Chapter 3

General Anaesthetics

INTRODUCTION

General anaesthetics are group of drugs that produces loss of consciousness, and therefore, loss of all sensations. The absolute loss of sensation is termed as anaesthesia. General anaesthetics bring about descending depression of the central nervous system (CNS), starting with the cerebral cortex, the basal ganglia, the cerebellum, and finally the spinal cord. These drugs are used in surgical operations to induce unconsciousness and, therefore, abolish the sensation of pain.

Horace Wills, a dentist, in 1844 successfully used N_2O as an anaesthetic for tooth extraction. Mortan, a dentist, demonstrated ether as an anaesthetic agent and it became popular. In 1847, chloroform was used by Simpson in Britain for obstetrical purposes. The first intravenous anaesthetic, thiopentone, was introduced in 1935. In 1901, Mayer and Overton pointed out a direct parallelism between lipid/water partition coefficient of general anaesthetics and their anaesthetic property known as minimal alveolar concentration (MAC).

MAC is the lowest concentration of an anaesthetic in pulmonary alveoli that is needed to produce immobility in response to a painful stimulus in 50% of the individuals. MAC of a number of general anaesthetics shows excellent correlation with their oil/gas partition coefficients. However, this only reflects the capacity of anaesthetics to enter into the CNS and attain sufficient concentration in the neuronal membrane.

The basic molecular targets show that the ligand-gated ion channels are the major target of anaesthetic action. Many inhalation anaesthetics, such as barbiturates, benzodiazepines, and propofal potentiate the action of inhibitory transmitter GABA to open chloride channels. The action of glycine transmitter, which also activates chloride channels in the spinal cord and medulla, is augmented by barbiturates, propofol, and many other inhalation anaesthetics. N_2O and ketamine do not act on GABA or glycine, but they selectively inhibit the excitatory *N*-methyl D-aspartate (NMDA) type of glutamate receptor.

Types of General Anaesthetics

General anaesthetics are usually given through inhalation or by intravenous injection.

Inhalation anaesthetics: Nitrous oxide, a gas at ambient temperature and pressure, continues to be an important compound of many anaesthesia regimens. Halothane, enflurane, isoflurone, desflurane, sevaflurane, and methoxyflurane are volatile liquids.

Intravenous anaesthetics: Several drugs are used intravenously, alone, or in combination with other drugs to achieve an anaesthetic state for minute surgery of the patients in the intensive care unit. These drugs include the following:

Barbiturates (thiopental, methohexitol)
Benzodiazepines (midazolam, diazepam)
Opiod analgesics (morphine, fentanyl, sulfentanyl, afentanil, remifentanil)
Propofol
Ketamine
Miscellaneous:
droperidol, etomidate, dexmedetomide.

Mode of action: General anaesthetics target the ligand gated ion channels and produce the anaesthetic action. The GABA receptor gated chloride channels are the most important sites and opens to perform the inhibitory action. N_2O and ketamine do not affect the GABA or glycine gated Cl^-channel, but they selectively inhibit the excitatory NMDA-type of glutamate receptor, which belongs to calcium-gated channels in the neurons and leads to neuronal hyper-polarization.

STAGES OF ANAESTHESIA

Stage I (analgesia): The patient is conscious and experience sensations of warmth, remoteness, drifting, falling, and giddiness. There is a marked reduction in the perception of painful stimuli. This stage is often used in minor surgery.

Stage II (delirium): This stage begins with the loss of consciousness. Depression of higher centres produces variety of effects including excitement, involuntary activity, and increased skeletal muscle tone, and the respiration is typically irregular.

Stage III (surgical anaesthesia): This is the stage of unconsciousness and paralysis of reflexes, respiration is regular and blood pressure is maintained. All surgical procedures are carried out in this stage.

Stage IV (medullary paralysis): Respiratory and circulatory failures take place as a result of the depression of the vital centres of the medulla, and brain stem occurs.

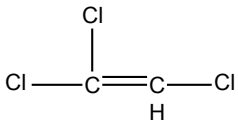
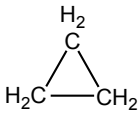
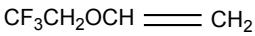
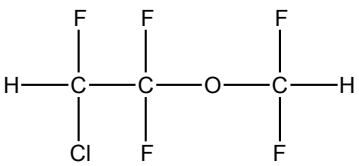
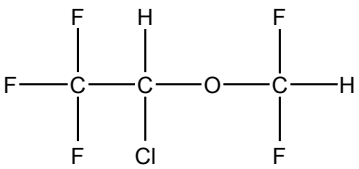
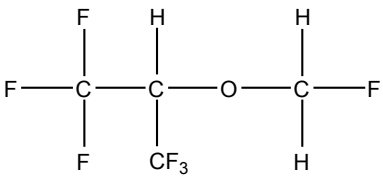
CLASSIFICATION

I. Volatile/Inhalation anaesthetics

S. No.	Name	Structure
1	Chloroform	$CHCl_3$
2	Diethyl ether	$C_2H_5OC_2H_5$

(*Continued*)

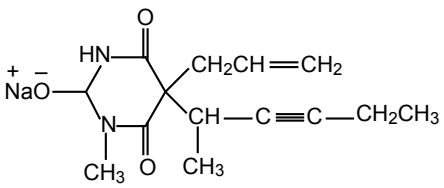
(*Continued*)

S. No.	Name	Structure
3	Divinyl ether	
4	Trichloro ethylene	
5	Ethyl chloride	CH_3CH_2Cl
6	Cyclo propane	
7	Halothane	$CF_3CHClBr$
8	Tribromo ethanol	Br_3CCH_2OH
9	Fluroxene	
10	Methoxy flurane	$CHCl_2CF_2OCH_3$
11	Enflurane	
12	Isoflurane	
13	Sevoflurane	

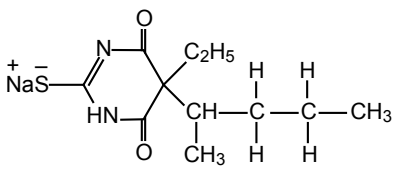
II. Nonvolatile or intravenous anaesthetics

a. Ultra short-acting barbiturates

Methohexital sodium

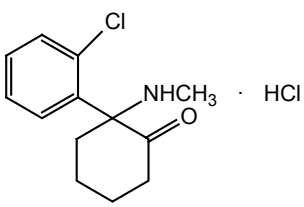


Thiopental sodium



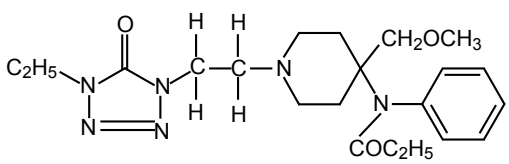
b. Aryl cyclohexylamines

Ketamine



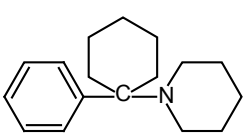
d. Narcotic analgesics

Alfentanyl

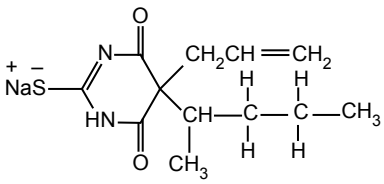


e. Miscellaneous

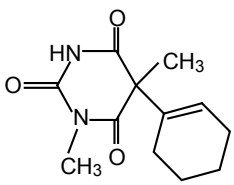
Phencyclidine



Thiomylal sodium

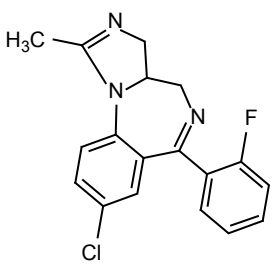


Hexobarbital

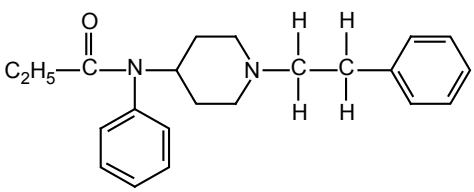


c. Benzodiazepines

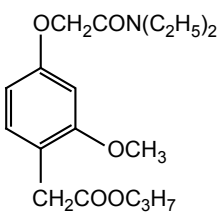
Midazolam



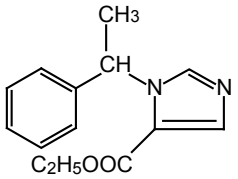
Fentanyl



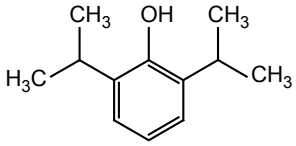
Propanidid



Etomidate



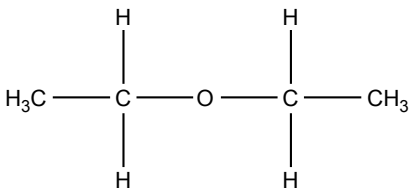
Propofol



SYNTHESIS AND DRUG PROFILE

I. Volatile/Inhalation anaesthetics

1. Ether (Diethyl ether)



1,1-Oxybisethane

Synthesis

(i) $C_2H_5OH + H_2SO_4 \xrightarrow{130 - 137°C} C_2H_5HSO_4 + H_2O$

$C_2H_5HSO_4 + C_2H_5OH \longrightarrow C_2H_5 — O — C_2H_5 + H_2SO_4$

Diethyl ether

(ii) Williamson's ether synthesis

$C_2H_5ONa + C_2H_5Br \longrightarrow C_2H_5OC_2H_5 + NaBr$

Sodium ethanolate — Bromoethane — Ethoxyethane

(iii) $H_2C = CH_2 + H_2SO_4 \longrightarrow C_2H_5HSO_4$

C_2H_5OH

$C_2H_5 — O — C_2H_5 + H_2SO_4$

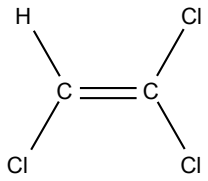
Diethyl ether

Properties and uses: It is a clear, colourless liquid, volatile, highly flammable, soluble in water, miscible with alcohol, methylene chloride, and with fatty oils. Low molecular weight ethers display anaesthetic activity that increases along with toxicity as the chain length increases. Introduction of unsaturation into the aliphatic ether increases potency and also shortens induction and emergence.

Ether is an absolute anaesthetic with pungent, irritant odour. It is flammable and explosive at concentrations necessary for anaesthesia.

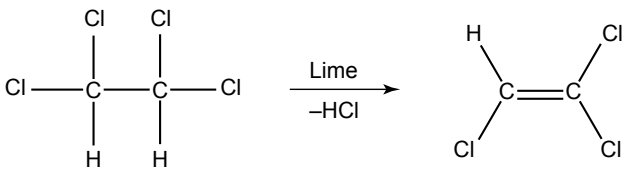
Storage: It should be stored in well-closed airtight containers and protected from light, stored at a temperature of 8°C–15°C.

2. Trichloro ethylene



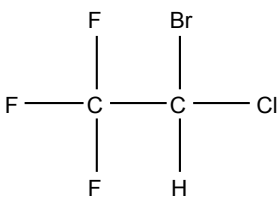
1,1,2-Trichloroethene

Synthesis



Tetrachloro ethane — Trichloro ethylene

Properties and uses: It may be used sporadically as a weak volatile anaesthetic, administered through inhalation. It possess an excellent analgesic property. It is frequently employed in short surgical operations, where a mild anaesthesia having potent analgesia is desired.

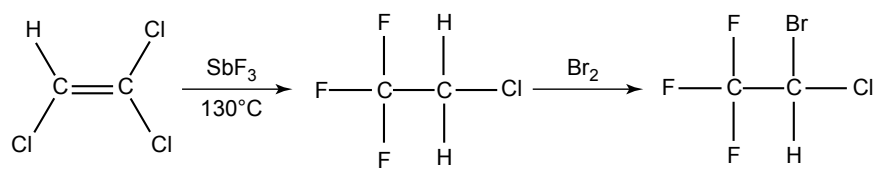


2-Bromo-2-chloro-1,1,1-trifluoro ethane

3. Halothane

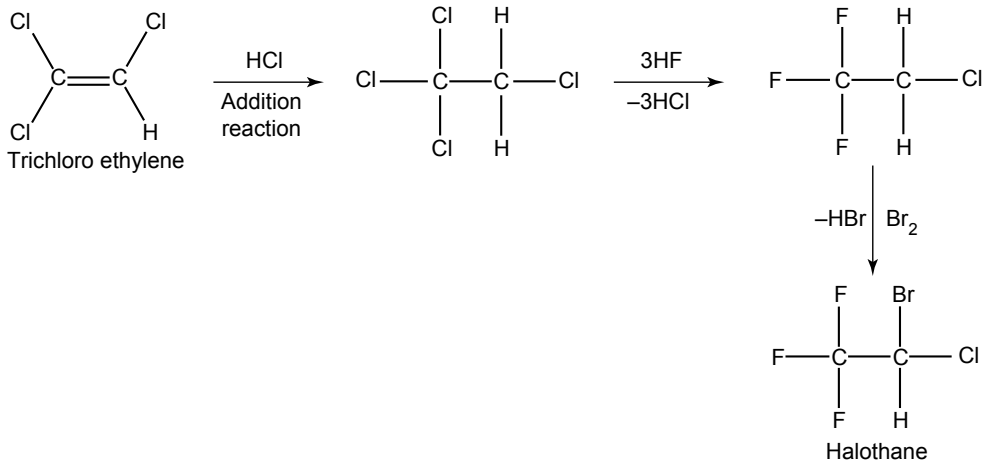
Synthesis

Route I. From: Trichloro ethylene

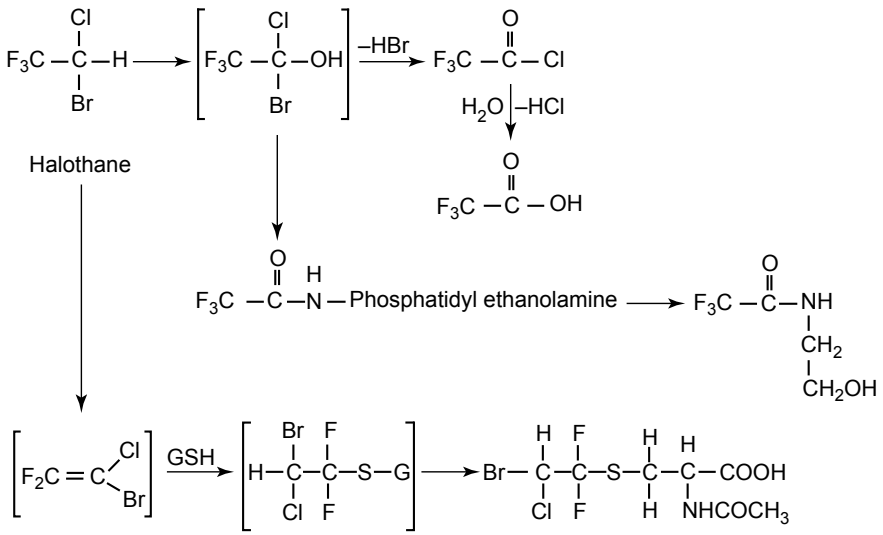


Trichloro ethylene — Halothane

Route II. From: Trichloro ethylene



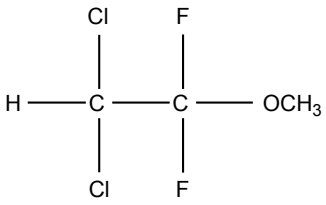
Metabolism: It is metabolized to three major metabolic products, trifluroacetic acid, *N*-trifluro acetyl ethanolamine, and *N*-acetyl-*s*-(2-bromo,2 chloro-1,1-difluro ethyl)-1-cysteine



Properties and uses: It is a clear, colourless, heavy, nonflammable liquid, slightly soluble in water, miscible with ethanol, and with trichloroethylene. Halothane lacks flammability. It may produce any depth of anaesthesia without causing hypoxia. Being a nonirritant, its inherent hypotensive effect retards capillary bleeding and renders a comparatively bloodless field. It is a potent, relatively safe general inhalation anaesthetic used in conjunction with N_2O. For skeletal muscle relaxation, it is used with succinyl choline or tubocurarine.

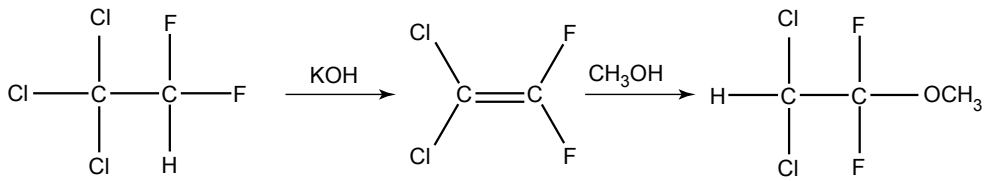
Storage: It should be stored in well-closed airtight containers, protected from light, at a temperature not exceeding 25°C in a nonreactive metal container.

4. Methoxy Flurane



(2,2-Dichloro-1,1-difluoro ethyl) (methyl) ether

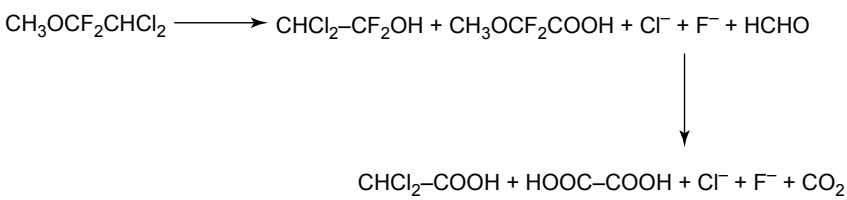
Synthesis



1,1-Difluoro-2,2,2-trichloro ethane

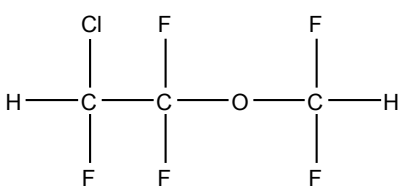
Methyl flurane

Metabolism: It is metabolized in the liver to produce fluoride ions, oxalic acid, difluoro methoxyacetic acid, and dichloroacetic acid. The high concentration of fluoride ions causes renal damage.



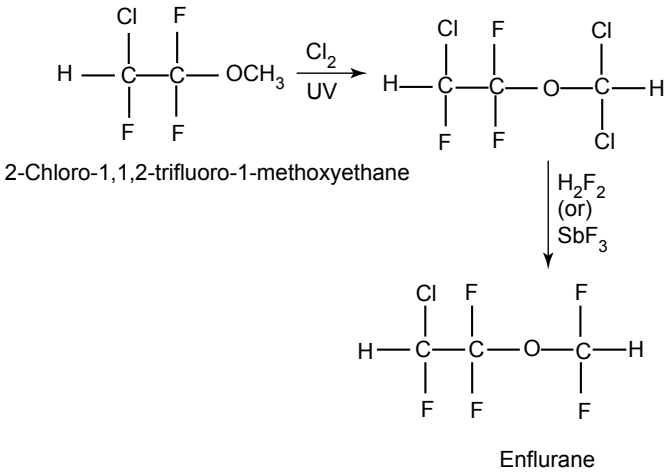
Properties and uses: It is a clear, colourless liquid, noninflammable and nonexplosive in air or oxygen in anaesthetic concentrations. It is the most potent of the inhalational agents. It is employed to cause light anaesthesia with deep analgesic and muscle relaxation feature, which makes it convenient for surgical operations.

5. Enflurane



(2-Chloro-1,1,2-trifluoro ethyl) (difluoro methyl) ether

Synthesis

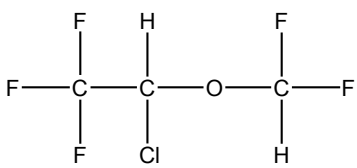


Metabolism: The principal metabolites are difluromethoxy difluroacetic acid and fluoride ion.

$$HCF_2O–CF_2–CHClF \longrightarrow \underset{\text{or}\ HOOC–CHClF}{HO–CF_2–CHClF} + CHF_2OCF_2COOH + F^- + Cl^-$$

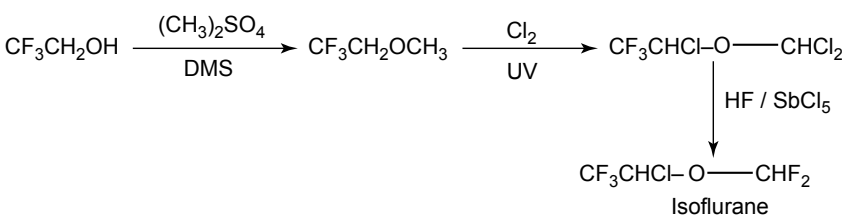
Properties and uses: It is a clear, colourless, volatile liquid with pleasant hydrocarbon-like odour. Soluble in water, miscible with organic solvents, chemically it is extremely stable. The induction of an emergence from anaesthesia and adjustment of anaesthetic depth during maintenance is smooth and moderately rapid. It is a noninflammable halogenated ether anaesthetic and provides rapid induction with no excitement.

6. Isoflurane

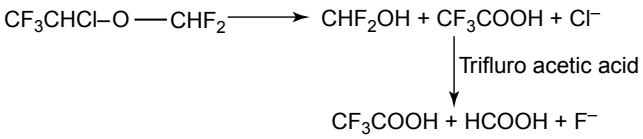


(1-Chloro-2,2,2-trifluoro ethyl)(difluoro methyl) ether

Synthesis



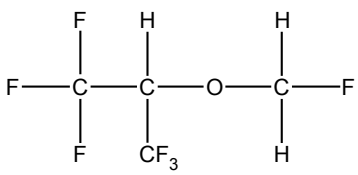
Metabolism: It is metabolized to trifluroacetic acid and fluoride ion.



Properties and uses: It is a clear, colourless, heavy liquid, insoluble in water, miscible with ethanol, and trichloroethylene. It resembles isomer enflurane in its properties. It is not flammable in air or oxygen. The depth of anaesthesia can be rapidly adjusted with it. Used for induction and maintenance of general anaesthesia.

Storage: It should be stored in well-closed airtight containers and protected from light.

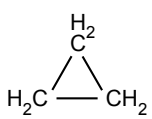
7. Sevoflurane



1,1,1,3,3,3-Hexafluoro-2- (fluoro methoxy) propane

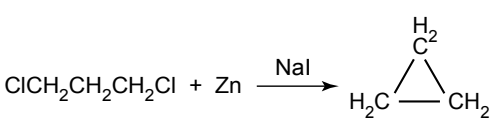
Properties and uses: Low boiling liquid with a slight odour; miscible with most organic solvents including fats or oils; practically insoluble in water. It is a nonflammable, nonirritating agent. The physical properties of this compound result in a more rapid induction and termination of anaesthetic when observed with the currently used agents.

8. Cyclopropane (Trimethylene)



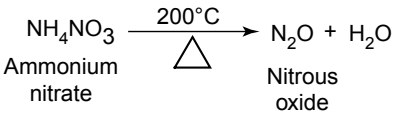
Cyclopropane

Synthesis



Properties and uses: It is nonirritant in nature and ensures rapid recovery from anaesthesia. The adverse effects are depressant effects on respiration, tendency to induce cardiac arrhythmias, and enhanced haemorrhage. Cyclopropane is an anaesthetic gas with a rapid onset of action. It may be used for analgesia, induction, or maintenance of anaesthesia.

9. Nitrous oxide (N_2O)



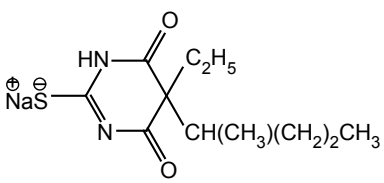
Properties and uses: It is a colourless gas, without appreciable odour to taste, soluble in water, freely soluble in alcohol, soluble in ether, or oils. This is the least toxic and least potent anaesthetic. It is a noninflammable, nonirritating, and a powerful analgesic agent. Nitrous oxide is a weak anaesthetic with good analgesic properties, and relatively no skeletal muscle relaxant properties. It is an inhalation anaesthetic of choice in dental surgery.

II. Nonvolatile or intravenous anaesthetics

a. Ultra short-acting barbiturates

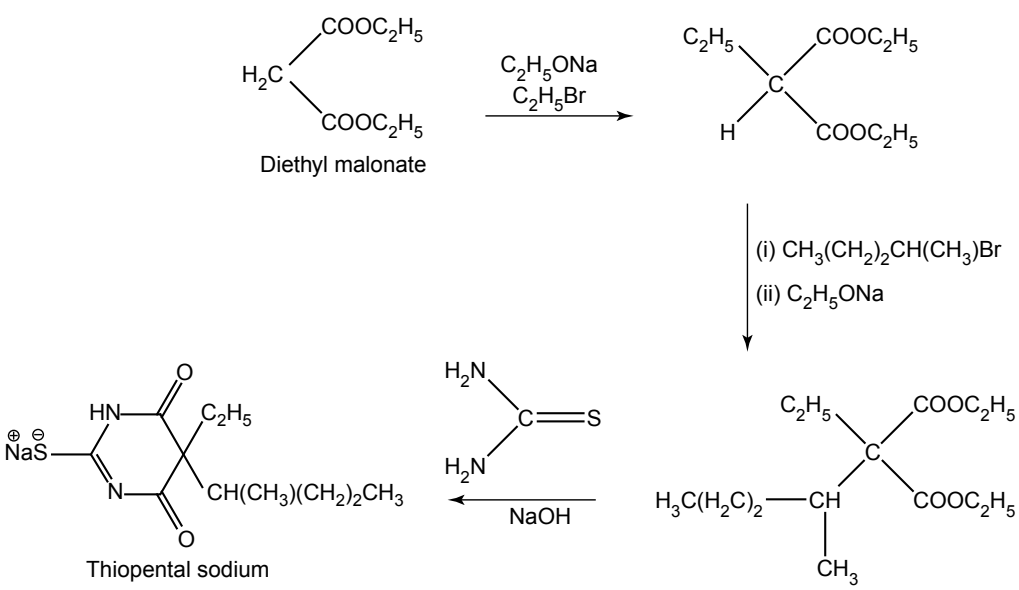
Metabolism of Barbiturates: This is discussed in Section III, Chapter 'Sedatives and Hypnotics'.

1. Thiopentone sodium (Thiopental)



Sodium salt of 5-ethyl-5(1-methyl butyl)-2-thio barbiturate

Synthesis



Properties and uses: A yellowish-white powder, hygroscopic, freely soluble in water, and partly soluble in ethanol. These are usually administered intravenously for the production of complete anaesthesia of a short duration. It belongs to the category of ultra short-acting barbiturates. Onset is rapid (about 30 sec) and duration is brief (10–30 min). By rectal route it is administered as a solution, suspension, or suppositories as basal anaesthetic. It is also used as a sedative, hypnotic, and anticonvulsant.

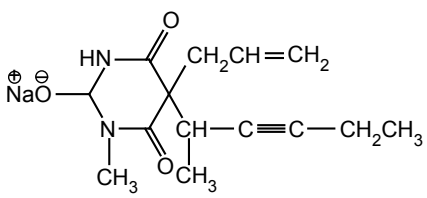
Assay for sodium: Dissolve the sample in water, add 0.1 ml of methyl red solution, and titrate with 0.1 M hydrochloric acid until a red colour is obtained. Boil the mixture gently for 2 min, cool it, and, if necessary, continue the titration with 0.1 M hydrochloric acid until the red colour is again obtained.

Assay for thiopental: Dissolve the sample in water, add 2 ml of dilute sulphuric acid, and shake with chloroform. Filter and evaporate the filtrate to dryness on a water-bath. Dissolve the residue in 30 ml of previously neutralized dimethylformamide and add thymol blue in methanol. Titrate immediately with 0.1 M lithium methoxide until a blue colour is obtained.

Storage: It should be stored in well-closed airtight containers and protected from light.

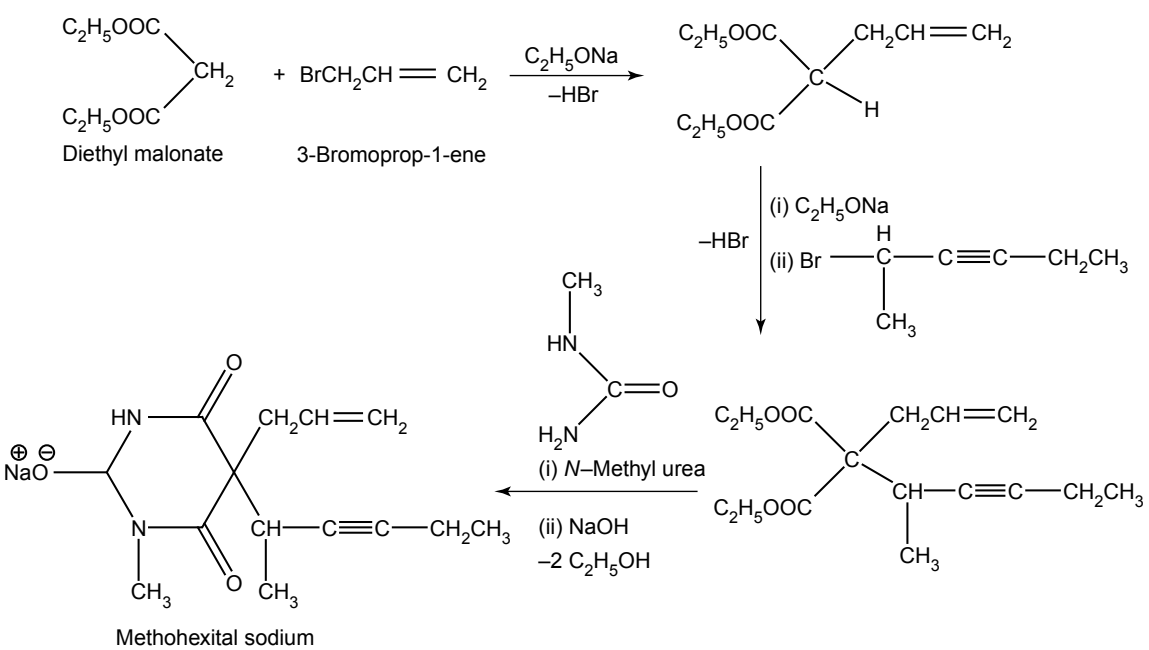
Dosage forms: Thiopental injection B.P.

2. Methohexital sodium



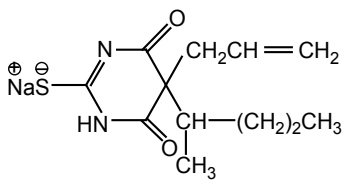
Sodium salt of 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbiturate

Synthesis



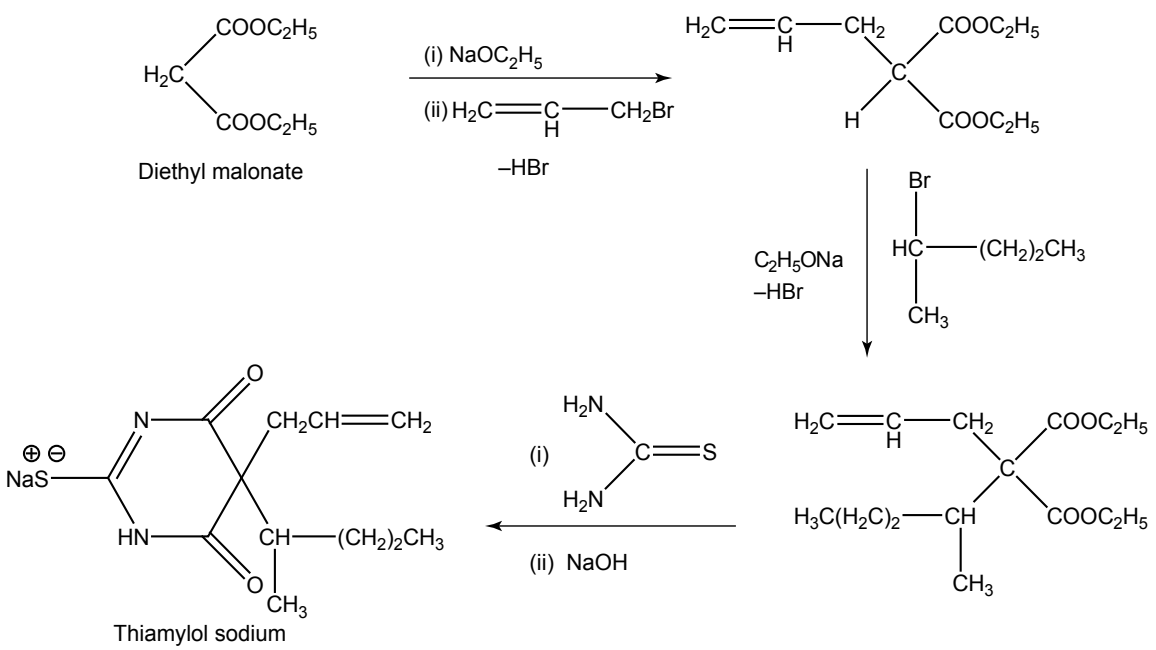
Properties and uses: White to off-white hygroscopic powder, essentially odourless, and the solution is alkaline to litmus, soluble in water. Methohexital produces more rapid recovery from unconsciousness than thiopental. It is more potent and has shorter duration of action. It is used for the induction of anaesthesia through the intravenous administration. It has two advantages over thiopental sodium. First, being it has less affinity towards fatty tissues and second, it has a greater potency. Its onset of action is quite speedy comparable to thiopental sodium while its recovery is more rapid. For these reasons, this intravenous anaesthetic is specifically useful for short surgical operations, such as oral surgery, gynaecological investigation, genitourinary procedures, and electroconvulsive therapy.

3. Thiomylal Sodium



Sodium salt of 5-allyl-5(1-methyl butyl)-2-thio barbiturate

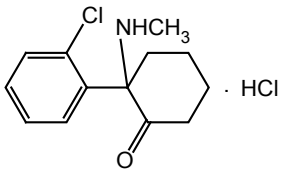
Synthesis



Properties and uses: Thiomylal is a highly hydrophobic thiobarbiturate having its structural features very much related to thiopental. Its biological activities are almost identical to thiopental. Used as intravenous anaesthetic.

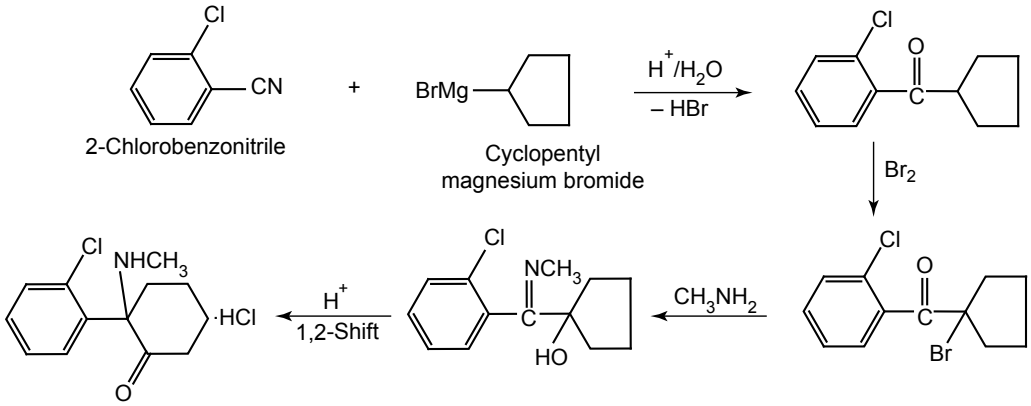
b. Arylcyclohexylamines

1. Ketamine HCl



2-(2-Chloro phenyl)-2-(methylamino) cyclohexanone

Synthesis



Properties and uses: It is a white or almost white crystalline powder, freely soluble in water, methanol, and ethanol. Its another name is 'dissociative anaesthetic' because it produces unpleasant hallucinations and strong feelings of dissociation from the environment. It is a rapidly acting nonbarbiturate general anaesthetic that produces anaesthesia and is characterized by profound analgesia.

Assay: Dissolve the substance in methanol and add 1.0 ml of 0.1 M hydrochloric acid, and perform potentiometric titration, using 0.1 M sodium hydroxide.

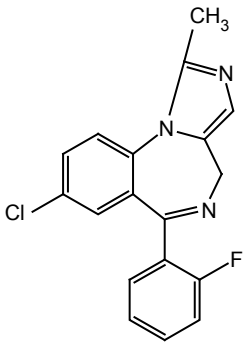
Storage: It should be stored in well-closed airtight containers, protected from light.

Dosage forms: Ketamine HCl injection I.P., B.P.

c. Benzodiazepines

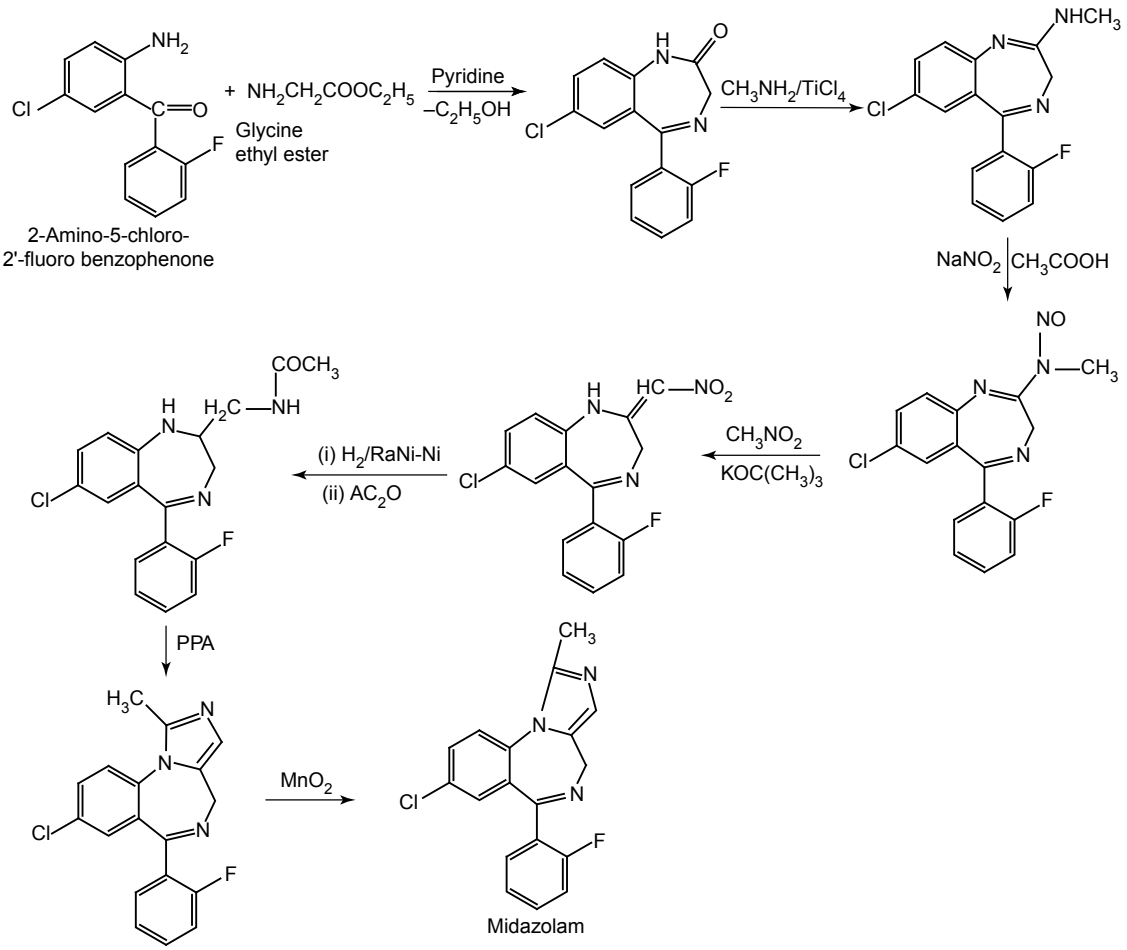
Metabolism: This is discussed in Sec III, Chapter 'Sedatives and Hypnotics'.

1. **Midazolam**



8-Chloro-6(2-fluoro phenyl)-2-methyl-imidazo benzodiazepine

Synthesis



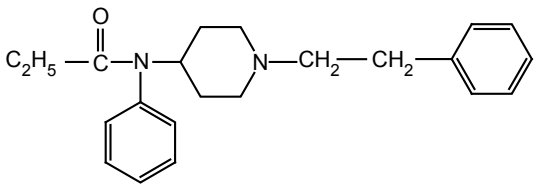
Properties and uses: It is a white or yellowish, crystalline powder, soluble in acetone, ethanol, and methanol, but insoluble in water. Midazolam has been used adjunctively with gaseous anaesthetics. The onset of CNS effect is slower than that of thiopental and it has a longer duration of action.

Assay: Dissolve the sample in anhydrous acetic acid and add aceticanhydride, titrate with 0.1 M perchloric acid and determine the end point potentiometrically.

Dosage forms: Midazolam injection B.P.

d. Narcotic analgesics

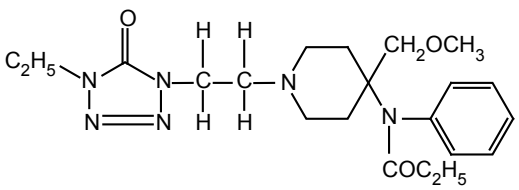
1. Fentanyl



N-(1-phenyl ethyl-4-piperidinyl) propionanilide

Synthesis and drug profile is discussed in Sec IV, Chapter 'Narcotic Analgesics'.

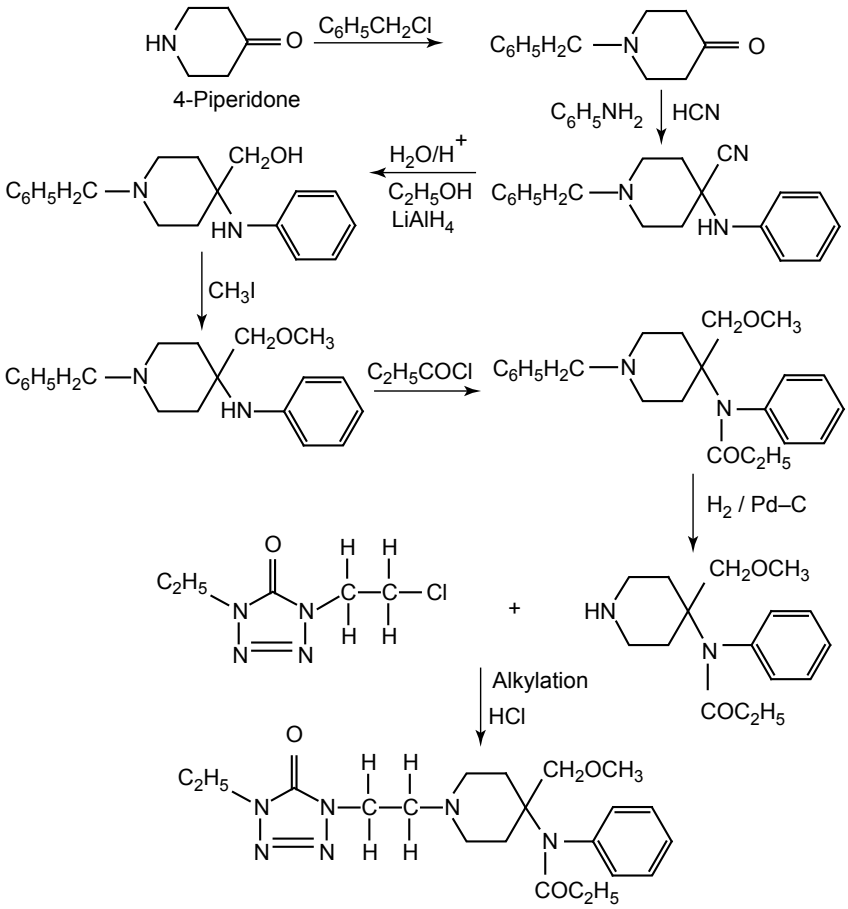
2. Alfentanyl



N-[1-[2-(4,5-dihydro-5-oxo-tetrazol-1-yl)ethyl]-4-(methoxy methyl) -4-piperidinyl]-*N*-phenyl propionamide

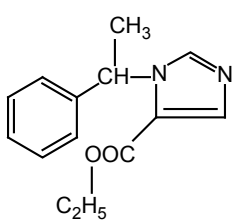
Properties and uses: It is closely related to fentanyl. It is a potent analgesic used as a primary anaesthetic or as an adjunct in the maintenance of anaesthesia. It has the same properties and side effects as fentanyl. It relieves moderate to severe break through pain.

Synthesis



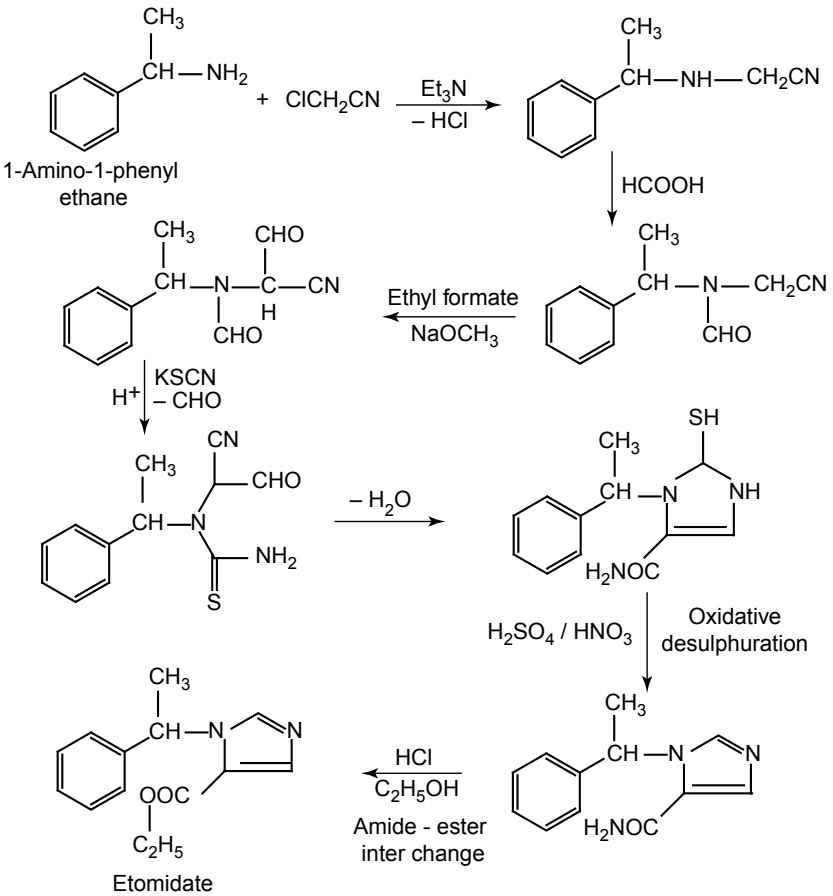
e. Miscellaneous

1. Etomidate



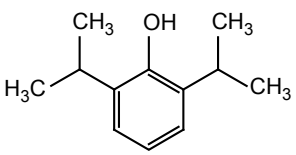
Ethyl-1-(1-methyl benzyl) imidazol-5-carboxylate

Synthesis



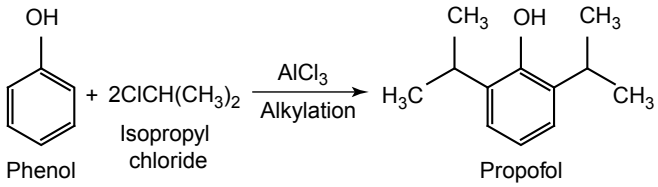
Properties and uses: It contains a 4-carboxylic acid ester-substituted imidazole moiety, which is also present in a number of compounds that are structural variants of the triazolo and imidazolo benzodiazepines. It is a positive allosteric modulator of GABA receptors.

2. Propofol



2,6-Diisopropyl phenol

Synthesis



Properties and uses: It is colourless or is a very light yellow in colour, clear liquid, very slightly soluble in water, miscible with hexane and with methanol. Propofol is useful for induction and maintenance of anaesthesia.

Assay: It is assayed by adopting liquid chromatography technique

Storage: It should be stored in well-closed airtight containers and protected from light under an inert gas.

Dosage forms: Propofol injection B.P.

PROBABLE QUESTIONS

1. Define and classify general anaesthetics. Outline the synthesis of any two drugs synthesis that belongs to intravenous anaesthetics.
2. Write the different stages of anaesthesia and explain the mode of action of general anaesthetics.
3. How will you classify general anaesthetics? Write the structure, chemical name, and uses of two drugs from each class.
4. Write the synthesis of general anaesthetic having pyrimidine nucleus.
5. Name the three derivatives of barbiturates that are used abundantly as intravenous anaesthetics. Write their structure, chemical name, and uses.
6. Mention a benzodiazepine derivative used as a general anaesthetic. Write its chemical name and synthesis.
7. Write a note on fluorinated compounds employed as inhalation anaesthetics.
8. Outline the synthesis and assay of the following general anaesthetics
   (a) Fluroxene and (b) Halothane
9. What are intravenous anaesthetics? Outline the synthesis of the following:
   (a)Thiopental sodium, (b) Ketamine hydrochloride, and (c) Methohexital sodium

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Chapter 4

Local Anaesthetics

INTRODUCTION

Local anaesthetics are drugs that when applied directly to the peripheral nervous tissue blocks nerve conduction and abolish all the sensations in that part supplied by the nerve. They are generally applied to the somatic nerves and capable of cutting on axons, cell body, dendrites, and synapses.

These are used in dentistry, in ophthalmology, in minor surgical operations, including endoscopy, and for relieving pain in certain medical conditions such as tumours growing in the spine. Local anaesthetics are also used topically for the temporary relief of pain from insect bites, burns, and other surface wounds.

Most local anaesthetic agents are weak bases, consisting of lipophilic groups connected by an intermediate chain to the tertiary amino groups. For therapeutic application, they are usually made available as salts to increase the solubility and the stability in the body. They exist either as the unchanged base or as a cation.

The clinically used local anaesthetics have minimal local irritant action and block sensory nerve endings, nerve trunks, neuromuscular junction, ganglionic synapse, and receptors that function through increased net (nerve) permeability. They also reduce the release of acetylcholine from motor nerve endings. Sensory and motor fibres are inherently and equally sensitive. The sensitivity is determined by the diameter of the fibres as well as by the fibre type. Diameters remaining the same, myelinated neurons are blocked earlier than nonmyelinated neurons. Autonomic fibres are generally more susceptible than somatic fibres. Among the somatic afferent order of blockade is pain, temperature, sense, touch and deep pressure sense, since pain is generally carried out by smaller diameter fibres than those carrying other sensations or motor impulses.

In clinical practice, a solution of local anaesthetic (except cocaine) often contains a vasoconstrictor (epinephrine, norepinephrine or phenylepinephrine). The vasoconstrictor serves dual purpose by decreasing the rate of absorption. It not only localizes the anaesthetic at the desired site, but also limits the rate at which it is absorbed into the circulation. The vasoconstrictor prolongs the action and lowers the systemic toxicity of local anaesthetics.

Mode of action: Local anaesthetics block both the generation and the conduction of the nerve impulse. The blockade probably results from the biochemical changes caused by the drug. Immediately after the nerve impulse had passed, the pores again become smaller. Sodium ions are pumped out of the fibre, at the same time potassium ions are transported into the fibre. Local anaesthetic decreases the permeability of cell membrane to sodium, thus preventing sodium depolarization.

Metabolism of local anaesthetics: Clinically available local anaesthetics are broadly divided into esters (e.g. procaine) and nonesters (e.g. lignocaine). The esters are hydrolyzed by esterases enzyme into *p*-amino benzoic acid and corresponding alcohols. The nonester types are primarily metabolized in the liver by CYP450, for example, lidocaine is converted primarily into 3-hydroxyl lidocaine to form 3-hydroxymono ethyl glycine-xylidine. Both may be excreted in their conjugated form. Lidocaine also metabolized into 4-hydroxy-2,6-dimethylanilide and 2-amino-3 methyl benzoic acid from the precursor metabolite 2,6-xylidine. The 2,6-xylidine is also directly excreted in its conjugated form, and it is formed from mono ethyl glycine xylidine, which is an immediate metabolite of lidocaine.

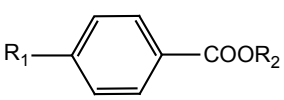
CLASSIFICATION

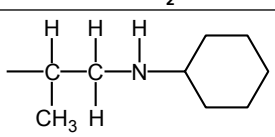
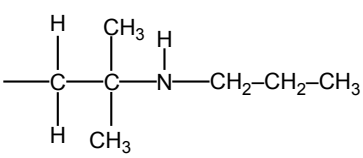
Local anaesthetics are generally classified into the following groups :

1. Natural agents
   a. Cocaine
2. Synthetic nitrogenous compounds
   a. Derivatives of benzoic acid
   b. Derivatives of para-amino benzoic acid
      i. Freely soluble: Procaine, Amethocaine.
      ii. Poorly soluble: Benzocaine, Orthocaine
   c. Derivatives of acetanilide: Lignocaine, Mepivacaine, Bupivacaine, Prilocaine, Etidocaine.
   d. Derivatives of quinoline: Cinchocaine, dimethisoquin
3. Synthetic non-nitrogenous agents: Benzyl alcohol, propanediol
4. Miscellaneous drugs with local action: Clove oil, phenol, chlorpromazine and certain antihistamines, for example, diphenhydramine

On the basis of chemical structure, local anaesthetics are classified as follows:

I. Benzoic acid derivatives



Name	R_1	R_2
Hexylcaine	–H	
Meprylcaine	–H	

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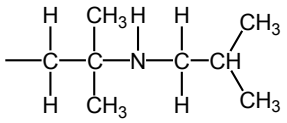
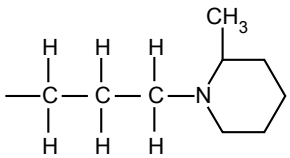
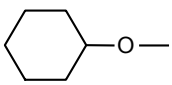
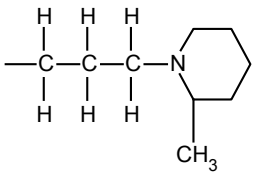
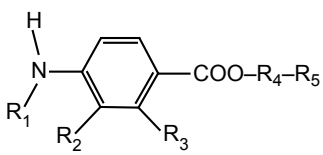
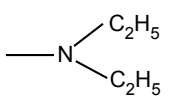
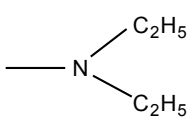
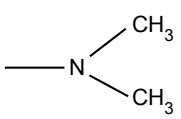
Name	R_1	R_2
Isobucaine	H	
Piperocaine	–H	
Cyclomethycaine		

II. *p*-Amino benzoic acid derivatives



Name	R_1	R_2	R_3	R_4	R_5
Benzocaine	–H	–H	–H	$-CH_2-CH_3$	–
Butamben	–H	–H	–H	$-(CH_2)_3\ CH_3$	–
Procaine	–H	–H	–H	$-CH_2-CH_2-$	
Chlorprocaine	–H	–H	–Cl	$-CH_2-CH_2-$	
Tetracaine	$-^{n}$Butyl	-H	–H	$-CH_2-CH_2-$	

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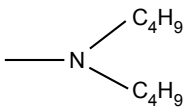
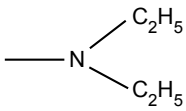
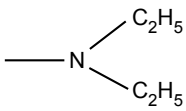
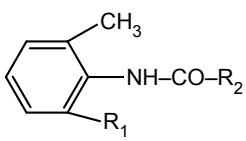
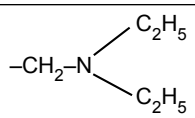
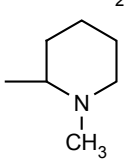
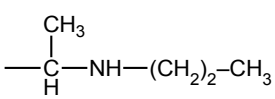
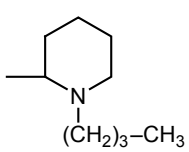
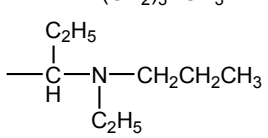
Name	R_1	R_2	R_3	R_4	R_5
Butacaine	–H	–H	–H	$-CH_2-CH_2-CH_2$	
Binoxinate	–H	^{n}Butoxy	–H	$-CH_2-CH_2-$	
Propoxycaine	–H	–H	^{n}Propoxy	$-CH_2-CH_2-$	

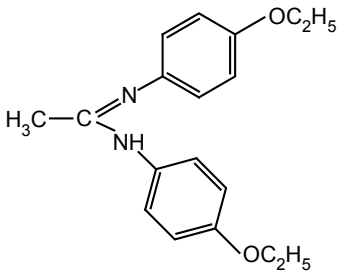
III. Anilide derivatives (2,6 Xylidines)



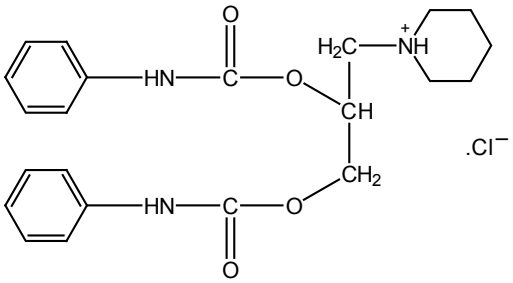
Name	R_1	R_2
Lidocaine/Lignocane	$-CH_3$	
Mepivacaine	$-CH_3$	
Prilocaine	–H	
Bupivacaine	$-CH_3$	
Etidocaine	$-CH_3$	

IV. Miscellaneous

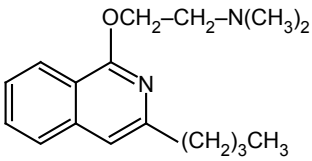
a. Phenacaine



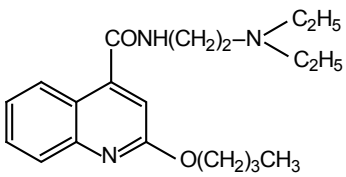
b. Diperodon HCl



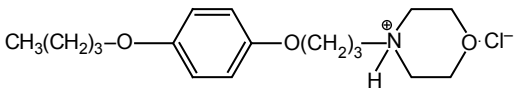
c. Dimethizoquine



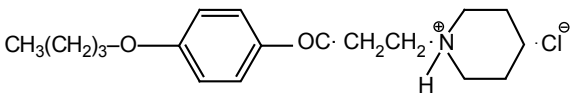
d. Dibucaine



e. Pramoxine HCl



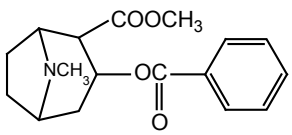
f. Dyclonine HCl



SYNTHESIS AND DRUG PROFILE

I. Benzoic acid derivatives

a. Cocaine

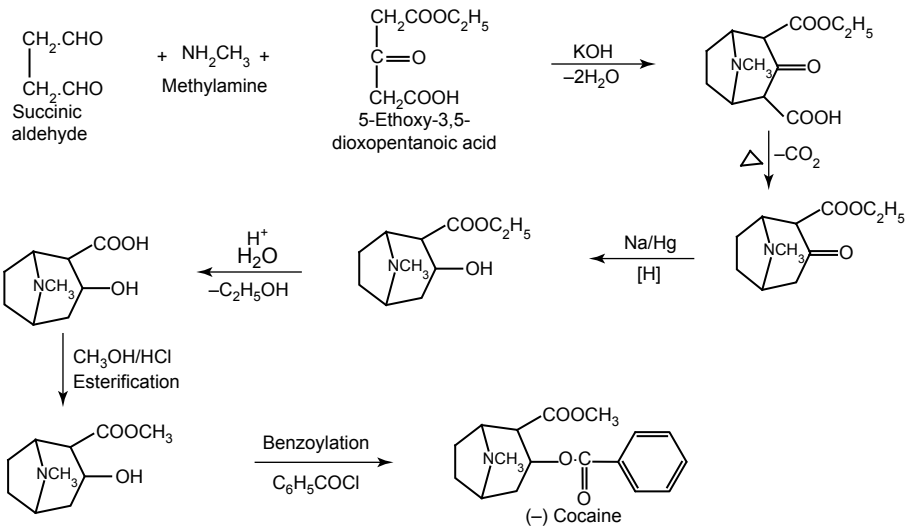


Properties and uses: Cocaine is the first local anaesthetic discovered; it is an alkaloid obtained from the leaves of *Erythroxylon cocca*. It is a white crystalline powder (or colourless crystals), very soluble in water, freely soluble in alcohol, and slightly soluble in methylene chloride. Though it is considered too toxic for any anaesthetic procedure requiring injection, it is still employed topically as a 1% or 2% solution for the anaesthesia of the ear, nose, throat, rectum, and vagina because of its intense vasoconstrictive action.

Assay: Dissolve the substance in a mixture of 0.01 M hydrochloric acid and alcohol. Perform potentiometric titration using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight containers and protected from light.

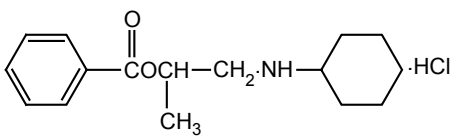
Synthesis



Dose: Employed topically in a 1% or 2% solution for anaesthesia of the ear, nose, throat, rectum, and vagina.

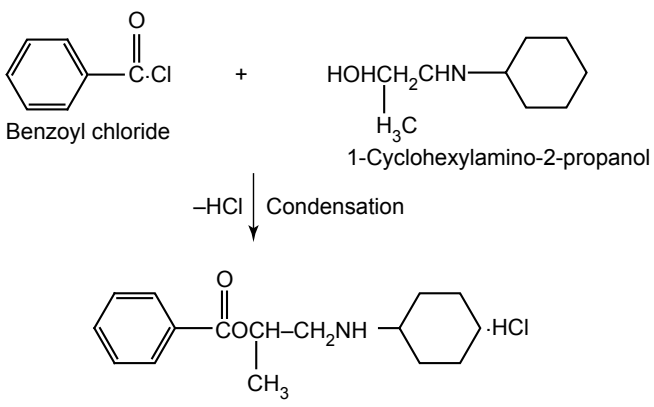
Dosage forms: Cocaine eye drops B.P.

b. Hexylcaine hydrochloride (Synonym: Cyanine)



1-(Cyclohexylamino)-2-propanol benzoate hydrochloride

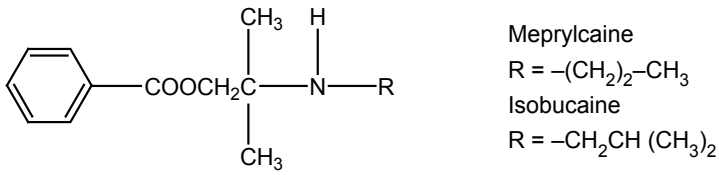
Synthesis



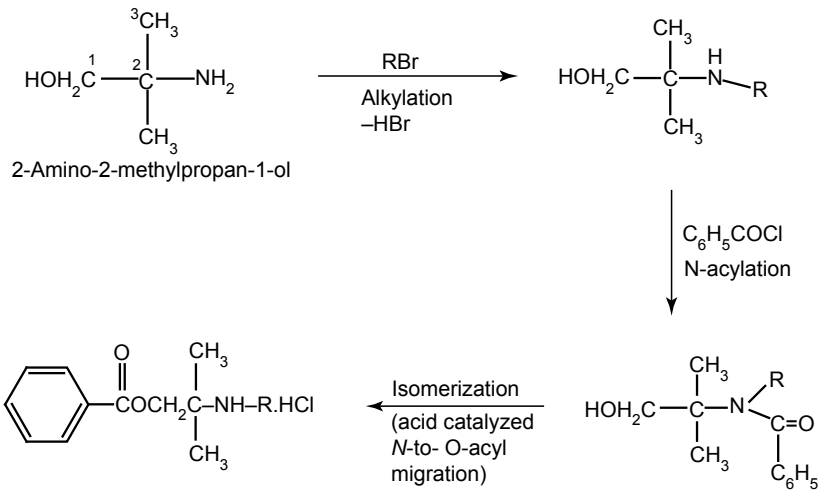
Properties and uses: It is a white powder, soluble in water, and chloroform. It is regarded as an all-purpose soluble local anaesthetic agent. The onset and duration of action is almost similar to that of lignocaine. It is mainly used as surface anaesthetic .

Dose: For infiltration anaesthesia, 1%; for nerve block anaesthesia, 1% and 2% solution; and for topical application to skin and mucous membrane, 1% to 5%.

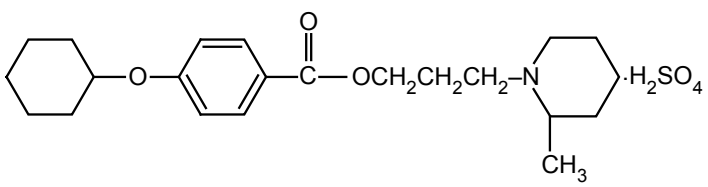
c. Meprylcaine and Isobucaine HCl



Synthesis



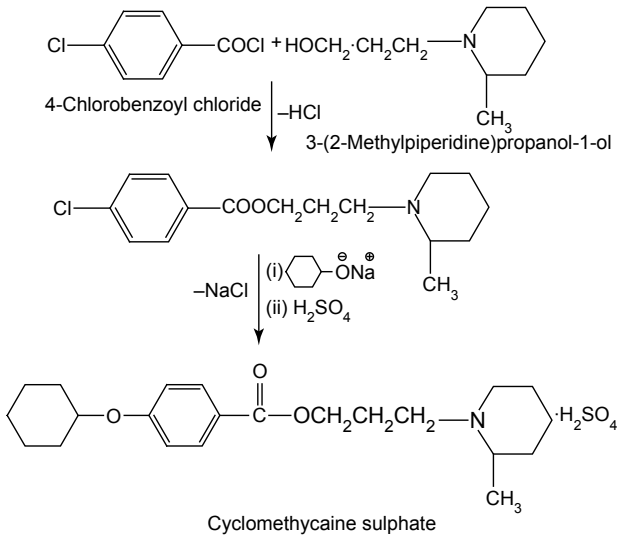
d. Cyclomethycaine sulphate



3-(2-Methyl piperidino)propyl-*p*-(cycloheyloxy)benzoate sulphate

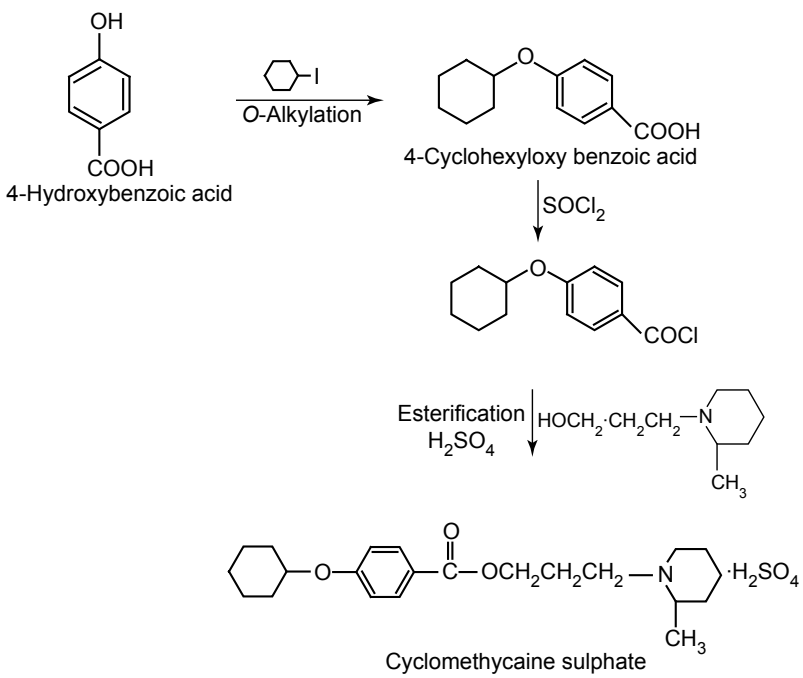
Synthesis

Route I. From: *p*-Chlorobenzoyl chloride



Cyclomethycaine sulphate

Route II. From: *p*-Hydroxy benzoic acid

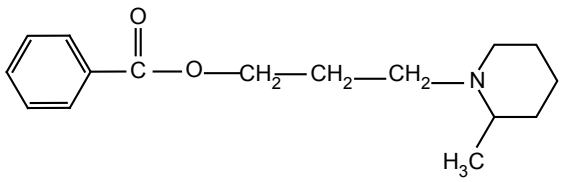


Cyclomethycaine sulphate

Properties and uses: It is a white crystalline powder, soluble in water, and chloroform. Used to releive pain from damaged skin, mucous membrane of rectum, vagina, and urinary bladder.

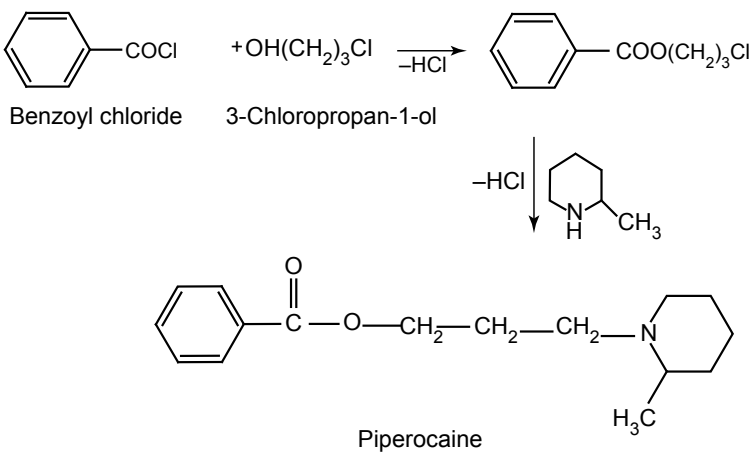
Dose: The usual dose for topical purpose is 0.25% to 1% in suitable form.

e. Piperocaine (Synonym: Metycaine)



3-(α-Methyl piperidino) propyl benzoate

Synthesis

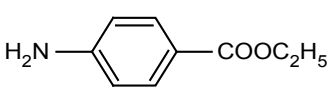


Piperocaine

Properties and uses: Piperocaine is small, white, crystalline powder, soluble in water and chloroform. It is used as surface anasthesia for eyes, throat and caudal analgesia.

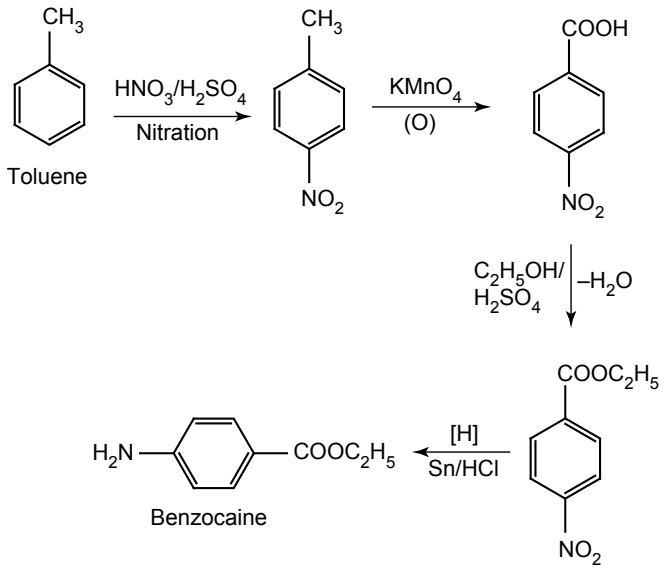
II. Para amino benzoic acid derivatives

a. Benzocaine (Americaine)



Ethyl-*p*-aminobenzoate

Synthesis



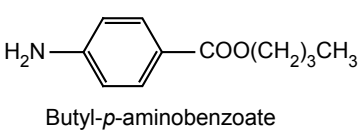
Properties and uses: It is a white crystalline powder or colourless crystals, freely soluble in alcohol, slightly soluble in water. Structurally, it lacks the terminal diethylamino group usually present in most of the anaesthetics, such as procaine. It is used to get rid of the pain caused by wounds, ulcers, and in mucous surface. It is nonirritant and nontoxic.

Assay: Dissolve the substance in a mixture of hydrochloric acid and water, and perform the determination of primary aromatic amino-nitrogen (diazotization method).

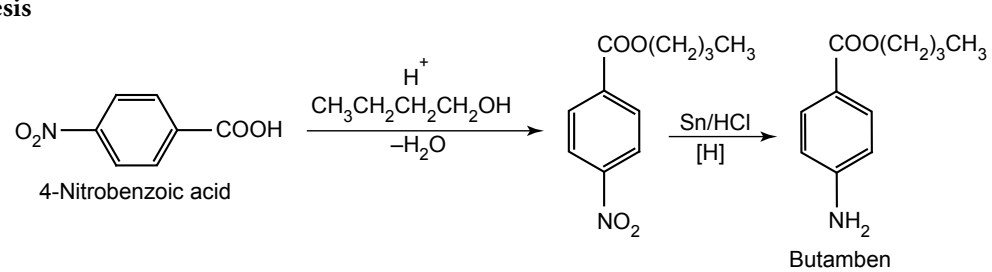
Storage: It should be stored in well-closed airtight container and protected from light.

Dose: Topical, 1% to 20% in ointment, cream, and aerosol for skin.

b. Butamben (Butesin)



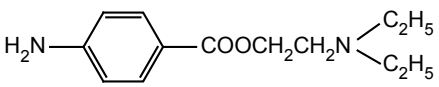
Synthesis



Properties and uses: It is a local anaesthetic of relatively low solubility and used in a similar manner to benzocaine. It is more efficacious than its corresponding ethyl ester when applied to intact mucous membranes.

Dose: Topical, 1% to 2% in conjunction with other local anaesthetics in creams, ointments, sprays, and suppositories.

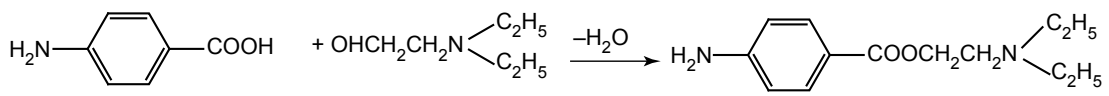
c. Procaine hydrochloride (Navocaine)



2-(Diethylamino)ethyl-*p*-aminobenzoate

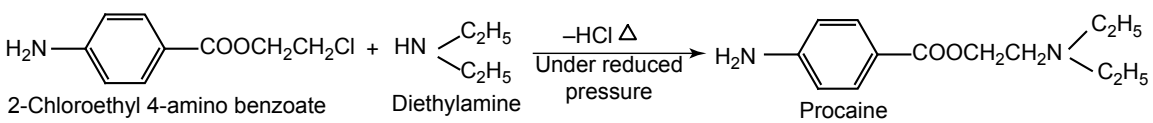
Synthesis

Route I. From: *p*-Amino benzoic acid



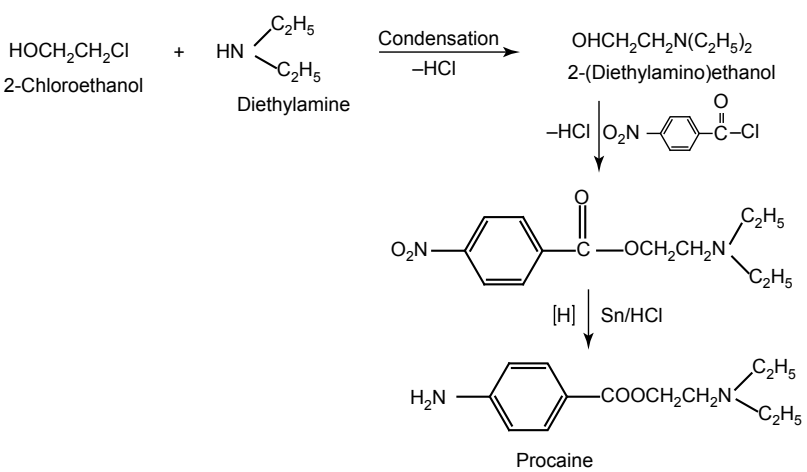
4-Aminobenzoic acid 2-(*N*,*N*-diethylamino)ethanol Procaine

Route II. From: 2-Chloro ethyl 4-amino benzoate



2-Chloroethyl 4-amino benzoate Diethylamine Procaine

Route III. From: 2-Chloro ethanol



2-Chloroethanol Diethylamine 2-(Diethylamino)ethanol Procaine

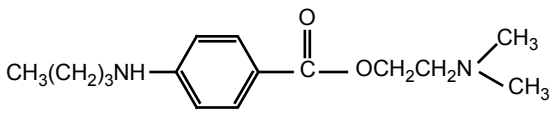
Properties and uses: It is a white crystalline powder or colourless crystals, soluble in water and alcohol. It has the advantage of lacking of local irritation, minimal systemic toxicity, longer duration of action, and low cost. It can be effectively used for causing anaesthesia by infiltration, nerve block, epidural block, or spinal anaesthesia.

Assay: Dissolve the substance in dilute hydrochloric acid and perform the determination of primary aromatic amino nitrogen (Diazotization method).

Storage: It should be stored in well-closed airtight container, protected from light.

Dose: Usual infiltration, 50 ml of a 0.5% solution; usual peripheral nerve block, 25 ml of a 1% or 2% solution; usual epidural, 25 ml of a 1.5% solution.

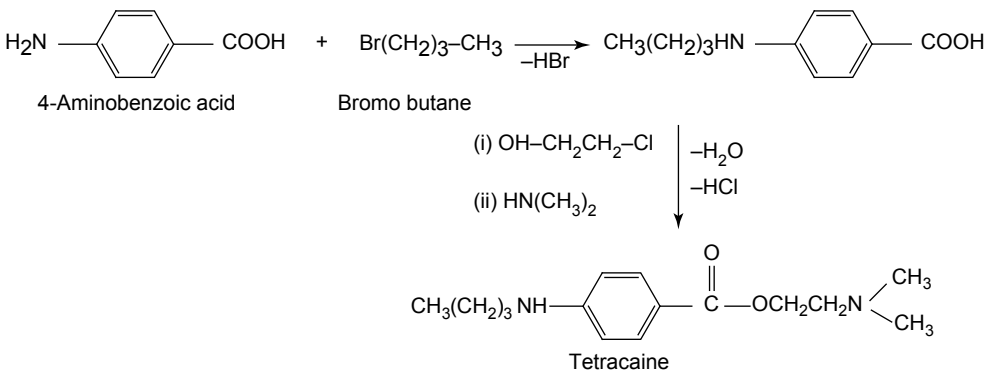
d. Tetracaine (Anethaine, Pontocaino hydrochloride)



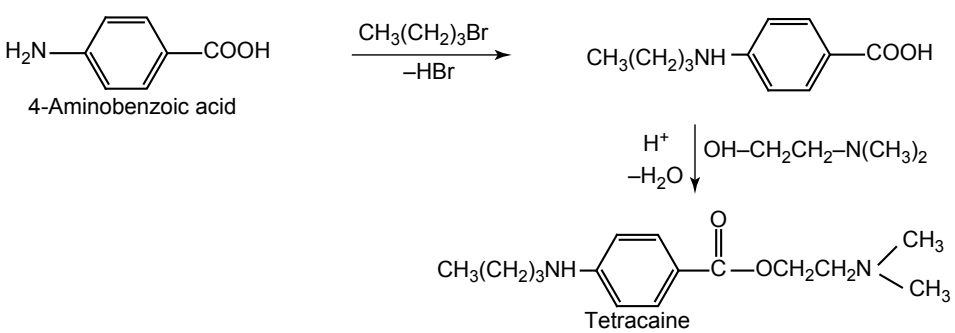
2-(Dimethyl amino) ethyl-*p*-(butyl amino) benzoate

Synthesis

Route I. From: 4-Amino benzoic acid



Route II. From: 4-Amino benzoic acid



Properties and uses: It is a white crystalline powder, slightly hygroscopic in nature, soluble in alcohol, and freely soluble in water. It is an all-purpose local anaesthetic drug used frequently in surface, infiltration block, caudal, and spinal anaesthesia. It is reported to be 10 times more toxic and potent than procaine. Its duration of action is twice than that of procaine.

Assay: Dissolve the substance in alcohol and add 0.01 M hydrochloric acid. Perform potentiometric titration, using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight container, protected from light.

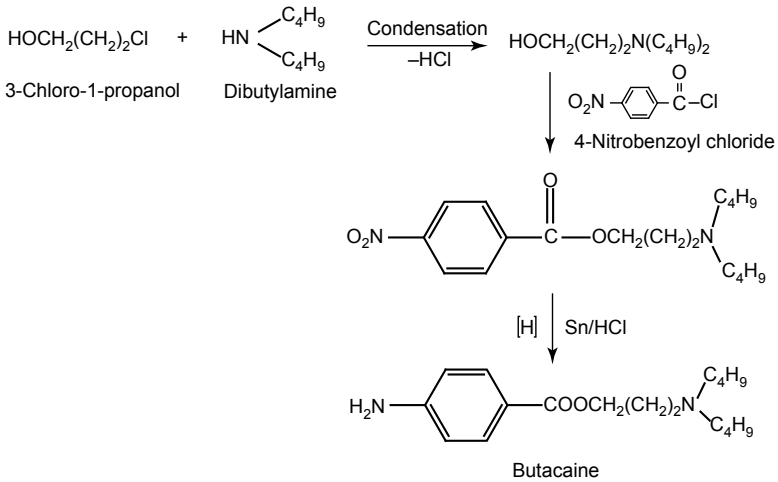
Dose: Usually, subarachnoid 0.5 to 2 ml as a 0.5% solution; topically, 0.1 ml of a 0.5% solution to the conjunctiva.

Dosage forms: Tetracaine eye drops B.P.

e. Butacaine (Butyn sulphate)

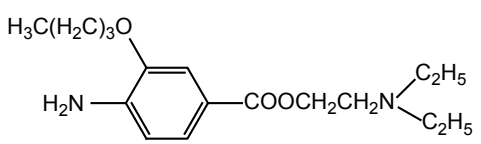
3-(Di-butyl amino)-1-propane-*p*-amino benzoate

Synthesis



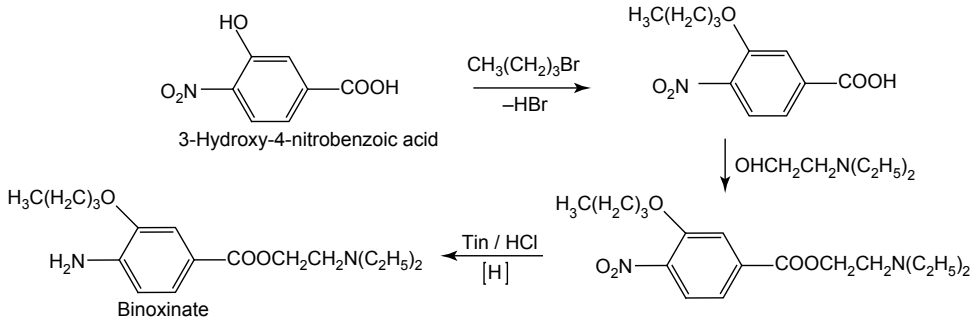
Dose: Several instillations of a 2% solution about 3 min apart allows most surgical procedures.

f. Binoxinate

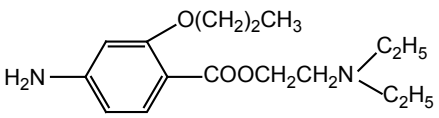


2-(Diethyl amino) ethyl-4-amino-3-butyloxy-benzoate

Synthesis

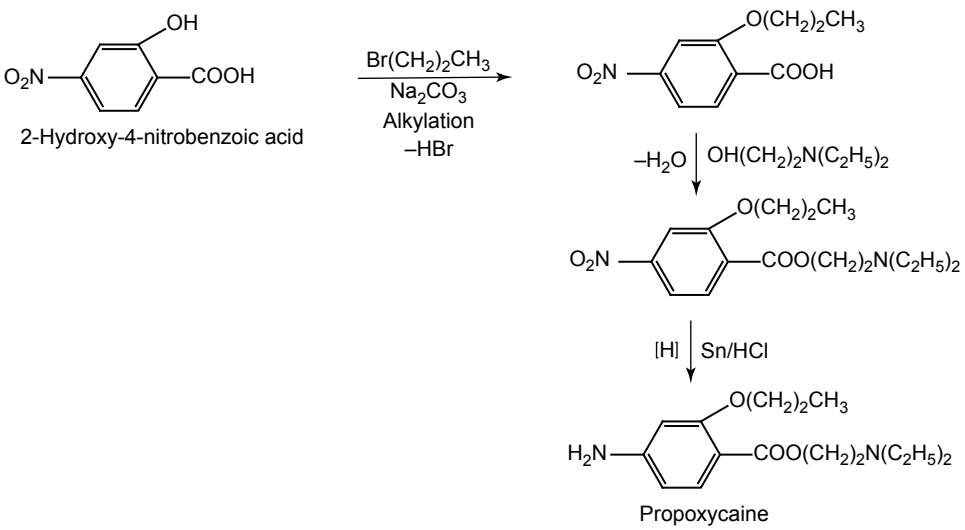


g. Propoxycaine (Blockhain)



2-(Diethyl amino) ethyl-4-amino-2-propoxy benzoate

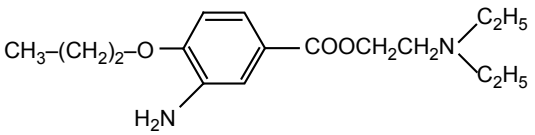
Synthesis



Properties and uses: Its local anaesthetic potency is reported to be 7 or 8 times more than that of procaine. It is a structural isomer of proparacaine, and is less toxic with slightly lower potency than proparacaine. It is mainly used for infiltration and nerve block anaesthesia.

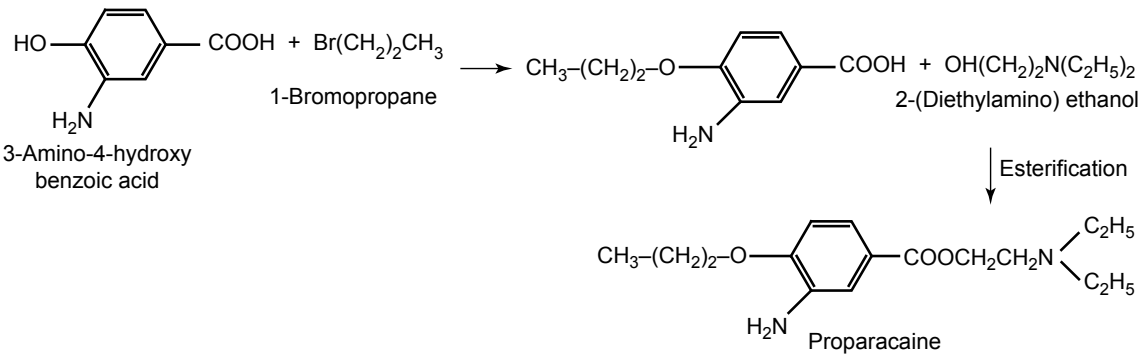
Dose: Usually, 2 to 5 ml of 0.5% solution.

h. Proparacaine



2-(Diethyl amino) ethyl-3-amino-4-propoxy benzoate.

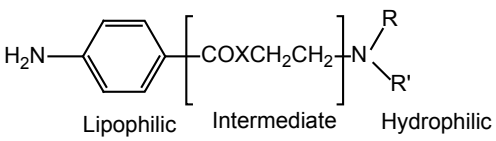
Synthesis



Properties and uses: An effective ester-type surface anaesthetic with potency about equal to that of tetracaine. It is a useful anaesthetic in ophthalmology and induces little or no initial irritation. It is useful for most occular procedures that require topical anaesthesia such as cataract extraction, tonometry, removal of foreign bodies and sutures, gonioscopy, conjunctival scraping for diagnosis and short-operative procedures involving the cornea and conjunctiva.

SAR OF BENZOIC ACID DERIVATIVES

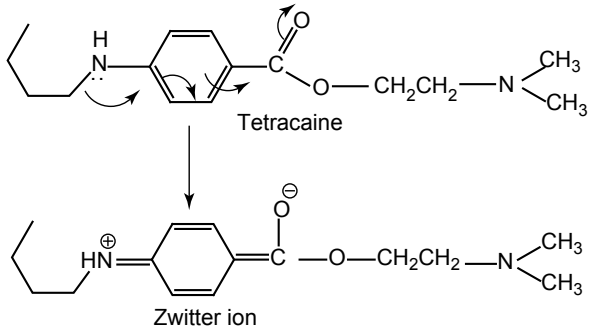
Most of these local anaesthetics are tertiary amines available as HCl salts with pKa in the range of 7.5–9.0. Any structural modification of the local anaesthetic that causes change in pKa will have pronounced effect to reach hypothetical receptor or the binding sites.



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 decreases the activity.



- 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 $C1^-$ 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.

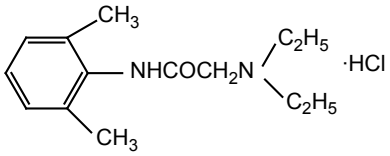
3. Hydrophilic portion

- 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 pyrolidino, 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.

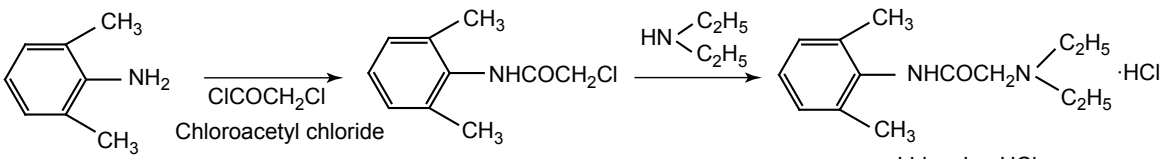
III. Anilides

Agents of this class are more stable to hydrolysis. They are more potent, have lower frequency of side effects, and induce less irritation than benzoic acid derivatives.

a. Lidocaine HCl (Synonym: Lignocaine, Xylocaine)



Synthesis



2,6-Xylidine

Metabolism: Undergoes *N*-de-ethylation to yield mono-ethyl glycinexylide followed by amidase action to *N*-ethyl glycine and 2, 6-dimethylaniline.

Properties and uses: It is a white crystalline powder, very soluble in water, freely soluble in alcohol. It is a potent local anaesthetic. It is reported to be twice as active as procaine hydrochloride in the same concentrations. It has local vasodilating action, but usually used with vasoconstrictor adrenaline to prolong the local anaesthetic activity. It is also used as class I anti-arrhythmic agent.

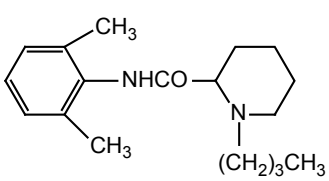
Assay: Dissolve the substance in alcohol and add 0.01 M hydrochloric acid. Perform potentiometric titration using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: Infiltration or epidural up to 60 ml (or 100 ml with epinephrine) as 0.5% solution.

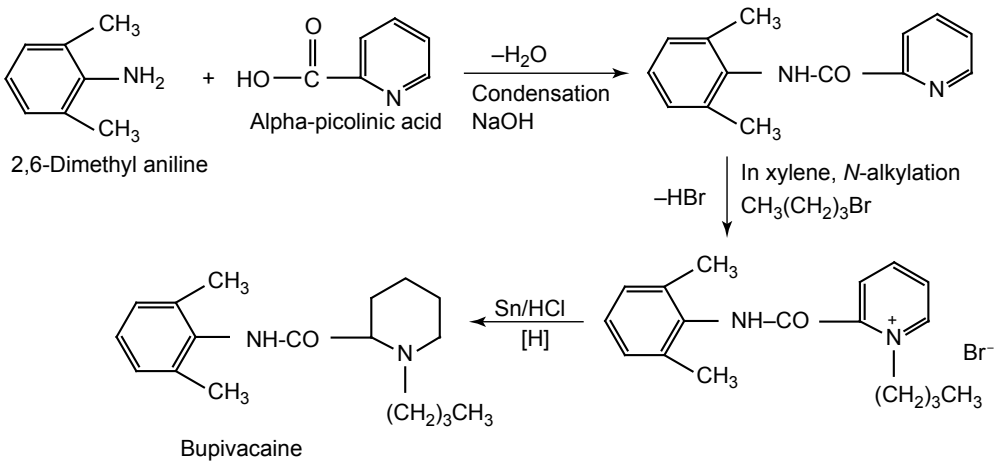
Dosage forms: Lidocaine gel B.P., Lidocaine and Chlorhexidine gel B.P., Lidocaine injection B.P., Lidocaine and adrenaline injection/Lidocaine and Epinephrine injection B.P., Sterile Lidocaine solution B.P.

b. Bupivacaine (Marcaine)



1-Butyl-*N*-(2, 6-dimethyl phenyl)-2-piperidin carboxamide

Synthesis



Properties and uses: It is a white crystalline powder or colourless crystals, soluble in water, freely soluble in alcohol. It is a long-acting local anaesthetic of the amide type, similar to mepivacaine and lidocaine, but about four times more potent. The effect of bupivacaine last longer than lidocaine hydrochloride. It is long-acting local anaesthetic mainly employed for regional nerve block.

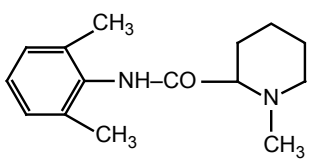
Assay: Dissolve the sample in a mixture of water and alcohol, to this add 0.01 M hydrochloric acid and carry out a potentiometric titration using 0.1 M ethanolic sodium hydroxide.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: Regional nerve block, 0.25% to 0.5% solutions; Lumbar epidural block, 15 to 20 ml of 0.25% to 0.5% solution; Caudal block, 15 to 40 ml of 0.2% solution.

Dosage forms: Bupivacaine HCl injection I.P., Bupivacaine injection B.P., Bupivacaine and Adrenaline injection/Bupivacaine and Epinephrine injection B.P.

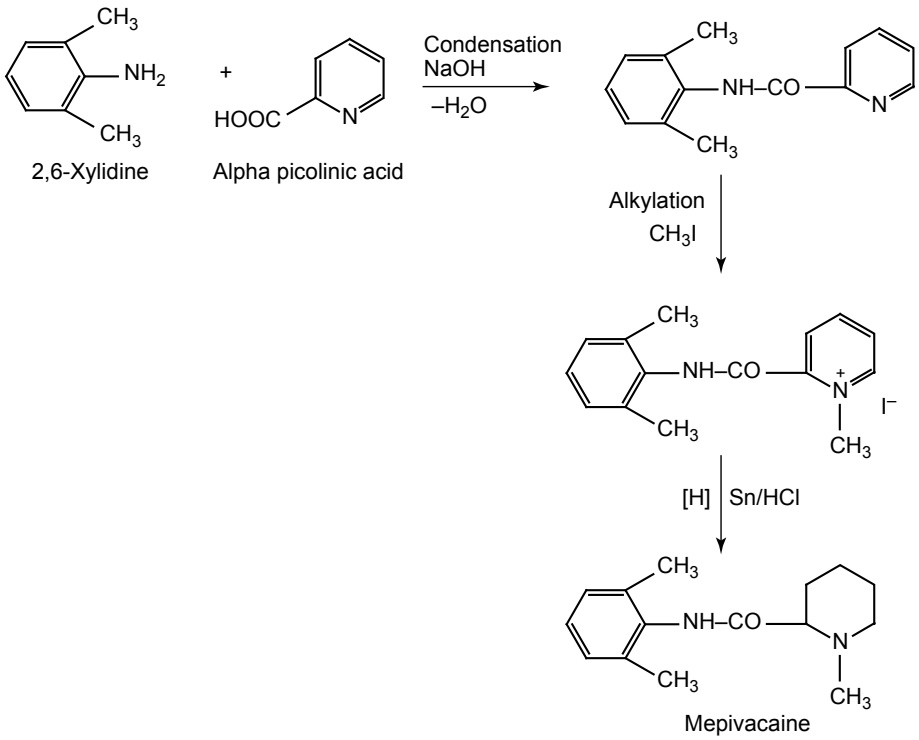
c. Mepivacaine (Carbocaine hydrochloride, Polocaine)



N-(2,6-dimethyl)-1-methyl-2-piperidin carboxamide

Properties and uses: It is a white crystalline powder, freely soluble in water and in alcohol, very slightly soluble in methylene chloride. The duration of action is significantly longer than that of lidocaine, even without adrenaline. It is of particular importance in subjects showing contraindication to adrenaline. It is a local anaesthetic used for infiltration, peridural, nerve block, and caudal anaesthesia.

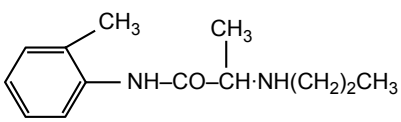
Synthesis



Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and alcohol. Perform potentiometric titration using 0.1 M sodium hydroxide.

Dose: In filtration and nerve block, 20 ml of 1% or 2% solution in sterile saline; caudal and peridural, 15 to 30 ml of 1%; 10 to 25 ml of 1.5% or 10 to 20 ml of a 2% solution in modified Ringer's solution.

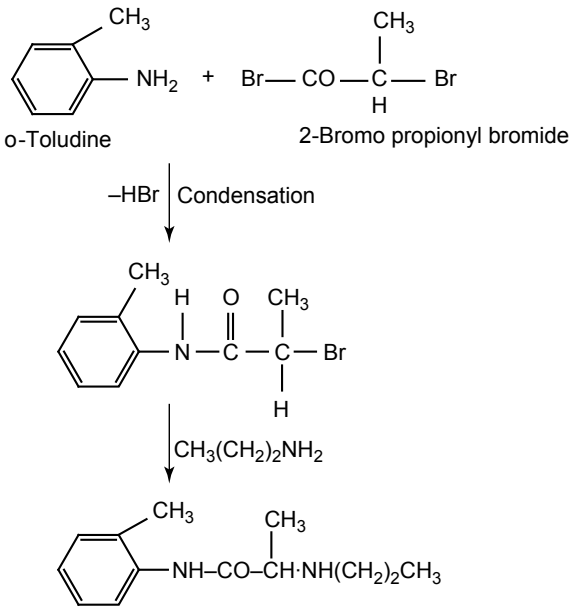
d. Prilocaine (Citanest hydrochloride)



2-(Propylamino)-*o*-propiono toludine

Properties and uses: It is a white crystalline powder or colourless crystals, very slightly soluble in acetone, freely soluble in water and alcohol. It is a local anaesthetic of the amide type, which is employed for surface infiltration and nerve block anaesthesia. Its duration of action is in between the shorter-acting

Synthesis



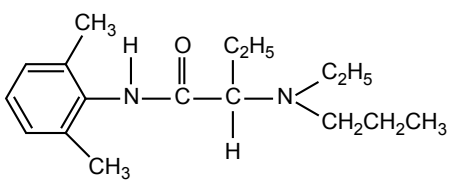
lidocaine and longer-acting mepivacaine. The solution of prilocaine HCl is specifically used for such patients who cannot tolerate vasopressor agents, patients having cardiovascular disorders, diabetes, hypertension, and thyrotoxicosis.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and alcohol and perform potentiometric titration, using 0.1 M sodium hydroxide.

Dose: Usually, therapeutic nerve block, 3 to 5 ml of a 1% or 2% solution; infiltration, 20 to 30 ml of a 1% or 2% solution; peridural, caudal, regional, 15 to 20 ml of a 3% solution; infiltration and nerve block, 0.5 to 5 ml of a 4% solution.

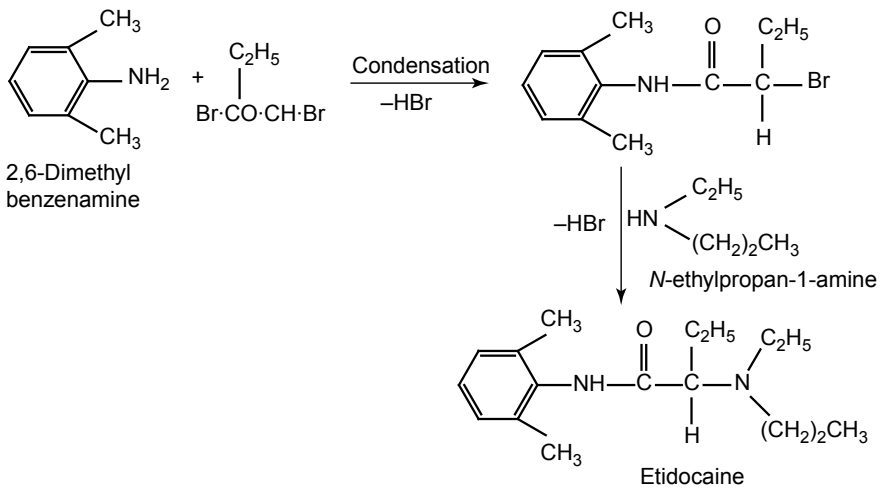
Dosage forms: Prilocaine injection B.P.

e. Etidocaine (Duranset)



2- (Ethyl propyl amino)-2', 6'-butyroxylide

Synthesis

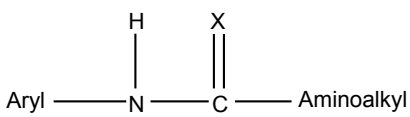


Properties and uses: It is a white crystalline powder, soluble in water, freely soluble in alcohol. It is used clinically in epidural, infiltrative, and regional anaesthesia. It has greater potency and longer duration of action than lidocaine.

Dose: Solution for injection: 1% without epinephrine and 1.5% with epinephrine.

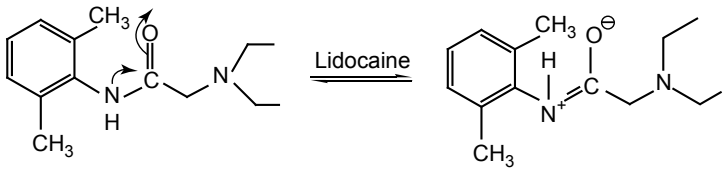
SAR of Anilides

General structure of anilides is represented as follows:



a. Aryl group

- The clinically useful local anaesthetics of this type possess a phenyl group attached to the sp^2 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

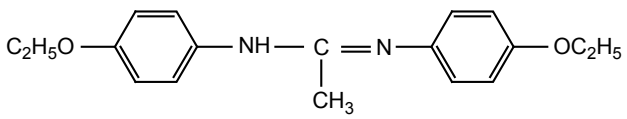
- 'X' may be carbon, oxygen, or nitrogen among them lidocaine series (X = O) has provided more useful products.

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.

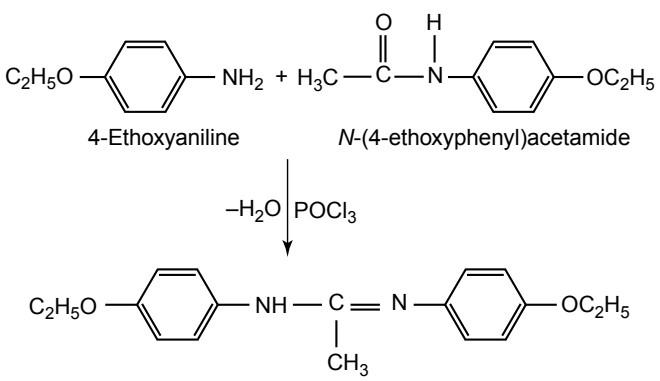
IV. Miscellaneous class

a. Phenacaine (Holocaine hydrochloride)



N, *N*'-bis(4-Ethoxyphenyl ethanindamide)

Synthesis

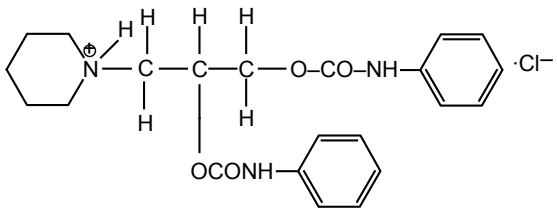


Phenacaine

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 sp^2 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.

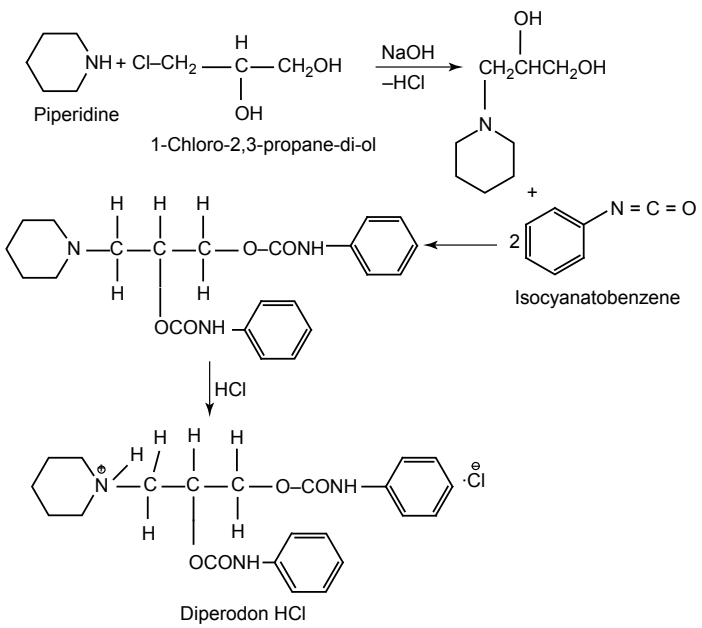
Dose: To the conjunctiva as 1%–2% ointment or as a 1% solution.

b. Diperodon HCl (Diothane)



3-(1-Piperidinyl)-bis (phenylcarbamate)-1, 2-propandiol

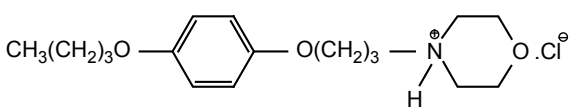
Synthesis



Properties and uses: It exists as white crystals, soluble in water, and potent surface anaesthetic; used primarily for anus. Very toxic in nature.

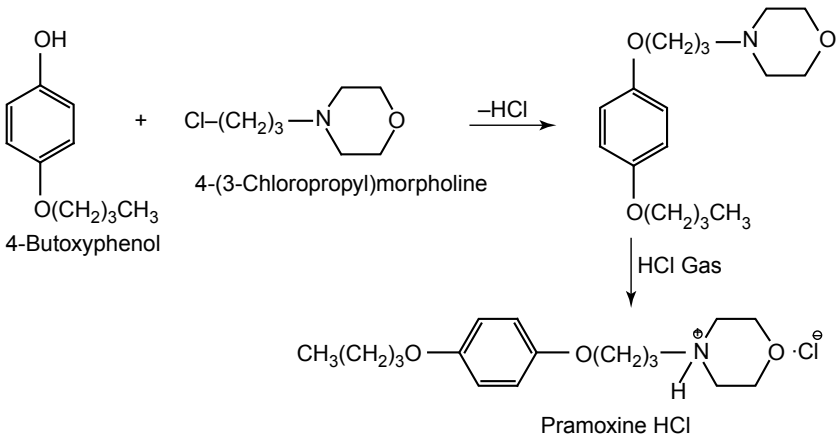
Dose: Topically, 0.5% to 1% solution, to the mucous membranes.

c. Pramoxine HCl (Traonaolene)



4-(-3(4-Butoxy phenoxy)propyl)morpholine.HCl

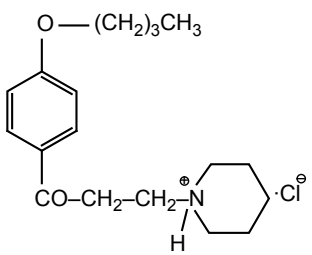
Synthesis



Properties and uses: White crystals or white crystalline powder, numbing taste, may have a slight aromatic odour. Soluble in chloroform, freely soluble in alcohol and water, very slightly soluble in ether. It is a surface anaesthetic, which possesses very low degree of toxicity and sensitization. It is applied locally as 1% solution in rectal surgery, itching, and minor burns. Structurally, it is unrelated to any of the amide type agents, simple ether linkage fulfils this function, and thus, exhibits the local anaesthetic activity.

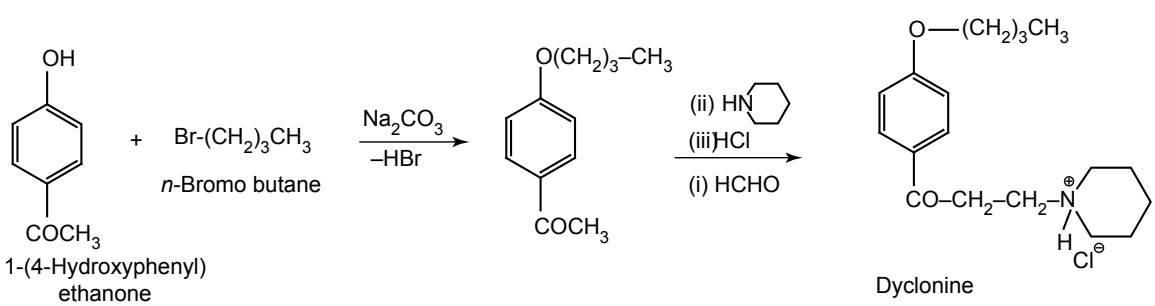
Dose: It is applied locally as 1% solution in rectal surgery, itching, and minor burns.

d. Dyclonine (Dyclone)



1-(4-Butoxy phenyl)-3-(1-piperidinyl)-1-propanone.HCl

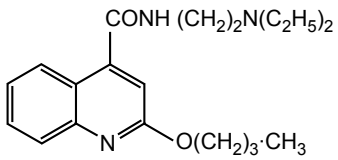
Synthesis



Properties and uses: Exists as white crystals or white crystalline powder and may have a slight odour. Soluble in water, alcohol, and chloroform, insoluble in ether and hexane. Dyclonine containing lozenges are used to relieve minor sore throat and mouth discomfort. It is used to anesthetize mucous membranes of mouth, trachea, and urethra prior to various endoscopic procedures.

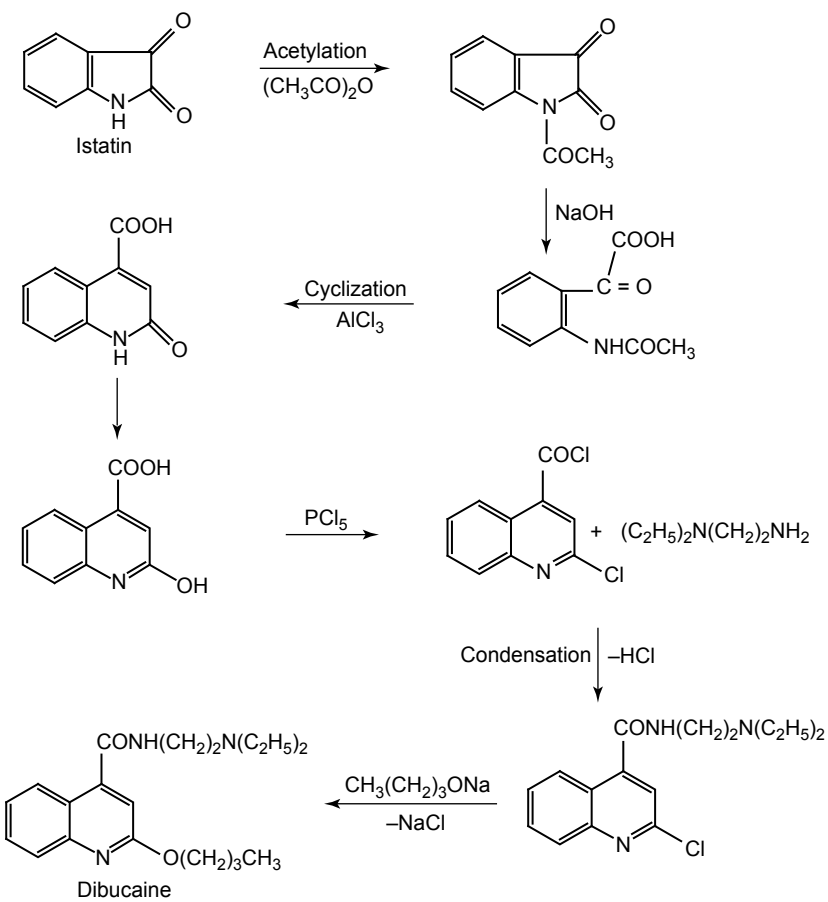
Dose: A 5% solution is used to relieve pain associated with oral or anogenital lesion.

e. Dibucaine (Nupercaine)



2-Butoxy-*N*-(2-(diethylamino)ethyl)-4-quinoline carboxamide

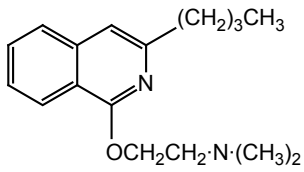
Synthesis



Properties and uses: Exists as white powder with slightly characteristic odour, somewhat hygroscopic, and darkens on exposure to light. Soluble in water, alcohol, chloroform, and in ether. Its anaesthetic activity is similar to those of procaine or cocaine when injected. It is several times more potent than procaine when injected subcutaneously and five times more toxic than cocaine, when injected intravenously. It is the most potent toxic and long-acting local anaesthetics used as infiltration, surface and spinal anaesthesia**.**

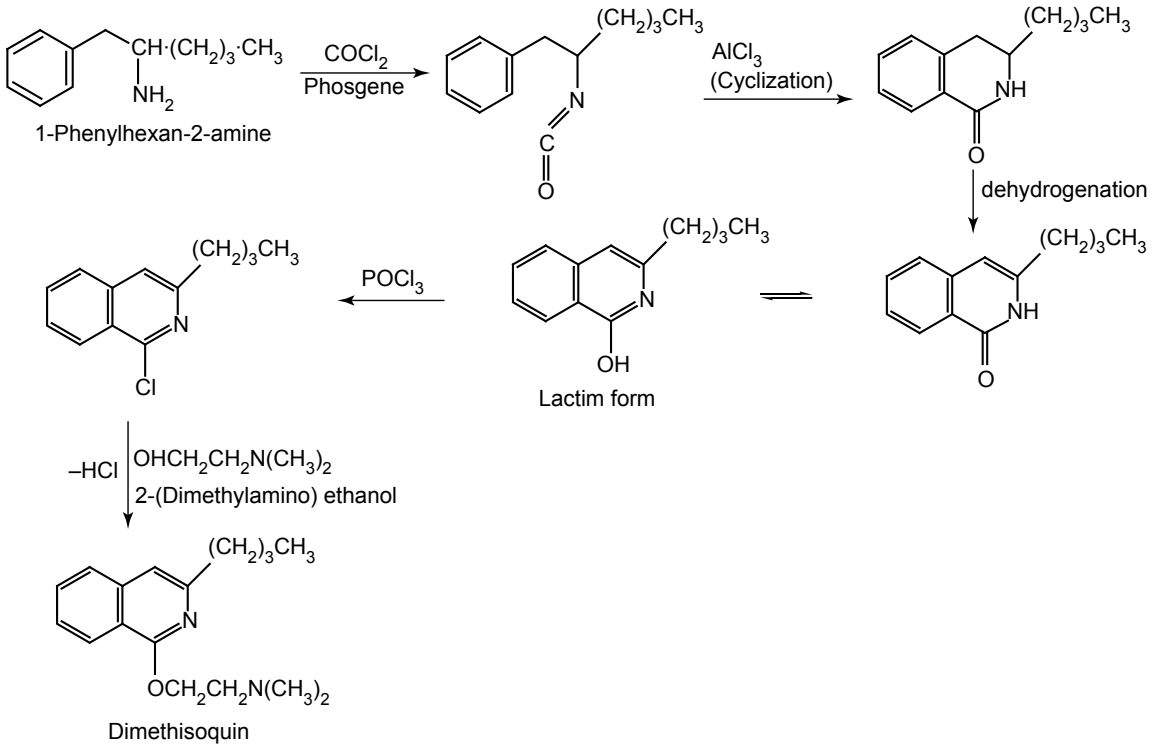
Dose: Subarachnoid, 0.5 to 2 ml of 0.5% solution; usually, 1.5 ml of a 0.5% solution.

f. Dimethisoquin (Synonym: Quinisocaine, Quotane)



3-Butyl-1-(2-(dimethylamino)ethoxy isoquinoline

Synthesis



Uses: It is a surface anaesthetic used as an ointment or lotion for relief from irritation, itching, pain, or burning.

Dose: Topically, to the skin as a 0.5% ointment or lotion 2 to 4 times/day.

PROBABLE QUESTIONS

1. Define and classify local anaesthetics with suitable examples. Outline the synthesis of any two drugs from different class.
2. Differentiate between the Local anaesthetics and the General anaesthetics. Is it necessary to include local anaesthetics as adjuncts in antiseptic creams used in severe burns and painful skin abrasions? Explain with typical examples.
3. Write the synthesis of local anaesthetics having the following functional group.
   (a) Ether (b) Amide (c) Morpholine
4. Outline the synthetic route leads to Procaine using the starting material
   (a) 2-Chloroethyl-*p*-amino benzoate
   (b) 4-Aminobenzoic acid
   (c) 4-Nitrobenzoic acid.
5. Justify why propoxycaine hydrochloride is more potent than procaine hydrochloride.
6. Mention a tropane derivative used as potent surface anaesthetic agent. Outline its synthesis starting from succinic aldehyde.
7. Write in detail about the SAR of Benzoic acid derivatives used as local anaesthetics.
8. Amides and esters constitute an important category of local anaesthetics. Mention the examples with their chemical structure; outline the synthesis of any one drug from each category.
9. Describe the synthesis of a quinoline analogue used as a local anaesthetic starting from isatin.
10. Write the mode of action and general metabolic pathway of local anaesthetics.
11. Write in brief about Anilides used as local anaesthetics.
12. Describe the synthesis of an isoquinoline analogue used as a local anaesthetic.

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