Chapter 18. Local Anaesthetics

- **SAR of LAs**
- **Benzoic acid derivativs:** Cocaine, Hexylcaine, Meprylcaine, Cycomethycaine, Piperocaine
- **Amino Benzoic acid derivativs:** Benzocain*, Butamben, Procain*, Butacain, Propoxycain, Tetracain, Benoxinate
- **Anilide derivetives:** Lidocain**,** Mepivacain**,** Prilocaine, Etidocaine
- **Misc.** Phenacaine, Diperodon, Dibucaine*

18.1. LOCAL ANESTHETICS

Local anesthetics (LAs) are drugs which used either topical of local injection for the anesthesia in the applied area. In the applied area they cause **reversible loss of sensory perception**, especially of pain by blocking the generation and conduction of nerve impulse within the neurons, without causing any structural damage.They interrupted both sensory as well as motor impulse, resulting in muscular paralysis and loss of autonomic control as well.

Classification:

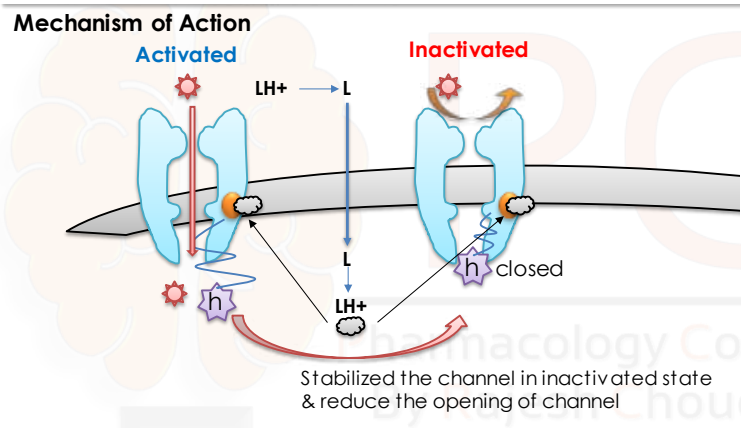
A. Injectable LAs

1. **Low potency, short duration**: Procaine Chloroprocaine
2. **Intermediate potency and duration**: Lidocaine (Lignocaine), Prilocaine
3. **High potency, long duration**: Tetracaine (Amethocaine), Bupivacaine, Ropivacaine, Dibucaine (Cinchocaine)

B. Surface LAs

1. **Soluble**: Cocain, Lidocaine, Tetracaine
2. **Insoluble**: Benzocaine, Butyl-amino-benzoate, Oxethazaine

Mechanism of Action:



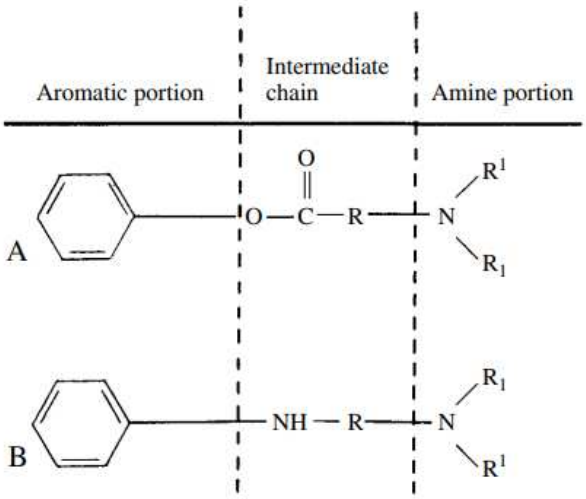
The LAs bind with the LA receptor located at Voltage gated Na+ Channel and stabilize the channel or prolongation in inactivated state and increase the threshold of channel opening and further lead to decreasing the impulse conduction.

Clinical Uses:

- ✓ Surface anesthesia
- ✓ Infiltration anesthesia
- ✓ Conduction block
- ✓ Spinal anesthesia

Pharmacology: https://youtu.be/dVQd-U9GPUk

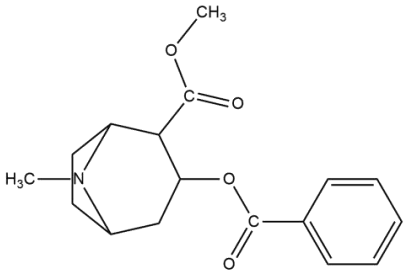
18.2. CHEMISTRY OF LOCAL ANESTHETICS



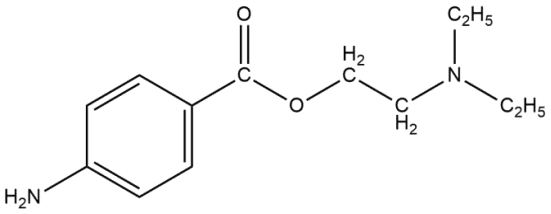
- The clinically useful LAs are weak bases with amphiphilic property
- The basic components in the structure of local anesthetics are the lipophilic aromatic portion (a benzene ring), an intermediate chain [either ester linkage (combination of an

aromatic acid and an amino alcohol)or amide linkage(combination of an aromatic amine and an amino acid)], and the hydrophilic amine portion

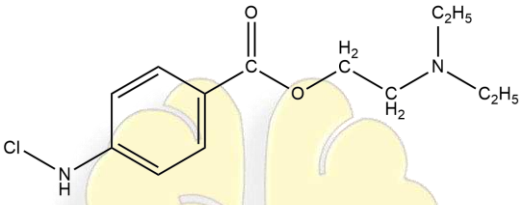
A. Ester-linked LAs: Cocaine, procaine, chloroprocaine, tetracaine, benzocaine.



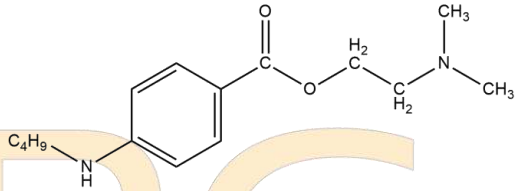
Cocain



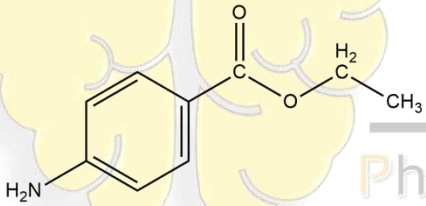
Procain



Chloroprocaine

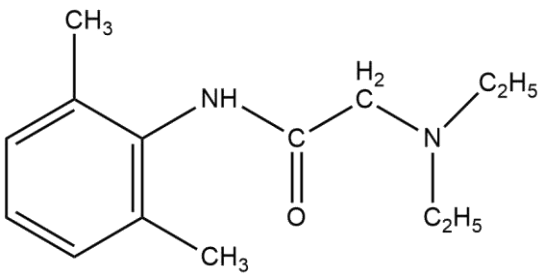


Tetracaine

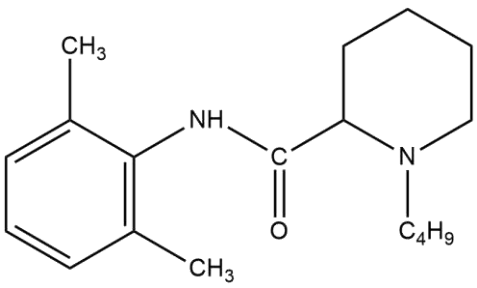


Benzocain

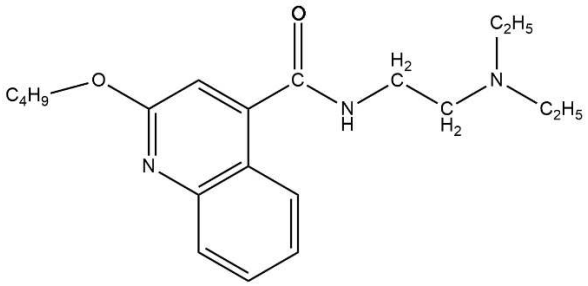
B. Amide-linked LAs: Lidocaine, bupivacaine, dibucaine, prilocaine, ropivacaine.



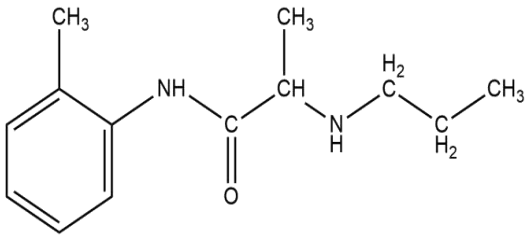
Lidocaine



Bupivacaine

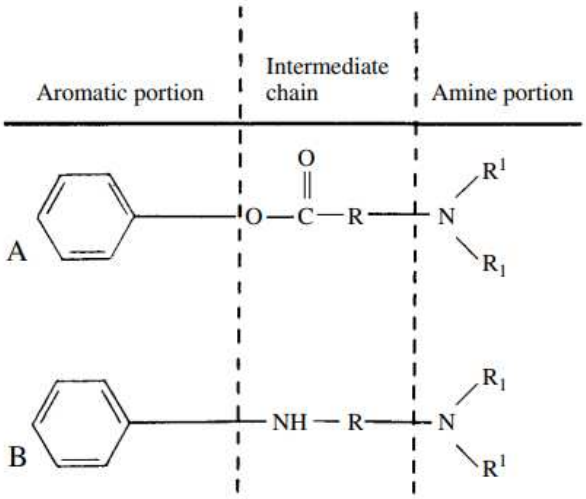


Dibucaine



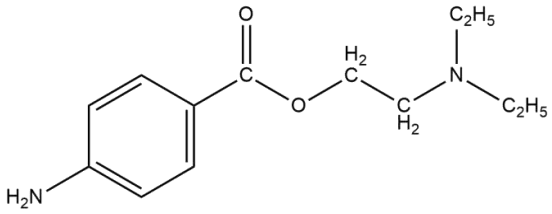
Prilocaine

SAR of Local Anesthetics



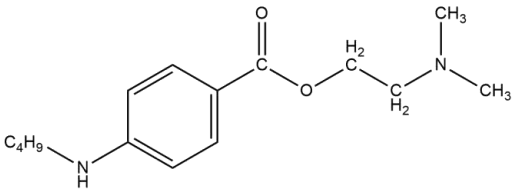
A. Aromatic Rings

- Aromatic ring and substituents at different position in LAs may add lipophilicity and enhace the penetrating capecity
- Substitution at para-position of aromatic ring in ester type Las enhance the ability to penetrate the nerve membrane and increase their affinity at the receptor site.



Procain

- Electron donating substitution at para-amino (R-NH-Ar) like alkoxy (**propoxycain**), alkylamino (**tetracain**) increase the potency. Becouse electron donating substitution enhance the rasonance between Aromatic ring and carbonyl group and resulting in increase the affinity to receptor.

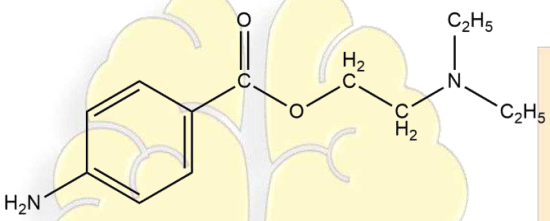


Tetracain

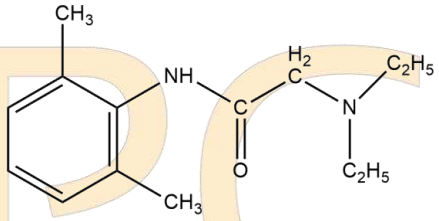
- Electron withdrawing substitution decrease the electron cloud around the carbonyl group and resulting in decrease in the LA activity.

B. Intermediate Linker

- The linker may be carbon, oxygen, nitrogen containing function moieties majorly ester and amide linkage.



Procain (Ester)

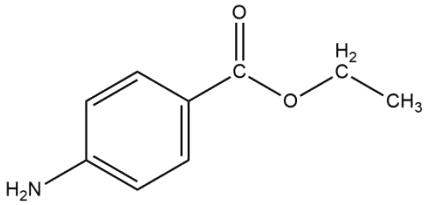


Lidocain (Amide)

- When length of alkyl chain of linker is increased, lipophilicity, protein binding, duration of action and toxicity may increase.
- Ester and amide linkage have similar binding affinity but amide linkage has differ in:-
  - ✓ Produce more intense and longer lasting anaesthesia
  - ✓ Bind to alfa 1 acid glycoprotein in plasma
  - ✓ Not hydrolysed by plasma esterases
  - ✓ Rarely cause hypersensitivity reactions; no cross sensitivity with ester LAs
- Branching of alfa-carbon will increase the duration of action in procain series but lidocain series does not show this effects.

C. Amino-alkyl Substitution

- Amino-alkyl group is important for drug water solubility not essential for activity. Eg. Benzocain have no amino-alkyl substitution.



Benzocain

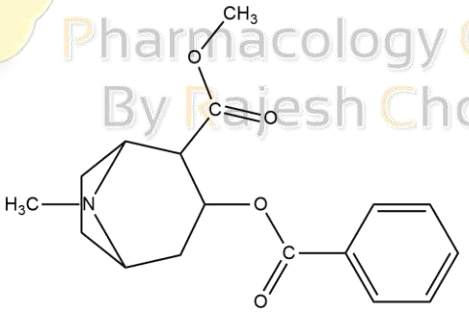
- Tertiary amine derivative are more potent and less toxic. Whereas, secondary amines may increase the duration but having irritative action and primary amines arte not suitabe due to less active & highly toxic

18.3. MEDICINAL CHEMISTRY OF SELECTED LOCAL ANESTHETICS

1. Benzoic Acid Derivativs

Drugs: Cocaine, Hexylcaine, Meprylcaine, Cycomethycaine, Piperocaine

A) Cocain

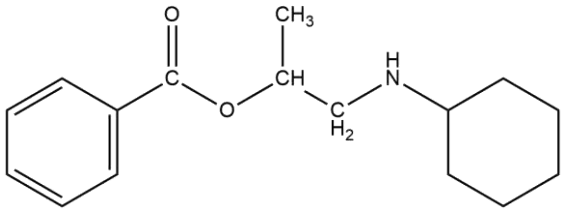


methyl (1*R*,2*R*,3*S*,5*S*)-3-benzoyloxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate

Uses

- ✓ Used as an LA in the inner lining of mouth during oral surgery, ophthalmology (4% solution), and nasal mucosa in otolaryngial procedure (10% solution)
- ✓ It has also vasoconstrictor properties, used to decrease bleeding & swelling from minor injuries.

B) Hexylcaine

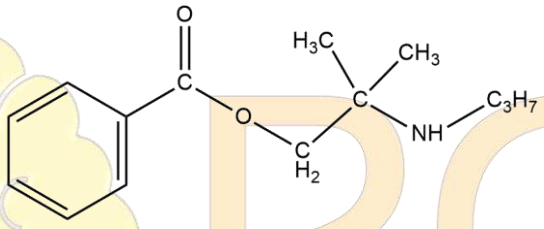


1-(Cyclohexyl amino) propan-2-yl benzoate

Uses

- ✓ Hexylcain acts a short acting LA used in oral surgery
- ✓ It is used as surface anesthesia (10-20%) and topical anesthesia

C) Meprylcaine

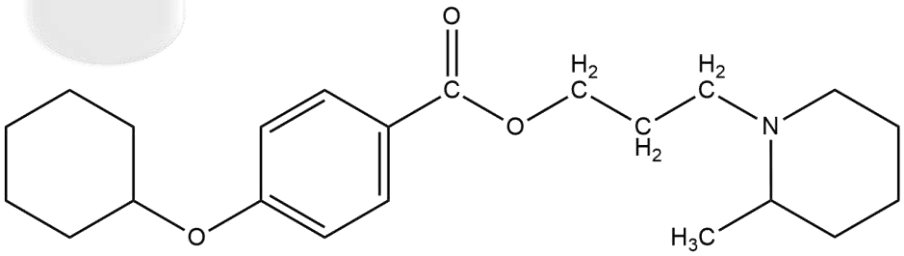


[2-methyl-2-(propylamino)propyl] benzoate

Uses

- ✓ It is used in dentistry (surface 0.5% or infiltration anesthetics)
- ✓ It is used as topical anesthesia
- ✓ Used in acute pain due to trauma, surgery, infection, etc.

D) Cycomethycaine

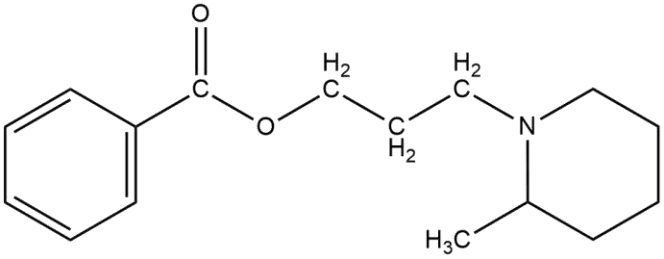


3-(2-methylpiperidin-1-yl) propyl 4-cyclohexyl-oxy-benzoate

Uses

- ✓ It is used as topical anesthesia (0.5-2% solution) in minor surgery

E) Piperocaine



3-(2-methylpiperidin-1-yl) propyl benzoate

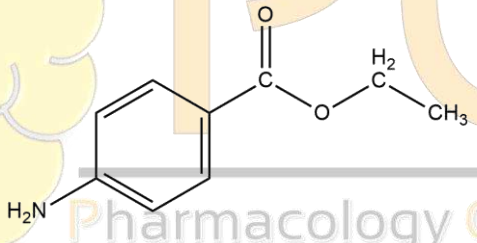
Uses

- ✓ It is used as surface anesthesia (0.5% solution) in ophthalmology, mouth ulcer
- ✓ Used in dentistry

2. Anino Benzoic Acid Derivativs

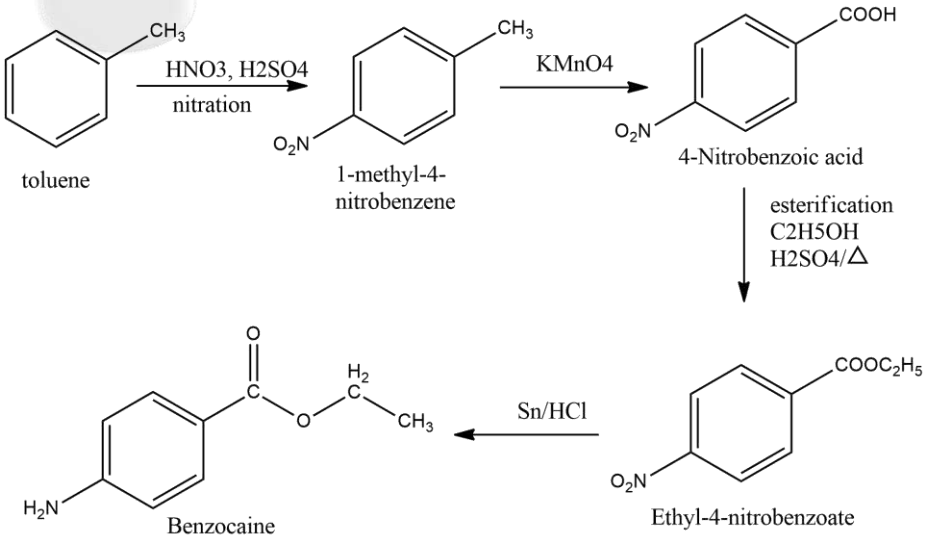
Drugs: Benzocain*, Butamben, Procain*, Butacain, Propoxycain, Tetracain, Benoxinate

A) Benzocain



Ethyl-4-amino benzoate

Synthesis:

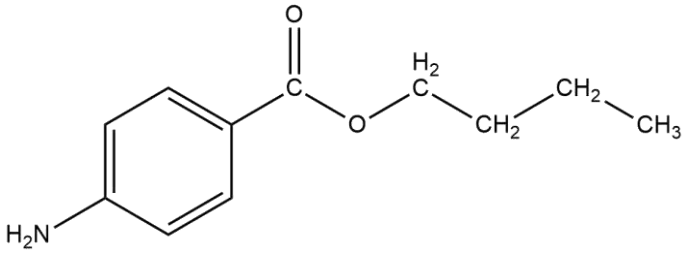


Uses:

- ✓ Used as surface anesthesia

- ✓ Used in dental pain, sore throat
- ✓ 10-20%, in ear drops, cream, ointment, sprays, etc for analgesia and topical anesthesia.

B) Butamben

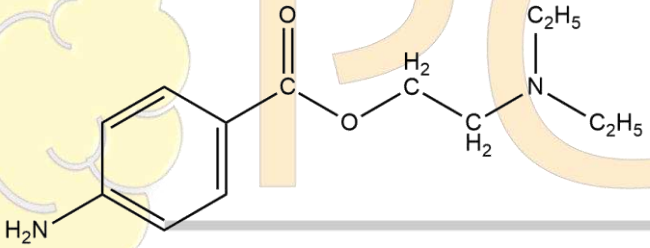


Butyl-4-amino benzoate

Uses:

- ✓ Used as surface anesthesia for skin mucous membrane
- ✓ Used in chronic pain

C) Procain

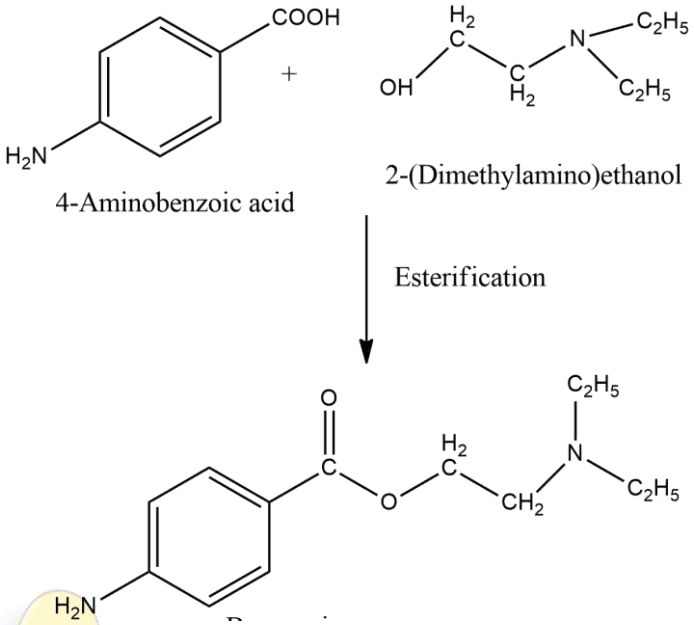


2-(diethyl amino) ethyl-4-amino benzoate

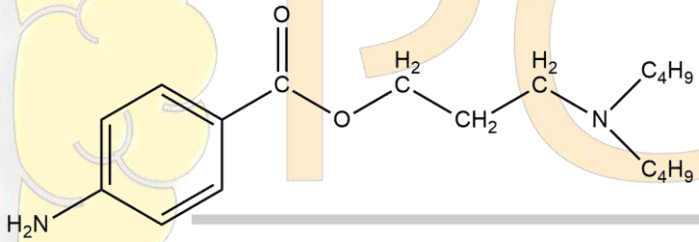
Uses

- ✓ Used as Infiltration anesthesia (0.25-0.5% solution)
- ✓ For peripheral nerve block dose of procaine HCl is 500 mg has used as 0.5% in 100 ml

Synthesis:



D) Butacain

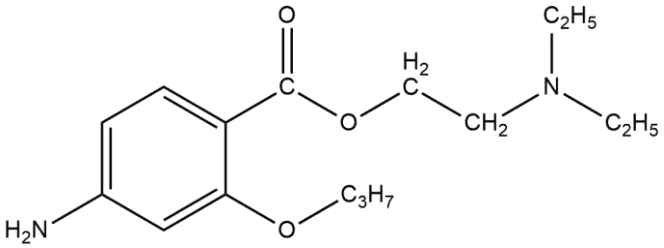


2-(dibutyl amino) propyl-4-amino benzoate

Uses

- ✓ Used as surface anesthesia
- ✓ Used in dental pain, ear and nasal drops.

E) Propoxycain

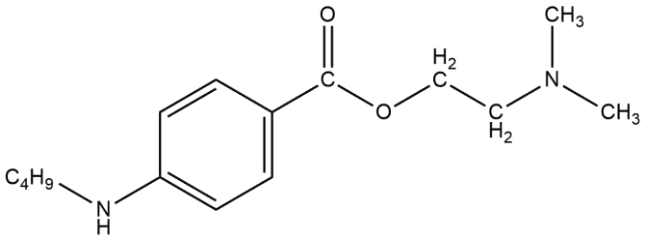


2-(diethyl amino) ethyl 4-amino-2-propoxybenzoate

Uses:

- ✓ Potent long acting local anesthetics
- ✓ Profound anesthesia when injected close to nerve sheath.

F) Tetracain (Amethocaine)

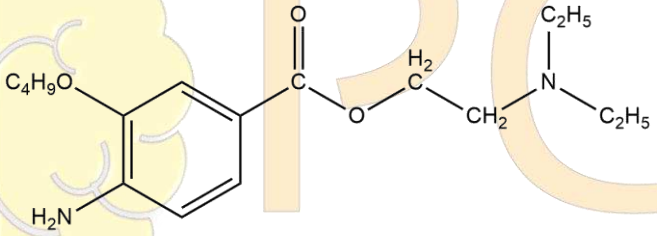


2-(dimethyl amino) ethyl 4-(butylamino)benzoate

Uses:

- ✓ Used spinal and topical anesthesia

G) Benoxinate



2-(diethyl amino)ethyl 4-amino-3-butoxy benzoate

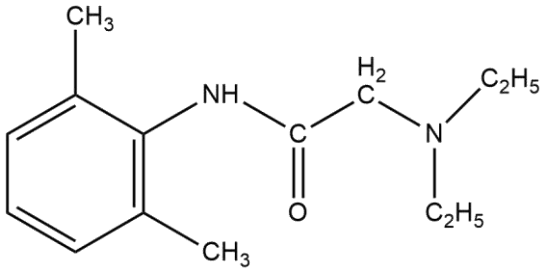
Uses:

- ✓ Used as surface anesthetic agent and used in ophthalmology, and brochoscopy.

3. Anilide Derivativs

Drugs: Lidocain**,** Mepivacain**,** Prilocaine, Etidocaine

A) Lidocain

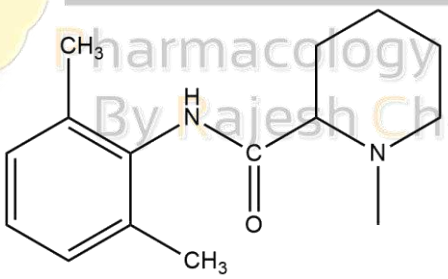


2-(diethylamino)-N-(2,6-dimethyl phenyl) acetamide

Uses:

- ✓ Lidocaine has a rapid onset of action, used as infiltration anesthesia (5-300 mg).
- ✓ 1% solution- block the stmpathetic nerve.
- ✓ 50 mg (5ml)- block the cervical & 50-100 mg (5-10 ml) block the lubmer.
- ✓ Used in eye drops (4%) for tonometry.
- ✓ Lidocain also used in cardiac arrhythmia.

B) Mepivacain

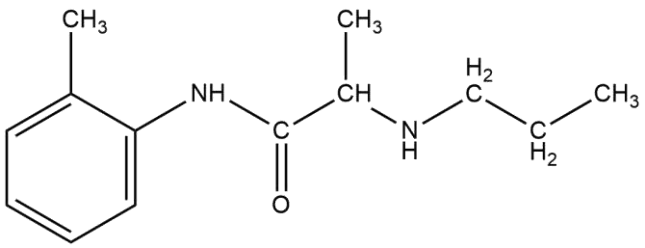


N-(2,6-dimethyl phenyl)-1-methylpiperidine-2-carboxamide

Uses:

- ✓ Used as local anesthesia for an epidural or spinal block and dental procedure.

C) Prilocaine

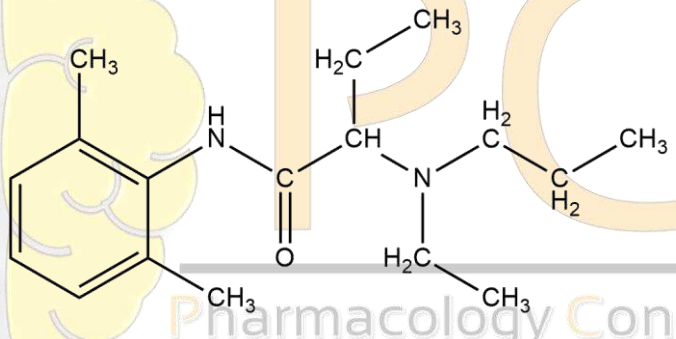


***N*-(2-methylphenyl)-2-(propyl amino) propenamide**

Uses:

- ✓ Used for i.v. regional anesthesia
- ✓ Used topical administration to decrease the painful needle sticks in children

D) Etidocaine



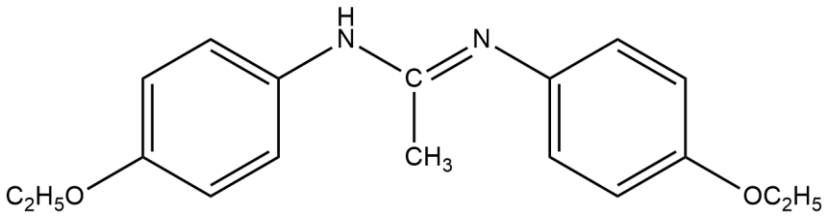
***N*-(2,6-dimethylphenyl)-2-[ethyl(propyl)amino]butanamide**

Uses:

- ✓ Used for epidural and topical anesthesia.
- ✓ Used for peripheral nerve or plexus block.

4. Misc. Drugs: Phenacaine, Diperodon, Dibucaine*

A) Phenacaine

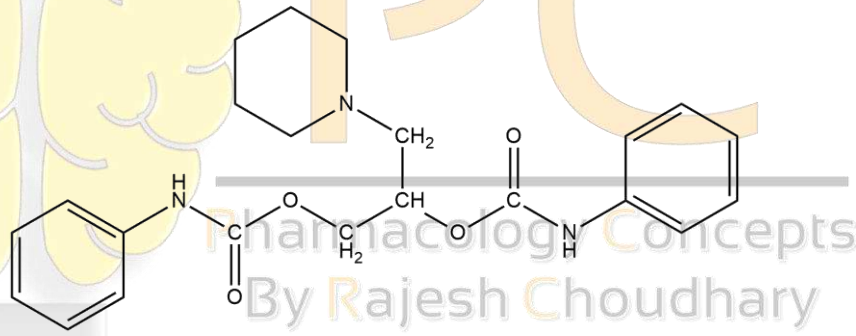


***N*,*N*'-bis(4-ethoxyphenyl)ethanimidamide**

Uses:

- ✓ 1% solution used as LA for ocular operation
- ✓ 1-3% solution used to treatment of skin operative procedure, dental and other minor surgery.

B) Diperodon

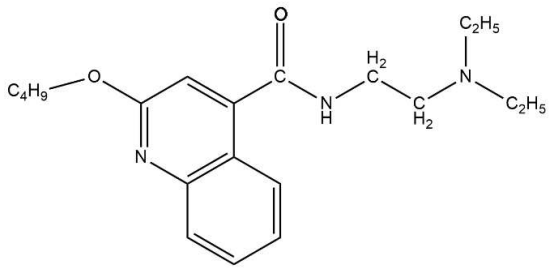


[2-(phenylcarbamoyloxy)-3-piperidin-1-ylpropyl] *N*-phenylcarbamate

Uses:

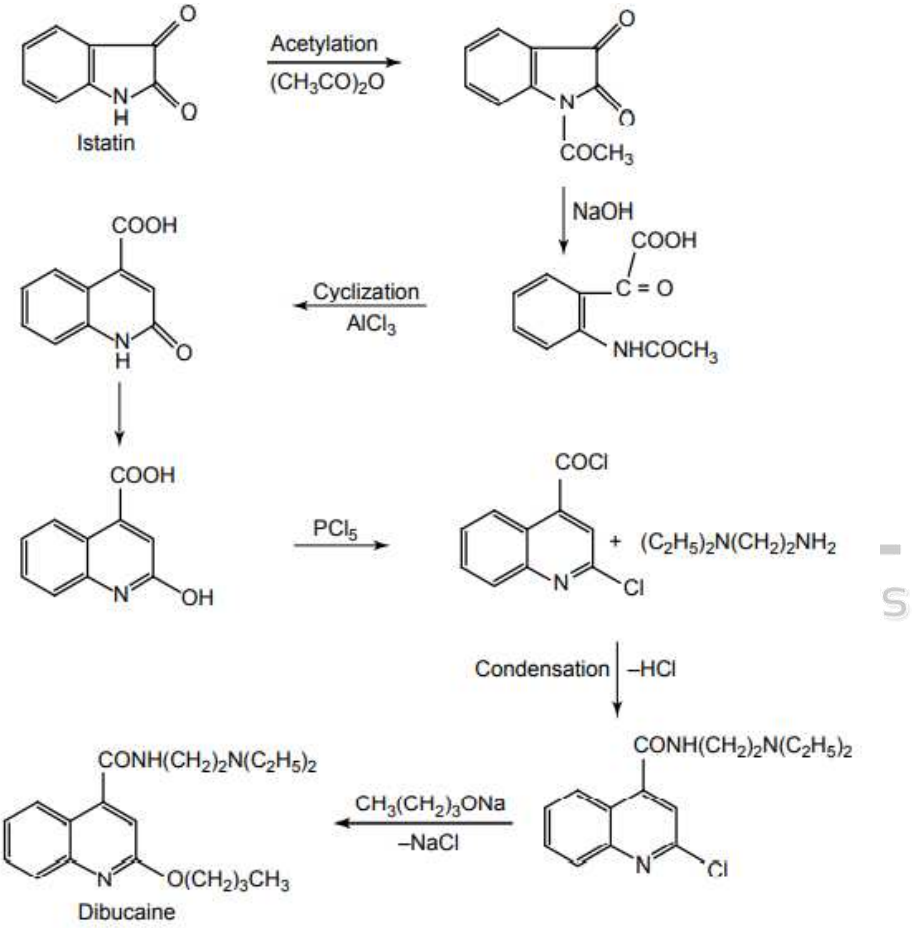
- ✓ Used to topical anesthesia for skin analgesia and minor surgery of skin.
- ✓ Used to nerve block
- ✓ Used to treatment of foot, and ankle disorders.

C) Dibucaine



2-butoxy-*N*-[2-(diethylamino)ethyl]quinoline-4-carboxamide

Synthesis



Uses:

- ✓ Used as surface anesthesia
- ✓ Used to relief pain and itching
- ✓ Used in puruties of skin
- ✓ Used to reduce swelling

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