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.

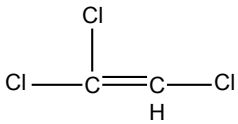
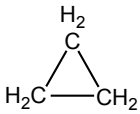
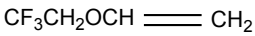
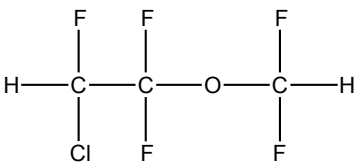
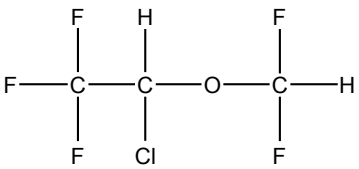
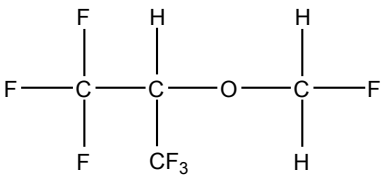
CLASSIFICATION

I. Volatile/Inhalation anaesthetics

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

(*Continued*)

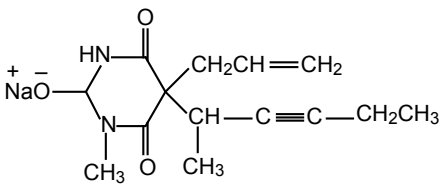
(*Continued*)

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	

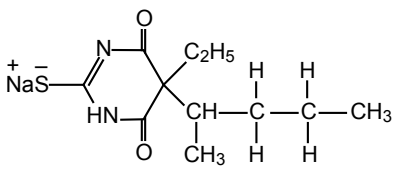
II. Nonvolatile or intravenous anaesthetics

a. Ultra short-acting barbiturates

Methohexital sodium

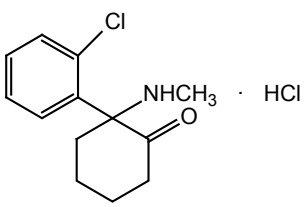


Thiopental sodium



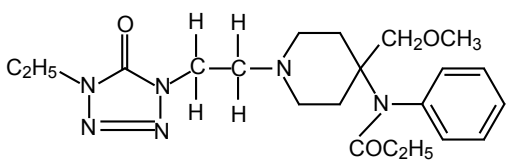
b. Aryl cyclohexylamines

Ketamine



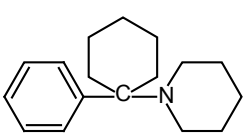
d. Narcotic analgesics

Alfentanyl

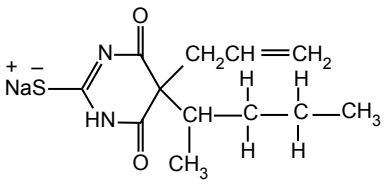


e. Miscellaneous

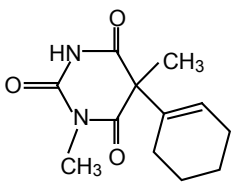
Phencyclidine



Thiomylal sodium

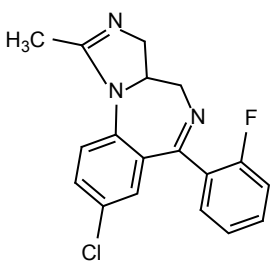


Hexobarbital

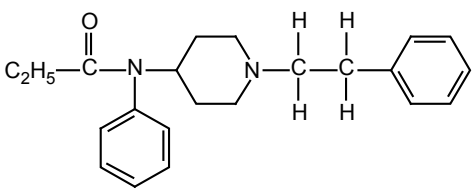


c. Benzodiazepines

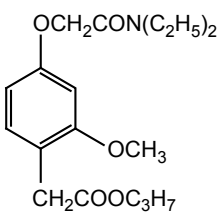
Midazolam



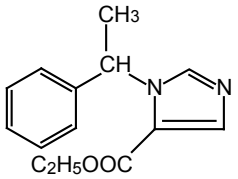
Fentanyl



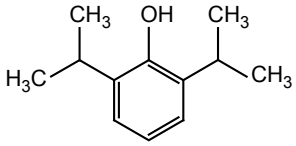
Propanidid



Etomidate



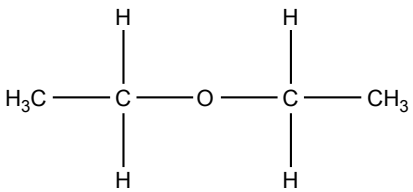
Propofol



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

$C_2H_5 — O — C_2H_5 + H_2SO_4$

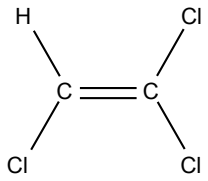
Diethyl ether

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.

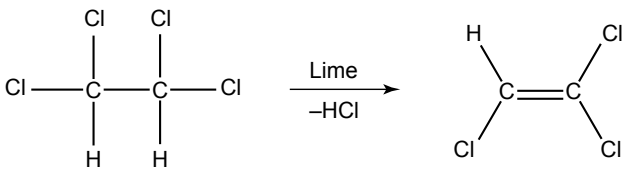
Storage: It should be stored in well-closed airtight containers and protected from light, stored at a temperature of 8°C–15°C.

2. Trichloro ethylene



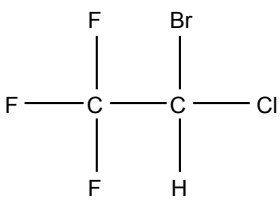
1,1,2-Trichloroethene

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.

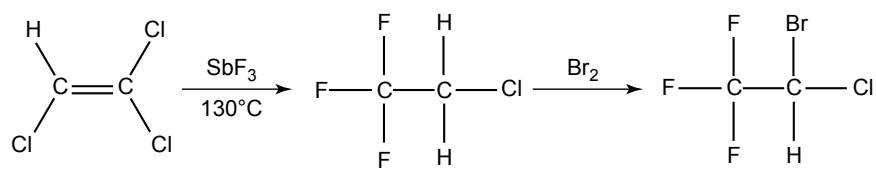


2-Bromo-2-chloro-1,1,1-trifluoro ethane

3. Halothane

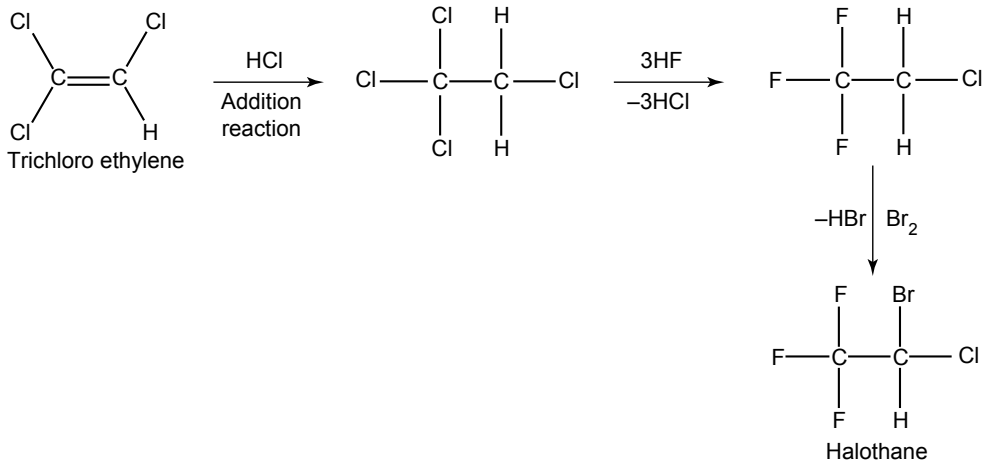
Synthesis

Route I. From: Trichloro ethylene

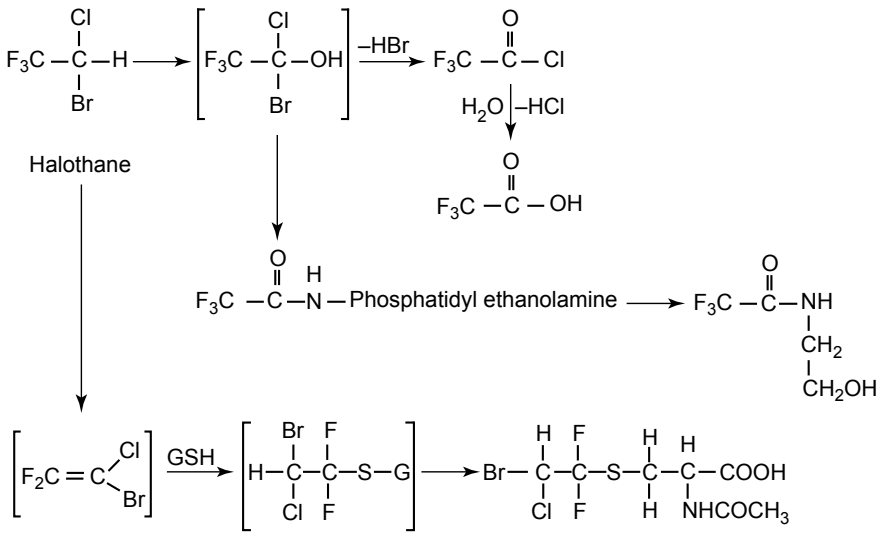


Trichloro ethylene — Halothane

Route II. From: Trichloro ethylene



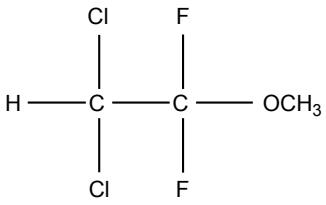
Metabolism: It is metabolized to three major metabolic products, trifluroacetic acid, *N*-trifluro acetyl ethanolamine, and *N*-acetyl-*s*-(2-bromo,2 chloro-1,1-difluro ethyl)-1-cysteine



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.

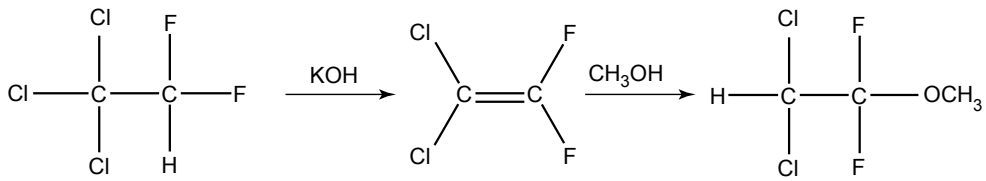
Storage: It should be stored in well-closed airtight containers, protected from light, at a temperature not exceeding 25°C in a nonreactive metal container.

4. Methoxy Flurane



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

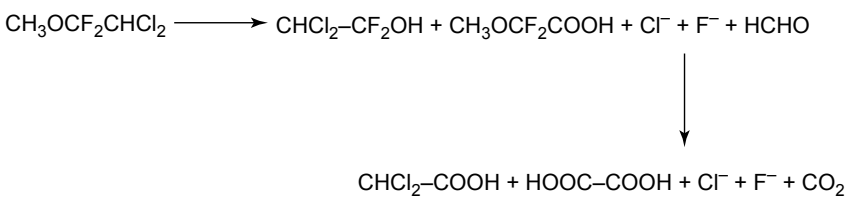
Synthesis



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

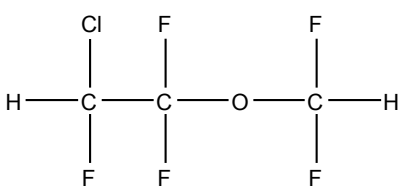
Methyl flurane

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.



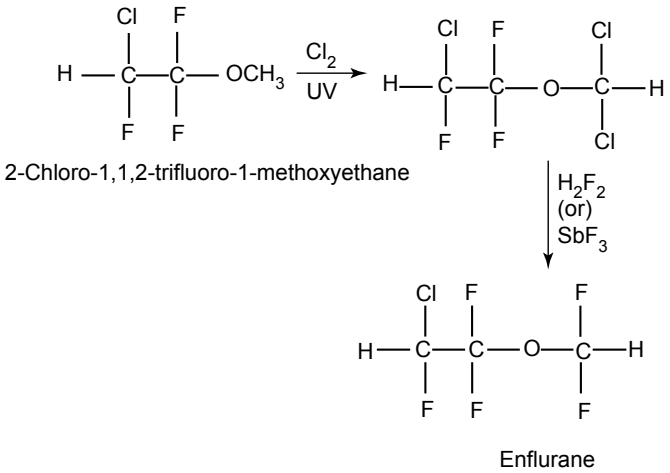
Properties and uses: It is a clear, colourless liquid, noninflammable and nonexplosive in air or oxygen in anaesthetic concentrations. It is the most potent of the inhalational agents. It is employed to cause light anaesthesia with deep analgesic and muscle relaxation feature, which makes it convenient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

5. Enflurane



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

Synthesis

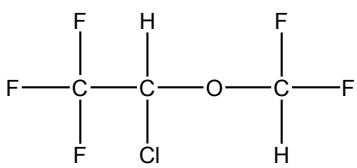


Metabolism: The principal metabolites are difluromethoxy difluroacetic acid and fluoride ion.

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

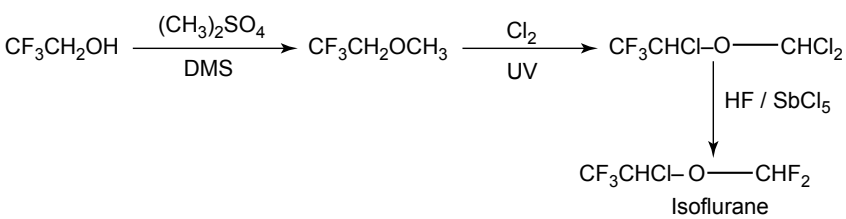
Properties and uses: It is a clear, colourless, volatile liquid with pleasant hydrocarbon-like odour. Soluble in water, miscible with organic solvents, chemically it is extremely stable. The induction of an emergence from anaesthesia and adjustment of anaesthetic depth during maintenance is smooth and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

6. Isoflurane

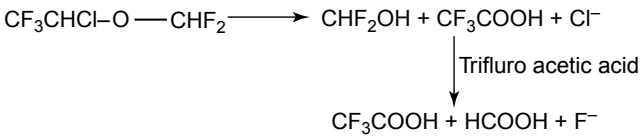


(1-Chloro-2,2,2-trifluoro ethyl)(difluoro methyl) ether

Synthesis



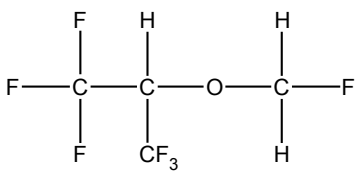
Metabolism: It is metabolized to trifluroacetic acid and fluoride ion.



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.

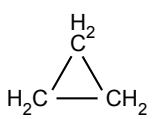
7. Sevoflurane



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

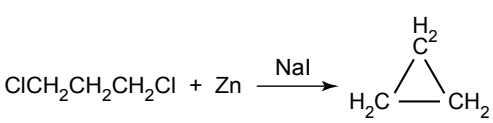
Properties and uses: Low boiling liquid with a slight odour; miscible with most organic solvents including fats or oils; practically insoluble in water. It is a nonflammable, nonirritating agent. The physical properties of this compound result in a more rapid induction and termination of anaesthetic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

8. Cyclopropane (Trimethylene)



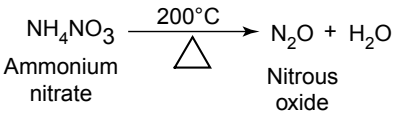
Cyclopropane

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)



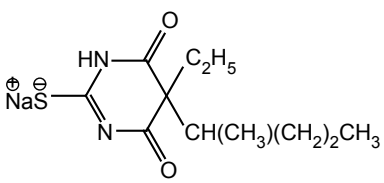
Properties and uses: It is a colourless gas, without appreciable odour to taste, soluble in water, freely soluble in alcohol, soluble in ether, or oils. This is the least toxic and least potent anaesthetic. It is a noninflammable, nonirritating, and a powerful analgesic agent. Nitrous oxide is a weak 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

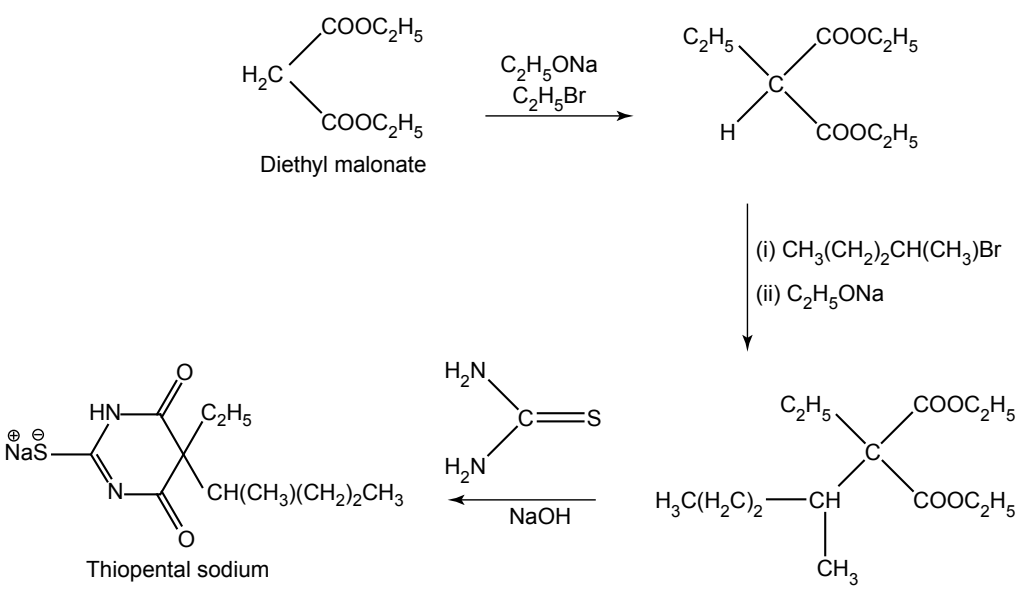
Metabolism of Barbiturates: This is discussed in Section III, Chapter 'Sedatives and Hypnotics'.

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.

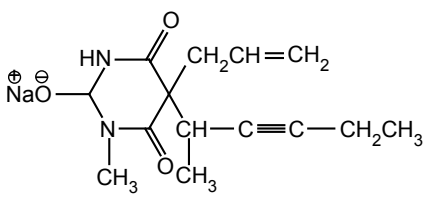
Assay for sodium: Dissolve the sample in water, add 0.1 ml of methyl red solution, and titrate with 0.1 M hydrochloric acid until a red colour is obtained. Boil the mixture gently for 2 min, cool it, and, if necessary, continue the titration with 0.1 M hydrochloric acid until the red colour is again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

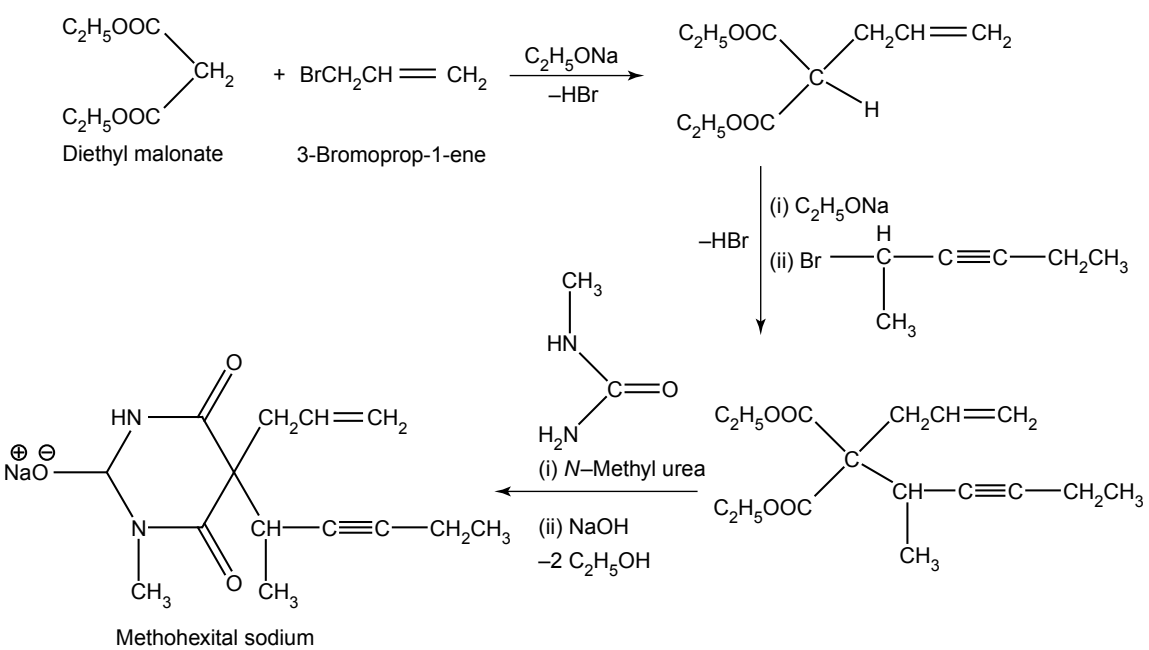
Dosage forms: Thiopental injection B.P.

2. Methohexital sodium



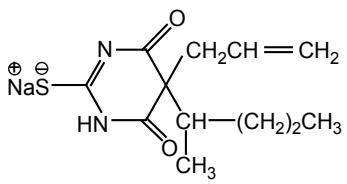
Sodium salt of 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbiturate

Synthesis



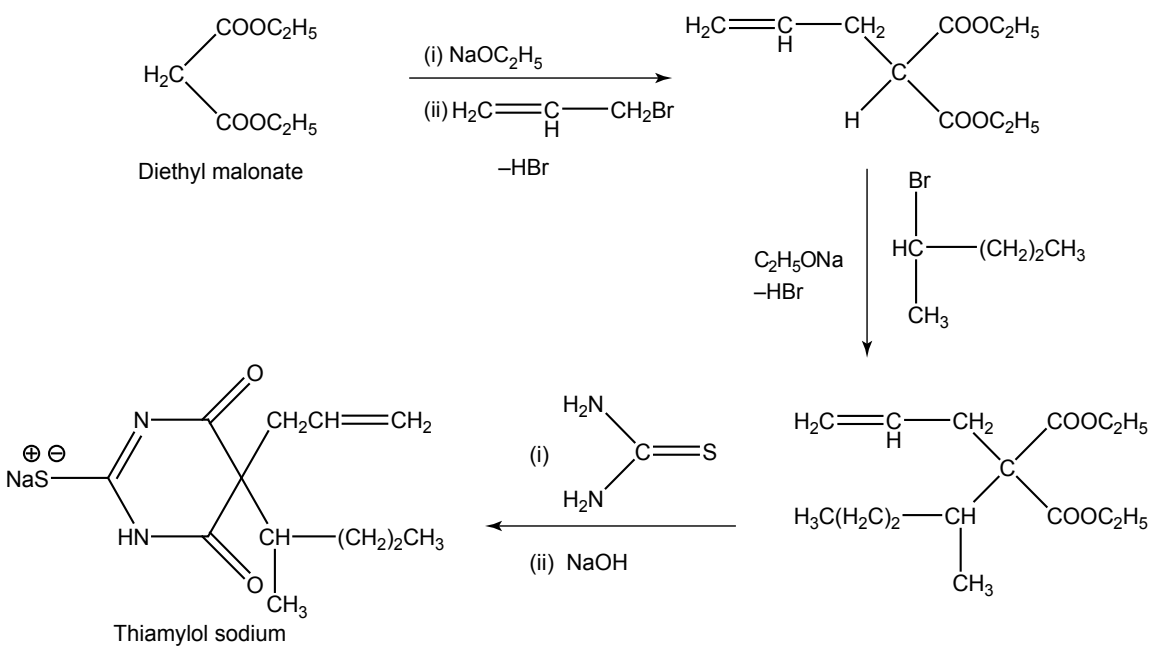
Properties and uses: White to off-white hygroscopic powder, essentially odourless, and the solution is alkaline to litmus, soluble in water. Methohexital produces more rapid recovery from unconsciousness than thiopental. It is more potent and has shorter duration of action. It is used for the induction 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

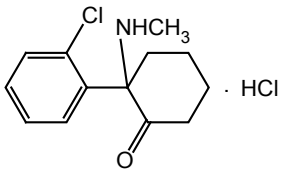
Synthesis



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.

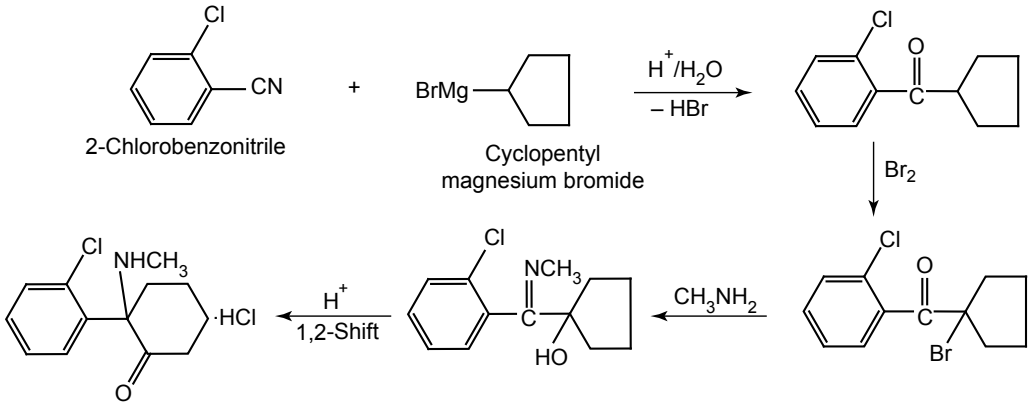
b. Arylcyclohexylamines

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.

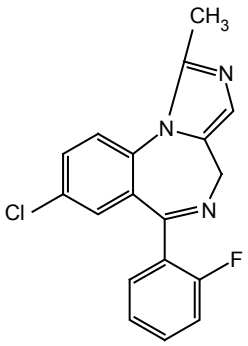
Storage: It should be stored in well-closed airtight containers, protected from light.

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

c. Benzodiazepines

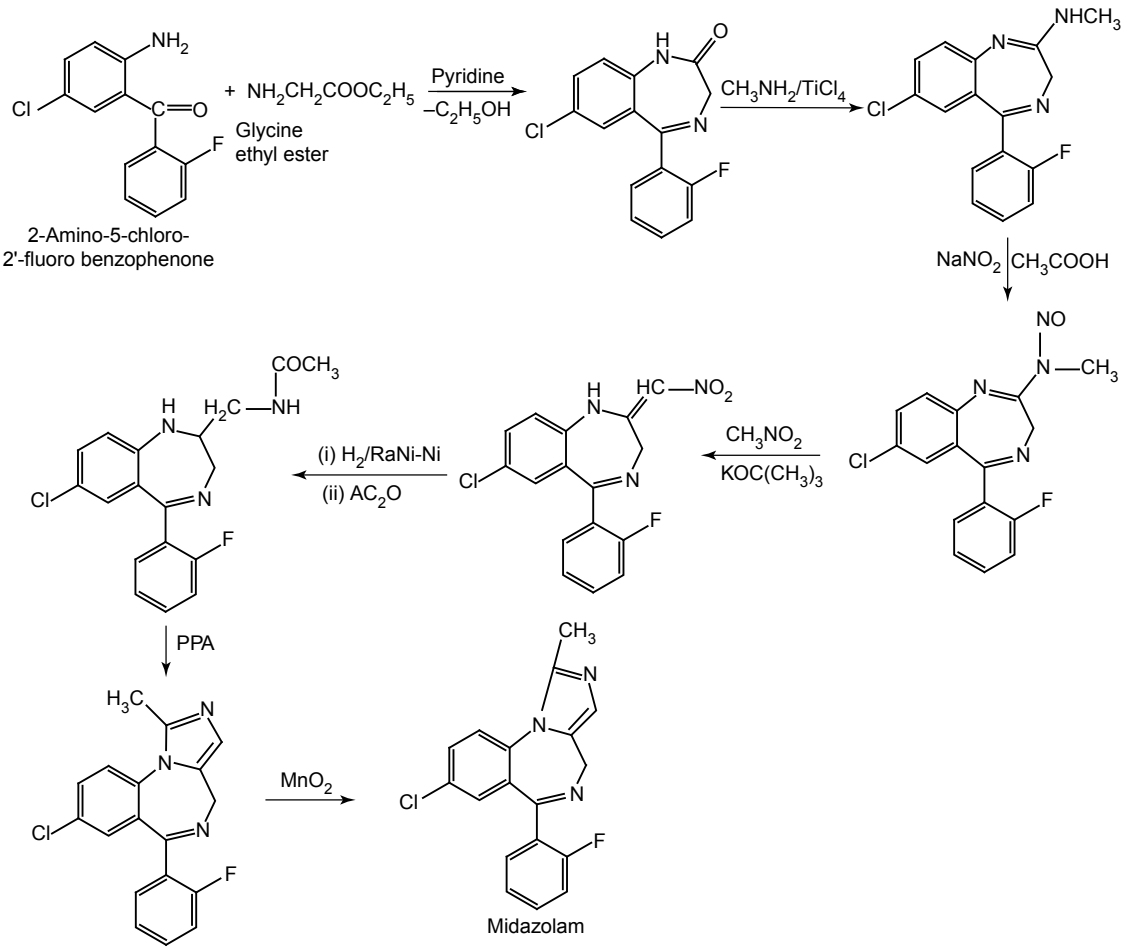
Metabolism: This is discussed in Sec III, Chapter 'Sedatives and Hypnotics'.

1. **Midazolam**



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

Synthesis



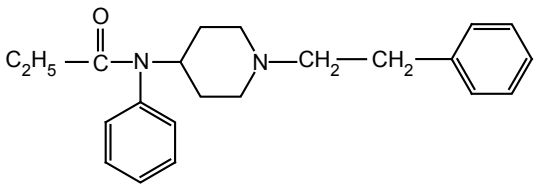
Properties and uses: It is a white or yellowish, crystalline powder, soluble in acetone, ethanol, and methanol, but insoluble in water. Midazolam has been used adjunctively with gaseous anaesthetics. The onset of CNS effect is slower than that of thiopental and it has a longer duration of action.

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

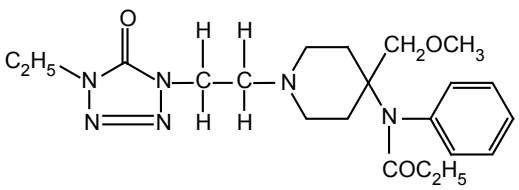
1. Fentanyl



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

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

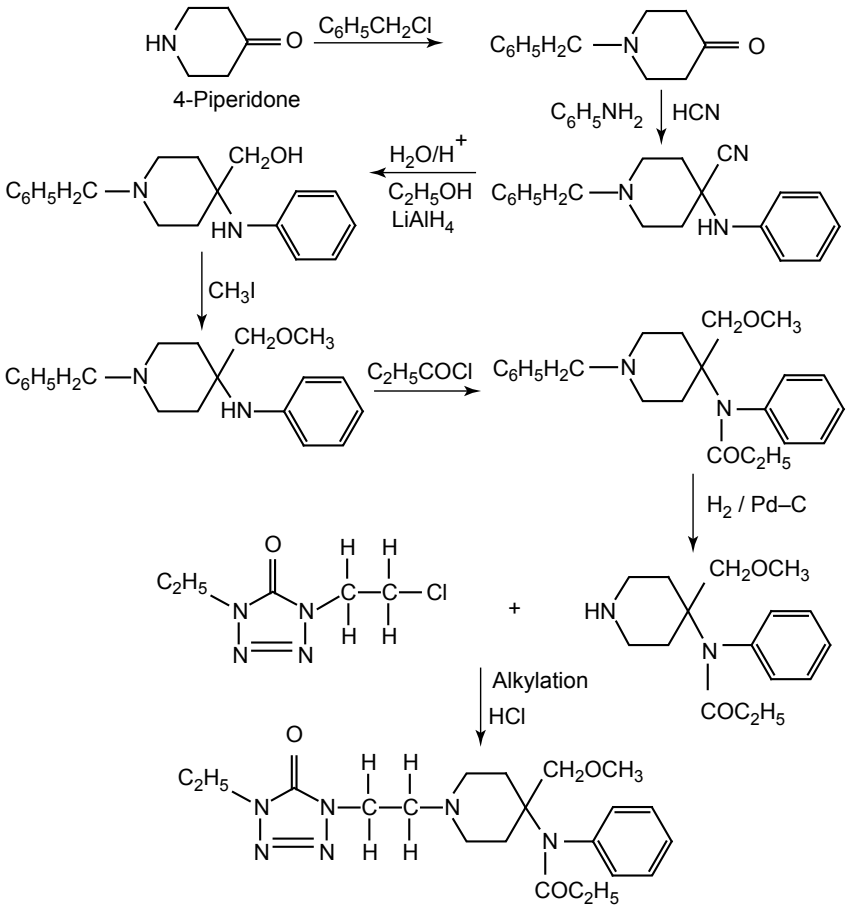
2. Alfentanyl



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

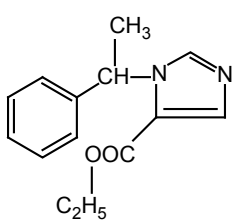
Properties and uses: It is closely related to fentanyl. It is a potent analgesic used as a primary anaesthetic or as an adjunct in the maintenance of anaesthesia. It has the same properties and side effects as fentanyl. It relieves moderate to severe break through pain.

Synthesis



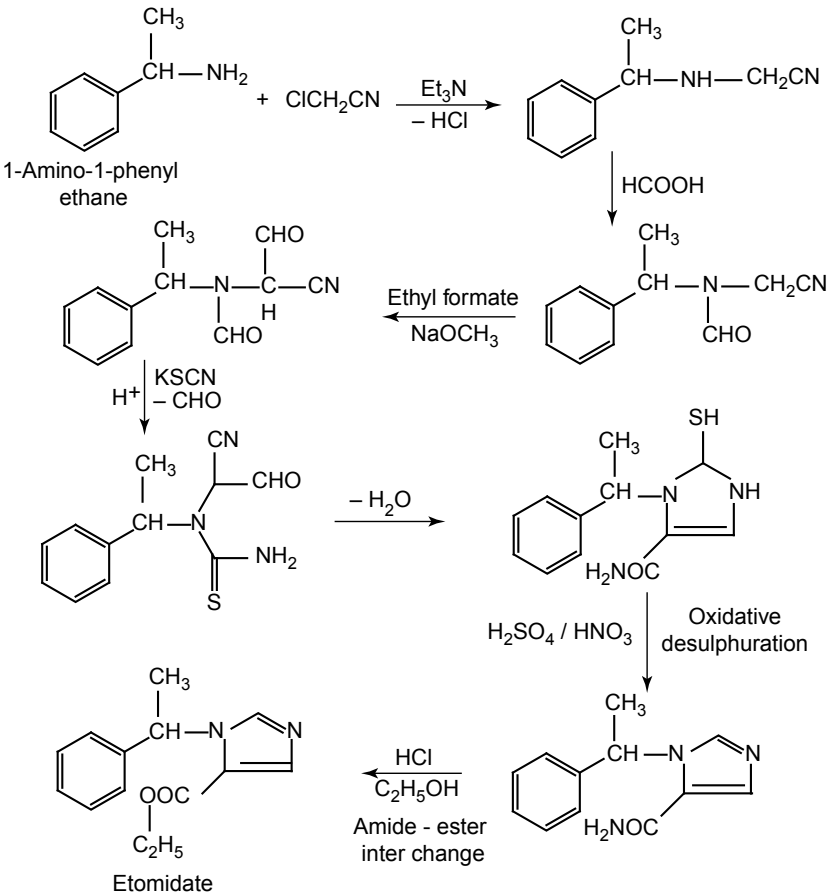
e. Miscellaneous

1. Etomidate



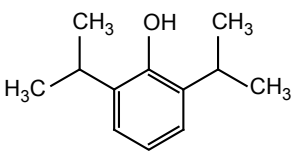
Ethyl-1-(1-methyl benzyl) imidazol-5-carboxylate

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