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MEDICINAL CHEMISTRY - II

UNIT 5

TOPIC :

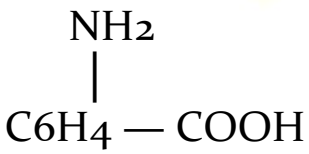
- **Amino Benzoic acid derivatives :** Benzocaine, *Butamben*, *Procaine*, Butacaine, Propoxycaine, Tetracaine, Benoxinate.

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

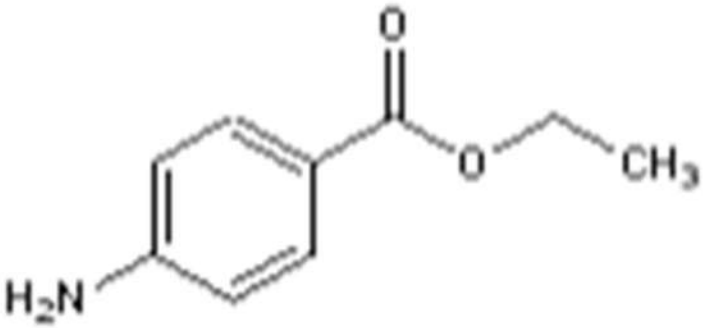
1. **Esterification:**
   PABA reacts with alcohols → PABA esters (used as local anesthetics or sunscreens).
   Example:
   PABA + C_2H_5OH → Ethyl p-aminobenzoate (Benzocaine) + H_2O
2. **Acylation:**
   Formation of amides → pharmaceutical intermediates.
3. **Diazotization:**
   Amino group can form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

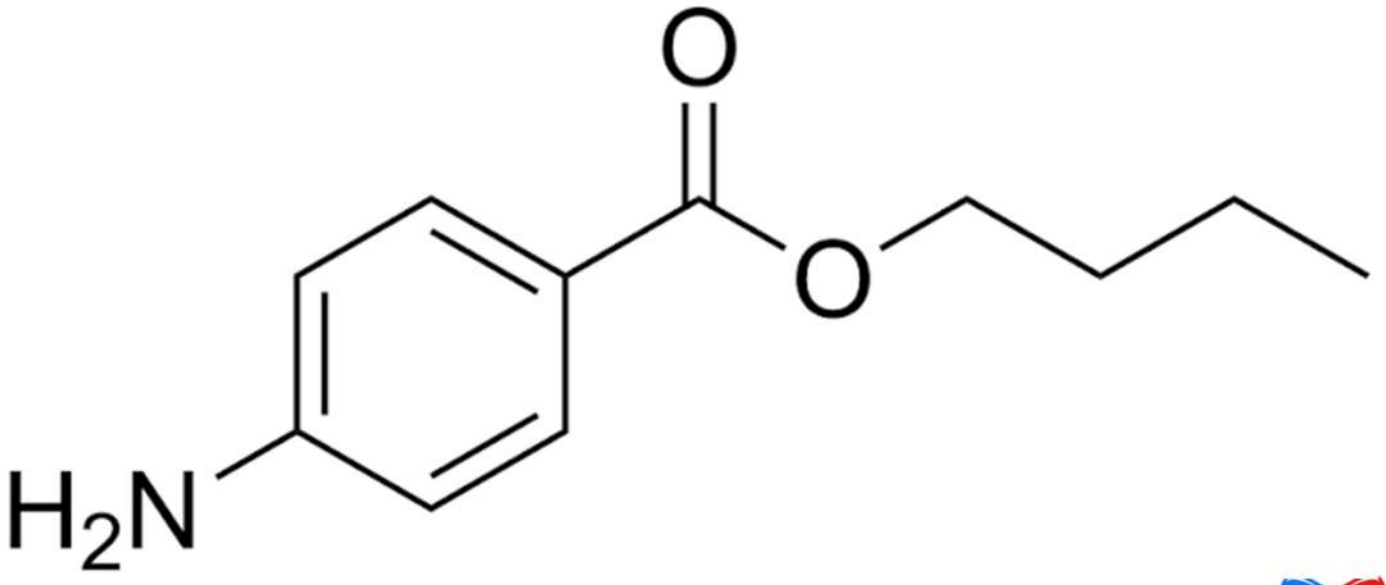
- **Topical anesthesia** for minor skin or mucous membrane irritation.
- In **dentistry**, used to relieve pain from sore gums or mouth ulcers.
- In **ENT procedures**, applied to nasal or throat mucosa to reduce discomfort.
- Sometimes included in **otological preparations** to relieve ear pain.
- Found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

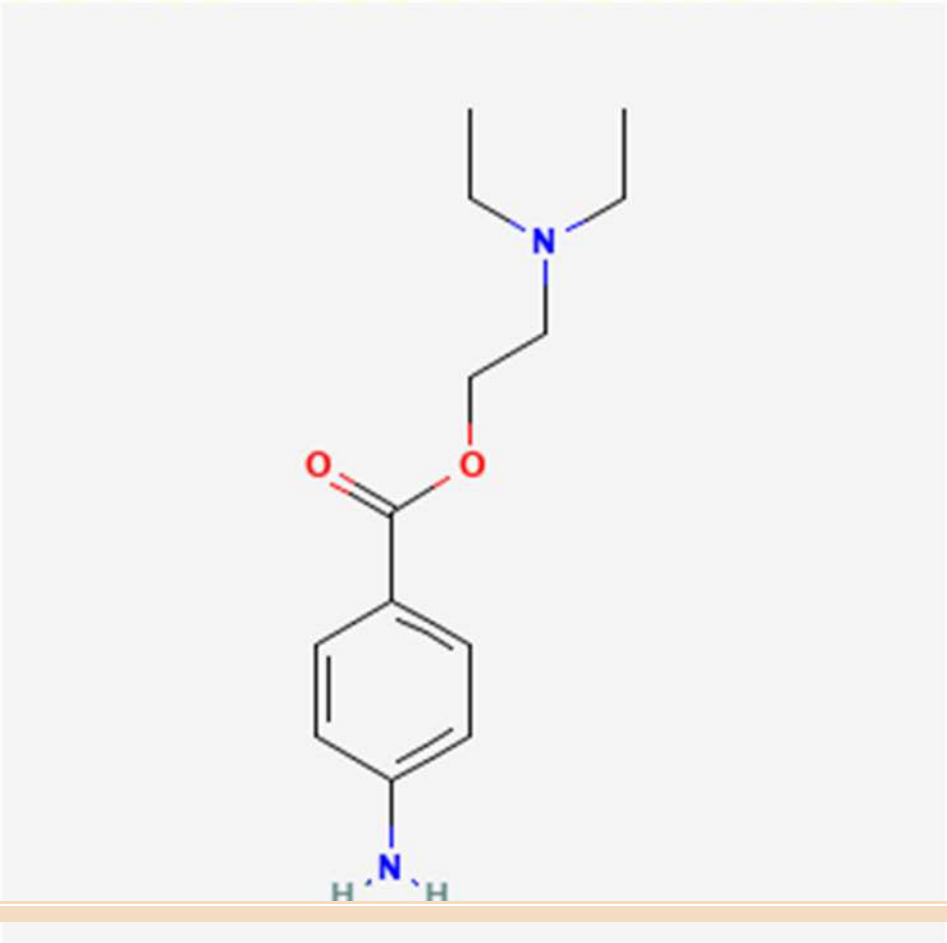
- **Topical anesthesia** for minor skin lesions and mucous membranes.
- **Dental anesthesia**, especially in combination with other anesthetics (e.g., lidocaine or benzocaine).
- **Infiltration anesthesia** for minor surgical procedures.
- Sometimes combined with other agents for **prolonged local anesthesia**.

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

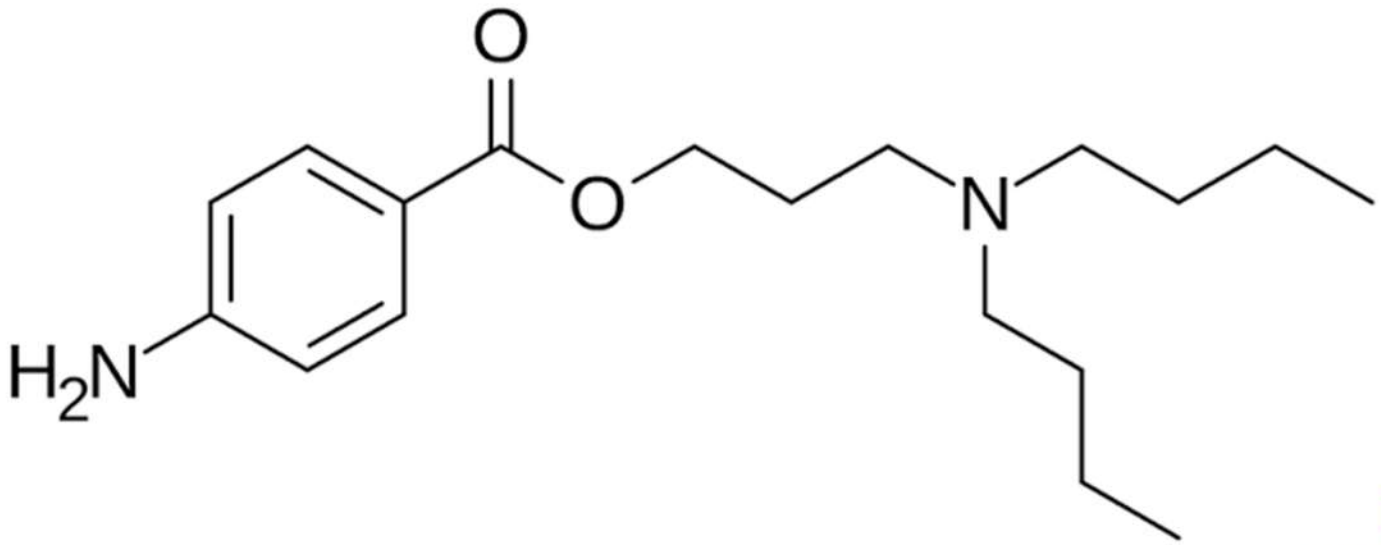
- **Infiltration anesthesia** for minor surgical procedures.
- **Peripheral nerve block** anesthesia.
- **Spinal anesthesia** for short procedures.
- Sometimes combined with **epinephrine** to **prolong action** and reduce bleeding.
- Historically, it was a **cocaine substitute** for topical anesthesia.

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

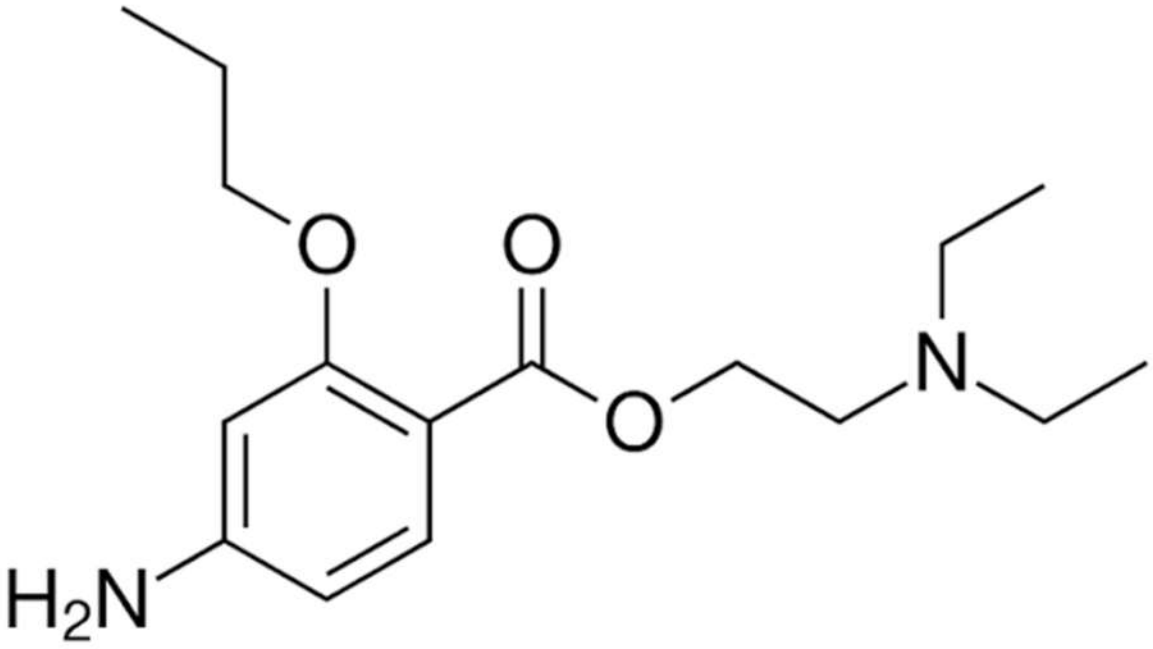
- **Topical anesthesia** for minor skin and mucous membrane procedures.
- **Dental anesthesia**, particularly for oral mucosa.
- **Minor surgical procedures** requiring short-term anesthesia.
- Sometimes used in combination with other anesthetics for **enhanced or prolonged local anesthesia**.

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

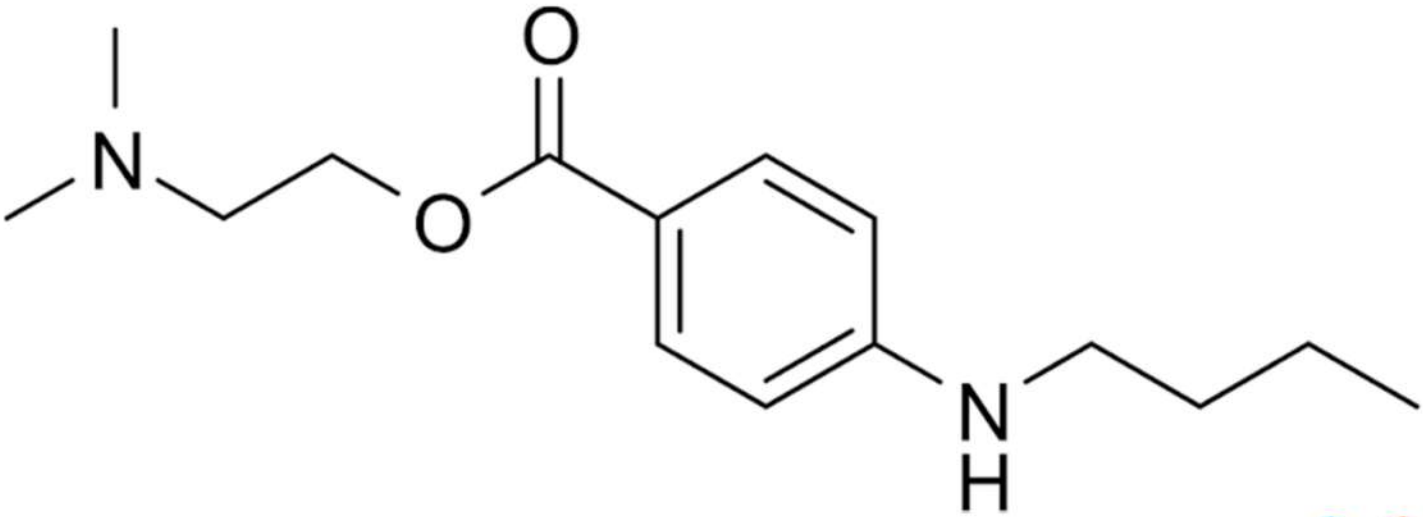
- **Topical anesthesia** for mucous membranes: eyes, nose, throat, urethra.
- **Minor surgical procedures** requiring surface anesthesia.
- **Diagnostic procedures**, e.g., ophthalmic examination, ENT endoscopy.
- Sometimes used in **dental procedures** as a surface anesthetic.

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

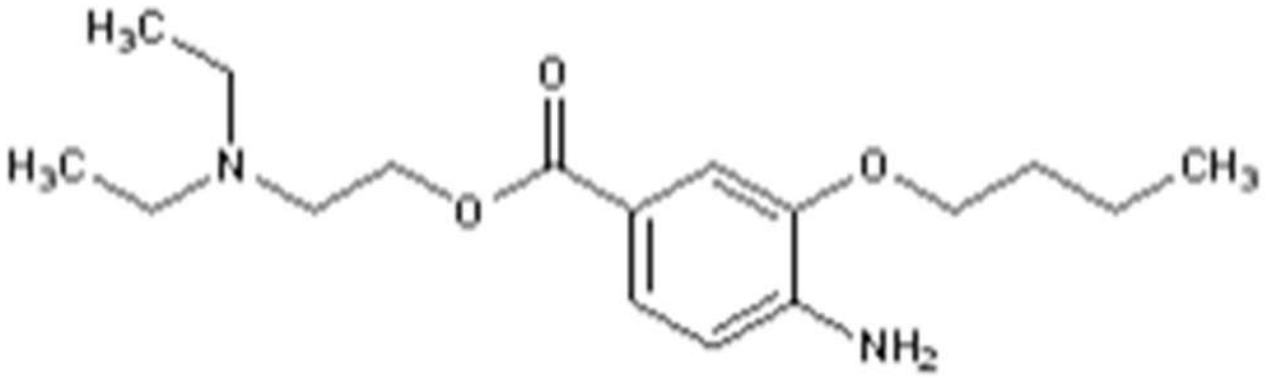
- **Topical anesthesia:** Skin, mucous membranes, and ophthalmic surfaces.
- **Spinal anesthesia:** Used for lumbar puncture and short-duration surgeries.
- **Infiltration anesthesia:** Minor surgical procedures.
- Sometimes combined with **vasoconstrictors** to prolong action and reduce systemic absorption.

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**.