Name of Unit	Drug acting on Central nervous system.
Course/Subject Code	BP402T
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Semester	IV
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Learning Outcome of Module 04

LO	Learning Outcome (LO)	Course Outcome Code
LO1	Psychosis , its mechanism	BP402.1
LO2	Antipsychotics and anticonvulsant classification	BP402.1
LO3	Therapeutic uses and adverse effects	BP402.2
LO4	Structure activity relationship.	BP402.3
LO5	Synthesis of drugs.	BP402.4

Content Table

Topic
• Introduction of Sedatives and hypnotics • Benzodiazepam • Barbiturates • Phenothiazines • Anticonvulsants • Synthesis • Important questions.

SEDATIVES AND HYPNOTICS

Nervous system: It is very important in helping to maintain the homeostasis (balance) of the human body. It control and coordinate the human body and it gives the quick response to our body.

CNS: It is the main system of nervous system. It regulates the whole body. It consist the brain and spinal cord.

These are those drugs which produce their effect on CNS

It can increase or decrease the activity of CNS.

Main category:

1. **Sedatives and hypnotics.**
2. **Anti Psychotics.**
3. **Anti Convulsant.**

Classification

Due to chemical differences, the sedative-hypnotics include several related families of drugs having common characteristics but somewhat diverse effects and therapeutic uses. These drugs are classified as follows

1. Barbiturates : Phenobarbitone, pentobarbitone, amobarbitone etc.

2. Non-barbiturates :

(a) Aldehydes and their derivatives : Chloral hydrate, paraldehyde, triclofossodium

(b) Piperidinederivatives : Glutethimide, methyprylone

(c) Quinazolinederivatives : Methaqualone

(d) Alcohols and their carbamate derivatives : Ethchlorvynol, meprobamate, ethinamate

(e) Benzodizepine derivatives : Chlordiazepoxide, diazepam, oxazepam, alprozolam, flurazepam, triazolam, prazepam, halazepam, temazepam, lorazepam.

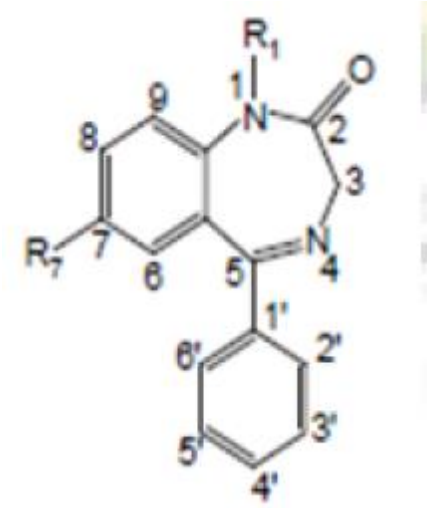
1. Benzodiazepines

Mode of action: Benzodiazepine receptors are present in the brain and they form a part of GABAA receptor's chloride ion channel macromolecular complex. Binding of benzodiazepines

to these receptors produces activation GABA receptor and increases chloride conductance by increasing the frequency of opening chloride ion channel. These in turn inhibit neuronal activity by hyper-polarization and de-polarization block.

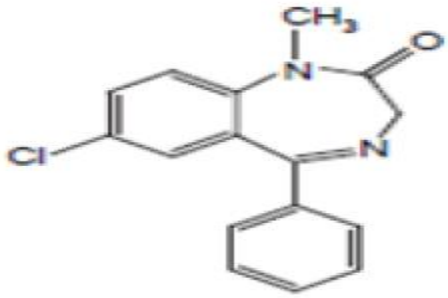
Metabolism of Benzodiazepines: Compounds without the hydroxyl group are nonpolar, and undergoes hepatic oxidation. Compounds with hydroxyl groups have more polarity and are readily converted into the glucuronide conjugates and excreted easily. These compounds are also metabolized by 3-hydroxylation of benzodiazepine ring.

SAR

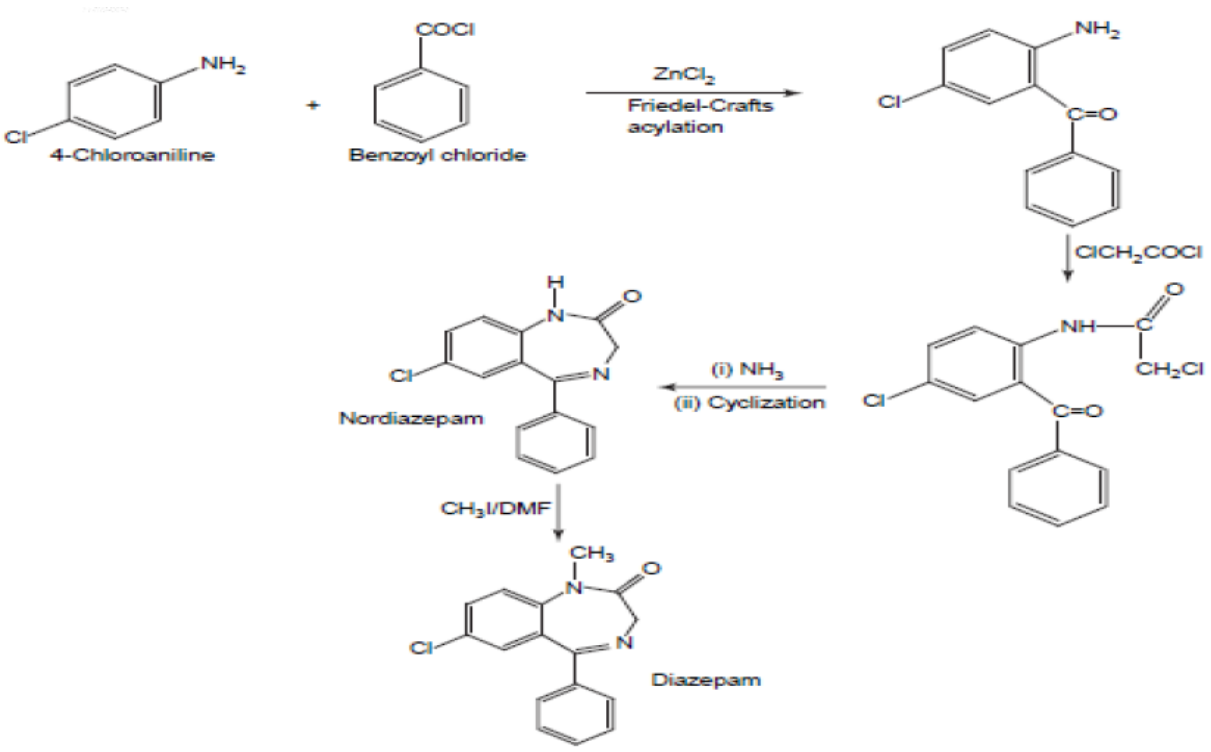


- The presence of electron attracting substituents (Cl, F, Br, NO_2) at position C-7 is required for the activity, and the more electron attracting substituents leads to potent activity.
- Position 6, 8, and 9 should be unsubstituted for the activity.
- Phenyl (or) pyridyl at the C-5 position promotes activity. If the phenyl ring substituted with electron attracting groups at 2' or 2', 6' position, then the activity is increased.
- On the other hand, substituents at 3', 4', and 5' positions decreases activity greatly.
- Saturation of 4, 5 double bond or shift of it to the 3, 4 position decreases the activity.
- Alkyl substitution at position 3 decreases the activity, but the presence or absence of hydroxyl group is essential. Compounds without 3-hydroxyl group are nonpolar and usually have long half-life. Compounds with the 3-hydroxyl group have short half-life because of rapid conjugation with glucuronic acid.
- Substitution at N^1 by alkyl, halo alkyl, and amino alkyl group increases the activity.
- Reduction of carbonyl function at C-2 position to CH_2 yields less potent compound.
- Triazolo benzodiazepine (Alprazolam) is found to be more potent, they do not require any substitution at 7th position.

Diazepam*

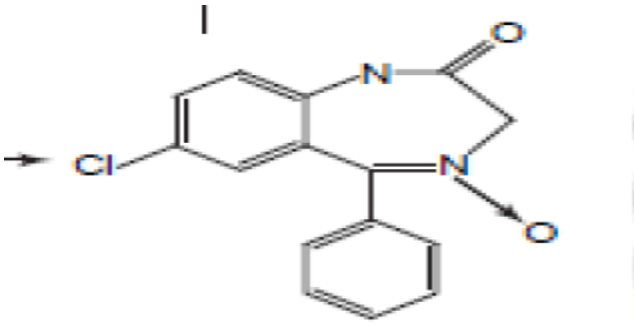


Synthesis



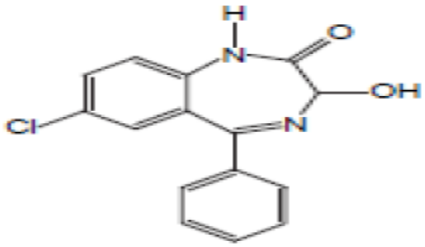
Properties and uses: It is a white or almost white crystalline powder soluble in ethanol and very slightly soluble in water. It is used as a skeletal muscle relaxant, anticonvulsant and antianxiety agent. It may take a long time to achieve sedative and antianxiety effects, during which time the patient can usually be maintained by giving the drug once or twice a day. Patients on the drug should be cautioned not to drive anautomobile or to operate dangerous machinery until a few days after the drug has been discontinued.

Chlordiazepoxide



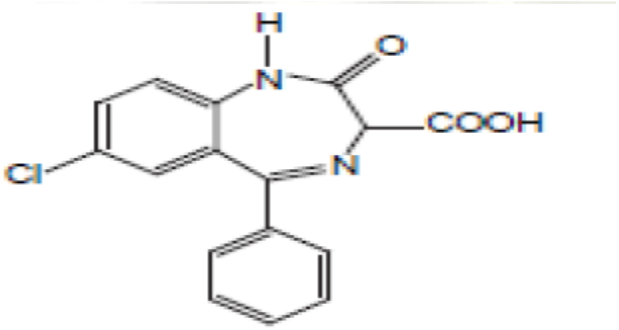
Properties and uses: It is a white or almost white crystalline powder soluble in ethanol and very slightly soluble in water. It shows polymorphism. It is used as sedative and hypnotic.

Oxazepam



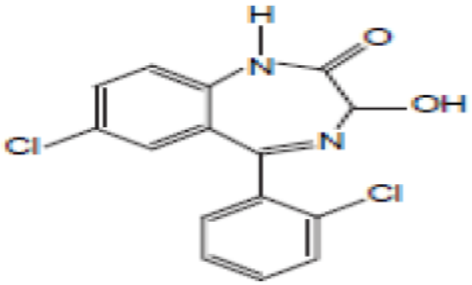
Properties and uses: It is a white or almost white crystalline powder slightly soluble in ethanol and insoluble in water. It is useful for the control of acute tremulousness, inebriation, or anxiety associated with alcohol withdrawal.

Chlorazepate



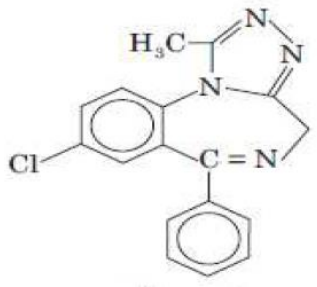
Uses: It is used as a sedative and hypnotic.

Lorazepam,



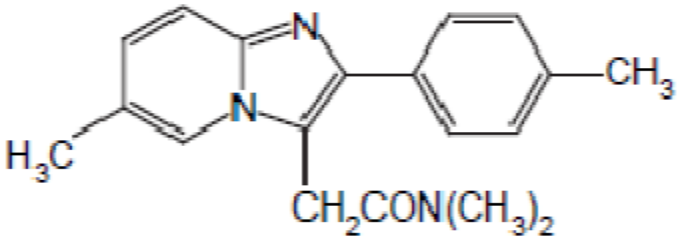
Properties and uses: It is a white or almost white crystalline powder, which is insoluble in water, sparingly soluble in ethanol, sparingly soluble in methylene chloride. It shows polymorphism. It is used as sedative and hypnotic. It has much more polarity than diazepam, for example, metabolism is relatively uncomplicated, and the duration of action is short.

Alprazolam



Properties and uses: It is a white crystalline powder, practically insoluble in water, freely soluble in methylenechloride sparingly soluble in acetone and in alcohol. It shows polymorphism. management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and early morning awakenings. The duration of action is short and the drug is a highly potent anxiolytic in doses of milligram. Titrate to the second point of inflexion.

Zolpidem

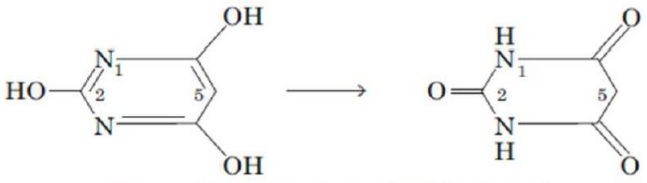


Properties and uses: It is a white or almost white crystalline powder, hygroscopic in nature, slightly soluble in water, sparingly soluble in methanol, and insoluble in methylene chloride. It is an imidazopyridine agent and is an agonist at the benzodiazepine α1 receptor subunit of the GABA-A receptor, used for the management of insomnia. The selective binding at α1 receptors Subunits of GABAA may explain the relative absence of myorelaxant and anticonvulsant effects as well as the preservation of deep sleep in human.

Barbiturtes:

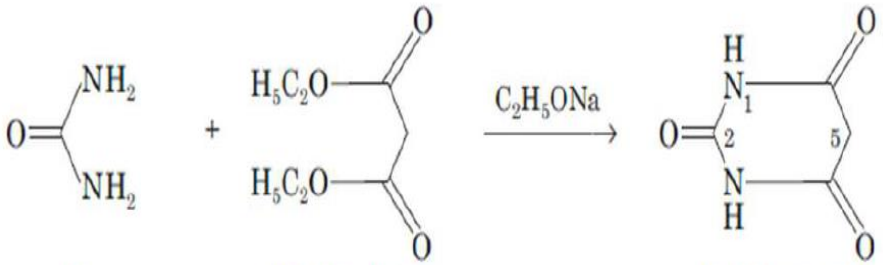
SAR of Barbiturates

1.Barbiturates are derivatives of barbituric acid (2,4,6- trioxyhexahydropyrimidine) which is devoid of hypnotic and sedative activities



Keto-enol tautomerism of barbituric acid

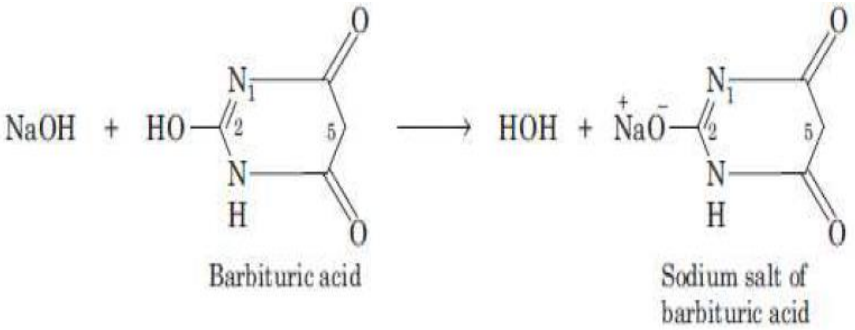
2. Barbituric acid may be described as a "cyclic ureide of malonic acid". Barbituric acid can be made by condensing urea with ethyl malonate in presence of sodium ethoxide.



Urea Ethylmalonate Barbituric acid

3**.** Clinically important hypnotic-sedative barbiturates have substitutions at sites 1, 2 and, especially, 5 of barbituric acid.

4. Keto-enoltautomerism of barbituric acid and barbiturates allows formation of watersolublesalts with a strong base.



Barbituric acid Sodium salt of barbituric acid

5. The barbiturates do not dissolve readily in water, their sodium salts dissolve readily in water.

6. Buffering action of Na2CO3 plus atmospheric CO2 maintains pH at 10 to 11.

In less alkaline solutions, these barbiturates may precipitate as the free acids; so do not reconstitute barbiturates with normal saline and do not mix with acidic solutions of other drugs.

SAR

1. Hypnotic activity. Side chains at position 5 (especially if one of them is branched) is essential for activity.

2. Potency and duration of action. Length of side chain at position 5 influences potency and duration of action. Ex: Secobarbital and thiamylal are slightly more potent than ntobarbital and thiopental, respectively.

3. More rapid onset and shorter duration of action Sulfur instead of oxygen atom at postion 2 has more rapid onset of action but shorter duration. Ex: thiamylal and thiopental have more rapid onset and shorter duration of action than secobarbital and pentobarbital, respectively.

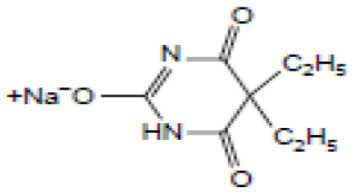
4. Increased incidence of excitatory side effects. Methylation at position 1 (methohexital) enhances excitatory side effects.

5. Increased potency, rate of onset and short action Generall an increase in the lipophilicity of the compound results in more rapid onset of action accompanied with an increase in potency.

6. Introduction of polar groups (hydroxyl, keto, amino, or carboxyl) into C 5-alkyl sidechain makes the compound more hydrophilic in nature**.** Due to the polar nature, hydrophilic barbiturates do not dissolve in microsomal membranes of liver and are excreted.

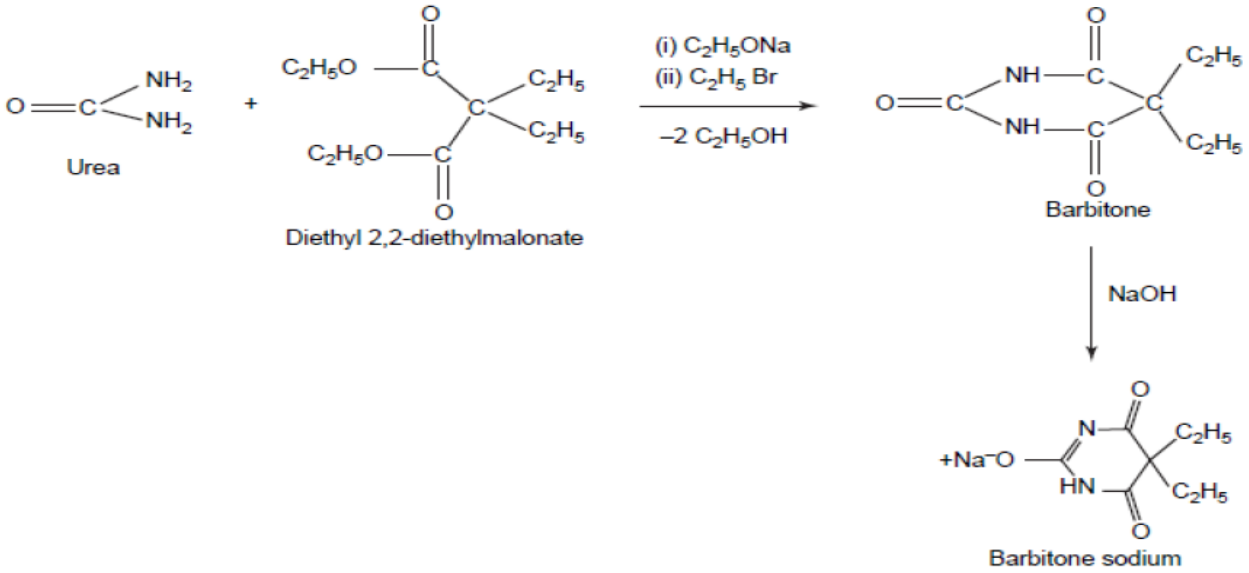
7. Branched, cyclic or unsaturated side chain at C-5 position. Generally reduce the duration of action due to an increased ease of metabolic conversion to a more polar, inactive metabolite.

Barbital*

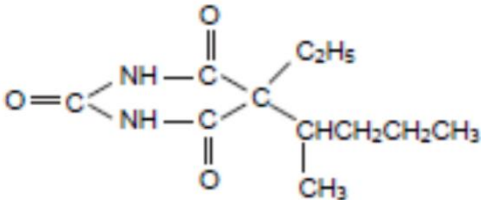


Properties and uses: Baritone sodium exists as white, crystalline powder or colourless crystals that is soluble in boiling water and in alcohol, but only slightly soluble in water. It forms water-soluble salts with sodium hydroxide. It is a powerful hypnotic drug and generally used in the treatment of epileptic seizures.

Synthesis

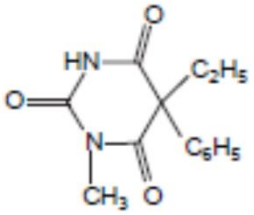


Phenobarbital



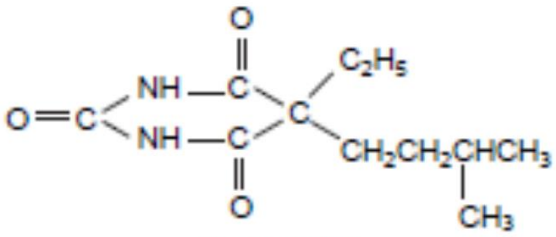
Properties and uses: Phenobarbital sodium is a hygroscopic substance. It is a white, crystalline powder, freely soluble in water and also soluble in alcohol. It is used as sedative, hypnotic and antiepileptic (drug of choice in the treatment of grandmal and petitmal epilepsy). It is useful in nervous and related tension states. An overdose of it can result in coma, severe respiratory depression, hypotension leading to cardiovascularcollapse, and renal failure.

Mephobarbital



Properties and uses: It is a white, crystalline powder, odourless, with a bitter taste, and a saturated is solution acid to litmus. Soluble in water, alcohol, chloroform, and in solutions of alkali hydroxides or carbonates. Mephobarbitone is a strong sedative with anticonvulsant action, but a relatively mild hypnotic. Hence, it is used for the relief of anxiety, tension, and apprehension, and is an antiepileptic in the management of generalized tonic- clonic and absence seizures.

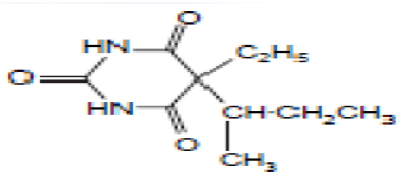
Amobarbital



Amobarbitol

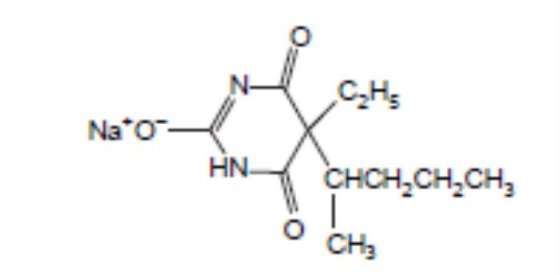
Properties and Uses: It can be used both as sedative and hypnotic at different dose intervals.

Butabarbital



Properties and uses: It is used as a sedative and hypnotic, especially used for the short-term treatment of insomnia. Because of tolerance, barbiturates lose efficacy after two weeks of use.

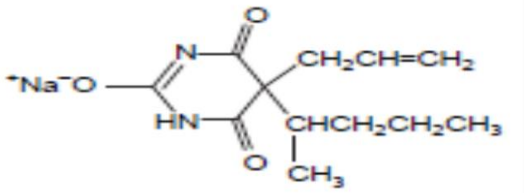
Pentobarbital



Properties and uses: It is hygroscopic in nature and a white crystalline powder, very soluble in water. It is used as a sedative or hypnotic for the short-term management of insomnia and is a

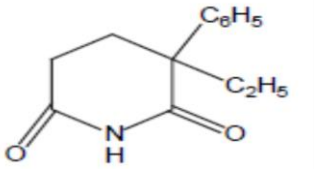
preanaesthetic medication, used in the treatment of strychnine poisoning. It is also indicated in the anaesthetic dose and administered intravenously, for the control of certain convulsive syndromes. This barbiturate is thought to reduce cerebral blood flow and, thereby, decrease oedema and intracranial pressure.

Secobarbital



Properties and uses: It is a white, hygroscopic powder having a bitter taste, with pH between 9.7 and 10.5, soluble in water and alcohol. It is used in status epilepticus and in toxic reactions to strychnine and as local anaesthetic.

Miscelleneous: Amides & imides: Glutethmide.



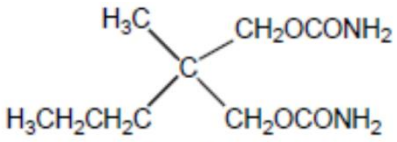
Properties and uses: It is used as a hypnotic drug to induce sleep without depressing respiration. Over dosage is less likely to depress respiration, but more likely to cause hypertension than most other barbiturates. Adverse reactions include a generalized rash, occasionally a purpuricor urticarial rash; exfoliative dermatitis has also been observed, rarely nausea, hangover, paradoxical excitation, and blurred vision have occurred. Some of these side effects may be due to the anticholinergic activity of this drug.

Alcohol & their carbamate derivatives:

Mode of action: These drugs elicit the action and is similar to the mechanism of barbiturates. These are general CNS depressants, which produce profound hypnosis. These are metabolized by alcohol dehydrogenase enzyme. Chloralhydrate undergoes oxidation to chloral and then to an

inactive metabolite, trichloroacetic acid, extensively metabolized to aryl glucuronides via conjugation with glucuronic acid and then excreted in urine.

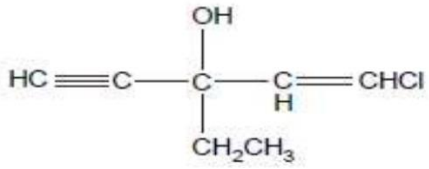
Meprobomate



Meprobamate

Properties and uses: It is a white or almost white amorphous or crystalline powder slightly soluble in water and freely soluble in alcohol. It is used in the treatment of anxiety disorders. It is also a centrally acting skeletal muscle relaxant. The agents in this group find use in a number of conditions, such as strains and sprains that may produce acute muscle spasm.

Ethchlorvynol.

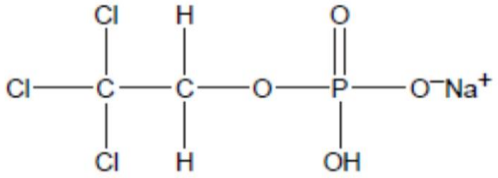


1-Chloro-3-ethyl-1-penten-4-yn-3-ol

Properties and uses: It also possesses muscle relaxant and anticonvulsant properties apart from CNS depressant action. Adverse effects include suppression of REM sleep, ataxia, and hypotension.

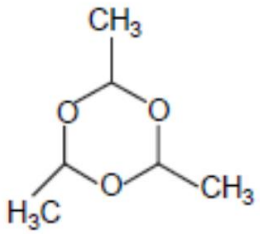
Aldehyde & their derivatives

Triclofos sodium



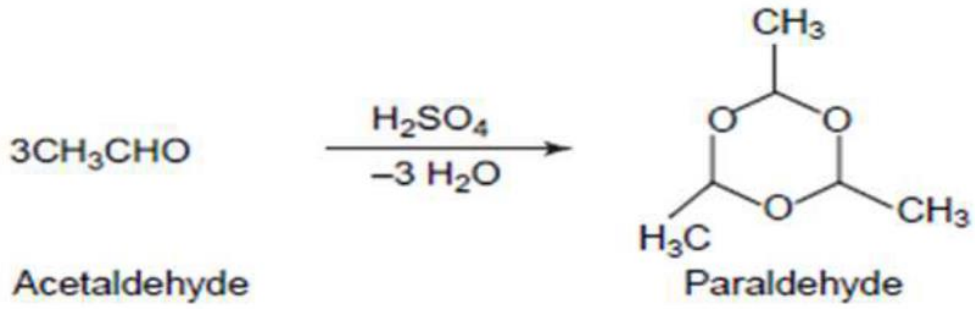
Properties and uses: It is a white or almost white powder, hygroscopic in nature. Freely soluble in water, slightly soluble in ethanol, practically insoluble in ether. Used as hypnotic.

Paraldehyde.



2, 4, 6-Trimethyl-1,3,5-trioxane

Synthesis



Properties and uses: It is a colourles or slightly yellow transparent liquid. It solidifies on cooling to form a crystalline mass. Miscible with alcohol and with essential oils, soluble in water, but less soluble in boiling water, it is exclusively used in the management of hospitalized patients undergoing alcohol withdrawal. Its CNS depressant activity resembles that of alcohol and chloral hydrates.

ANTIPSYCHOTICS

Psychoactive or psychotropic drugs are also known as tranquilizers. These drugs are used in the treatment of psychiatric disorders i.e. abnormalities of mental function. The psychoactive drugs render the patient calm and peaceful by reducing agitation and anxiety. Psychoactive drugs does not cure mental disorders but the available drugs do control most symptomatic manifestations and behavioral deviances, facilitate the patient's tendency toward remission and improve the capacity of patient for social, occupational, and familiar adjustment. The primary characteristic feature of these drugs is that they alter the mental state and behavior in a predictable way

The psychoactive drugs are classified as:

1. Antipsychotic drugs
2. Anti depressant drugs
3. Anti anxiety drugs

ANTIPSYCHOTIC AGENTS: Antipsychotic drugs are used to treat psychoses like schizophrenia, mania, senile dementia and behaviour disorders in children. These drugs act by depressing the central nervous system (by decreasing dopamine levels) and by producing sedation without producing sleep. Thus the antipsychotics are employed to reduce excitation, agitation, agressiveness and impulsiveness. Hence they are also known as antischizophrenic drugs or neuroleptic drugs or major **tranquilizers.**

Classification

1. Phenothiazines

a. Aliphatic side chain: Promazine, Chlorpromazine, triflupromazine

b. Piperidine side chain: Thioridazine

c. Piperazine side chain: Trifluoperazine, fluphenazine, Piperacetazine HCl, Prochlorperazine.

2.Butyrophenones: Haloperidol, Droperidol, Trifluperidol, Penfluridol

3.Thioxanthenes: Flupenthixol,Chlorprothixene, Thiothixene,

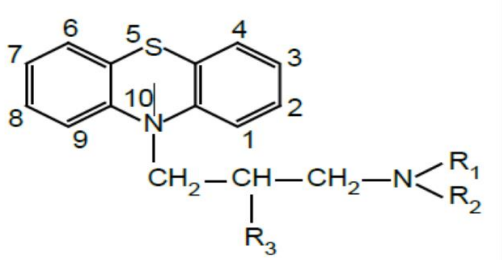
4. Other heterocyclics: Pimozide, Loxapine

5. Atypical antipsychotics: Clozapine, risperidone, olanzapine,

6. Benzamides: Sulpieride.

7. Beta amino ketones: Molindone hydrochloride.

1. Phenothiazeines: Phenothiazines act exclusively on specific postsynaptic receptors and block the postsynaptic dopamine receptors. They work on the positive symptoms of psychosis such as hallucinations, delusions, disorganized speech, looseness of association, and bizarre behavior. Phenothiazines are chemically constituted by a lipophilic, linearly fused tricyclic system having a hydrophilic basic amino alkyl chain. The following is the general structure ofantipsychotic drugs.



SAR of Phenothiazeines. Activity of phenothazines is determined by the following:

1. Nature of alkyl side chain at C-10.
2. Amino group of side chain.
3. Substituents on aromatic ring.

1. Modification of alkyl side chain

1. Potency is maximum when there is three carbon between two 'N' atom (ring and side chain N
2. Introduction of methyl group at C-1 decreases antipsychotic activity and produces imipramine-like activity.
3. If C-1 is incorporated into cyclopropane ring imipramine-like activity is obtained.
4. When oxygen is introduced into C-1 results in potent antidepressant effect.

Example: Chloracizine.

5.Addition of –CH3 at C-2 or C-3 has very little effect on activity.

6. Bridging of position 3 of side chain to position 1 of phenothiazine nucleus decreases neuroleptic activity

2. Amino group modification

1. 3° nitrogen shows maximum potency and 2° or 1° nitrogen shows reduced or abolished activity. N-alkylation with more than one carbon decreases activity.
2. Activity is decreased when dimethylamino group is replaced by pyrolidinyl, morpholinyl, or thiomorpholinyl groups. However, piperidine or piperazine is more potent than dimethylamino group.
3. Bridged piperidinederivates retain high degree of activity although bulky.
4. Introduction of OH, CH3, CH3CH2 OH at C-4 of piperazine results in increased activity.

5. Piperazine and phenothiazines may be esterified with long-chain fatty acids to produce slowly absorbed long-acting lipophilic prodrugs. Due to the slow release from oily deposition, significant activity is retained

6. When N-4 piperazine substituents are as large as phenyl, ethyl, or p-amino phenyl ethyl (e.g. Azaspirane, Chlorspirane) are active.

3. Phenothiazine ring

1.Substitution at C-2 position is optimal for neuroleptic activity. In general, potency at different positions increases in the following order 1 < 4 < 3 < 2. Potency of the various groups increase in the following order OH < H< CN < CH3 <Cl< CF3.

2. Disubstitution (or) trisubstitution of the C-2 substituted drugs results in harmful potency.

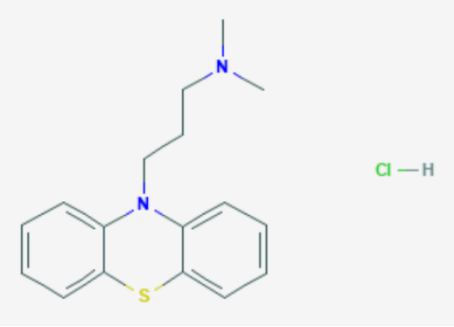
3. CF3 is more potent than Cl, but EPS appears, hence, chlorpromazine is much used, rather than trifluprom azine.

4. The electro-negative chlorine atom at C-2 is responsible for imparting asymmetry to this molecule and the attraction of the amine side chain towards the ring containing the chlorine atom indicate an important structural feature of such molecules.

5. Oxidation of the sulphur at 5th position of antipsychotic phenothiazine
decreases activity.

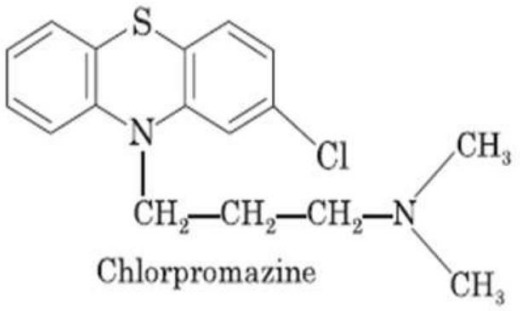
A. Phenothiazines with Aliphatic side chain

a. Promazine hydrochloride.



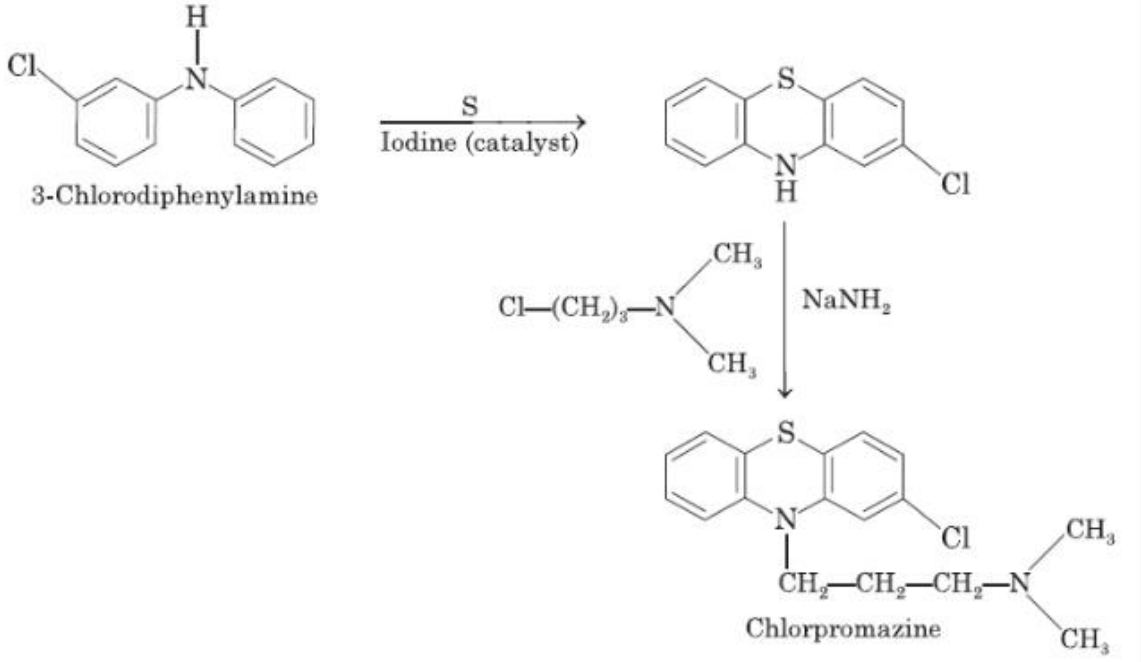
Properties and uses: It is a white or almost white crystalline powder, slightly hygroscopic in nature. It is well soluble in water, alcohol, and methylene chloride. It has low clinical potency, medium extrapyramidal toxicity, high sedative effect, and high hypotensive action. It is used as dopamine receptor antagonist and neuroleptic.

b. Chlorpromazine hydrochloride*



Chlorpromazine

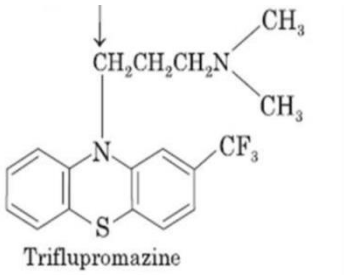
Synthesis



Chlorpromazine

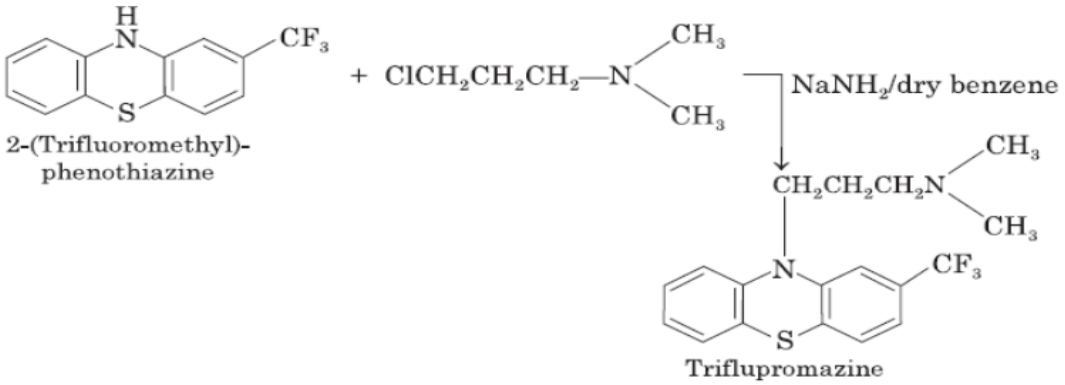
Properties and uses: It is a white or almost white crystalline powder, freely soluble in ethanol and well soluble in water. It is demethylated, sulphoxidized, hydroxylated, and glucuronidated to yield 7-o-glu-nor chlorpromazine. The drug has significant sedative and hypotensive properties, possibly reflecting central and peripheral α1--noradrenergic blocking activity and also effects the peripheral anticholinergic activity, used as dopamine receptor antagonist and neuroleptic. It decomposes on exposure to air and light, hence, it should be stored in well-closed airtight containers and protected from light.

Triflupromazine



Triflupromazine

Synthesis



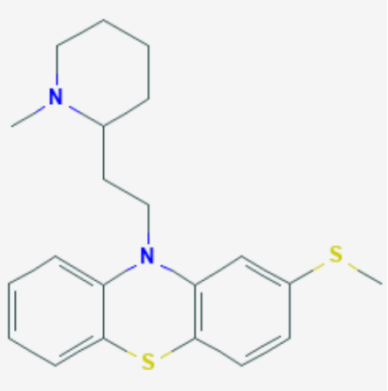
2-(Trifluoromethyl)-phenothiazine

Triflupromazine

Properties and uses: It is a white to pale yellow, crystalline powder, hygroscopic in nature, soluble in alcohol and freely soluble in water. It has lower sedative and hypotensive effects than chlorpromazine, and greater milligram potency as an antipsychotic, used as dopamine receptor antagonist and neuroleptic.

B. Phenothiazines with Piperidine side chain

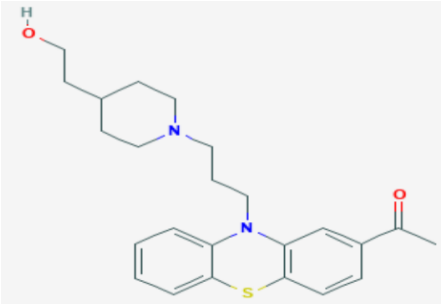
a .Thioridazine hydrochloride



Properties and uses: It is a white or almost white crystalline powder, soluble in ethanol, freely soluble in water and in methanol. The drug exerts minimum antiemetic activity and there by gives rise to minimal extrapyramidal stimulation. The drug has sedative and hypotensive activity in common with chlorpromazine. It is effective in the management and manifestations of psychotic disorders, used as Dopamine receptor antagonist and neuroleptic.

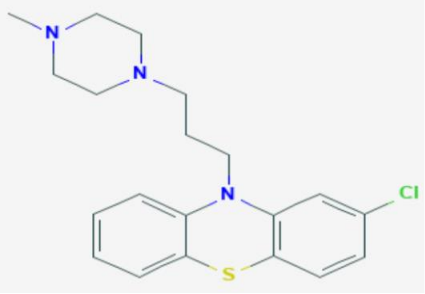
C. Phenothiazines with Piperazine side chain

a. Piperacetazine hydrochloride



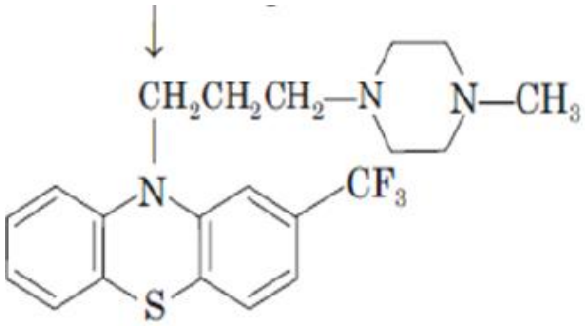
Properties and uses: It is a white or pale yellow crystalline powder, well soluble in water and alcohol. It is mainly used for anti-emetic effect, used as dopamine receptor antagonist and neuroleptic.

b. Prochlorperazine maleate.

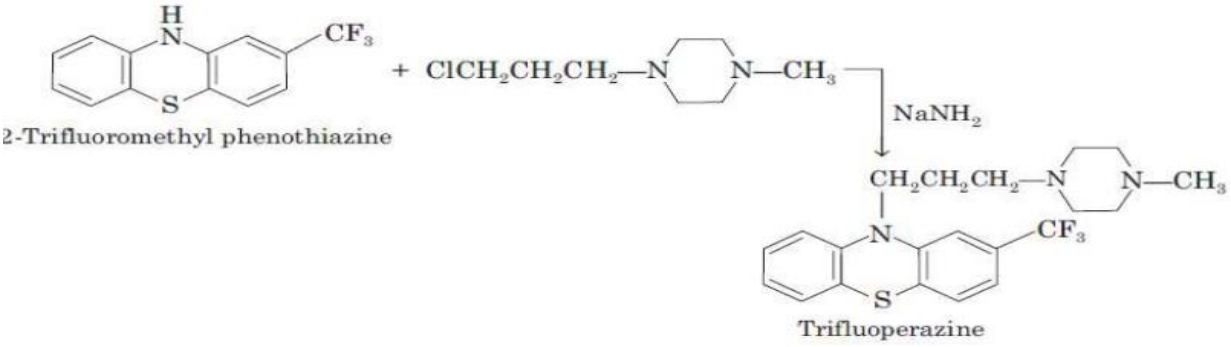


Properties and uses: It is a white or pale yellow crystalline powder, well soluble in water and alcohol. It is more potent on a milligram basis than its alkylamino counterpart, chlorpromazine because of the high prevalence of extra-pyramidal symptom (EPS). It is mainly used for anti-emetic effect, not for its anti-psychotic effect, used as dopamine receptor antagonist and neuroleptic.

c. Trifluoperazine hydrochloride.

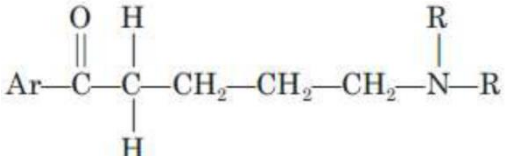


Synthesis



Properties and uses. Trifluoperazine occurs as hydrochloride sale salt. Trifluoperazine HCl is white to pale yellow, crystalline powder. It is freely soluble in water and should be protected from light and moisture. Trifluoperazine has been used to control psychotic disorders. It is effective to control excessive anxiety, tension, aggressiveness and agitation.

2. Butyrophenones: The antipsychotic properties of butyrophenones is due to the presence of the following general structure



1. Intact carbonyl group of butyrophenones is necessary for antipsychotic activity.

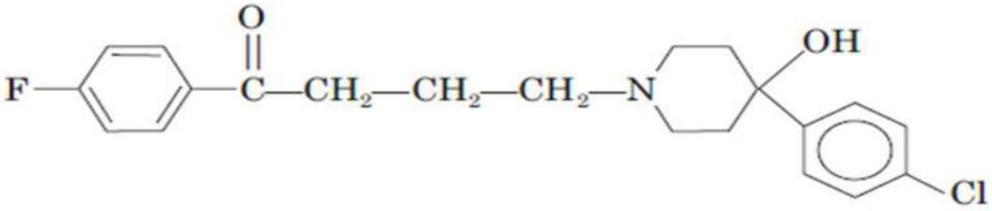
2. Replacement of carbonyl group by functional groups such as CH(OH), —CH (X), —O—, —S, —SO2—etc., decreases activity.

3. All butyrophenones must have a fluorine atom in para-position of aryl group. The antipsychotic activity is markedly decreased by introducing H, Cl, CH3, OCH3 or Ar instead of fluorine at para position in aryl group.

4. Propylene bridge is required for antipsychotic properties. Shortening or lengthening or branching of propylene bridge decreases antipsychotic activity.

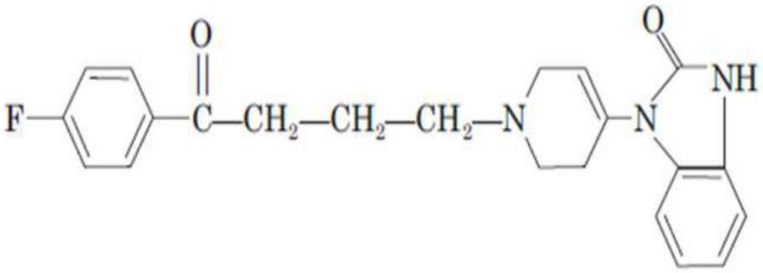
5. Incorporation of basic nitrogen into 6-membered rings is important for CNS depressant activity.

a. Haloperidol.



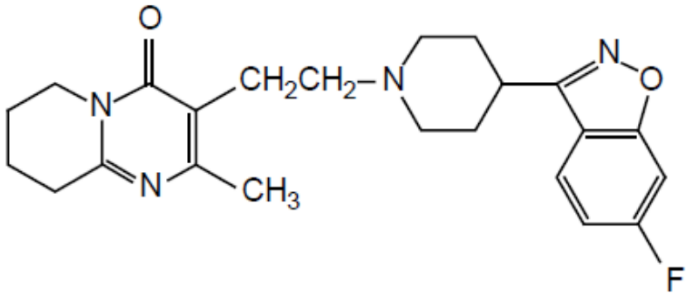
Properties and uses: It is useful in the management of psychotic reactions, hostility, and hyperactivity. It is a drug of choice for Tourett's syndrome. Haloperidol is an effective neuroleptic and also possesses antiemetic properties

b. Droperidol



Properties and uses: It is a white or almost white powder insoluble in water, sparingly soluble in alcohol, freely soluble in dimethylformamide and in methylene chloride. The drug exhibits relatively low therapeutic potency, medium extrapyramidal toxicity, high sedative effect, and above all high hypotensive action. It is frequently used in combination with the nacrotic agents pre-anaesthetically. It is a neuroleptic used as an adjunct to anaesthesia to produce sedation and reduce incidence of nausea and vomiting. Also used as β1 adrenoceptor agonist α-adrenoceptor agonist.

c. Risperidone.

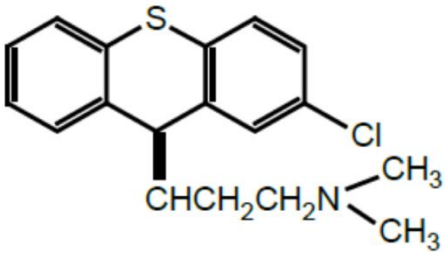


Properties and uses: It is a white or almost white powder, dissolves in dilute acid solutions, insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol. It is a typical antipsychotic and neuroleptic. Its adverse effects include nasal congestion, orthostastic hypotension, insomnia, and possible EPS. Causes more EPS than other atypical agents. May cause weight gain and an increased tendency for glucose intolerance. Risperidone has structural features of hybrid molecules between butyrophenone and trazodone. It is a typical antipsychotic, effective against the negative symptoms of schizophrenia. It should be stored in well-closed airtight containers and protected from light.

3. Thioxanthenes:

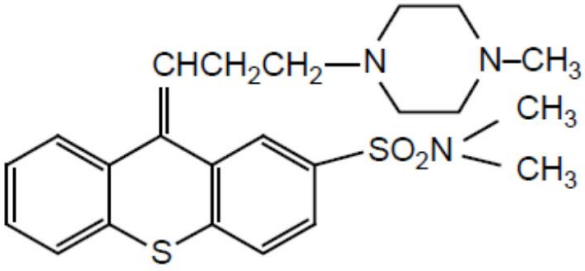
Ring Analogues of Phenothiazeines:

a. Chlorprothixene.



Properties and uses: It is a white or almost white crystalline powder, slightly soluble in methylene chloride, and soluble in water and alcohol. It is used in the treatment of acute and chronic schizophrenia, psychotic and other conditions in which anxiety, agitation, and tension predominate

b. Thiothixene.

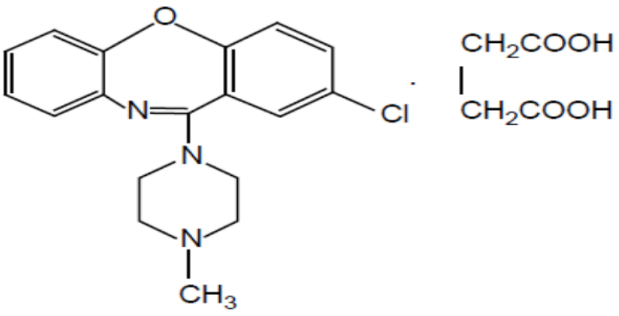


Properties

Properties and uses: White, or nearly white crystalline powder with slight odour, and affected by light, soluble in water, anhydrous alcohol, or chloroform, practically insoluble in benzene, acetone, or ether. The substituent in the second position produces Z and E isomers. The Z isomers are the more active antipsychotic isomers. It was introduced as an antipsychotic agent useful in the management of schizophrenia and other psychotic states. It is also helpful in the management of secondary symptoms of schizophrenia, such as hallucinations, tension, and suspiciousness. It also shows antidepressant property.

4. Other Hetrocyclics

a. Loxapine succinate

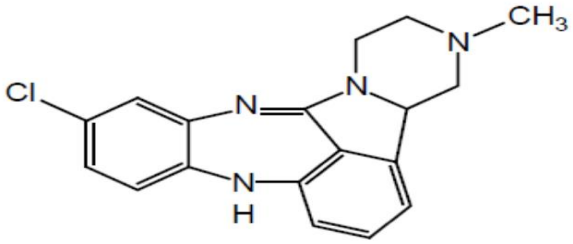


Properties

Properties and uses: Exist as white to off-white crystalline powder, slightly soluble in water or alcohol. It may give rise to possible anticholinergic and antiadrenergic activity It is used for symptomatic control of schizophrenia.

5. Atypical antipsychotics

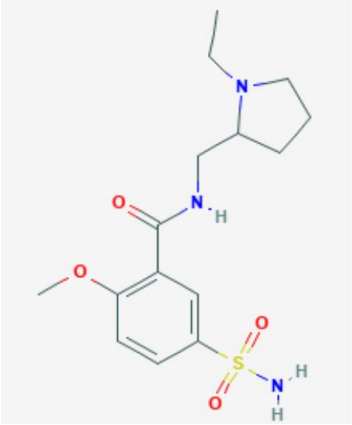
a. Clozapine.



Properties and uses: It is a yellow crystalline powder, dissolves in dilute acetic acid, insoluble in water, freely soluble in methylene chloride, and soluble in alcohol. It has more affinityfor D1 and less for D2 dopamine receptors. It may have its unique profi le due to the blockade of D1 receptors and M1 muscarinic activity. It has high potentially fatal agranulocytosis. Other adverse side effects include drowsiness, dizziness, and doserelatedseizures. It is effective in individuals suffering from disorganization. For example, loose associations, inappropriate affect, incoherence, and reduction in rational thought processes.

6. Benzamides:

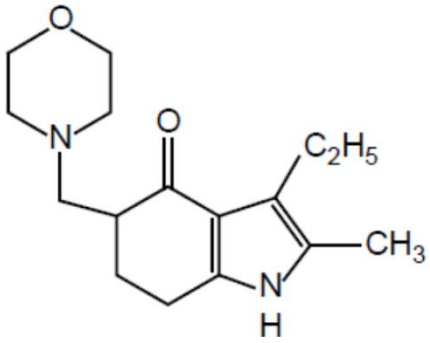
a. Sulpieride.



Properties and uses: Exists as white crystals, freely soluble in water or alcohol.mSulpiride, sold under the brand name Dogmatil among others, is an atypical antipsychotic medication of the benzamide class which is used mainly in the treatment of psychosis associated with schizophrenia and major depressive disorder.

7. Beta amino ketones:

a. Molindone hydrochloride



Properties and uses: Exists as white crystals, freely soluble in water or alcohol, it is a potent antipsychotic as trifluoperazine and all the side effects resemble those of the phenothiazines. It is used in the treatment of schizophrenia and other psychosis.

Anticonvulsants

The epilepsies are a group of disorders characterized by chronic, recurrent, paroxysmal changes in neuralgic function caused by abnormalities in electrical activity of the brain. They are one of the common neuralgic disorders, estimated to affect 0.52% of the population and can occur at any age. The terms convulsion and seizure are often used interchangeably and basically have the same meaning. For many years, treatment options for epilepsy were limited. Over the last decade, however, many new pharmacological therapies have been introduced, and several more are in development.Anticonvulsants are a diverse group of pharmacological agents used in the treatment of epileptic seizures. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder and borderline personality disorder, since many seem to act as mood stabilizers, and for the treatment of neuropathic pain. Types of Epilepsy. There are four types of epilepsy. Certain signs and symptoms characterize each type ;

(a) Grand Mal. Grand Mal is the most common type of epilepsy. In this type of epilepsy, the person often experiences an aura (this can consist of certain sounds, fear discomfort) immediately before a seizure. Then the patient loss consciousness and has tonic-clonic convulsions. The seizures generally last from 2 to 5 minutes.

(b) Petit Mal. This type of epilepsy is most frequently found in children. Brief periods of blank spells or loss of speech characterizes petit mal. During the seizures, which usually last from 1 to

30 seconds, the person stops what he is doing and after the seizure resumes what he was doing before the seizure. Many persons are not aware that they have had a seizure.

(c) Jacksonian (Focal). This type of epilepsy is rare. It is usually associated with lesion of a certain part of the brain (cerebral cortex). Jacksonian epilepsy is characterized by focal or local clonic type convulsions of localized muscle groups (for example, thumb, big toe, and so forth). The seizures normally last from 1 to 2 minutes.

(d) Psychomotor. Psychomotor epilepsy is rare. It is characterized by periods of abnormal types of behavior (for example, extensive chewing or swallowing). Psychomotor seizures occur most often in children 3 years of age through adolescence. The individual may experiencean aura with perceptual alterations, such as hallucinations or a strong sense of fear. Thelocalized seizures may advance to generalized convulsions with resultant loss of consciousness.

Classification of anticonvulsants

1. Barbiturates: Phenobarbitone, Methabarbital.

2. Hydantoins: Phenytoin*, Mephenytoin, Ethotoin.

3. Oxazolidine diones: Trimethadione, Paramethadione .

4. Succinimides: Phensuximide, Methsuximide, Ethosuximide*

5. Urea and monoacylureas: Phenacemide, Carbamazepine*

6. Benzodiazepines: Clonazepam

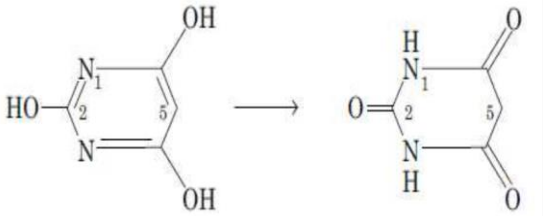
7. Miscellaneous: Primidone, Valproic acid , Gabapentin, Felbamate

1. Barbiturates: Barbiturates are central nervous system (CNS) depressants (medicines that cause drowsiness).Barbiturates produce a wide spectrum of CNS depression, from mild sedation to coma,and have been used as sedatives, hypnotics, anesthetics and anticonvulsants. But, they can be addictive and abused. Excessive doses can cause depression, slurred speech, slowed reflexes and confusion.urate, diethylbarbituric acid, was synthesized by Fischer and Mering in 1903. A number of other hypnotic-sedative barbiturates were developed and tested, but all had too slow onset and too long duration of action. In 1932 Weese and Schapff synthesized the first rapid onset, short duration barbiturate, the methylated oxybarbiturate hexobarbital. Unfortunately, hexobarbital caused undesirable excitatory side effects. Thiopental was first administered by Waters (Wisconsin) and Lundy (Mayo Clinic) in 1934.

Thiopental proved to be fast and brief acting and devoid of excitatory side effects. In 1950 Brodie et al demonstrated that barbiturate hypnotic-sedative activity was terminated not by metabolism, but by redistribution from centra neural sites of action to other body tissues. It was later shown (Price, 1960) that during prolonged infusions, redistribution becomes less effective because redistribution sites approach equilibrium.

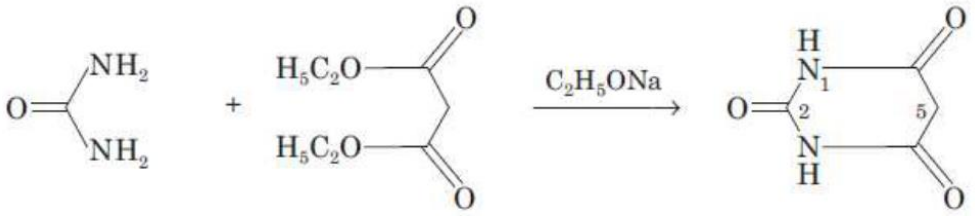
Chemistry

1. Barbiturates are derivatives of barbituric acid (2,4,6- trioxyhexahydropyrimidine) which is devoid of hypnotic and sedative activities.



Keto-enol tautomerism of barbituric acid

2. Barbituric acid may be described as a "cyclic ureide of malonic acid". Barbituric acid can be made by condensing urea with ethyl malonate in presenceof sodium ethoxide.



Urea + Ethylmalonate → Barbituric acid

SAR

1. Hypnotic activity. Side chains at position 5 (especially if one of them is branched) is essential for activity.

2. Potency and duration of action. Length of side chain at position 5 influences potency and duration of action. Ex: Secobarbital and thiamylal are slightly more potent than pentobarbital and thiopental, respectively.

3. More rapid onset and shorter duration of action. Sulfur instead of oxygen atom at postion 2 has more rapid onset of action but shorter duration. Ex: thiamylal and thiopental have more rapid onset and shorter duration of action than secobarbital and pentobarbital, respectively.

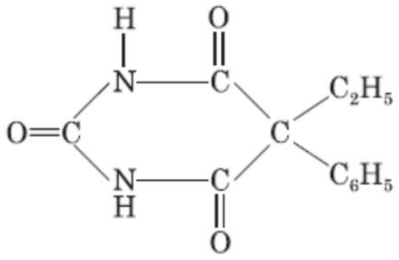
4. Increased incidence of excitatory side effects. Methylation at position 1 (methohexital) enhances excitatory side effects.

5. Increased potency, rate of onset and short action. Generally an increase in the lipophilicity of the compound results in more rapid onset of action accompanied with an increase in potency.

6. Introduction of polar groups (hydroxyl, keto, amino, or carboxyl) into C-5- alkyl sidechain makes the compound more hydrophilic in nature. Due to the polar nature, hydrophilic barbiturates do not dissolve in microsomal membranes of liver and are excreted.

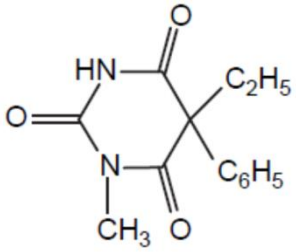
7. Branched, cyclic or unsaturated side chain at C-5 position generally reduce the duration of action due to an increased ease of metabolic conversion to a more polar, inactive metabolite.

a. **Phenobarbitone.**



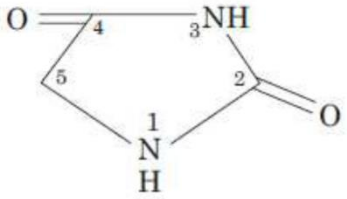
Properties and uses: Phenobarbital sodium is a hygroscopic substance. It is a white, crystalline powder, freely soluble in water and also soluble in alcohol. It is used as sedative, hypnotic and antiepileptic (drug of choice in the treatment of grandmal and petitmal epilepsy). It is useful in nervous and related tension states. An overdose of it can result in coma, severe respiratory depression, hypotension leading to cardiovascular collapse, and renal failure.

b.Methabarbital.



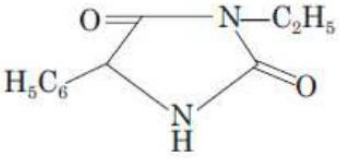
Properties and uses: It is a white, crystalline powder, odourless, with a bitter taste, and a saturated is solution acid to litmus. Soluble in water, alcohol, chloroform, and in solutions of alkali hydroxides or carbonates. Mephobarbitone is a strong sedative with anticonvulsant action, but a relatively mild hypnotic. Hence, it is used for the relief of anxiety, tension, and apprehension, and is an antiepileptic in the management of generalized tonic clonic and absence seizure

1. Hydantoins are cyclic monoacylureas. They possess imidazoline-2, 4-dione heterocyclic system. Hydantoins are structurally related to barbiturates, differing in lacking the 6-oxo moiety**.**

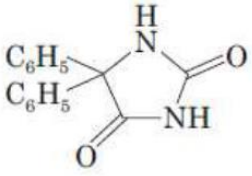


2. Hydantoins are weakly acidic than barbiturates. Thus aqueous solution of sodium salts provide strongly alkaline solutions.

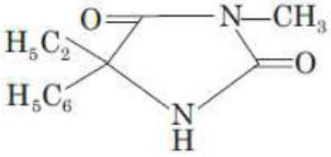
3. A clinically useful hydantoin possess an aryl substituent at the 5-position.



Ethotoin



Phenytoin



Mephenytoin

4. Hydantoin derivatives possessing of lower alkyl substituents have absence activity.

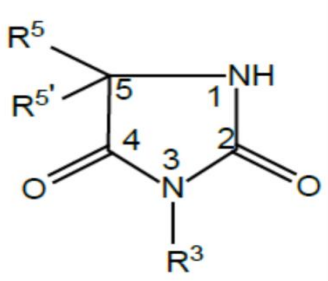
5. Hydantoins activate Na+-K+-dependent and Ca++-dependent ATPase and increase Na+ transport.

SAR

1. 5-phenyl or other aromatic substitution is essential for activity.

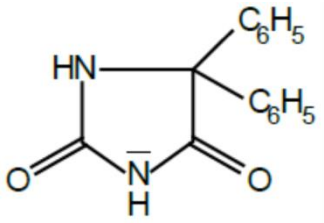
2. Alkyl substituent at position 5 may contribute to sedation, a property absent in phenytoin.

3. Among other hypnotics 1,3-disubstituted hydantoins, exhibit activity against chemically induced convulsion, while it remains ineffective against electric shock induced convulsion

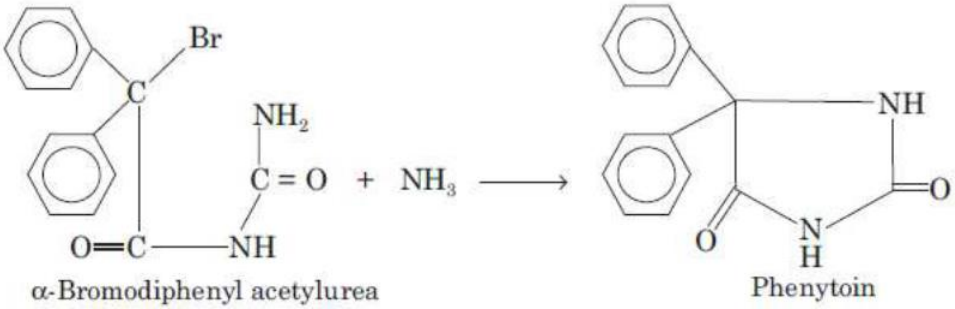


Mode of action: Hydantoins prevent repetitive detonation of normal brain cells during depolarization shift. This is achieved by prolonging the inactivated state of voltage gate sensitive sodium channels and governs the refractory period of specific neurons, moreover, reduces the calcium infl ux and inhibits the glutamate activity. Intracellular storation of Na+ leads to the prevention of repetitive firing.

a. Phenytoin



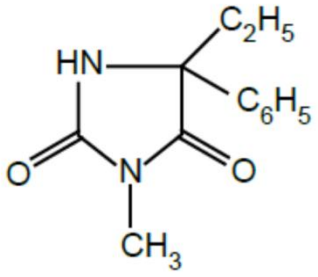
Synthesis



Properties and uses: It is a white crystalline powder, slightly hygroscopic, insoluble in methylene chloride, soluble in water and alcohol. Phenytoin is the first anticonvulsant in which it was clearly demonstrated that anticonvulsant activity could definitely be separated from sedative-hypnotic activity. A common side effect is gingival hyperplasia, a reaction that seldom

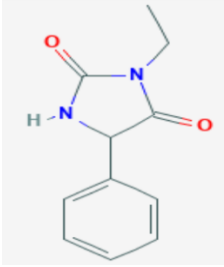
occurs with me phenytoin, and apparently, never with cardiac arrhythmias. It is one of the most widely used antiepileptic agents and it is effective in most forms of epilepsy, except absence of seizures.

b. Mephenytoin

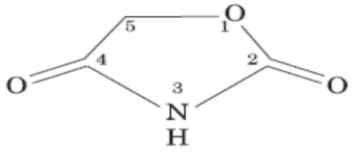


Properties and uses: It is one of the fi rst hydantoin introduced into therapy. It is converted into N-demethyl metabolite 5-phenyl-5-ethyl hydantoin It was introduced as a sedative-hypnotic and anticonvulsant under the name Nirvanol, but it was withdrawn because of toxicity.

c.Ethotoin

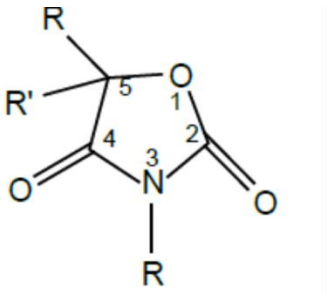


3. Oxazolidinediones : Oxazolidine-2, 4-dione is analogous to hydantoin differs in having of oxygen atom at position 1 instead of NH. Ex: Trimethadione, paramethadione.



SAR

1. Replacement of the -NH group at position 1 of the hydantoin system with an oxygen atom yields the oxazolidine 2-2,4-dione system.

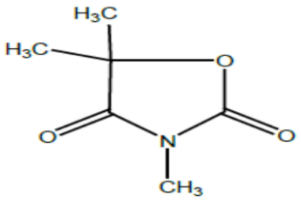


2. 3,5,5-Trimethadione (tridione) was the first drug introduced specifically for treating absence seizures. It is also important as a prototype structure.

3. The nature of the substituent on C-5 is important, example, lower alkyl substituents towards antipetitmal activity while acyl substituents towards antigrandmal activity.

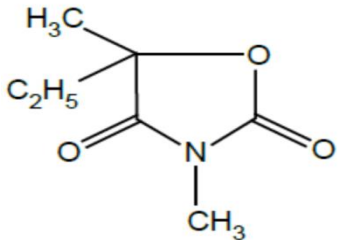
4. The N-alkyl substituent does not alter or afford the activity since all the clinically used agents from this class undergo N-dealkylation in metabolism.

a.Trimethadione



Properties and uses: It is a colourless or almost colourless crystals, soluble in water and alcohol. It is first drug introduced specifi cally for treating absence seizures. It is important as a prototype structure for antiabsence seizure compounds. It is metabolized by N-demethylation to putative active metabolite dimethadone and it is further excreted unchanged. It is used as an antipetitmal agent. It causes nephrosis, aplastic anaemia and bone marrow depression.

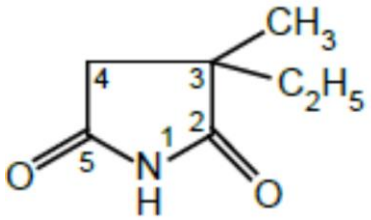
b.Paramethadione .



Properties and uses: It is an oily liquid, slightly soluble in water and freely soluble in ethanol. It is used as an anticonvulsant.

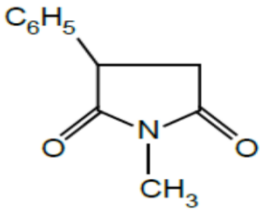
4. Succinimides:

SAR



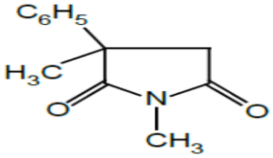
1. The activity of antiepileptic agents, such as the oxazolidine 2,4-dione with substituted succinamides (CH2 replace O) was logical choice for synthesis and evaluation.
2. N-demethylation occurs to yield the putative active metabolite.
3. Both phensuximide and the N-demethyl metabolite are inactivated by p- hydroxylation and conjugation.

a. Phensuximide.



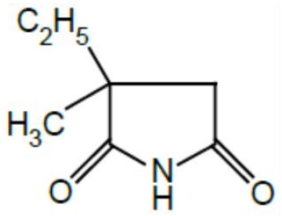
Properties and uses: It is a crystalline solid, soluble in water and freely soluble in ethanol. N-demethylation occurs to yield active metabolite, both phensuximide and N-demethyl metabolites are inactived by para hydroxylation and conjugation. It has low potency and is therefore relegated to secondary status. The phenyl substituent confers some activity against generalized tonic clonic and partial seizures.

b. Methsuximide

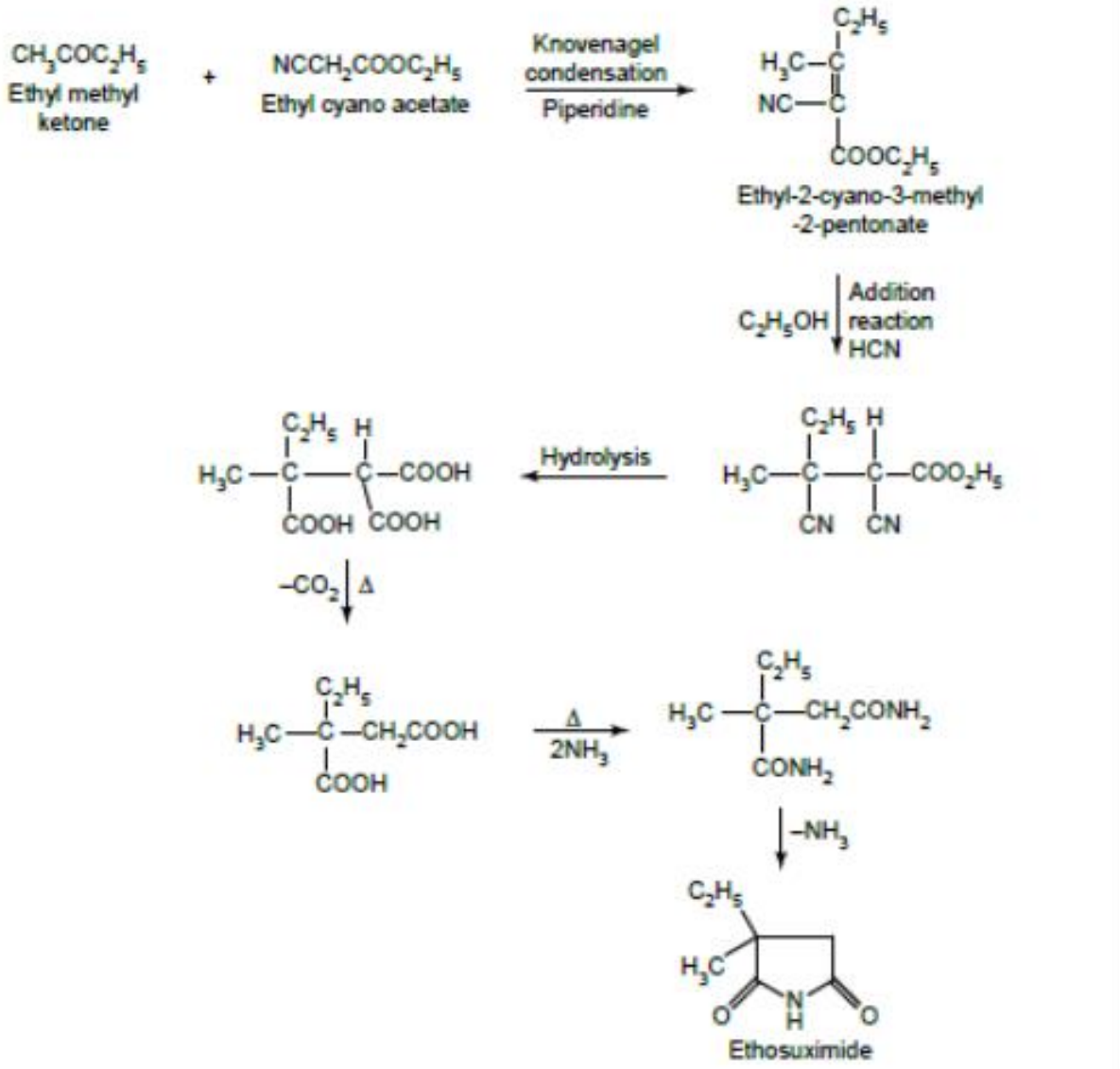


Properties and uses: It is more active than phensuximide, and used in thetreatment of petitmal epilepsy. It is metabolized into N-demethylsuximide and the metabolite is also an active compound.

c. Ethosuximide*



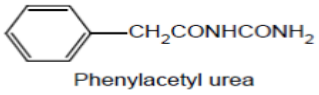
Synthesis



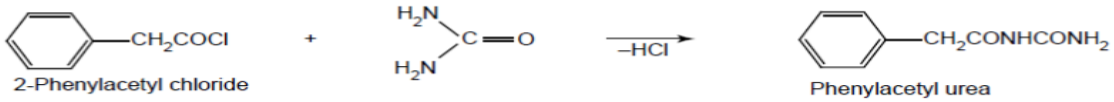
Properties and uses: It is a white or an almost white powder or waxy solid. Freely soluble in water, ethanol, and methylene chloride. It is metabolized into 3-(1-hydroxyethyl) compound. It conforms very well to the general structural pattern for antiabsence activity. The drug is more active and less toxic thanTrimethadione. It is a calcium-T channel blocking drug, effective in the cure of petitmal epilepsy.It should be stored in well-closed airtight containers.

5. Urea and monoacylureas

a. Phenacemide

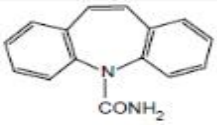


Synthesis

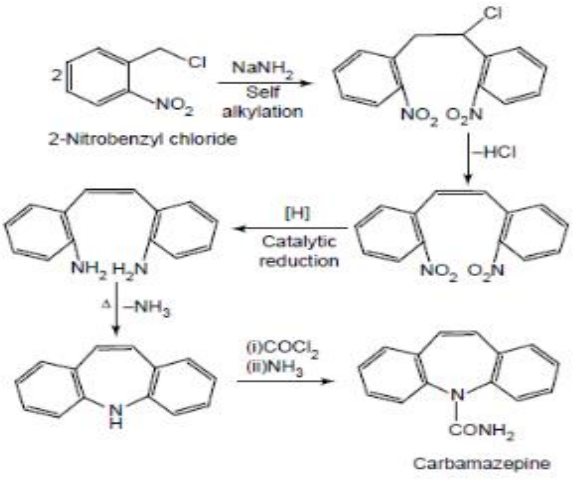


Uses: Used mainly in psychomotor epilepsy.

b.Carbamazepine*



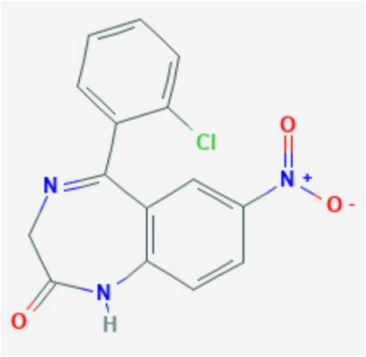
Synthesis



Propeties and uses: It is a white or almost white crystalline powder and it shows polymorphism, slightly soluble in water, freely soluble in methylene chloride, but sparingly soluble in acetone and ethanol ,antiseizure agent, but is toxic, used to treat partial seizures and grandmal seizures. It is also useful in the treatment of pain associated with trigeminal neuralgia.

6. Benzodiazepines: Benzodiazepines are the most commonly used anxiolytics and hypnotics. They act at benzodiazepine receptors, which are associated with gamma-aminobutyric acid (GABA) receptors. Clinically useful benzodiazepines to treat anxiety are diazepam, chlordiazepoxide, oxazepam, prazepam, alprazolam, lorazepam, chlorazepate

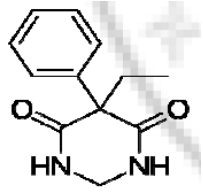
a. Clonazepam

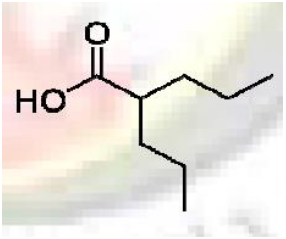


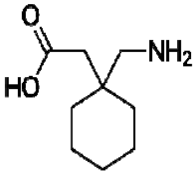
Properties and uses: A triazolobenzodiazepine derivative that structurally resembles alprazolam and triazolam. Itis useful in the management of insomnia.

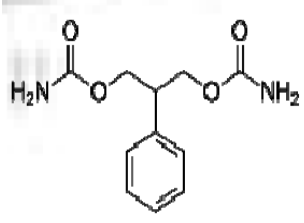
7. Miscellaneous:

a. Primidoneb **b. Valproic acid** **c. Gabapentind** **d. Felbamate**









Long Questions: (10 Marks)

1. Classify sedative hypnotic drugs. Give the chemical feature of each class.
2. Explain MOA, SAR and therapeutic uses of the following drugs.

Chlordiazepoxide, Alprazolam,Oxazepam and Diazepam.

3. Explain MOA and SAR of Barbiturates with examples.
4. Give SAR of phenothiazines with examples and structures.
5. Write a note on butyrophenones.
6. Write about chlorpromazine in detail along with its synthesis.
7. Classify anticonvulsant drugs and discuss its MOA in brief.
8. Write a note on benzodiazepam.
9. Write about valporic acid as anticonvulsant.
10. Write a note on phenothiazines.

Short questions: (5 Marks)

1. Write some clinical uses of benzodiazepines.
2. Differentiate between sedatives and hypnotics.
3. How does benzodiazepine affect the action of GABA?
4. Write the structure of haloperidol.
5. Write the structure and uses of Phenobarbital.
6. What is depolarization?
7. Write the side effects of chlorpromazine.
8. What do you mean by thioxanthenes.
9. Write the synthesis of Chlorpromazine.
10. Write a synthetic scheme of phenytoin.