Chapter 2

Sedatives and Hypnotics

INTRODUCTION

Sedatives are central nervous system (CNS) depressant drugs that reduce excitement, tension, and produce relaxation. Hypnotics are drugs that depress the CNS and produce sleep similar to that of natural sleep. Both sedative and hypnotic action may reside in the same drug. At lower dose, the drug may act as sedative, while at a higher dose the same drug may act as hypnotic.

Agents used as sedatives and hypnotics include a large number of compounds of diverse chemical structure given in classification and pharmacological properties, which have the common ability to induce a nonselective, reversible depression of the CNS.

Sedative and hypnotic drugs are frequently used in preanaesthetic medication and as an adjunctive therapy in psychiatry. A large number of sedative and hypnotic drugs cross the placental barrier, consequently their chronic use during pregnancy may cause withdrawal effect in the newborn infant. Many of these substances are excreted into the breast milk, and hence, their chronic use during breast-feeding may cause sedation to the infant.

Sedatives and hypnotics are also used as the following:

- antianxiety agents
- anticonvulsants
- muscle relaxants
- general anaesthetics
- preanaesthetic medication
- antipsychiatrics
- to potentiate analgesic drugs
- adjuvant to anaesthesia
- a co-drug in the treatment of hypertension

The clinical pharmacology of the sedatives and hypnotics include the following:

Treatment of Anxiety States

The psychological behaviour and physiological responses that characterizes anxiety may be in many forms. Typically, the psychic awareness of anxiety is accompanied by an enhanced motor tension and autonomic hyperactivity. The benzodiazepines continue to be widely used for the management of anxiety states. Since anxiety symptoms may be relieved by many benzodiazepines, it is not easy to demonstrate the superiority of one individual drug over another.

Treatment of Sleep Problems

Nonpharmacological therapies are sometimes useful for sleep problems including proper diet and exercise, avoiding stimulants before retiring and ensuring a comfortable sleeping environment. In some cases, the patient will need and should be given a sedative and hypnotic. Benzodiazepines can cause a dose-dependent decrease in both rapid eyeball movement and non rapid eyeball movement and slowly cause sleep, although to a lesser extent than barbiturates. Zolpidem and zaleplon are less likely to change sleep pattern than the benzodiazepines.

Other Therapeutic Uses

Long-acting drugs such as chlordiazepoxide, diazepam, and to a lesser extent phenobarbital are administered in progressively decreasing doses to patients during withdrawal from psychological dependence on ethanol or other sedative hypnotics. Meprobamate and other benzodiazepines are frequently used as skeletal muscle relaxants.

MOLECULAR BASIS OF INHIBITORY NEUROTRANSMITTERS

Gamma-aminobutyric acid (GABA) is the main inhibitory transmitter in the brain. GABA is formed from glutamate by the action of glutamic acid decarboxylase. Its action is terminated by reuptake, but also by deamination catalyzed by GABA transaminase. There are two types of GABA receptors, that is, $GABA_A$ and $GABA_B$. $GABA_A$ receptors, which occur mainly postsynaptically, are directly coupled to chloride channels, opening of which reduces membrane excitability. Other drugs that interact with GABA receptors and channels include benzodiazepines, neurosteroids, including endogenous progesterone metabolites and other CNS depressants, such as barbiturates, which facilitate the action of GABA. $GABA_B$ receptors are G protein-coupled receptors linked to the inhibition of cAMP formation. They cause pre and postsynaptic inhibition by inhibiting Ca^{2+} channel openings and increasing K^+ conductance. Baclofen is a $GABA_B$ receptor agonist used to treat spasticity. Glycine is another inhibitory transmitter functionally similar to GABA action.

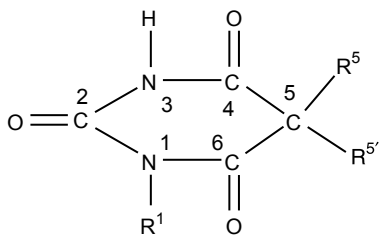
CLASSIFICATION

Sedatives and hypnotics are classified on the basis of their chemical structure, as follows:

1. Barbiturates
2. Benzodiazepines
3. Acyclic hypnotics containing nitrogen
4. Cyclic hypnotics containing nitrogen
5. Alcohols and aldehydes
6. Acetylene derivatives

7. Miscellaneous
   a. Inorganic salts
   b. Acids and esters
   c. Antihistaminic and anticholinergic agents
   d. Suphones
   e. Plant extracts
   f. Endogenous substances
   g. Other opioids: morphine, pethidine
   h. Neuroleptics: chlorpromazine, triflupromazine
8. Newer agents

1. Barbiturates

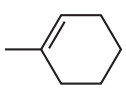


Barbiturates are further classified on the basis of duration of their action.

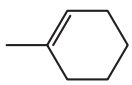
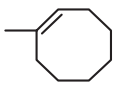
a. Long-acting barbiturates (6 h or more than 6 h)

Name	R^1	R^5	$R^{5'}$
Barbital	–H	$-C_2H_5$	$-C_2H_5$
Phenobarbital	–H	$-C_2H_5$	$-C_6H_5$
Mephobarbital	$-CH_3$	$-C_2H_5$	$-C_6H_5$
Metharbital	$-CH_3$	$-C_2H_5$	$-C_2H_5$

b. Intermediate-acting barbiturates (3–6 h)

Name	R^1	R^5	$R^{5'}$
Amobarbital	–H	$-C_2H_5$	$-CH_2CH_2CH(CH_3)(CH_3)$
Butabarbital	–H	$-C_2H_5$	$-CH(CH_3)-CH_2-CH_3$
Aprobarbital	–H	$CH_2=CH-CH_2-$	$(CH_3)_2CH-$
Talbutal	–H	$CH_2=CH-CH_2-$	$CH_3CH_2CH(CH_3)-$
Butalbital	–H	$CH_2=CH-CH_2-$	$(CH_3)_2CHCH_2-$
Hexobarbital	$-CH_3$	$-CH_3$	

c. Short-acting barbiturates (less than 3 h)

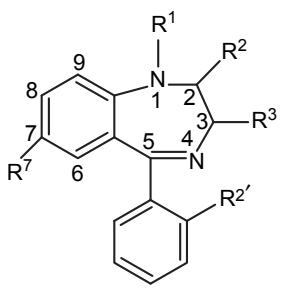
Name	R^1	R^5	$R^{5'}$
Pentobarbital	–H	$-C_2H_5$	$CH_3CH_2CH_2CH(CH_3)$–
Secobarbital	–H	$CH_2=CH-CH_2-$	$CH_3(CH_2)_2CH(CH_3)$–
Cyclobarbital	–H	$-C_2H_5$	
Heptabarbital	–H	$-C_2H_5$	

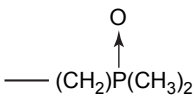
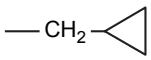
d. Ultra short-acting barbiturates (15 min)

Name	R^1	R^5	$R^{5'}$
Thiopentone	–H	$-C_2H_5$	$CH(CH_2)_2CH_3$ CH_3

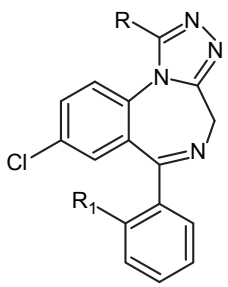
(At C – 2 = S instead of = O)

2. Benzodiazepines

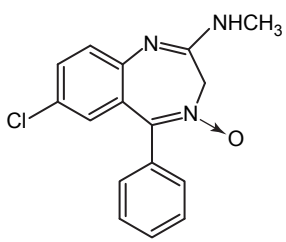


Name	R^1	R^2	R^3	R^7	$R^{2'}$
Diazepam	$-CH_3$	= O	–H	–Cl	–H
Oxazepam	–H	= O	–OH	–Cl	–H
Chlordesmethyl diazepam	–H	= O	–H	–Cl	–Cl
Fosazepam		= O	–H	–Cl	–H
Prazepam		= O	–H	–Cl	–H
Nitrazepam	–H	= O	–H	$-NO_2$	–H
Nordiazepam	–H	= O	–H	–Cl	–H
Nimetazepam	$-CH_3$	= O	–H	$-NO_2$	–H
Flunitrazepam	$-CH_3$	= O	–H	$-NO_2$	–F
Flurazepam	$-(CH_2)_2N(C_2H_5)_2$	= O	–H	–Cl	–F
Quazepam	$-CH_2CF_3$	= S	–H	–Cl	–F
Halozepam	$-CH_2CF_3$	= O	–H	–Cl	–H
Temazepam	$-CH_3$	= O	–OH	–Cl	–H
Lorazepam	–H	= O	–OH	–Cl	–Cl
Clonazepam	–H	= O	–H	$-NO_2$	–Cl
Doxefazepam	$-CH_2OH$	= O	–OH	–Cl	–F

Triazolo benzodiazepines



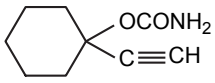
Name	R	R_1
Alprazolam	$-CH_3$	–H
Triazolam	$-CH_3$	– Cl
Estazolam	–H	–H



Chlordiazepoxide

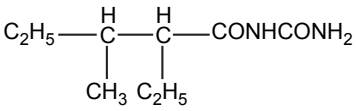
3. Acyclic hypnotics containing nitrogen (acyclic ureides)

a. Urethanes

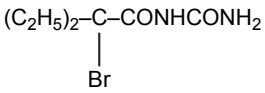


Ethinamate

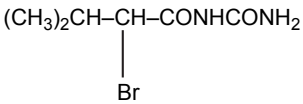
b. Ureides



Capuride

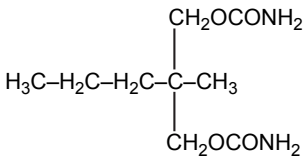


Carbromal



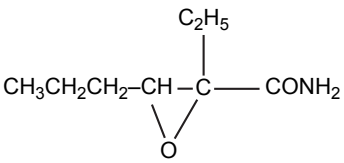
Bromovalurea

c. Carbamates

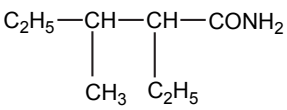


Meprobamate

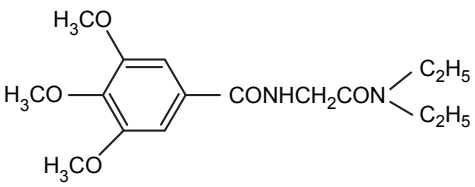
d. Amides



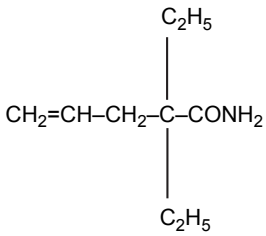
Oxanamide



Valnoctamide



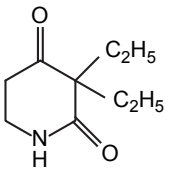
Trimethoxy benzglycine



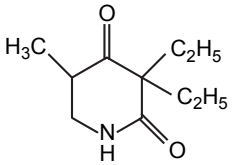
Diethyl allyl acetamide

4. Cyclic hypnotics containing nitrogen

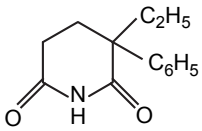
a. Piperidinediones



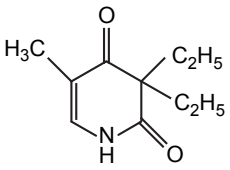
Dihydroprylone



Methyprylone

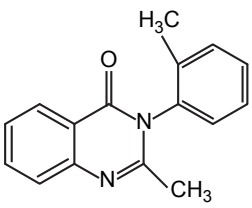


Glutethimide

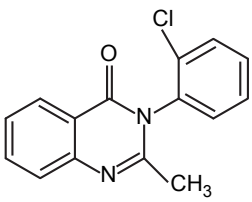


Ethypicone

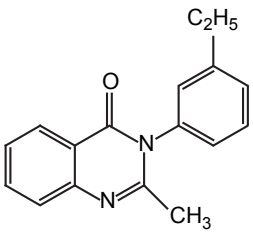
b. Quinazolinones



Methaqualone

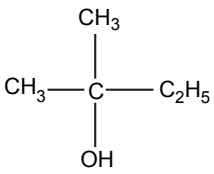


Mecloqualone

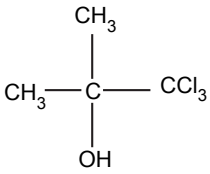


Ethinazone

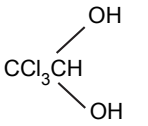
5. Alcohols and aldehydes



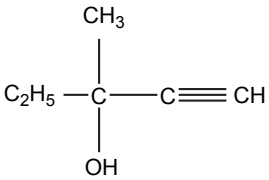
Amylene hydrate



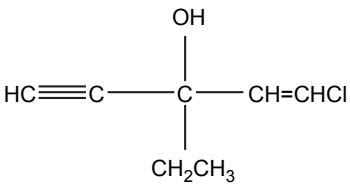
Chlorbutanol



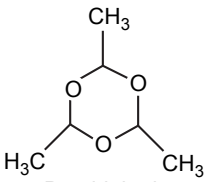
Chloral hydrate



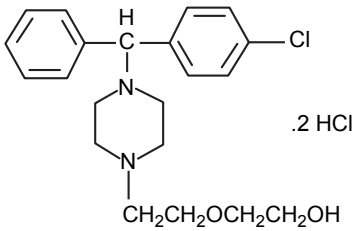
Methyl pentynol



Ethychlorvynol

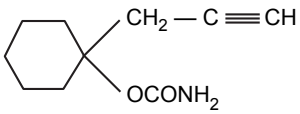


Paraldehyde

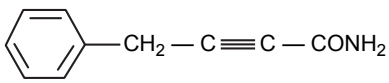


Hydroxyzine HCl

6. Actylene derivatives



Hexapropymate



Carfimate

7. Miscellaneous

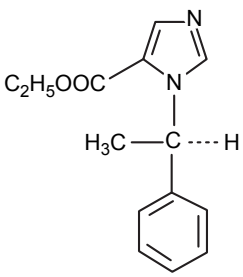
a. Inorganic salts

KBr, magnesium sulphate

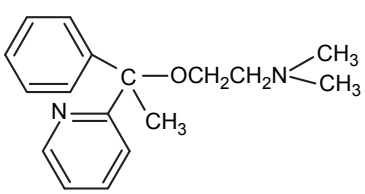
b. Acids and esters

Tryptophan, 5-hydroxy tryptophan

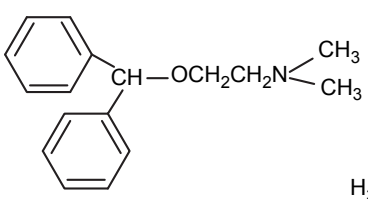
Etomidate



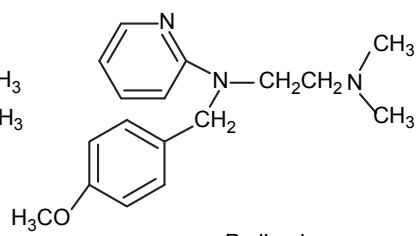
c. Antihistamines and anticholinergics



Doxylamine



Diphenhydramine



Pyrilamine

d. Sulphones

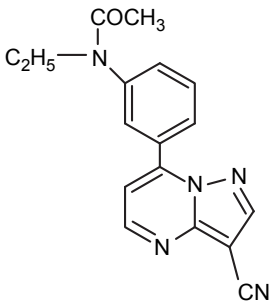
Toxic-not used

e. Plant extracts of

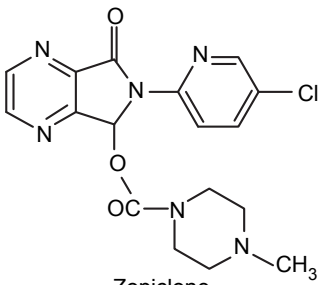
Radix valerianae
Rauwolfia serpentina
Avana sativa
Glandula lupuli

f. Endogenous substances: peptides

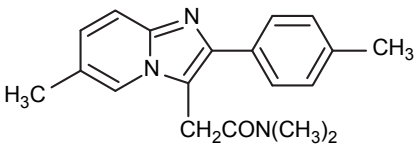
8. Newer agents



Zaleplon



Zopiclone



Zolpidem

SYNTHESIS AND DRUG PROFILE

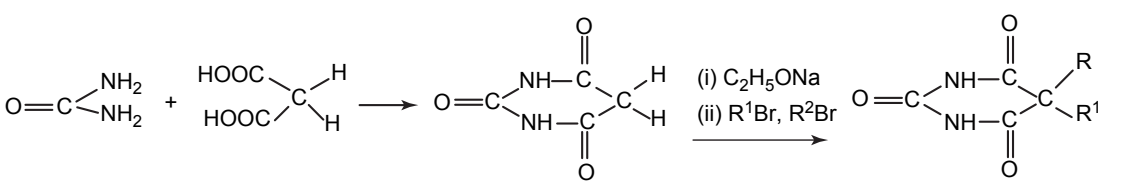
1. Barbiturates

Barbiturates are derivatives of barbituric acid. Their hypnotic activity is conferred by the replacement of H-atom attached to the C-5 position by aryl or alkyl radicals. They are generally synthesized by adopting the following route of synthesis.

Mode of action: Barbiturates primarily act on GABA: benzodiazepin receptor Cl^- channel complex and potentiate GABA ergic inhibitory action by increasing the lifetime of Cl^- channel opening induced by GABA. Barbiturates do not bind to benzodiazepine receptor promptly, but it binds to another site on the same macromolecular complex to exert the GABA ergic facilitator actions. The barbiturate site appears to be located on α and *ß* subunit. At high concentrations, barbiturates directly increases Cl^- conductance and inhibit Ca^{2+} dependent release of neurotransmitters and they also depress glutamate-induced neuronal depolarization.

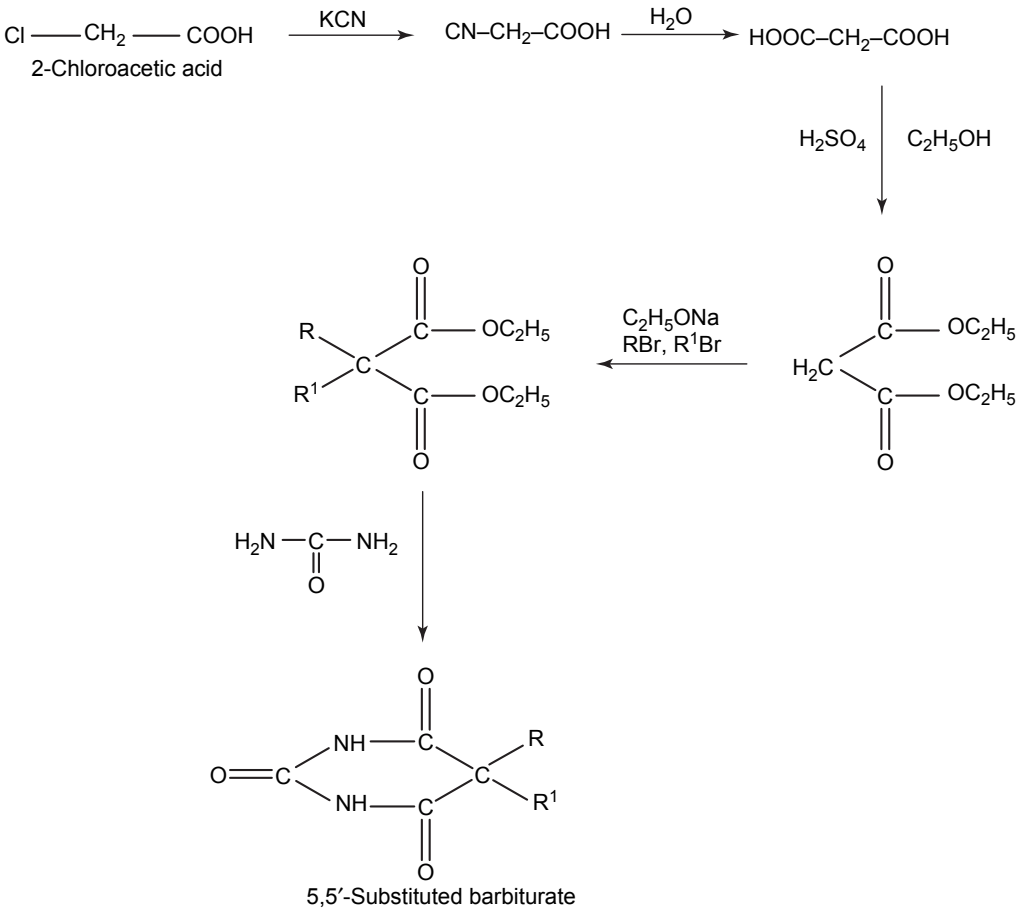
Synthesis

Route I: From urea and malonic acid



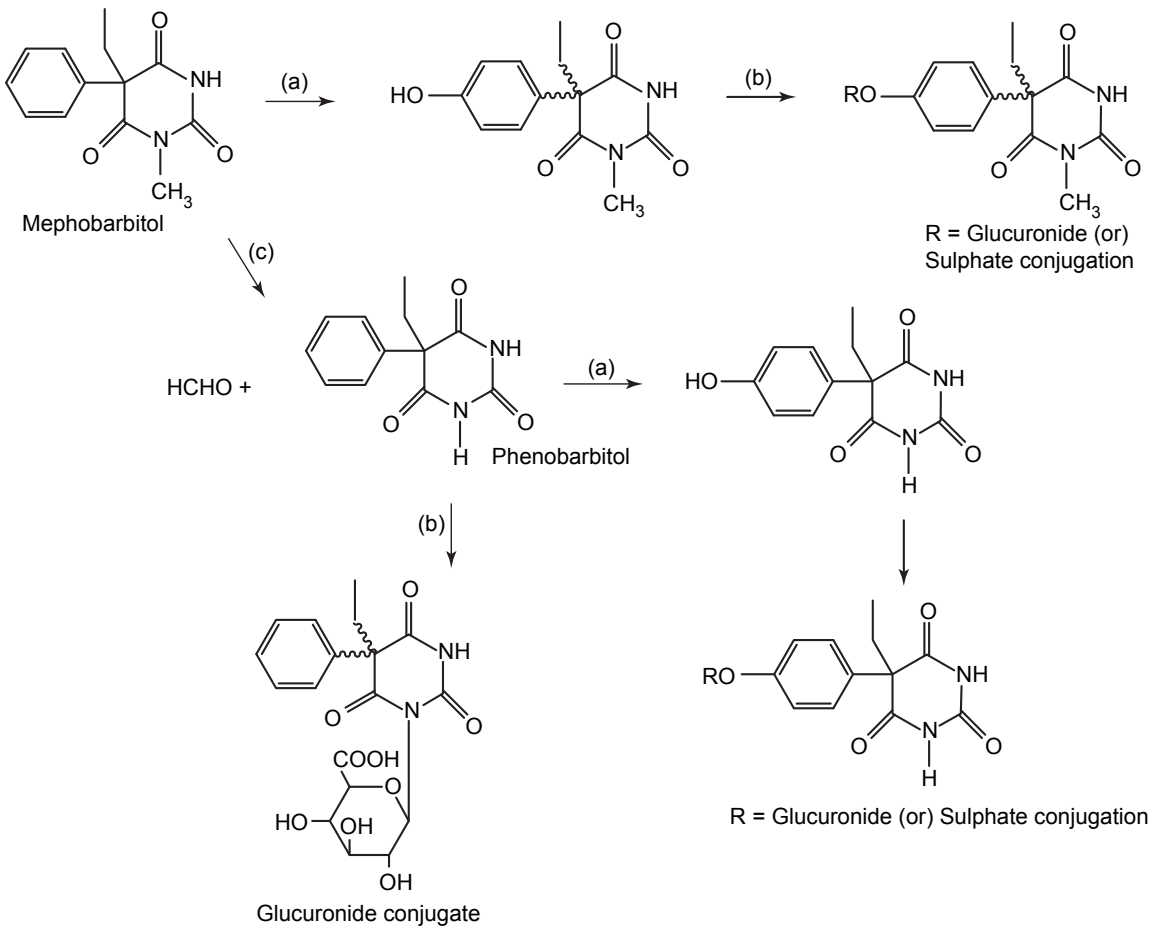
Urea Malonic acid Barbituric acid 5,5[1]-Substituted barbiturate

Route II: From chloroacetic acid



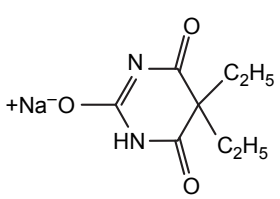
Metabolism of barbiturates: These drugs are metabolized in the liver and forms less lipophilic compounds. These are mediated through glucuronide or sulphate conjugation.

1. Oxidation of a substituent at C-5 forms alcohols or phenols, and these undergo further oxidation to form ketones or carboxylic acids. The barbiturates containing a propene at the fifth position inactivates CYP450 by alkylation of the porphyrin ring of CYP450.
2. The conjugation of heterocyclic nitrogen with glucuronic acid is due to the oxidative metabolism in the biotransformation of 5,5-disubstituted barbiturates (phenobarbital and amobarbital).
3. It undergoes oxidative *N*-dealkylation at nitrogen.
4. Oxidative desulphation of 2-thio barbiturates yields more hydrophilic barbiturates, which is excreted through urine.



Uses: They are used as sedative, hypnotic and anticonvulsant. They are administered through the intravenous (IV) route for inducing anaesthesia.

1. Barbitone sodium (Barbital sodium)



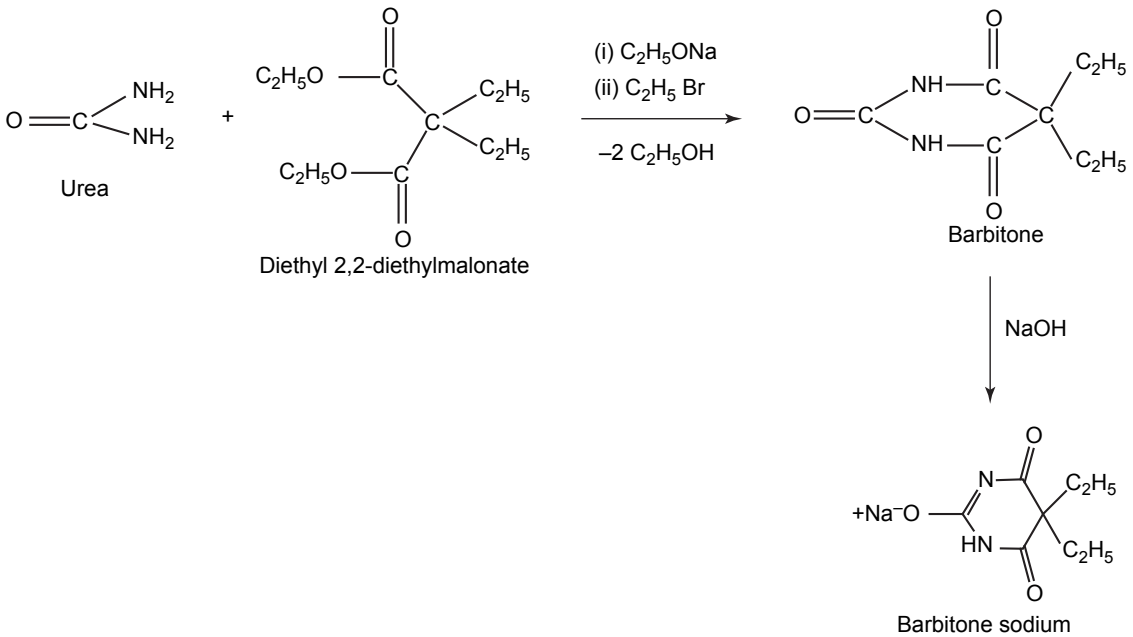
Sodium-5,5′-diethylbarbiturate

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

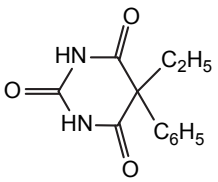
with sodium hydroxide. It is a powerful hypnotic drug and generally used in the treatment of epileptic seizures.

Assay: Dissolve the substance in pyridine and to this add thymolphthalein solution and silver nitrate solution in pyridine and titrate the solution with 0.1 methanolic sodium hydroxide. Endpoint is the appearance of blue colour.

Synthesis

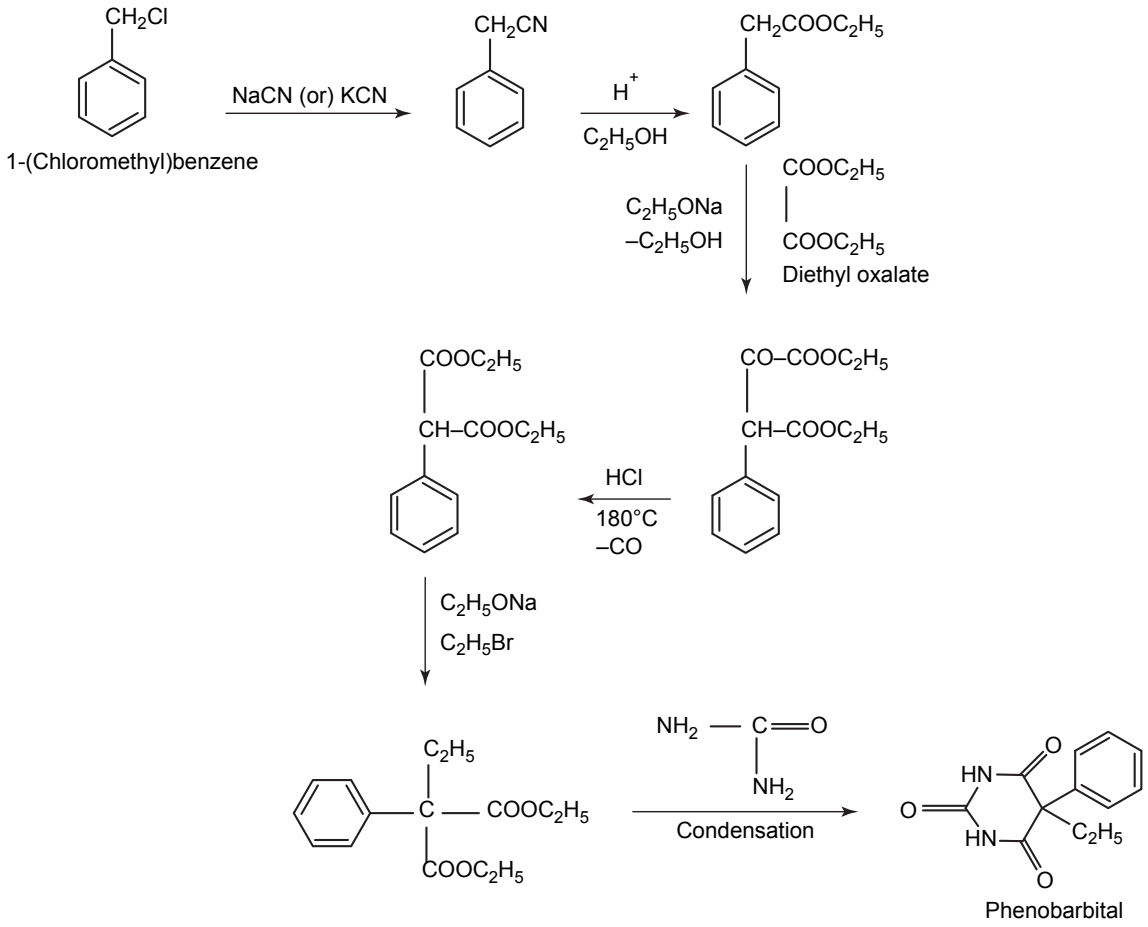


2. Phenobarbitone (Phenobarbital, Luminal)



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.

Synthesis



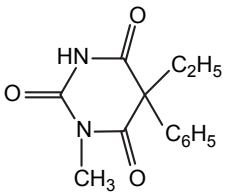
Assay: Dissolve the sample in water and add 0.05 M sulphuric acid. Heat the mixture to boiling point and then cool it. Add methanol and shake until dissolution is complete. Perform a potentiometric titration using 0.1 M sodium hydroxide. After the first point of inflexion, interrupt the addition of sodium hydroxide, add 10 ml of pyridine, mix, and continue the titration. Read the volume added between the two points of inflexion.

Storage: It should be stored in well closed airtight container.

Dose: For sedation: Adult: 30–120 mg/day in 2–3 divided doses. Children: 6 mg/kg/day. For hypnotic: Adult: 100–320 mg at bedtime. Do not administer for more than 2 weeks for the treatment of insomnia. Through IV route for preoperative sedation: Child: 1–3 mg/kg 1–1.5 h before procedure.

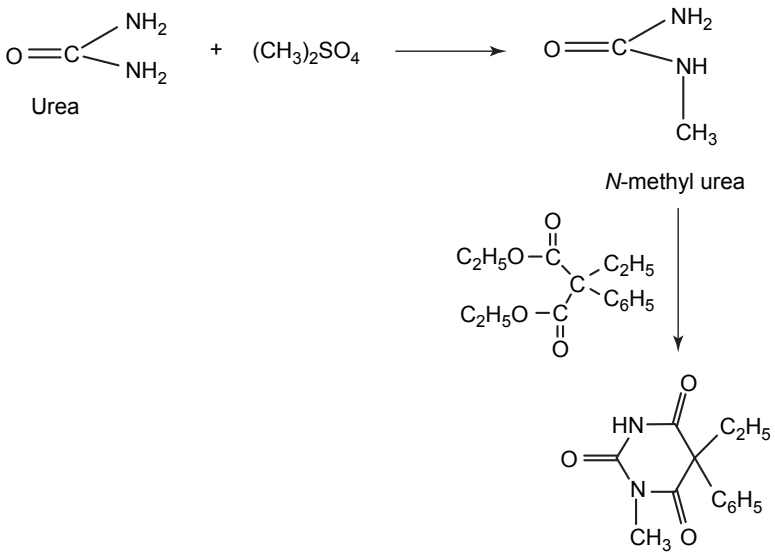
Dosage forms: Phenobarbital sodium tablets I.P., B.P., Phenobarbital sodium injection I.P., Phenobarbitone tablets I.P., Phenobarbital injection B.P., Paediatric phenobarbital oral solution B.P.

3. Methyl phenobarbitone (Mephobarbital)



5-Ethyl-1-methyl-5-phenyl barbituric acid

Synthesis

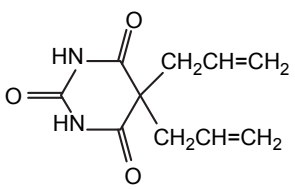


Methyl phenobarbitone

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.

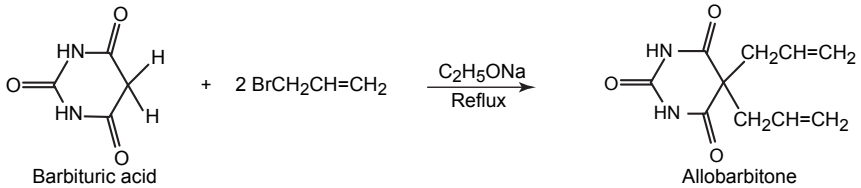
Dose: As a sedative 30–100 mg 3–4 times/day; as an anticonvulsant 400–600 mg daily.

4. Allobarbitone



5-5′- Diallyl barbituric acid

Synthesis

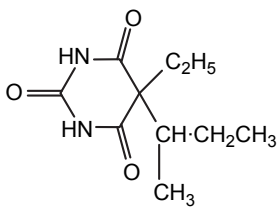


Barbituric acid — Allobarbitone

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

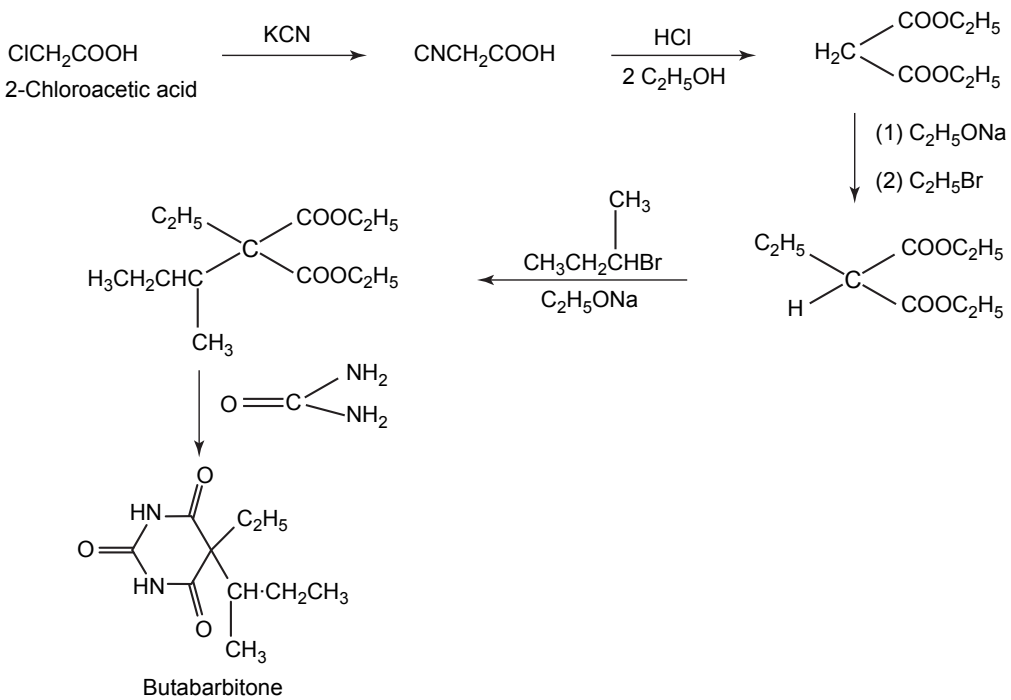
Dose: As a sedative 30 mg 3–4 times a day; as a hypnotic 100–200 mg at night.

6. Butabarbitone (Neonal)



5-(1-methyl propyl)-5-ethyl barbituric acid

Synthesis

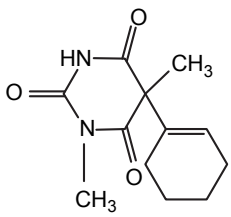


Butabarbitone

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.

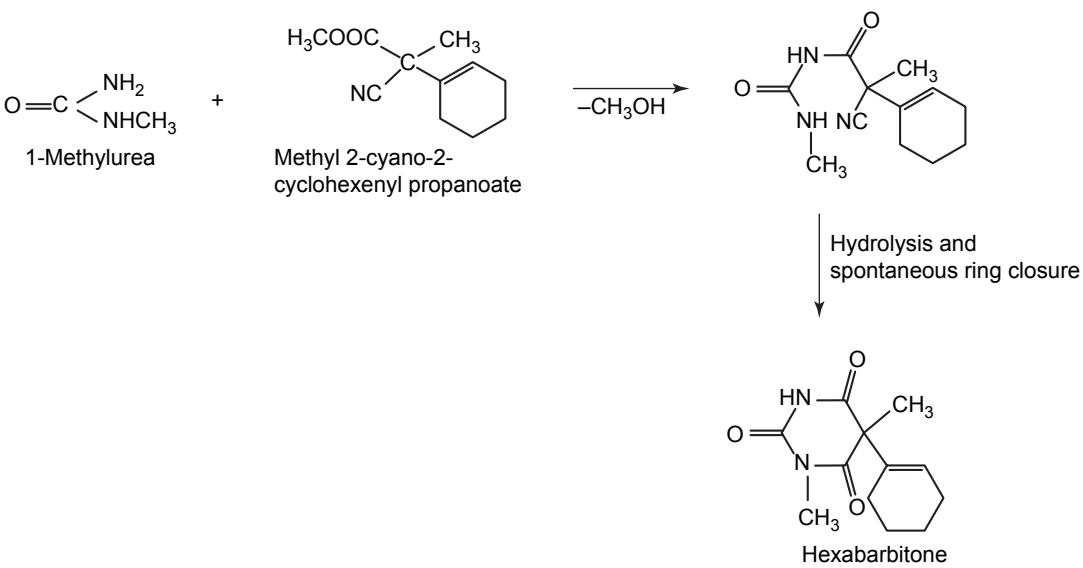
Dose: 30 mg as a sedative and 100–200 mg at night as a hypnotic.

5. Hexabarbitone (Hexobarbital, Evipal, Sombulex)



5-Cyclohexenyl-1,5-dimethylpyrimidin-2,4,6-trione

Synthesis

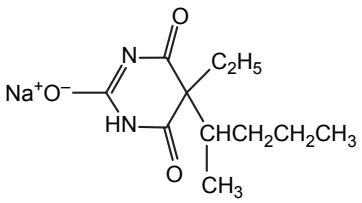


Properties and uses: It is a white, crystalline powder, very slightly soluble in water, sparingly soluble in alcohol. It forms sodium salt with sodium hydroxide, which is soluble in water. It is used as hypnotic.

Assay: Dissolve the sample in ethanol; to this add thymolphthalein solution and silver nitrate solution in pyridine. Titrate with 0.1 Methanolic sodium hydroxide. Endpoint is the appearance of blue colour.

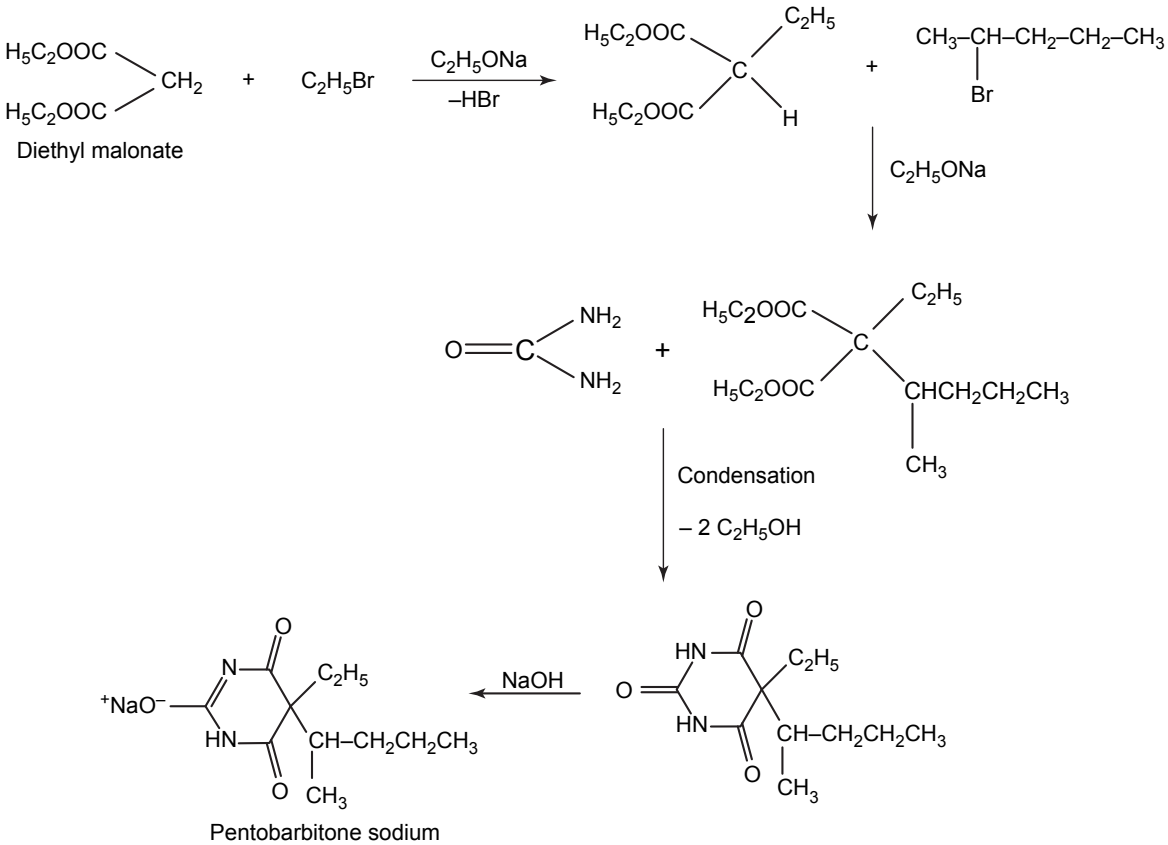
Dose: The usual dose for adult, oral hypnotic is 250–500 mg.

6. Pentobarbitone sodium (Pentobarbital sodium, Palapent, Sodital)



Sodium-5-ethyl-5-1(1-methylbutyl) barbiturate

Synthesis



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 doses 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.

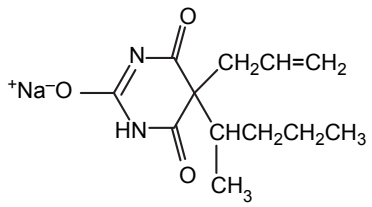
Assay: Dissolve the sample in silver nitrate solution in pyridine and titrate with 0.1 methanolic sodium hydroxide until a pure blue colour is obtained, using 0.5 ml of thymolphthalein solution as indicator.

Storage: It should be stored in well-closed airtight containers.

Dose: The usual oral sedative dose for adult is 30 mg 2–4 times daily. Through I.M. route, for preoperative, sedative, 150–200 mg. Through IV route, anticonvulsant, 100 mg initially up to 400 mg.

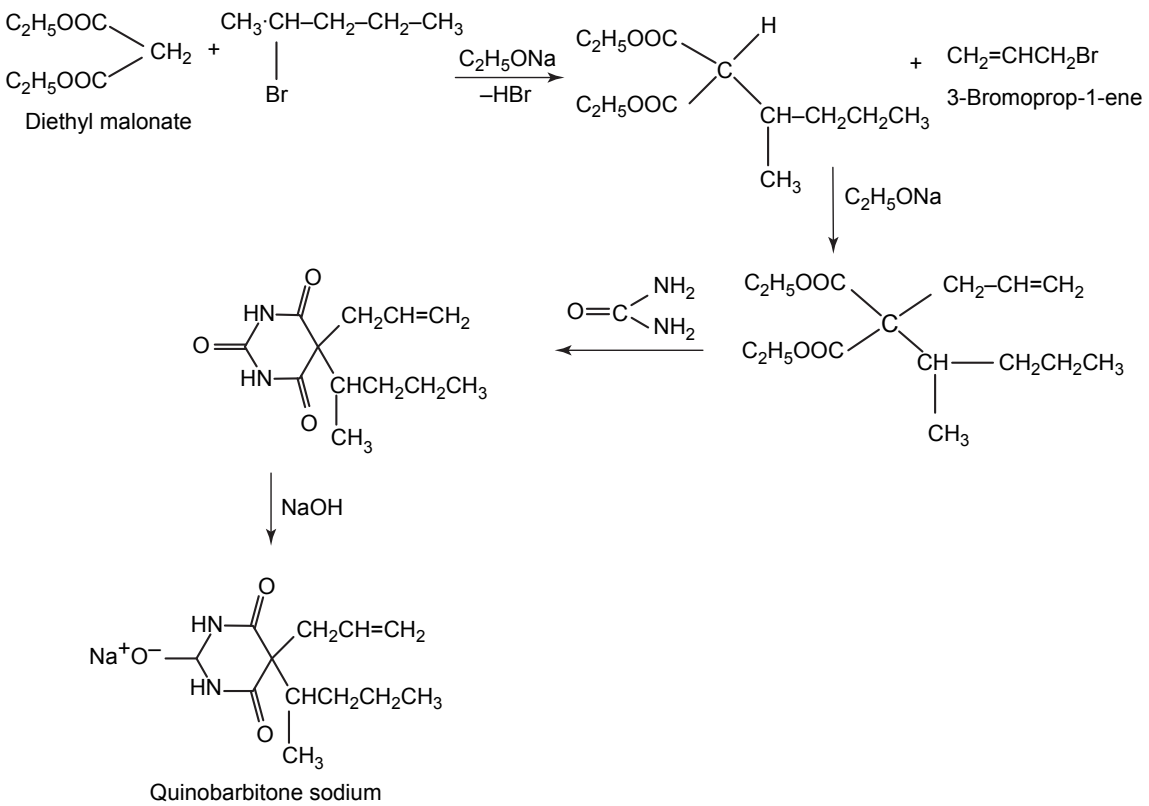
Dosage forms: Pentobarbital tablets I.P., B.P.

7. Quinobarbitone sodium (secobarbital sodium)



Sodium-5-allyl-5-(1-methylbutyl) barbiturate

Synthesis



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.

Dose: The usual adult dose is 50–200 mg.

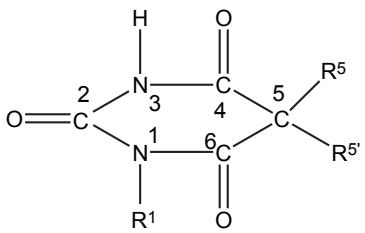
SAR of Barbiturates

A good hypnotic barbituric acid derivative must have the following properties:

1. The acidity value within certain limits to give proper ratio of ionized (dissociated) and unionized forms, which is important to cross blood brain barrier (BBB). It takes approximately 40%–60% dissociation to enable a barbiturate to cross BBB and exert effects on CNS. Determination of the pKa can thus be predictive of the CNS activity.
2. Lipid water solubility (partition coefficient) should be in certain limits.

1. Acidity

On the basis of acidity values, barbiturates are divided into two classes:



Active class

i. 5,5′-disubstituted barbituric acids
ii. 5,5′-disubstituted thiobarbituric acids
iii. 1,5,5′-trisubstituted barbituric acids

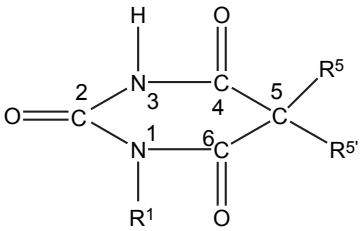
Inactive class

i. 1-substituted barbituric acids
ii. 5-substituted barbituric acids
iii. 1,3-disubstituted barbituric acids
iv. 1,5-disubstituted barbituric acids
v. 1,3,5,5′-tetrasubstituted barbituric acids

They are inactive since they are not acidic. These classes of agents depend on metabolism to produce 1,5,5′ trisubstituted barbituric acids, which are acidic. Attachment of alkyl substituent to both N^1 and N^3 renders the drug nonacidic, making them inactive.

2. Lipid water solubility

Once the acidity value criteria is satisfied, the lipid-water solubility or partition co-efficient is calculated to find out whether the compound is active or not. The following structural skeleton is essential for hypnotic activity:

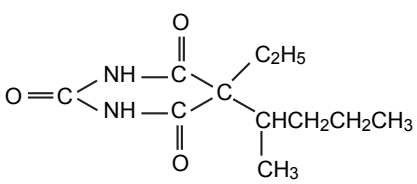


- The sum of the carbon atoms of both the substituents at c-5 should be between 6 and 10, in order to attain optimal hypnotic activity. This sum is also an index of the duration of action.

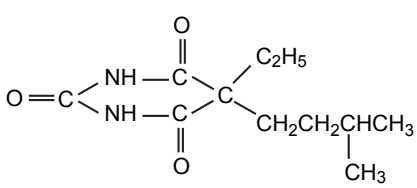
Sum of value	Duration of action
7–9	Rapid onset and shortest duration
5–7	Intermediate duration of action
4	Slowest onset and longest duration (two ethyl group or ethyl and phenyl)

- Within the same series, the branched chain has greatest lipid solubility and hypnotic activity, but has shorter duration of action.
- Branched cyclic or unsaturated chains at C-5 position, generally, reduce the duration of action, due to increased ease of metabolic conversion to more polar inactive metabolite.
- The greater the branching, more potent will be the drug.

Example: pentobarbital is more potent than amobarbital.



Pentobarbital



Amobarbitol

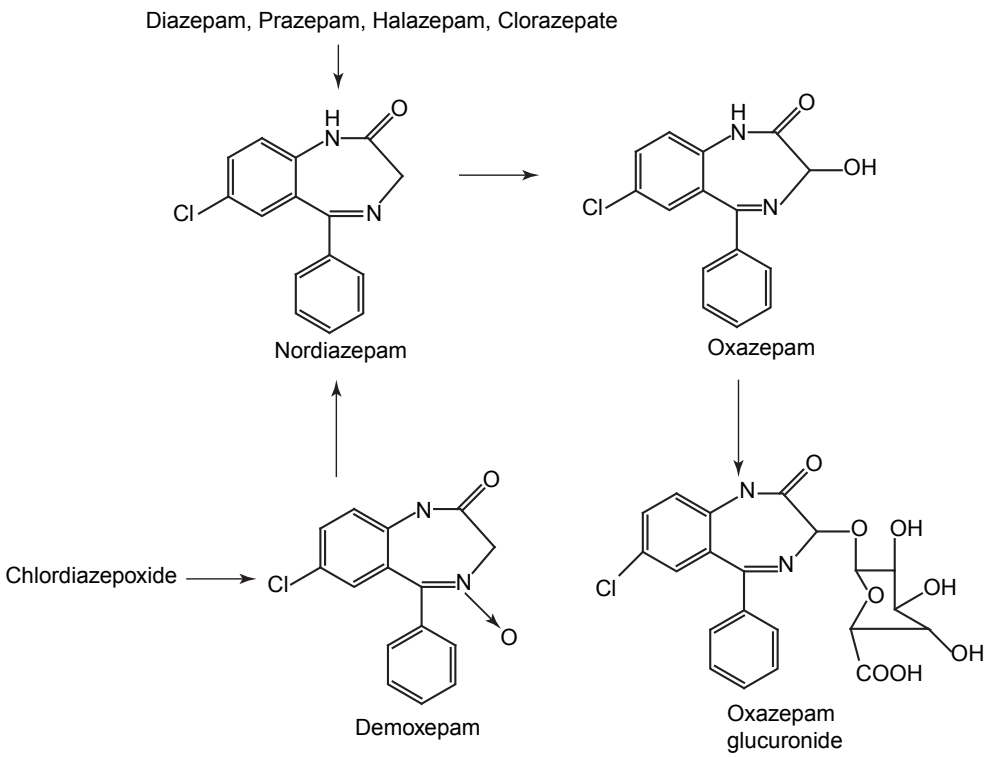
- However, the stero-isomers posses approximately the same potencies.
- Within the series, the unsaturated analogues (i.e. alkyl, alkenyl, and cycloalkenyl) may result in greater potency than the saturated analogues, with the same number of carbon atoms.
- Alicyclic or aromatic substituted analogues are more potent than analogues of aliphatic substitutions with the same number of carbon atoms.
- Introduction of a halogen atom into the C-5 substituents increase potency.

- Introduction of a polar substituents (OH, NH_2, COOH, CO, RNH, and SO_3H) into the aromatic group at C-5 results in decreased lipid solubility and potency.
- Alkylation at 1 or 3 position may result in compounds having shorter onset and duration of action since *N*-methyl group reduces acidity value.
- Replacement of oxygen by sulphur atoms at C-4 and C-6 position reduces the hypnotic activity.
- Replacement of oxygen by sulphur atom at C-2 position leads to rapid onset and shorter duration of action.

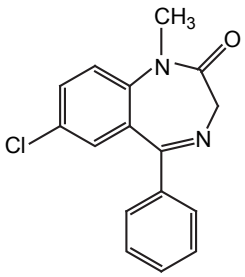
II. Benzodiazepines

Mode of action: Benzodiazepine receptors are present in the brain and they form a part of $GABA_A$ receptor's chloride ion channel macromolecular complex. Binding of benzodiazepines to these receptors produces activation of $GABA_A$ 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.

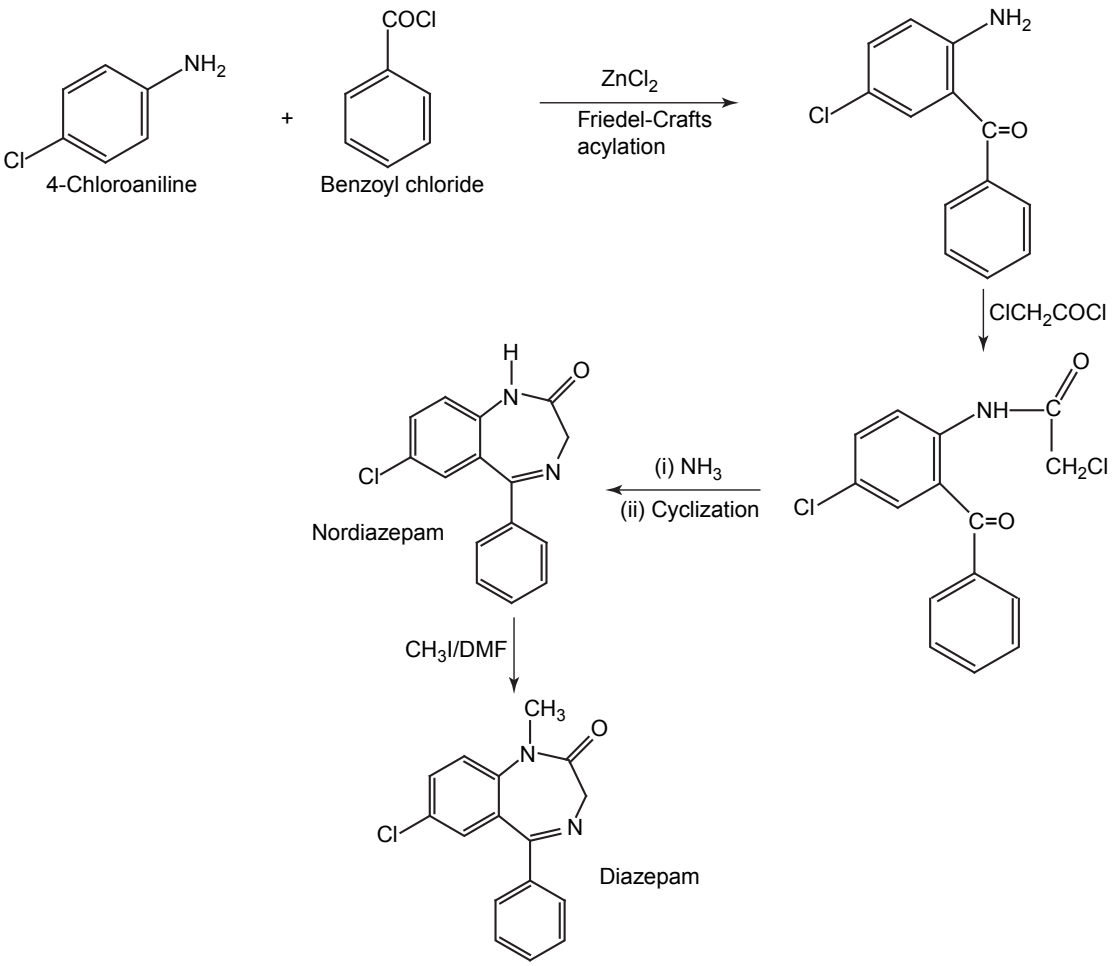


1. Diazepam (Calmpose, Valium, Diazep)



7-Chloro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one

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 an automobile or to operate dangerous machinery until a few days after the drug has been discontinued.

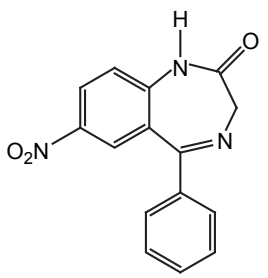
Assay: Dissolve the sample in acetic anhydride and titrate with 0.1 M perchloric acid and determine the endpoint potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: For short-term management of anxiety: Adult: 2 mg three times a day. Maximum: 30 mg daily. For insomnia associated with anxiety—Adult: 5–15 mg at bedtime. Sleepwalking; night terrors—Children and adolescents (up to 18 years): 1–5 mg at bedtime. Anaesthetic premedication—Adult: 5–15 mg given before general anaesthesia. Child: 1–12 month: 250 μg/kg; 1–5 year; 2.5 mg; 5–12 year; 5 mg. For adjunct in the management of seizures— Adult: 2–60 mg daily in divided doses. For muscle spasms—Adult: 2–15 mg daily in divided doses, increased up to 60 mg daily in severe spastic disorders. Maximum: 60 mg/day. Child: 1–12 month, 250 μg/kg; 1–5 years, 2.5 mg; 5–12 years, 5 mg; 12–18 year; 10 mg. Maximum: 40 mg/day. Elderly: Dose reduction may be required.

Dosage forms: Diazepam tablets I.P., B.P., Diazepam injection I.P., B.P., Diazepam capsules I.P., Diazepam oral solution B.P., Diazepam rectal solution B.P.

2. Nitrazepam (Dormin, Nipam, Nitorsun)



7-Nitro-5-phenyl-1,4-benzodiazepin-2-one

Properties and uses: It is a yellow crystalline powder slightly soluble in alcohol and insoluble in water. It is used as sedatives and hypnotics, and in the management of myoclonic seizures.

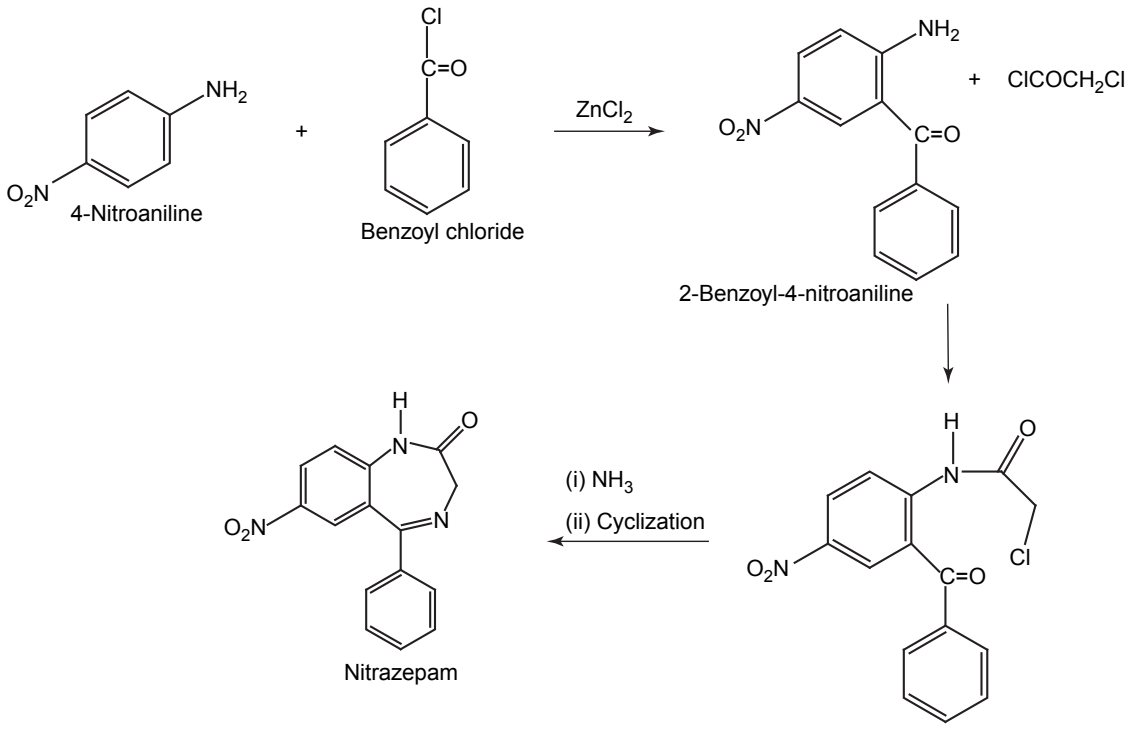
Assay: Dissolve the sample in acetic anhydride. Titrate the solution with 0.1 M perchloric acid and determine the endpoint potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

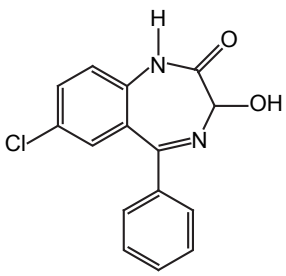
Dose: For short-term management of insomnia—Adult: 5 mg at night; can increase to 10 mg, if necessary. Elderly and debilitated patients: less than the normal adult dose. For infantile spasms: Child and infant, 125 μg/kg two times a day; gradually increase to 250–500 μg/kg two times a day.

Dosage forms: Nitrazepam tablets I.P., B.P., Nitrazepam oral suspension B.P.

Synthesis



3. Oxazepam (Serepax)



7-Chloro-3-hydroxy-5-phenyl-1,4-benzodiazepin-2-one

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. Side effects that have been observed include rashes, nausea, lethargy, oedema, slurred speech, tremor, and altered libido. More severe reactions include leucopenia and jaundice.

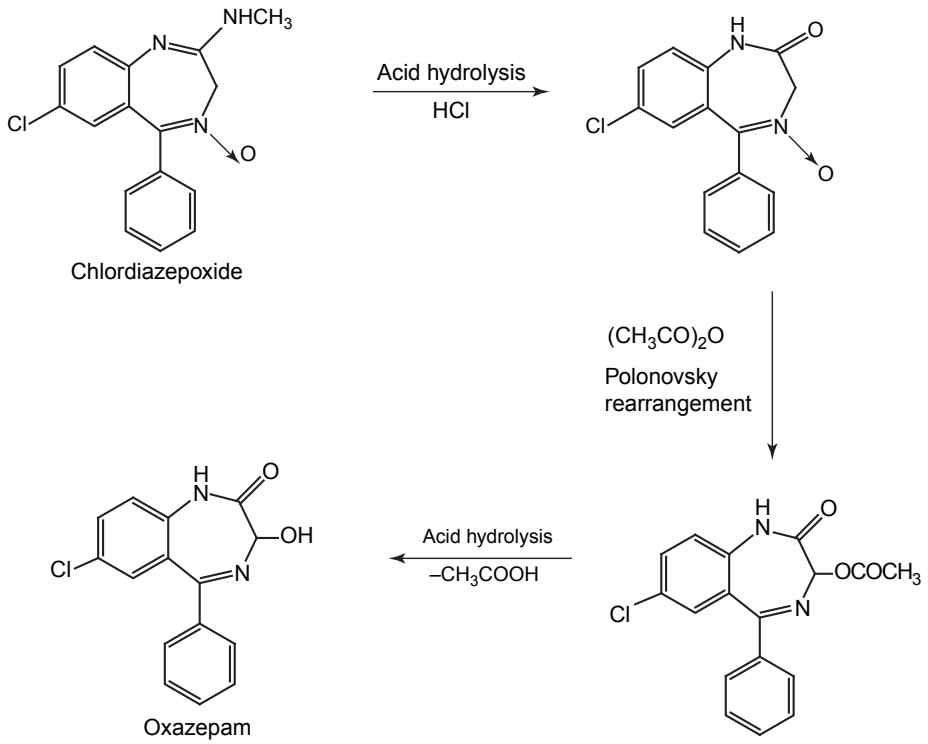
Assay: Dissolve the sample in anhydrous acetic acid and acetic anhydride. Titrate with 0.1 M perchloric acid and determine the endpoint potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

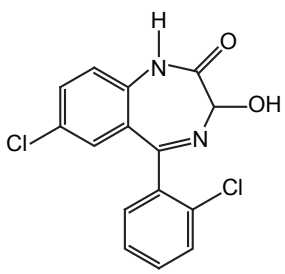
Dose: For anxiety, alcohol withdrawal syndrome—Adult: 15–30 mg 3 or 4 times/day. Elderly or debilitated patients: Initially, 10 mg thrice/day; increase up to 10–20 mg 3 or 4 times/day, if necessary. For insomnia associated with anxiety: Adult: 15–25 mg given 1 h before bedtime. Up to 50 mg may be occasionally required.

Dosage forms: Oxazepam tablets B.P.

Synthesis

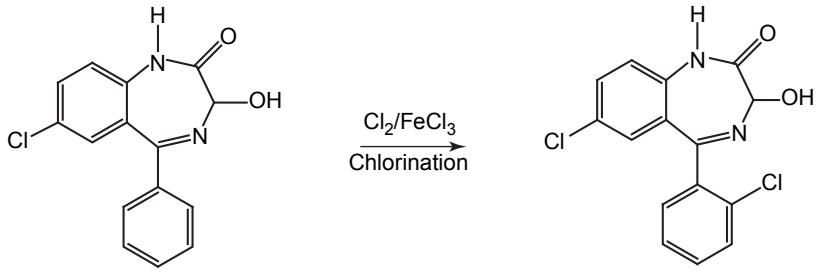


4. Lorazepam (Larposa, Lorvan)



7-Chloro-5-(2-chlorophenyl)-3-hydroxy-1,4-benzodiazepin-2-one

Synthesis



Oxazepam Lorazepam

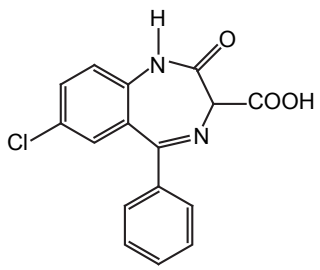
Properties and uses: It is a white or almost white crystalline powder, which is insoluble in water, sparingly soluble in ethanol, sparingly soluble in methylene chloride. It shows polymorphism. It is used as sedative and hypnotic. It has much more polarity than diazepam, for example, metabolism is relatively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

Assay: Dissolve the sample in dimethylformamide. Titrate with 0.1 M tetrabutylammonium hydroxide and determine the endpoint potentiometrically.

Dose: For Anxiety—Adult: Usual dose 1–6 mg daily in 2 or 3 divided doses. Largest dose taken at night. Up to 10 mg daily has been used. Elderly: Initial dose of 1–2 mg daily in 2 or 3 divided doses. Adjust as necessary. For insomnia associated with anxiety; Adult: 1–4 mg as a single dose given at bedtime. Elderly: 1–2 mg initially, adjust as needed.

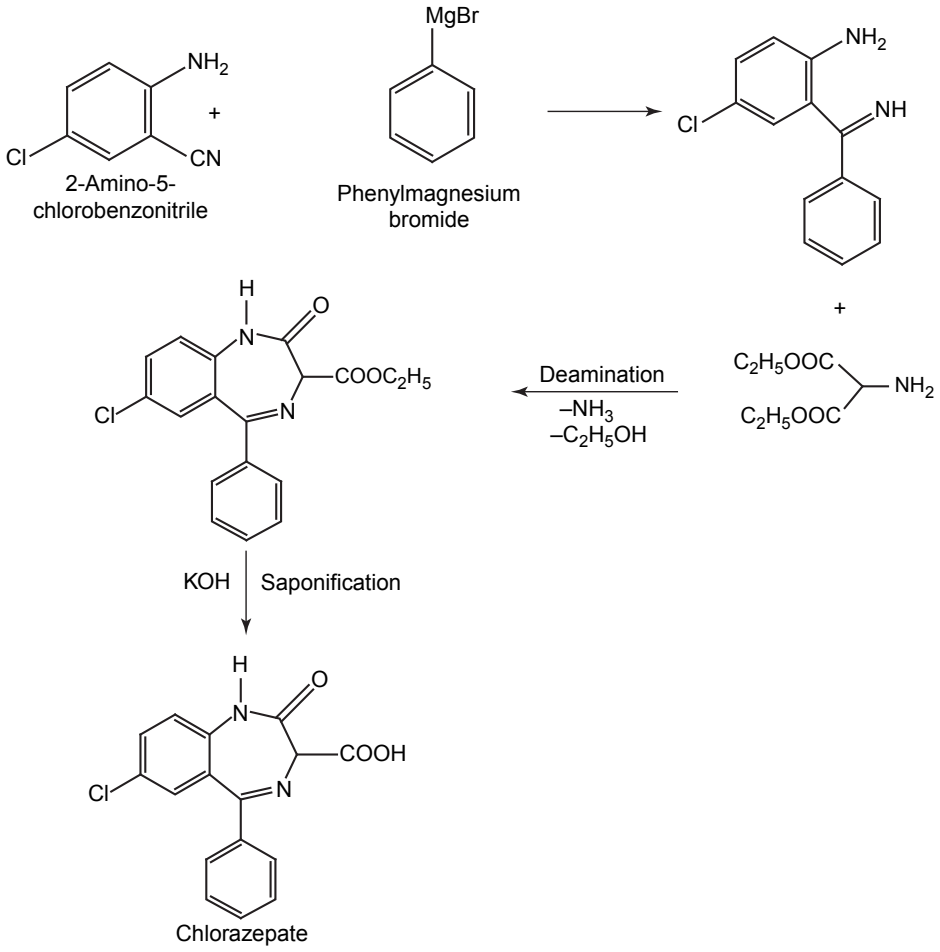
Dosage forms: Lorazepam injection B.P., Lorazepam tablets B.P.

5. Chlorazepate



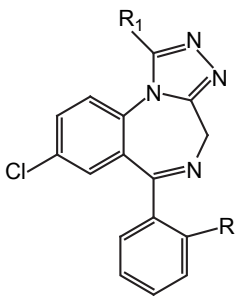
7-Chloro-2-oxo-5-phenyl-1, 4-benzodiazepin-3-carboxylic acid

Synthesis

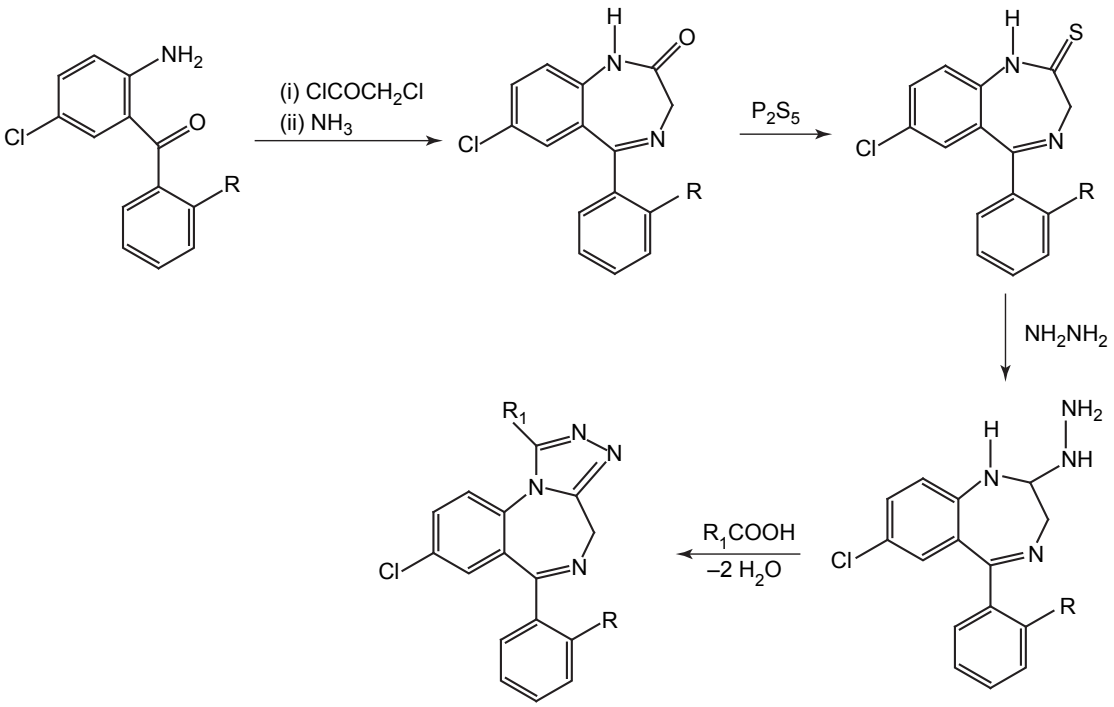


Uses: It is used as a sedative and hypnotic.

6. Triazolobenzodiazepines



Synthesis: Estazolam, Triazolam, Alprazolam



Estazolam R = H, R_1 = H
Triazolam R = Cl, R_1 = CH_3
Alprazolam R = H, R_1 = CH_3

Metabolism of Alprazolam: The methyl group of this drug is metabolized by oxidation reaction to methyl alcohol and conjugation reaction takes place.

Properties and uses

Estazolam: A triazolobenzodiazepine derivative that structurally resembles alprazolam and triazolam. It is useful in the management of insomnia. It has an intermediate half-life and the peak plasma concentration reaches 1.5 to 2 h after oral administration. It undergoes hepatic microsomal oxidation and has an elimination half-life 2 to 15 h. It causes more serious toxicity and withdrawal reactions than other benzodiazepines.

Dose: The usual required dose is 2 mg.

Triazolam (Halcion)**:** It is freely soluble in water and the metabolites, has little hypnotic action and is useful in the management of insomnia. The common adverse effects include drowsiness, dizziness, and headache.

Dose: The usual oral dose for an adult is 0.25–0.5 mg at bedtime.

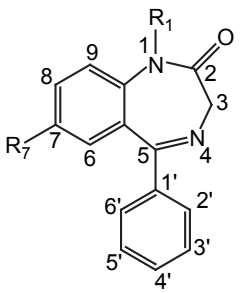
Alprazolam: It is a white crystalline powder, practically insoluble in water, freely soluble in methylene chloride sparingly soluble in acetone and in alcohol. It shows polymorphism. It is useful in the short-term

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.

Assay of Alprazolam: Dissolve the sample in a mixture of 3 volumes of anhydrous acetic acid and 2 volumes of acetic anhydride. Titrate with 0.1 M perchloric acid and determine the endpoint potentiometrically. Titrate to the second point of inflexion.

Storage: It should be stored in well-closed airtight containers and protected from light.

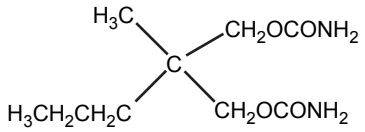
SAR of Benzodiazepines



- 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.

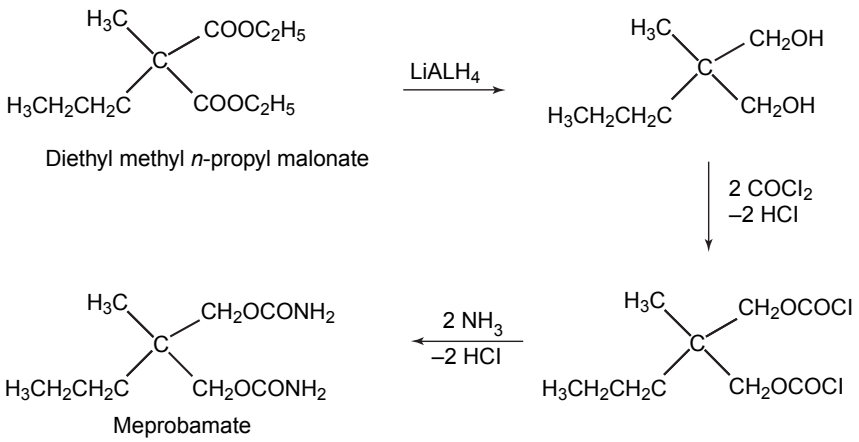
III. Acyclic hypnotics containing nitrogen

1. Meprobamate (Miltown, Equanil)



2-Methyl-2-propyl-1,3-propanediol dicarbamate

Synthesis



Diethyl methyl *n*-propyl malonate

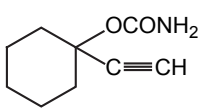
Meprobamate

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.

Assay: Dissolve the sample in 25% V/V solution of sulphuric acid and boil under a reflux condenser for 3 h. Cool and dissolve by cautiously adding 30 ml of water, cool again and place in a steam-distillation apparatus. Add 40 ml of strong sodium hydroxide solution and distil immediately by passing steam through the mixture. Collect the distillate into 40 ml of a 40 g/l solution of boric acid R until the total volume in the receiver reaches about 200 ml. Add 0.25 ml of methyl red mixed solution. Titrate with 0.1 M hydrochloric acid until the colour changes from green to violet.

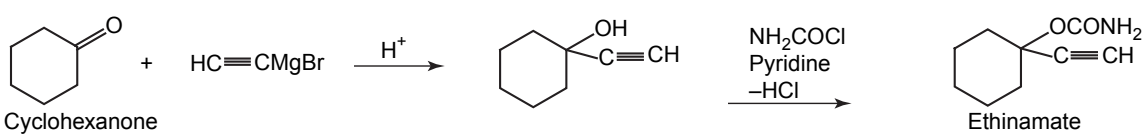
Dose: The usual oral dose for an adult is 400 mg.

2. Ethinamate



1-Ethynyl-cyclohexyl carbamate

Synthesis



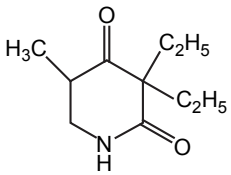
Cyclohexanone

Ethinamate

IV. Cyclic Hypnotics Containing Nitrogen

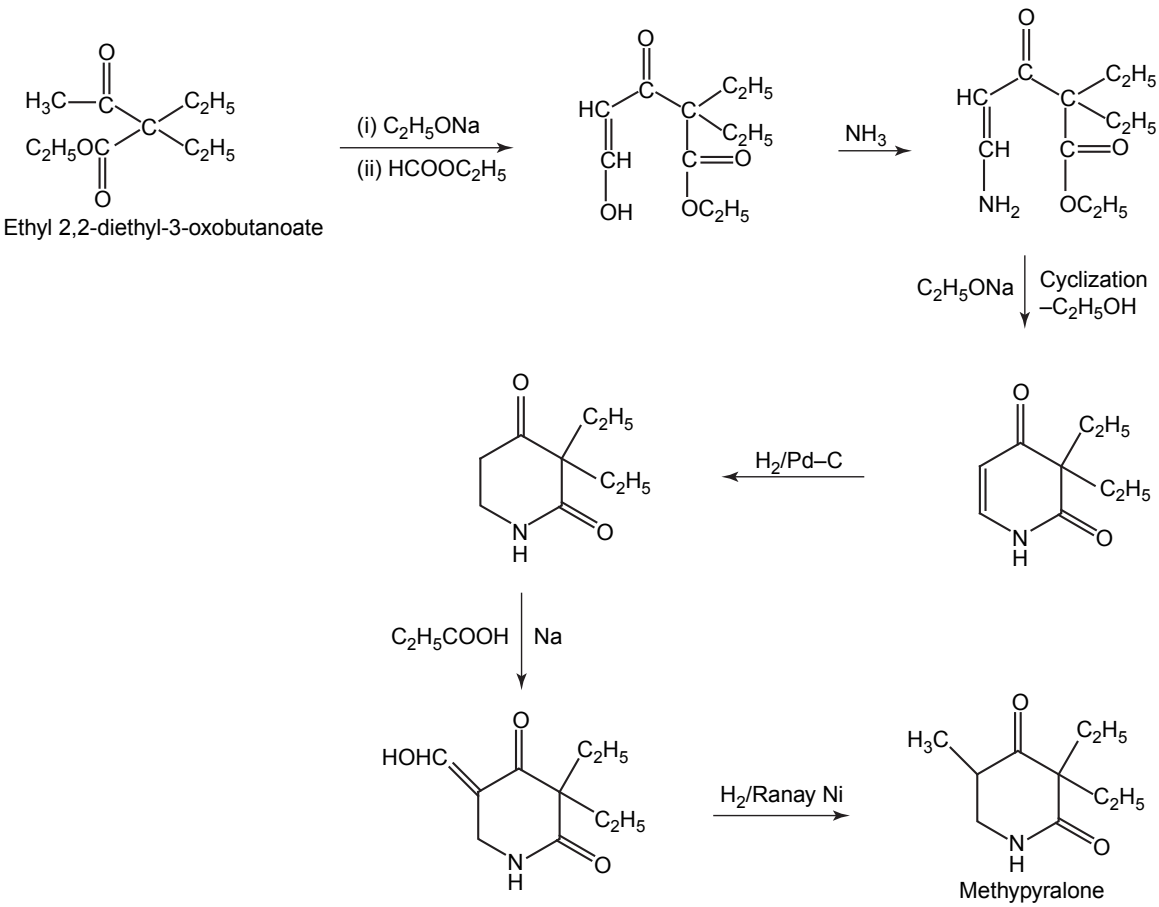
1. Piperidinedione derivatives

a. Methyprylone (Noludar)



3,3-Diethyl-5-methylpiperidine-2,4-dione

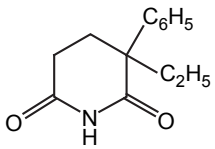
Synthesis



Properties and uses: Methyprylone exists as white crystalline powder and soluble in water. Used as a hypnotic agent useful in the management of insomnia of varied etiology.

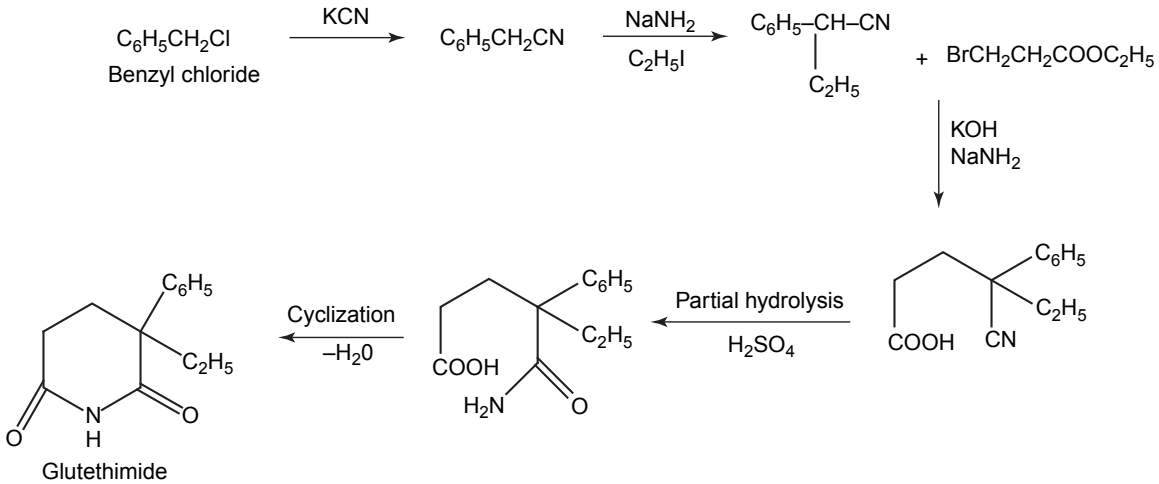
Dose: The usual adult dose is 200–600 mg for hypnotic; 50–100 mg for sedative.

b. Glutethimide



3-Ethyl-3-phenyl piperidine-2,6-dione

Synthesis



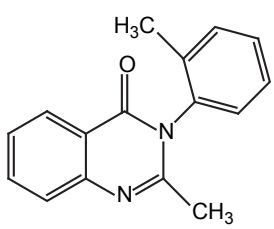
Glutethimide

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 purpuric or 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.

Dose: The usual adult dose is 250–500 mg.

2. Quinazolinone derivatives

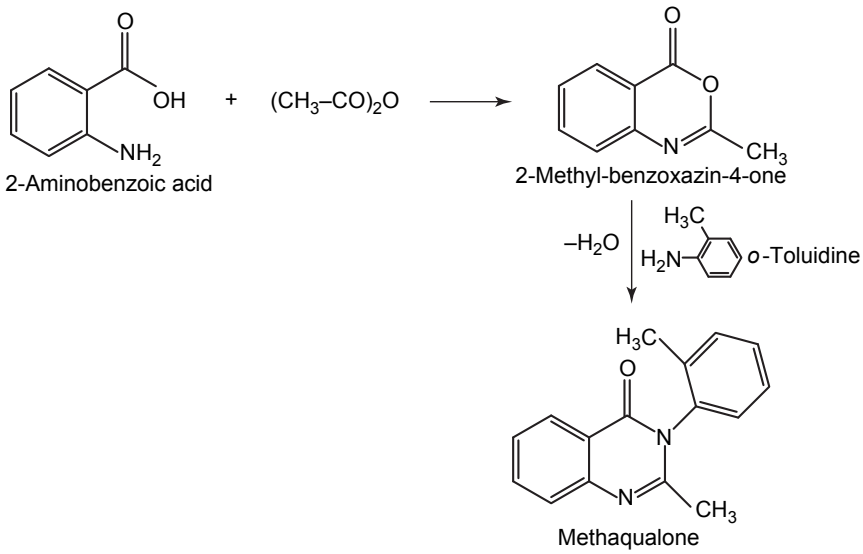
a. Methaqualone (Mequin)



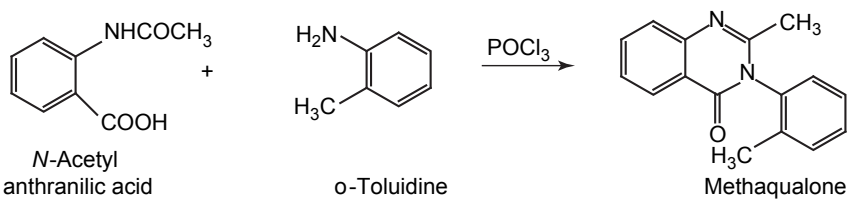
2-Methyl-3-*o*-tolylquinazolin-4(3H)-one

Synthesis

Route I. From: Anthranilic acid



Route II.From: *N*-Acetyl anthranilic acid



Properties and uses: It is a white or almost white crystalline powder. It dissolves in dilute sulphuric acid and very slightly soluble in water and also soluble in alcohol. It is used as a hypnotic drug to induce sleep and as a daytime sedative. It may be administered along with an antihistaminic agent such as diphenhydramine

Assay: Dissolve the sample in anhydrous acetic acid. Titrate with 0.1 M perchloric acid and determine the endpoint potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

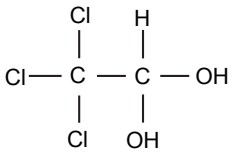
Dose: The usual adult dose is 50–150 mg.

V. Alcohols and Aldehydes

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.

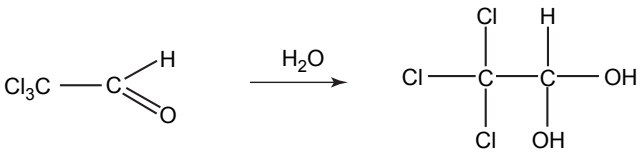
Metabolism: These are metabolized by alcohol dehydrogenase enzyme. Chloralhydrate undergoes oxidation to chloral and then to an inactive metabolite, trichloroacetic acid, via aldehyde dehydrogenase, which also is extensively metabolized to aryl glucuronides via conjugation with glucuronic acid and then excreted in urine.

1. Chloral hydrate (Noctec)



2,2,2-Trichloro-1,1-ethanediol

Synthesis



Chloral Chloral hydrate

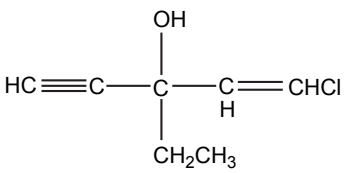
Properties and uses: Colourless, transparent crystals, very soluble in water and freely soluble in alcohol. Used principally for the short-term treatment of insomnia, it is used pre-operatively to allay anxiety and to induce sedation/sleep. It is used post-operatively as an adjuvant to opiates and other analgesics to control pain. It has also been used to produce sleep prior to electroencephalogram (EEG) evaluations. It is also effective in reducing anxiety associated with withdrawal of alcohol and other drugs, such as opiates and barbiturates.

Assay: Dissolve the sample in water and add 1 M sodium hydroxide solution. Allow to stand for exactly 2 min and titrate with 0.5 M sulphuric acid, using phenolphthalein solution as indicator. Titrate the neutralized solution with 0.1 M silver nitrate, using potassium chromate solution as an indicator.

Storage: It should be stored in well closed airtight container.

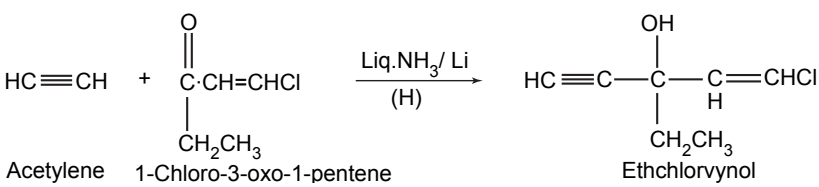
Dose: The usual adult dose is 500–1000 mg for hypnotic and 250 mg for sedative.

2. Ethchlorvynol (Placidyl)



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

Synthesis

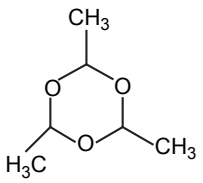


Acetylene 1-Chloro-3-oxo-1-pentene Ethchlorvynol

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.

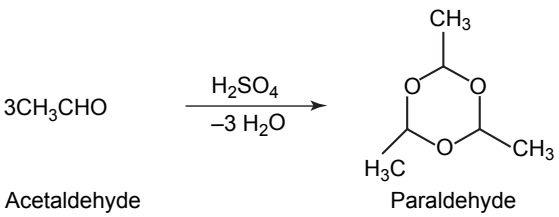
Dose: The usual adult dose is 500–1000 mg hypnotic and 100–200 mg sedative.

3. Paraldehyde



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

Synthesis

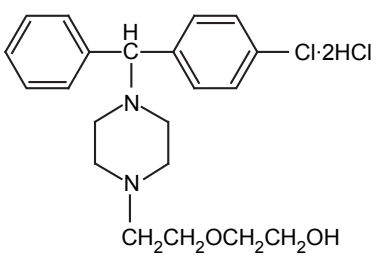


Properties and uses: It is a colourless or slightly yellow transparent liquid. It solidifies on cooling to form a crystalline mass. Miscible with alcohol and with essential oils, soluble in water, but less soluble in boiling water, it is exclusively used in the management of hospitalized patients undergoing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

Storage: It should be stored in well-closed airtight containers and protected from light. If the substance has solidified, the whole contents of the container must be liquefied before use.

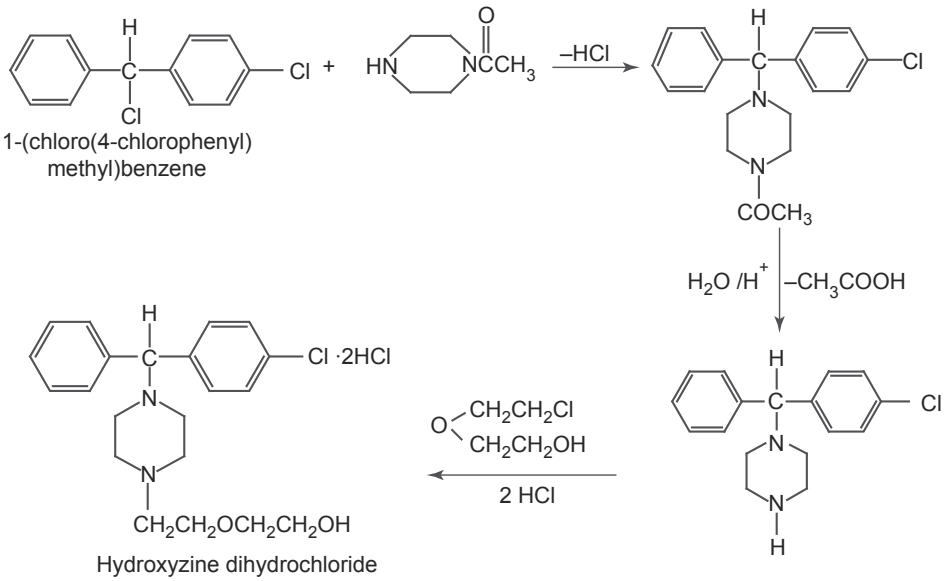
Dosage forms: Paraldehyde injection B.P.

4. Hydroxyzine hydrochloride



2-(2-(4-[(4-Chloro phenyl) phenyl methyl)-1-Piperazinyl]-ethoxy) ethanol dihydrochloride

Synthesis



Properties and uses: It is a hygroscopic crystalline powder, white or almost white in colour, freely soluble in water and in alcohol, very slightly soluble in acetone. It is useful in psychosomatic disturbances, nervous tension, and anxiety.

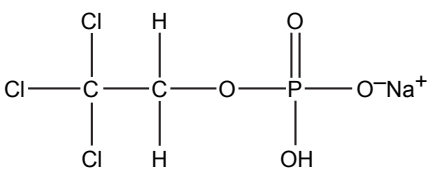
Assay: Dissolve the sample in 10 ml of anhydrous acetic acid and 40 ml of acetic anhydride. Titrate with 0.1 M perchloric acid and determine the endpoint potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: Adult: I.M. injection as the hydrochloride in doses of 25–100 mg every 4–6 h; Children: 1 mg per kg body weight I.M for pre and postoperative sedation.

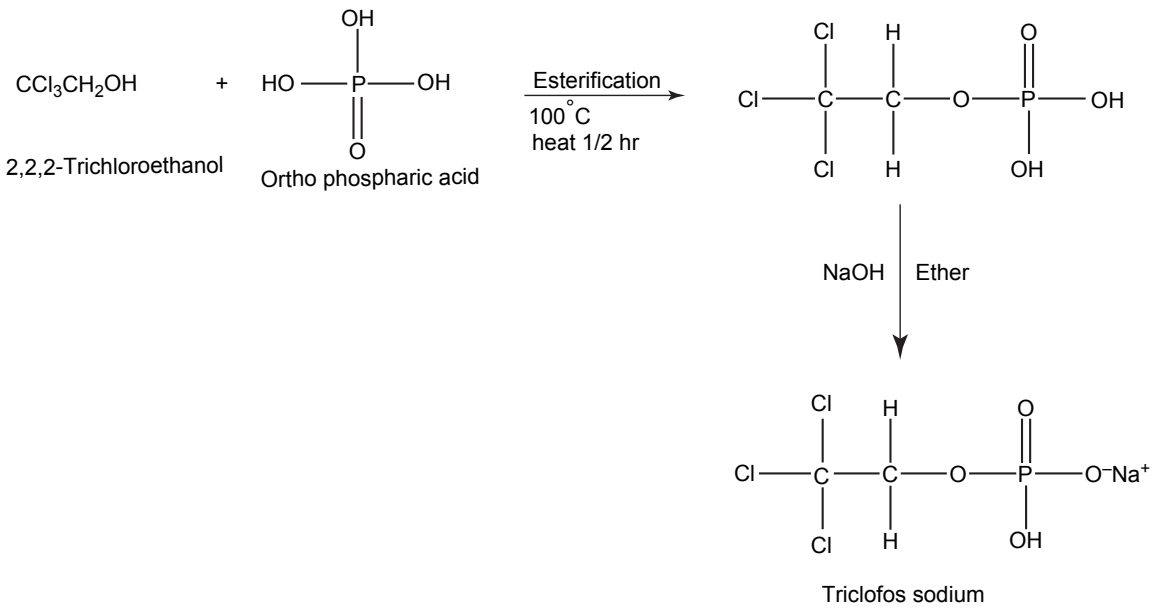
VII. Miscellaneous Class

1. Triclofos sodium



2, 2, 2,-Trichloro ethanol dihydrogen phosphate monosodium.

Synthesis

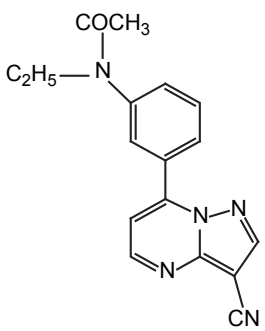


Properties and uses: It is a white or almost white powder, hygroscopic in nature. Freely soluble in water, slightly soluble in ethanol, practically insoluble in ether. Used as hypnotic.

Preparation: Triclofos oral solution B.P.

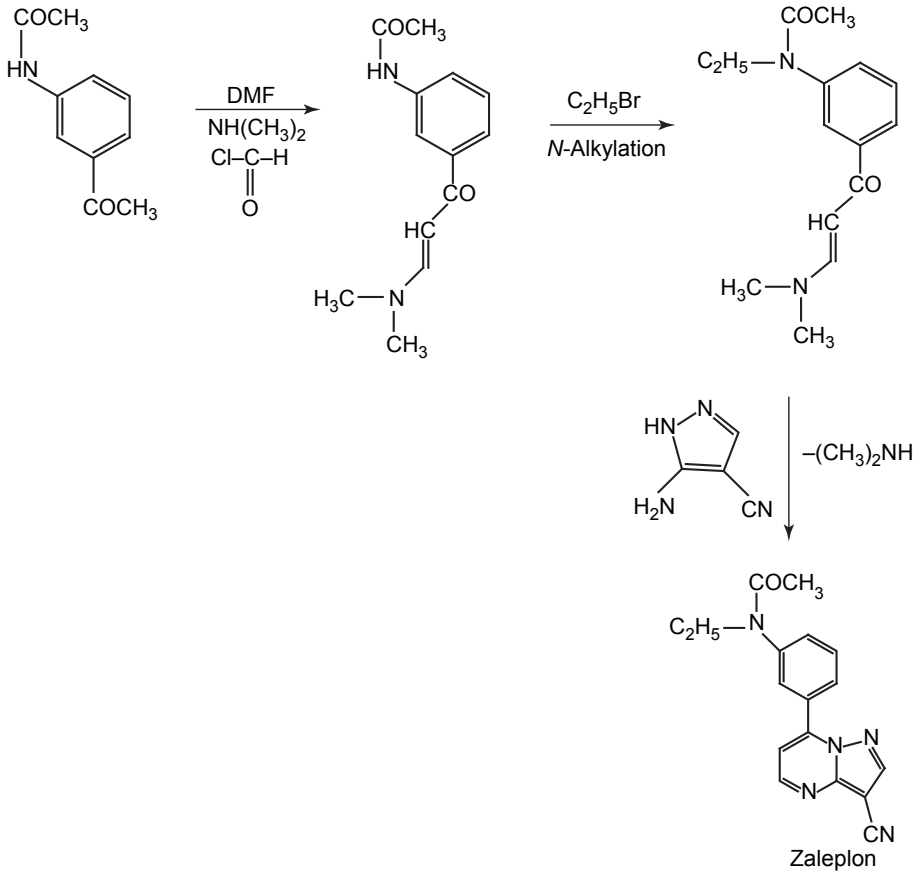
VIII. Newer Agents

1. Zaleplon (Zaplon, Zaso)



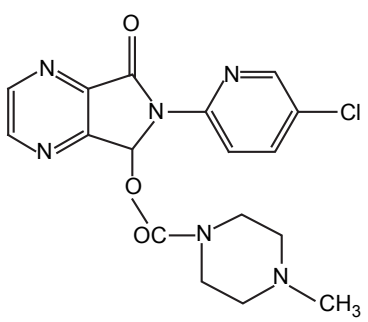
Properties and uses: Zaleplone is a nonbenzodiazepine pyrazolo pyrimidine derivative of a short-acting sedative and hypnotic. It acts as a selective agonist at the benzodiazepine α_1 receptor subunit on the $GABA_A$ receptor complex in the brain. Subunit modulation of the GABA-BZD receptor is hypothesized to be responsible for its hypnotic properties.

Synthesis

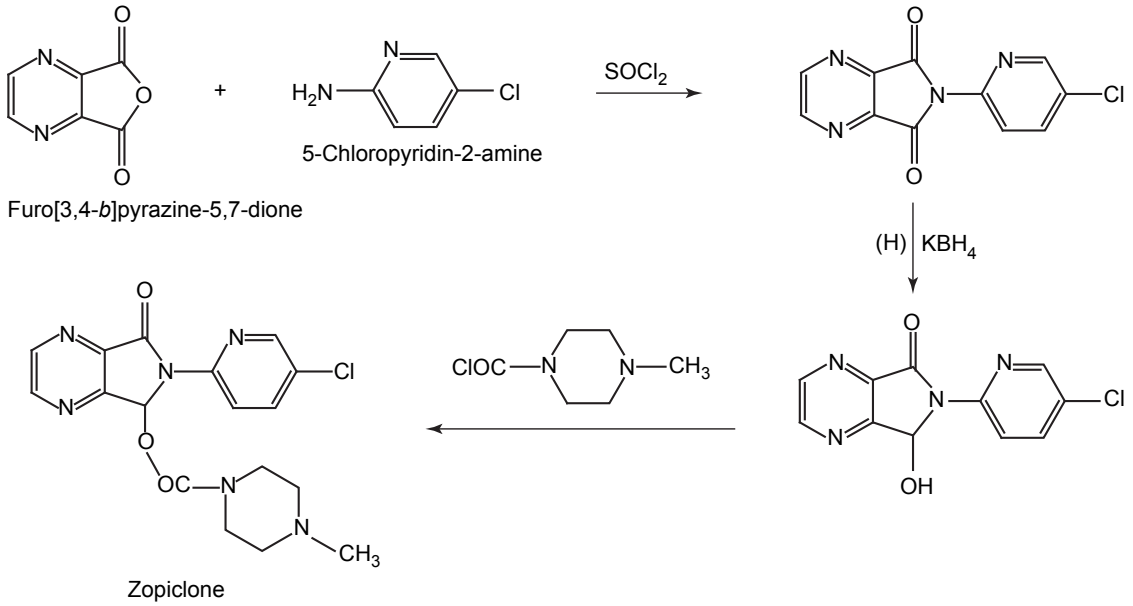


Dose: For insomnia—Adult: 10 mg before bedtime. Maximum: 20 mg daily. Elder less than 65 year: 5 mg before bedtime. Maximum 10 mg daily.

2. Zopiclone (Ziclone, Zopicon, Zonap)



Synthesis



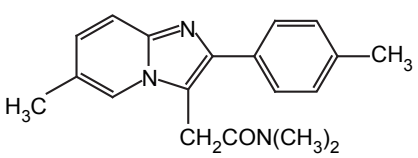
Properties and uses: It is a white or slightly yellowish powder, insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, insoluble in alcohol. It dissolves in dilute mineral acids. It is a new hypnotic agent structurally unrelated to barbiturates and benzodiazepines. It binds to the $GABA_A$ benzodiazepine receptor complex.

Assay: Dissolve the sample in a mixture of 10 ml of anhydrous acetic acid and 40 ml of acetic anhydride. Titrate with 0.1 M perchloric acid and determine the endpoint potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: For short-term management of insomnia—Adult: 7.5 mg at bedtime. Elderly: Initially, 3.75 mg at bedtime

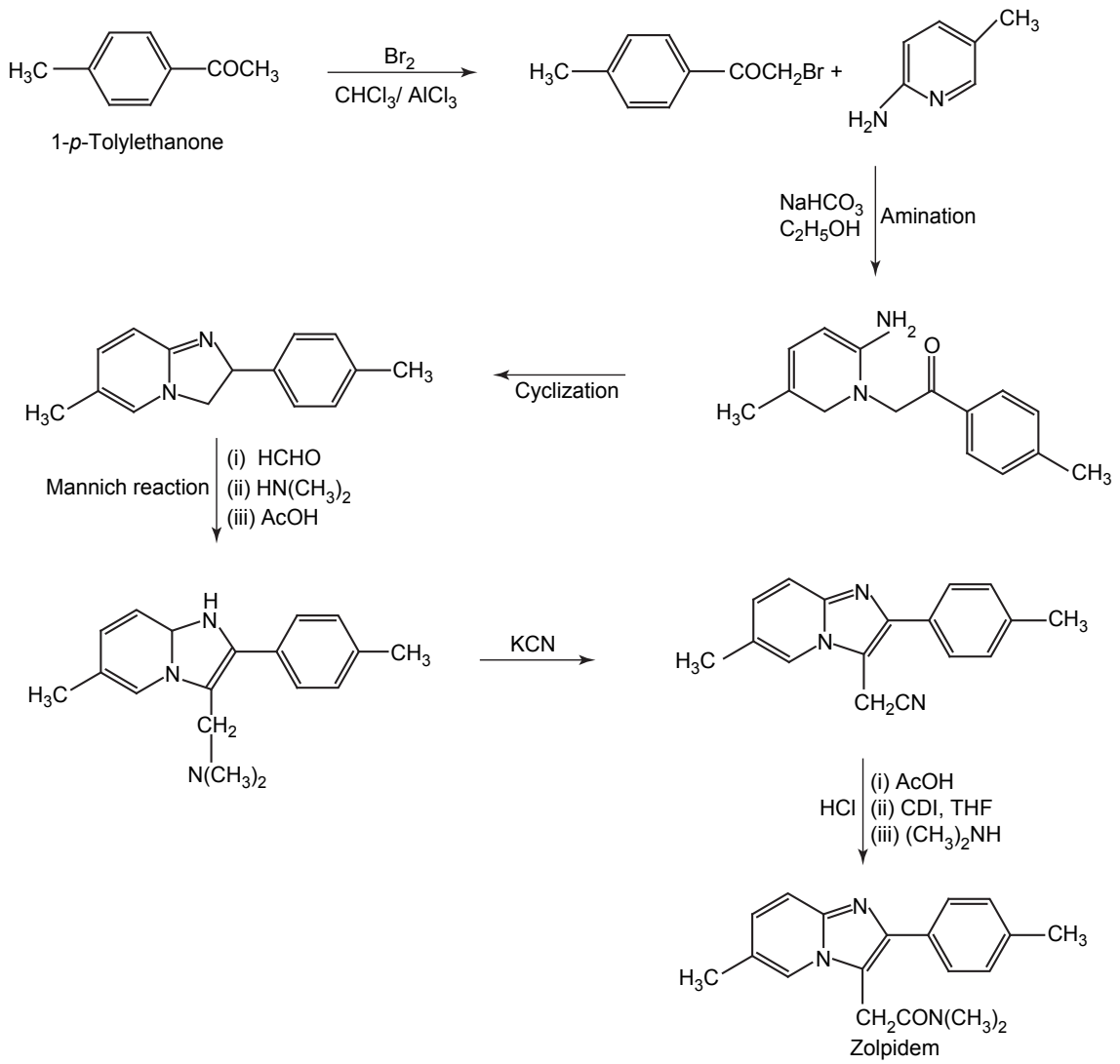
3. Zolpidem



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 α_1 receptor subunit of the $GABA_A$ receptor, used for the management of

insomnia. The selective binding at α_1 receptors Subunits of $GABA_A$ may explain the relative absence of myo-relaxant and anticonvulsant effects as well as the preservation of deep sleep in human.

Synthesis



Assay: Dissolve the sample in a mixture of 20 ml of anhydrous acetic acid and 20 ml of acetic anhydride. Titrate with 0.1 M perchloric acid and determine the endpoint potentiometrically.

Storage: It should be stored in well-closed airtight containers and protected from light.

PROBABLE QUESTIONS

1. Define and classify sedatives and hypnotics. Explain how the cyclic ureide barbituric acid may be prepared from (a) urea and malonyl dichloride and (b) urea and diethyl malonate.
2. Why the thiobarbiturates get metabolized in vivo faster than the barbiturates? Explain.
3. Explain the SAR of benzodiazepines.
4. How does the long-acting barbiturate phenobarbitone sodium can be synthesized.
5. Name the barbiturate having allyl group at C-5 in the barbituric acid. Write its synthesis and uses.
6. Mention a drug having pyrimidine nucleus used as sedative and hypnotic. Write its structure, chemical name, synthesis, and uses.
7. A class of barbiturates find their use in the treatment of insomnia and preoperative medication. Name two potent drugs and discuss the synthesis of any one of them.
8. Write a note on triazolo benzodiazepines used as sedative and hypnotic.
9. Based on quinazolinone nucleus, a potent hypnotic drug was introduced. Name the compound and write its structure, synthesis, and uses.
10. Outline the metabolic pathway and mode of action of benzodiazepines and barbiturates.
11. Outline the synthesis of meprobamate and nitrazepam.
12. Write the structure, chemical name, and uses of a potent hypnotic drug having a benzodiazepine nucleus. Outline its synthesis and metabolic pathway.
13. Explain the following with suitable examples: (a) mode of action of barbiturates and (b) SAR of barbiturates.
14. A brand of barbiturates are usually employed to cause general anaesthesia and control convulsions. Name any one potent member and write its synthesis and metabolism in vivo.
15. Write a note on long-acting barbiturates.

SUGGESTED READINGS

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