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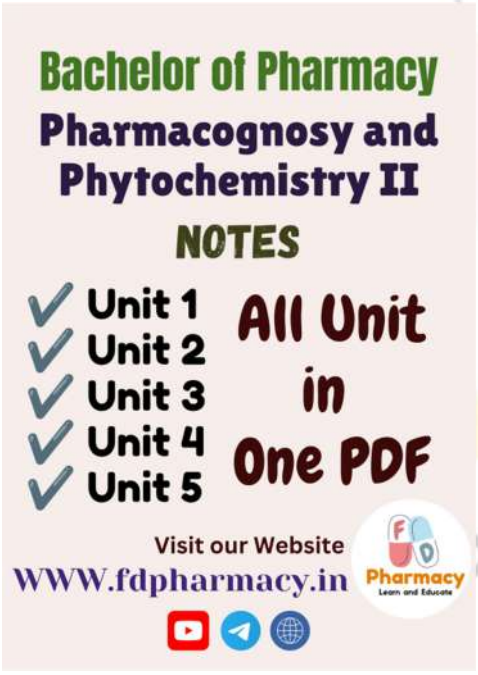
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MEDICINAL CHEMISTRY - II

UNIT 5

TOPIC :

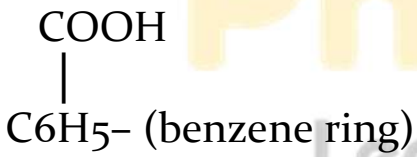
- **Benzoic Acid derivatives :** Cocaine, Hexylcaine, Meprylcaine, Cyclomethycaine, Piperocaine.

Benzoic Acid Derivatives

- Benzoic acid derivatives are a broad class of aromatic carboxylic acid compounds derived from benzoic acid (C_6H_5COOH).
- 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: C_6H_5COOH
Structure:
An aromatic benzene ring attached to a carboxylic acid functional group (–COOH).



- The –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 (pKa ≈ 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

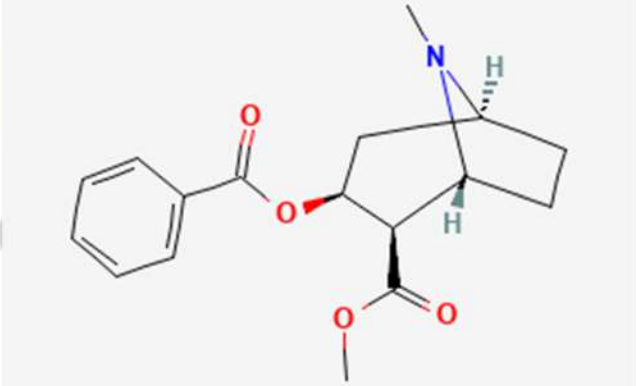
1. Esterification:
   Benzoic acid reacts with alcohols in presence of acid catalyst → Benzoate esters (used in perfumery & anesthetics).
   Example:
   $C_6H_5COOH + C_2H_5OH \rightarrow C_6H_5COOC_2H_5 + H_2O$
2. Amidation:
   With amines to form benzamides, which have medicinal value (e.g., benzamide 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

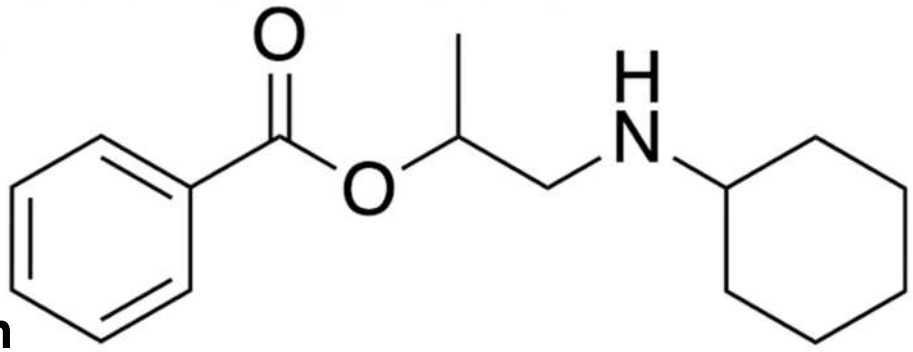
- Therapeutic Uses:
    1. Local anesthesia in ENT (ear, nose, throat) procedures, especially nasal and laryngeal surgeries.
    2. Used in ophthalmic surgery (occasionally) due to its vasoconstrictor property.
    3. Acts as a topical anesthetic with vasoconstriction, which reduces bleeding.
- Non-medical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

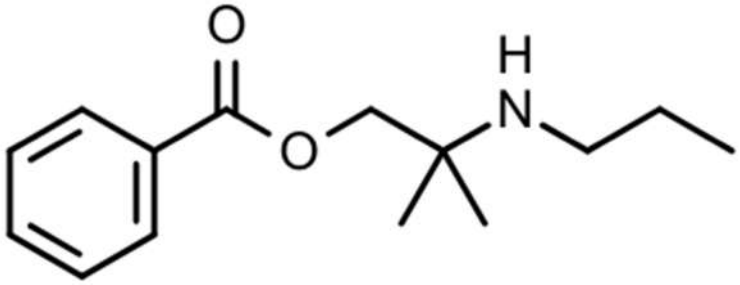
- Used for topical anesthesia on mucous membranes (nose, throat, and urethra).
- Acts as a surface anesthetic in minor procedures.
- Sometimes used in dental and ophthalmic applications.
- May be used as an alternative to cocaine due to lower addiction risk.
- Provides rapid local anesthesia with good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

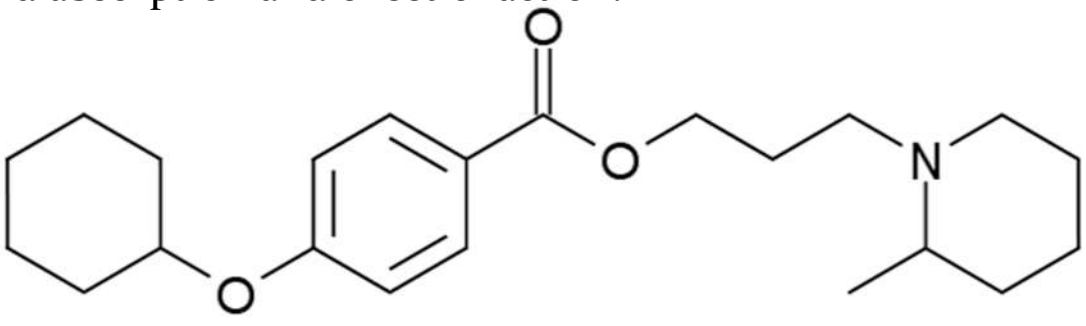
- Cyclomethycaine is a local anesthetic belonging to the ester type of anesthetics.
- It is used primarily for surface (topical) anesthesia of mucous membranes in the nose, throat, and urethra.
- The drug has rapid onset and short to moderate duration of action.
- Cyclomethycaine was introduced as an 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

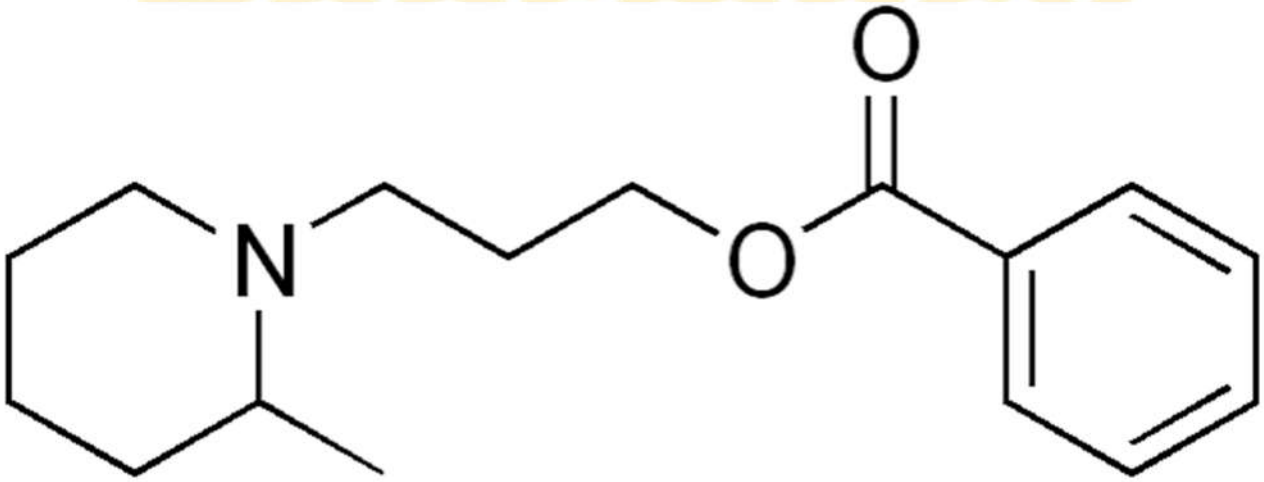
- Used for topical anesthesia on mucous membranes of the:
  - Nose and throat during endoscopic or diagnostic procedures.
  - Urethra before catheterization.
- Acts as a surface anesthetic in minor surgical or dental applications.
- Provides rapid numbing with minimal irritation.
- Sometimes used as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