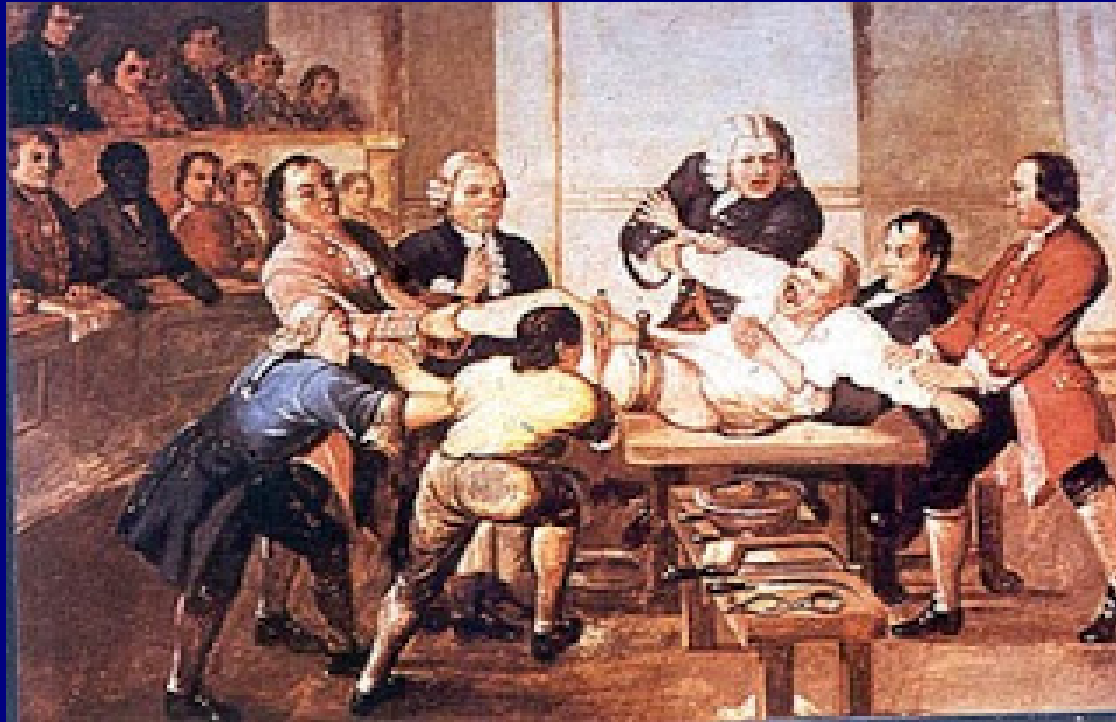


# NERVOUS SYSTEM DRUGS

## Surgery Before Anesthesia



NEPHAR 305

Pharmaceutical Chemistry I

# The Nervous System

- ✓ The nervous system helps all the parts of the body to communicate with each other. It also reacts to changes both outside and inside the body.
- ✓ Problems of the nervous system include epilepsy, meningitis, multiple sclerosis (MS) and Parkinson's disease.

## Central nervous system

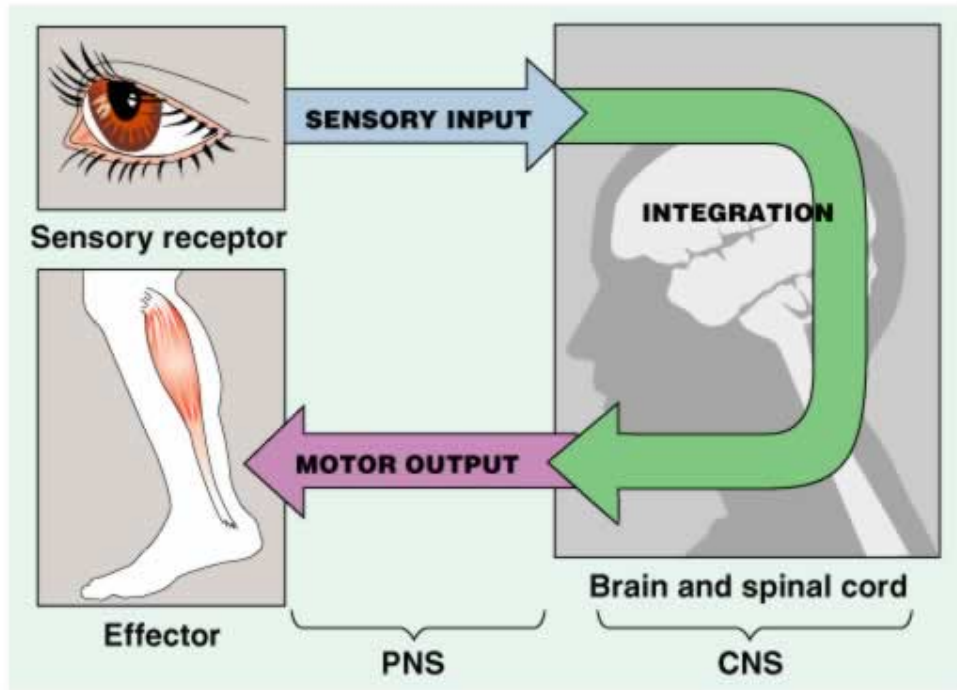
The brain and the spinal cord make up the central nervous system.

**The peripheral nervous system** - It is made up of two main parts

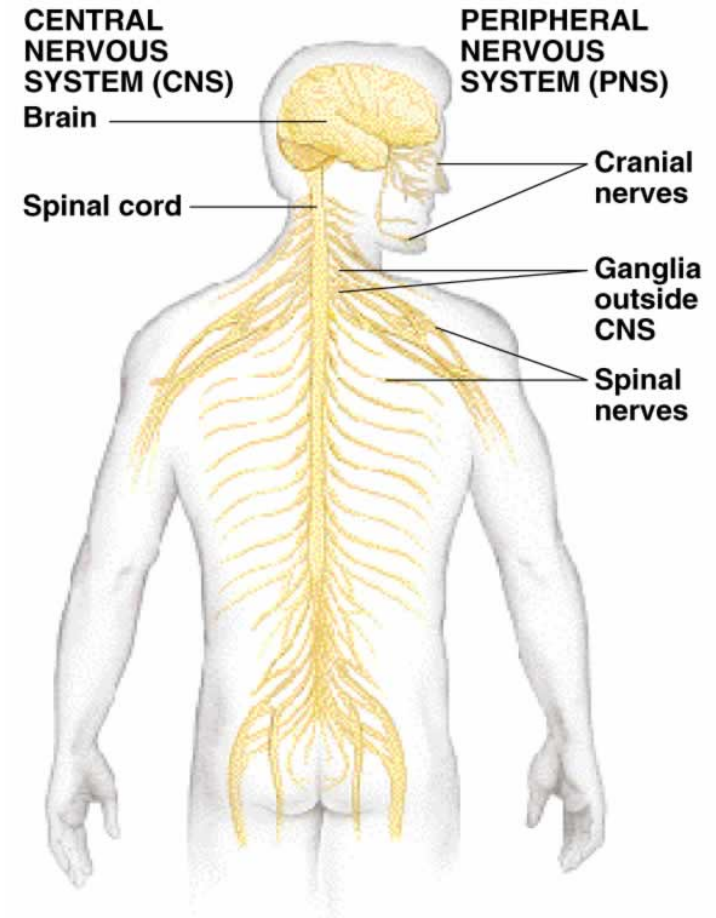
**the autonomic:** one of its main roles is to regulate glands and organs without any effort from our conscious minds

**somatic nervous systems:** One of its roles is to relay information from the eyes, ears, skin and muscle to the central nervous system (brain and spinal cord).

# Central nervous system & peripheral nervous system



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# Classification of The Nervous System Drugs

- ✓ **Hallucinogens**
- ✓ **General anesthetics**
- ✓ **Local anesthetics**
- ✓ **Sedative-Hypnotics**
- ✓ **Tranquilizers**
- ✓ **Antidepressants**
- ✓ **Antiepileptics**
- ✓ **Antipsychotics**
- ✓ **Antiepileptics**
- ✓ **Analeptics**
- ✓ **Analgesics**
- ✓ **Muscle relaxants**
- ✓ **Antitussives**
- ✓ **Expectorants**
- ✓ **Mucolytic**
- ✓ **Cholinergic**
- ✓ **Antiparkinson**
- ✓ **Alzheimer**

# General Anesthetics

- ✓ General anesthesia is the induction of a state of unconsciousness with the absence of pain sensation over the entire body, through the administration of anesthetic drugs medications.
- ✓ General anesthetic drugs cause **amnesia, analgesia, muscle paralysis, and sedation.**
- ✓ It results in a controlled, reversible state of unconsciousness.
- ✓ It is used during certain medical and surgical procedures.

## Mechanism of Action of General Anesthetics

- ✓ Exact mechanism is **still not understood** since the drug apparently does not bind to any receptor on the cell surface and does not seem to affect the release of chemicals that transmit nerve impulses (neurotransmitters) from the nerve cells.
- ✓ Possibly, general anesthesia works by altering the flow of sodium molecules into nerve cells (neurons) through the cell membrane.
- ✓ It is known, that when the sodium molecules do not get into the neurons, nerve impulses are not generated and the brain becomes unconscious, does not store memories, does not register pain impulses from other areas of the body, and does not control involuntary reflexes.

✓ Molecular structures of general anesthetics widely used in medicine are very simple and diverse so that there is **no obvious structure–activity relationship**

**Some examples of structures of general anesthetics widely used in medicine:**

**Ethanol,  $\text{CH}_3\text{CH}_2\text{OH}$**

**Chloroform,  $\text{CHCl}_3$**

**Diethyl ether,  $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$**

**Fluroxene,  $\text{CF}_3\text{CH}_2\text{OC}=\text{CH}_2$**

**Halothane,  $\text{CF}_3\text{CHClBr}$**

**Methoxyflurane,  $\text{CHCl}_2\text{CF}_2\text{OCH}_3$**

**Enflurane,  $\text{CFHClCF}_2\text{OCF}_2\text{H}$**

**Sevoflurane,  $\text{CF}_3\text{CH}(\text{CF}_3)\text{OCH}_2\text{F}$**

# Classification of General Anesthetic Drugs

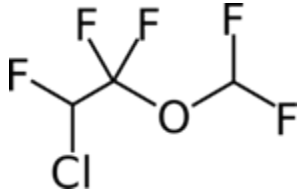
1. INHALATION agents
2. INTRAVENOUS (injection) agents

## 1. Inhalation anesthetic agents

- ✓ **Inhalation anesthetic agents** are very diverse drugs: ether, nitrous oxide, halogenated hydrocarbons.
- ✓ Most are liquids @ room temperature in closed containers, but easily volatilize when open to the atmosphere.
- ✓ Exceptions are nitrous oxide is a gas, and desflurane (lowest volatility).
- ✓ All are non-explosive, do not support combustion(except nitrous oxide) and are non-irritating when inhaled (except desflurane).

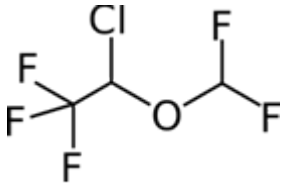


# Examples of Inhalation Anesthetics



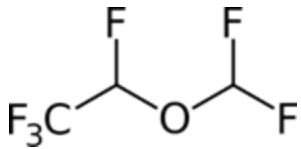
**Enflurane**, (Enthane®)

2-chloro-1,1,2-trifluoroethyl-difluoromethyl ether



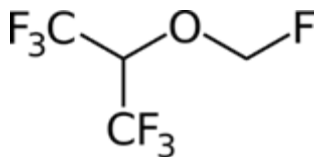
**Isoflurane** (Forane®)

(1-chloro-2,2,2-trifluoroethyl difluoromethyl ether)



**Desflurane** (Suprane®)

(1,2,2,2-tetrafluoroethyl difluoromethyl ether)



**Sevoflurane** (Ultane®)

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

**Halothane** (Fluothane®)  $\text{CF}_3\text{-CHClBr}$

**Nitrous oxide**,  $\text{N}_2\text{O}$

**Chloroform**,  $\text{CHCl}_3$

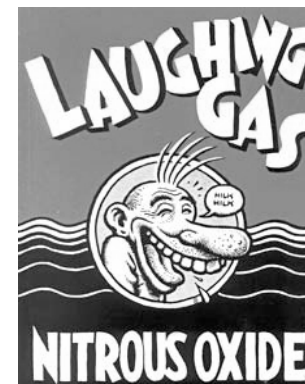
**Diethyl ether**,  $\text{CH}_3\text{CH}_2\text{-O-CH}_2\text{CH}_3$

# Inhalation Anesthetics

## Nitrous oxide (N<sub>2</sub>O)

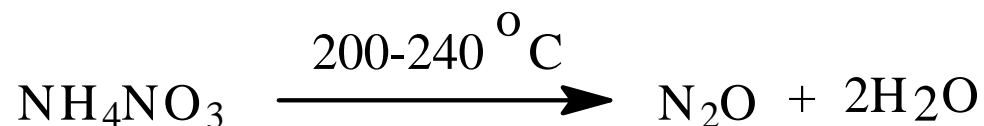
- Low potency (must be combined with other agents)
- Rapid induction and recovery
- Good analgesic properties

It has no color, smell, and doesn't irritate



**Structure:** N=N=O, N≡N-O

**Synthesis:** Ammonium nitrate heated to high temperatures gives N<sub>2</sub>O.



# Inhalation Anesthetics

- **Ether** ( $\text{CH}_3\text{CH}_2\text{-O-CH}_2\text{CH}_3$ )
  - Obsolete (except in underdeveloped regions)
  - Slow onset and recovery
  - Post-operative nausea, vomiting
  - Highly explosive

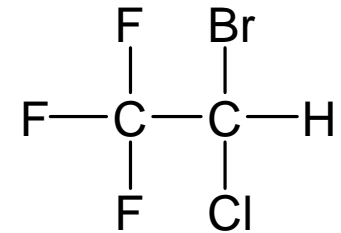


**Synthesis:** Substitution reaction of ethanol under acidic conditions gives diethyl ether. For purification, the ether is then dried over anhydrous calcium chloride for 24 hours and distilled on a water bath, collecting the fraction boiling



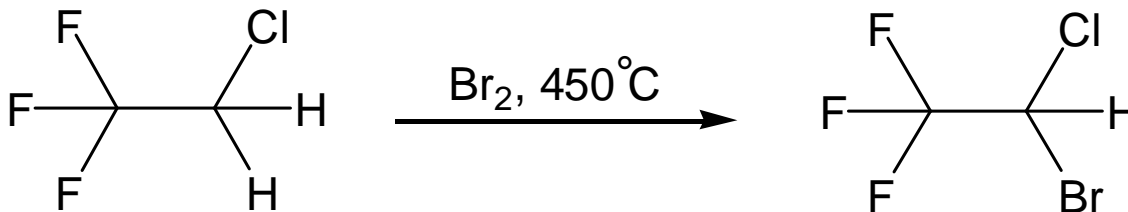
# Inhalation Anesthetics - Halothane

**Halothane** (Fluothane) 2-Bromo-2-chloro-1,1,1-trifluoroethane



- Widely used agent
- Potent, non-explosive and non-irritant
- It is colorless and pleasant-smelling, but unstable in light
- 30% metabolized in liver => repeated use can cause liver damage
- No analgesic properties

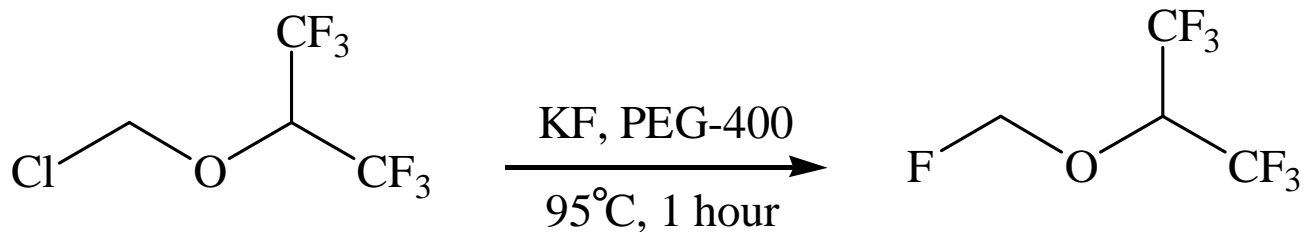
**Synthesis:** 2-chloro-1,1,1-trifluoroethane is reacted with bromine at 450 °C to produce halothane



## Inhalation Anesthetics - Sevoflurane

- ✓ **Sevoflurane** also called **fluoromethyl hexafluoroisopropyl ether**, is a sweet-smelling, nonflammable, highly fluorinated methyl isopropyl ether used for induction and maintenance of general anesthesia

**Synthesis:** Nucleophilic fluorination of  $\alpha$ -chloro ethers with metal fluorides has traditionally been the method mostly used to obtain simple  $\alpha$ -fluoro ethers.



**Sevoflurane**

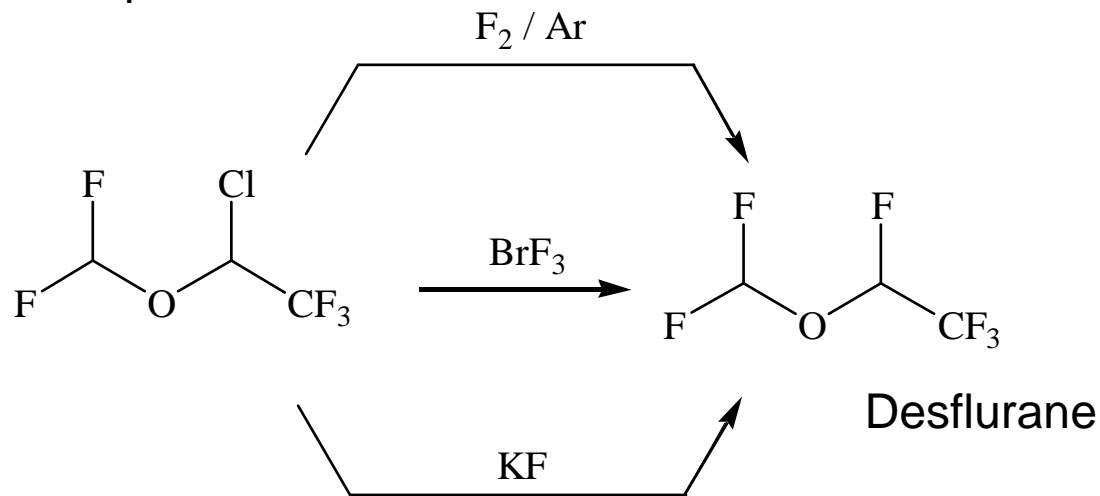
1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane

# Inhalation Anesthetics - Desflurane

- Though desflurane vaporises very readily, it is a liquid at room temperature.
- Like halothane, enflurane and isoflurane, it is a racemic mixture of (*R*) and (*S*) optical isomers
- It has the most rapid onset and offset of the volatile anesthetic drugs used for general anesthesia due to its low solubility in blood.

**Synthesis:** The final product can be obtained by fluorination of isoflurane [2-(difluoromethoxy)-2-chloro-1,1,1-trifluorethane] (II) in three different ways:

- 1) With fluorine in argon at  $-10\text{ }^{\circ}\text{C}$ .
- 2) With KF in diethyl glycol at  $195\text{ }^{\circ}\text{C}$ .
- 3) With  $\text{BrF}_3$  at room temperature.



## 2. INTRAVENOUS ANESTHETIC AGENTS

**Intravenous anesthetic agents** are medication that produces anesthesia when injected into the circulatory system

Advantages of IV anesthesia include rapid and smooth induction of anesthesia, little equipment requirement and easy administration of drugs compared to most of the inhalational agents

### **Physicochemical properties of ideal IV anesthetic agent**

- Water soluble
- Stable formulation, nonpyrogenic
- Non irritating, painless on IV injection
- Small volume needed for induction
- Inexpensive to prepare and formulate

# Classification of intravenous anesthetics

## Classification of intravenous anesthetics

### Rapidly acting (primary induction) agents

#### Barbiturates:

Methohexital

Thiobarbiturates – thiopental, thiamylal

Imidazole compounds - etomidate

Sterically hindered alkyl phenols - propofol

Steroids – etanolone, althesin (none currently available)

### Slower acting (basal narcotic) agents

Ketamine

Benzodiazepines – diazepam, flunitrazepam, midazolam

Large-dose opioids – fentanyl, alfentanil, sufentanil, remifentanil

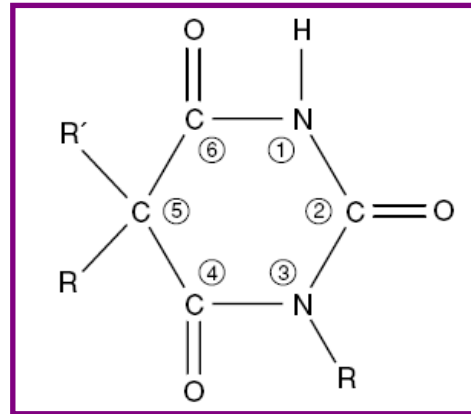
Neuroleptic combination – opioid + neuroleptic



# Intravenous Anesthetic Agents - Barbiturates

Barbiturates are a class of drugs that act on the GABAA receptor in the brain and spinal cord. The GABAA receptor is an inhibitory channel that decreases neuronal activity, and barbiturates enhance the inhibitory action of the GABAA receptor.

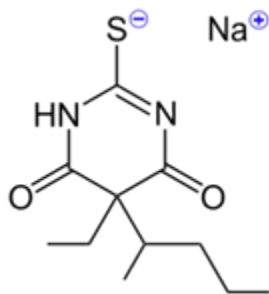
## Structure of a Barbiturate Ring



## Structure Activity Relationship of Barbiturates (Thiobarbiturates)

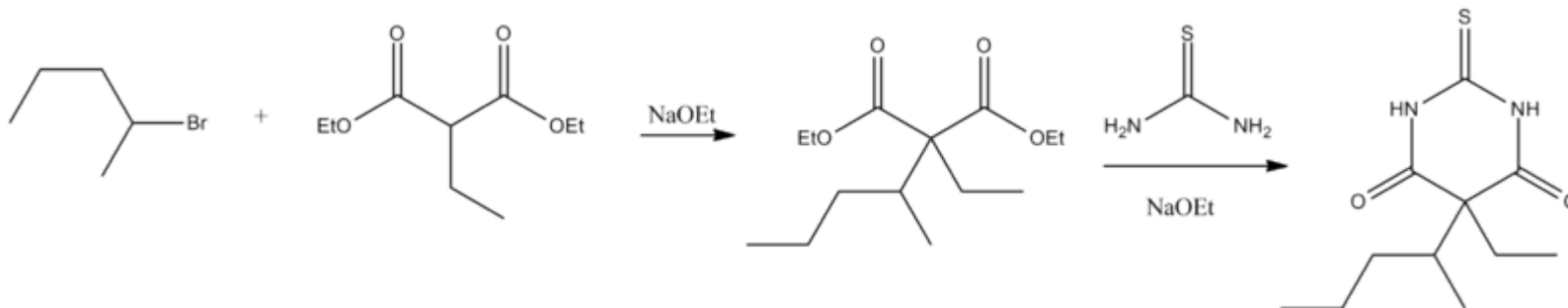
- ❑ Barbiturates are weak acids that are poorly soluble in water at neutral pH.
- ❑ The mostly used thiopental, thiamylal and methohexital are formulated as racemic mixtures of their water soluble sodium salts.
- ❑ The substitution of sulfur for oxygen at C2 increases lipophilicity, which results in increased potency, more rapid onset and shorter duration of action
- ❑ Alkylation of N1 also increases lipophilicity and speeds onset

**Sodium thiopental**, also known as **thiopental** is an ultra-short-acting barbiturate and has been used commonly in the induction phase of **general anesthesia**

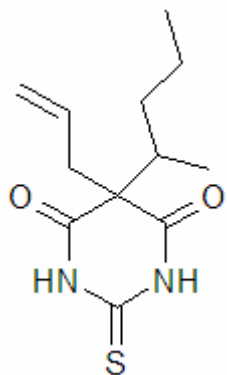


sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate.

**Synthesis :** Thiopental, 5-ethyl-5-(1-methylbutyl)2-thiobarbituric acid, is synthesized by the alkylation of ethylmalonic ester with 2-bromopentane in the presence of sodium ethoxide. The product ethyl-(1-methylbutyl)malonic ester undergoes heterocyclization with thiourea, using sodium ethoxide as a base. Changes into soluble form when treated with bases.

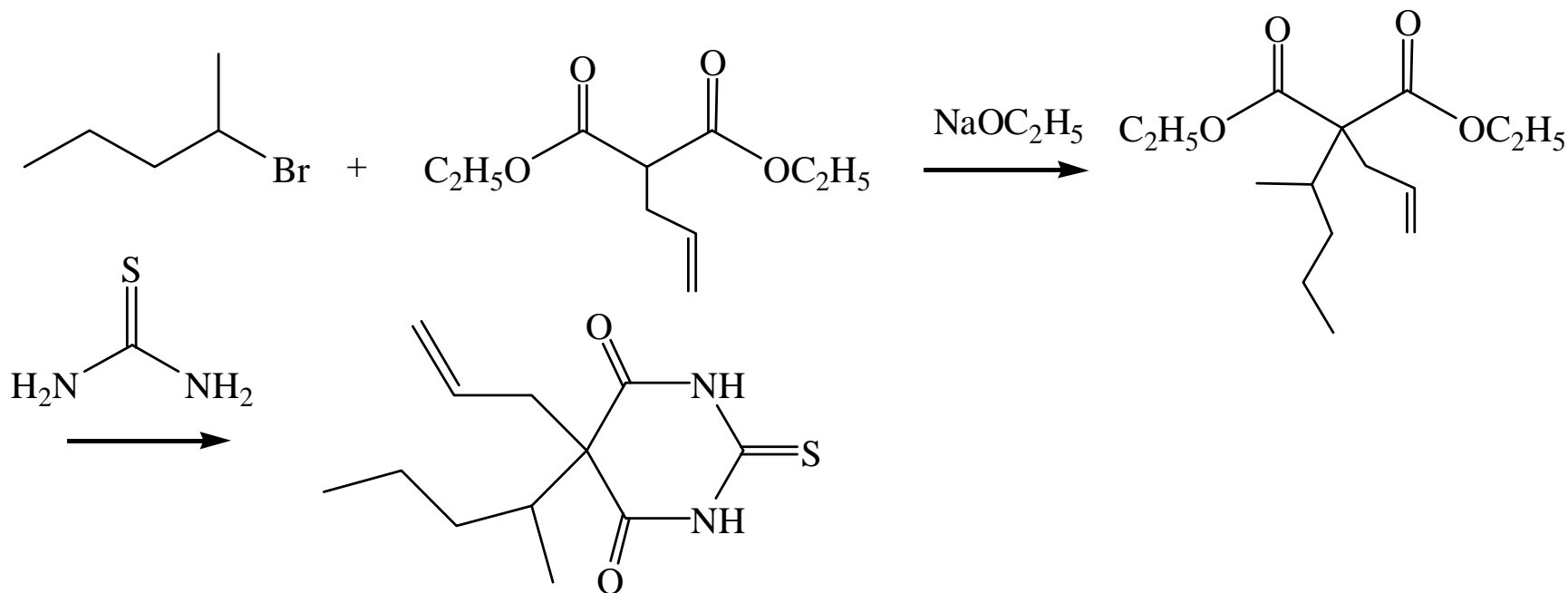


**Thiamylal (Surital)** is a barbiturate derivative and is used as a strong but short acting sedative



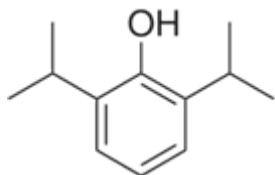
5-Allyl-5-(1-methylbutyl)-2-thiobarbituric acid

**Synthesis :** Classical synthesis of barbiturates is used.  $\alpha$ -Allyl- $\alpha$ -(1-methylbutyl) malonic acid diethyl ester and thiourea reaction gives **Thiamylal**.



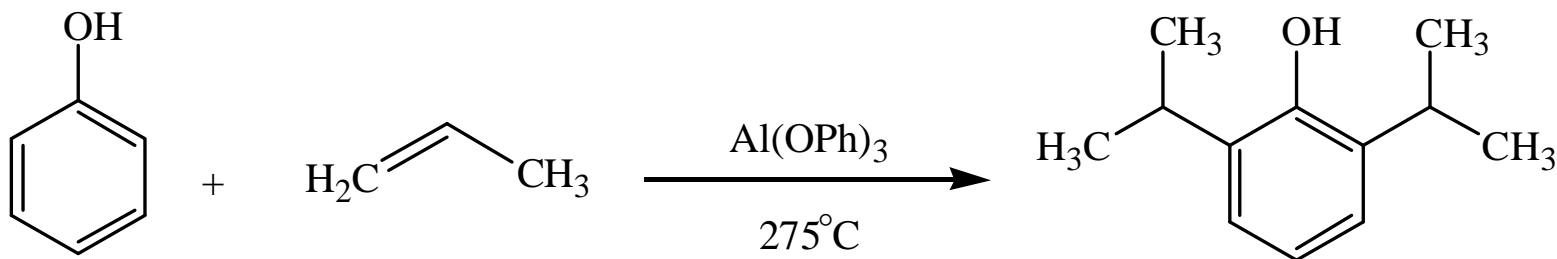
# Intravenous Anesthetic Agents - Propofol

**Propofol** (Diprivan) is a short-acting, intravenous anesthetic. Propofol is extremely lipid-soluble, but almost insoluble in water.



2,6-Bis(1-methylethyl)phenol

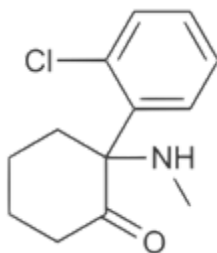
**Synthesis :** By condensation of phenol (I) with propylene (II) at temperatures ranging from 230°C to 275°C and pressures up to 3000 atm. in an autoclave, using aluminum phenoxide as catalyst.



# Intravenous Anesthetic Agents - Ketamine

**Ketamine** is a drug used in human and veterinary medicine, for the induction and maintenance of general anesthesia.

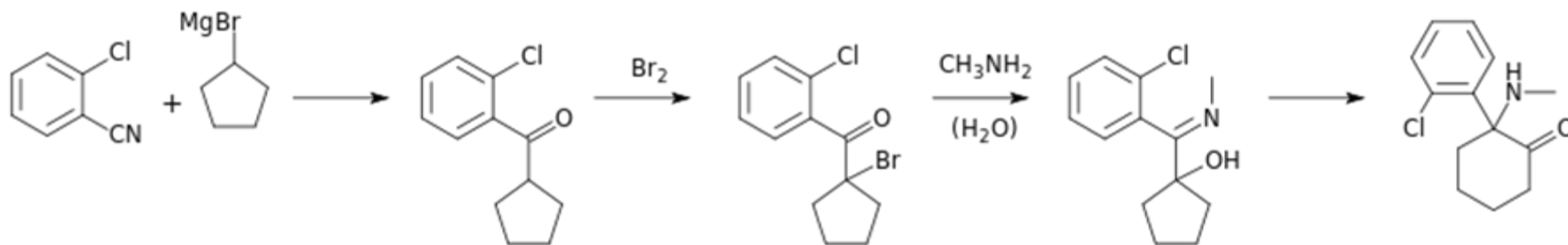
- It is soluble in water.



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

## Synthesis :

- 2-chlorobenzonitrile reacts with the Grignard reagent cyclopentylmagnesium bromide to give 1-(2-chlorobenzoyl)cyclopentane.
- The next step is bromination forming bromoketone, which upon reaction with an aqueous solution of methylamine forms the methylimino derivative.
- During this reaction, a simultaneous hydrolysis of the tertiary bromine atom occurs.
- On heating the reaction product in decalin, a ring-expansion rearrangement occurs, forming ketamine



## Müstahzarlar:

**Enfluran:** Ethrane volatil ( Abbott )

**Halotan:** Fluothane (Zeneca), Halotan (Sanofi-Doğu), Halothan (Hoechst Marion Roussel)

**İzofluran:** Forane (Abbott)

**Ketamin:** Ketalar (E.Warner Lambert )

**Kloroform:** Kamfoform ( Sano)

**Midazolam:** Dormicum (Roche )

**Propanidid:** Epontol (Bayer )

**Sevofluran:** Sevorane (Abbott)

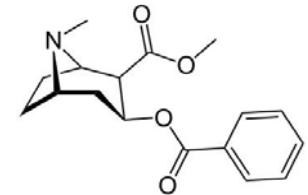
**Tiyopental sodyum:** Pental sodyum ( İ.E.Ulagay ),  
Pentothal sodyum (Abbott )

# Local Anesthetic Agents

✓ Local anesthesia is drug-induced reversible local blockade of pain sensation in a specific part of the body that does not alter consciousness or block sensation in other parts.

✓ First local anesthetic is **Cocaine**: isolated from coca leaves in 1859 by Niemann

✓ First analog of cocaine synthesized for use as a local anesthetic is procaine (1905)



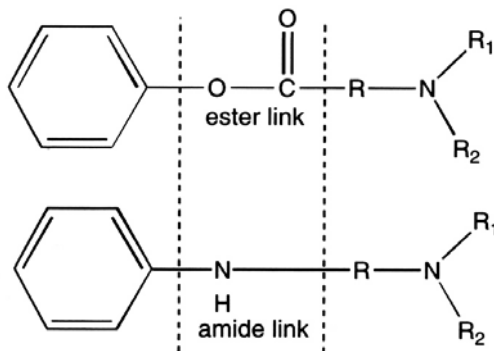
## General Properties of Local Anesthetic Agents:

- Are lipophilic, weak bases ( $pK_a=8-9$ ) => mainly ionized at physiological pH
- Poorly soluble in water
- Act in their ionized form, but penetrate the cell membrane in the non-ionized form

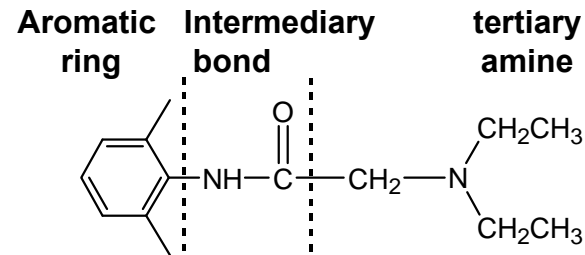
• **Mechanism of action:** inactivates Na channels thus reversibly inhibiting  $Na^+$ -influx

# Chemical Structure of Local Anesthetics

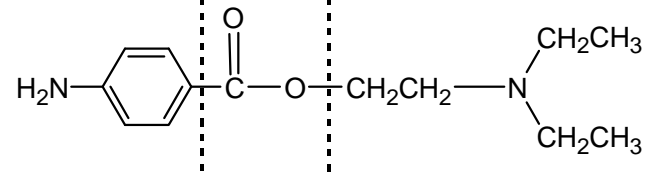
- Aromatic part linked by ester or amide bond to basic side chain:



**Lidocaine**



**Procaine**



## Esters:

- Inactivated quickly by non-specific esterases in the plasma and tissue

## Amides:

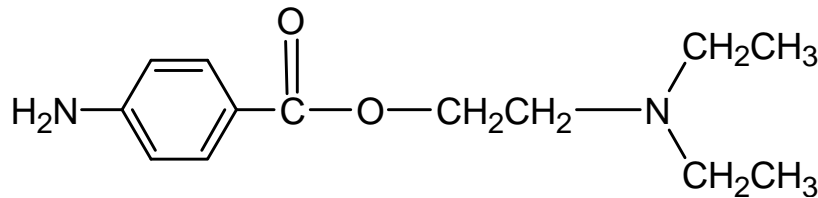
- More stable, longer plasma half-lives



# Chemical Structure of Local Anesthetic

- Local anesthetics (LAs) consist of a lipophilic and a hydrophilic portion separated by a connecting hydrocarbon chain
- An **ester** (-CO-) or an **amide** (-NHC-) bond links the hydrocarbon chain to the lipophilic aromatic ring.
- The **hydrophilic group** is usually a **tertiary amine** (can also be a **secondary amine**), whereas the **lipophilic** portion is usually an **aromatic ring**.
- the nature of this bond determines many of the properties of the agent; the **ester** linkage is hydrolysed easier than amides during metabolism

eg., **procaine** can be divided into **three main portions**,



- a. the aromatic acid - para-aminobenzoic acid
- b. the alcohol - ethanol
- c. the tertiary amide - diethyl amine

# Examples of Local Anesthetics

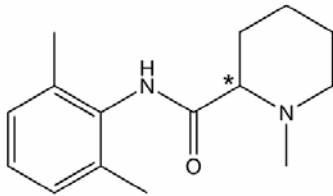
- ❑ Esters include cocaine, procaine, 2-chloroprocaine, tetracaine and benzocaine.
- ❑ Amides include lidocaine, bupivacaine, levobupivacaine, mepivacaine, etidocaine, prilocaine, ropivacaine and articaine.
- ❑ Stereo-isomerism is found in bupivacaine, prilocaine, ropivacaine, etidocaine and mepivacaine.
- ❑ Most are marketed as racemic mixtures with the exception of levobupivacaine (S-bupivacaine) and ropivacaine (S-ropivacaine).

# Examples of Local Anesthetic Agents

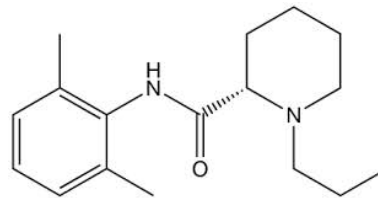
<p><b>BUPIVACAINE</b></p> <p><chem>CC1=CC=C(C=C1)C(=O)N(C2=CC=C(C=C2)C)C3CCCCC3NCCCC</chem></p>	<p><b>ETIDOCAINE</b></p> <p><chem>CC1=CC=C(C=C1)C(=O)N(C2=CC=C(C=C2)C)CC(C)N(CC)CC</chem></p>
<p><b>LIDOCAINE</b></p> <p><chem>CC1=CC=C(C=C1)C(=O)N(C2=CC=C(C=C2)C)CCN(CC)CC</chem></p>	<p><b>MEPIVACAINE</b></p> <p><chem>CC1=CC=C(C=C1)C(=O)N(C2=CC=C(C=C2)C)C3CCCCC3N</chem></p>
<p><b>ROPIVACAINE</b></p> <p><chem>CC1=CC=C(C=C1)C(=O)N(C2=CC=C(C=C2)C)C3CCCCC3NCCC</chem></p>	<p><b>2-CHLOROPROCAINE</b></p> <p><chem>CC1=CC=C(C=C1)C(=O)N(C2=CC=C(C=C2)N)C3CCCCC3N(CC)CC</chem></p>
<p><b>PRILOCAINE</b></p> <p><chem>CC1=CC=C(C=C1)C(=O)N(C2=CC=C(C=C2)C)CC(C)N(C)CC</chem></p>	<p><b>PROCAINE</b></p> <p><chem>CC1=CC=C(C=C1)C(=O)N(C2=CC=C(C=C2)N)C3CCCCC3N(CC)CC</chem></p>
<p><b>ARTICAINE</b></p> <p><chem>CC1=CC=C(C=C1)C(=O)N(C2=CC=C(C=C2)C)CC(C)N(C)CC</chem></p>	<p><b>TETRACAINE</b></p> <p><chem>CC1=CC=C(C=C1)C(=O)N(C2=CC=C(C=C2)N)C3CCCCC3N(C)CC</chem></p>

# Structure Activity Relationships of Local Anesthetic

- ❑ changes to any part of the molecule lead to changes in activity & toxicity
- ❑ increases in the length of the intermediate alcohol group, up to 2-3 carbon atom chain result in greater anesthetic potency beyond this critical length, increased toxicity results
- ❑ compounds with an ethyl ester, such as procaine, exhibit the least toxicity
- ❑ the length of the two terminal groups on the tertiary amino-N group are similarly important
- ❑ the addition of a butyl group to mepivacaine results in bupivacaine, which differs by,
  - increased lipid solubility & protein binding
  - greater potency
  - a longer duration of action



mepivacaine

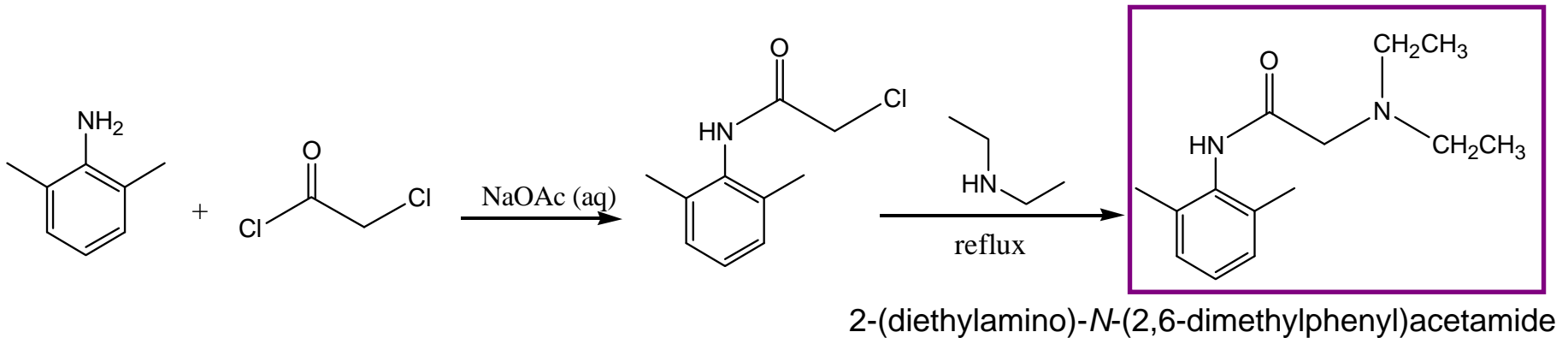


bupivacaine

# Local Anesthetic Agents - Lidocaine

- ✓ One of the most widely used local anesthetics across the world

**Synthesis:** Lidocaine may be prepared in two steps by the reaction of 2,6-xylidine with chloroacetyl chloride, followed by the reaction with diethylamine

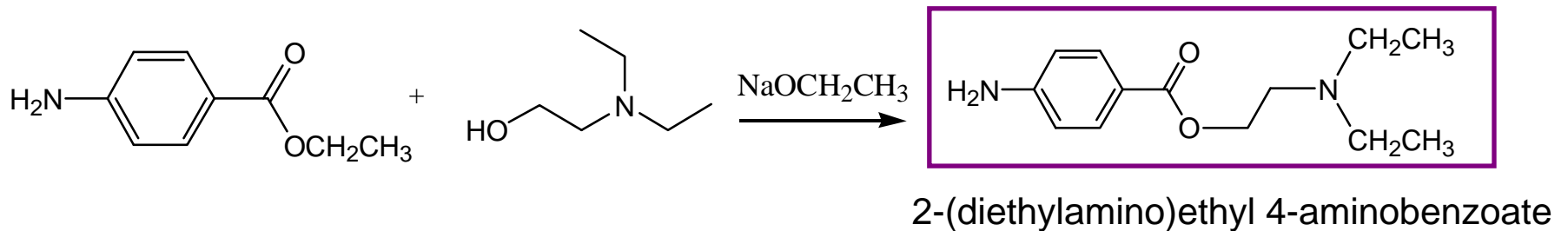


# Local Anesthetic Agents - Procaine

✓ Procaine is a weak agent with a relatively slow onset and short duration of action.

**Synthesis:** Procaine, is synthesized in two ways.

**1:** The first way consists of the direct reaction of the 4-aminobenzoic acid ethyl ester with 2-diethylaminoethanol in the presence of sodium ethoxide.



## Local Anesthetic Agents - Procaine

**2:** The **second way** is by reacting 4-nitrobenzoic acid with thionyl chloride, the resulting acid chloride is then esterified with 2-diethylaminoethanol. Finally, the nitro group is reduced by hydrogenation over Raney nickel catalyst.

