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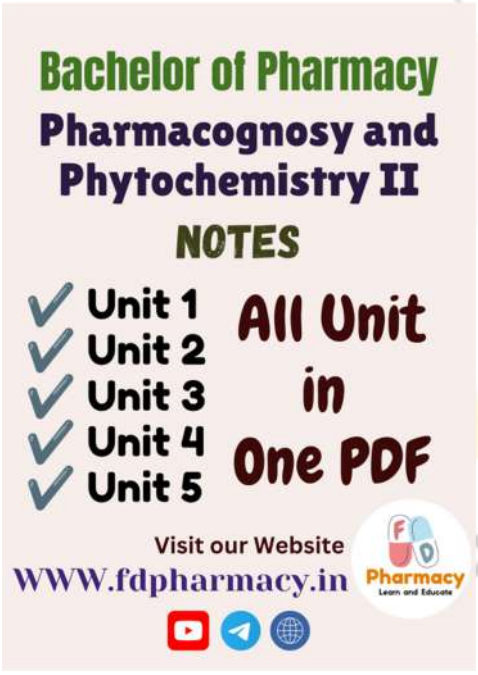
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MEDICINAL CHEMISTRY - II

UNIT 5

TOPIC :

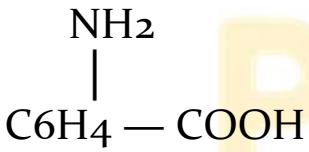
- **Amino Benzoic acid derivatives :** Benzocaine, *Butamben*, *Procaine*, Butacaine, Propoxycaine, Tetracaine, Benoxinate.

Amino Benzoic Acid Derivatives

- Amino benzoic acid derivatives are compounds derived from benzoic acid (C_6H_5COOH) in which one or more hydrogen atoms on the benzene ring are replaced by amino group ($–NH_2$).
- These derivatives are important aromatic amino acids with significant pharmaceutical and biological importance.
- Depending on the position of the amino group on the benzene ring relative to the carboxyl group (–COOH), they exist in three isomeric forms:
    1. Ortho-amino benzoic acid (Anthranilic acid)
    2. Meta-amino benzoic acid
    3. Para-amino benzoic acid (PABA)
- Among these, p-Aminobenzoic acid (PABA) is the most pharmacologically significant.

General Structure

General formula: $C_6H_4(NH_2)(COOH)$



- Functional groups:
    - Carboxylic acid group (–COOH)
    - Amino group ($–NH_2$)
- The position of $–NH_2$ on the benzene ring determines chemical reactivity and biological activity.

Isomeric Forms

Isomer	Common Name	Position of $-NH_2$	Key Uses
2-Amino benzoic acid	Anthranilic acid	Ortho (2-position)	Intermediate for dyes, perfumes, drugs
3-Amino benzoic acid	Meta-amino benzoic acid	Meta (3-position)	Chemical intermediate
4-Amino benzoic acid	Para-aminobenzoic acid (PABA)	Para (4-position)	Vitamin factor, drug precursor, sunscreen agent

Chemical Reactions

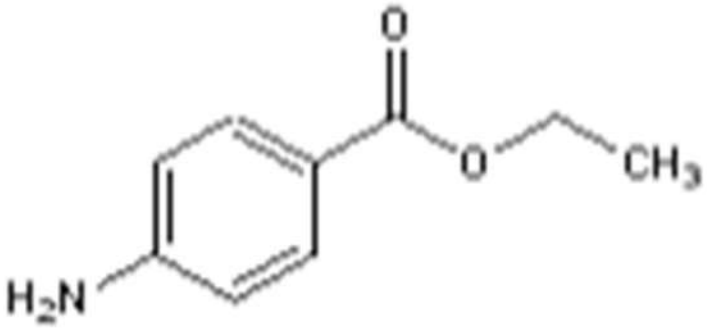
1. Esterification:
   PABA reacts with alcohols → PABA esters (used as local anesthetics or sunscreens).
   Example:
   PABA + C_2H_5OH → Ethyl p-aminobenzoate (Benzocaine) + H_2O
2. Acylation:
   Formation of amides → pharmaceutical intermediates.
3. Diazotization:
   Amino group can form diazonium salts → dyes and intermediates.

Benzocaine

- Benzocaine is a local anesthetic belonging to the ester type.
- It is commonly used for topical anesthesia on skin, mucous membranes, and minor injuries.
- Benzocaine is widely found in over-the-counter formulations such as sprays, gels, lozenges, and ointments.
- It has a rapid onset of action but a short duration.
- Unlike injectable local anesthetics, Benzocaine is poorly soluble in water, so it is mainly used topically.

Chemical Structure

- Chemical Name: Ethyl 4-aminobenzoate
- Molecular Formula: $C_9H_{11}NO_2$
- Molecular Weight: 165.19 g/mol
- Chemical Class: Ester-type local anesthetic; derivative of p-aminobenzoic acid (PABA)
- Structural



Mechanism of Action

- Benzocaine acts by blocking voltage-gated sodium (Na^+) channels in nerve cell membranes.
- This prevents depolarization, inhibiting nerve impulse generation and conduction.
- The result is a reversible loss of sensation at the application site.
- It primarily affects sensory neurons, producing local anesthesia without affecting motor function.
- Onset is rapid due to its lipid solubility, but duration is limited by poor water solubility and surface application.

Synthesis

Starting Material: p-Aminobenzoic acid (PABA)

1. Esterification: PABA is reacted with ethanol in the presence of an acid catalyst (like sulfuric acid).
2. Purification: The product, ethyl 4-aminobenzoate (Benzocaine), is purified by recrystallization.

Uses

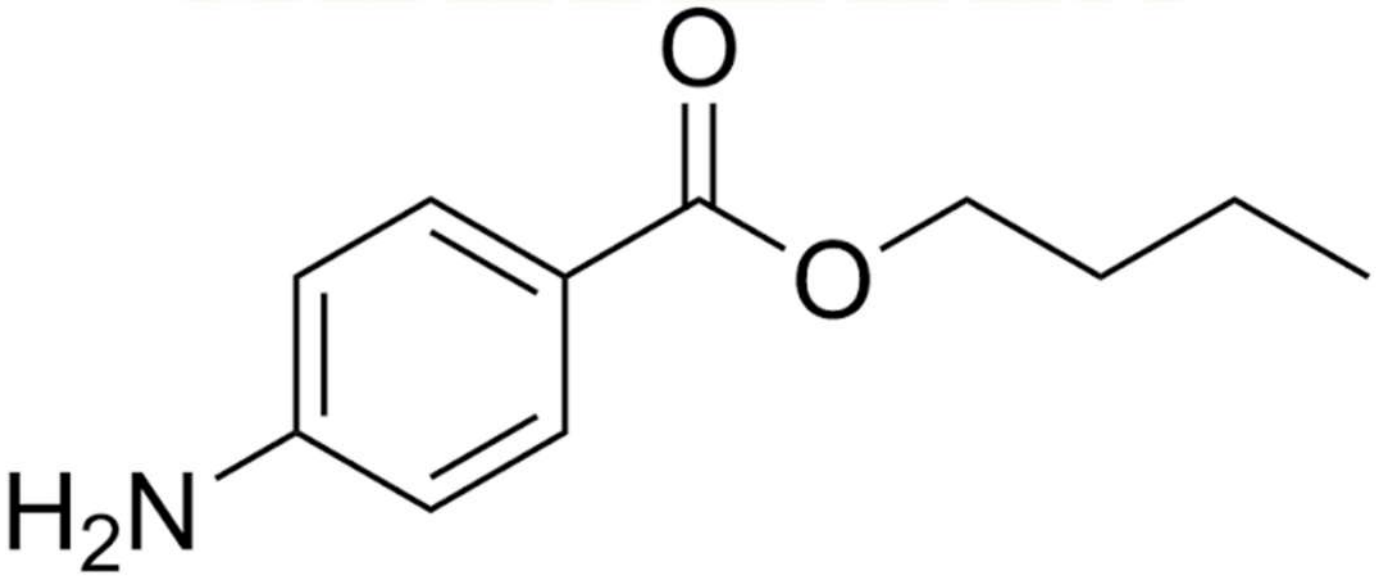
- Topical anesthesia for minor skin or mucous membrane irritation.
- In dentistry, used to relieve pain from sore gums or mouth ulcers.
- In ENT procedures, applied to nasal or throat mucosa to reduce discomfort.
- Sometimes included in otological preparations to relieve ear pain.
- Found in over-the-counter throat lozenges, sprays, gels, and ointments.

Butamben

- Butamben (Butyl 4-aminobenzoate) is a local anesthetic of the ester type.
- It is primarily used for topical and infiltration anesthesia, particularly in dental and minor surgical procedures.
- Butamben provides rapid onset and moderate duration of anesthesia.
- Compared to other ester anesthetics, it is less soluble in water, so it is mainly formulated as suspensions or combined with other anesthetics for prolonged effect.
- It is generally used as Butamben base or Butamben hydrochloride.

Chemical Structure

- Chemical Name: Butyl 4-aminobenzoate
- Molecular Formula: $C_{11}H_{15}NO_2$
- Molecular Weight: 193.24 g/mol
- IUPAC Name: Butyl 4-aminobenzoate
- Chemical Class: Ester-type local anesthetic; derivative of p-aminobenzoic acid (PABA)
- Structural



Mechanism of Action

- Butamben works by blocking voltage-gated sodium (Na^+) channels on neuronal membranes.
- This prevents depolarization and inhibits nerve impulse conduction, producing reversible loss of sensation.
- It primarily affects sensory nerves, sparing motor function.
- The action terminates once the drug diffuses away and is hydrolyzed by plasma esterases.

Synthesis

Starting Material: p-Aminobenzoic acid (PABA)

Steps:

1. Esterification: PABA is reacted with butanol in the presence of an acid catalyst (e.g., sulfuric acid).
2. Purification: The product, Butyl 4-aminobenzoate (Butamben), is purified by recrystallization.

Uses

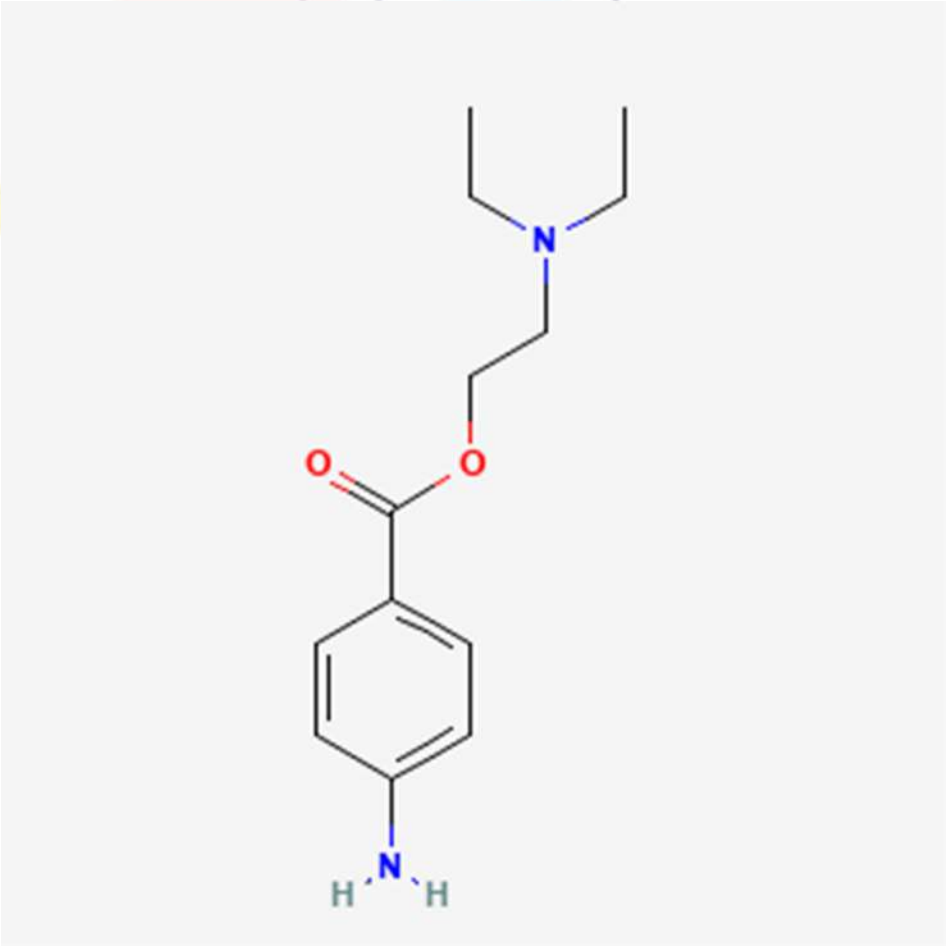
- Topical anesthesia for minor skin lesions and mucous membranes.
- Dental anesthesia, especially in combination with other anesthetics (e.g., lidocaine or benzocaine).
- Infiltration anesthesia for minor surgical procedures.
- Sometimes combined with other agents for prolonged local anesthesia.

Procaine

- Procaine is a synthetic ester-type local anesthetic, first synthesized in 1905 by Alfred Einhorn.
- It is widely used for infiltration, nerve block, and spinal anesthesia.
- Procaine is known for its rapid onset and short duration of action.
- It is mainly used as Procaine hydrochloride for clinical administration.
- Historically, Procaine was introduced as a safer alternative to cocaine, with less toxicity and no addictive potential.

Chemical Structure

- Chemical Name: 2-(Diethylamino)ethyl 4-aminobenzoate
- Molecular Formula: $C_{13}H_{20}N_2O_2$
- Molecular Weight: 236.31 g/mol
- IUPAC Name: 2-(diethylamino)ethyl 4-aminobenzoate
- Chemical Class: Ester-type local anesthetic
- Structural



Mechanism of Action

- Procaine acts by blocking voltage-gated sodium (Na^+) channels on neuronal membranes.
- This prevents depolarization, thereby inhibiting the conduction of nerve impulses.
- Primarily affects sensory neurons, causing local anesthesia without affecting consciousness.
- The action is reversible and terminated by hydrolysis of the ester linkage by plasma pseudocholinesterases.
- Onset is rapid, but duration is short, making repeated doses necessary for prolonged procedures.

Synthesis

Starting Materials: p-Aminobenzoic acid (PABA) and 2-diethylaminoethanol

Steps:

1. Esterification: p-Aminobenzoic acid is reacted with 2-diethylaminoethanol in the presence of acid or dehydrating agent to form Procaine base.
2. Salt Formation: The base is treated with hydrochloric acid to yield Procaine hydrochloride, the water-soluble form used clinically.

Uses

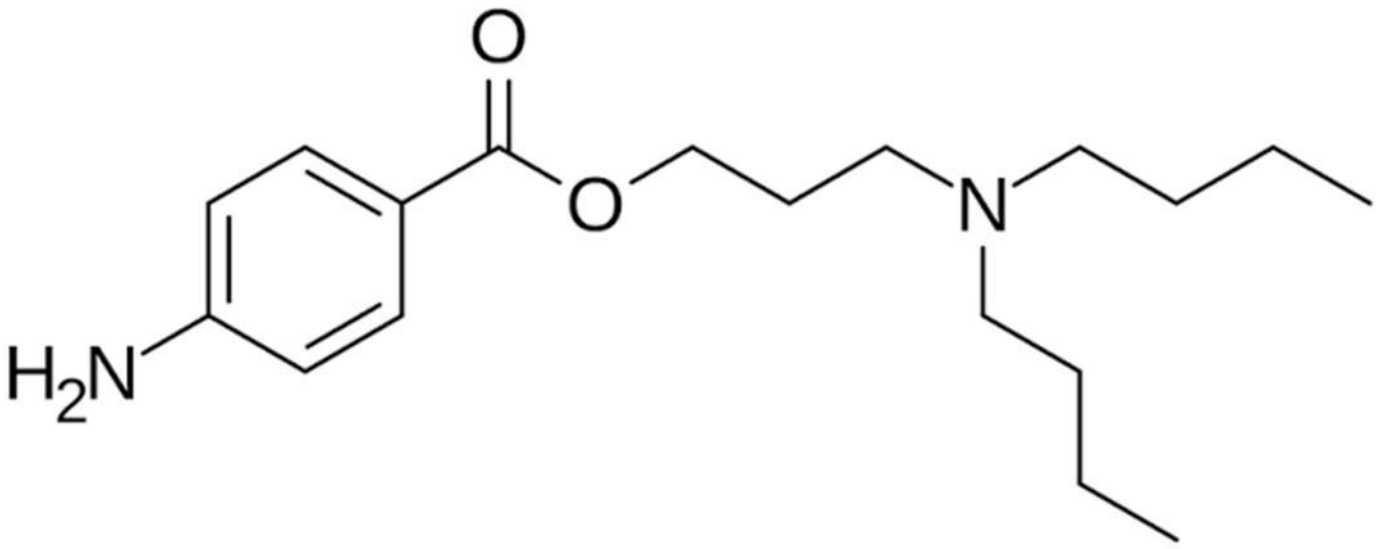
- Infiltration anesthesia for minor surgical procedures.
- Peripheral nerve block anesthesia.
- Spinal anesthesia for short procedures.
- Sometimes combined with epinephrine to prolong action and reduce bleeding.
- Historically, it was a cocaine substitute for topical anesthesia.

Butacaine

- Butacaine is a local anesthetic of the ester type, closely related to procaine and benzocaine.
- It is primarily used for topical anesthesia on skin and mucous membranes.
- Butacaine provides rapid onset and moderate duration of anesthesia.
- Its lipid solubility allows for good penetration into nerve membranes, making it suitable for minor surgical procedures and dental applications.
- It is commonly formulated as Butacaine hydrochloride, the water-soluble salt for clinical use.

Chemical Structure

- Chemical Name: Butyl 4-(diethylamino)benzoate
- Molecular Formula: $C_{15}H_{23}NO_2$
- Molecular Weight: 245.35 g/mol
- IUPAC Name: Butyl 4-(diethylamino)benzoate
- Chemical Class: Ester-type local anesthetic; derivative of p-aminobenzoic acid (PABA)
- Structural



Mechanism of Action

- Butacaine produces local anesthesia by blocking voltage-gated sodium (Na^+) channels in the neuronal membrane.
- This prevents depolarization and inhibits nerve impulse conduction, producing a reversible loss of sensation.
- It primarily affects sensory fibers, sparing motor function.
- The ester bond is hydrolyzed by plasma esterases, terminating its action.

Synthesis

Starting Material: p-Aminobenzoic acid (PABA)

Steps:

1. Alkylation: The amino group of PABA is reacted with diethylamine to form the diethylamino derivative.
2. Esterification: The carboxyl group is esterified with butanol under acidic conditions to form Butacaine base.
3. Salt Formation: The base is converted to Butacaine hydrochloride by treatment with HCl, yielding a water-soluble form suitable for clinical use.

Uses

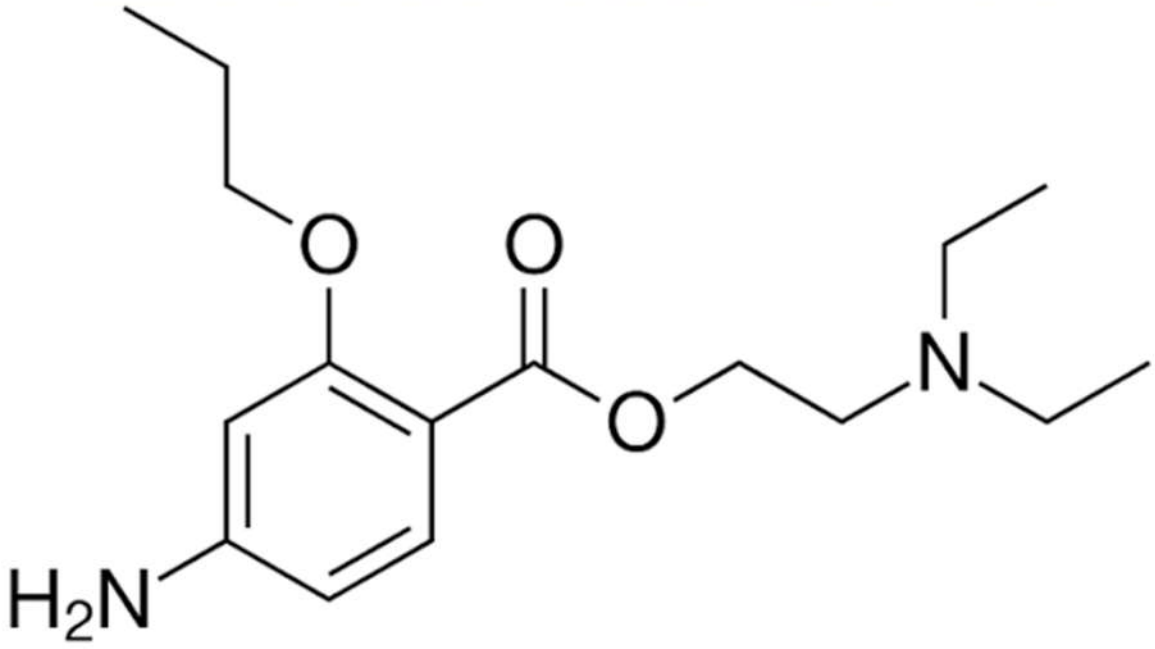
- Topical anesthesia for minor skin and mucous membrane procedures.
- Dental anesthesia, particularly for oral mucosa.
- Minor surgical procedures requiring short-term anesthesia.
- Sometimes used in combination with other anesthetics for enhanced or prolonged local anesthesia.

Propoxycaine

- Propoxycaine is a synthetic local anesthetic of the ester type.
- It is used primarily for surface anesthesia on mucous membranes, including eye, throat, and nasal passages.
- Propoxycaine has a rapid onset and moderate duration of action, making it suitable for diagnostic and minor surgical procedures.
- It is typically administered as Propoxycaine hydrochloride, the water-soluble salt form.
- Developed as an alternative to cocaine, it offers effective anesthesia with reduced toxicity and no addictive potential.

Chemical Structure

- Chemical Name: 2-(Diethylamino)ethyl 4-propoxybenzoate hydrochloride
- Molecular Formula: $C_{15}H_{23}NO_3 \cdot HCl$
- Molecular Weight: 293.81 g/mol
- Chemical Class: Ester-type local anesthetic; derivative of p-aminobenzoic acid (PABA)
- Structural



Mechanism of Action

- Propoxycaine produces local anesthesia by blocking voltage-gated sodium (Na^+) channels in nerve membranes.
- This prevents depolarization, thereby inhibiting nerve impulse conduction.
- The effect is reversible, resulting in temporary loss of sensation.
- Primarily affects sensory neurons, sparing motor neurons.
- Termination of action occurs through hydrolysis by plasma esterases.

Synthesis

Starting Materials: p-Hydroxybenzoic acid (or derivative) and 2-diethylaminoethanol

Steps:

1. Ether formation: The hydroxyl group of p-hydroxybenzoic acid is reacted with propanol to form p-propoxybenzoic acid.
2. Esterification: p-Propoxybenzoic acid is esterified with 2-diethylaminoethanol to form Propoxycaine base.
3. Salt formation: The base is treated with hydrochloric acid to form Propoxycaine hydrochloride, which is water-soluble for clinical use.

Uses

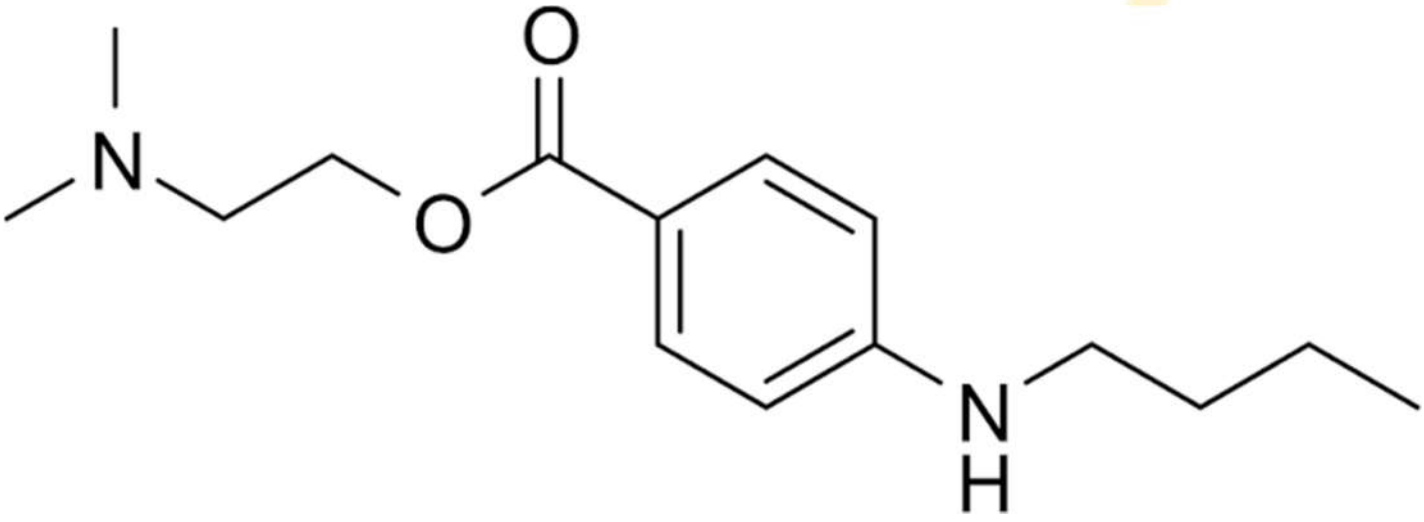
- Topical anesthesia for mucous membranes: eyes, nose, throat, urethra.
- Minor surgical procedures requiring surface anesthesia.
- Diagnostic procedures, e.g., ophthalmic examination, ENT endoscopy.
- Sometimes used in dental procedures as a surface anesthetic.

Tetracaine

- Tetracaine (also called Amethocaine) is a potent ester-type local anesthetic.
- It is widely used for topical, spinal, and infiltration anesthesia.
- Tetracaine has a rapid onset and longer duration of action compared to other ester anesthetics such as procaine or benzocaine.
- It is typically administered as Tetracaine hydrochloride, a water-soluble salt form.
- It is particularly useful for ophthalmic, spinal, and epidural anesthesia due to its potency and prolonged effect.

Chemical Structure

- Chemical Name: 4-(Butylamino)benzoic acid 2-(dimethylamino)ethyl ester hydrochloride
- Molecular Formula: $C_{15}H_{24}N_2O_2 \cdot HCl$
- Molecular Weight: 302.82 g/mol
- IUPAC Name: 2-(Dimethylamino)ethyl 4-(butylamino)benzoate hydrochloride
- Chemical Class: Ester-type local anesthetic; derivative of p-aminobenzoic acid (PABA)
- Structural



Mechanism of Action

- Tetracaine acts by blocking voltage-gated sodium (Na^+) channels in nerve membranes.
- This prevents depolarization, inhibiting the generation and propagation of nerve impulses, resulting in reversible local anesthesia.
- It primarily affects sensory neurons, sparing motor neurons.
- Its longer duration is due to higher lipid solubility and slower hydrolysis by plasma esterases compared to other esters.

Synthesis

Starting Materials: p-Aminobenzoic acid (PABA) and 2-dimethylaminoethanol

Steps:

1. Alkylation: The amino group of PABA is reacted with butyl halide to form 4-(butylamino)benzoic acid.
2. Esterification: The carboxyl group is esterified with 2-dimethylaminoethanol to form Tetracaine base.
3. Salt Formation: The base is treated with hydrochloric acid to form Tetracaine hydrochloride, a water-soluble clinical form.

Uses

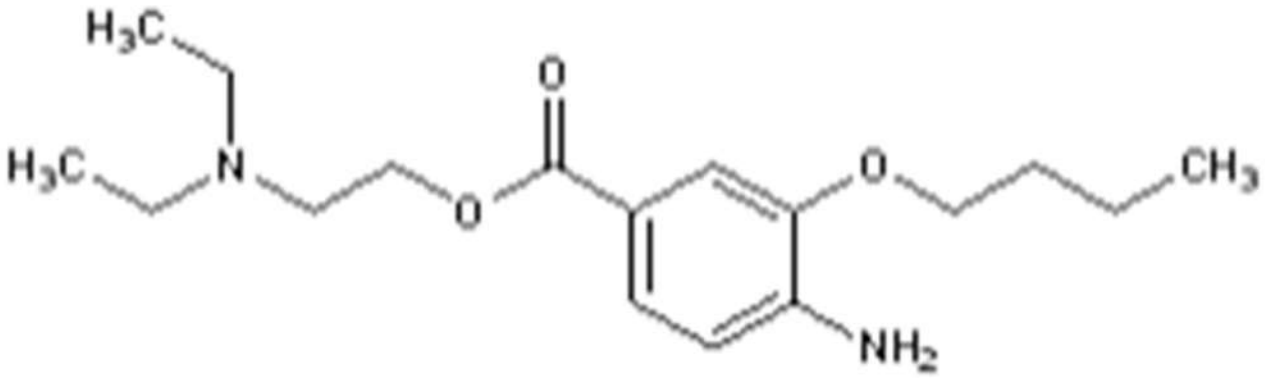
- Topical anesthesia: Skin, mucous membranes, and ophthalmic surfaces.
- Spinal anesthesia: Used for lumbar puncture and short-duration surgeries.
- Infiltration anesthesia: Minor surgical procedures.
- Sometimes combined with vasoconstrictors to prolong action and reduce systemic absorption.

Benoxinate

- Benoxinate (also called oxybuprocaine) is a potent ester-type local anesthetic.
- It is primarily used for ophthalmic anesthesia in procedures such as tonometry, cataract extraction, and minor eye surgery.
- Benoxinate has a rapid onset of action and moderate duration.
- Typically administered as Benoxinate hydrochloride in ophthalmic drops, providing topical anesthesia of the cornea and conjunctiva.
- It is preferred in eye procedures due to its minimal systemic absorption and low toxicity.

Chemical Structure

- Chemical Name: 2-(Diethylamino)ethyl 4-aminobenzoate hydrochloride (Note: similar to oxybuprocaine derivative)
- Molecular Formula: $C_{15}H_{24}N_2O_2 \cdot HCl$
- Molecular Weight: 302.82 g/mol
- Chemical Class: Ester-type local anesthetic; derivative of p-aminobenzoic acid (PABA)
- Structural



Mechanism of Action

- Benoxinate produces anesthesia by blocking voltage-gated sodium (Na^+) channels in nerve membranes.
- This prevents depolarization, inhibiting nerve impulse conduction.
- Primarily affects sensory nerves, producing reversible loss of corneal and conjunctival sensation.
- Action is terminated by hydrolysis of the ester bond by plasma esterases.

Synthesis

Starting Materials: p-Aminobenzoic acid (PABA) and 2-diethylaminoethanol

Steps:

1. Alkylation: The amino group of PABA is modified with a suitable butyl or diethyl group to form the desired derivative.
2. Esterification: The carboxyl group is esterified with 2-diethylaminoethanol to form the Benoxinate base.
3. Salt Formation: The base is treated with hydrochloric acid to form Benoxinate hydrochloride, the ophthalmic preparation.

Uses

- Topical ocular anesthesia for:
  - Tonometry (measuring intraocular pressure)
  - Cataract surgery
  - Minor ophthalmic procedures and diagnostic tests
- Sometimes used in combination with other agents for enhanced ophthalmic anesthesia.