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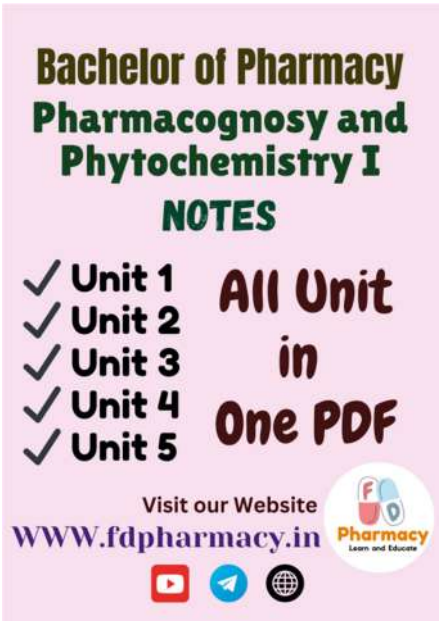
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MEDICINAL CHEMISTRY – I

UNIT 4

TOPIC :

- **Drugs acting on Central Nervous System**

  A. Sedatives and Hypnotics :

  Benzodiazepines : SAR of Benzodiazepines, Chlordiazepoxide, Diazepam*, Oxazepam, Chlorazepate, Lorazepam, Alprazolam, Zolpidem*

  Barbiturtes : *SAR of barbiturates, Barbital*, Phenobarbital, Mephobarbital, Amobarbital, Butabarbital, Pentobarbital, Secobarbital

  Miscelleneous :

  Amides & imides: Glutethmide.

  Alcohol & their carbamate derivatives: Meprobomate, Ethchlorvynol.

  Aldehyde & their derivatives: Triclofos sodium, Paraldehyde

Drugs Acting on Central Nervous System (CNS)

- Drugs acting on the CNS are pharmacological agents that specifically influence the functions of the brain and spinal cord.
- These drugs modify mental activity, mood, consciousness, perception, and behavior.
- They are widely used in the management of neurological disorders (like epilepsy, Parkinsonism) and psychiatric disorders (like depression, schizophrenia, anxiety, insomnia, etc.).
- Mechanism: They act by altering the function of neurotransmitters (e.g., GABA, dopamine, serotonin, acetylcholine, norepinephrine) either by enhancing or inhibiting their activity.

Major Classes of CNS-Acting Drugs

1. Sedative-Hypnotics
2. Antipsychotics (Neuroleptics / Major Tranquilizers)
3. Antidepressants
4. Antiepileptics (Anticonvulsants)
5. Anti-Parkinsonian Drugs

Sedatives and Hypnotics

- Sedatives: Drugs that calm the patient, reduce anxiety, and produce relaxation without necessarily inducing sleep.
- Hypnotics: Drugs that induce sleep resembling natural sleep.
- Both groups act as CNS depressants in a dose-dependent manner:
  - Low dose → Sedation (anxiolysis, relaxation)
  - Higher dose → Hypnosis (sleep induction)
- They are commonly prescribed for insomnia, anxiety, pre-anesthetic medication, and seizure control.

Classification of Sedatives and Hypnotics

1. **Benzodiazepines**
   - Chlordiazepoxide
   - Diazepam
   - Oxazepam
   - Chlorazepate
   - Lorazepam
   - Alprazolam
   - Zolpidem (structurally different but benzodiazepine-like action)
2. **Barbiturates**
   - Phenobarbital
   - Barbital
   - Mephobarbital
   - Amobarbital
   - Butabarbital
   - Pentobarbital
   - Secobarbital
3. **Miscellaneous Agents**
   - Alcohols: Ethchlorvynol
   - Carbamates: Meprobamate
   - Amides & Imides: Glutethimide
   - Aldehyde derivatives: Triclofos sodium
   - Other hypnotics: Zopiclone, Zaleplon

Benzodiazepines

- Definition: Class of CNS depressants that reduce anxiety, induce sedation, relax muscles, and help in sleep.
- History: Accidentally discovered in 1961 (first: Chlordiazepoxide).
- Examples:
  - Chlordiazepoxide
  - Diazepam
  - Oxazepam
  - Chlorazepate
  - Lorazepam
  - Alprazolam
  - Zolpidem

Mechanism of Action

- Benzodiazepines act by enhancing the action of GABA (Gamma Amino Butyric Acid) at the GABA-A receptor complex.
- GABA is the major inhibitory neurotransmitter in the brain.
- Binding of benzodiazepines increases the frequency of chloride ion channel opening, causing neuronal hyperpolarization and CNS depression.
- Effects:
  - Anxiolytic (reduce anxiety)
  - Hypnotic (induce sleep)
  - Muscle relaxant
  - Anticonvulsant
  - Pre-anesthetic

SAR (Structure–Activity Relationship) of Benzodiazepines

Benzodiazepines consist of three main rings: A (benzene), B (diazepine), C (phenyl).

Ring A (Benzene ring)

- Essential for binding to GABA-A receptor.
- Electron withdrawing group at position 7 (e.g., –Cl, –NO_2) enhances activity.
- Substitutions at 6, 8, or 9 positions usually reduce potency.

Ring B (Diazepine ring)

- Contains two nitrogen atoms.
- Substitution at N1 (alkyl, haloalkyl, aminoalkyl) increases activity.
- Hydroxy group at position 3 → Increases water solubility & faster metabolism → shorter duration of action.
- Phenyl group at position 5 is essential for activity.

Ring C (Phenyl ring at position 5)

- Increases binding affinity to GABA-A receptor.
- Ortho substitution (2-position) with electron-withdrawing groups enhances potency.
- Para substitution generally decreases activity.

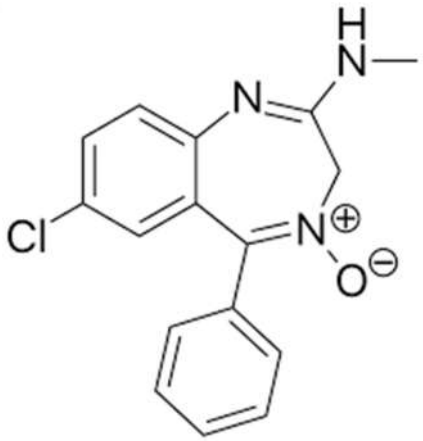
Therapeutic Uses of Benzodiazepines

- Anxiety disorders (Diazepam, Lorazepam)
- Insomnia (Temazepam, Triazolam)
- Epilepsy and seizures (Clonazepam, Diazepam)
- Muscle relaxation (Diazepam)
- Pre-anesthetic medication (Midazolam, Lorazepam)
- Alcohol withdrawal syndrome (Chlordiazepoxide, Diazepam)

Chlordiazepoxide

Structure

- Belongs to benzodiazepines (first-generation).
- Tricyclic structure: benzene ring fused to a seven-membered diazepine ring.
- Chlorine atom at position 7 enhances pharmacological activity.
- Chemically, it is a 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine.



Mechanism of Action (MOA)

- Acts as a positive allosteric modulator of GABA-A receptors in the CNS.
- Enhances GABA activity, increasing chloride ion influx → hyperpolarization of neurons.
- Pharmacological effects:
  - Sedation and anxiolysis (calms CNS activity).
  - Muscle relaxation.
  - Anticonvulsant activity.
  - Hypnotic effect at higher doses.

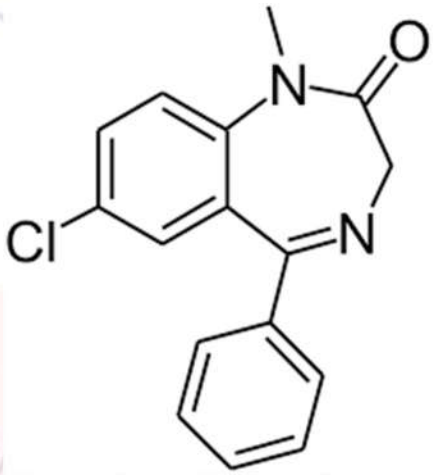
Therapeutic Uses

- Anxiety disorders (short-term management).
- Alcohol withdrawal (reduces agitation and risk of seizures).
- Preoperative sedation.
- Occasionally used for muscle relaxation and insomnia.

Diazepam

Structure

- Belongs to benzodiazepines (long-acting).
- Tricyclic structure: benzene ring fused to a seven-membered diazepine ring.
- Chlorine atom at position 7 enhances activity.
- Chemically, it is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.



Mechanism of Action (MOA)

- Positive allosteric modulator of GABA-A receptors in the CNS.
- Enhances GABAergic inhibition → increases chloride influx → hyperpolarization of neurons.
- Pharmacological effects:
  - Anxiolytic (reduces anxiety).
  - Sedative–hypnotic (induces calmness and sleep).
  - Anticonvulsant (raises seizure threshold).
  - Muscle relaxant (by CNS depression).

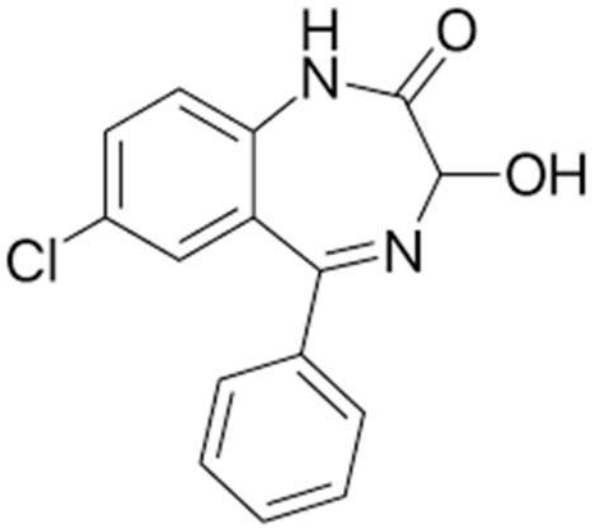
Therapeutic Uses

- Anxiety disorders.
- Status epilepticus (IV route).
- Muscle spasm and spasticity.
- Preoperative sedation and amnesia.
- Alcohol withdrawal management.

Oxazepam

Structure

- Belongs to benzodiazepines (intermediate-acting).
- Tricyclic structure: benzene ring fused to a seven-membered diazepine ring.
- Hydroxyl group at position 3 → increases water solubility and allows phase II metabolism (conjugation).
- Chemically, it is 7-chloro-3-hydroxy-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.



Mechanism of Action (MOA)

- Positive allosteric modulator of GABA-A receptors in the CNS.
- Enhances GABAergic inhibition → increases chloride influx → hyperpolarizes neurons.
- Pharmacological effects:
  - Sedative and anxiolytic (reduces anxiety).
  - Muscle relaxation (less pronounced than other benzodiazepines).
  - Hypnotic effect (induces sleep at higher doses).

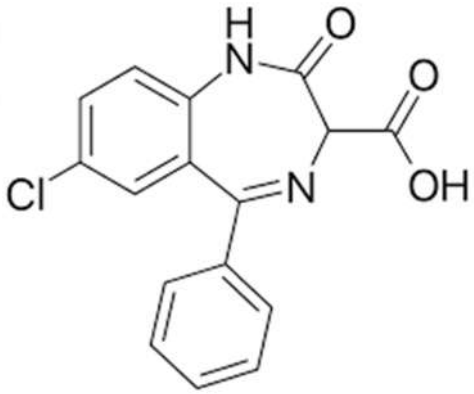
Therapeutic Uses

- Anxiety disorders, especially in elderly or hepatic-impaired patients (due to safe metabolism via conjugation).
- Insomnia associated with anxiety.
- Alcohol withdrawal symptoms.

Chlorazepate

Structure

- Benzodiazepine class (long-acting prodrug).
- Tricyclic structure: benzene ring fused to a seven-membered diazepine ring.
- Carboxylic acid ester at position 2 → converted in vivo to desmethyldiazepam (active metabolite).
- Chemically: 2-(aminomethyl)-3H-1,4-benzodiazepin-3-one 7-chloro derivative.



Mechanism of Action (MOA)

- Prodrug: rapidly converted in the body to desmethyldiazepam, the active form.
- Acts as a positive allosteric modulator of GABA-A receptors.
- Enhances GABAergic inhibition → increased chloride influx, hyperpolarizing neurons.
- Pharmacological effects:
  - Sedation and anxiolysis.
  - Muscle relaxation.
  - Anticonvulsant activity.

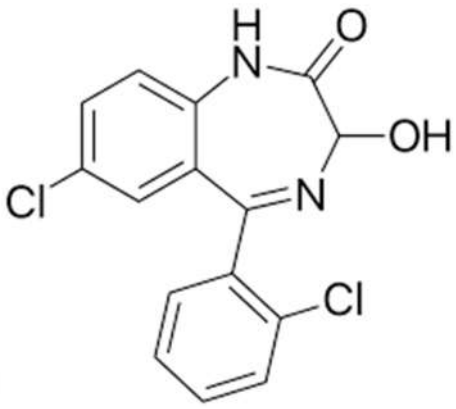
Therapeutic Uses

- Anxiety disorders (especially chronic anxiety).
- Alcohol withdrawal symptoms.
- Seizure disorders (as adjunct therapy).
- Preoperative sedation.

Lorazepam

Structure

- Belongs to benzodiazepines (intermediate-acting).
- Tricyclic structure: benzene ring fused to a seven-membered diazepine ring.
- Hydroxyl group at position 3 → allows phase II metabolism (glucuronidation) → safer in hepatic impairment.
- Chemically: 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one.



Mechanism of Action (MOA)

- Positive allosteric modulator of GABA-A receptors in the CNS.
- Enhances GABA-mediated chloride influx → hyperpolarizes neurons → CNS depression.
- Pharmacological effects:
  - Sedative and anxiolytic.
  - Anticonvulsant.
  - Muscle relaxant (mild).
  - Hypnotic effect at higher doses.

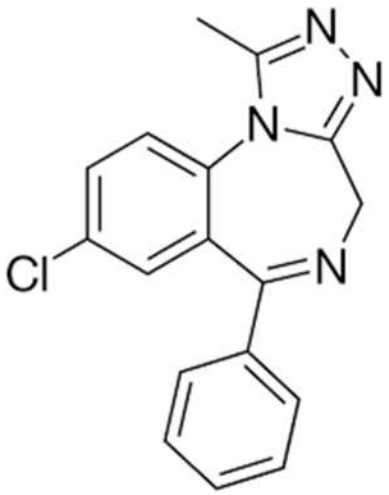
Therapeutic Uses

- Anxiety disorders.
- Status epilepticus (IV route).
- Preoperative sedation.
- Alcohol withdrawal symptoms.
- Insomnia associated with anxiety.

Alprazolam

Structure

- Belongs to benzodiazepines (short-acting, triazolobenzodiazepine).
- Tricyclic structure: benzene fused to diazepine ring with an additional triazole ring at position 1.
- Chemically: 8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine.
- Lipophilic → rapid onset of action.



Mechanism of Action (MOA)

- Positive allosteric modulator of GABA-A receptors in CNS.
- Enhances GABA-mediated chloride influx → hyperpolarizes neurons → reduces CNS excitability.
- Pharmacological effects:
  - Anxiolytic (primary use).
  - Sedative-hypnotic (less pronounced than long-acting benzodiazepines).
  - Muscle relaxant (mild).
  - Anticonvulsant (short-term use).

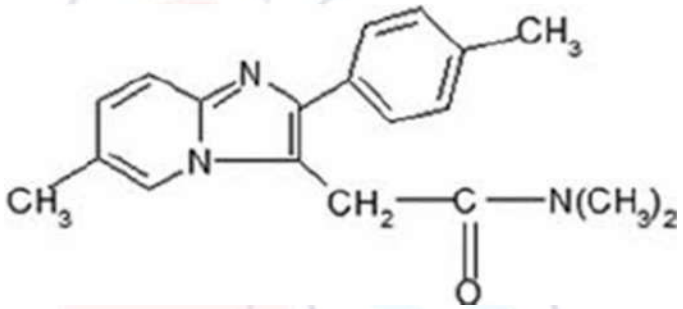
Therapeutic Uses

- Generalized anxiety disorder (GAD).
- Panic disorder (with or without agoraphobia).
- Short-term insomnia treatment (secondary use).
- Adjunct in depression with anxiety.

Zolpidem

Structure

- Belongs to non-benzodiazepine hypnotics (Imidazopyridines).
- Structurally different from classical benzodiazepines but selectively binds to BZ1 (omega-1) receptor subtype of GABA-A receptor.
- Chemically: N,N,6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide.
- Rapidly absorbed orally, highly lipophilic → fast onset of action.



Mechanism of Action (MOA)

- Selective positive allosteric modulator of GABA-A receptors (BZ1 subtype).
- Enhances GABA-mediated chloride influx → hyperpolarizes neurons → CNS depression.
- Produces sedative-hypnotic effect with minimal anxiolytic, anticonvulsant, or muscle relaxant activity.

Therapeutic Uses

- Short-term treatment of insomnia, especially difficulty in sleep initiation.
- Used in patients who cannot tolerate benzodiazepines or for short-term hypnotic therapy.
- Not preferred for long-term use due to risk of tolerance and dependence.

Barbiturates

- Barbiturates are potent CNS depressants derived from barbituric acid.
- They act as sedative-hypnotics and anticonvulsants, but due to their narrow therapeutic index and risk of dependence/respiratory depression, their medical use has declined in favor of safer benzodiazepines.
- They produce a dose-dependent CNS depression:
  - Low dose → Sedation (calming effect)
  - Moderate dose → Hypnosis (sleep induction)
  - High dose → Surgical anesthesia
  - Toxic dose → Coma, death (respiratory failure)

Examples of Barbiturates

- Phenobarbital
- Barbital
- Mephobarbital
- Amobarbital
- Butabarbital
- Pentobarbital
- Secobarbital

Mechanism of Action

- Barbiturates act on the GABA-A receptor complex (different binding site from benzodiazepines).
- They enhance the action of GABA by increasing the duration of chloride ion channel opening → neuronal hyperpolarization → CNS depression.
- At high concentrations, barbiturates can directly open chloride channels, even without GABA → explains their high toxicity compared to benzodiazepines.

Structure–Activity Relationship (SAR) of Barbiturates

Parent nucleus: Barbituric acid (not active itself).
Biological activity depends on substitution at C-5, N-1/N-3, and unsaturation/aromaticity.

1. C-5 Substitution (critical for activity)
    - Dialkyl or Aryl/Alkyl substitution → increases lipid solubility and CNS activity.
    - Example: Phenyl group at C-5 (Phenobarbital) → anticonvulsant activity.
    - Branched or unsaturated alkyl groups → faster onset and shorter duration of action.
    - Aromatic groups → prolong action.
2. N-1 or N-3 Substitution
    - Alkylation reduces polarity → increases lipophilicity and potency.
    - However, N-alkyl substitution usually reduces anticonvulsant activity, but may enhance hypnotic activity.
3. Unsaturation / Aromaticity
    - Introducing double bonds or aromatic substituents enhances lipid solubility.
    - This increases hypnotic potency and decreases duration of action.

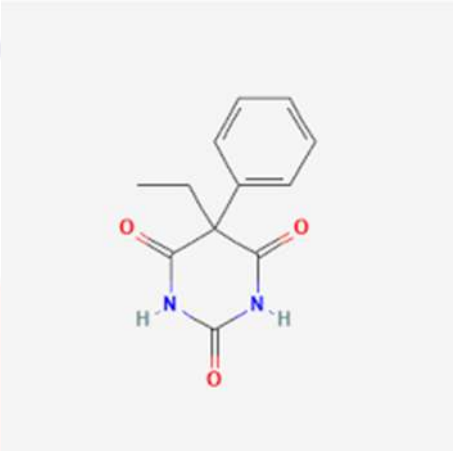
Therapeutic Uses

- Sedative-hypnotic (insomnia, but rarely used now).
- Anticonvulsant (Phenobarbital for epilepsy).
- Pre-anesthetic medication (Thiopental).
- Euthanasia / lethal injection (due to strong CNS depression).

Phenobarbital

Structure

- Belongs to barbiturates (long-acting).
- Barbituric acid derivative: cyclic ureide with two nitrogen atoms and three keto (C=O) groups.
- Chemically: 5-ethyl-5-phenylbarbituric acid.
- Lipophilic → crosses blood-brain barrier slowly → longer onset, long duration.



Mechanism of Action (MOA)

- Positive allosteric modulator of GABA-A receptors in CNS.
- Enhances GABA-mediated chloride influx → hyperpolarizes neurons → CNS depression.
- At high concentrations: may directly open chloride channels independent of GABA.
- Pharmacological effects:
  - Anticonvulsant.
  - Sedative and hypnotic.
  - Minimal muscle relaxant effect.

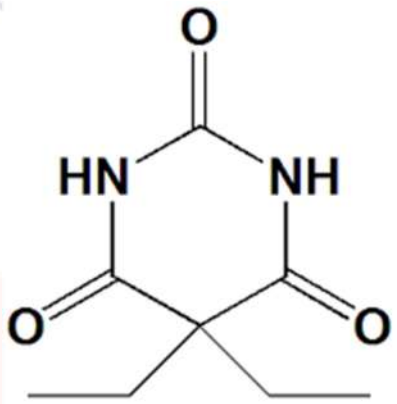
Therapeutic Uses

- Epilepsy: especially generalized tonic-clonic and partial seizures.
- Sedation: preoperative or short-term use.
- Occasionally used for status epilepticus (less preferred than benzodiazepines).

Barbital

Structure

- Belongs to barbiturates (long-acting).
- Barbituric acid derivative: cyclic ureide with two nitrogen atoms and three keto (C=O) groups.
- Chemically: 5,5-diethylbarbituric acid.
- Lipophilic → CNS penetration is moderate → slow onset and long duration.



Barbital

Mechanism of Action (MOA)

- Positive allosteric modulator of GABA-A receptors in CNS.
- Enhances GABA-mediated chloride influx → hyperpolarizes neurons → CNS depression.
- Produces sedative and hypnotic effects; anticonvulsant effects are mild.

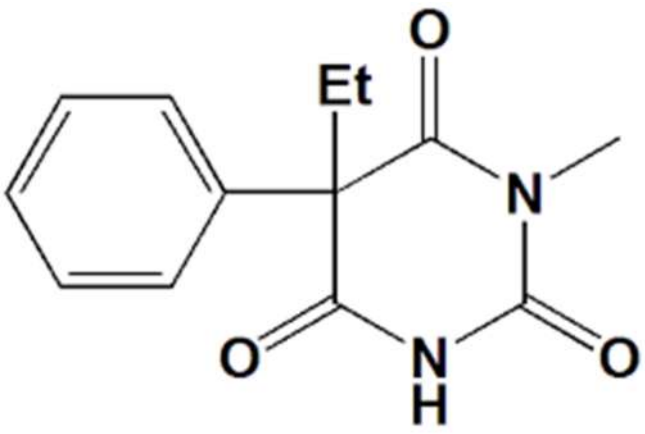
Therapeutic Uses

- Sedation: to calm patients in anxiety or mild agitation.
- Hypnotic: short-term treatment of insomnia.
- Occasionally used in epilepsy (less common now).
- Largely replaced by safer benzodiazepines due to better safety profile.

Mephobarbital

Structure

- Belongs to barbiturates (long-acting).
- Barbituric acid derivative with a methyl group on the nitrogen (N-1 position): 1-methyl-5-phenylbarbituric acid.
- Lipophilic → CNS penetration is moderate → slow onset, long duration.



Mephobarbital

Mechanism of Action (MOA)

- Positive allosteric modulator of GABA-A receptors in CNS.
- Enhances GABA-mediated chloride influx → hyperpolarizes neurons → CNS depression.
- Produces anticonvulsant and sedative effects; less hypnotic potency compared to other barbiturates.

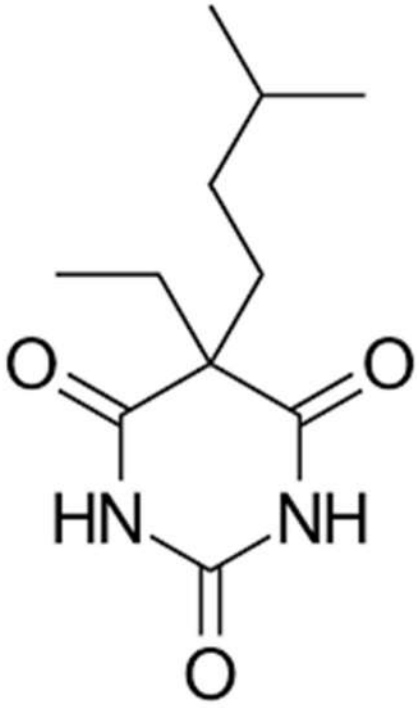
Therapeutic Uses

- Epilepsy: used in generalized tonic-clonic and partial seizures.
- Sedation: mild calming effect.
- Less commonly used today due to availability of safer alternatives like benzodiazepines.

Amobarbital

Structure

- Belongs to barbiturates (intermediate-acting).
- Barbituric acid derivative: 5-ethyl-5-(3-methylbutyl)barbituric acid.
- Lipophilic → moderate CNS penetration → intermediate onset and duration.



Mechanism of Action (MOA)

- Positive allosteric modulator of GABA-A receptors in CNS.
- Enhances GABA-mediated chloride influx → hyperpolarizes neurons → CNS depression.
- Produces sedative, hypnotic, and anticonvulsant effects.

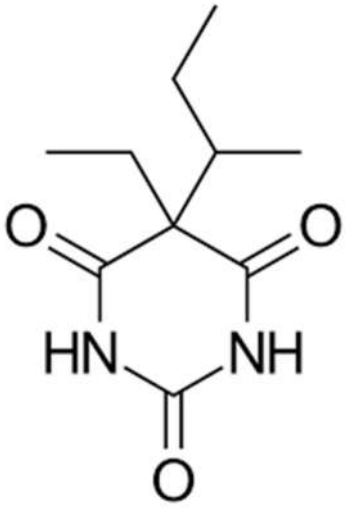
Therapeutic Uses

- Sedation: preoperative or short-term calming.
- Hypnotic: treatment of insomnia.
- Occasionally in epilepsy (less preferred than phenobarbital).
- Largely replaced by safer benzodiazepines in modern therapy.

Butabarbital

Structure

- Belongs to barbiturates (intermediate-acting).
- Barbituric acid derivative: 5-sec-butyl-5-ethylbarbituric acid.
- Lipophilic → moderate CNS penetration → intermediate onset and duration.



Mechanism of Action (MOA)

- Positive allosteric modulator of GABA-A receptors in CNS.
- Enhances GABA-mediated chloride influx → hyperpolarizes neurons → CNS depression.
- Produces sedative, hypnotic, and anticonvulsant effects.

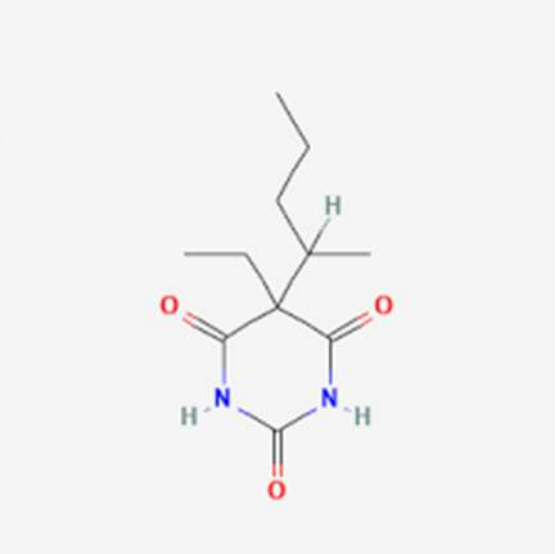
Therapeutic Uses

- Sedation: short-term calming or preoperative sedation.
- Hypnotic: treatment of insomnia.
- Occasionally used in epilepsy (less common today).
- Has largely been replaced by benzodiazepines due to improved safety.

Pentobarbital

Structure

- Belongs to barbiturates (short-acting).
- Barbituric acid derivative: 5-ethyl-5-(1-methylbutyl)barbituric acid.
- Highly lipophilic → rapid CNS penetration → fast onset, short duration.



Mechanism of Action (MOA)

- Positive allosteric modulator of GABA-A receptors in CNS.
- Enhances GABA-mediated chloride influx → hyperpolarizes neurons → CNS depression.
- Produces sedative, hypnotic, and anticonvulsant effects.
- At high doses → can induce anesthesia.

Therapeutic Uses

- Short-term insomnia (hypnotic).
- Sedation for preoperative procedures.
- Emergency treatment of seizures (less preferred now).
- Occasionally used as anesthetic induction agent in hospitals.

Secobarbital

Structure

- Belongs to barbiturates (short-acting).
- Barbituric acid derivative: 5-(pent-2-en-1-yl)-5-(1-methylbutyl)barbituric acid.
- Highly lipophilic → rapid CNS penetration → fast onset, short duration.

Mechanism of Action (MOA)

- Positive allosteric modulator of GABA-A receptors in CNS.
- Enhances GABA-mediated chloride influx → hyperpolarizes neurons → CNS depression.
- Produces sedative, hypnotic, and anticonvulsant effects.
- At higher doses → can induce anesthesia.

Therapeutic Uses

- Short-term insomnia (hypnotic).
- Preoperative sedation.
- Rarely used today due to availability of safer benzodiazepines.

Miscelleneous

Amides

- Amides are a miscellaneous class of sedative-hypnotic agents.
- They are synthetic derivatives that act as CNS depressants similar to barbiturates but with slightly different chemical structures.
- Their clinical use today is limited, as safer drugs (benzodiazepines and Z-drugs) are available.

Examples

- **Glutethimide**

Mechanism of Action

- Act on the GABA-A receptor complex in the CNS.
- Enhance the inhibitory action of GABA by facilitating chloride ion influx, producing sedation, hypnosis, and anticonvulsant activity.
- Unlike benzodiazepines, they do not have a specific antagonist (like flumazenil).

Structure–Activity Relationship (SAR) of Amide Hypnotics

- Based on cyclic or acyclic amide nucleus.
- Lipophilicity determines potency and duration of action:
  - More lipophilic → faster onset, shorter duration.
- Alkyl or aryl substitutions on the amide nucleus enhance sedative-hypnotic activity.
- Halogen substitution → increases potency but also toxicity.

Therapeutic Uses

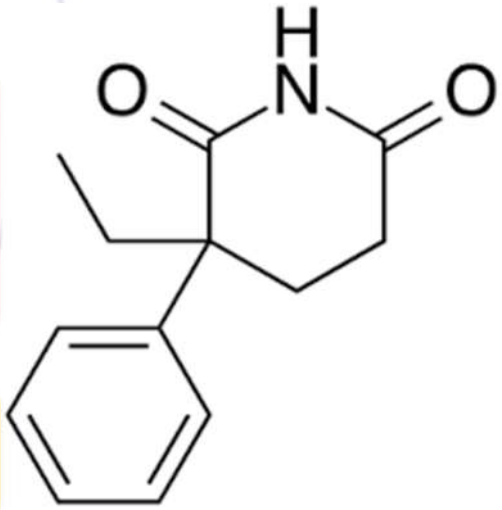
- Historically used as:
  - Hypnotics (treatment of insomnia).
  - Sedatives (for anxiety).

- Glutethimide was once used as a substitute for barbiturates in insomnia and epilepsy.
- Currently, they are rarely prescribed because of:
  - High risk of dependence and tolerance.
  - Toxicity and drug abuse potential.

Glutethimide

Structure

- Belongs to non-barbiturate sedative-hypnotics.
- Chemical class: Piperidine derivative (cyclic imide).
- Structure: γ-substituted piperidinedione → lipophilic → CNS penetration moderate.



Mechanism of Action (MOA)

- Enhances GABA-A receptor activity → increases chloride influx → hyperpolarization of neurons.
- Produces sedative and hypnotic effects.
- Less potent than barbiturates but still CNS depressant.

Therapeutic Uses

- Short-term insomnia.
- Sedation for anxiety or agitation (historical use).
- Rarely used today due to risk of dependence and overdose.

Amides and Imides

- **Amides:**
  - Functional group in which nitrogen is attached to one carbonyl group (C=O) through a single sigma bond.
  - General structure:

$$R\text{-}C(=O)\text{-}NH_2 \quad \text{or} \quad R\text{-}C(=O)\text{-}NR_2$$

- **Imides:**
  - Functional group in which nitrogen is attached to two carbonyl groups (C=O) via single sigma bonds.
  - General structure:

$$R\text{-}CO\text{-}NH\text{-}CO\text{-}R$$

Examples

- Glutethimide

Mechanism of Action (MOA)

- Amides (Local anesthetics):
  - Block voltage-gated sodium channels in neuronal membranes.
  - Prevent generation and propagation of action potentials.
  - Result → Loss of pain sensation (analgesia/local anesthesia).
- Imides (Anticonvulsants):
  - Many act on T-type calcium channels (e.g., Ethosuximide in absence seizures).
  - Some act indirectly on GABA-A receptor complex enhancing inhibitory neurotransmission.
  - Result → CNS depression, anticonvulsant, or hypnotic effects.

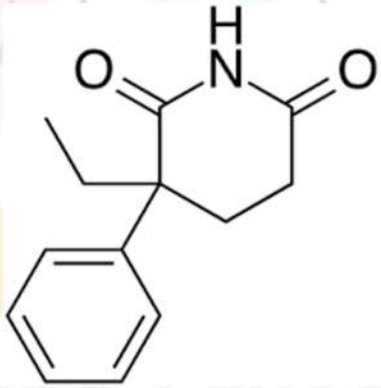
Therapeutic Uses

- Amides:
  - Local anesthesia (Lidocaine, Bupivacaine).
  - Sedation and hypnosis (older cyclic amide derivatives).
- Imides:
  - Treatment of epilepsy (Ethosuximide for absence seizures).
  - Historically used as sedative-hypnotics (Glutethimide, Methyprylon).

Glutethmide

Structure

- Belongs to non-barbiturate sedative-hypnotics.
- Chemical class: γ-substituted piperidinedione (cyclic imide derivative).
- Lipophilic → allows moderate CNS penetration.



Mechanism of Action (MOA)

- Acts as a positive allosteric modulator of GABA-A receptors.
- Enhances GABA-mediated chloride influx → hyperpolarizes neurons → CNS depression.
- Produces sedative and hypnotic effects.

Therapeutic Uses

- Short-term insomnia.
- Sedation for anxiety or agitation (historical use).
- Rarely used today due to risk of dependence, tolerance, and overdose.

Alcohols and their Carbamate Derivatives

General Formula

- **Alcohols:**

where R = alkyl or aryl group, and –OH = hydroxyl group.

- Classification (based on number of hydroxyl groups):
  - Monohydric alcohols → contain one –OH group (e.g., Ethanol: $CH_3–CH_2–OH$)
  - Dihydric alcohols (glycols) → contain two –OH groups (e.g., Ethane-1,2-diol: $HO–CH_2–CH_2–OH$)
  - Trihydric alcohols → contain three –OH groups (e.g., Propane-1,2,3-triol / Glycerol: $HO–CH_2–CHOH–CH_2OH$)

Examples

- Meprobomate,
- Ethchlorvynol.

Mechanism of Action (MOA)

- Alcohols:
  - Enhance the effect of GABA (γ-aminobutyric acid) at GABA-A receptors.
  - Cause CNS depression, producing sedation, hypnosis, anxiolysis, and in higher doses anesthesia or respiratory depression.
  - Ethanol also affects other receptors (NMDA inhibition, dopamine release), contributing to its psychoactive effects.
- Carbamate derivatives:
  - Act similarly to barbiturates by potentiating GABA-A receptor activity.

- Increase inhibitory neurotransmission → sedation, muscle relaxation, and anxiolytic effects.

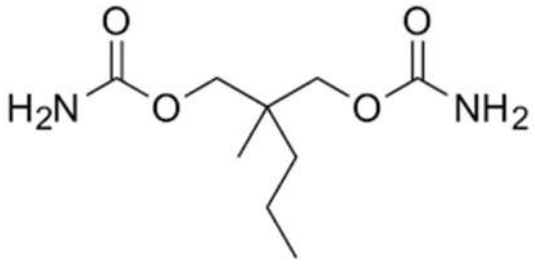
Therapeutic Uses

- Alcohols:
  - Ethanol: historically used as sedative-hypnotic; now used in methanol poisoning (as antidote).
  - Glycerol: osmotic diuretic, laxative.
  - Ethylene glycol: not used therapeutically (toxic, causes renal failure).
- Carbamates:
  - Meprobamate: used as anxiolytic and sedative-hypnotic (historically).
  - Carisoprodol: centrally acting muscle relaxant.
  - Felbamate: anticonvulsant (used in epilepsy).

Meprobamate

Structure

- Belongs to carbamate derivative sedative-hypnotics.
- Chemical formula: $C_{10}H_{22}N_2O_4$
- Structure: 2-methyl-2-propyl-1,3-propanediol dicarbamate.
- Lipophilic → allows CNS penetra



Mechanism of Action (MOA)

- Enhances GABA-A receptor activity → increases chloride influx, hyperpolarizing neurons.
- Produces sedative, anxiolytic, and muscle relaxant effects.
- Less potent than barbiturates; lower risk of respiratory depression.

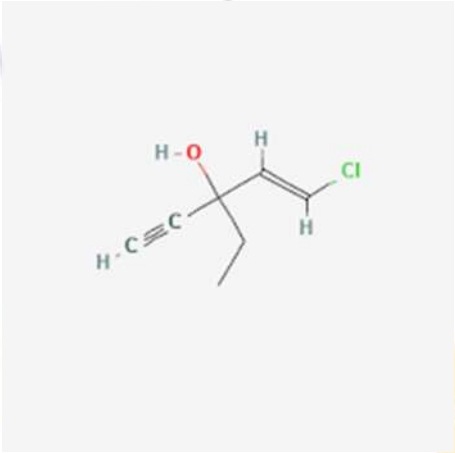
Therapeutic Uses

- Anxiety disorders (short-term management).
- Tension and agitation.
- Historically used as sedative, now largely replaced by benzodiazepines due to safety concerns.

Ethchlorvynol

Structure

- Belongs to non-barbiturate sedative-hypnotics.
- Chemical class: Hydroxyvinyl derivative.
- Structure: 2-chloro-1-ethenyl-1-cyclohexanol.
- Lipophilic → allows CNS penetration.



Mechanism of Action (MOA)

- Enhances GABA-A receptor activity → increases chloride influx, hyperpolarizing neurons.
- Produces sedative and hypnotic effects.
- Less potent than barbiturates; lower risk of respiratory depression.

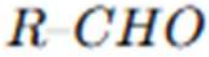
Therapeutic Uses

- Short-term insomnia.
- Sedation for agitation or anxiety (historical use).
- Rarely used today due to dependence, tolerance, and availability of safer drugs.

Aldehydes and their Derivatives

- Aldehyde functional group:
  A carbon atom is attached by:
  - A double bond to oxygen (C=O, carbonyl group)
  - A single bond to hydrogen (–H)
  - A single bond to another atom or group (–R)

  General formula:



  where R = alkyl or aryl group.

Examples

- Triclofos sodium,
- Paraldehyde.

Mechanism of Action (MOA)

- Aldehyde derivatives act as CNS depressants.
- They enhance the inhibitory effect of GABA (γ-aminobutyric acid) at GABA-A receptors.
- Result: Increased chloride ion influx → neuronal hyperpolarization → reduced brain excitability.
- Produce sedation, hypnosis, and anxiolysis by slowing down brain activity.

Therapeutic Uses

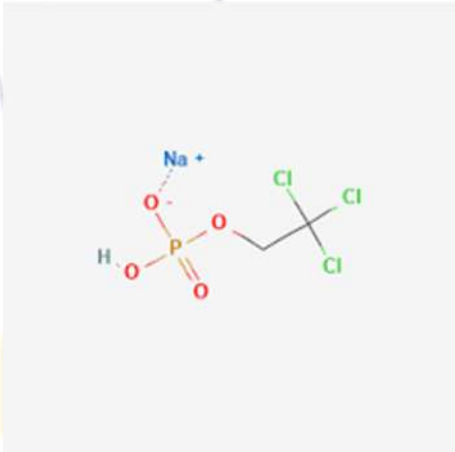
- Chloral hydrate:
  - Used as a hypnotic (induces sleep).
  - Used in children for sedation before diagnostic procedures.
  - Rarely used today due to better alternatives (benzodiazepines).

- Triclofos sodium:
  - More palatable derivative of chloral hydrate.
  - Used as a pediatric sedative and hypnotic.
- Paraldehyde:
  - Was used as a sedative and in treatment of delirium tremens (alcohol withdrawal), but now obsolete.

Triclofos Sodium

Structure

- Belongs to non-barbiturate sedative-hypnotics.
- Chemical class: Organophosphate derivative (phosphate ester of trichloroethanol).
- Prodrug → metabolized in the liver to trichloroethanol, which is the active sedative agent.



Mechanism of Action (MOA)

- Active metabolite trichloroethanol enhances GABA-A receptor activity.
- Increases chloride influx → hyperpolarization of neurons → CNS depression.
- Produces sedative and hypnotic effects.

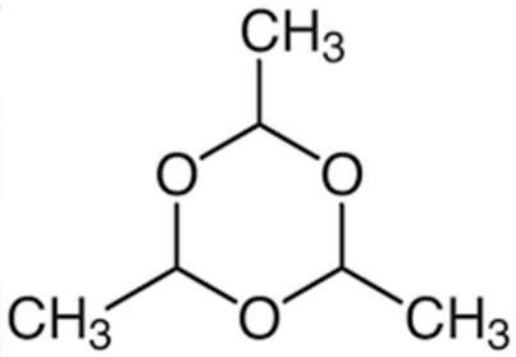
Therapeutic Uses

- Short-term insomnia, especially in children.
- Occasionally used as preoperative sedation.
- Safer alternative to barbiturates in pediatric sedation, but rarely used today due to availability of safer hypnotics.

Paraldehyde

Structure

- Chemical class: Cyclic polymer of acetaldehyde.
- Molecular formula: $(C_2H_4O)_3$
- Physical properties: Colorless, oily liquid with a pungent odor; highly lipophilic, allowing rapid CNS penetration.



Mechanism of Action (MOA)

- CNS depressant acting on multiple sites.
- Enhances GABA-A receptor activity, increasing chloride ion influx → hyperpolarization of neurons → sedation and anticonvulsant effect.
- Also has direct membrane-stabilizing effects on neurons.

Therapeutic Uses

- Sedation in severe agitation or delirium tremens.
- Anticonvulsant in status epilepticus (historical use).
- Rarely used today due to unpleasant odor, irritant properties, and availability of safer alternatives.