# LOCAL ANESTHETIC

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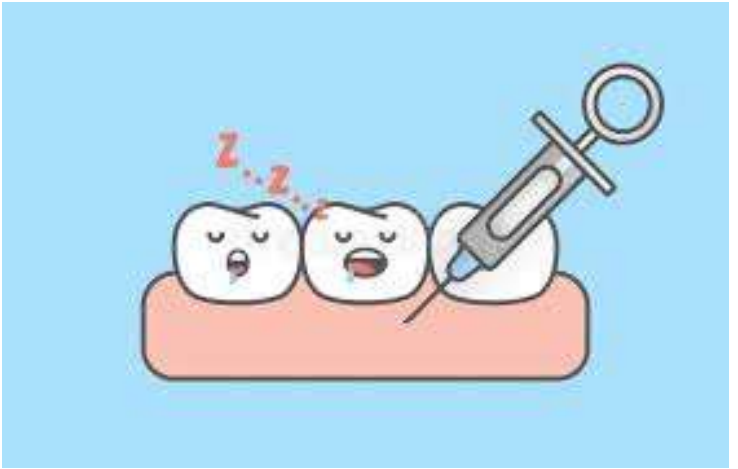


# LOCAL ANESTHETICS

- Local anesthetic agents are drugs that, when given either topically or administered directly into a localized area, produce a state of local anesthesia by reversibly blocking nerve conductances that transmit the sensations of pain from this localized area to the brain.
- Local anaesthetics block both the generation and the conduction of the nerve impulse.
- Anesthesia produced by local anesthetics is without loss of consciousness or impairment of vital central cardiorespiratory functions


Wolters Kluwer
Lippincott
Williams & Wilkins
Do you prefer a local anesthesia?
I would rather prefer an imported one.

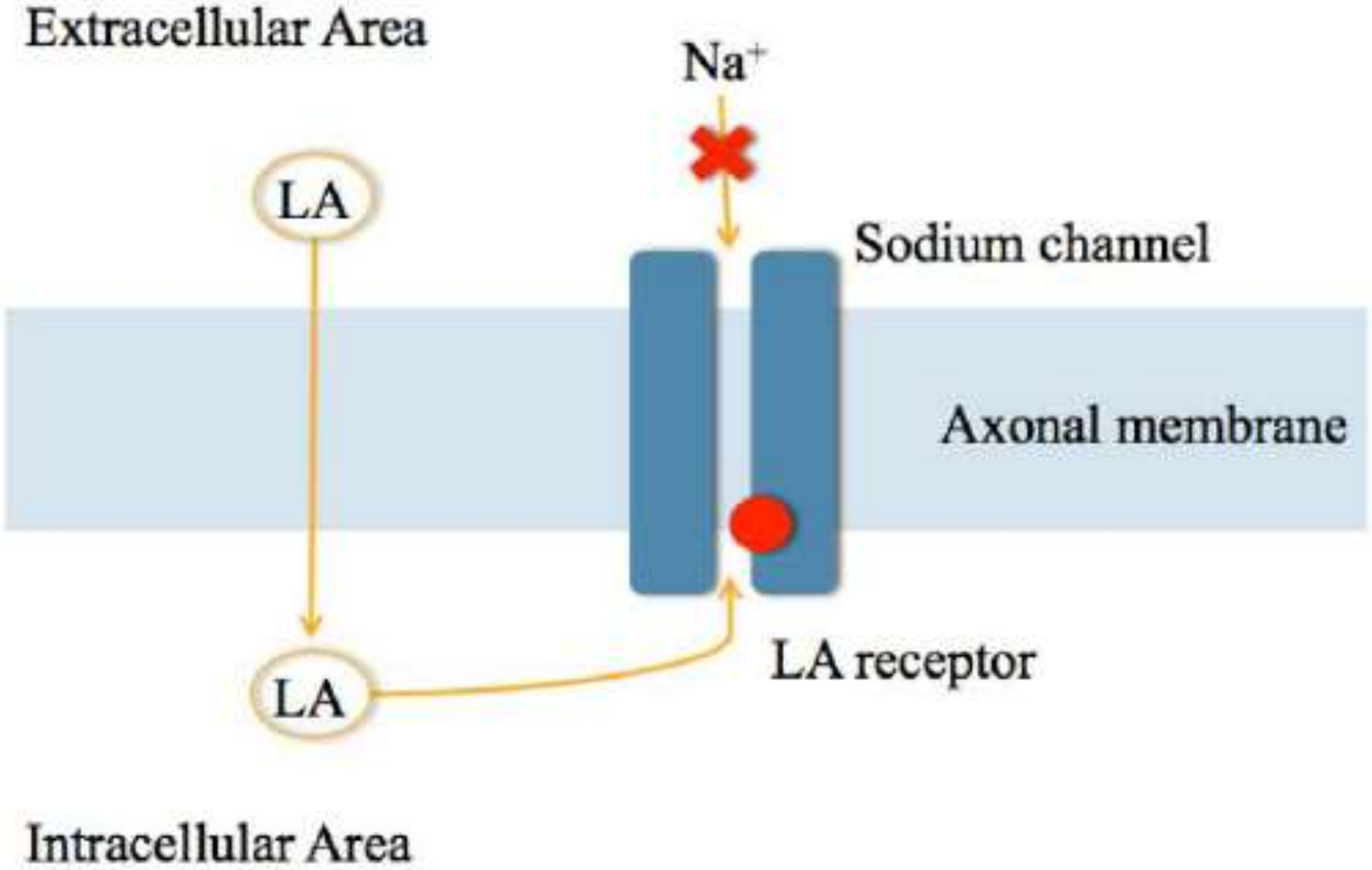
# HOW DO THEY WORK???

- Local anesthetics block nerve conductance by binding to selective sites on the Na+ channels in the excitable membranes, thereby reducing Na+ passage (i.e., conductance) through the pores and, thus, interfere with the generation of action potentials.
- Although local anesthetics decrease the excitability of nerve membranes, they do not affect the neuron's resting potential. Local anesthetics, in contrast to analgesic compounds, do not interact with the pain receptors or inhibit the release or the biosynthesis of pain mediators.

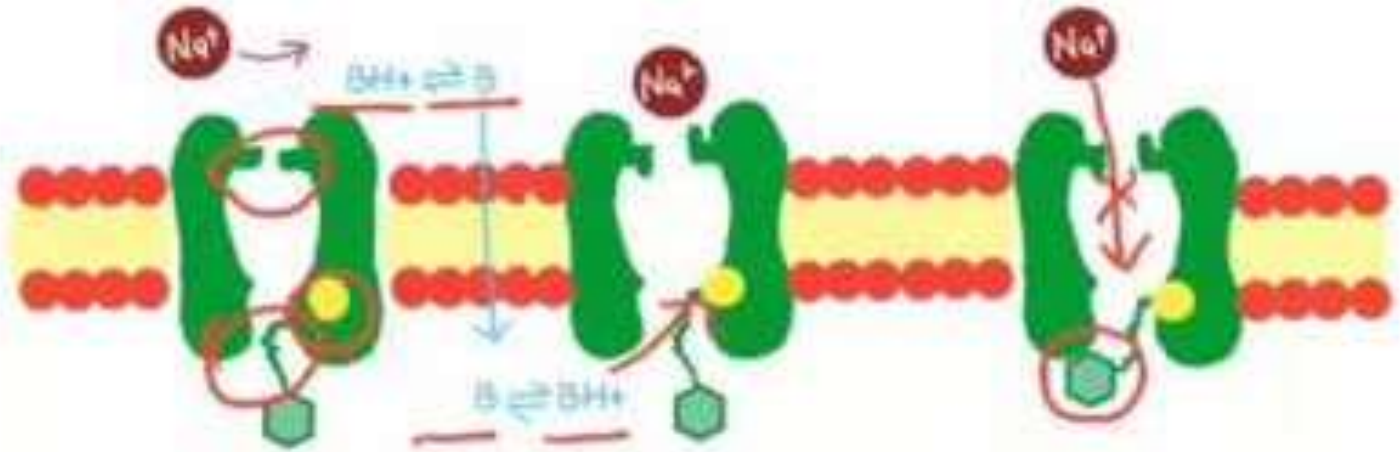
# MECHANISM OF ACTION

- Local anesthetics act by decreasing the excitability of nerve cells without affecting the resting potential.
- Because the action potential, or the ability of nerve cells to be excited, is associated with the movement of Na+ across the nerve membranes, anything that interferes with the movement of these ions will interfere with cell excitability.
- All LAs are membrane-stabilizing drugs; they reversibly decrease the rate of depolarization and repolarization of excitable membranes (like nociceptors) at peripheral nerve ending.
- Though many other drugs also have membrane-stabilizing properties, not all are used as LAs (propranolol, for example, though it has LA properties).
- LA drugs act mainly by inhibiting sodium influx through sodium-specific ion channels in the neuronal cell membrane, in particular the so-called voltage-gated sodium channels.
- When the influx of sodium is interrupted, an action potential cannot arise and signal conduction is inhibited.
- The receptor site is thought to be located at the cytoplasmic (inner) portion of the sodium channel.
- Local anesthetic drugs bind more readily to sodium channels in an activated state, thus onset of neuronal blockade is faster in rapidly firing neurons. This is referred to as state-dependent blockade.

- The LAs interact with a receptor situated within the voltage sensitive Na+ channel and raise the threshold of channel opening: $Na^+$ permeability fails to increase in response to an impulse or stimulus.
- Impulse conduction is interrupted when the $Na^+$ channels over a critical length of the fibre (2–3 nodes of Ranvier in case of myelinated fibres) are blocked.
- At physiological pH, the LA molecule is partly ionized. The equilibrium between the unionized base form (B) and the ionized cationic form ($BH^+$ ) depends on the pKa of the LA.
- Potency of a LA generally corresponds to the lipid solubility of its base form (B), because it is this form which penetrates the axon.
- However, the predominant active species is the cationic form of the LA which is able to approach its receptor only when the channel is open at the inner face, and it binds more avidly to the activated and inactivated states of the channel, than to the resting state.
- Binding of the LA prolongs the inactivated state. The channel takes longer to recover → refractory period of the fibre is increased.
- The degree of blockade is frequency dependent: greater blockade occurs at higher frequency of stimulation. Moreover, exposure to higher concentration of $Ca^{2+}$ reduces inactivation of $Na^+$ channels and lessens the degree of block.
- Blockade of conduction by LA is not due to hyperpolarization; in fact, resting membrane potential is unaltered because $K^+$ channels are blocked only at higher concentrations of LA.


Extracellular Area
Na+
LA
Sodium channel
Axonal membrane
LA
LA receptor
Intracellular Area

## Mechanism:




Resting state → Activated state → Inactivated state

# ADVERSE EFFECTS

- Systemic toxicity on rapid i.v. injection is related to the intrinsic anaesthetic potency of the LA. However, toxicity after topical application or regional injection is influenced by the relative rates of absorption and metabolism. Those rapidly absorbed but slowly metabolized are more toxic.

(1) CNS effects are light-headedness, dizziness, auditory and visual disturbances, mental confusion, disorientation, shivering, twitchings, involuntary movements, finally convulsions and respiratory arrest. This can be prevented and treated by diazepam.

(2) Cardiovascular toxicity of LAs is manifested as bradycardia, hypotension, cardiac arrhythmias and vascular collapse.

(3) Injection of LAs may be painful, but local tissue toxicity of LAs is low. However, wound healing may be sometimes delayed. Addition of vasoconstrictors enhances the local tissue damage.

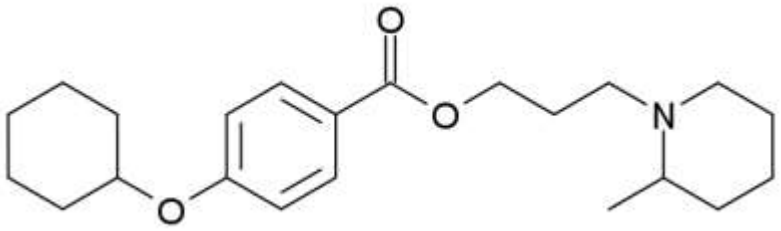
(4) Hypersensitivity reactions like rashes, angioedema, dermatitis, contact sensitization, asthma and rarely anaphylaxis occur.

# CLASSIFICATION

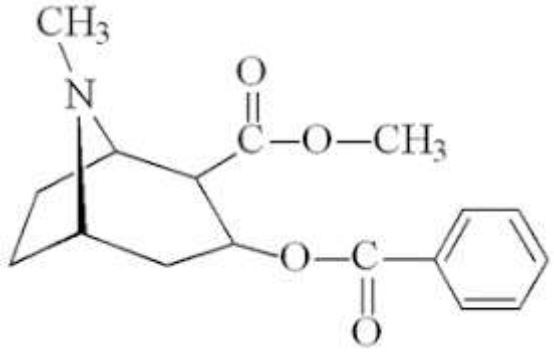
| S.NO. | CLASS | EXAMPLES |
|---|---|---|
| 1. | BENZOIC ACID DERIVATIVE | Meprylcaine, Cyclomethycaine, Piperocaine, Hexylcaine, Isobucaine, Cyclomethycaine. |
| 2 | P-AMINO BENZOIC ACID DERIVATIVE | Benzocaine, Procaine, Butacaine, Propoxycaine, Tetracaine. |
| 3 | LIDOCAINE/ANILIDE DERIVATIVE | Lignocaine/Lidocaine, Mepivacaine, Prilocaine, Etidocaine, Bupivacaine |
| 4 | MISCELLANEOUS | Phenacaine, Diperodon HCl, Dimethizoquine, Dibucaine, Pramoxine HCl, Dyclonine HCl |

# 1. BENZOIC ACID DERIVATIVES:

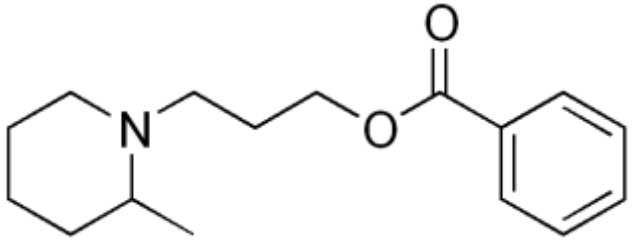
Cyclomethycaine

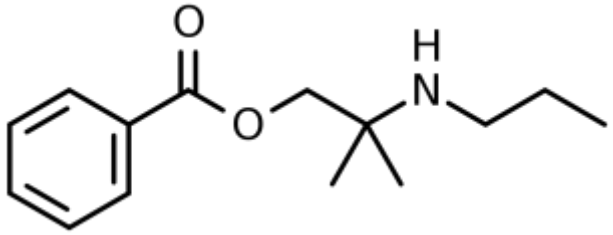


Cocaine

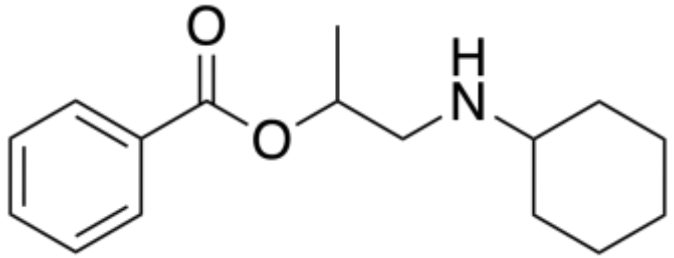


Piperocaine



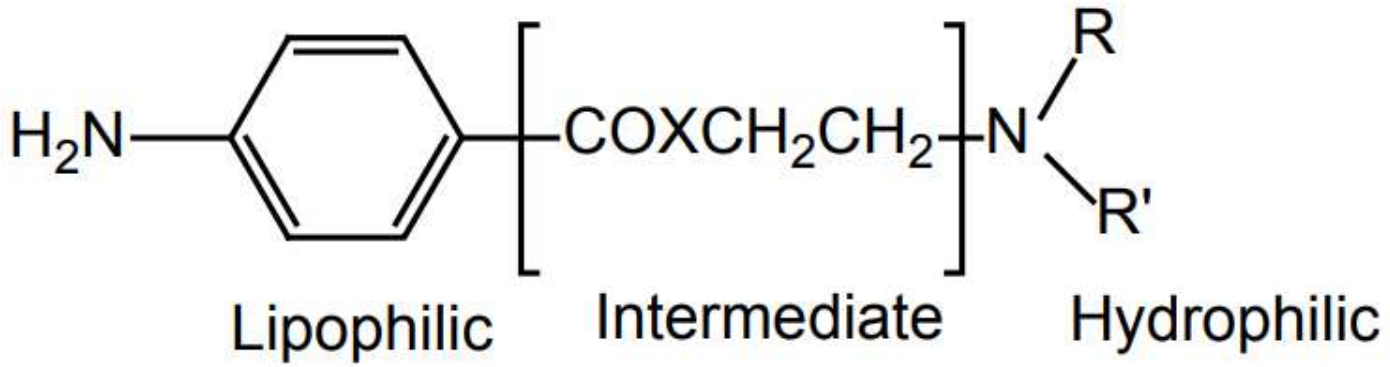


Meprylcaine



Hexylcaine

# SAR OF BENZOIC ACID DERIVATIVES




- The structure of most local anesthetic agents consists of three parts as shown above.
- They contain

(a) a lipophilic ring that may be substituted,

(b) a linker of various lengths that usually contains either an ester or an amide, and

(c) an amine group that is usually a tertiary amine

## 1. Lipophilic

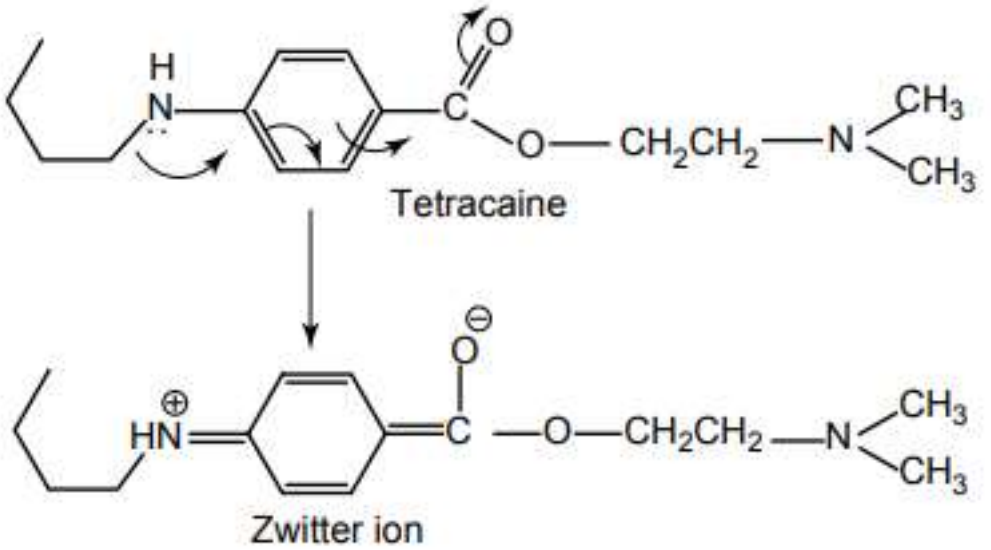
• The clinically useful local anaesthetics of this class possess an aryl radical that is attached directly to the carbonyl group and are highly liphophilic.

• They appear to play an important role in the binding of local anaesthetics to the channel receptor protein.

• Placement of aryl group with substituents that increases the electron density of the carbonyl oxygen enhances the activity.

• Structural modification leads to change in physical and chemical properties. Electron withdrawing substituents in ortho or para or at both the positions leads to an increase of its local anaesthetic property.

• Amino (procaine, butacaine) alkyl amino (tetracaine) alkoxyl (cyclomethycaine) group can contribute to electron density in the aromatic ring by both resonance and inductive effects. Hence the increase in local anaesthetic property.




- Any substitution that enhances zwitterion formation will be more potent. Hence m-position substitution dec. Tetracaine is more potent than procaine (40–50 times).
- Although the butyl group present in it increases lipid solubility, the potentiation is partly due to electron releasing property of the n-butyl group via inductive effect, which intend to increase the formation of the Zwitterion.
- Presence of electron withdrawing group such as Cl– ortho to carbonyl pulls electron density away from carbonyl group, thus, making it more susceptible for nucleophilic attack by the esterase.

## 2. Intermediate

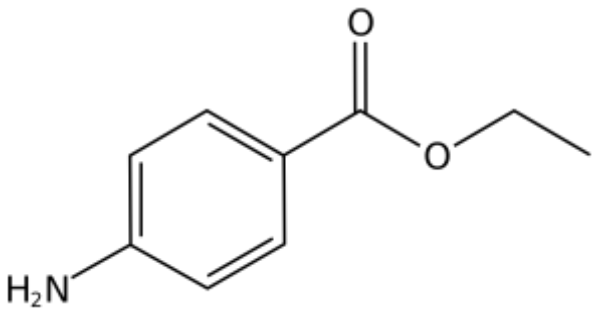
- In procaine series, anaesthetic potency decreases in the following order sulphur, oxygen, carbon, and nitrogen.
- Modifications also affect the duration of action and toxicity. In general, amides (X= N) are more resistant to metabolic hydrolysis than esters (X = O). Thioesters (X = S) may cause dermatitis.
- Placement of small alkyl groups (branching) around ester group (hexylcaine/meprylcaine) or the amide function also hinder hydrolysis, and hence, increase in duration of action.

## 3. Hydrophilic portion

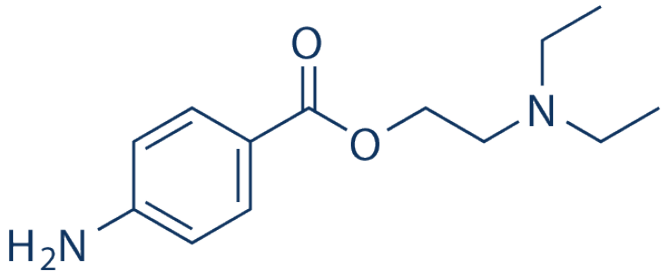
- The amino alkyl group is not necessary for local anaesthetic activity, but it is used to form water soluble salts such as HCl salts.
- Tertiary amines are more useful agents. The secondary amines appear to have a longer duration of action, but they are more irritating. Primary amines are not active/cause irritation.
- The tertiary amino group may be diethyl amino, piperidine, or pyrrolidine, leading to a product that exhibit same degree of activity, essentially.
- The more hydrophilic morpholino group usually leads to diminished potency.
- In general, the local anaesthetic drug should have increased lipid solubility and lower pKa values that leads to rapid onset and lower toxicity.

# 2. PARA-AMINO BENZOIC ACID DERIVATIVE

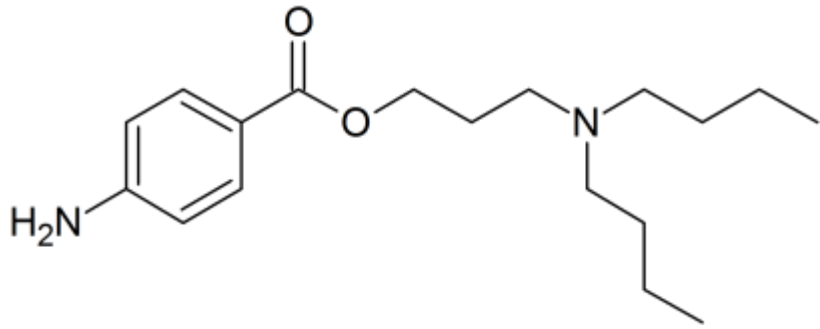
Benzocaine



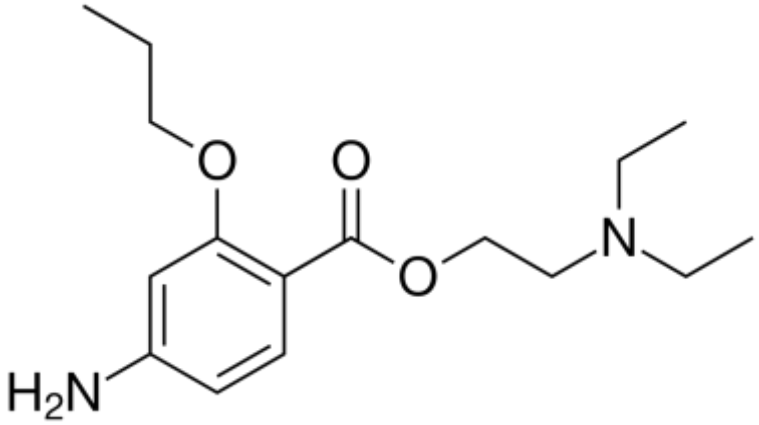

Procaine



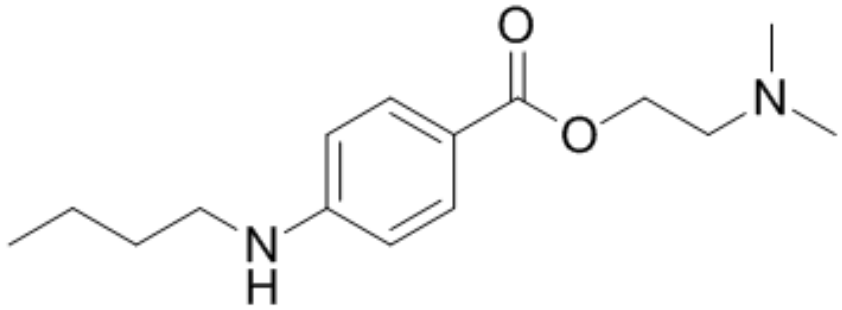

Butacaine



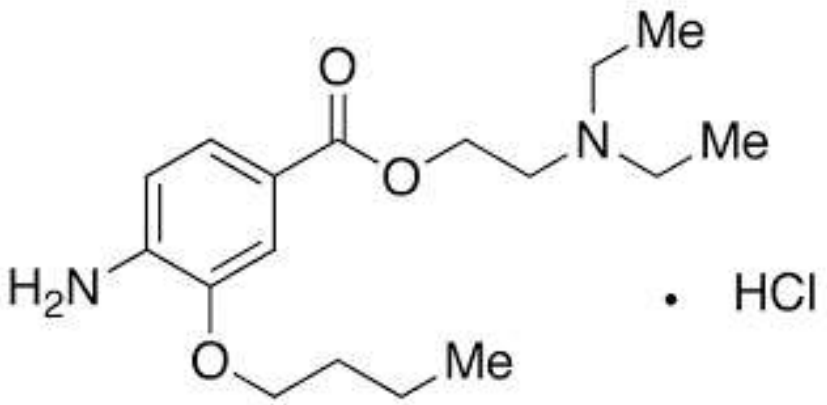

Propoxycaine



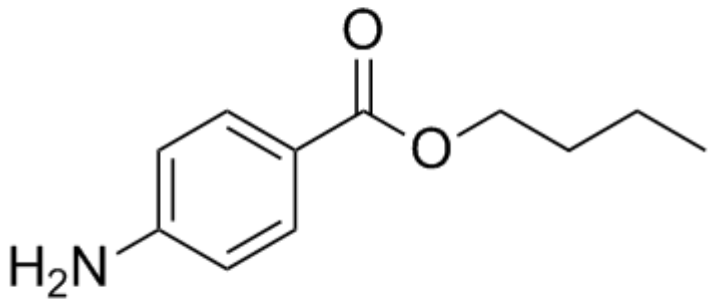

Tetracaine



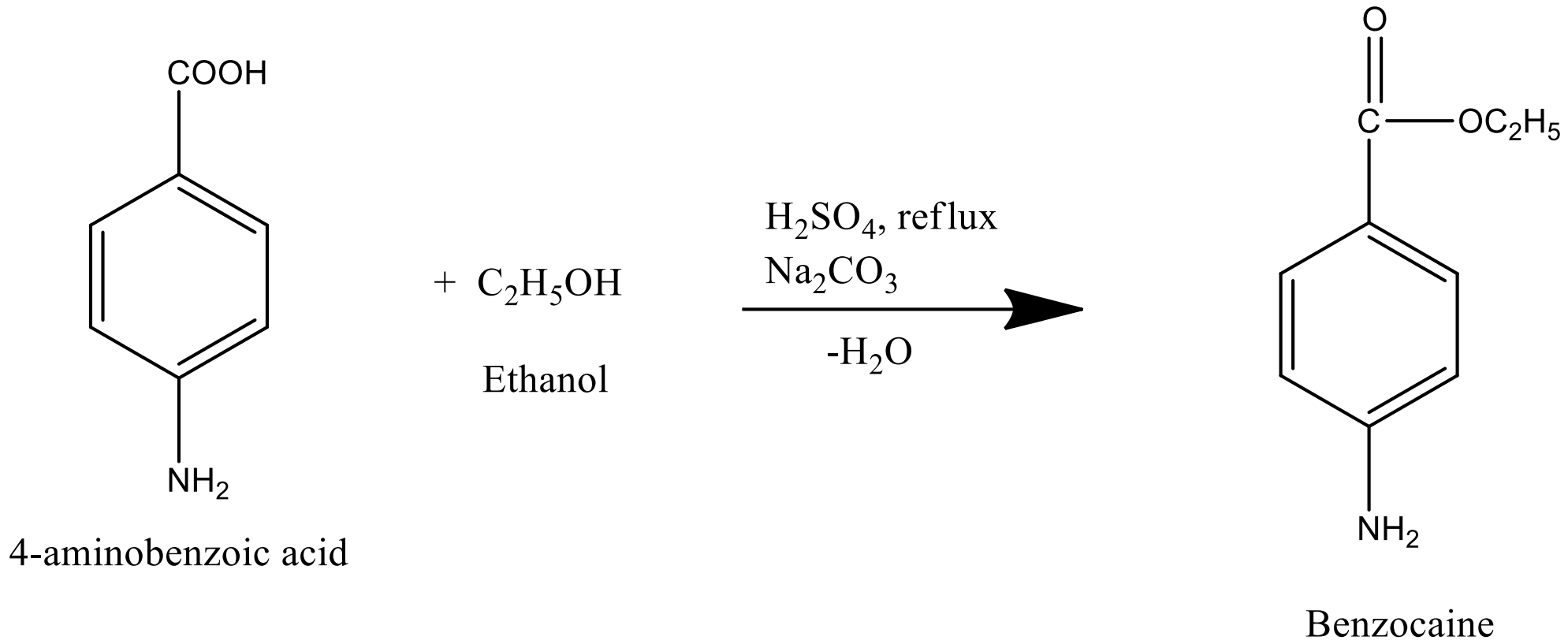
Benoxinate




Butamben



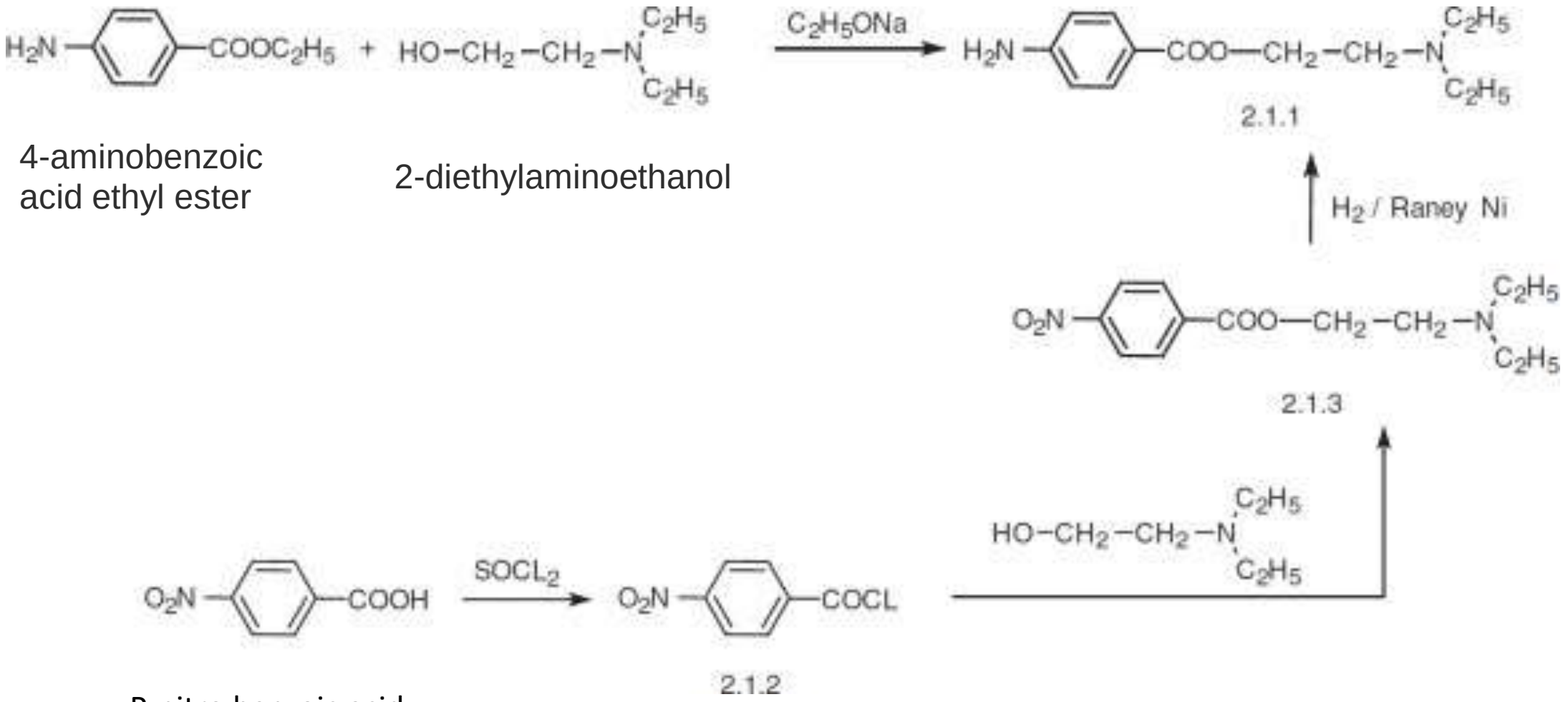
# SYNTHESIS OF BENZOCAINE:




4-aminobenzoic acid

Benzocaine

# Synthesis of Procaine:



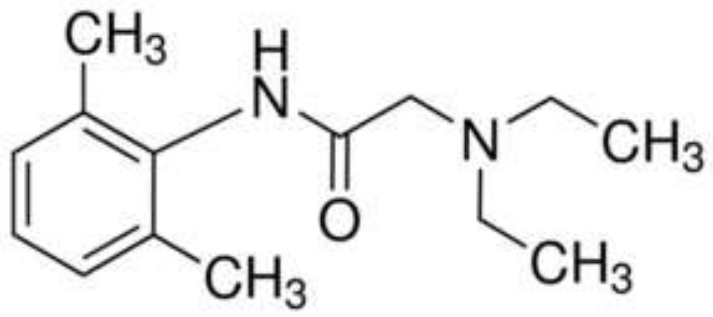

4-aminobenzoic acid ethyl ester

2-diethylaminoethanol

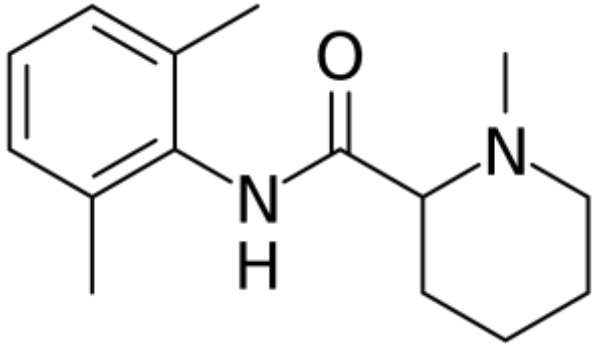
P-nitro benzoic acid

# 3. ANILIDE DERIVATIVES

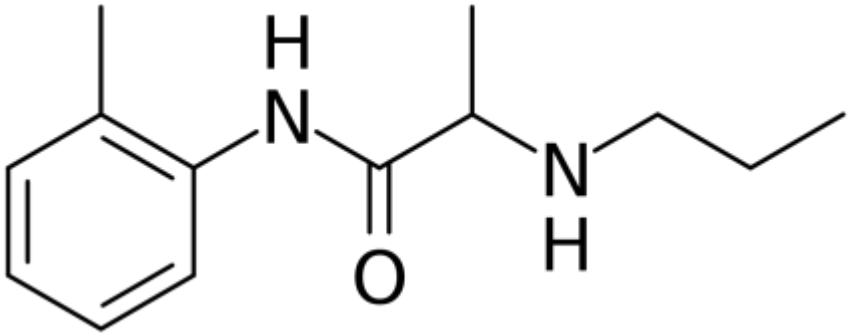
Lignocaine



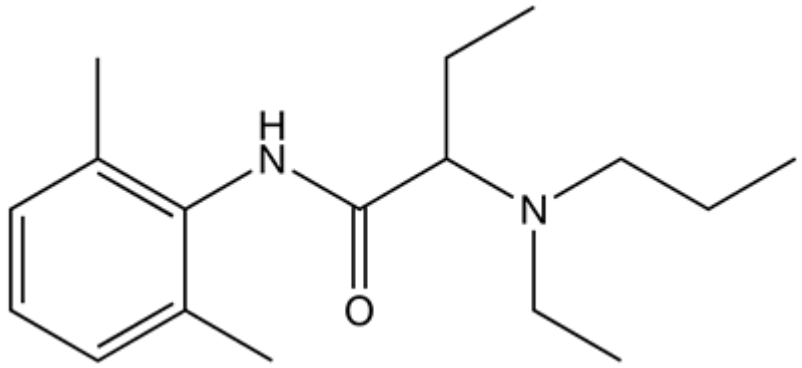

Mepivacaine




Prilocaine




Etidocaine



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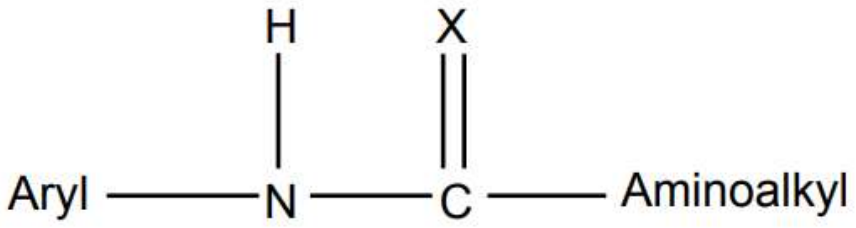
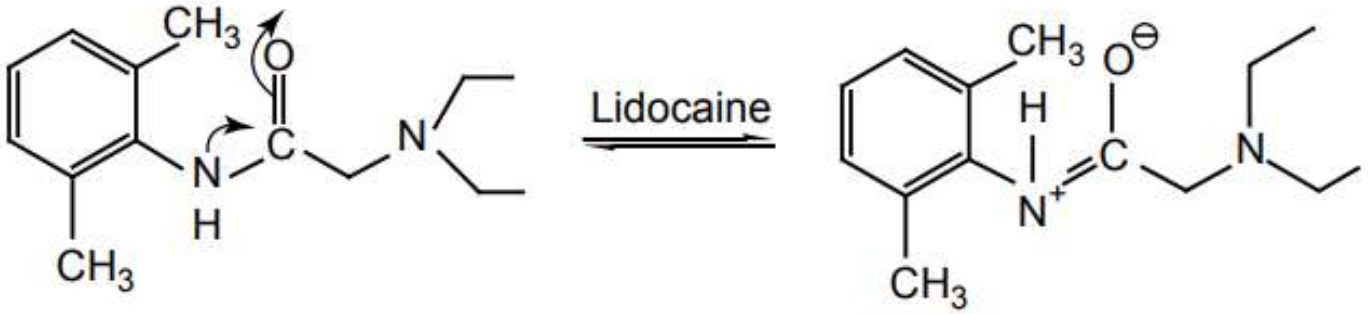



**a. Aryl group**

- The clinically useful local anaesthetics of this type possess a phenyl group attached to the sp2 carbon atom through a nitrogen bridge.
- Placement of substituents on the phenyl ring with a methyl group in the 2 (or) 2 and 6-position enhances the activity.
- In addition, the methyl substituent provides steric hindrance to hydrolysis of the amide bond and enhances the coefficient of distribution.
- Any substitution on the aryl ring that enhances zwitterion formation will be more potent.




Lidocaine Zwitterion

## b. Substituent X

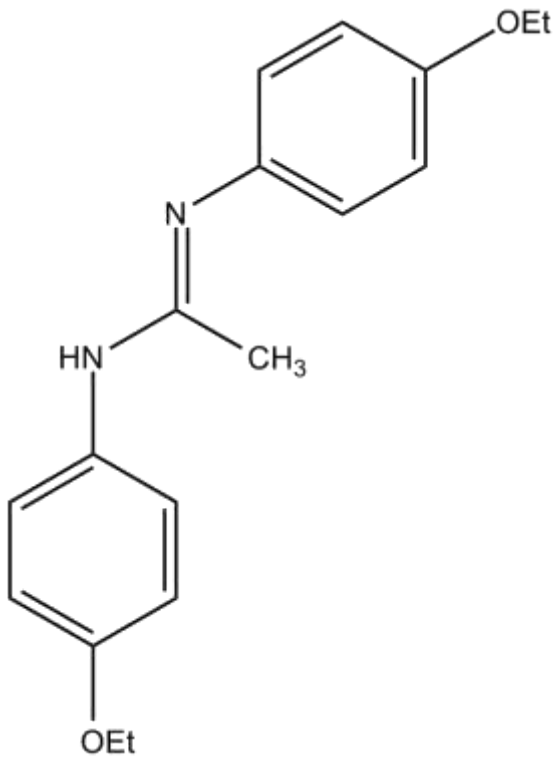
- ‘X’ may be carbon, oxygen, or nitrogen among them lidocaine series (X = O) has provided more useful products.

## c. Amino alkyl group

- The amino function has the capacity for salt formation and is considered as the hydrophilic portion of the molecule.
- Tertiary amines (diethyl amine, piperidine) are more useful because the primary and secondary amines are more irritating to tissues.

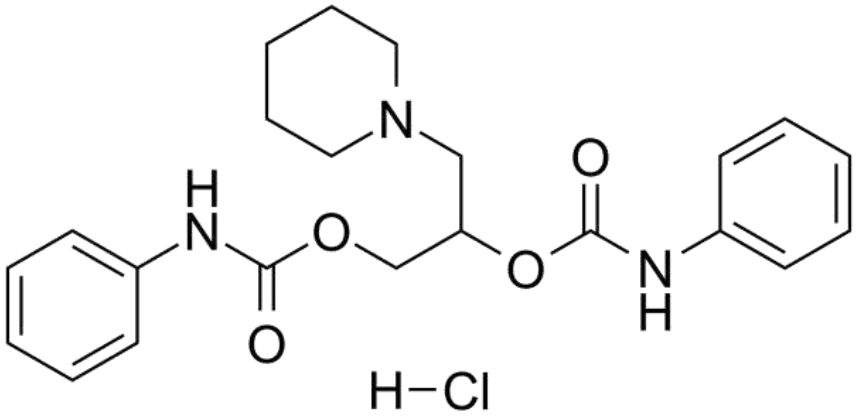
# 4. MISCELLANEOUS AGENTS

Phenacaine

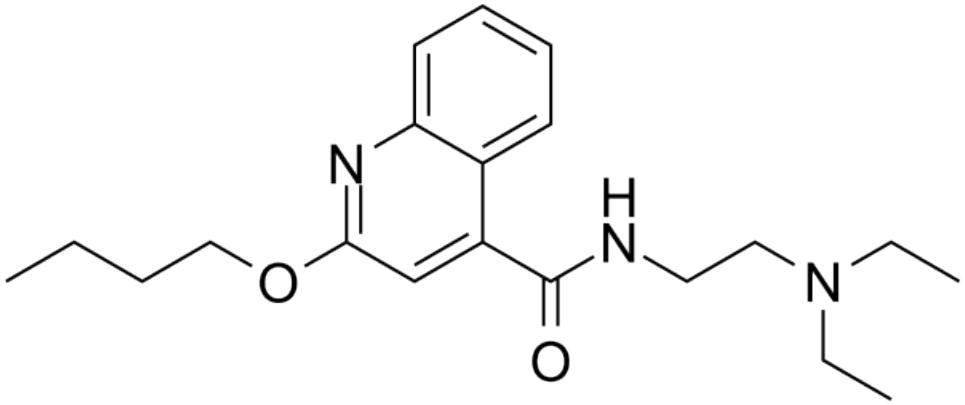



**Properties and uses**: It exists as small white odourless and crystalline powder. Structurally, it is related to anilides in that the aromatic ring is attached to a sp2 carbon through a nitrogen bridge. It is one of the oldest synthetic local anaesthetic. It is used mainly for producing local anaesthesia of the eye

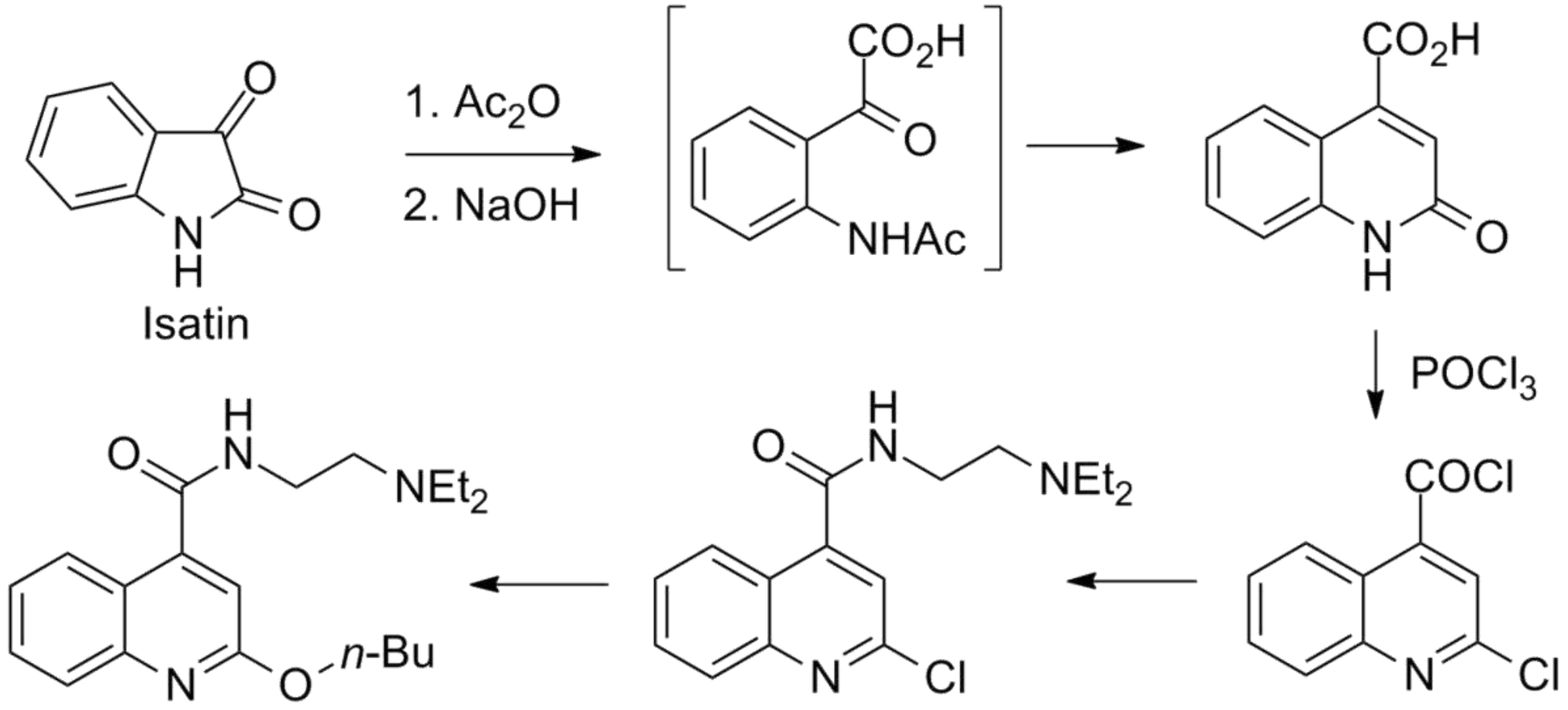
Diperodon



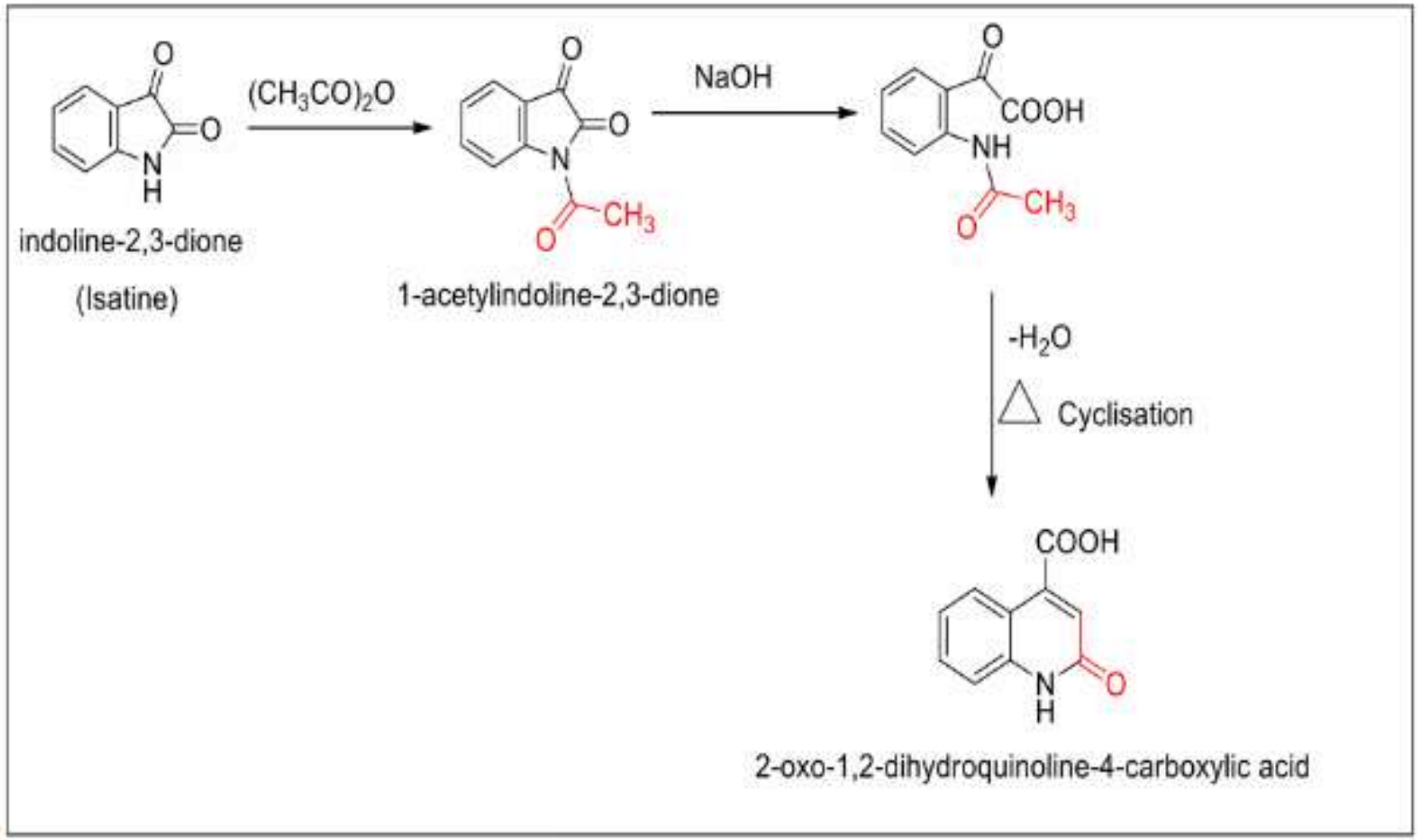

Dibucaine

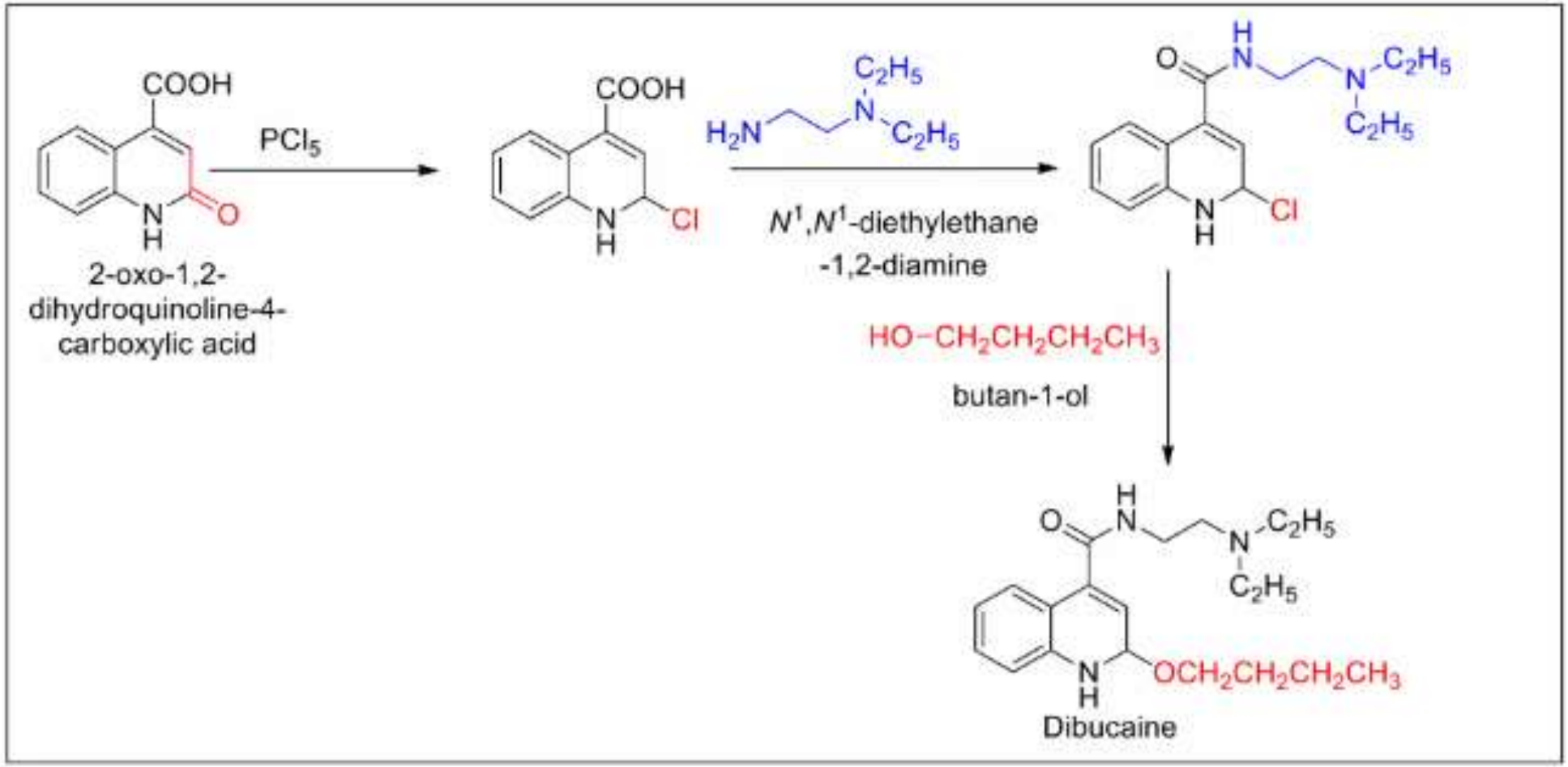


Dibucaine synthesis:



Dibucaine synthesis:




COOH
PCl5
2-oxo-1,2-dihydroquinoline-4-carboxylic acid
COOH
Cl
H2N
C2H5
N1,N1-diethylethane-1,2-diamine
HO–CH2CH2CH2CH3
butan-1-ol
OCH2CH2CH2CH3
Dibucaine

# THERAPEUTIC USES

LA are used when:

- surgery is minor and does not require general or regional anesthesia
- the procedure can be done quickly and the patient does not need to stay overnight
- the operation does not need the muscles to be relaxed or for the patient to be unconscious

LAs may be used for

- neuraxial analgesia and anesthesia,
- Spinal anesthesia
- Epidural anesthesia
- peripheral nerve blocks,
- Intravenous regional anesthesia
- subcutaneous and tissue infiltration, and
- topical anesthesia.
- Brachial plexus block
- Iontophoresis
- Dental surgery, the removal of a verruca, a mole, or a cataract, and biopsies

# Thank You!