Pharmaceutical Chemistry

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Synthesis of Essential Drugs

By *R.S. Vardanyan* and *V.J. Hruby*, Elsevier, 2006

2. Local Anesthetics

Local anesthetics are medications used for the purpose of **temporary** and **reversible elimination of painful feelings** in **specific areas of the body** by **blocking transmission of nerve fiber impulses**.

These drugs, unlike general anesthetics, cause a **loss of feeling in specific areas** while **keeping the patient conscious**.

In clinical situations, local anesthetics are widely used for **pain relief** in situations ranging from dental procedures to gynecological interventions, soreness, itching, and irritation associated with disturbance of the integrity of the skin and mucous membranes (cuts, bites, wounds, rashes, allergic conditions, fungal infections, skin sores, and cracking).

They are used during opthalmological procedures such as tonometry, gonioscopy, removal of foreign bodies, and during minor surgical interventions.

Local anesthetics **reversibly block nerve transmission**, cause **local loss of feeling** while **relieving local pain** and **preventing muscle activity** in the process.

Local anesthetics can be differentiated by their method of clinical use:

1. Topical anesthesia: Local use on the mucous membranes of the nose, mouth, larynx, tracheobrachial tree, eyes, urinary tract, and gastrointestinal tract causes superficial anesthesia.

Drugs: benzocaine, cyclomethycaine, hexylcaine, cocaine, lidocaine, and tetracaine

2. Infiltration anesthesia: Direct introduction of local anesthetic into the skin or deeper tissue for surgical intervention.

Drugs: lidocaine, mepivacaine, bupivacaine, ethidocaine, and procaine

3. Block or regional anesthesia: Introduction of local anesthetic into an individual nerve or group of nerves during minor surgical interventions with the purpose of blocking the feeling and motor action is frequently called block or regional anesthesia.

This method is often used during surgical intervention of the shoulder, arm, neck, or leg.

Drugs: Lidocaine, mepivacaine, and bupivacaine

4. Spinal anesthesia: Introduction of local anesthetics directly into the spinal fluid, which causes a sympathetic blockage, or loss of feeling as well as muscle relaxation resulting from the interaction of anesthetic with every spinal nerve tract.

This method is used during major surgical interventions.

Drugs: lidocaine, mepivacaine, and bupivacaine

5. Epidural anesthesia: Introduction of local anesthetic into the spinal cord membrane of the intervertebral space.

It is used during obstetrical and gynecological interventions that do not require a fast development of anesthesia.

Drugs: lidocaine, mepivacaine, bupivacaine, ethidocaine, and chloroprocaine

History:

The alkaloid cocaine was first used in 1884 as a local anesthetic in a clinical opthalmological intervention. Due to the danger of drug addiction and high toxicity, its use is severely limited.

The synthetic local anesthetic drug appeared in clinical practice in 1905.

In 1947, lidocaine was introduced and bupivacaine in 1963.

Mechanism:

As agents blocking conductivity in axons and dendrites, local anesthetics differ from the compounds that block neuron transmission in synapses.

Mechanism for local anesthetic action: they serve as sodium channel blockers

The molecular targets of local anesthetic action are the voltage-requiring sodium channels, which are present in all the neurons.

After introduction of local anesthetic (in the form of a water-soluble salt) into the organism, equilibrium is established between the neutral and cationic forms of the drug (depending on the pK_a of the drug and the pH of the interstitial fluid).

The neutral drug can pass through connective tissue surrounding the nerve fiber and through the phospholipid plasma membrane into the axoplasm. In the axoplasm, the base is once again ionized until it reaches an appropriate value determined by intracellular pH.

These drugs selectively bind with the intracellular surface of sodium channels and block the entrance of sodium ions into the cell. This leads to stop the depolarization process, which is necessary for the diffusion of action potentials, elevation of the threshold of electric nerve stimulation, and thus the elimination of pain.

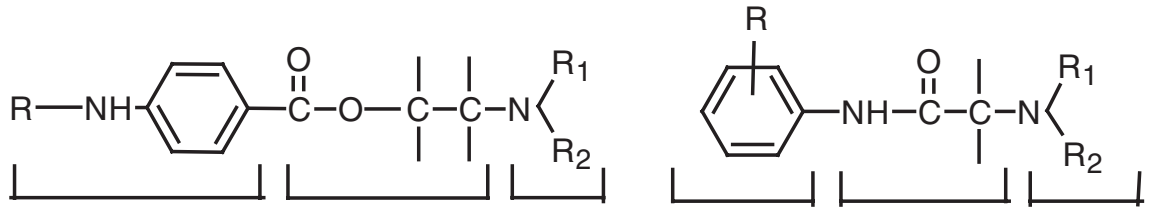
Since the binding process of anesthetics to ion channels is reversible, the drug diffuses into the vascular system where it is metabolized, and nerve cell function is completely restored.

The mechanism of benzocaine action differs slightly, since it presumably acts by diffusing across the phospholipid membrane and then stretching it out. This deforms the sodium channels and lowers sodium conduction.

An analogous mechanism of stretching (changing the fluidity) of the membrane was also suggested as an explanation for the action mechanism of general anesthetics.

Structure:

General anesthetics can be classified as **esters** of *n*-aminobenzoic acid and dialkylaminoalkanols, or as **anilides** of *N*,*N*-dialkyl substituted α-aminoacids.



They are made up of three parts:

aromatic ring (lipophilic region), intermediate hydrocarbon chain, and amine region (hydrophilic group).

A **substitution** in the aromatic ring and in the amine region changes both the **solubility** and the extent of binding of anesthetics to the receptors, which in turn determines the **strength** and **duration of the action** of the drugs.

The ability to cause **allergic reactions**, stability and toxicity is determined by the structure of the connecting chain, which also determines the site of biotransformation and inactivation of the drug: either by fermentative hydrolysis in the plasma (ester anesthetics), or decomposition in the liver (aminoamide anesthetics).

It is interesting that a number of antihistamine, anticholinergic, and adrenergenic drugs having analogous chemical structures, also exhibit local anesthetic properties.

Amino-ester series

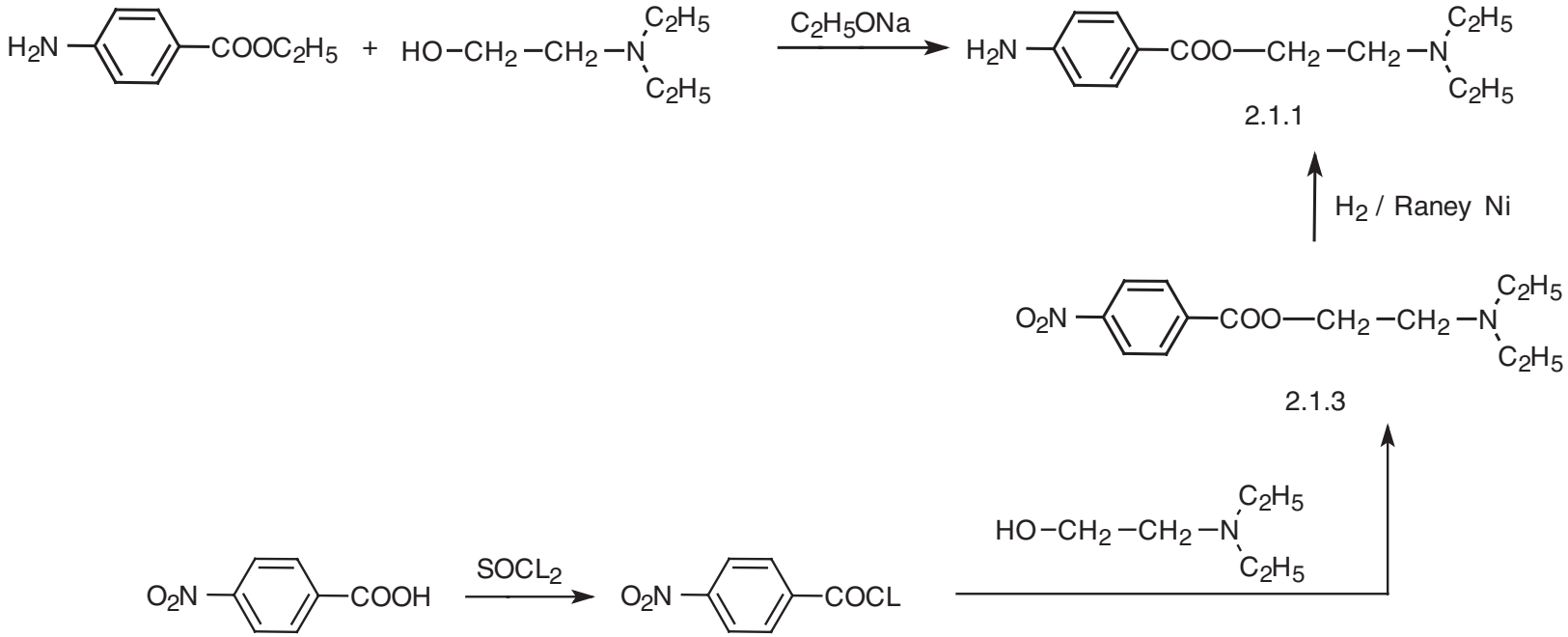
Procaine

a short-acting local anesthetic.

used in infiltration, block, epidural, and spinal cord anesthesia, and for potentiating activity of basic drugs during general anesthesia.

It may cause allergic reactions.

Synonym: of procaine are novocaine, adrocaine, impletol, and melkaine.

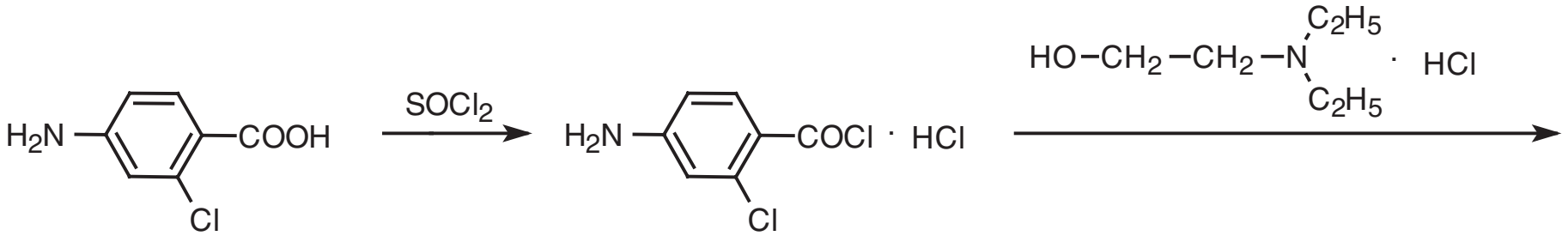


Chloroprocaine

used in situations requiring fast-acting pain relief.

It is also used in infiltration anesthesia, blocking peripheral nerve transmission, and in spinal and epidural anesthesia.

Synonym: Nesacaine is a for chloroprocaine.



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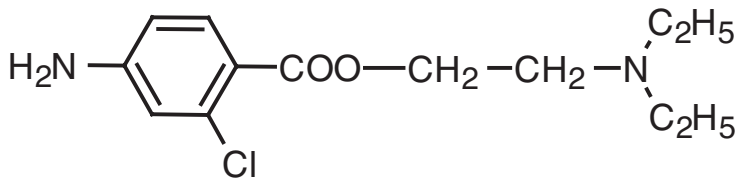
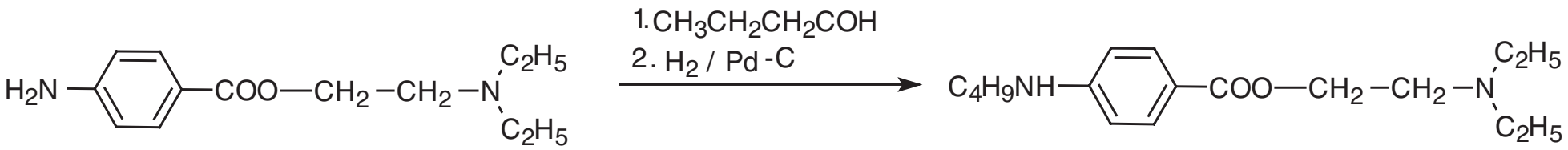


Tetracaine

Strong and long-lasting local anesthetic.

It is primarily used in spinal cord anesthesia.

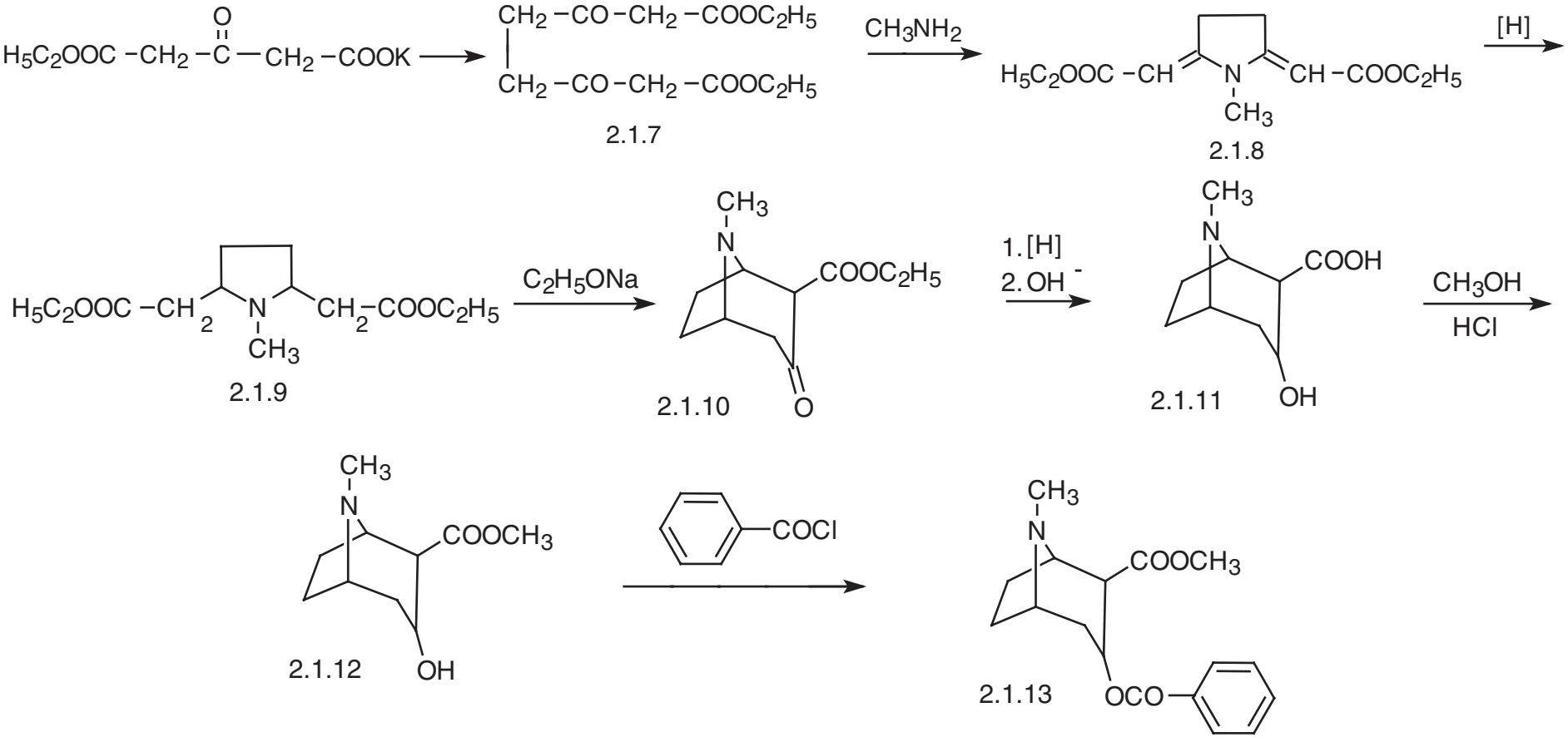
Synonyms: pontocaine and butylcaine

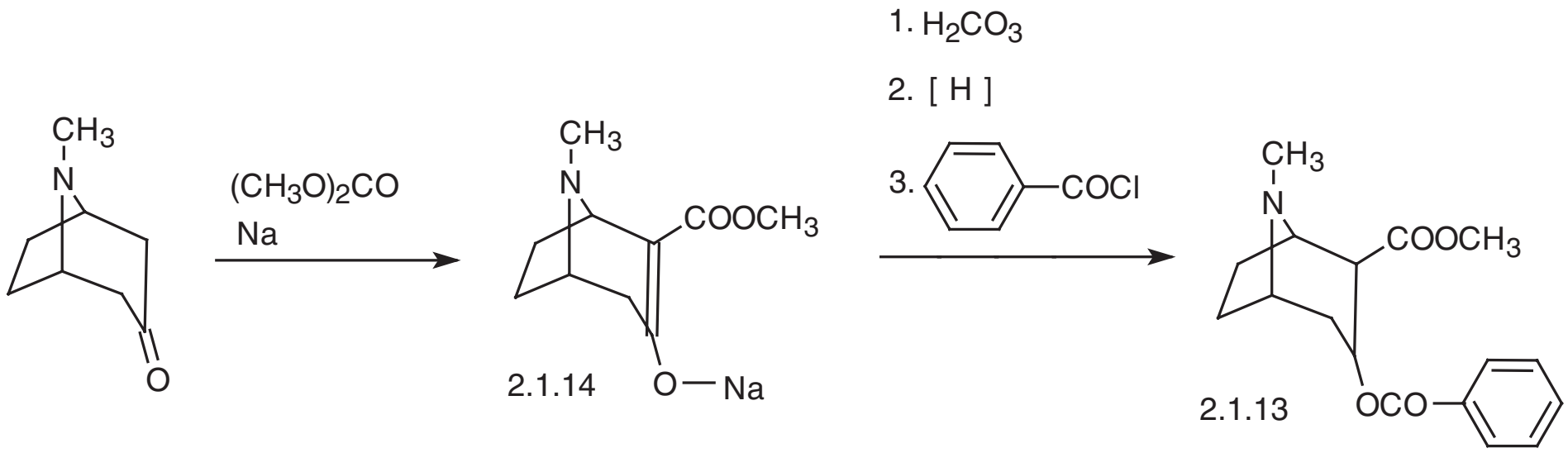


Cocaine

The alkaloid cocaine was isolated in 1860 from leaves of the cocaine shrub (Erthroxylon coca), which contains various alkaloids that are ecogonic derivatives (2.1.11), of which cocaine makes up a significant portion.

Its structure was established in 1898. The first synthesis of cocaine was proposed in 1902.





The final product is a racemate from which the levorotary isomer is isolated.

Cocaine is only used in exceptional cases as a topical anesthetic in ophthalmology due to the fast onset of addiction and its powerful effect on the CNS.

Amino-amide series

Lidocaine

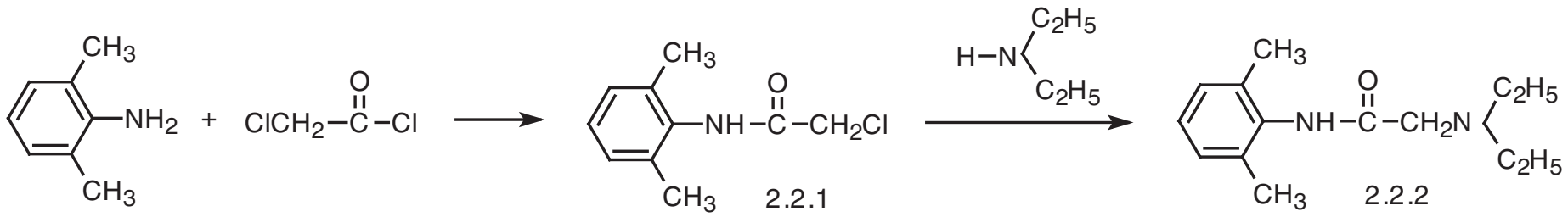
Its excellent therapeutic activity is fast-acting and lasts sufficiently long to make it suitable for practically any clinical use.

It stabilizes cell membranes, blocks sodium channels, facilitates the secretion of potassium ions out of the cell, and speeds up the repolarization process in the cell membrane.

It is used for terminal infiltration, block, epidural, and spinal anesthesia during operational interventions in dentistry, otolaryngology, obstetrics, and gynecology.

It is also used for premature ventricular extrasystole and tachycardia, especially in the acute phase of cardiac infarction.

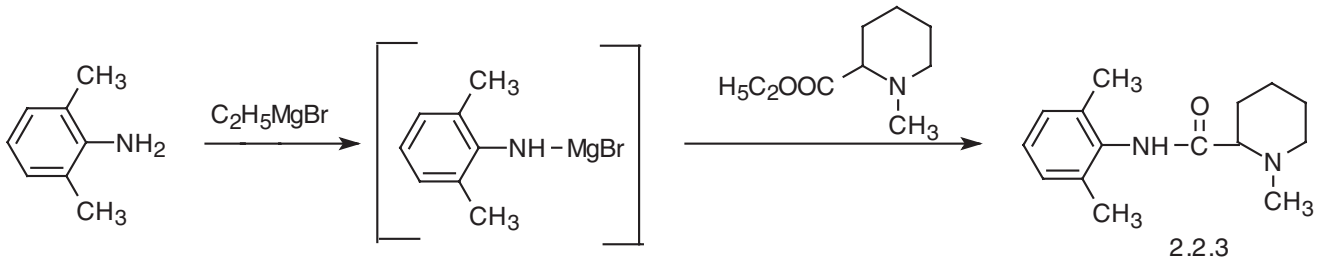
Synonym: xylocaine and neflurane



Mepivacaine

Similar to lidocaine in terms of properties; however, it has longer lasting effects.

Synonym: carbocaine and estradurin



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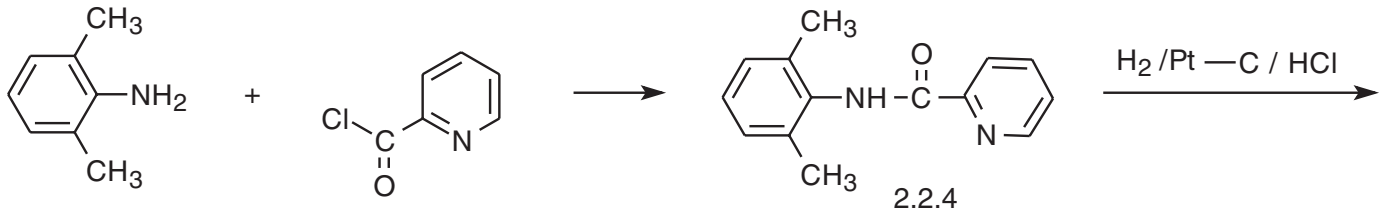

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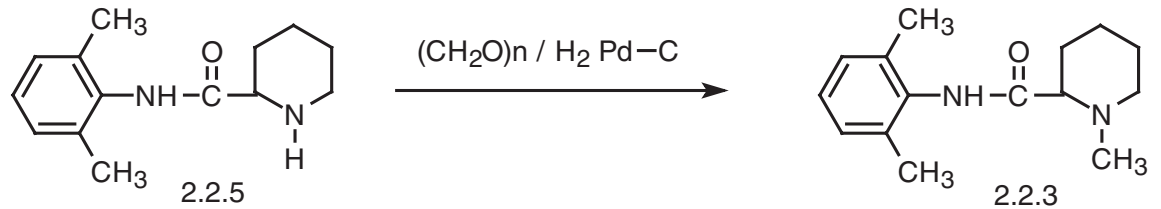

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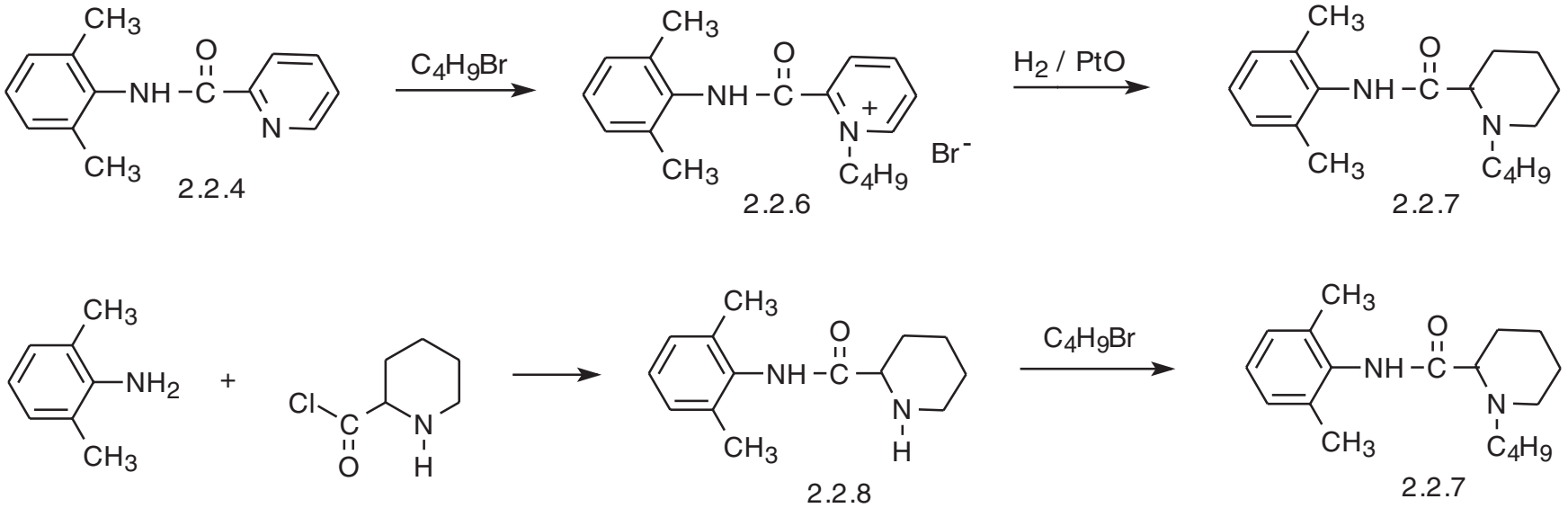
Bupivacaine

used in infiltration, spinal, and epidural anesthesia in blocking nerve transmission.

Its most distinctive property is its long-lasting action. It is used for surgical intervention in urology and in lower thoracic surgery from 3 to 5 h in length, and in abdominal surgery lasting from 45 to 60 min.

It is used to block the trifacial nerve, the sacral and brachial plexuses, in resetting dislocations, in epidural anesthesia, and during Cesarian sections.

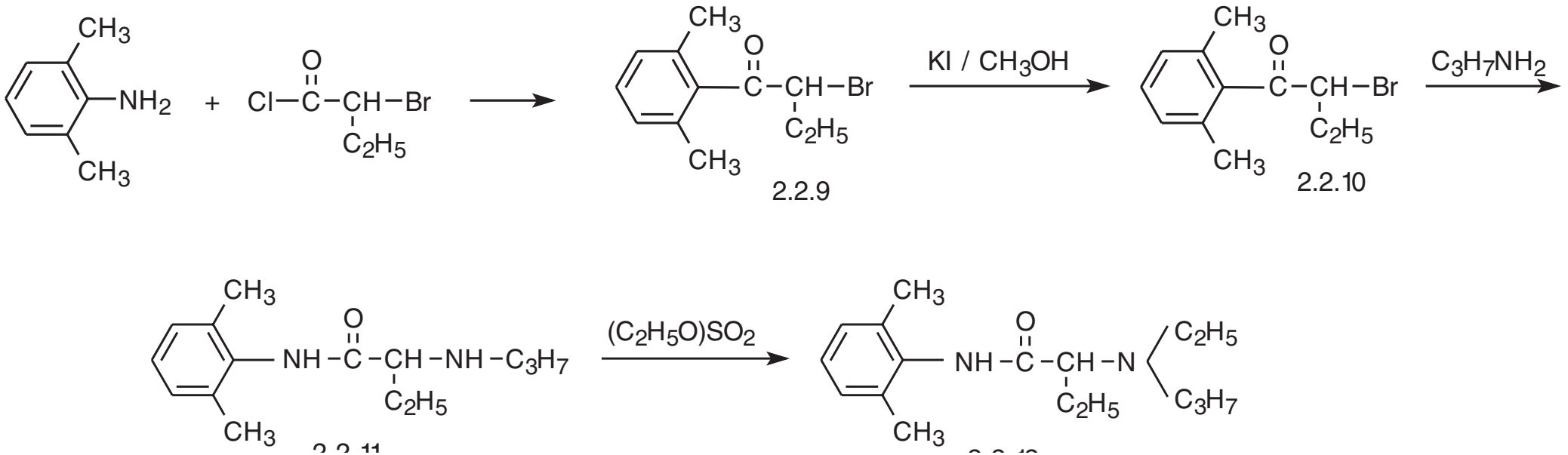
Synonym: marcaine



Ethidocaine

Similar to mepivacaine in terms of its pharmacological properties; however, it possesses muscle relaxant properties to some extent.

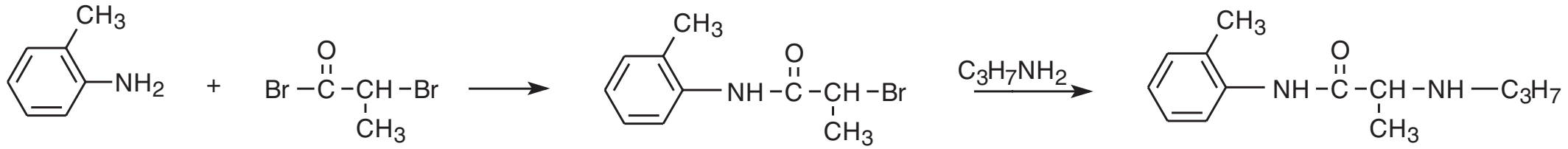
Synonym: duranest



Prilocaine

In terms of pharmacological parameters, prilocaine is comparable to lidocaine; however, because of a number of toxic manifestations, it is **rarely used in medical practice**.

Synonym: Citanest and xylonest



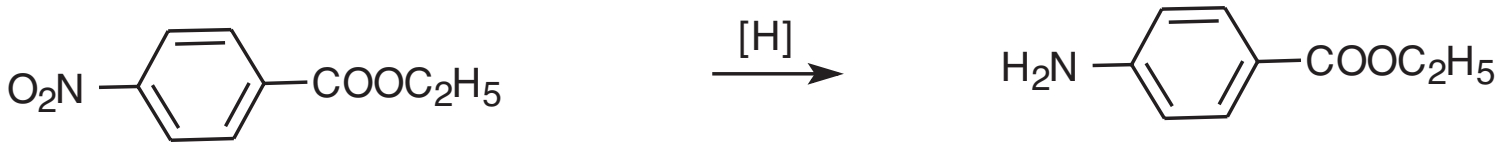
TOPICAL ANESTHETICS

Benzocaine

Used in topical anesthesia on the skin and mucous membranes in the form of **aerosols**, or as **creams** for reduction of pain caused by itching, cuts, bites, etc.

It begins to work 15–30 sec after application and lasts 12–15 min.

Synonym: anestezin and dermoplast



Cyclomethycaine

Used in topical anesthesia on the skin or mucous membranes for cuts, bites, and also for urological examinations.

Synonym: surfacaine.