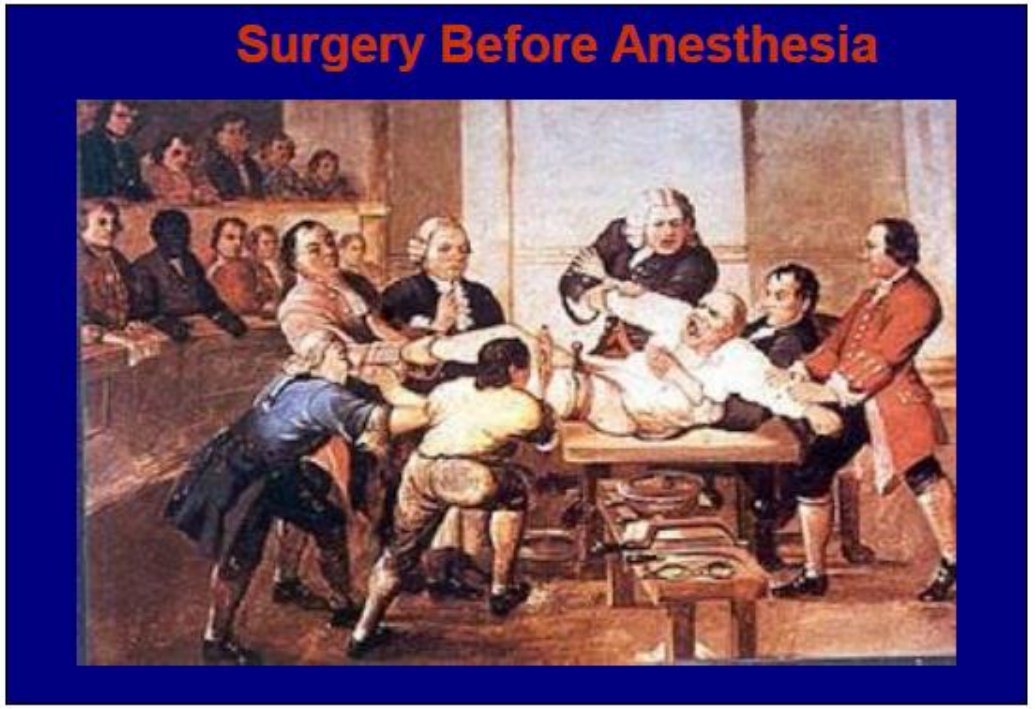
NERVOUS SYSTEM DRUGS



Anesthetic Drugs
8. Lecture

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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.

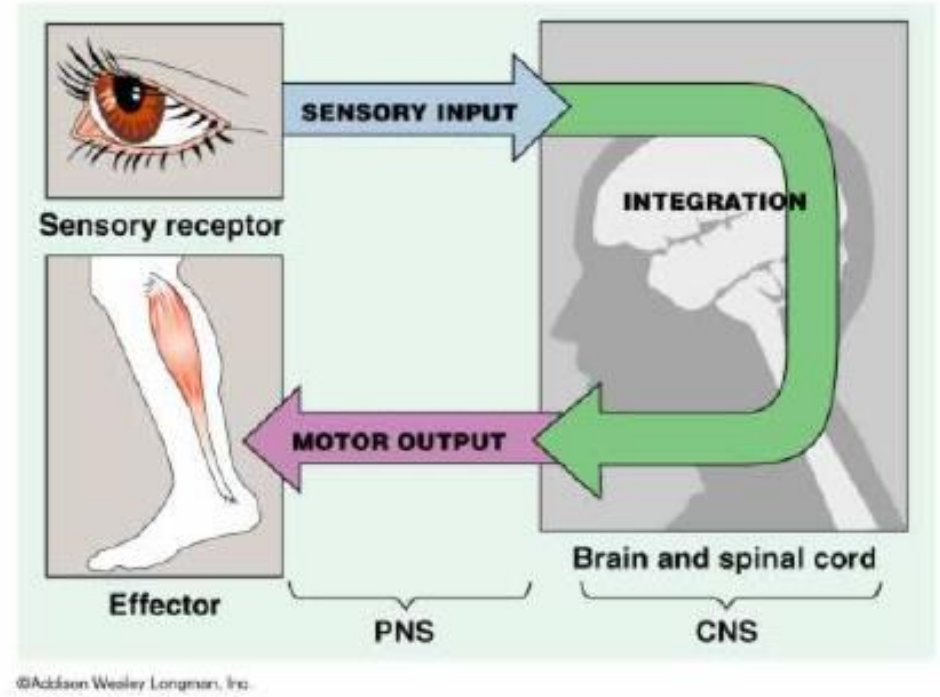
Central nervous system
The brain and the spinal cord make up the central nervous system.

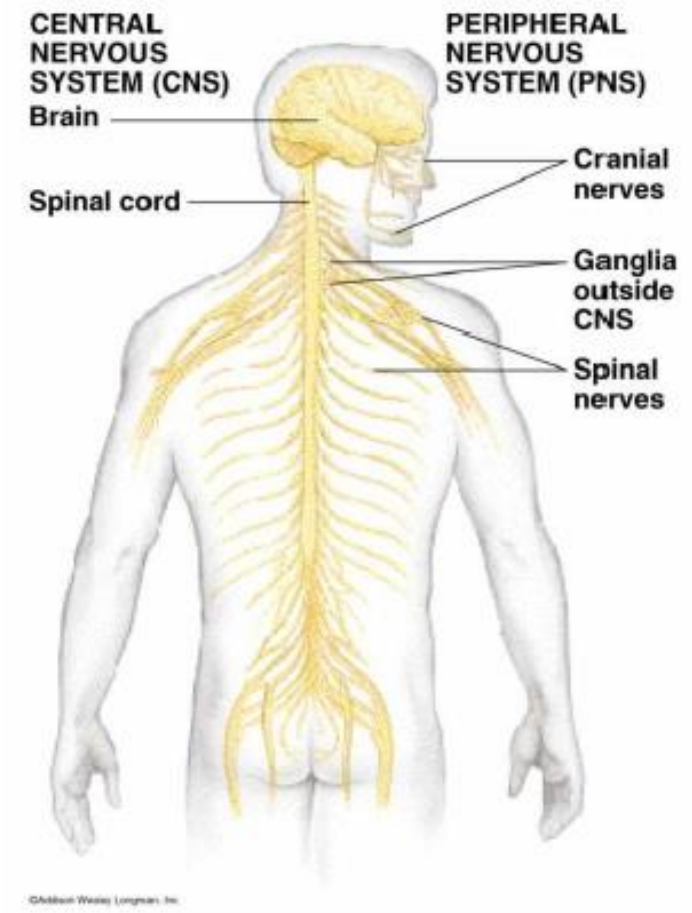
The peripheral nervous system - It is made up of two main parts

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
- ✓ Analeptics
- ✓ Analgesics
- ✓ Muscle relaxants
- ✓ Antitussives
- ✓ Expectorants
- ✓ Mucolytic
- ✓ Cholinergic
- ✓ Antiparkinson
- ✓ Alzheimer

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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, CH_3CH_2OH

Chloroform, $CHCl_3$

Diethyl ether, $CH_3CH_2OCH_2CH_3$

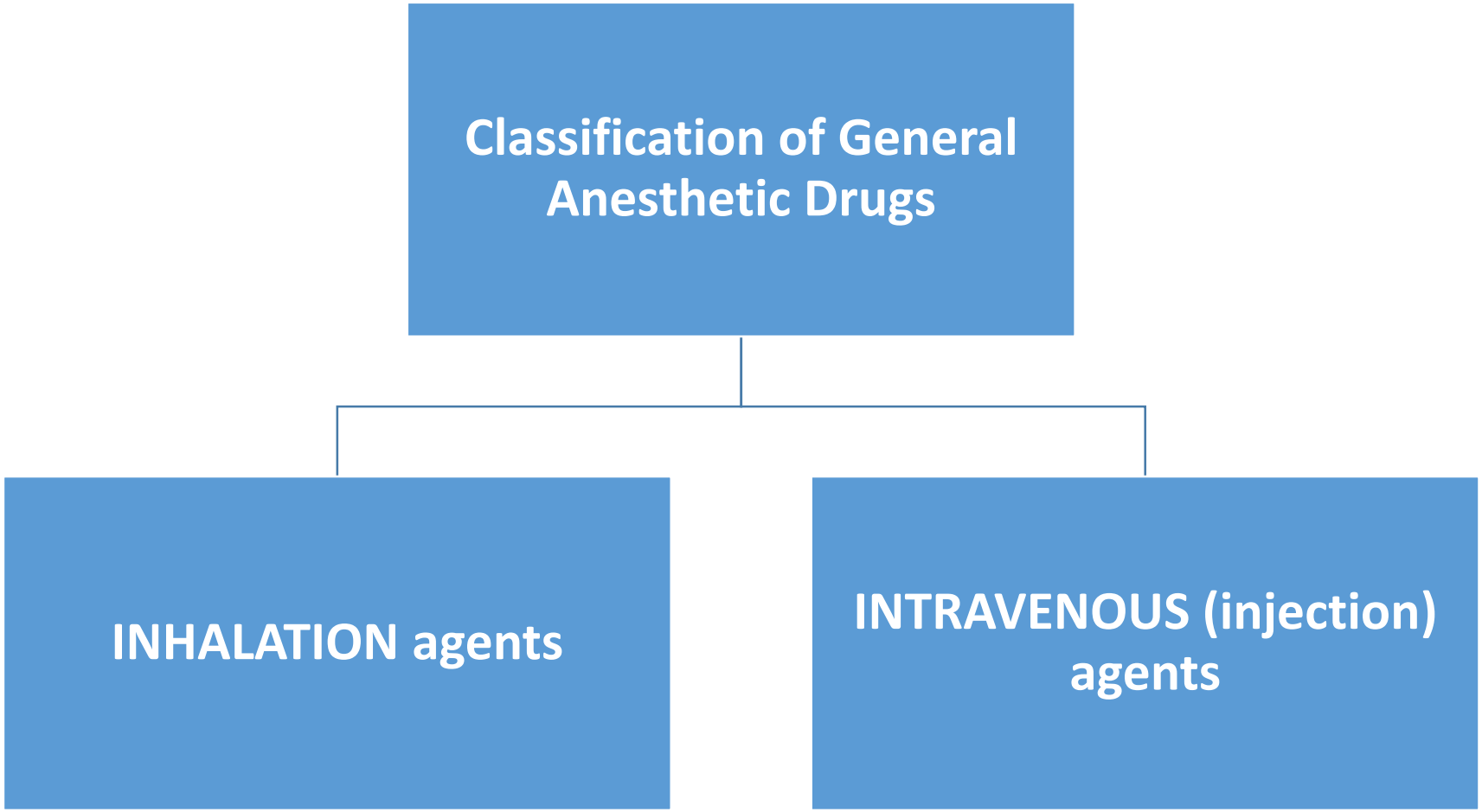
Fluroxene, $CF_3CH_2OC{=}CH_2$

Halothane, $CF_3CHClBr$

Methoxyflurane, $CHCl_2CF_2OCH_3$

Enflurane, $CFHClCF_2OCF_2H$

Sevoflurane, $CF_3CH(CF_3)OCH_2F$


Classification of General Anesthetic Drugs
INHALATION agents
INTRAVENOUS (injection) agents

Classification of General Anesthetic Drugs

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).

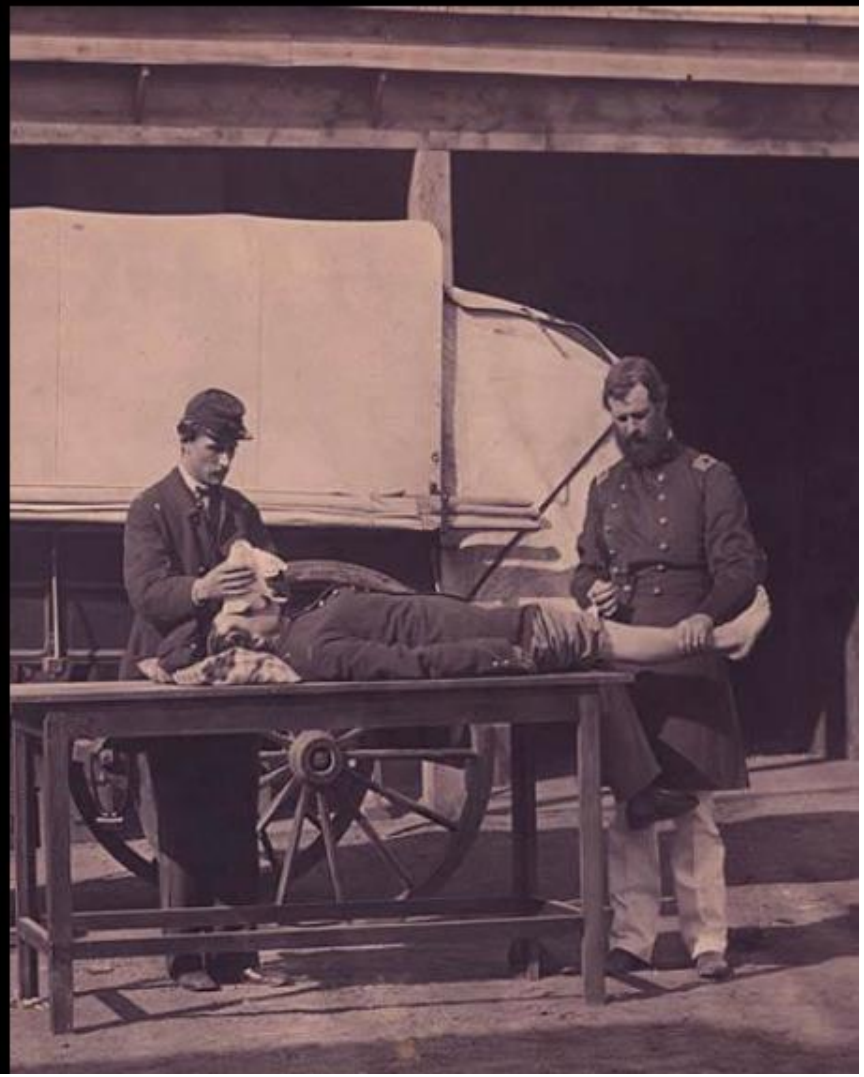
History:

Ether:

Accepted in 1846 due to William Morton

showed it worked in dental procedures in Boston.

- American civil war amputations 1860s



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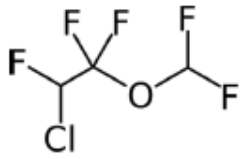
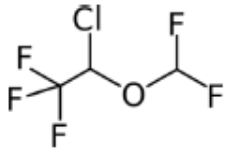
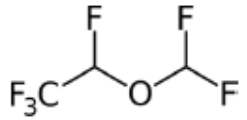
Examples of Inhalation Anesthetics



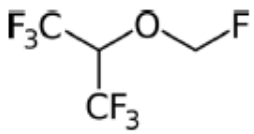
Enflurane, (Enthrane®)
2-chloro-1,1,2,-trifluoroethyl-difluoromethyl ether



Isoflurane (Forane®)
(1-chloro-2,2,2-trifluoroethyl difluoromethyl ether)



Desflurane (Suprane®)
(1,2,2,2-tetrafluoroethyl difluoromethyl ether)

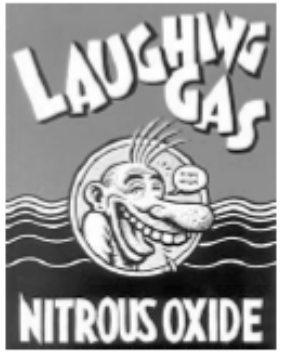


Sevoflurane (Ultane®)
1-trifluoromethyl-2,2,2-trifluoroethyl fluoromethyl ether

Halothane (Fluothane®) CF_3-CHClBr
Nitrous oxide, N_2O
Chloroform, $CHCl_3$
Diethyl ether, CH_3CH_2-O-CH_2CH_3

Inhalation Anesthetics – Nitrous Oxide

Nitrous oxide (N_2O)
– 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_2O.

$$NH_4NO_3 \xrightarrow{200\text{-}240\ ^{o}C} N_2O + 2H_2O$$

Inhalation Anesthetics - Ether

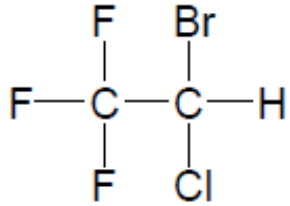
- **Ether** (CH_3CH_2-O-CH_2CH_3)
  - Obsolete (except in underdeveloped regions)
  - Slow onset and recovery
  - Post-operative nausea, vomiting
  - Highly explosive

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

$$CH_3CH_2OH + CH_3CH_2OH \xrightarrow{H_2SO_4} CH_3CH_2OCH_2CH_3$$

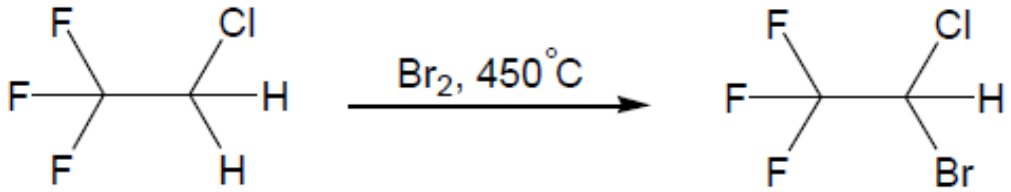
Inhalation Anesthetics - Halothane

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

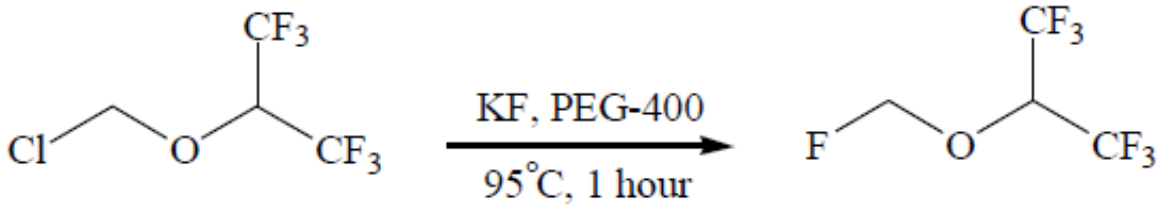
Synthesis: 2-chloro-1,1,1-trifluoroethane is reacted with bromine at 450 °C to produce halothane



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 a-chloro ethers with metal fluorides has traditionally been the method mostly used to obtain simple a-fluoro ethers.



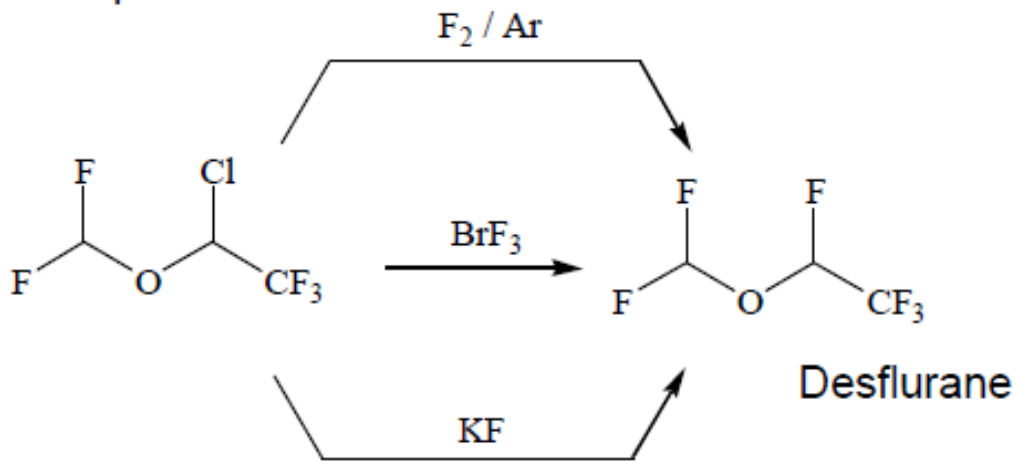
Sevoflurane

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 °C.
2) With KF in diethyl glycol at 195 °C.
3) With BrF_3 at room temperature.



Classification of General Anesthetic Drugs

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 Anesthetic Drugs

Classification of intravenous anesthetics
Rapidly acting (primary induction) agents Barbiturates: Methohexital Thiobarbiturates – thiopental, thiamylal
Imidazole compounds - etomidate
Sterically hindered alkyl phenols - propofol
Steroids – elanolone, althesin (none currently available)
Slower acting (basal narcotic) agents Ketamine
Benzodiazepines – diazepam, flunitrazepam, midazolam
Large-dose opioids – fentanyl, alfentanil, sulfentanil, remifentanil
Neuroleptic combination – opioid + neuroleptic

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Structure Activity Relationships (SAR)

>is the relationship between chemical structure and pharmacoligical activity for a series of compounds.

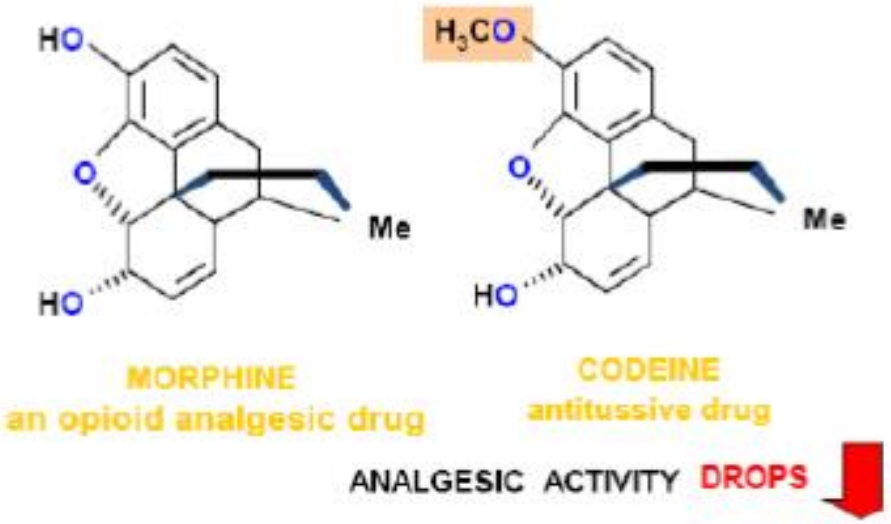
SAR – identifies which functional groups are importand for binding and activity

Method

- Alter, remove or mask a fuctional group
- Test the analogue for activity
- Method of testing: in vitro – for binding interactions with target (e.g. enzyme)

in vivo – for target binding interactions – pharmacokinetic properties

Structure Activity Relationships (SAR)



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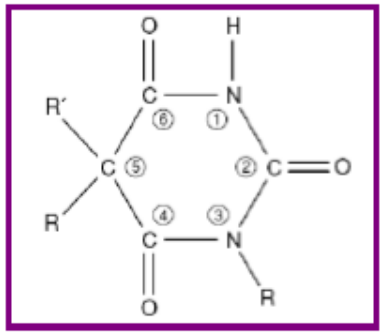
Intravenous Anesthetic Agents - Barbiturates

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

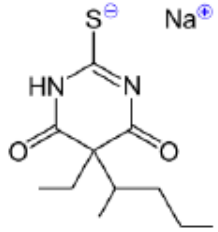


Structure Activity Relationship of Barbiturates (Thiobarbiturates)

- 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

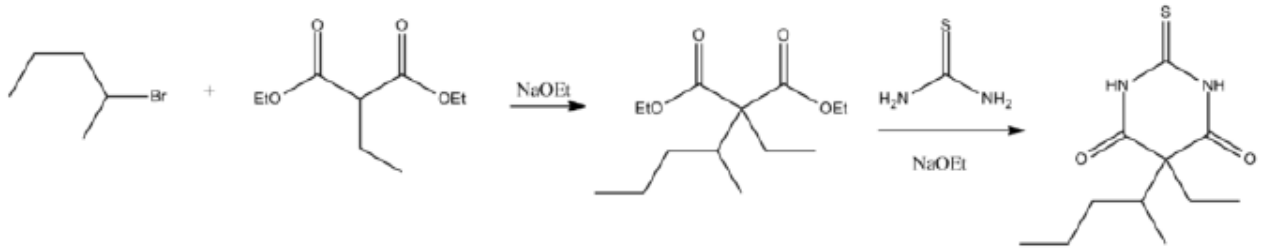
Intravenous Anesthetic Agents – Sodium Thiopental

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.



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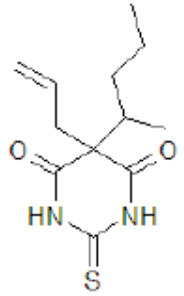
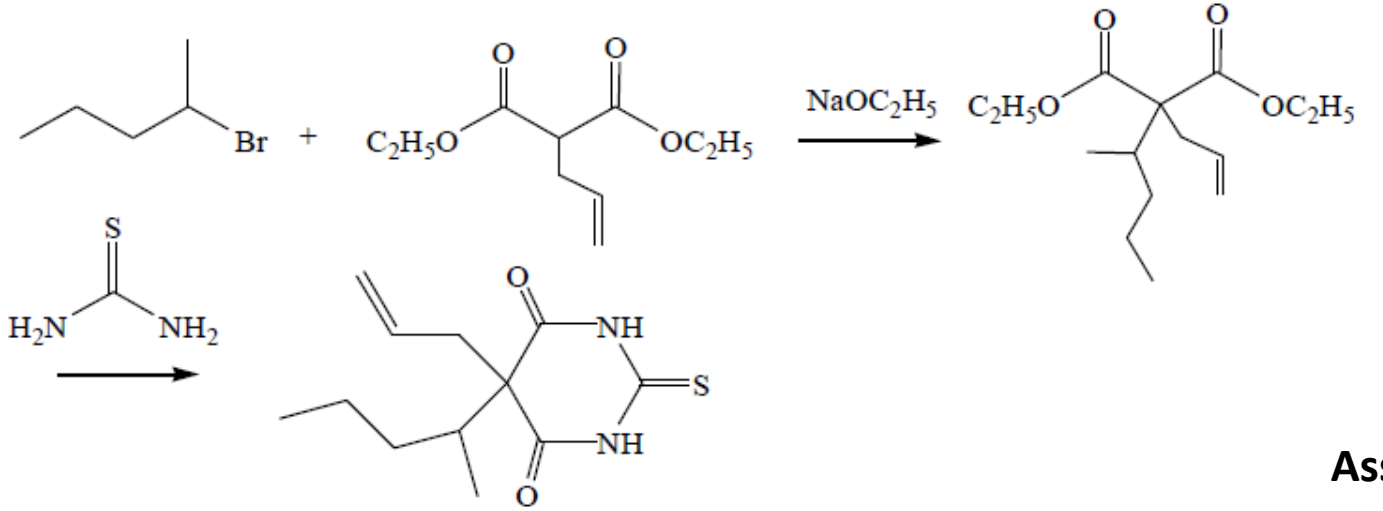
Intravenous Anesthetic Agents – Thiamylal

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. α-Allyl-α-(1-methylbutyl) malonic acid diethyl ester and thiourea reaction gives **Thiamylal.**



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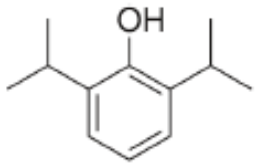
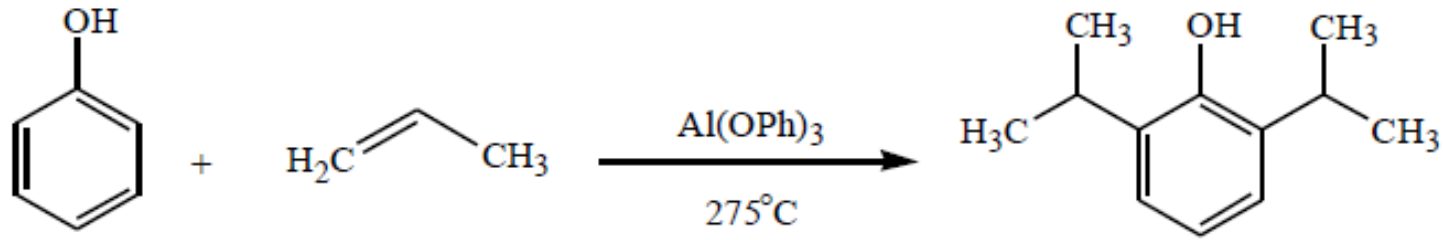
Intravenous Anesthetic Agents – Propofol

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



2,6-Bis(1-methylethyl)phenol

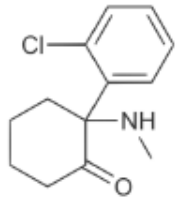
Synthesis : By condensation of phenol (I) with propylene (II) at temperatures ranging from 230°C to 275°C and pressures up to 3000 atm. in an autoclave, using aluminum phenoxide as catalyst.



Intravenous Anesthetic Agents – Ketamine

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

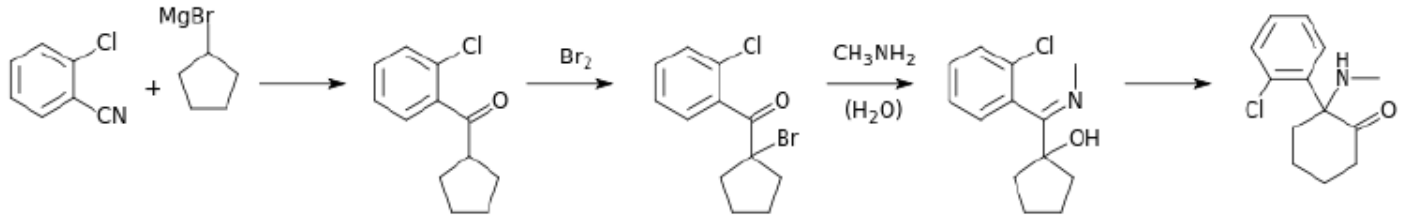
- It is soluble in water.



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

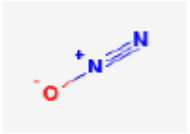
Synthesis :

- 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

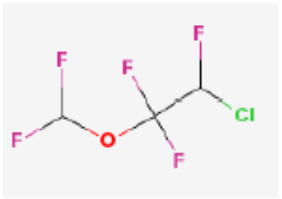


Commonly Inhaled Anesthetics

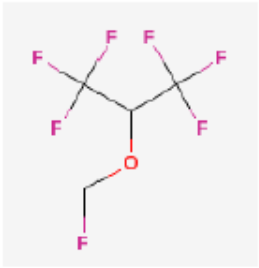
Nitrous Oxide



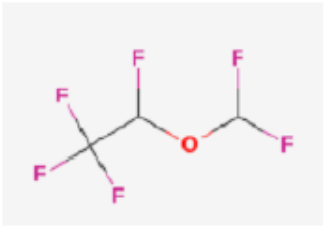
Enflurane (Ethrane ®)



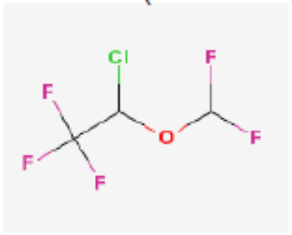
Sevoflurane (Ultane ®)



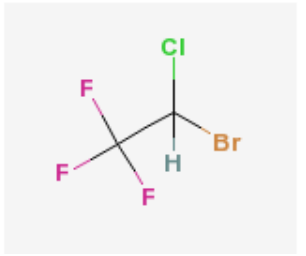
Desflurane (Suprane®)



Isoflurane (Forane®)



Halothane



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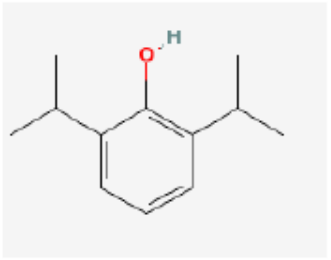
Common Intravenous Anesthetics

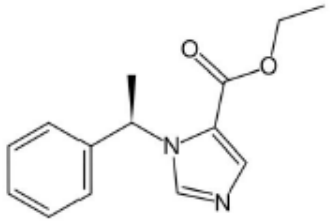
Propofol (Diprivan®)



–analgesic properties (non barbiturate). New class of hypnotic sedatives: diisopropylphenols

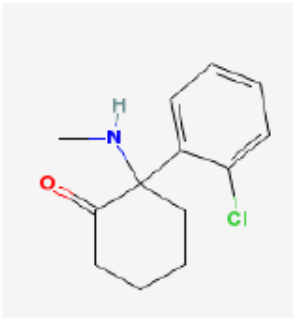
–Binds GABAa receptor.

Etomidate

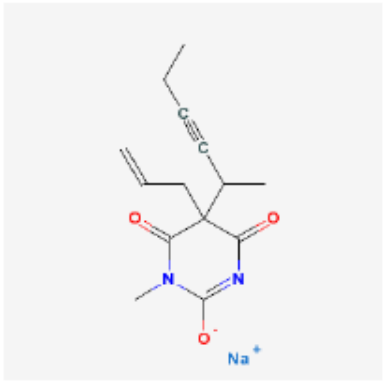


Binds to GABAa receptor

Ketamine (Ketalar®)



Methohexital (Brevital®)



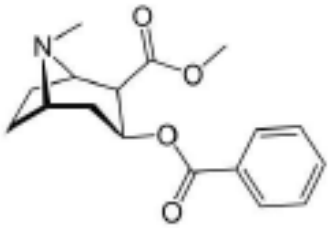
Barbiturate binding to GABAa receptors

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)



Local Anesthetic Agents

General Properties of Local Anesthetic Agents:

– Are lipophilic, weak bases (pK_a=8-9) => mainly ionized at physiological pH

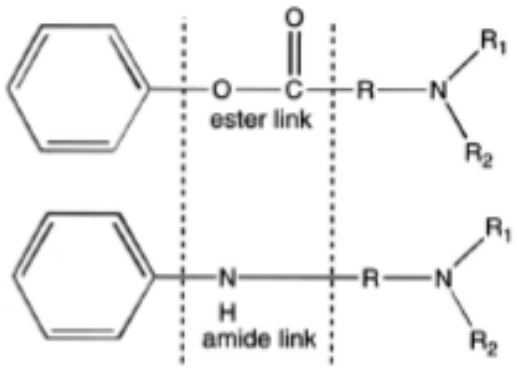
– Poorly soluble in water

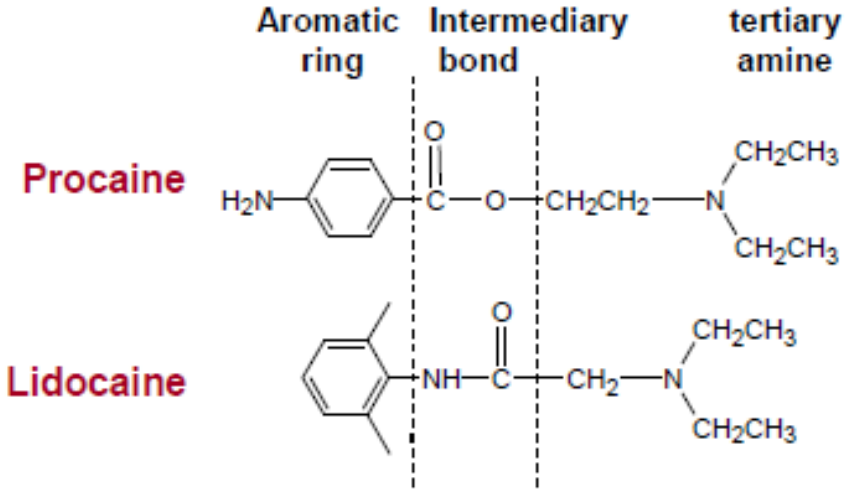
– Act in their ionized form, but penetrate the cell membrane in the non-ionized form

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

Chemical Structure of Local Anesthetic Agents

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





Esters:

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

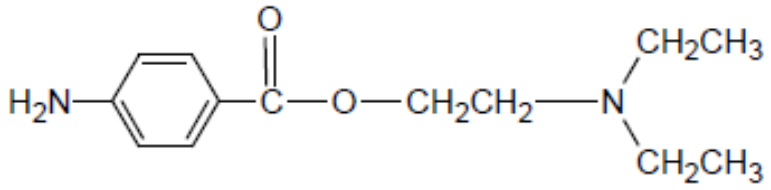
Amides:

– More stable, longer plasma half-lives

Chemical Structure of Local Anesthetic Agents

- 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

Example of Local Anesthetic Agents

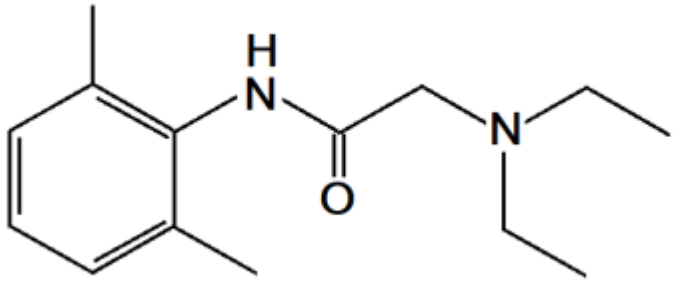
- Esters include cocaine, procaine, 2-chloroprocaine, tetracaine and benzocaine.

- Amides include lidocaine, bupivacaine, levobupivacaine, mepivacaine, etidocaine, prilocaine, ropivacaine and articaine.

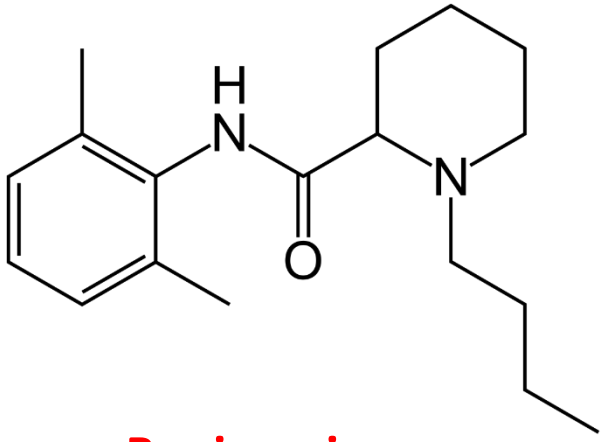
- Stereo-isomerism is found in bupivacaine, prilocaine, ropivacaine, etidocaine and mepivacaine.

- Most are marketed as racemic mixtures with the exception of levobupivacaine (S-bupivacaine) and ropivacaine (S-ropivacaine).

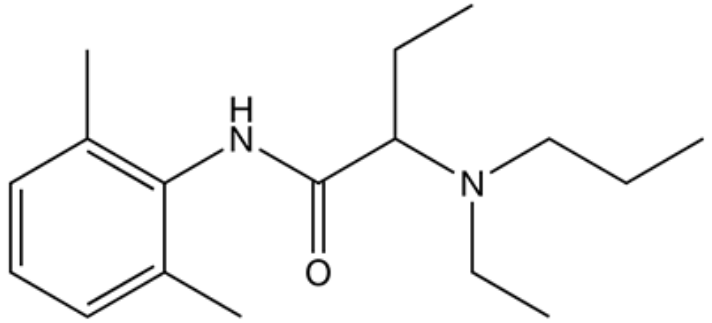
Chemical Structure of Local Anesthetic Agents



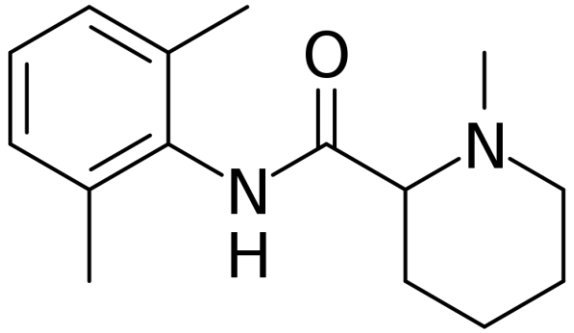
Lidocaine



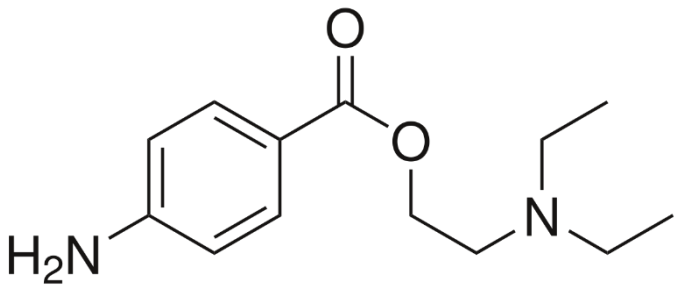
Bupivacaine



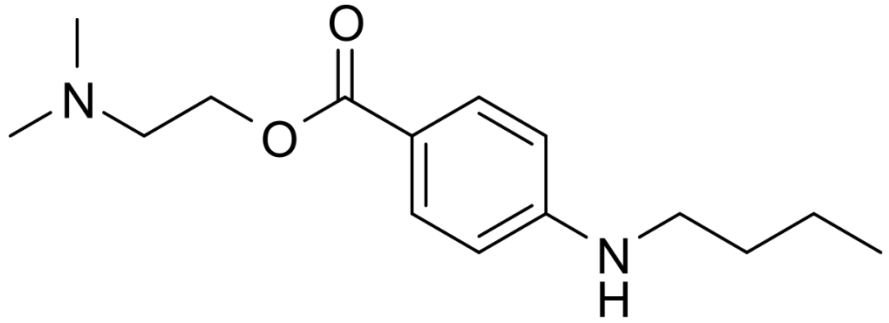
Etidocaine



Mepivacaine



Procaine



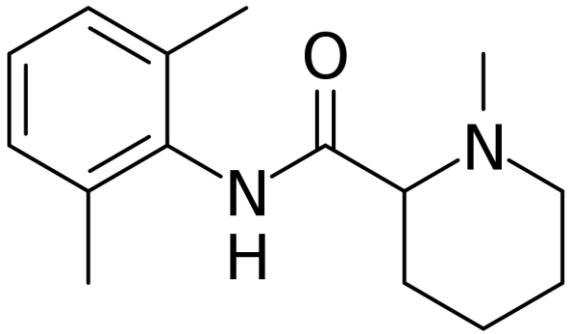
Tetracaine

Assoc.Prof. Omer Tahir Gunkara

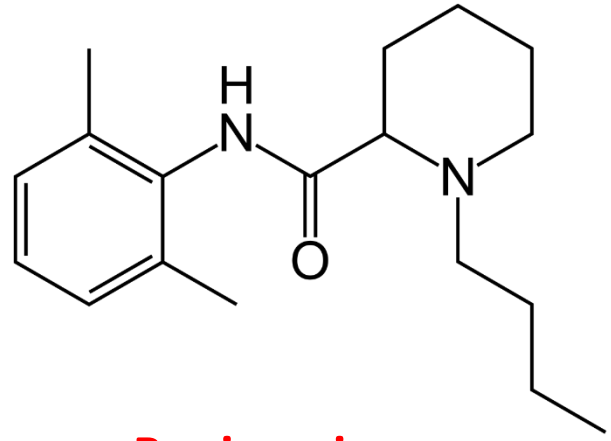
Structure Activity Relationships of Local Anesthetic Agents

- 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,

a. increased lipid solubility & protein binding
b. greater potency
c. a longer duration of action



Mepivacaine

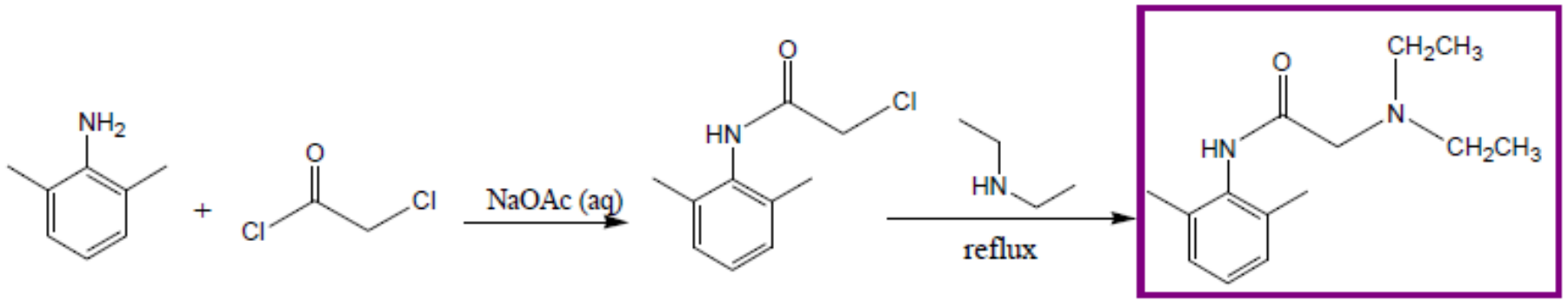


Bupivacaine

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



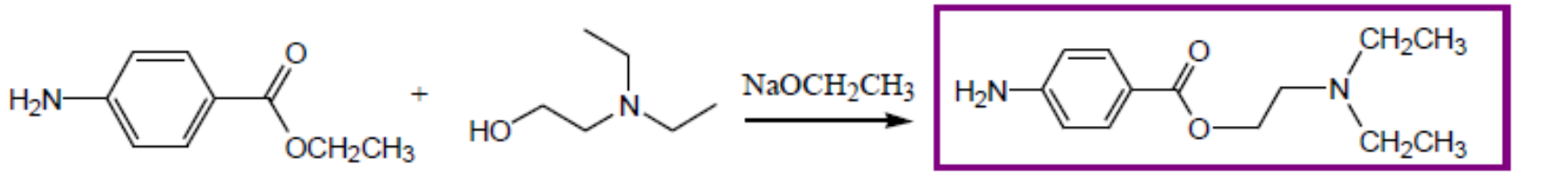
2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide

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.



2-(diethylamino)ethyl 4-aminobenzoate

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.