Sedatives and Hypnotics

Presented By;-

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Specialization:- Pharmaceutical Chemistry

Sedatives and Hypnotics

Sedatives

Sedatives are **CNS depressant drugs** that **reduce** **anxiety, tension, and excitement** *without causing sleep*. They produce a **calming effect** and help in **anxiolysis**.

Hypnotics

Hypnotics are **CNS depressants** that **induce and maintain sleep**. They produce a **stronger CNS depression** compared to sedatives.

Classification Sedatives and Hypnotics

1. **Benzodiazepines:-** Chlordiazepoxide, Diazepam*, Oxazepam, Chlorazepate, Lorazepam, Alprazolam, Zolpidem
2. **Barbiturtes:-** Barbital*, Phenobarbital, Mephobarbital, Amobarbital, Butabarbital, Pentobarbital, Secobarbital
3. **Miscelleneous:-**
    i. **Amides & imides:-** Glutethmide.
    ii. **Alcohol & their carbamate derivatives:-** Meprobomate, Ethchlorvynol.
    iii. **Aldehyde & their derivatives:-** Triclofos sodium, Paraldehyde.

Introduction of Benzodiazepines

- Benzodiazepines are a class of **CNS depressant drugs** widely used as **sedatives, hypnotics, anxiolytics, muscle relaxants, and anticonvulsants**. They were introduced in the 1960s as safer alternatives to barbiturates.
- They act primarily on the **GABAergic system** and enhance inhibitory neurotransmission in the brain. Common examples include **diazepam, lorazepam, alprazolam, clonazepam, and midazolam**.

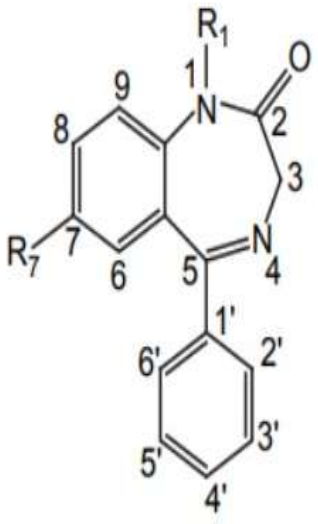
Mechanism of Action - Benzodiazepines

Benzodiazepines act on the **GABA-A receptor**, which is a **ligand-gated chloride ion channel**.

Step-by-step MOA

1. Benzodiazepines **bind to a specific site** on the GABA-A receptor (the **benzodiazepine binding site**).
2. They **do not directly open the chloride channel**, but they **enhance the effect of GABA**, the main inhibitory neurotransmitter.
3. They **increase the frequency of chloride channel opening** when GABA is present.
4. Increased **Cl^- influx → hyperpolarization** of the neuronal membrane.
5. This makes neurons **less excitable**, producing:
    - ✓ Anxiolytic effect
    - ✓ Sedation and hypnosis
    - ✓ Anticonvulsant action
    - ✓ Muscle relaxation

SAR of Benzodiazepines



Position	Structural Requirement/Modification	Effect on Activity/Properties
C-7	Electron-withdrawing group (Cl, F, Br, NO_2)	Essential for activity; increases sedative and hypnotic potency. Electron-donating groups decrease activity.
C-5	Phenyl or pyridyl ring	Essential for activity.
C-5 Phenyl Ring	Electron-withdrawing group at ortho or 2',6' positions (e.g., F, Cl)	Increases activity (e.g., Lorazepam, Triazolam). Substitutions at meta or para positions decrease activity.
C-2	Carbonyl group (C=O)	Required for the primary depressant effects (e.g., diazepam). Reduction to $–CH_2$ group results in less potent compounds.
N-1	Small alkyl group (e.g., methyl)	Increases activity and potency (e.g., diazepam). Larger substituents decrease activity. Can also be fused with an additional triazole or imidazole ring (e.g., alprazolam, midazolam).
C-3	Unsubstituted or hydroxyl group (-OH)	Alkyl groups decrease activity. A hydroxyl group (e.g., Oxazepam, Lorazepam) retains activity but results in a shorter half-life due to altered metabolism.
C-4, C-5	Double bond	Saturation or shifting of the 4,5 double bond decreases or abolishes activity.
C-6, C-8, C-9	Unsubstituted	Substituents at these positions generally decrease activity.
N-4	Position 4,5 double bond present	The nitrogen should ideally be part of a 1,4-diazepin-2-one structure for standard activity.

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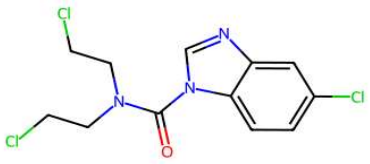
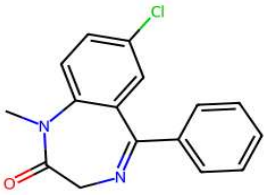
Benzodiazepines

Drug Name	Introduction (Class, Half-life)	Mechanism of Action (MOA)	Uses
Chlordiazepoxide	Benzodiazepine (long-acting, 24-48 hrs half-life). The first discovered benzodiazepine (1955).	Enhances the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) at the GABA-A receptor, increasing the frequency of chloride channel opening, which leads to CNS depression.	Management of anxiety disorders, acute alcohol withdrawal symptoms, and preoperative apprehension.
Diazepam	Benzodiazepine (long-acting, 20-50 hrs half-life).	Enhances GABA's inhibitory effects at the GABA-A receptor by increasing the frequency of chloride channel opening, leading to general CNS-depressant effects.	Anxiety, alcohol withdrawal, muscle spasms/spasticity, and as an adjunctive treatment for seizures/status epilepticus.
Oxazepam	Benzodiazepine (intermediate-acting).	Enhances GABA's inhibitory effects at the GABA-A receptor, increasing chloride ion conduction.	Management of anxiety disorders, anxiety with depressive symptoms, and acute alcohol withdrawal.
Clorazepate	Benzodiazepine (long-acting, converted to active metabolite desmethyldiazepam).	Undergoes decarboxylation in gastric juice to its active form, desmethyldiazepam, which then enhances GABA-A receptor activity.	Adjunct treatment for anxiety disorders and focal (partial) onset seizures.
Lorazepam	Benzodiazepine (intermediate-acting, 10-20 hrs half-life).	Binds to benzodiazepine receptors on the GABA-A receptor complex, enhancing GABA's inhibitory effects at multiple CNS sites.	Anxiety disorders, preoperative sedation, insomnia, and first-line treatment for convulsive status epilepticus. Preferred for use in patients with liver dysfunction.
Alprazolam	Benzodiazepine (intermediate-acting).	Enhances the effects of GABA at the GABA-A receptor, producing anxiolytic, sedative, and muscle relaxant effects.	Treatment of anxiety disorders and panic disorders (including agoraphobia).
Zolpidem	Non-benzodiazepine (Z-drug, short-acting hypnotic).	Binds selectively to the benzodiazepine-1 (BNZ-1) receptor subtype of the GABA-A complex, which primarily mediates sleep.	Short-term treatment of insomnia (specifically for sleep onset and maintenance).

Chemical Structure Benzodiazepines

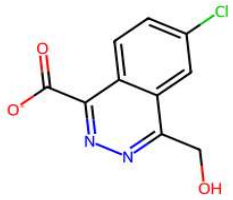


Chlordiazepoxide



Diazepam

Oxazepam



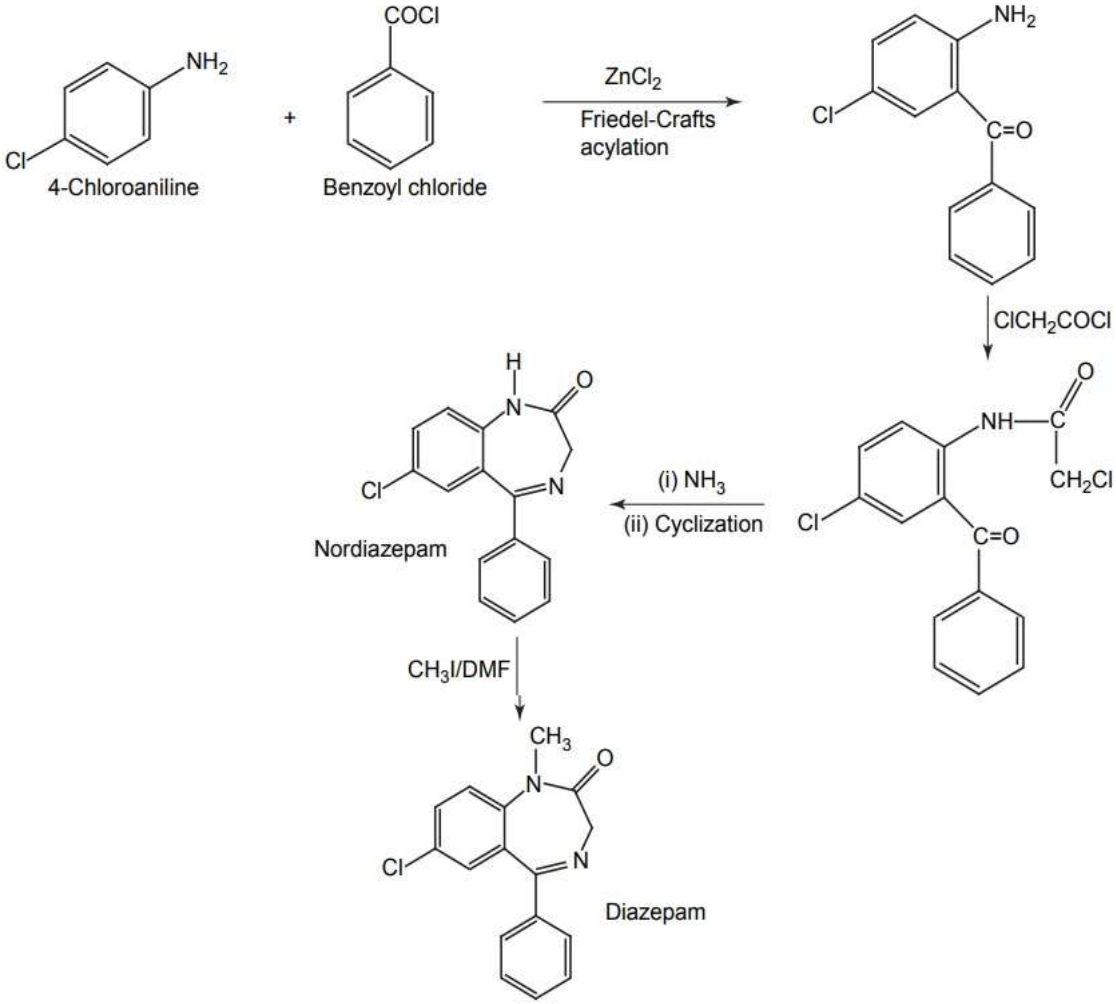
Chlorazepate

Lorazepam

Alprazolam

Zolpidem

Synthesis of Diazepam

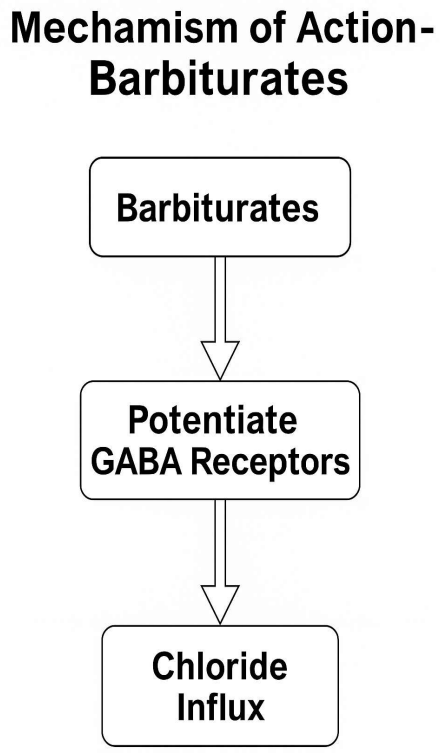


Introduction of Barbiturates

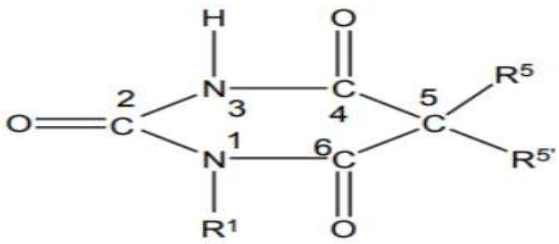
1. Barbiturates are **CNS depressant drugs** derived from **barbituric acid**.
2. They were widely used as sedatives, hypnotics, anticonvulsants, and anesthetic agents before the advent of safer drugs like benzodiazepines.

Mechanism of Action - Barbiturates

1. **Binding to the GABA-A Receptor:-** Barbiturates bind to specific allosteric sites on the GABA-A receptor complex, which are distinct from where GABA itself or benzodiazepines bind.
2. **Enhancing GABA Action:-** Once bound, barbiturates potentiate the effect of GABA.
3. **Prolonging Chloride Channel Opening:-** Unlike benzodiazepines which increase the *frequency* of the chloride channel opening, barbiturates increase the *duration* of time that the chloride ion channel remains open.
4. **Chloride Ion Influx:-** The prolonged opening of the channel allows a greater influx of negatively charged chloride ions into the postsynaptic neuron.
5. **Neuronal Hyperpolarization:-** This influx of negative ions hyperpolarizes the cell membrane (makes it more negative), increasing the threshold required for the neuron to fire an action potential.
6. **Central Nervous System (CNS) Depression:-** The overall result is decreased neuronal excitability and reduced nerve transmission, leading to a general depression of the CNS.



SAR of barbiturates

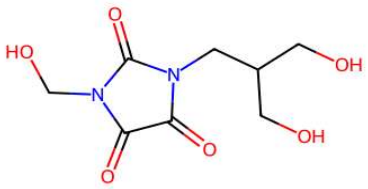


Position	Modification	Effect on Activity
C-5	Replacing both hydrogens is essential for hypnotic activity.	Optimal activity requires a total of 4–10 carbon atoms in the two side chains.
C-5 side chain length	Increasing the length of the side chain.	Increases duration of action.
C-5 side chain branching	Introducing a branched chain.	Increases potency and shortens duration.
C-5 double bonds	Introducing double bonds into the side chains.	Increases vulnerability to oxidation, leading to a shorter duration of action.
C-5 rings	Replacing aliphatic groups with aromatic or alicyclic rings.	Increases potency more than an equivalent-length aliphatic group.
C-5 polar groups	Adding polar groups (e.g., -OH, -NH2, -COOH) to the C-5 side chain.	Makes the compound more hydrophilic.
C-2	Replacing the oxygen atom with a sulfur atom.	Leads to a more rapid onset of action, but a shorter duration of action.
N-1	Methylation at position 1.	Increases excitatory side effects.
Overall Lipophilicity	Increasing the overall lipophilicity of the compound.	Leads to a more rapid onset and shorter duration of action.

Barbiturates

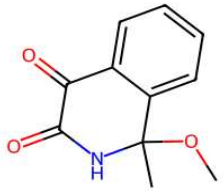
Drug	Introduction	Mechanism of Action (MOA)	Uses
Barbital*	Long-acting barbiturate; early hypnotic agent; slow onset.	Enhances GABA-A action by ↑ duration of Cl^- channel opening → CNS depression.	Hypnotic (historical use), sedative. Rarely used now.
Phenobarbital	Long-acting; least lipid-soluble; widely used anticonvulsant.	Prolongs GABA-A chloride channel opening; also suppresses glutamate.	Epilepsy (tonic-clonic, partial seizures), sedation.
Mephobarbital	N-methyl derivative of phenobarbital; long-acting.	Enhances GABA-mediated Cl^- influx; depresses CNS.	Anticonvulsant (similar to phenobarbital), mild sedative.
Amobarbital	Intermediate-acting barbiturate; moderate lipid solubility.	Potentiates GABA-A inhibition → ↑ Cl^- channel open time.	Sedation, hypnosis, pre-anesthetic medication.
Butabarbital	Short-acting barbiturate; faster onset.	Enhances GABA-A mediated inhibition → neuron hyperpolarization.	Short-term hypnotic, pre-operative sedation.
Pentobarbital	Short-acting; potent CNS depressant; high lipid solubility.	Increases duration of GABA-A Cl^- channel opening; inhibits glutamate at high dose.	Insomnia (rarely now), pre-surgical sedation, control of seizures.
Secobarbital	Short-acting; high lipid solubility; strong hypnotic.	Potentiates GABA-A receptor → hyperpolarization of neurons.	Hypnotic, pre-operative sedation, treatment of refractory seizures.

Chemical Structure Barbiturates

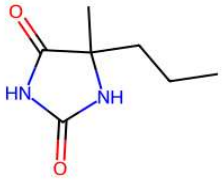


Barbital

Phenobarbital

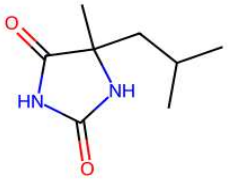


Mephobarbital



Amobarbital

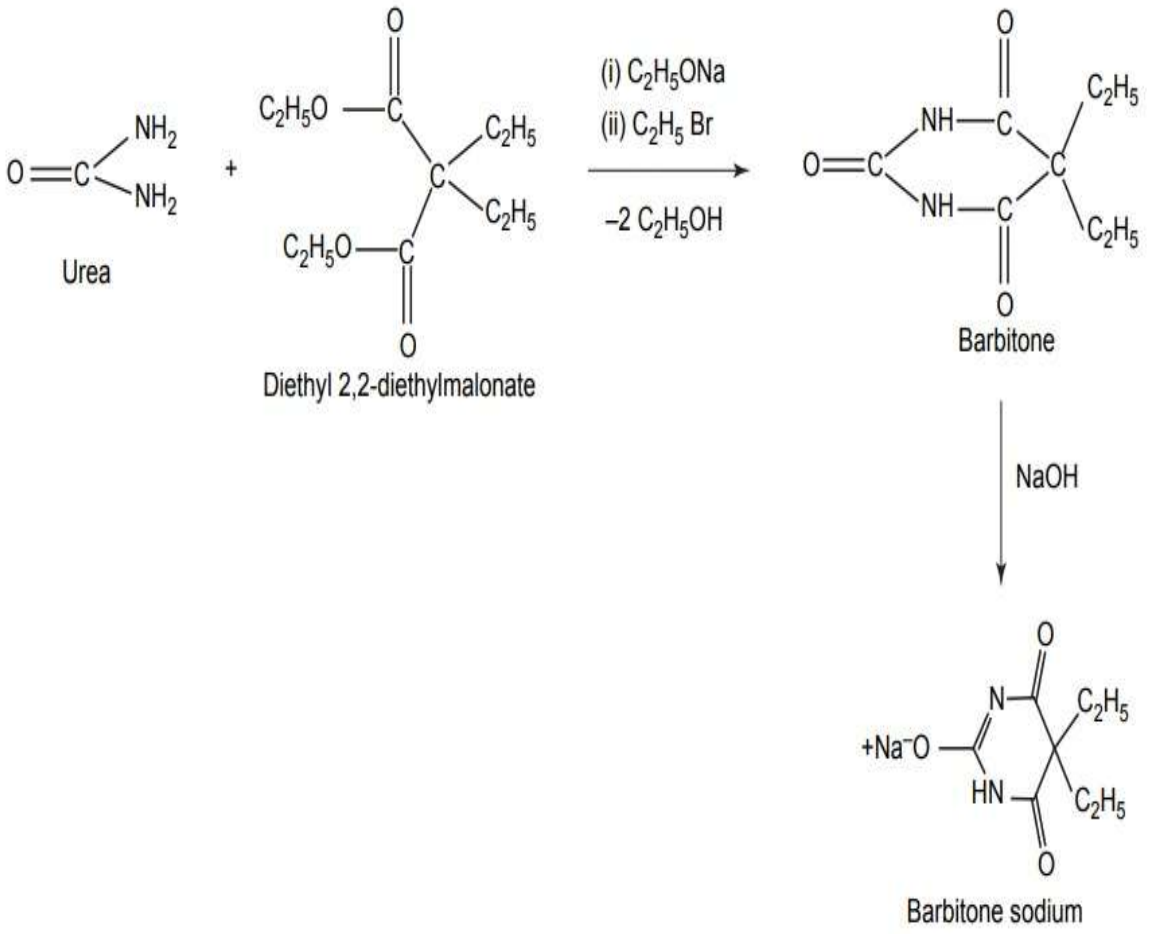
Butabarbital



Pentobarbital

Secobarbital

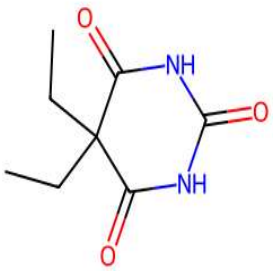
Synthesis of Barbital



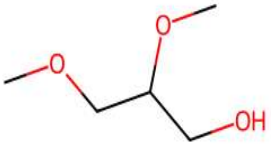
Miscellaneous Drugs

Drug Class	Drug	Introduction / Nature	Mechanism of Action (MOA)	Uses
Amides & Imides	**Glutethimide**	Non-barbiturate sedative–hypnotic; structurally related to barbiturates.	Enhances GABA-A receptor activity; increases Cl^- channel opening → CNS depression.	Hypnotic for insomnia (rarely used today due to abuse potential).
Alcohols & Carbamate derivatives	**Meprobamate**	Carbamate derivative; anxiolytic; related to barbiturates.	Binds to GABA-A receptor; increases Cl^- conductance; at high doses directly opens Cl^- channel.	Anxiety disorders, short-term sedation.
	Ethchlorvynol	Chlorinated tertiary alcohol; rapid-acting sedative–hypnotic.	Enhances GABA-A activity; depresses CNS function.	Short-term treatment of insomnia.
Aldehydes & Derivatives	**Triclofos sodium**	Prodrug of trichloroethanol; pediatric sedative.	After metabolism to trichloroethanol, enhances GABA-A function → sedation.	Pediatric sedation, sleep induction in children.
	Paraldehyde	Cyclic polymer of acetaldehyde; old sedative–hypnotic.	GABA-A enhancement; CNS depression.	Status epilepticus (in children), delirium tremens, sedation (historical use).

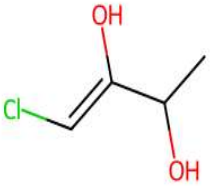
Chemical Structure Miscellaneous Drugs



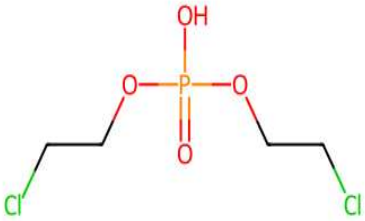
Glutethimide



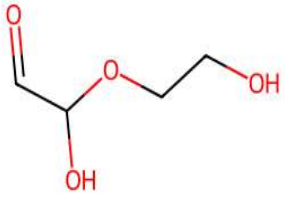
Meprobamate



Ethchlorvynol



Triclofos sodium



Paraldehyde

Thank you

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