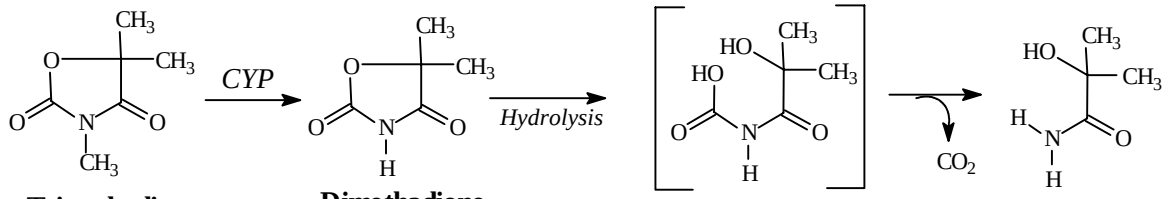


Barbiturate

Oxazolidinediones
Trimethadione: R = CH_3
Paramethadione: R = CH_2CH_3

Structure, Chemistry and Actions: Trimethadione and the other oxazolidinediones are "ring-contracted" analogues of the barbiturates (one carbonyl removed) or can be viewed as isosteres of the hydantoins (one ring N replaced with O). These compounds have physicochemical properties similar to the barbiturates, except they are not acidic (no imide). Unlike hydantoins and anticonvulsant barbiturates, the oxazolidinediones modifies maximal seizure pattern in humans receiving electroconvulsive therapy. These agents have a sedative effect, which may increase to ataxia with excessive doses.

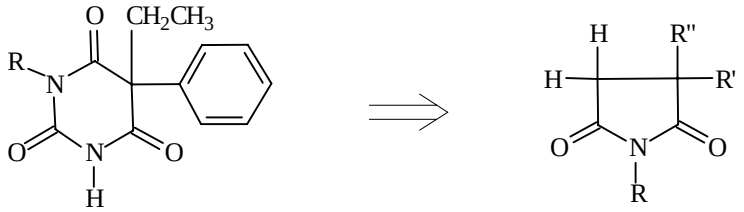
Absorption and Metabolism: Somewhat erratic absorption. Extensive hepatic CYP-mediated OND to active demethyl metabolites. Dimethadione is formed from trimethadone Dimethadione may be further metabolized to acids via ring cleavage and the acids then decarboxylated resulting in inactive metabolites and carbon dioxide. Trimethadione has a plasma half-life of 16 to 24 hours; dimethadione's plasma half-life is 6 to 13 days



Trimethadione **Dimethadione *(ACTIVE)***

Excretion: Parent drug (3%) and metabolites in urine. The excretion rate of the metabolite dimethadione can be enhanced by alkalinizing the urine or increasing urine volume. Due to its acidity (OND product!)

VI. Ethosuximide (Zarontin®) and the Succinimides



Barbiturate

Succinimides

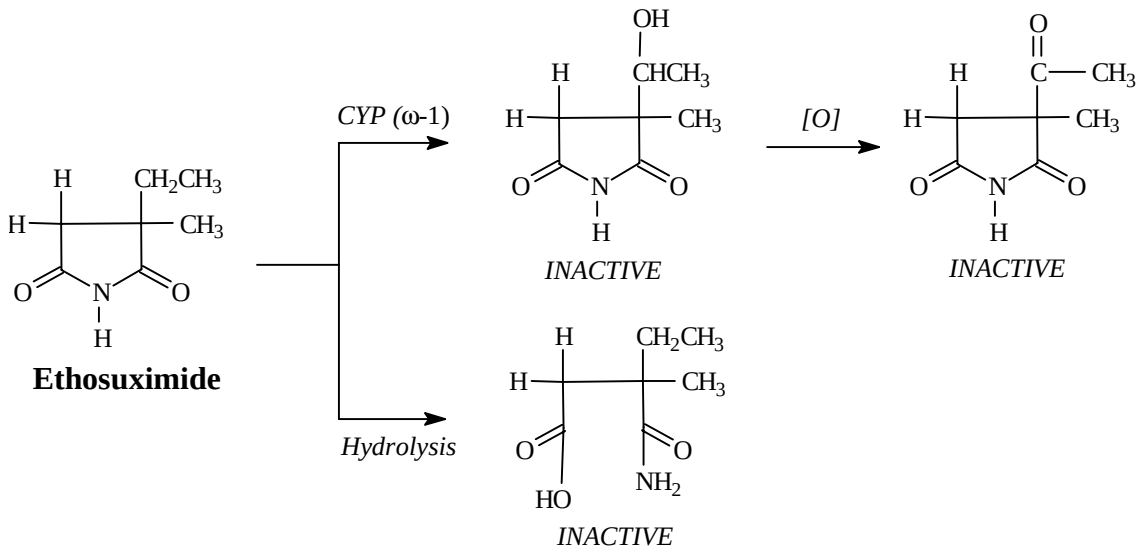
Ethosuximide: R = H, R' = CH_3, R" = CH_2CH_3

Methsuximide: R = CH_3, R' = CH_3, R" = 

Phensuximide: R = CH_3, R' = H, R" = 

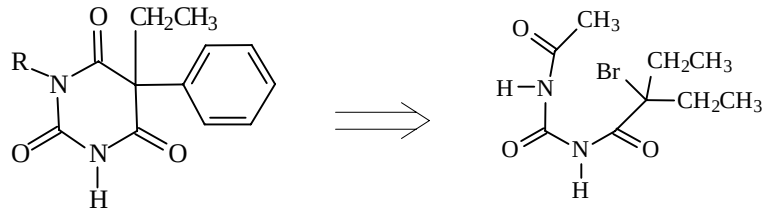
Structure, Chemistry and Actions: Ethosuximide and the other succinimides are "ring-contracted" analogues of the barbiturates (one carbonyl removed) or can be viewed as isosteres of the hydantoins (one ring N replaced with CH_2). These compounds have physicochemical properties similar to the barbiturates, except only ethosuximide has an imide N-H and is acidic (pKa 9.5). The antiepileptic (petit mal) actions of the succinimdes may be related to synaptic inhibition brought about by the GABA mediated chloride conductants

Absorption/ Metabolism/Execretion: These agents are readily absorbed from the GI tract with a T_{max} of 3-7 hours. Ethosuximide is extensively metabolized to inactive metabolites; only about20% is excreted unchanged via the kidneys. The plasma half-life is 30 hours in children and 60 hours in adults. Less than 1% of a dose of methsuximide is recovered unchanged in urine; plasma half-lives range from 2.6 to 4 hours. Phensuximide is excreted in urine and in bile; half-life is » 4 hours.



Ethosuximide

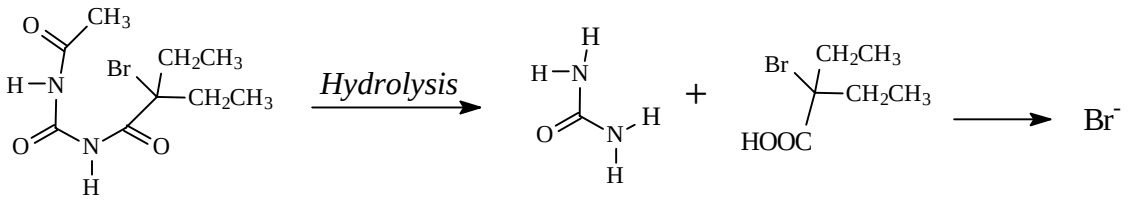
VII. Acetylcarbromal



Barbiturate **Acetylcarbromal**

Structure and Chemistry: Acetylcarbromal is a "ring-opened" barbiturate analogue. It contains two acidic imide protons like barbiturates. It is unique in that it contains bromide. Acetylcarbromal is a short-acting CNS depressant used as a daytime sedative and as a hypnotic and has anticonvulsant activity. Its antiepileptic activity is believed to result from metabolism which releases bromide which is produces "secondary anion potentiation" of gamma-aminobutyric acid (GABA) channels in the CNS (anion at chloride channels). The bromide ion is thought to be responsible for the toxicity of this agent as well. It has generally been replaced by safer, more effective products.

Metabolism: Hydrolyzed to urea and bromide acid which liberates Br-. The metabolites are readily eliminated by renal route.



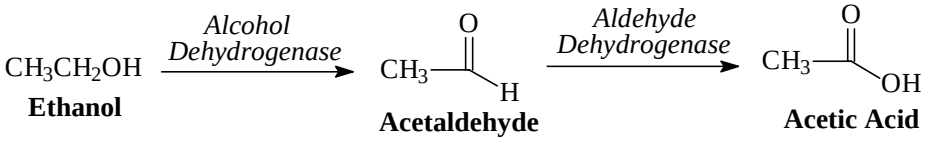
Acetylcarbromal **Urea**

ALCOHOLS, ALDEHYDES AND CARBAMATES

I. Ethanol

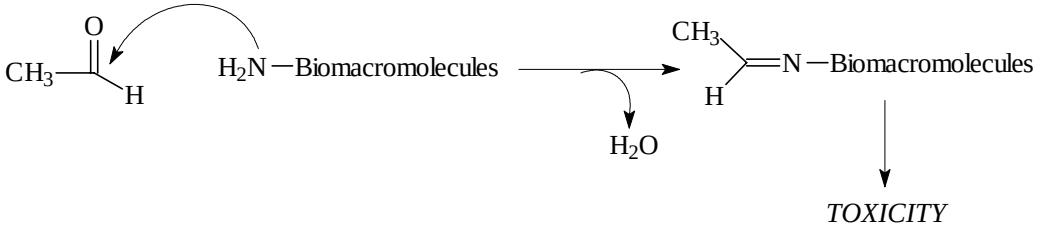
Actions: Acts at the $GABA_A$ receptor to potentiate the action of GABA. ALso inhibts NMDA glutamate receptors. These actions result in an array of actions including CNS depression (**See Pharmacology Notes**).

Kinetics: Rapidly absorbed and distributed to all tissues (small molecule). Rapidly and complete oxidized alcohol dehydrogenase to acetaldehyde. The acetaldehyde formed is oxidized to acetic acid by aldehyde dehdyrogenases/oxidases.

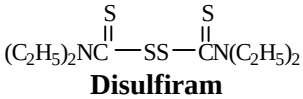


Ethanol **Acetaldehyde** **Acetic Acid**

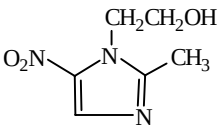
Ethanol Toxicity: Ethanol may produce a variety of acute and toxic effects by a number of mechanisms. The metabolic intermediate acetaldehyde has been implicated in a number of ethanol-associated toxicities. This intermediate contains an electrophilic carbonyl which can react with nucleophilic groups (such as amines) on biomacromolecules as shown below. These complexes may compromise cellular structure and viability and result in toxicity:



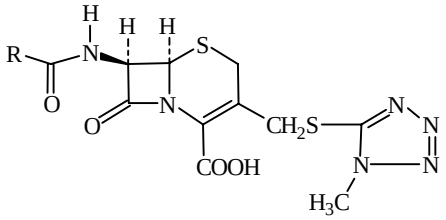
Inhibition of Ethanol metabolism: A number of drugs including disulfiram, metronidazole, N-methylthiotetrazole cephalosporins and oral hypoglycemics inhibit aldehyde dehydrogenase and thereby allow for accumulation of acetaldehyde and enhanced ethanol toxicity:



Disulfiram



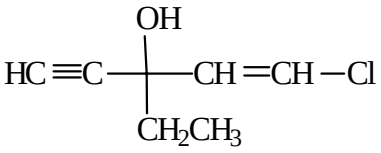
Metronidazole



NMTT Cephalosporins

Aldehyde Dehydrogenase Inhibitors

II. Ethchlorvynol (Placidyl®)

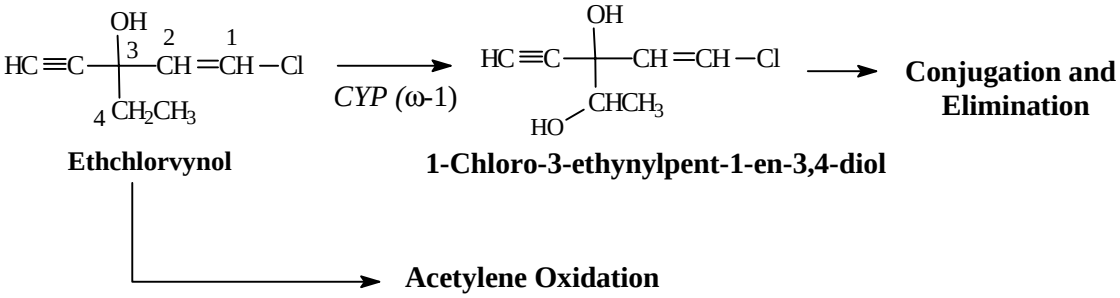


Ethchlorvynol

Structure, Chemistry and Actions: A tertiary, lipophilic alcohol; the addition of ethinyl and chlorovinyl groups to ethanol greatly enhance lipophilic character. This drug is chemically stable and as a tertiary alcohol is resistant to alcohol dehydrogenase ooxdaition. It is metabolized, hjowever, by CYP-mediated hydroxylation as shown below. Ethchlorvynol has sedative-hypnotic, anticonvulsant and muscle relaxant properties and produces EEG patterns similar to those produced by barbiturates. ethchlorvynol has generally been replaced by safer and more effective agents.

Absorption: Lipophilic drug that is rapidly absorbed producing peak plasma concentrations within 2 hours. Nearly 90% of the drug is destroyed in the liver. There is extensive tissue concentration, particularly in adipose tissue.

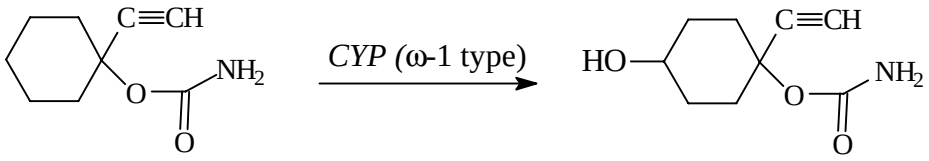
Metabolism/Execretion: Most of the dose is excreted in the urine, mostly as metabolites. The free and conjugated forms of the major metabolite, the diol of ethchlorvynol, in the urine accounts for about 40% of the dose. The parent compound and its metabolites undergo extensive enterohepatic recirculation. Plasma half-life of parent compound is 10 to 20 hrs.



III. Ethinamate (Valmid®)

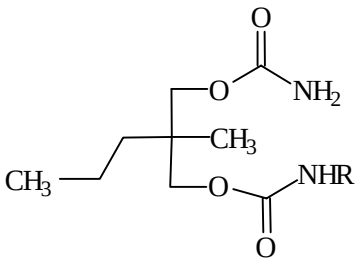
Structure, Chemistry and Actions: Carbamate analogue of acetylenic alcohol. The site of action and mechanism of action of ethinamate have not been studied. It is a short-acting hypnotic to which tolerance rapidly develops; it is indicated only for periods of 7 days or less. Ethinamate has largely been replaced by safer and more effective agents.

Metabolism: resistant to alcoholo-type metabolism but is extensively metabolized by other pathways including CYP-mediated hydroxylation of the cyclohexyl ring to 4-hydroxyethinamate followed by glucuronidation.



Ethinamate **4-Hydroxyethinamate**

IV. Meprobamate (Equanil, Miltown®)



R = H: Meprobamate
R = $CH(CH_3)_2$: Carisoprodol

Structure, Chemistry and Actions: A bis-carbamate–1,3-propanediol derivative. Meprobamate is an antianxiety agent that has selective effects at multiple sites in the CNS, including the thalamus and limbic system. It also appears to inhibit multineuronal spinal reflexes. Meprobamate is mildly tranquilizing, and has some anticonvulsant and muscle relaxant properties. The mechanism of action is unknown!

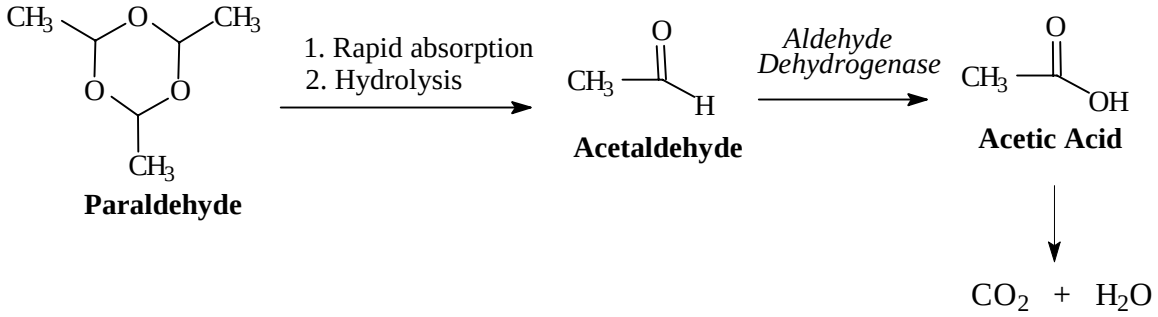
Absorption/Distribution: Meprobamate is well absorbed from the GI tract; yielding peak plasma concentrations within 1 to 3 hours. Plasma protein binding is approximately 15%.

Metabolism/Execretion: The liver metabolizes 80-92% of the drug; the remainder is excreted unchanged in the urine. Following a single dose, the plasma half-life ranges from 6 to 17 hours, but during chronic administration, may be as long as 24 to 48 hours. Meprobamate can induce some hepatic microsomal enzymes, but does not appear to induce its own metabolism. Excretion is mainly renal (90%), with < 10% appearing in feces.

V. Paraldehyde

Structure, Chemistry and Actions: A trimer of acetaldehyde, is a colorless, bitter tasting liquid with a strong, unpleasant odor. It produces nonspecific, reversible depression of the CNS and has been used as a rapid-acting hypnotic. With usual therapeutic doses, paraldehyde has little effect on respiration and blood pressure; large doses may cause

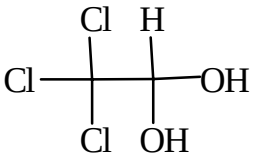
respiratory depression and hypotension. It has generally been replaced by safer and more effective agents.



Absorption/Distribution: Paraldehyde is rapidly absorbed after oral administration giving peak serum concentrations within 30-60 minutes. Paraldehyde distributes to the CNS rapidly, producing sleep within 10 to 15 minutes after a therapeutic dose; sleep lasts about 8 to 12 hours.

Metabolism/Execretion: Plasma half-life ranges from 3.4 to 9.8 hours. Approximately 70-80% of the drug is metabolized in the liver, 11% to 28% is exhaled unchanged via the lungs and a negligible amount is excreted in the urine. The major primary metabolite formed, acetaldehyde is reported to be inactive. In hepatic disease, elimination rate is decreased and more drug is excreted through the lungs.

VI. Chloral hydrate (Noctec®)



Chloral Hydrate (CH)

Structure, Chemistry and Actions: The hydrate of trichloroacetaldehyde (TCA) and thus is a relatively lipophilic compound. In vivo this compound is readily hydrolyzed by a chemical mechanism to TCA. TCA is reduced by ADH to **trichloroethanol** (TCE), the principal active metabolite. Chloral hydrate an onset of action that correlates with absorption and conversion to trichloroethanol (TCE). This metabolite readily penetrates the CNS (lipophilicity) and produces CNS depression by an unknown mechanism, but may be similar to ethanol. Hypnotic doses produce mild cerebral depression and quiet, deep sleep. In therapeutic doses, chloral hydrate has little effect on respiration, blood pressure and reflexes. "Hangover" is less common with chloral hydrate than with most barbiturates and some benzodiazepines. This drug has generally been replaced by safer and more effective agents.

Kinetics: TCE has a plasma half-life of 7 to 10 hours; plasma protein binding is 35% to 41%. TCE is converted in the liver and kidney to trichloroacetic acid (TCAA) which is **inactive** and excreted in the urine and bile. Although inactive, TCAA is 71% to 88% protein bound and has a very long half-life. TCAA also can displace other acidic drugs from plasma protein binding sites. TCE can also be conjugated as a glucuronide and eliminated renally