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MEDICINAL CHEMISTRY - II

UNIT 5

TOPIC :

- **Benzoic Acid derivatives :** Cocaine, Hexylcaine, Meprylcaine, Cyclomethycaine, Piperocaine.



Benzoic Acid Derivatives

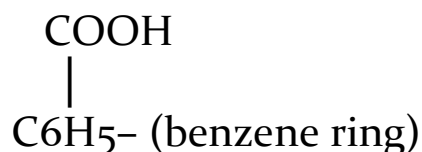
- Benzoic acid derivatives are a broad class of aromatic carboxylic acid compounds derived from benzoic acid ($\text{C}_6\text{H}_5\text{COOH}$).
- The benzene ring in benzoic acid allows substitution at various positions, forming derivatives with diverse physicochemical and pharmacological properties.
- These derivatives are important in pharmaceutical chemistry due to their use as:
 - Antiseptics and preservatives
 - Local anesthetics
 - Analgesic and antipyretic agents
 - Anti-inflammatory agents
 - Excipients and intermediates in drug synthesis

Structure of Benzoic Acid

Molecular formula: $\text{C}_6\text{H}_5\text{COOH}$

Structure:

An aromatic benzene ring attached to a carboxylic acid functional group ($-\text{COOH}$).



- The $-\text{COOH}$ group is the reactive site.
- Substitutions on the ring (ortho, meta, para positions) modify the chemical reactivity and pharmacological properties.

General Properties of Benzoic Acid and Its Derivatives

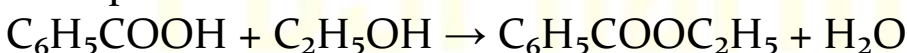
Property	Description
Physical state	Colorless crystalline solid
Odor	Slightly aromatic
Solubility	Sparingly soluble in cold water, soluble in alcohol, ether, and chloroform
Melting point	~122°C
Acidity	Weak acid ($pK_a \approx 4.2$), stronger than aliphatic carboxylic acids due to resonance stabilization
Chemical reactions	Undergoes typical aromatic substitution and carboxylic acid reactions

Chemical Reactions of Benzoic Acid

1. Esterification:

Benzoic acid reacts with alcohols in presence of acid catalyst → Benzoate esters (used in perfumery & anesthetics).

Example:



2. Amidation:

With amines to form benzamides, which have medicinal value (e.g., benzamide derivatives as antipyretics).

3. Nitration, Halogenation, Sulfonation:

Occur at meta-position (since $-COOH$ is meta-directing).

4. Reduction:

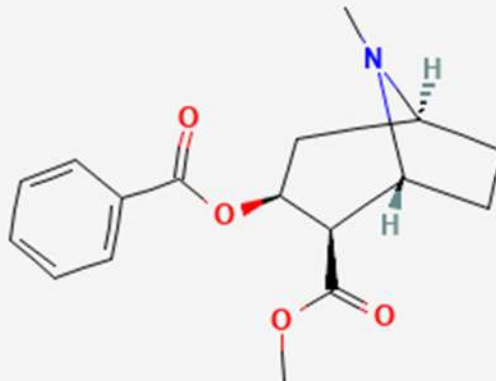
Benzoic acid → Benzyl alcohol (by reducing agents like $LiAlH_4$).

Cocaine

- **Cocaine** is a **natural alkaloid** obtained from the leaves of the plant *Erythroxylon coca* (family *Erythroxylaceae*).
- It is a **powerful local anesthetic** and a **central nervous system (CNS) stimulant**.
- In medicine, it is used **topically for anesthesia**, particularly in the **eye, ear, nose, and throat** procedures.
- Cocaine was the **first local anesthetic** discovered and used clinically before synthetic agents like lidocaine were developed.
- Because of its **addictive and euphoric properties**, its medical use is now **strictly limited**.

Chemical Structure

- **Chemical Name:** Methyl (1R,2R,3S,5S)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate
- **Molecular Formula:** $C_{17}H_{21}NO_4$
- **Molecular Weight:** 303.35 g/mol
- **Chemical Class:** Tropane alkaloid; Ester-type local anesthetic
- **Structural**



Mechanism of Action

Cocaine acts by **blocking the reuptake of neurotransmitters** and **inhibiting voltage-gated sodium channels**.

A. Local Anesthetic Action (Peripheral Action):

1. Cocaine **blocks voltage-gated Na^+ channels** on neuronal membranes.
2. Prevents depolarization and **inhibits generation and conduction of nerve impulses**.

3. Leads to **loss of sensation** in the area of application.

B. Central Nervous System (CNS) Stimulant Action:

1. Cocaine **blocks reuptake** of **dopamine, norepinephrine, and serotonin** in the synaptic cleft.
2. Increases neurotransmitter concentration → causes **euphoria, alertness, and excitation**.
3. At higher doses, may cause **restlessness, convulsions, and dependence**.

Synthesis

Cocaine is a **natural product**, primarily obtained by **extraction** from the leaves of *Erythroxylon coca*.

However, **synthetic routes** exist for laboratory production.

Simplified Outline of Natural Extraction:

1. **Leaves of Erythroxylon coca** are dried and macerated.
2. The alkaloids are extracted using **organic solvents** (like kerosene or gasoline).
3. The crude extract is acidified and purified to yield **cocaine hydrochloride**.

Uses

• Therapeutic Uses:

1. **Local anesthesia** in ENT (ear, nose, throat) procedures, especially nasal and laryngeal surgeries.
2. Used in **ophthalmic surgery** (occasionally) due to its vasoconstrictor property.
3. Acts as a **topical anesthetic with vasoconstriction**, which reduces bleeding.

• Non-medical (Illicit) Use:

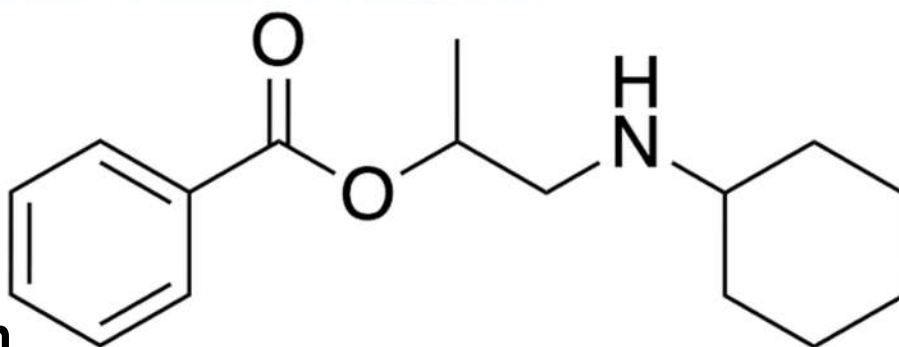
- Used as a **recreational drug** due to its **euphoric and stimulant effects** on the CNS.
- However, **illegal use** can cause severe **addiction and toxicity**.

Hexylcaine

- Hexylcaine is a **local anesthetic** belonging to the **ester type** of anesthetics.
- It is used primarily for **surface (topical) anesthesia** of mucous membranes.
- It acts by **blocking nerve impulse conduction**, producing a reversible loss of sensation.
- It has a **moderate onset and duration** of action.
- Structurally and pharmacologically, it is related to **procaine** and **cocaine**, but with **greater potency** and **less toxicity**.
- It is available as **Hexylcaine hydrochloride** for clinical use.

Chemical Structure

- **Chemical Name:** 2-(Diethylamino)ethyl 1-hexyl-1-hydroxybenzoate hydrochloride
- **Molecular Formula:** $C_{17}H_{29}NO_2 \cdot HCl$
- **Molecular Weight:** 315.88 g/mol
- **Structural Class:** Ester-type local anesthetic containing a benzoic acid derivative with an aliphatic chain and tertiary amine.
- **Structure**



Mechanism of Action

- Hexylcaine acts by **blocking voltage-gated sodium (Na^+) channels** in the neuronal membrane.
- This **prevents depolarization** and inhibits the initiation and propagation of nerve impulses.

- The blockade is **reversible** — normal nerve function returns once the drug diffuses away from the nerve.
- It primarily affects **sensory neurons**, leading to loss of pain sensation without affecting consciousness.
- The effectiveness depends on **lipid solubility**, **pKa**, and **degree of ionization** at tissue pH.

Synthesis

1. **Starting material:** p-Hydroxybenzoic acid.
2. **Esterification:** Reacted with **1-hexanol** to form **1-hexyl p-hydroxybenzoate**.
3. **Alkylation:** The product is then reacted with **2-diethylaminoethyl chloride** in presence of a base to form **Hexylcaine base**.
4. **Conversion to hydrochloride salt:** The base is treated with **hydrochloric acid** to yield **Hexylcaine hydrochloride** (the active form).

Overall Reaction:

p-Hydroxybenzoic acid → 1-hexyl p-hydroxybenzoate → Hexylcaine base
→ Hexylcaine hydrochloride

Uses

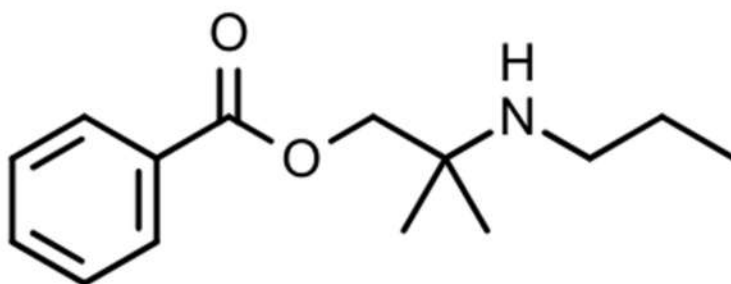
- Used for **topical anesthesia** on mucous membranes (nose, throat, and urethra).
- Acts as a **surface anesthetic** in minor procedures.
- Sometimes used in **dental** and **ophthalmic** applications.
- May be used as an **alternative** to cocaine due to lower addiction risk.
- Provides **rapid local anesthesia** with good tissue penetration.

Meprylcaine

- **Meprylcaine** is a **local anesthetic** of the **ester type**, similar in structure and action to **procaine** and **benzocaine**.
- It is used for **local and infiltration anesthesia** and sometimes in **topical preparations**.
- It has **rapid onset** and **short to moderate duration** of action.
- Meprylcaine shows **both anesthetic and mild stimulant effects** on the central nervous system.
- It is usually administered as **Meprylcaine hydrochloride**, the water-soluble salt form.

Chemical Structure

- **Chemical Name:** 2-(Methylamino)propyl p-toluate hydrochloride
- **Molecular Formula:** $C_{13}H_{20}ClNO_2$
- **Molecular Weight:** 257.76 g/mol
- **IUPAC Name:** Propan-2-yl 4-methylbenzoate with an N-methylamino group in the side chain.
- **Structural**



Mechanism of Action

- Meprylcaine works by **blocking voltage-gated sodium (Na^+) channels** in nerve cell membranes.
- This **prevents depolarization**, thereby **inhibiting conduction** of nerve impulses.
- The blockade is **reversible**, leading to **temporary loss of sensation**.
- It affects **sensory neurons** primarily, causing local anesthesia without affecting consciousness.
- Like other ester anesthetics, its action is terminated by **hydrolysis by plasma esterases**.

Synthesis

1. **Starting material:** *p*-Toluic acid (4-methylbenzoic acid).
2. **Esterification:** React *p*-toluic acid with **2-methylamino-1-propanol** to form the corresponding ester (*Meprylcaine base*).
3. **Salt formation:** Treat the base with **hydrochloric acid (HCl)** to form **Meprylcaine hydrochloride**, the active, water-soluble form.

Uses

- Used as a **local anesthetic** for:
 - Infiltration anesthesia
 - Nerve block anesthesia
 - Surface (topical) anesthesia
- Sometimes used in **dental** and **minor surgical** procedures.
- May have mild **CNS stimulant** properties; occasionally explored for **psychiatric research** (historically).

Cyclomethycaine

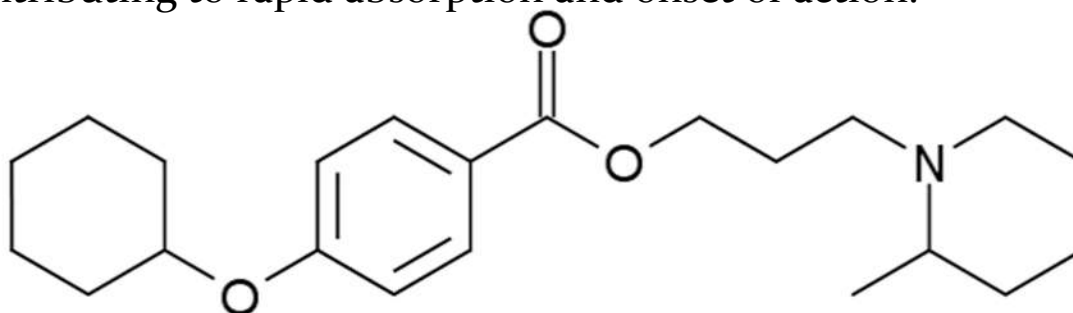
- **Cyclomethycaine** is a **local anesthetic** belonging to the **ester type** of anesthetics.
- It is used primarily for **surface (topical) anesthesia** of mucous membranes in the **nose, throat, and urethra**.
- The drug has **rapid onset** and **short to moderate duration** of action.
- Cyclomethycaine was introduced as an alternative to **cocaine**, offering similar local anesthetic effects but **less toxicity and no addictive potential**.
- It is available clinically as **Cyclomethycaine hydrochloride**, a water-soluble salt form suitable for topical application.

Chemical Structure

- **Chemical Name:** 2-(Diethylamino)ethyl 4-butylaminobenzoate hydrochloride
- **Molecular Formula:** $C_{16}H_{27}NO_2 \cdot HCl$
- **Molecular Weight:** 317.85 g/mol
- **Chemical Class:** Ester-type local anesthetic derived from *p*-aminobenzoic acid.

Structure Description:

- Cyclomethycaine has a **benzene ring** substituted with an **amino group** and an **ester linkage**.
- It possesses a **diethylaminoethyl chain**, which provides the basic nitrogen necessary for receptor binding.
- The **aliphatic butyl side chain** enhances **lipid solubility**, contributing to rapid absorption and onset of action.



Mechanism of Action

- Cyclomethycaine acts by **blocking voltage-gated sodium (Na^+) channels** in the neuronal membrane.
- This **prevents depolarization** and inhibits the generation and conduction of **nerve impulses**.
- The result is a **reversible loss of sensation** in the localized area.
- It affects **sensory neurons** more than motor neurons, so normal movement is usually preserved.
- The effect wears off once the drug diffuses from the nerve membrane and is **hydrolyzed by plasma esterases**.

Synthesis

1. **Starting Material:** *p*-Aminobenzoic acid (PABA).
2. **Esterification:** PABA is esterified with **2-diethylaminoethanol** to form **2-(diethylamino)ethyl p-aminobenzoate**.
3. **Substitution:** The amino group on the benzene ring is substituted or alkylated with a **butyl group** (via butylamine or related agent).
4. **Salt Formation:** The product is treated with **hydrochloric acid** to yield **Cyclomethycaine hydrochloride**.

Uses

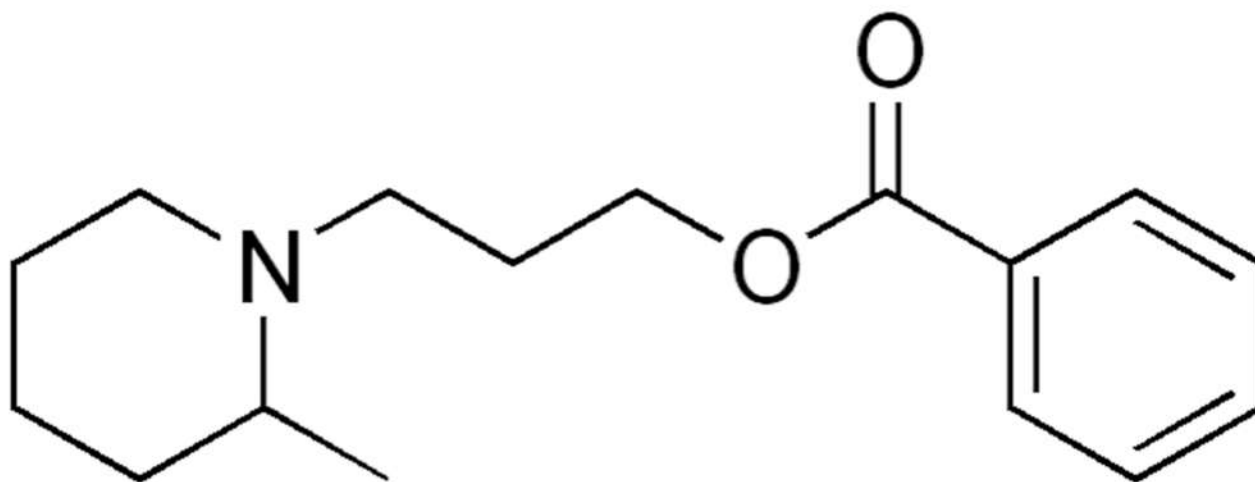
- Used for **topical anesthesia** on mucous membranes of the:
 - **Nose and throat** during endoscopic or diagnostic procedures.
 - **Urethra** before catheterization.
- Acts as a **surface anesthetic** in minor surgical or dental applications.
- Provides **rapid numbing** with minimal irritation.
- Sometimes used as a **replacement for cocaine** in mucosal anesthesia.

Piperocaine

- **Piperocaine** is a **local anesthetic** of the **ester type**, structurally related to **procaine**.
- It is mainly used for **infiltration anesthesia**, **nerve block**, and **spinal anesthesia**.
- Piperocaine has a **longer duration of action** and **greater potency** than procaine due to increased lipid solubility.
- It is generally used as **Piperocaine hydrochloride**, a water-soluble salt form suitable for injection.
- The drug produces **reversible loss of sensation** by blocking nerve conduction without affecting consciousness.

Chemical Structure

- **Chemical Name:** 3-(2-Methylpiperidino)propyl benzoate hydrochloride
- **Molecular Formula:** $C_{15}H_{24}ClNO_2$
- **Molecular Weight:** 285.81 g/mol
- **IUPAC Name:** 3-(2-methylpiperidin-1-yl)propyl benzoate hydrochloride
- **Chemical Class:** Ester-type local anesthetic (benzoate ester derivative).
- **Structural**



Mechanism of Action

- Piperocaine acts by **blocking voltage-gated sodium (Na^+) channels** in the neuronal membrane.
- This **prevents depolarization**, thereby **inhibiting conduction** of nerve impulses.
- The blockade is **reversible**, and sensation returns once the drug diffuses away or is metabolized.
- It primarily affects **sensory fibers**, producing local anesthesia without loss of consciousness.
- Hydrolysis by **plasma esterases** terminates its action, producing **benzoic acid and alcohol derivatives** as metabolites.

Synthesis

1. **Starting Material:** *p*-Hydroxybenzoic acid or benzoic acid.
2. **Esterification:** Benzoic acid is esterified with **3-(2-methylpiperidino)propanol** to form **Piperocaine base**.
3. **Salt Formation:** The base is treated with **hydrochloric acid** to yield **Piperocaine hydrochloride**.

Uses

- Used as a **local anesthetic** for:
 - **Infiltration anesthesia** (subcutaneous tissue).
 - **Peripheral nerve block**.
 - **Spinal and epidural anesthesia**.
- Provides **long-lasting local anesthesia** with minimal irritation.
- Occasionally used in **minor surgical procedures** and **dentistry**.