General anesthetics

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Background

- **General anesthesia was absent until the mid-1800's**
- **William Morton** administered ether to a patient having a neck tumor removed at the Massachusetts General Hospital, Boston, in October 1846.
- The discovery of the **diethyl ether** as general anesthesia was the result of a search for means of eliminating a patient's pain perception and responses to painful stimuli.

What are General Anesthetics?

- A drug that brings about a reversible loss of consciousness
- generally administered by an anesthesiologist in order to induce or maintain general anesthesia to facilitate surgery.

General Anaesthesia (GA)

- A variety of drugs are given to the patient that have different effects with the overall aim of ensuring unconsciousness, amnesia and analgesia.

Stages of general anesthesia

- **Stage I:** analgesia and sedation
- **Stage II:** excitation
- **Stage III:** anesthesia for surgery
- **Stage IV:** intoxication, respiratory arrest

MAC (minimum alveolar concentration)

- A measure of potency of inhaled anesthetics
- MAC is the concentration necessary to prevent responding in 50% of population.

Pharmacokinetics of Inhaled Anesthetics

1. Amount that reaches the brain

   Indicated by oil:gas ratio (lipid solubility)

2. Solubility of gas into blood

   The lower the blood:gas ratio, the more anesthetics will arrive at the brain

Features of ideal anesthetic

- Not disturbing smell
- Fast acting
- Low solubility in blood- fast transport to brain
- Stable when stored, not reacting with other chemicals
- Non- flamable, non- explosive
- Low methabolism in body, fast elimination, no accumulative effect
- No depressing effect on circulatory and respiratory systems

Gas Inhalation Anesthetics

-Hidrocarbons

Ethylene ($CH_2=CH_2$);

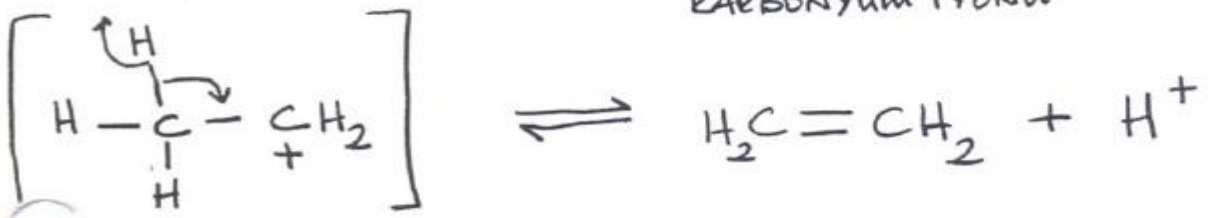
1) ETİL ALKOL ÜN DEHİDRATASYONU

$$CH_3-CH_2-OH \xrightarrow[H_2SO_4]{180^\circ C} H_2C=CH_2 + H_2O$$

$$CH_3-CH_2-OH \xrightarrow[Al_2O_3]{400^\circ C} H_2C=CH_2 + H_2O \text{ (SANAYİDE)}$$

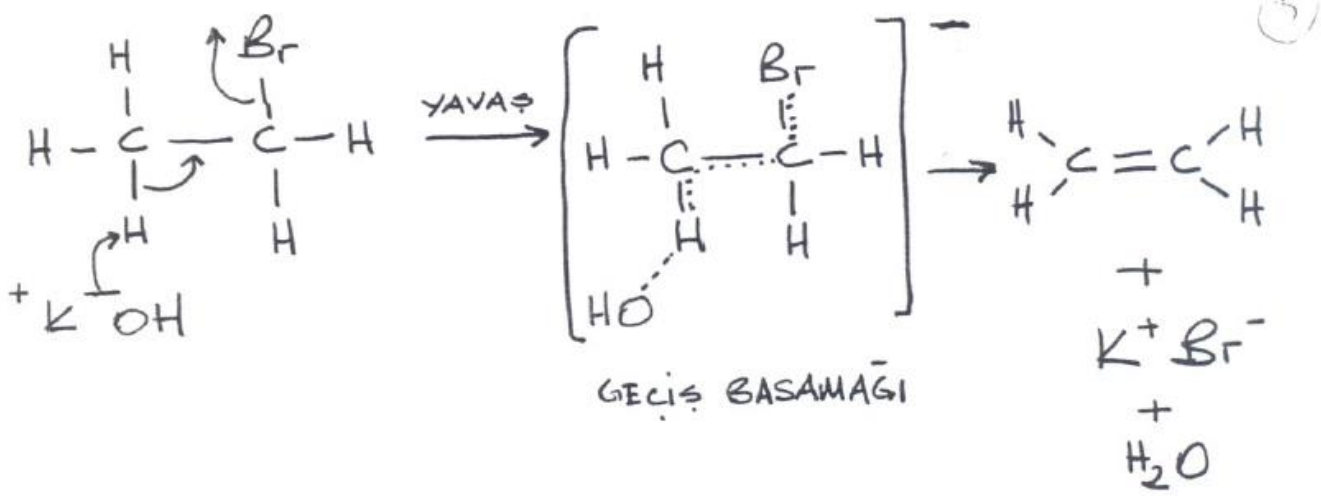
OKSONYUM IYONU

KARBONYUM IYONU



2) ETİL BROMÜR'ÜN DEHİDROHALEJOSYONU

$$CH_3-CH_2-Br \xrightarrow[KOH]{EtOH} H_2C=CH_2 + HBr$$



3) ÇİNKO ARACILIĞI İLE DEHALOJENASYON

$$H_2C(Br)-CH_2(Br) \xrightarrow{Zn^\circ} H_2C=CH_2 + ZnBr_2$$

It's explosive with air.

Despite its low side effects, it has lost its significance in recent years due to its explosive nature and low activity.

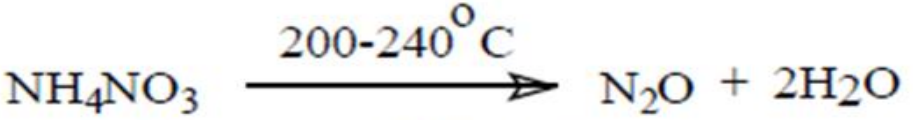
Cyclopropane

- Although air is explosive, it is a stronger anesthetic compound than ethylene (5 times stronger narcotics)
- Elimination is slow.
- Reaction of dibromopropane with zinc gives cyclopropane

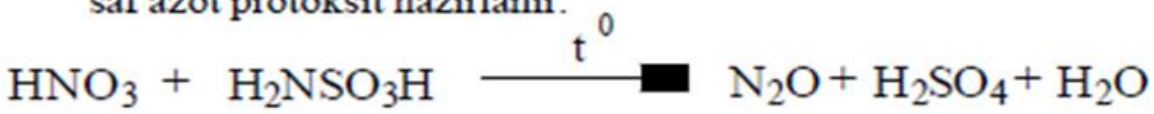
Nitrous Oxide

- widely used
- Potent analgesic
- Produce a light anesthesia
- Do not depress the respiration/vasomotor center
- Used ad adjunct to supplement other inhalationals

Amonyum nitratın yüksek derecede ısıtılmasıyla elde edilir.



Nitrik asitin aminosülfonik asit ile sıcakta reaksiyona sokulmasıyla daha saf azot protoksit hazırlanır.

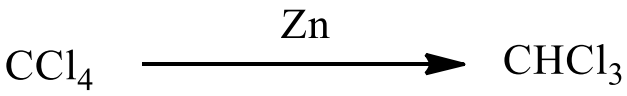


Volatile liquid inhalation anesthetics

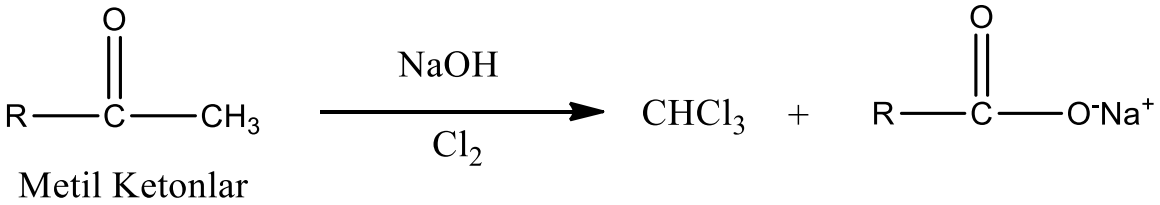
- **Halogenated hydrocarbons**

Chloroform (Trichloromethane);

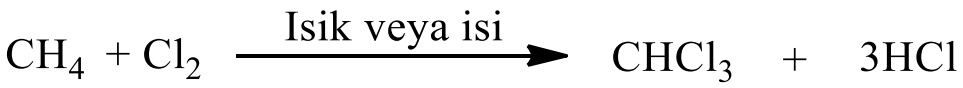
- Synthesized by reduction of carbon tetrachloride;



- Synthesized by Haloform reaction;



- Through photochemical halogenation;



- It is the cheapest and easiest component.

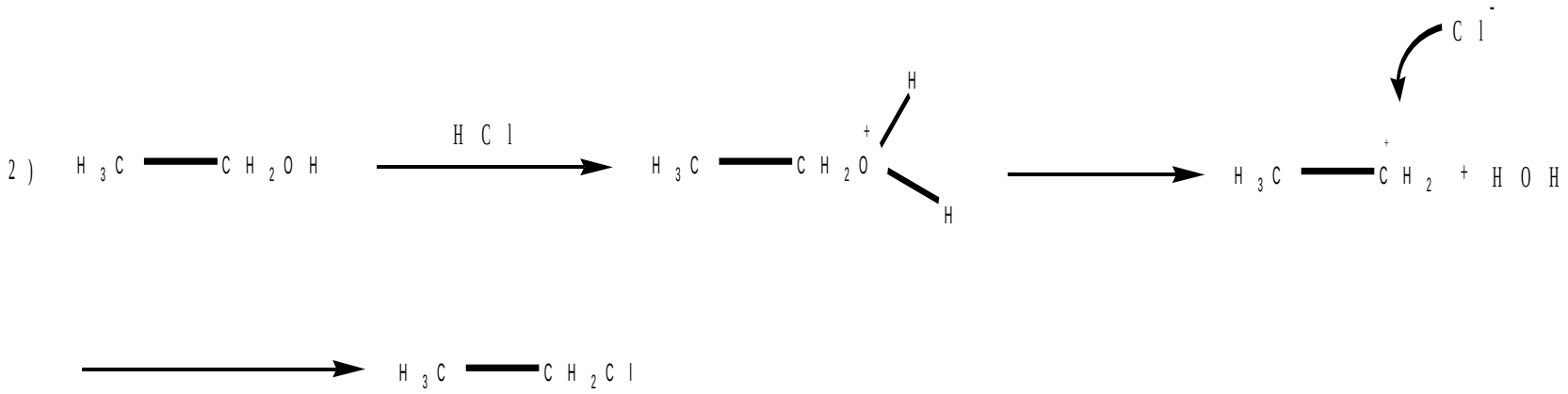
- Chloroform is metabolized by oxidation in the body and transforms into phosgene. Phosgene is a lethal and very toxic gas. For this reason, it is not currently used as an anesthetic.

Ethyl Chloride (Chloroethane)

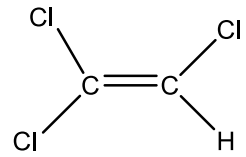
- It has no use today because it has the side effects more than chloroform.

Synthesis;

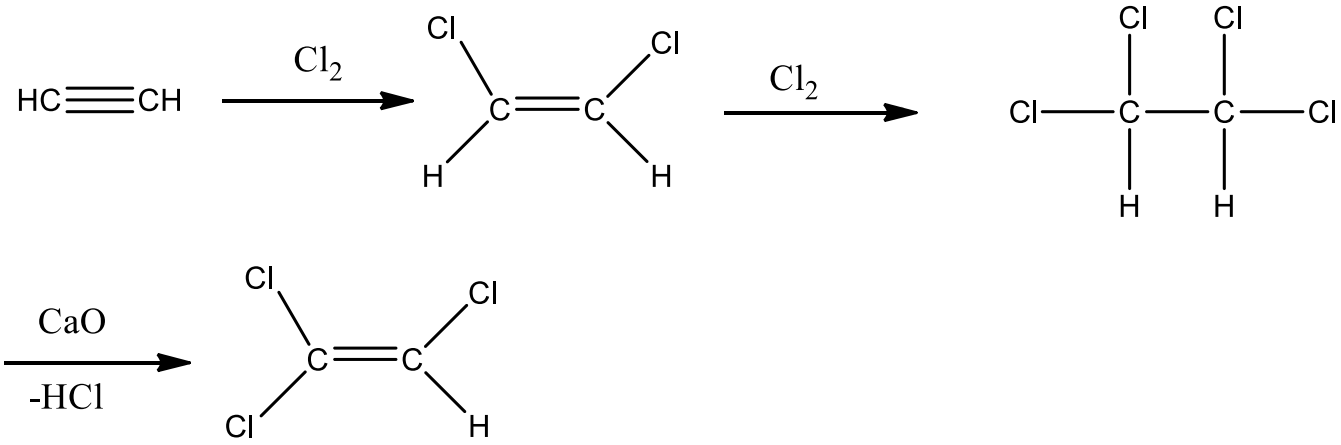
1) $H_2C{=}CH_2 \xrightarrow{HCl} H_3C{-}CH_2Cl$



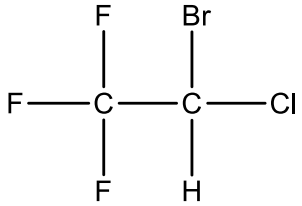
TRICHLORETHYLENE (1,1,2-trichloroethylene)



- Not enough muscular relaxation for surgical intervention.
- Used in short-term small operations for analgesic effect .
- Synthesized by chlorine addition to acetylene



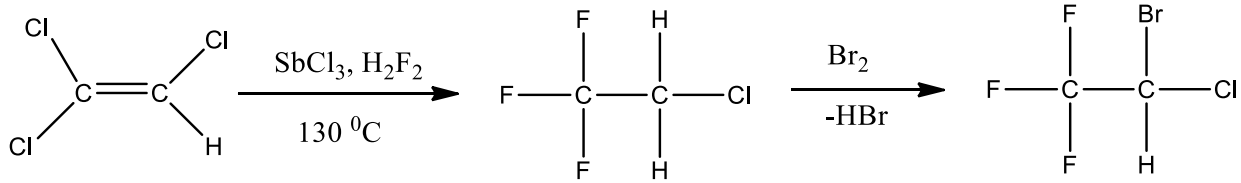
Halothane



2- bromo-2-chloro-1,1,1-trifluoro ethane

- It is used with nitrogen protoxide because the analgesic effect is not good.
- Used for many years with good effect
- First non-flamable volatile fluid anesthetic
- MAC high
- Depression of circulatory system
- May destroy liver
- Nowadays used only in pediatric anesthesia

Synthesis;



Ether and Halogenated Ethers

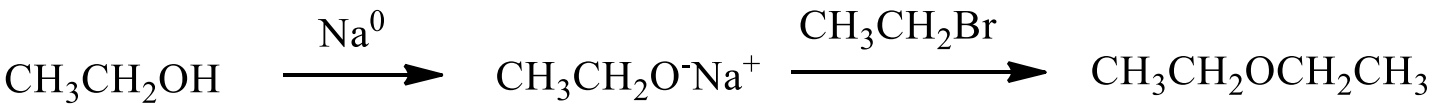
Ether (Diethylether);

$CH_3CH_2OCH_2CH_3$

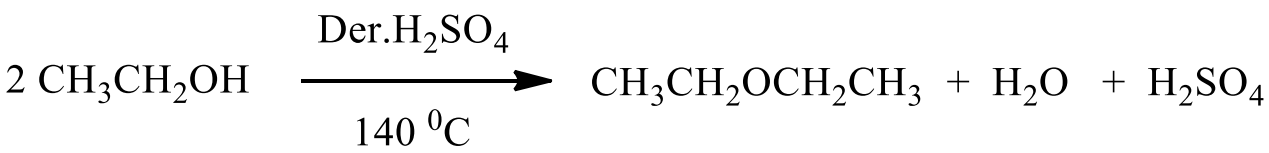
- It flames easily, the mixture with air explodes.
- Good analgesic and muscle relaxant properties.

Synthesis;

1) Williamson Synthesis :



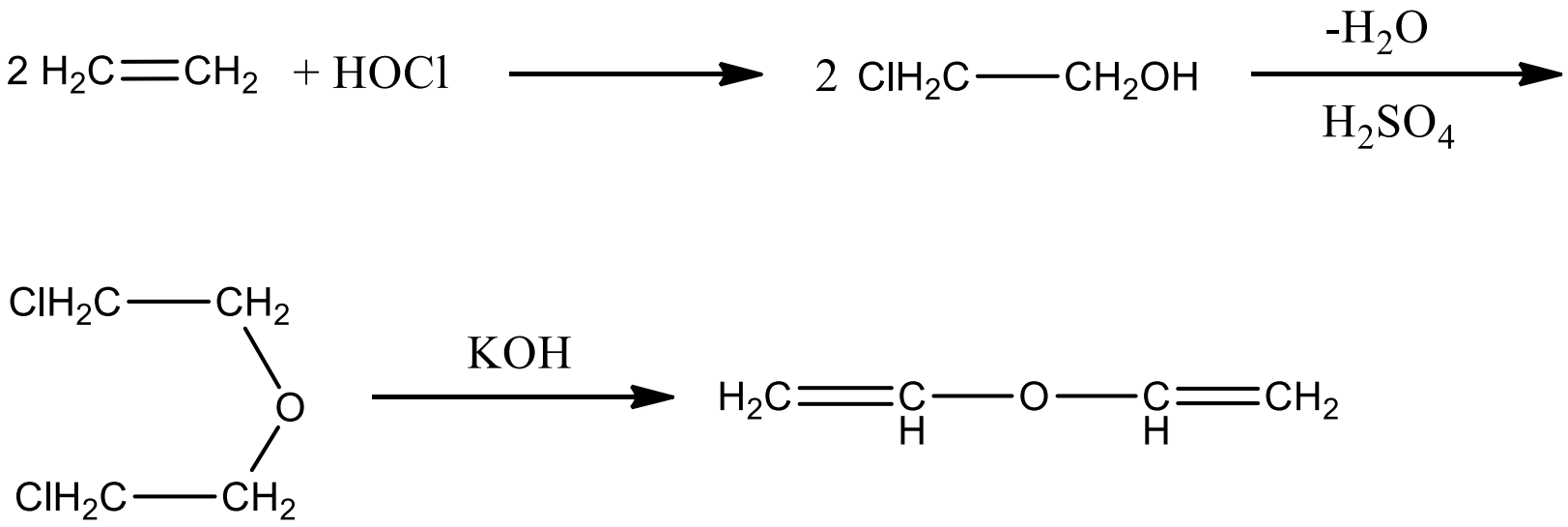
2)



Divinyl ether (Divinyl Oxide, Vinethene®)

$H_2C=CH-O-CH=CH_2$

Synthesis;

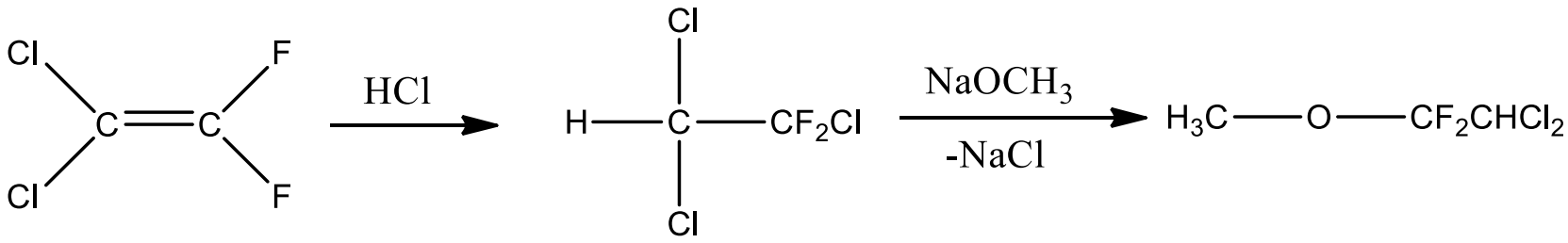


Metoxiflurane (Penthrane)

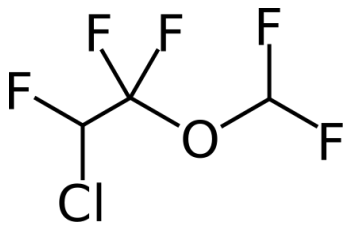
$CH_3OCF_2CHCl_2$

2,2-Dichloro-1,1-difluoroethyl methyl ether

- It's the most powerful general anesthetic.
- It is not explosive and flammable.
- Used with N2O.
- It is hepatotoxic in the liver because the metabolic end result with F-ion.

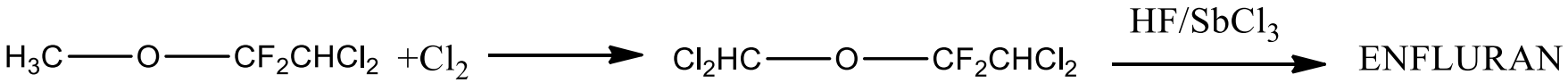


Enflurane



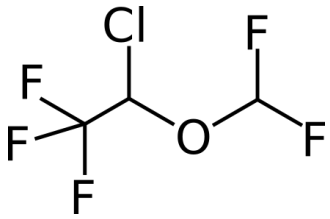
- 2-Chloro-1,1,2-trifluoroethyl difluoromethyl ether

- Rapid, smooth induction and maintenance
  - 2-10% metabolized in liver

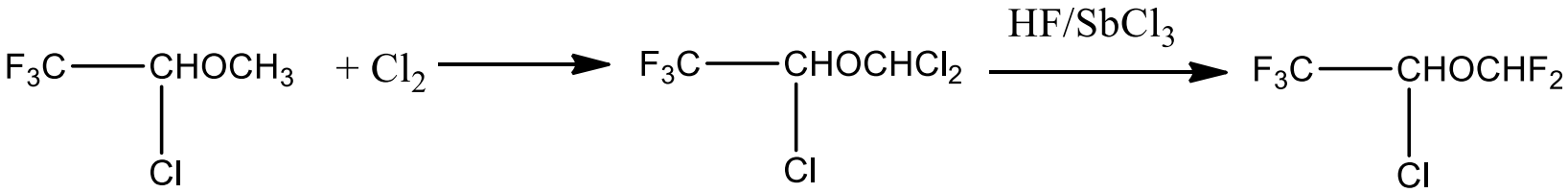


Chlorination of methoxyflurane, than reaction of 1,1,2-trifluoro-2-chloro-1-difluoromethoxyethane with antimony trichloride gives the Enflurane

Isoflurane



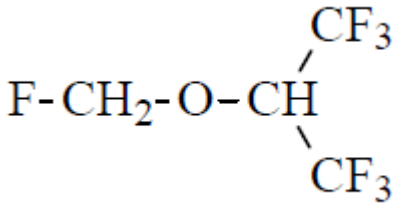
(2-chloro-2-(difluoromethoksi)-1,1,1-trifluoro-ethane)



The chlorination of 1-chloro-2,2,2-trifluoroethyl methyl ether is followed by the reaction with hydrofluoric acid in the presence of antimony trichloride.

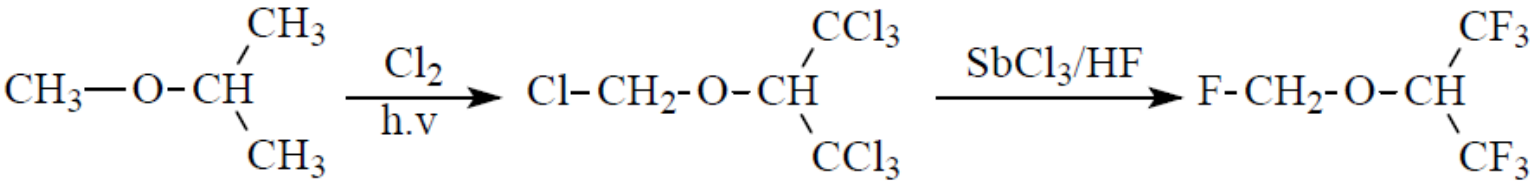
- smooth and rapid induction and recovery
- very little metabolism (0.2%)
- no reports of hepatotoxicity or renotoxicity

Sevoflurane



1- (trifluoromethyl) -2,2,2-trifluoroethyl fluoromethyl ether

- The methyl isopropyl ether is firstly chlorinated and then reacted with hydrofluoric acid in the presence of antimony trichloride.



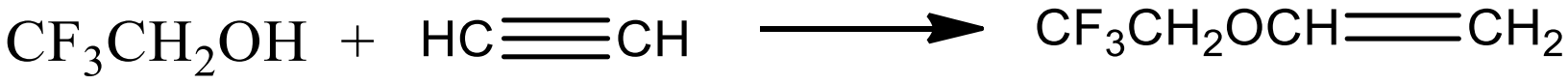
Metil izopropil eter

Fluoroxene (Fluoromar®)

$CF_3CH_2OCH=CH_2$

2,2,2-Trifluoroethyl vinyl ether

- It is synthesized from 2,2,2-trifluoroethanol and acetylene in a basic medium under pressure.



Physical and Chemical Properties of Inhaled Anesthetics

- Although halogenations of hydrocarbons and ethers increase anesthetic potency, it also increase the potential for inducing cardiac arrhythmias in the following order F<Cl<Br.
- Ethers that have an asymmetric halogenated carbon tend to be good anesthetics.
- Halogenated methyl ethyl ethers are more stable, are more potent, and have better clinical profile than halogenated diethyl ethers.
- Fluorination decrease flammability and increase stability of adjacent halogenated carbons.
- The presence of double bonds tends to increase chemical reactivity and toxicity.

Intravenous Anesthetics

- Most exert their actions by potentiating $GABA_A$ receptor

- GABAergic actions may be similar to those of volatile anesthetics, but act at different sites on receptor

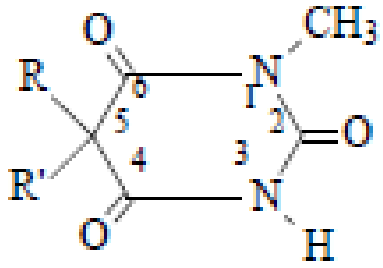
Organ Effects

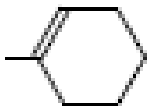
- Most decrease cerebral metabolism and intracranial pressure
- Most cause respiratory depression
- May cause apnea after induction of anesthesia

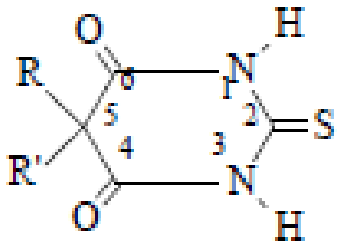
Cardiovascular Effects

- Barbiturates, benzodiazepines and propofol cause cardiovascular depression.

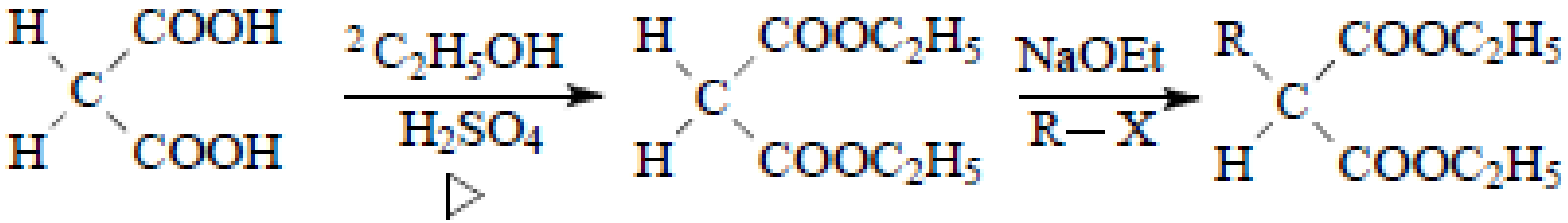
Barbiturates



	R	R^1
Metoheksital 5-Allil-5-(1-metil-2-pentinil)-1-metilbarbitürik asit	$-CH_2CH=CH_2$	$-CH(CH_3)-C\equiv C-C_2H_5$
Hekzobarbital 5-Metil-5-siklohekzenil-1-metilbarbitürik asit	$-CH_3$	

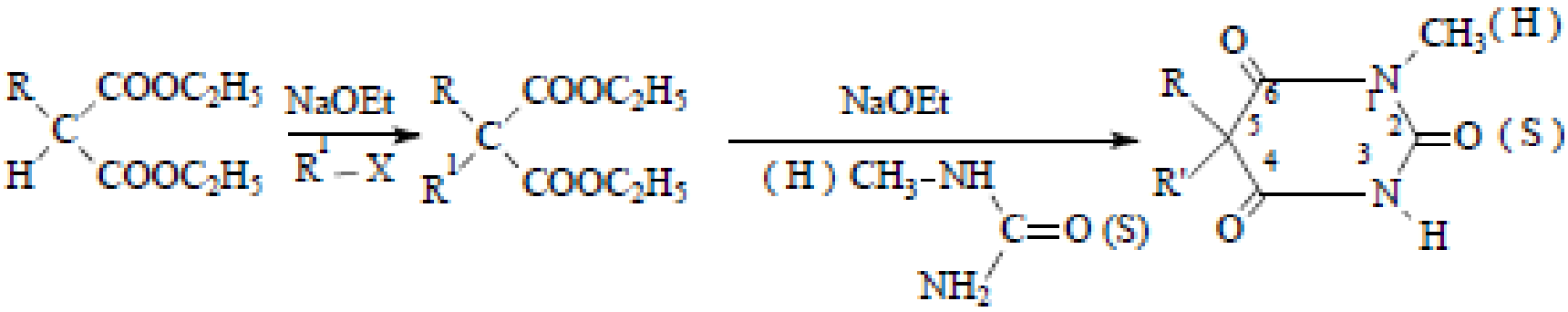


	R	R^1
Tiyopental 5-Etil-5-(1-metilbutil)- 2-tiyobarbitürik asit	$-C_2H_5$	$-CH(CH_3)-C_3H_7$
Tiyamilal 5-Allil-5-(1-metilbutil)- 2-tiyobarbitürik asit	$-CH_2-CH=CH_2$	$-CH(CH_3)-C_3H_7$



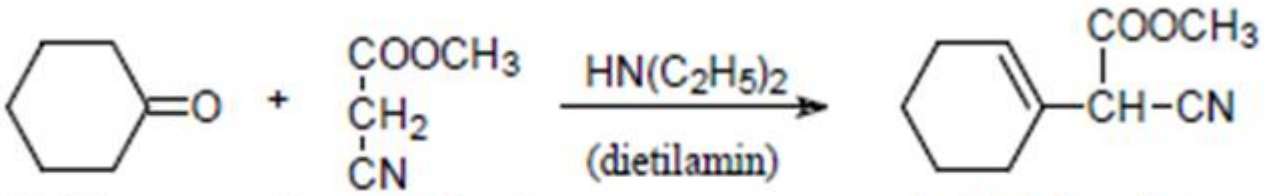
Malonik Asit

Dietilmalonat



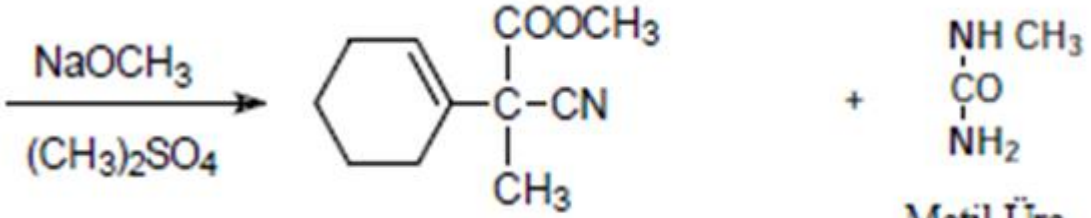
Metil Üre
veya
Tiyo Üre

Metoheksital
Tiyopental
Tiyamilal



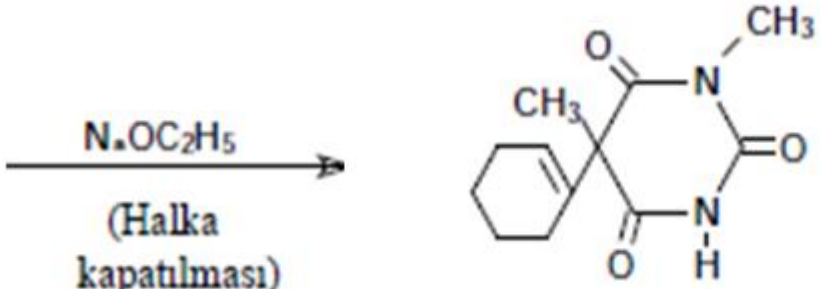
1-Siklohekzanon siyanoasetik asit metil esteri

1-siklohekzenilsiyano asetik asit metil esteri



2-siyano-2-(1-siklohekzenil) propiyonik asit metil esteri

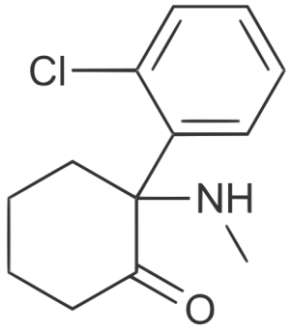
Metil Üre



Hekzobarbital

Cyclohexanones

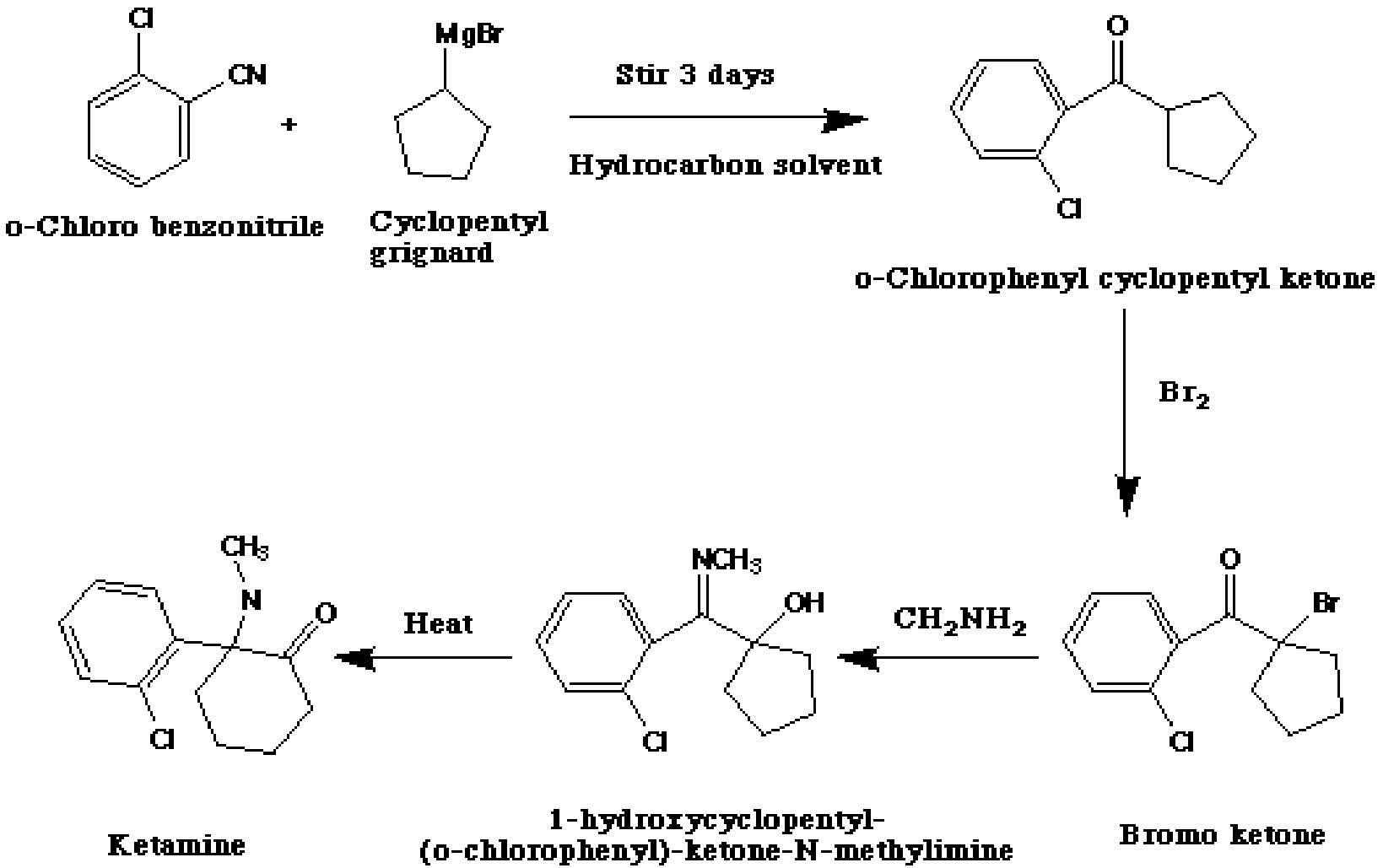
Ketamine



(*RS*)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone

- NMDA Receptor Antagonist
- usually stimulate rather than depress the circulatory system.
- It is a solid general anesthetic compound that can be administered intravenously and intramuscularly.
- strong analgesic effect
- the effect is observed 10-15 minutes after administration of the drug

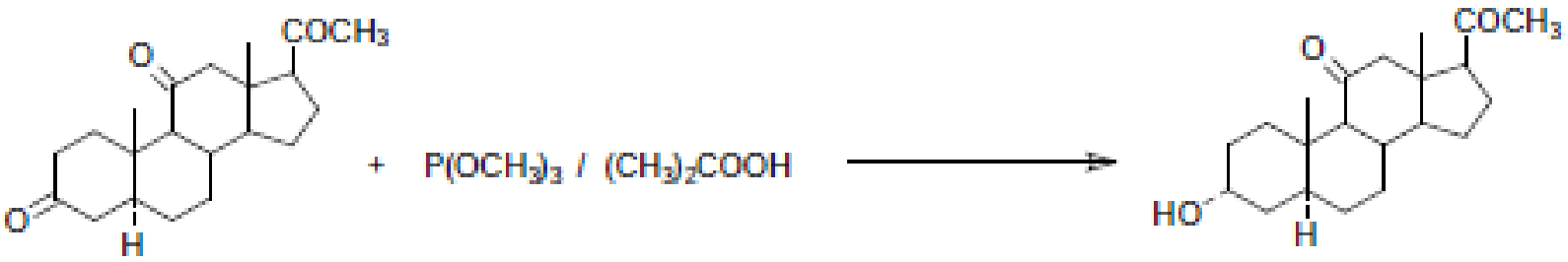
Synthesis of Ketamine



Steroids

Alphaxalone;

3 α -Hydroxy-5 α -pregnane-11,20-dione



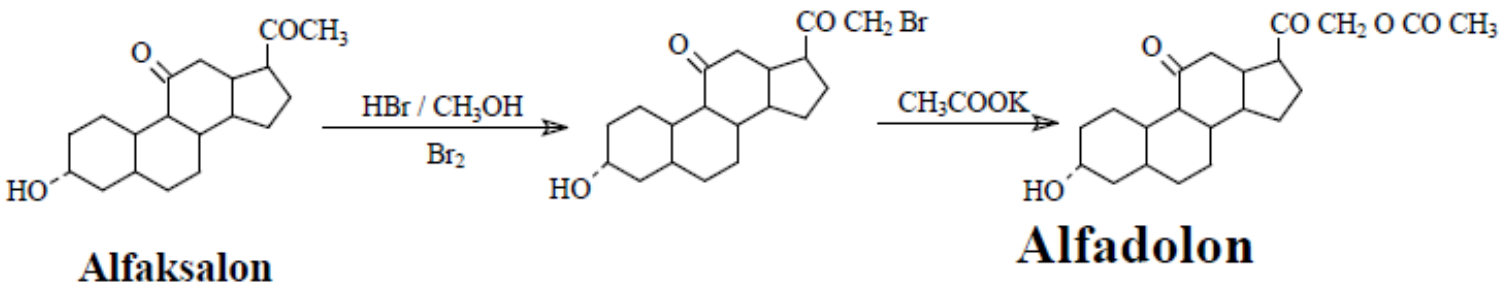
3,11,20-triokso-5α-pregnanın trimetilfosfit

Alfaksalon

Alphadolone

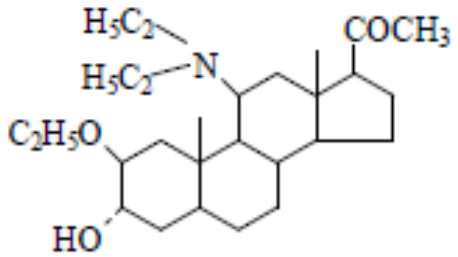
3α,21-Dyhidroxy-5 α -pregnane-11,20-dione-21-acetate

- Synthesized by the reaction of the alphaxalone with bromine followed by potassium acetate.



Alfaksalon **Alfadolon**

Minaxolone



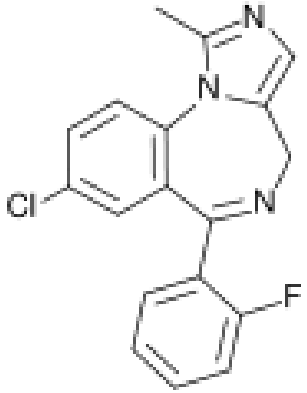
3 α -hydroxy-2-ethoxy-11-diethylaminopregnan-20-one

Benzodiazepines

- Although not known as anesthetic compounds, some benzodiazepines are used in premedication.

- Diazepam,
- flurazepam and
- Midazolam is the most commonly used compound in anesthesia.

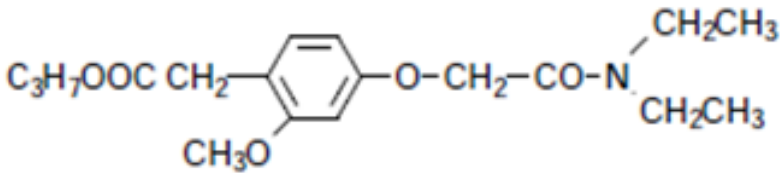
MİDAZOLAM (DORMİCUM)® :



- Benzodiazepine derivative.
- Provides rapid induction.
- No analgesic effect.
- It is used for sedation in the patient before surgery and endoscopy.

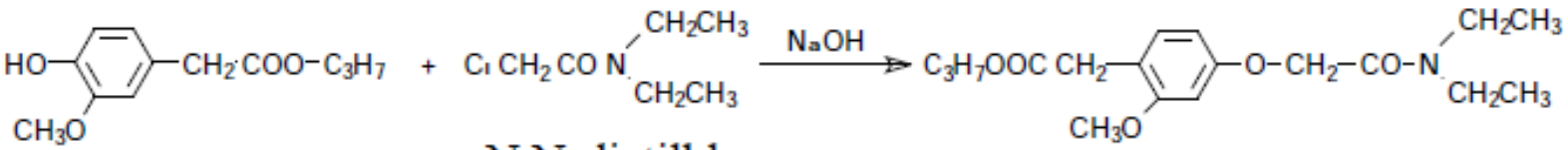
Others

- **Propanidid**



4- [2- (Diethylamino) -2-oxoethoxy] -3-methoxyphenyl acetic acid propyl ester

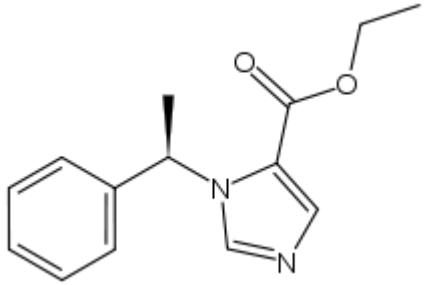
Synthesis;



4-hidroksi-3-metoksifenil asetik asit propil esteri

N,N-dietilkloro asetamit

Etomidate



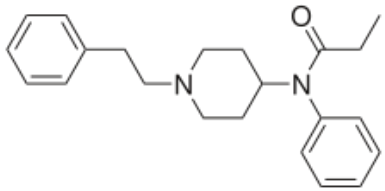
1- (1-Phenylethyl) -1H-imidazole-5-carboxylic acid ethyl ester

- Marketed as Amidate
- A short-acting intravenous anaesthetic agent used for the induction of general anaesthesia and sedation.
- The effect starts quickly and ends quickly.
- No analgesic effect.
- It is used in combination with fentanyl or similar drugs because it causes involuntary contractions.

SHORT-ACTING OPIOIDS

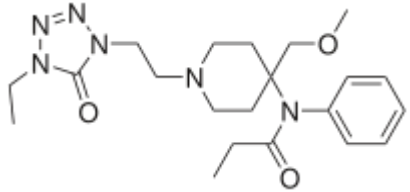
- They are generally used for induction.
- They can be used for preanesthetic medication or for the management of surgical anesthesia.

Fentanyl;



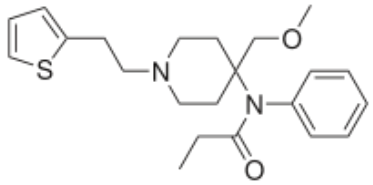
N-(1-(2-phenylethyl)-4-piperidinyl)-*N*-phenylpropanamide

Alfentanyl ;



N-{1-[2-(4-ethyl-5-oxo-4,5-dihydro-1*H*-1,2,3,4-tetrazol-1-yl)ethyl]-4-(methoxymethyl)piperidin-4-yl}-*N*-phenylpropanamide

Sufentanyl;



N-[4-(methoxymethyl)-1-(2-thiophen-2-ylethyl)-4-piperidyl]-*N*-phenylpropanamide

General anesthesia

- Induction
- Maintenance

Maintenance

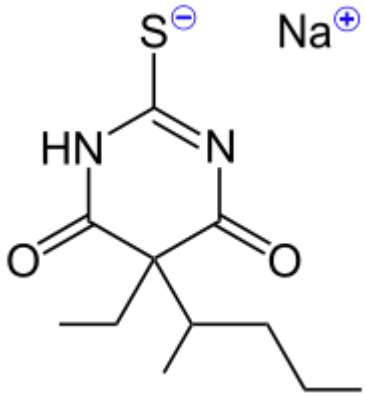
- In order to prolong anaesthesia for the required duration
- breathe to a carefully controlled mixture of oxygen, nitrous oxide, and a volatile anaesthetic agent
- transferred to the patient's brain via the lungs and the bloodstream, and the patient remains unconscious
- Inhaled agents are supplemented by intravenous anaesthetics, such as opioids (usually fentanyl or morphine)

Intravenous Induction Agents

- Used in combination with Inhaled anesthetics to:
  - Supplement general anesthesia
  - Maintain general anesthesia
  - Provide sedation
  - Control blood pressure
  - Protect the brain

- Propofol
- Thiopental sodium

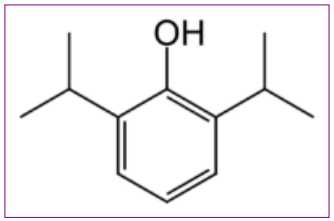
Thiopental sodium



RS)-[5-ethyl-4,6-dioxo-5-(pentane-2-yl)-1,4,5,6-tetrahydropirimidine-2-yl]sulfanid sodyum

- rapid onset (20 sec)
- short-acting
- oil:water ratio is so high /reaches the brain so quickly
- It is used with nitrogen protoxide because the analgesic effect is not good.

Propofol



2,6-bis(propan-2-yl)phenol

- Short-acting agent used for the induction
- maintenance of GA and sedation
- Onset within one minute of injection

Mechanism of Propofol

- Action of anesthetics on the $GABA_A$ receptor
  - Binding of anesthetics to specific sites on the receptor protein
- Parenteral anesthetic
  - Small, hydrophobic, substituted aromatic or heterocyclic compound
- Propofol partitions into lipophilic tissues of the brain and spinal cord
  - Produces anesthesia within a single circulation time

Metabolism and Toxicity

- Propofol is extensively metabolized
  - 88% of an administered dose appearing in the urine
- Eliminated by the hepatic conjugation of the inactive glucuronide metabolites which are excreted by the kidney