SEDATIVE-HYPNOTICS

Sedative is a drug that reduces excitement and calms the subject without inducing sleep, though drowsiness may be produced; while **Hypnotic** is a drug that induces and/or maintains sleep, similar to normal arousable sleep.

The sedatives and hypnotics are more or less CNS depressants with somewhat differing time-action and dose-action relationships. Hypnotics given in high doses can produce general anaesthesia. Thus, sedation—hypnosis—general anaesthesia may be regarded as increasing grades of CNS depression.

Treatment of insomnia is the most important use of this class of drugs.

Sleep

The duration and pattern of sleep varies considerably among individuals. Age has an important effect on quantity and depth of sleep. It has been recognized that sleep is an architectured cyclic process.

The different phases of sleep and their characteristics are—

Stage 0 (awake): From lying down to falling asleep and occasional nocturnal awakenings; constitutes 1–2% of sleep time. Eye movements are irregular or slowly rolling.

Stage 1 (dozing): Eye movements are reduced but there may be bursts of rolling. Neck muscles relax. Occupies 3–6% of sleep time.

Stage 2 (unequivocal sleep): little eye movement; subjects are easily arousable. This comprises 40–50% of sleep time.

Stage 3 (deep sleep transition): Eye movements are few; subjects are not easily arousable; comprises 5–8% of sleep time.

Stage 4 (cerebral sleep): Eyes are practically fixed; subjects are difficult to arouse. Night terror may occur at this time. It comprises 10–20% of sleep time. During stage 2, 3 and 4 heart rate, BP and respiration are steady and muscles are relaxed.

Stages 3 and 4 together are called slow wave sleep (SWS).

REM sleep (paradoxical sleep): There are marked, irregular and darting eye movements; dreams and nightmares occur, which may be recalled if the subject is aroused. Heart rate and BP fluctuate; respiration is irregular. Muscles are fully relaxed, but irregular body movements occur occasionally. About 20–30% of sleep time is spent in REM.

Normally stages 0 to 4 and REM occur in succession over a period of 80–100 min. Then stages 1–4–REM are repeated cyclically.

CLASSIFICATION

1. **Barbiturates**

Long acting : Phenobarbitone

Short acting: Butobarbitone,

Pentobarbitone

Ultra-short acting: Thiopentone,

Methohexitone

2. **Benzodiazepines**

Hypnotic: Diazepam,

Flurazepam,

Lorazepam,

Temazepam,

Nitrazepam,

Alprazolam,

Triazolam

Antianxiety: Diazepam,

Chlordiazepoxide,

Oxazepam

Lorazepam,

Alprazolam.

Anticonvulsant: Diazepam,

Clonazepam,

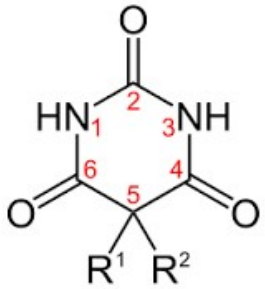
Clobazam

3. **Newer nonbenzodiazepine hypnotics:**
   Zopiclone
   Zolpidem
   Zaleplon

Chloral hydrate, Triclophos, Paraldehyde, Glutethimide, Methyprylon, Methaqualone and Meprobamate are historical sedative-hypnotics no longer used.

BARBITURATES

Barbiturates are substituted derivatives of barbituric acid (malonyl urea). Barbituric acid as such is not a hypnotic but compounds with alkyl or aryl substitution on C-5 are. Replacement of O with S at C-2 yields thiobarbiturates which are more lipid-soluble and more potent. Barbiturates have variable lipid solubility, the more soluble ones are more potent and shorter acting. They are insoluble in water but their sodium salts dissolve yielding highly alkaline solution.



Barbiturates have been popular hypnotics and sedatives of the last century upto 1960s, but are not used now to promote sleep or to calm patients. However, they are described first because they are the prototype of CNS depressants.

PHARMACOLOGICAL ACTIONS

Barbiturates are general depressants for all excitable cells, the **CNS is most sensitive** where the effect is almost global, but certain areas are more susceptible.

1. CNS : Barbiturates produce dose-dependent effects:
sedation → sleep → anaesthesia → coma.
Hypnotic dose shortens the time taken to fall asleep and increases sleep duration. The sleep is arousable, but the subject may feel confused and unsteady if waken early. Night awakenings are reduced. REM and stage 3, 4 sleep are decreased; REM-NREM sleep cycle is disrupted. The effects on sleep become progressively less marked if the drug is taken every night consecutively. A rebound increase in REM sleep and nightmares is often noted when the drug is discontinued after a few nights of use and it takes several nights for normal pattern to be

restored. Hangover (dizziness, distortions of mood, irritability and lethargy) may occur in the morning after a nightly dose.

Sedative dose (smaller dose of a longer acting barbiturate) given at daytime can produce drowsiness, reduction in anxiety and excitability. However, they do not have selective antianxiety action. Barbiturates can impair learning, shortterm memory and judgement. They have no analgesic action; small doses may even cause hyperalgesia. Euphoria may be experienced by addicts.

Barbiturates have anticonvulsant property. The 5-phenyl substituted compounds (phenobarbitone) have higher anticonvulsant: sedative ratio, i.e. they have specific anticonvulsant action *independent of general CNS depression*.

Barbiturates depress all areas of the CNS, but reticular activating system is the most sensitive; its depression is primarily responsible for inability to maintain wakefulness.

Mechanism of action Barbiturates appear to act primarily at the GABA: BZD receptor–Cl^- channel complex and potentiate GABAergic inhibition by increasing the lifetime of Cl^- channel opening induced by GABA (contrast BZDs which enhance frequency of Cl^- channel opening). They do not bind to the BZD receptor, but bind to another site on the same macromolecular complex to exert the GABA facilitatory action. The barbiturate site appears to be located on α or β subunit, because presence of only these subunits is sufficient for their response. Presence of γ subunit is not necessary as is the case with BZDs. They also enhance BZD binding to its receptor. At high concentrations, barbiturates directly increase Cl^- conductance (GABA-mimetic action; contrast BZDs which have only GABA-facilitatory action) and inhibit Ca2+ dependent release of neurotransmitters. In addition they depress glutamate induced neuronal depolarization through AMPA receptors (a type of excitatory amino acid receptors). At very high concentrations, barbiturates depress voltage sensitive Na+ and K+ channels as well. A dose-dependent effect on multiple neuronal targets appears to confer the ability to produce any grade of CNS depression.

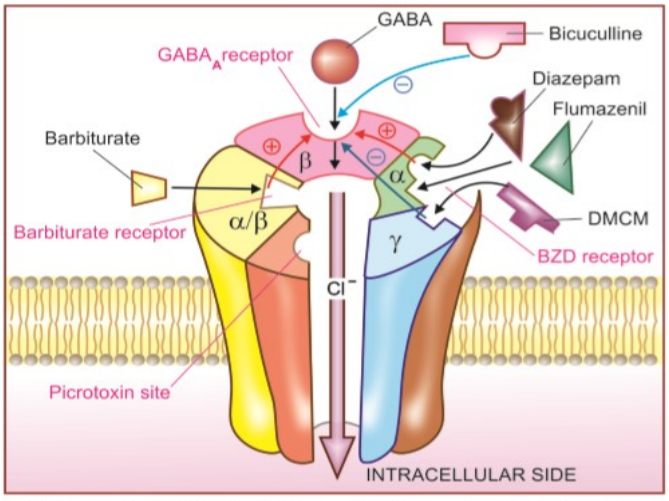


Fig. 29.3: Schematic depiction of GABA$_A$-benzodiazepine receptor-chloride channel complex
The chloride channel is gated by the primary ligand GABA acting on GABA$_A$ receptor located on the β subunit. The benzodiazepine (BZD) receptor located on the interface of α and γ subunits modulates GABA$_A$ receptor in either direction: agonists like diazepam facilitate, while inverse agonists like DMCM hinder GABA mediated Cl^- channel opening, and BZD antagonist flumazenil blocks the action of both. The barbiturate receptor, located either on α or β subunit also facilitates GABA and is capable of opening Cl^- channel directly as well. Bicuculline blocks GABA$_A$ receptor, while picrotoxin blocks the Cl^- channel directly

2. Other systems

Respiration is depressed by relatively higher doses. Neurogenic, hypercapneic and hypoxic drives to respiratory centre are depressed in succession. Barbiturates donot have selective antitussive action.

CVS: Hypnotic doses of barbiturates produce a slight decrease in BP and heart rate. Toxic doses produce marked fall in BP due to vasomotor centre depression, ganglionic blockade and direct decrease in cardiac contractility. Reflex tachycardia can occur, though pressor reflexes are depressed. However, the dose producing cardiac arrest is about 3 times larger than that causing respiratory failure.

Skeletal muscle: Hypnotic doses have little effect but anaesthetic doses reduce muscle contraction by action on neuromuscular junction.

Smooth muscles: Tone and motility of bowel is decreased slightly by hypnotic doses; more profoundly during intoxication. Action on bronchial, ureteric, vesical and uterine muscles is not significant.

Kidney: Barbiturates tend to reduce urine flow by decreasing BP and increasing ADH release. Oliguria attends barbiturate intoxication.

USES

Except for phenobarbitone in epilepsy and thiopentone in anaesthesia no other barbiturate is used now. As hypnotic and anxiolytic they have been superseded by BZDs. They are occasionally employed as adjuvants in psychosomatic disorders.

Phenobarbitone 30–60 mg oral OD–TDS; 100–200 mg i.m./i.v. GARDENAL 30, 60 mg tab, 20 mg/5 ml syr; LUMINAL 30 mg tab; PHENOBARBITONE SOD 200 mg /ml inj.

ADVERSE EFFECTS

Side effects: Hangover was common after the use of barbiturates as hypnotic. On repeated use they accumulate in the body—produce tolerance and dependence. Mental confusion, impaired performance and traffic accidents may occur (also see Ch. 30).

Idiosyncrasy: In an occasional patient barbiturates produce excitement. This is more common in the elderly. Precipitation of porphyria in susceptible individuals is another idiosyncratic reaction.

Hypersensitivity: Rashes, swelling of eyelids, lips, etc.— more common in atopic individuals.

Tolerance and dependence: Both cellular and pharmacokinetic (due to enzyme induction) tolerance develops on repeated use. However, fatal dose is not markedly increased: addicts may

present with acute barbiturate intoxication. There is partial cross tolerance with other CNS depressants. Psychological as well as physical dependence occurs and barbiturates have considerable abuse liability. This is one of the major disadvantages. Withdrawal symptoms are—excitement, hallucinations, delirium, convulsions; deaths have occurred.

Acute barbiturate poisoning: Mostly suicidal, sometimes accidental. It is infrequently encountered now due to inavailability of barbiturates. However, the principles of treatment apply to any CNS depressant poisoning.

Manifestations are due to excessive CNS depression— patient is flabby and comatose with shallow and failing respiration, fall in BP and cardiovascular collapse, renal shut down, pulmonary complications, bullous eruptions. Lethal dose depends on lipid solubility. It is 2–3 g for the more lipid-soluble agents (short-acting barbiturates) and 5–10 g for less lipid-soluble phenobarbitone.

Treatment:

1. Gastric lavage; leave a suspension of activated charcoal in the stomach to prevent absorption of the drug from intestines.

2. Supportive measures: such as, patent airway, assisted respiration, oxygen, maintenance of blood volume by fluid infusion and use of vasopressors—dopamine may be preferred for its renal vasodilating action.

3. Alkaline diuresis: with sodium bicarbonate 1 mEq/kg i.v. with or without mannitol is helpful only in the case of longacting barbiturates which are eliminated primarily by renal excretion.

4. Haemodialysis and haemoperfusion (through a column of activated charcoal or other adsorbants) is highly effective in removing long-acting as well as short-acting barbiturates. There is no specific antidote for barbiturates. In the past, analeptics like metrazol, bemegride, etc. have been used in an attempt to awaken the patient. This is dangerous, may precipitate convulsions while the patient is still comatose— mortality is increased. The emphasis now is on keeping the patient alive till the poison has been eliminated.

Interactions:

1. Barbiturates induce several CYP isoenzymes, including glucuronyl transferase, and increase the metabolism of many drugs and reduce their effectiveness—warfarin, steroids (including contraceptives), tolbutamide, griseofulvin, chloramphenicol, theophylline.

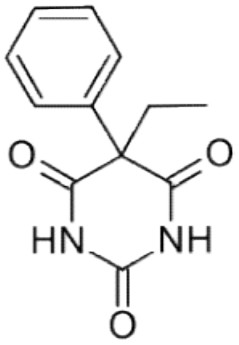
2. Additive action with other CNS depressants —alcohol, antihistamines, opioids, etc.

3. Sodium valproate increases plasma concentration of phenobarbitone.

4. Phenobarbitone competitively inhibits as well as induces phenytoin and imipramine metabolism: complex interaction.

5. Phenobarbitone decreases absorption of griseofulvin from the g.i.t.

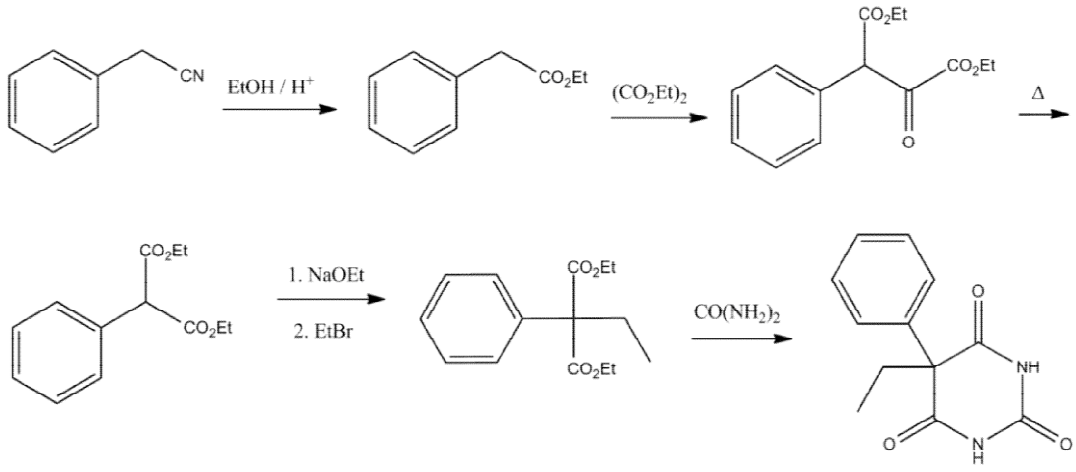
Phenobarbitone



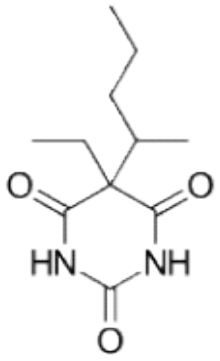
5-Ethyl-5-phenyl-1,3-diazinane-2,4,6-trione

Synthesis:

The synthetic method consists of a Pinner reaction of benzyl cyanide, giving phenylacetic acid ethyl ester. Subsequently, this ester undergoes cross Claisen condensation using diethyl oxalate, giving diethyl ester of phenyloxobutandioic acid. Upon heating this intermediate easily loses carbon monoxide, yielding diethyl phenylmalonate. Malonic ester synthesis using ethyl bromide leads to the formation of α-phenyl-α-ethylmalonic ester. Finally a condensation reaction with urea gives phenobarbital.



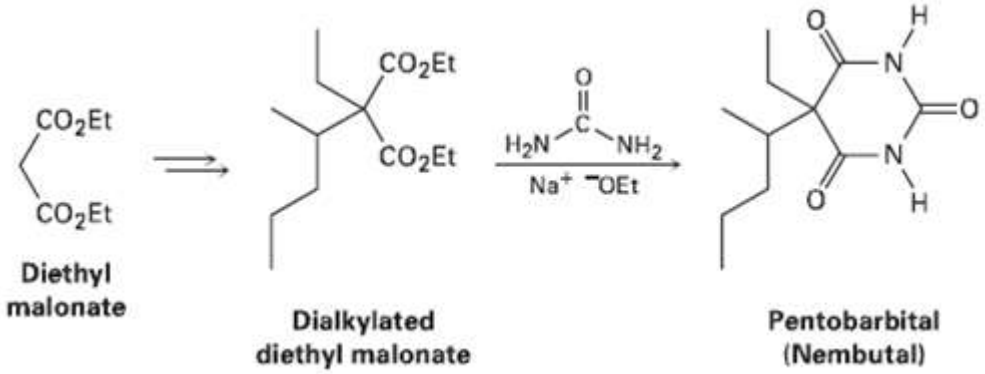
Pentobarbitone



5-Ethyl-5-(1-methylbutyl)-2,4,6(1H,3H,5H)-pyrimidinetrione

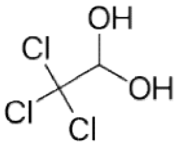
Pentobarbital (US English) or pentobarbitone (UK English) is a short-acting barbiturate. Pentobarbital can occur as both a free acid and as salts of elements such as sodium and calcium. The free acid is only slightly soluble in water and ethanol

Synthesis:



Uses: Typical applications for pentobarbital are sedative, hypnotic for short term, preanesthetic and control of convulsions in emergencies.It is also used as a veterinary anesthetic agent.Pentobarbital also has an application in reducing intracranial pressure in Reye's syndrome, traumatic brain injury and induction of coma in cerebral ischemia patients. Pentobarbital-induced coma has been advocated in patients with acute liver failure refractory to mannitol

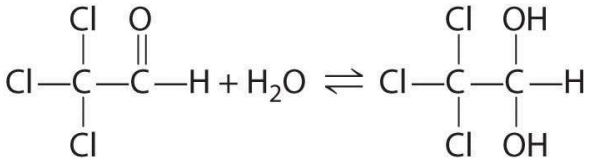
Chloral Hydrate



2,2,2-Trichloroethane-1,1-diol

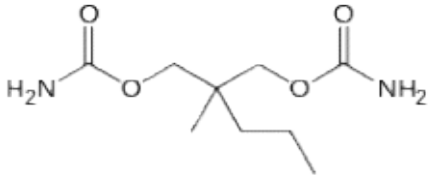
Chloral hydrate is an organic compound with the formula $C_2H_3Cl_3O_2$. It is a colorless solid. It has limited use as a sedative and hypnotic pharmaceutical drug. It is also a useful laboratory chemical reagent and precursor.

Synthesis: It is derived from chloral (trichloroacetaldehyde) by the addition of one equivalent of water.



Uses: Chloral hydrate is used for the short-term treatment of insomnia and as a sedative before minor medical or dental treatment. It was largely displaced by barbiturates and subsequently by benzodiazepines.

Meprobalmate



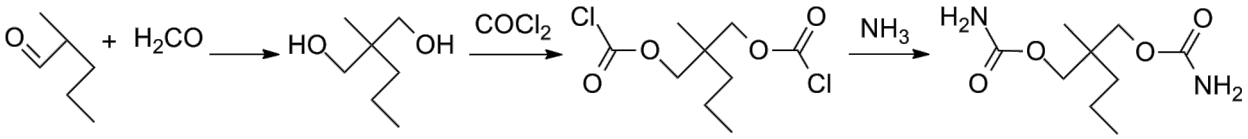
[2-(carbamoyloxymethyl)-2-methyl-pentyl] carbamate

Meprobalmate is a carbamate derivative used as an anxiolytic drug. It was the best-selling minor tranquilizer for a time, but has largely been replaced by the benzodiazepines due to their wider therapeutic index (lower risk of toxicity at therapeutically prescribed doses) and lower incidence of serious side effects.

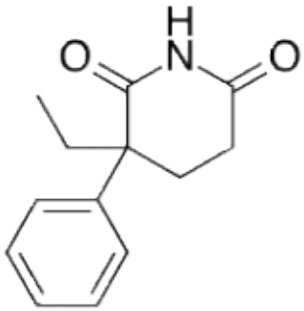
Synthesis:

Meprobamate, 2-methyl-2-propyl-1,3-propandiol dicarbamate is synthesized by the reaction of 2-methylvaleraldehyde with two molecules of formaldehyde and the subsequent transformation

of the resulting 2-methyl-2-propylpropan-1,3-diol into the dicarbamate via successive reactions with phosgene and ammonia.



Glutethimide

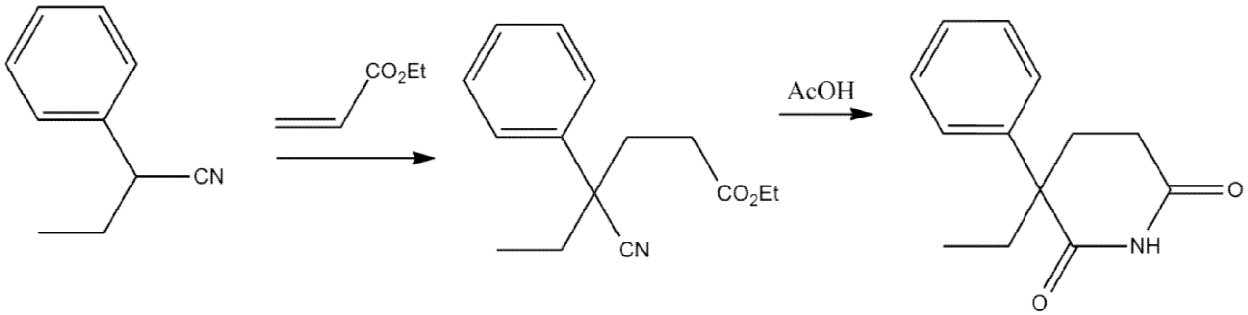


3-ethyl-3-phenyl-piperidine-2,6-dione

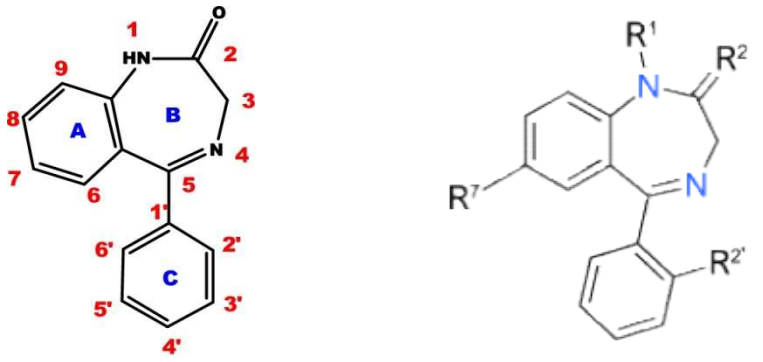
Glutethimide is a hypnotic sedative that was introduced by Ciba in 1954 as a safe alternative to barbiturates to treat insomnia. Before long, however, it had become clear that glutethimide was just as likely to cause addiction and caused similarly severe withdrawal symptoms- not used today.

Synthesis:

Glutethimide (2-ethyl-2-phenylgutarimide) is synthesized by addition of 2-phenylbutyronitrile to the methylacrylate (Michael reaction), and the subsequent alkaline hydrolysis of the nitrile group in the obtained compound into an amide group, and the subsequent acidic cyclization of the product into the desired glutethimide. The (R) isomer has a faster onset and more potent anticonvulsant activity in animal models than the (S) isomer.



BENZODIAZEPINES (BZDs)



Core structure **Common substitutions**

Fig. The core structure of benzodiazepines. "R" labels denote common locations of side chains, which give different benzodiazepines their unique properties.

Chlordiazepoxide and diazepam were introduced around 1960 as antianxiety drugs. Since then this class has proliferated and has replaced barbiturates as hypnotic and sedative as well, because—

1. BZDs produce a lower degree of neuronal depression than barbiturates. They have a high therapeutic index. Ingestion of even 20 hypnotic doses does not usually endanger life—there is no loss of consciousness (though amnesia occurs) and patient can be aroused; respiration is mostly not so depressed as to need assistance

2. Hypnotic doses do not affect respiration or cardiovascular functions. Higher doses produce mild respiratory depression and hypotension which is problematic only in patients with respiratory insufficiency or cardiac/haemodynamic abnormality.

3. BZDs have practically no action on other body systems. Only on i.v. injection the BP falls (may be marked in an occasional patient) and cardiac contractility decreases. Fall in BP in case of diazepam and lorazepam is due to reduction in cardiac output while that due to midazolam is due to decrease in peripheral resistance. The coronary arteries dilate on i.v. injection of diazepam.

4. BZDs cause less distortion of sleep architecture; rebound phenomena on discontinuation of regular use are less marked.

5. BZDs do not alter disposition of other drugs by microsomal enzyme induction.

6. They have lower abuse liability: tolerance is mild, psychological and physical dependence, drug seeking and withdrawal syndrome are less marked.

7. A specific BZD antagonist *flumazenil* is available which can be used in case of poisoning.

CNS actions The overall action of all BZDs is qualitatively similar, but there are prominent differences in selectivity for different facets of action, and in their time-course of action. Different members are used for different purposes. In contrast to barbiturates, they are not general depressants, but exert relatively selective anxiolytic, hypnotic, muscle relaxant and anticonvulsant effects in different measures. Even when apparently anaesthetic dose of diazepam is administered i.v., some degree of awareness is maintained, though because of anterograde amnesia (interference with establishment of memory trace) the patient does not clearly recollect the events on recovery.

Antianxiety: Some BZDs exert relatively selective antianxiety action which is probably not dependent on their sedative property. With chronic administration relief of anxiety is maintained, but drowsiness wanes off due to development of tolerance.

Sleep: While there are significant differences among different BZDs, in general, they hasten onset of sleep, reduce intermittent awakening and increase total sleep time (specially in those who have a short sleep span). Time spent in stage 2 is increased while that in stage 3 and 4 is decreased. They tend to shorten REM phase, but more REM cycles may occur, so that effect on total REM sleep is less marked than with barbiturates. Nitrazepam has been shown to actually increase REM sleep. Night terrors and body movements during sleep are reduced and stage shifts to stage 1 and 0 are lessened. Most subjects wake up with a feeling of refreshing sleep. Some degree of tolerance develops to the sleep promoting action of BZDs after repeated nightly use.

Muscle relaxant: BZDs produce centrally mediated skeletal muscle relaxation without impairing voluntary activity (see Ch. 25). Clonazepam and diazepam have more marked muscle relaxant property. Very high doses depress neuromuscular transmission.

Anticonvulsant: Clonazepam, diazepam, nitrazepam, lorazepam and flurazepam have more prominent anticonvulsant activity than other BZDs. Diazepan and lorazepam are highly effective for short-term use in status-epilepticus, but their utility in long-term treatment of epilepsy is limited by development of tolerance to the anticonvulsant action.

Site and mechanism of action

Benzodiazepines act preferentially on midbrain ascending reticular formation (which maintains wakefulness) and on limbic system (thought and mental functions). Muscle relaxation is produced by a primary medullary site of action and ataxia is due to action on cerebellum.

BZDs act by enhancing presynaptic/postsynaptic inhibition through a specific BZD receptor which is an integral part of the $GABA_A$ receptor–Cl^- channel complex. The subunits of this complex form a pentameric transmembrane anion channel (Fig.29.3) gated by the primary ligand (GABA), and modulated by secondary ligands which include BZDs. Only the α and β subunits

are required for GABA action, and most likely the binding site for GABA is located on the β subunit, while the α/γ subunit interface carrys the BZD binding site. The modulatory BZD receptor increases the frequency of Cl^- channel opening induced by submaximal concentrations of GABA. The BZDs also enhance GABA binding to $GABA_A$ receptor. The $GABA_A$ antagonist bicuculline antagonizes BZD action in a noncompetitive manner. It is noteworthy that the BZDs do not themselves increase Cl^- conductance; have only GABA facilitatory but no GABA mimetic action. This probably explains the lower ceiling CNS depressant effect of BZDs.

USES

Currently, BZDs are one of the most frequently prescribed drugs. They have also been combined with many other categories of drugs with a view to improve efficacy by relieving attendant anxiety.

1. As hypnotic: A hypnotic should not be casually prescribed for every case of insomnia. Understanding the pattern and cause of insomnia in the specific patient is important, and use of a variety of other measures can avoid unnecessary hypnotic medication. When indicated, BZDs or the newer non-BZDs like zolpidem, zaleplon are the hypnotic of choice.

2. Other uses

(a) As anxiolytic and for day-time sedation.

(b) As anticonvulsant, especially emergency control of status epilepticus, febrile convulsions, tetanus, etc.

(c) As centrally acting muscle relaxant.

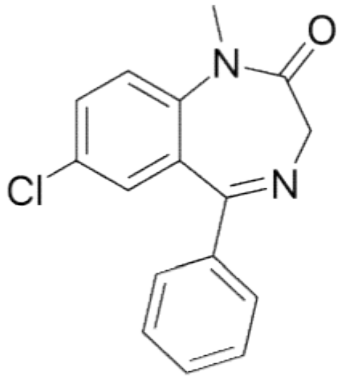
(d) For preanaesthetic medication, i.v. anaesthesia and conscious sedation.

(e) Before ECT, electrical cardioversion of arrhythmias, cardiac catheterization, endoscopies, in obstetrics and many minor procedures—diazepam i.v. has gained popularity because of its calming-amnesicanalgesic and muscle relaxant properties and relative safety.

(f) Alcohol withdrawal in dependent subjects.

(g) Along with analgesics, NSAIDs, spasmolytics, antiulcer and as adjuvants to treat ‘gas’ or nonspecific dyspeptic symptoms.

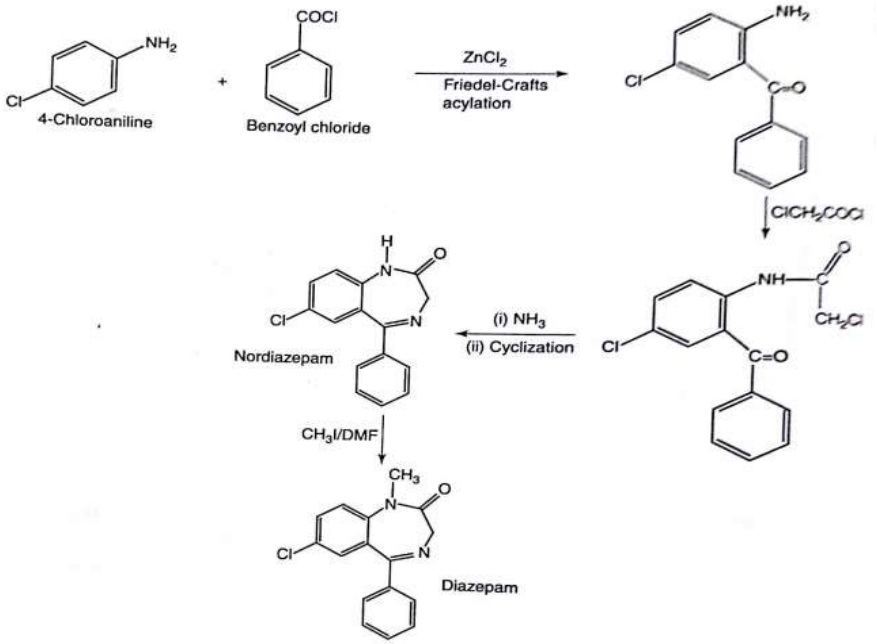
Diazepam



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

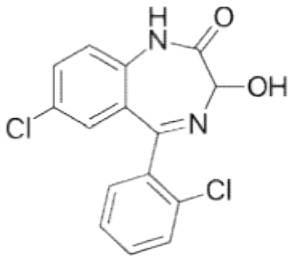
Diazepam is prototypical and was the first member of the benzodiazepine-2-one group to be introduced. It is very lipophilic and is thus rapidly and completely absorbed after oral administration. Maximum peak blood concentration occurs in 2 hours and elimination is slow, with a half-life of about 46 hours. It is the oldest and all purpose BZD, used as anxiolytic, hypnotic, muscle relaxant, premedicant, anaesthetic and for emergency control of seizures due to its broad spectrum activity. It generates active metabolites (desmethyl-diazepam, oxazepam). On occasional use it is free of residual effects. With regular use accumulation occurs and prolonged anxiolytic effect may be obtained. It is less likely to cause rebound insomnia on discontinuation of chronic use. Withdrawal phenomena are mild.

Synthesis:



Dose: VALIUM 2, 5, 10 mg tab., 10 mg/2 ml inj., CALMPOSE 2.5, 5, 10 mg tab, 2 mg/5 ml syr, 10 mg/2 ml inj, PLACIDOX 2, 5, 10 mg tab, 10 mg/2 ml inj.

Lorazepam

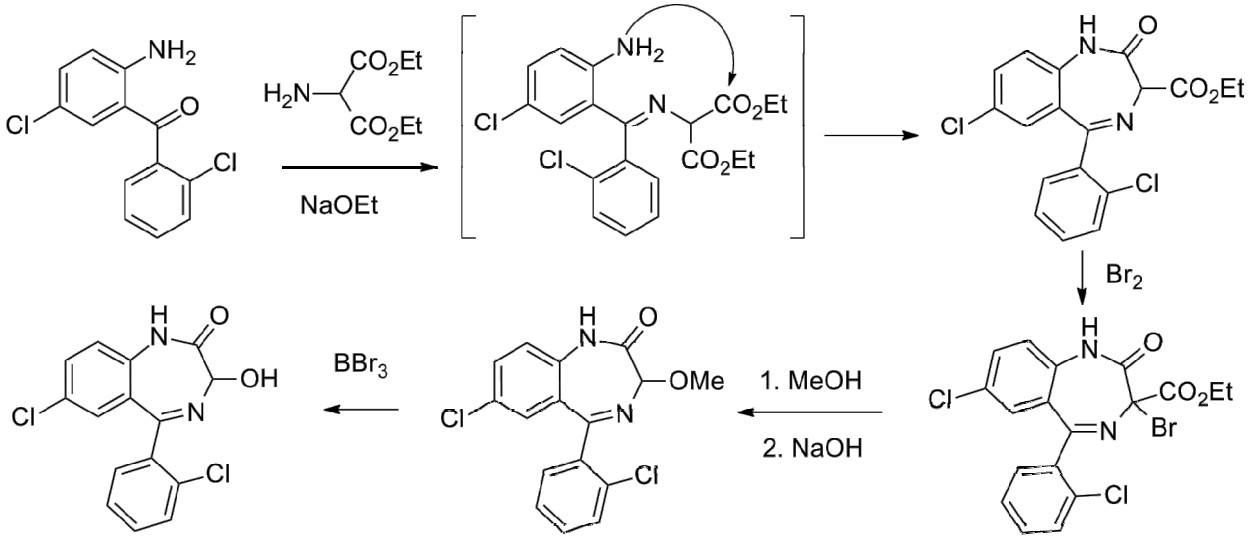


7-chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-1,4-benzodiazepin-2-one

Lorazepam is the 2' -chloro derivative of oxazepam. In keeping with overall SARs, the 2'-chloro substituent increases activity. As with oxazepam, metabolism is relatively rapid and uncomplicated because of the 3-hydroxyl group in the compound. Thus, it also has short half-life (2–6 hours) and similar pharmacological activity.

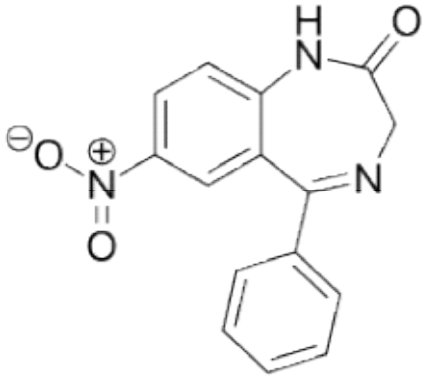
Lorazepam has anxiolytic, sedative, hypnotic, amnesic, anticonvulsant, and muscle relaxant properties. It is a high-potency and an intermediate-acting benzodiazepine.

Synthesis:



Uses: It is used to treat anxiety disorders, trouble sleeping, active seizures including status epilepticus, for surgery to interfere with memory formation, sedate those who are being mechanically ventilated, alcohol withdrawal, and chemotherapy induced nausea and vomiting.

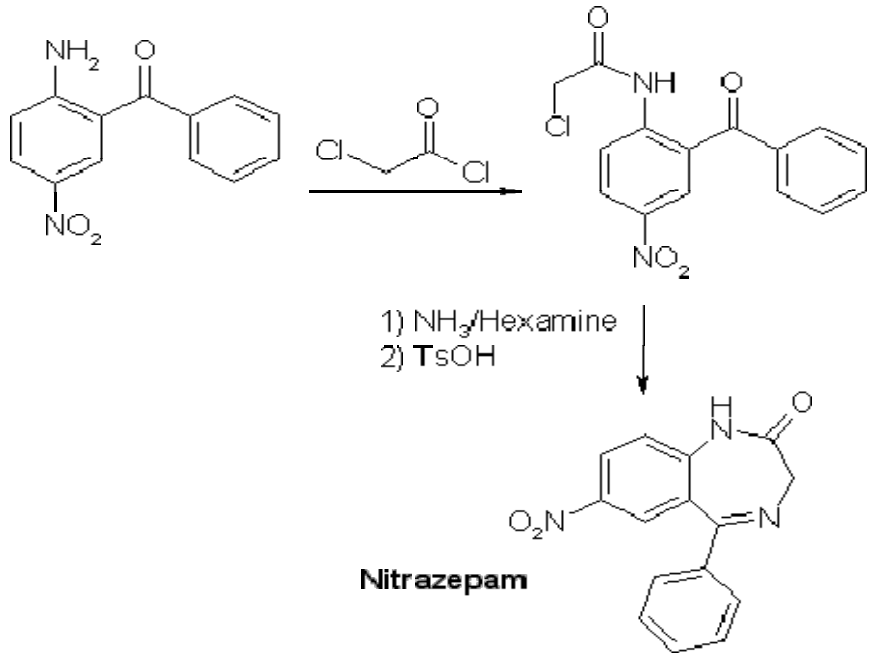
Nitrazepam



7-nitro-5-phenyl-1H-benzo[e][1,4]diazepin-2(3H)-one

Nitrazepam is dose to dose equipotent as diazepam. Accumulation and residual effects can be avoided only if ingestion is occasional. Good for patients with frequent nocturnal awakenings, when some day time sedation is acceptable.

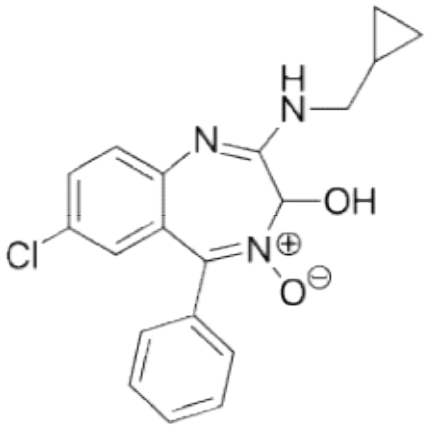
Synthesis:



Uses: Nitrazepam is used to treat short-term sleeping problems (insomnia), namely difficulty falling asleep, frequent awakening, early awakening, or a combination of each. Nitrazepam is sometimes tried to treat epilepsy when other medications fail.

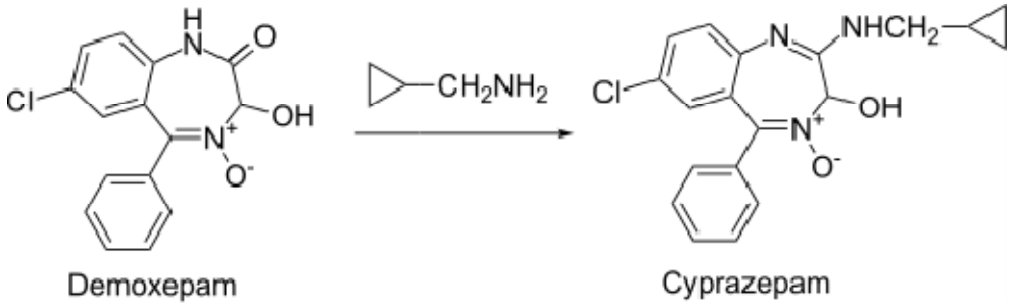
SEDAMON, HYPNOTEX, NITRAVET 5 mg tab., 5, 10 mg cap.

Cyprazepam



10-chloro-N-(cyclopropylmethyl)-3-hydroxy-2-phenyl-3,6-diazabicyclo[5.4.0]undeca-1,6,8,10-tetraen-5-imine

Synthesis:



Uses: Cyprazepam is a drug which is a sedative-hypnotic benzodiazepine derivative. It has anxiolytic properties, and presumably also has hypnotic, skeletal muscle relaxant, anticonvulsant and amnestic properties.