General anaestetics

Functions of general anaesthesia

•neither terapeutic nor diagnostic

•make surgical and other painful procedures easier

Demands on effects of general anaesthetics

1. Analgesia (pain relief)
2. Amnesia
3. Lost of conciousness
4. Decrease of movability of skeletal musculature
5. Atenuation of autonomic responses
6. Reversibility of effect

•all anaesthetics do not reach all demands

Classification of general anesthetics according to the route of administration

1. Inhaltion – gases, volatile liquids

•effect is less dependent on a particular stucture more on lipophilicity

2. Intravenous

•more specific - receptor mechanisms of action

Sites of action

CNS: Brain cortex, reticular system, thalamus, spinal cord

Effect

Anaesthetics block nervous impulses transfer

- **decrease of activity of excitably acting synapses**
- **increase of activity of inhibitory synapses**
- **synaptic channels for Ca^{2+} and Cl^- ligand-activated ones = Cl^- channels activated by GABA or glycine are influenced by anaesthetics (propofol, barbiturates, benzodiazepins, inhalation ansestetics)**
- increase of quiescent steady state membrane potential – hyperpolarization
- attenuation of neurons forming impulses – not elucidated – ventilation and heart frequence also influenced by anaesthetics

Mechanisms of action of general anaesthetics

Lipide theory

- anaesthetic is dissolved in a lipide membrane and causes some changes of physical properties of the membrane
- based on the Meyer-Overton rule
- higher lipids solubility expressed as $P_{oil/air}$ implies higher anaesthetic potency i.e. lower minimal alveolar concentration
- valid for **inhalation anaesthetics** only

Protein theory

- interaction of anaesthetic with a hydrophobic part of an integral transmembane protein

Mixed effect on the protein-lipide interface

Dependence of effect of inhalation anaesthetic on $P_{oil/air}$

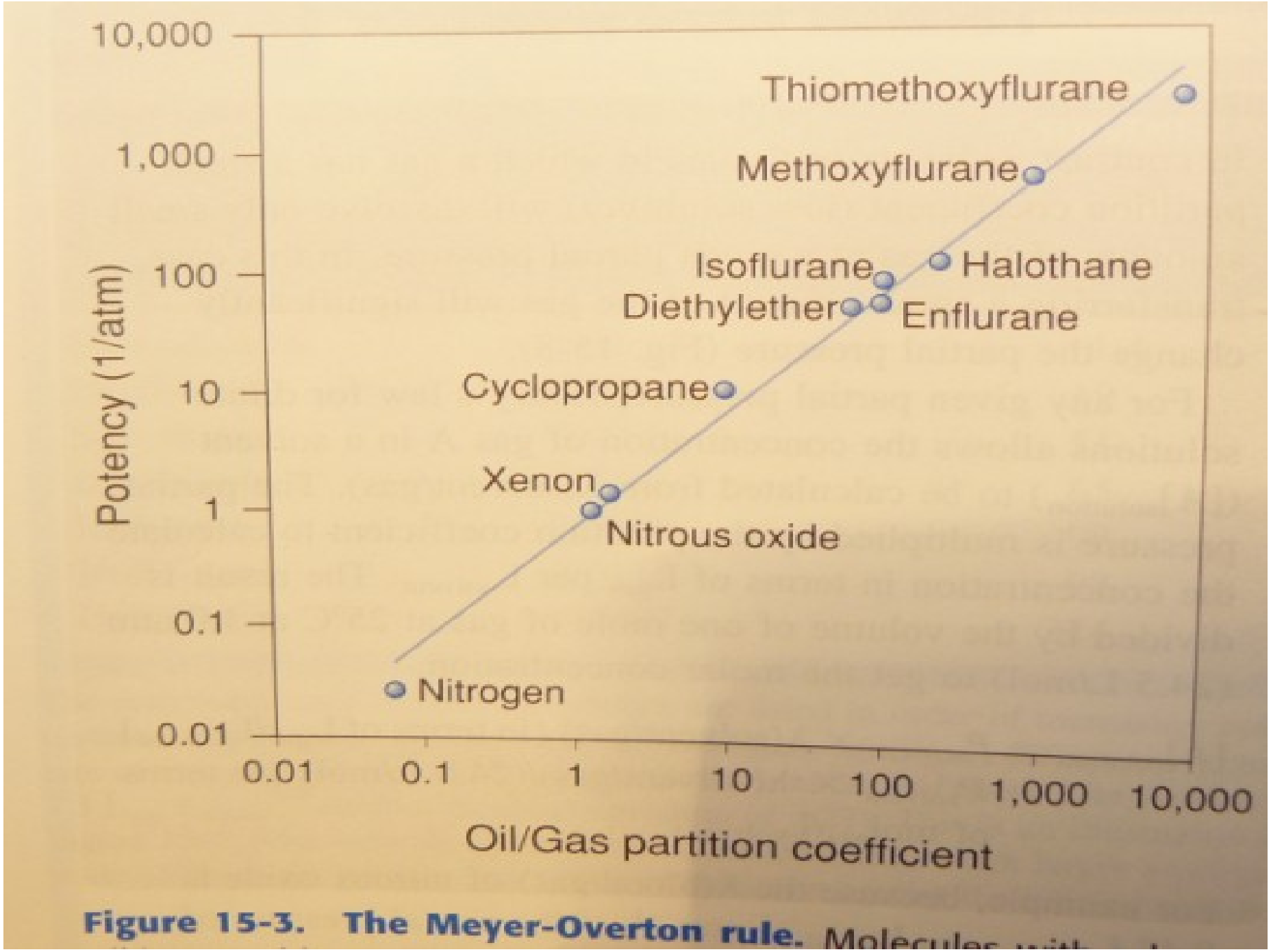
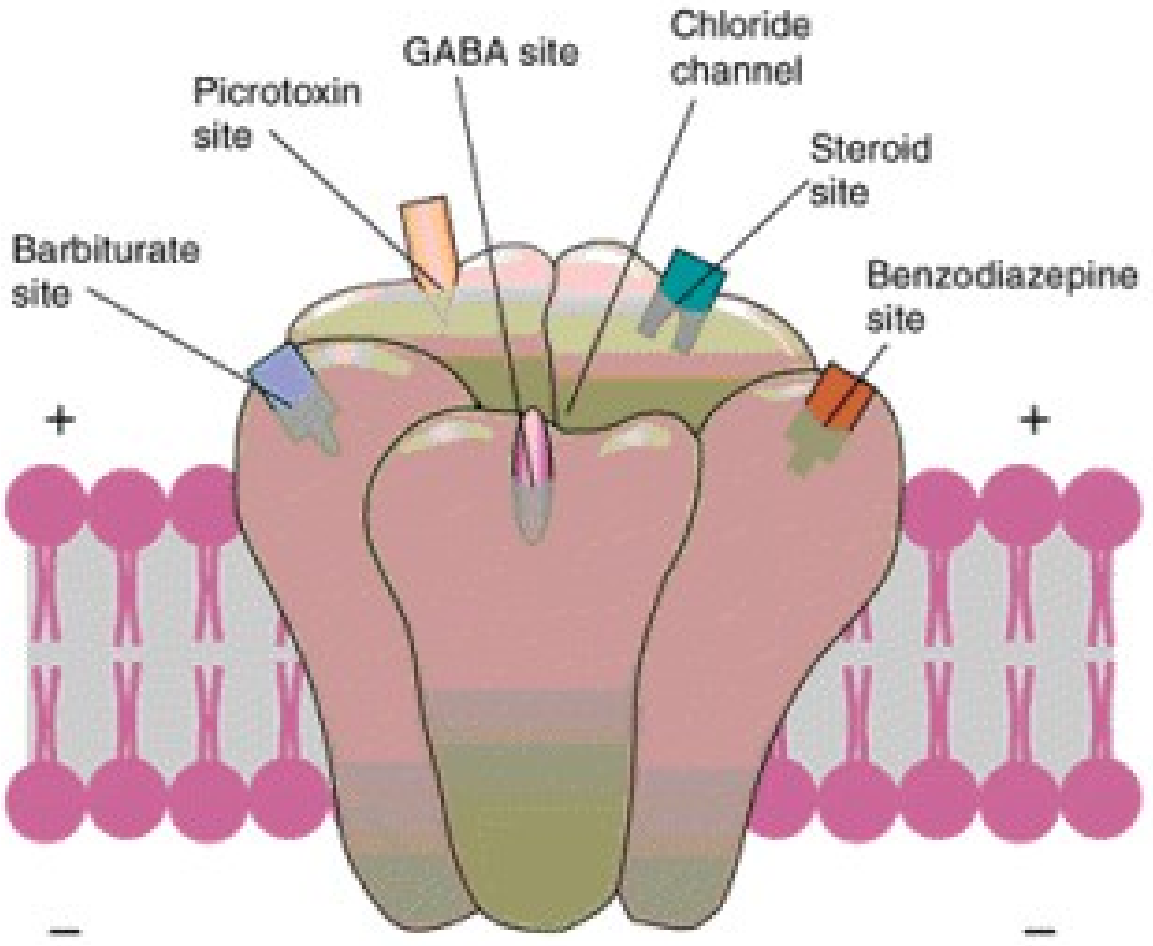


Figure 15-3. The Meyer-Overton rule. Molecules

$GABA_A$ receptor

► **Schematic Illustration of a $GABA_A$ Receptor, with Its Binding Sites**

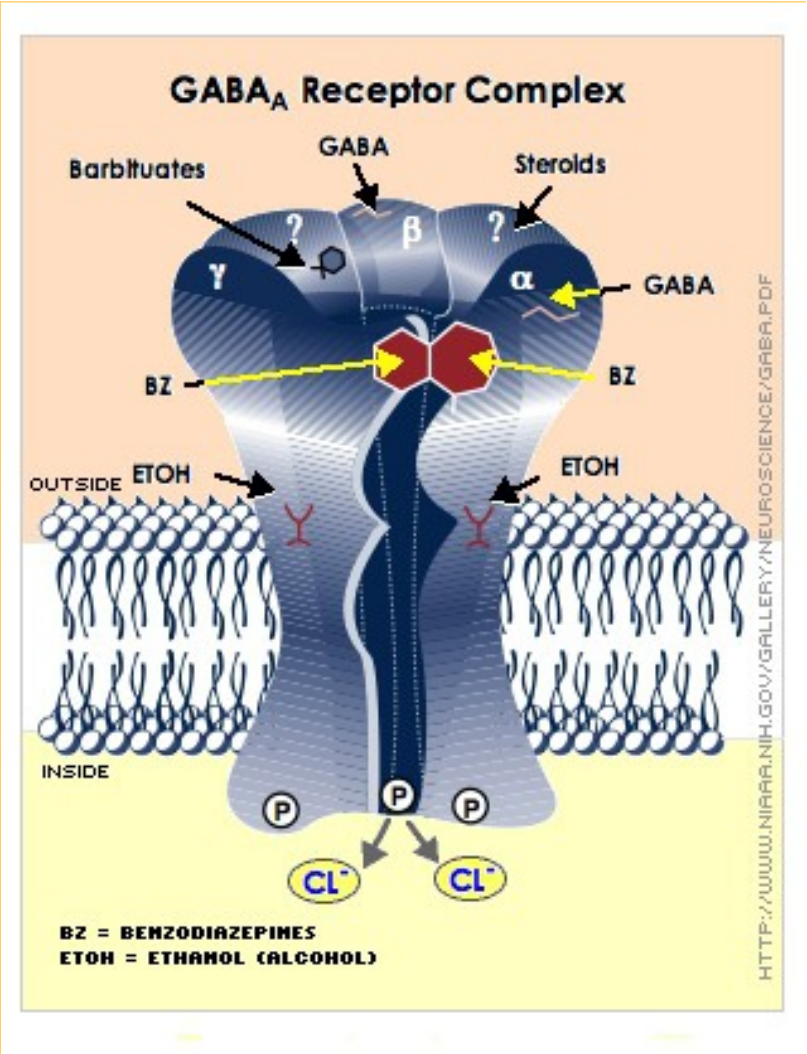


$GABA_A$ receptor and its role in general anaesthesia

$GABA_A$ receptor = ligand controled chloride channel

•opening of the channel causes cell hyperpolarization and thus its insensitiveness to impulses

•agonists: GABA, barbiturates, benzodiazepins, steroids (have identified binding sites)

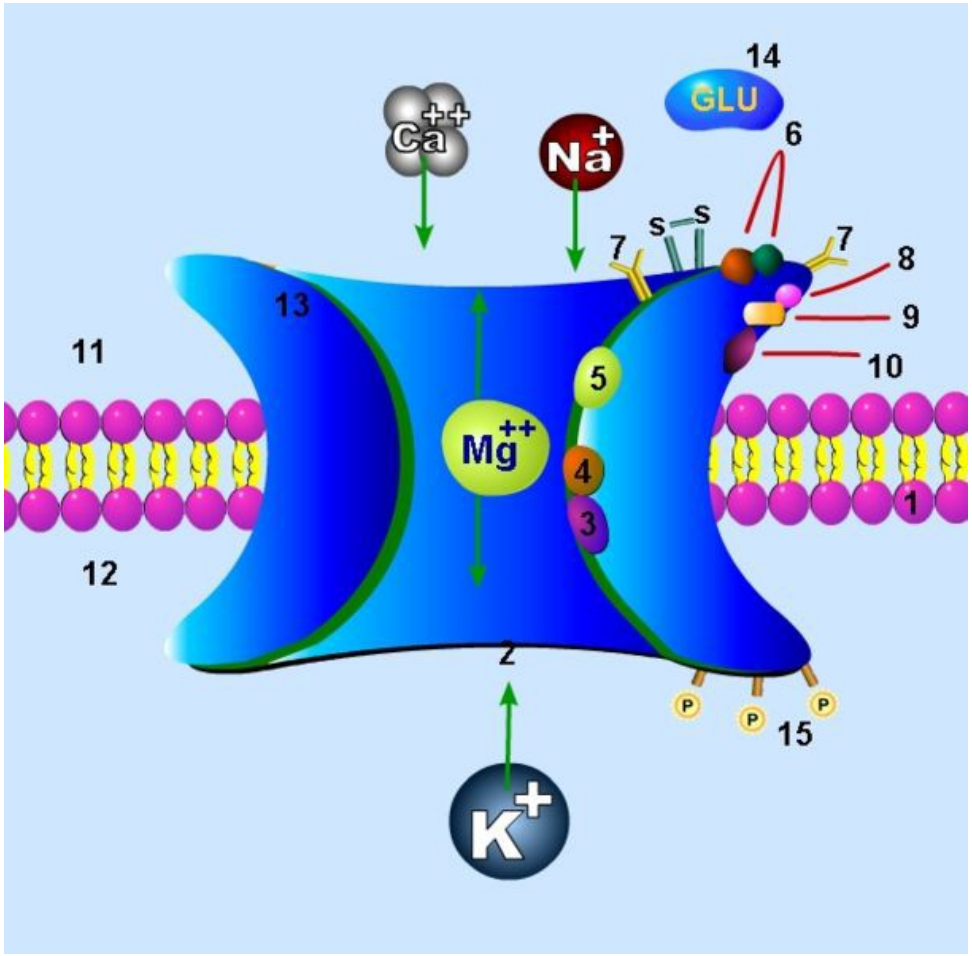


NMDA (N-methyl-D-aspartate) receptor

- a subtype of glutamate receptor
- anaesthetics are its **antagonists**

activation $\Rightarrow$ cell **depolarization** by entrance of Ca^{2+} and Na^{+}

- takes part in effects of N_2O, Xe a ketamine

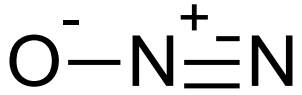


Inhalation general anesthetics
1. Gases

Nitrous oxide N_2O

„laughing gas“, „Lachgas“

- used since 19th century (dentist Wells 1845)
- patient reaction badly predictable
- contemporarirly sometimes in obstetrics – rather analgesia with conciousness retention



Preparation: heating of ammonium nitrate to 180 – 250°C:

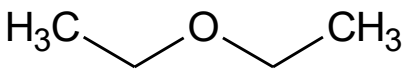
$NH_4NO_3 \rightarrow N_2O + H_2O$

Xenon Xe

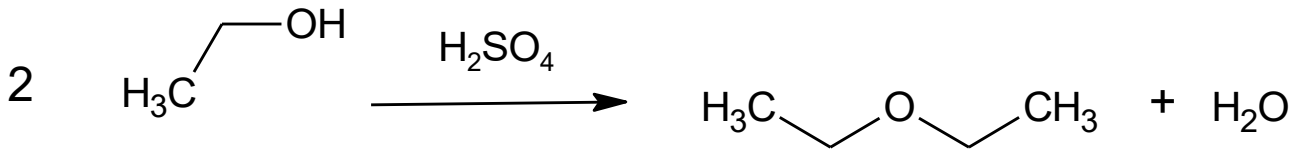
- inert gas
- name from Greek „xenos“ - stranger
- invented by Sir W. Ramsay and M.W. Travers 1898
- modern and secure inhalation anaesthetic

Inhalation general anaesthetics
2. Volatile liquids
2.1 Ethers

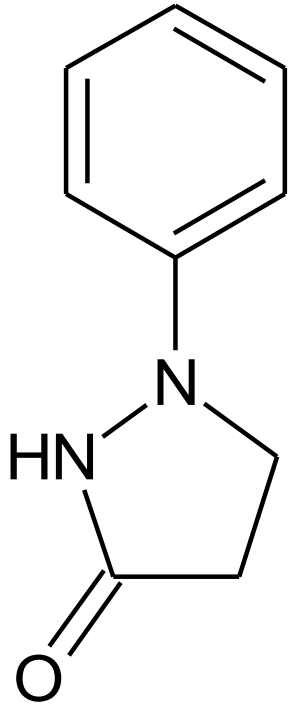
Diethylether, aether, „aether sulphuricus“



Preparation



- known since 10th -11th century: Abu al-Khasim al-Zahravi Ibn Zuhr, an Arab alchemist
- as an anaesthetic used since 1846 (William Morton; the first patient Gilbert Abbott)
- well controlled introduction of a patient into anaesthesia: all phases clearly expressed
- disadvantages: highly inflammable, mixture of vapours with air highly explosive
- forming of explosive peroxides $\Rightarrow$ stabilization needed (Cu sealing of bottles, phenidone)
- *Ether anaestheticus, Ether solvens PhEur*, *Aether pro narcosi* PhBs IV

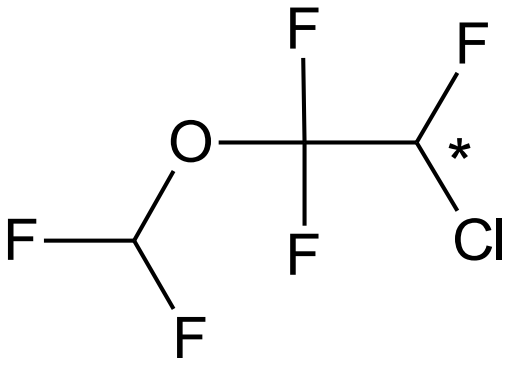


1-phenylpyrazolidin-3-one
phenidone

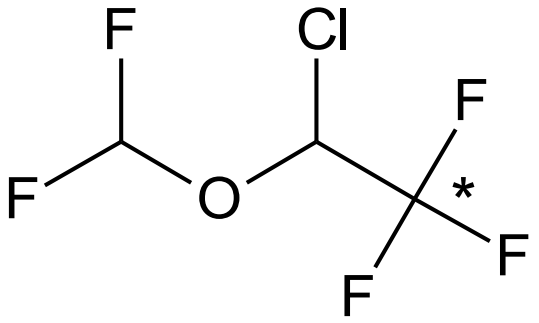
•antioxidant stabilizing agent added into diethylether according to some pharmacopoeias

Ether anaesthesia in U.S. army at the end of 19th century

Halogenated ethers
•non-toxic, non-inflammable



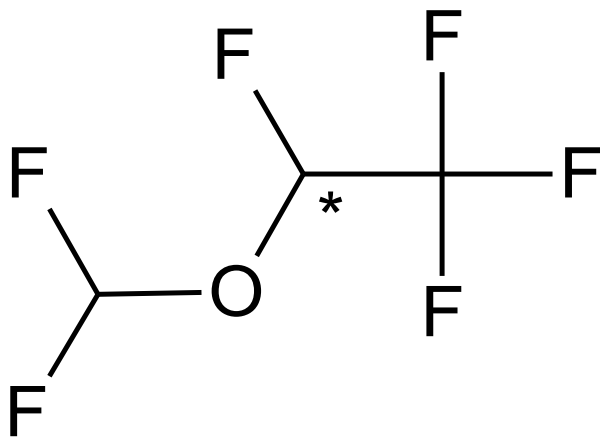
enfluran



isofluran

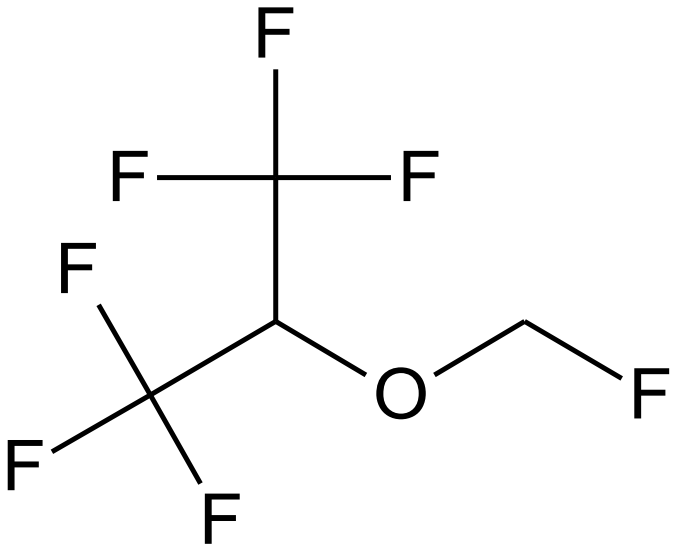
Isofluranum PhEur

Halogenated ethers

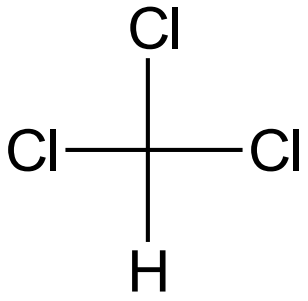


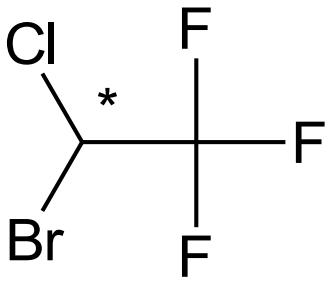
desfluran

Desfluranum PhEur



sevofluran





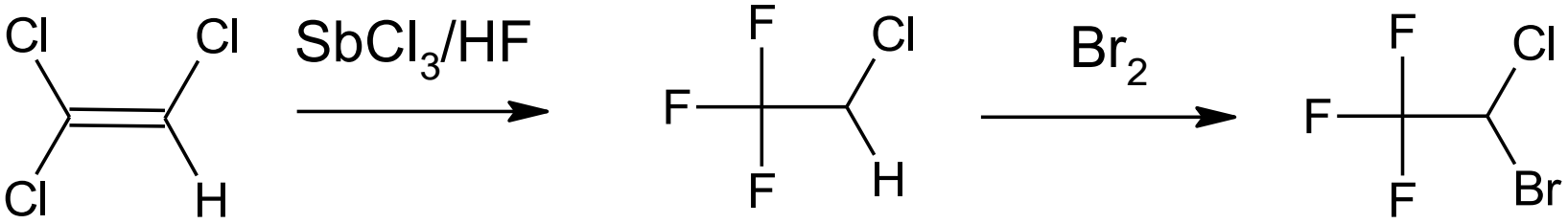
chloroform

trichloromethane

halothan

•at first Simpson 1847
•strongly hepatotoxic, suspect cancerogene, not used as anaesthetic now (decomposition to $COCl_2$)

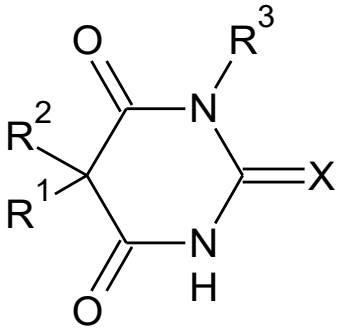
Halothanum PhEur
b. p. 49 - 51°C



Synthesis of halothan

3. Intravenous general anaesthetics

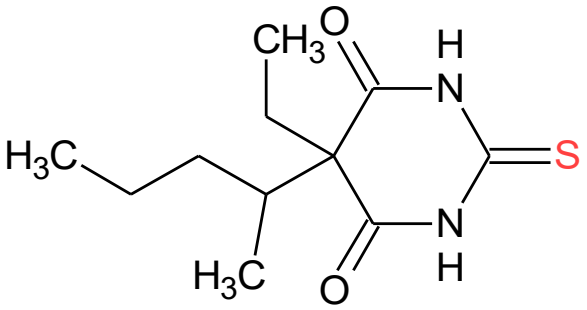
Barbiturates and thiobarbiturates



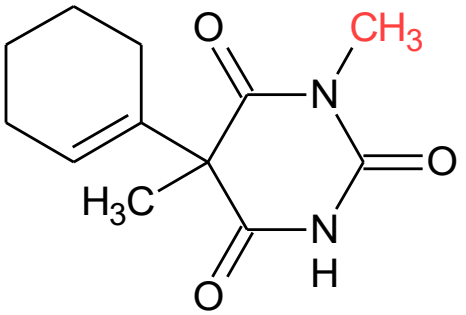
$R^1=R^2=R^3=H$; X=O barbituric acid

R^1, R^2= alkyl, aryl, R^3= H or alkyl; X=O barbiturates

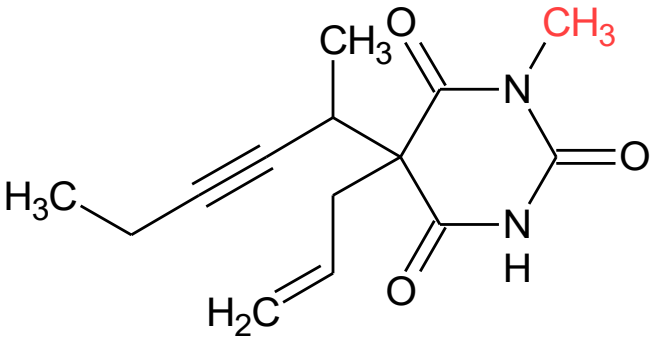
R^1, R^2= alkyl, aryl, R^3= H or alkyl; X=S thiobarbiturates



thiopental



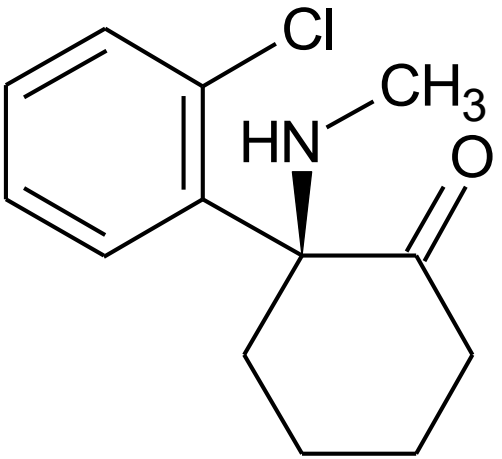
hexobarbital



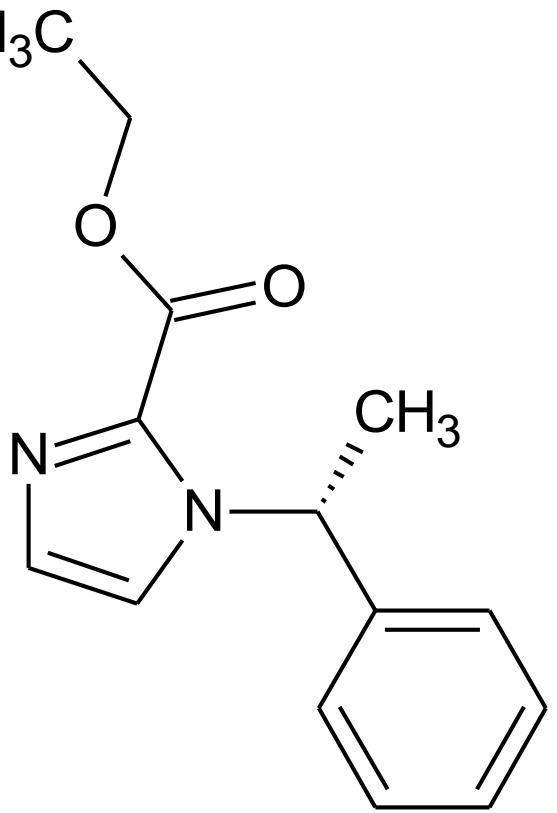
methohexital

•one- or dibasic acids (lactame/lactime-tautomerism ⇒ N- or O-/S-acids ⇒ used as water soluble Na^+ salts

Intravenous general anaesthetics



(S)-(+)-**ketamine**



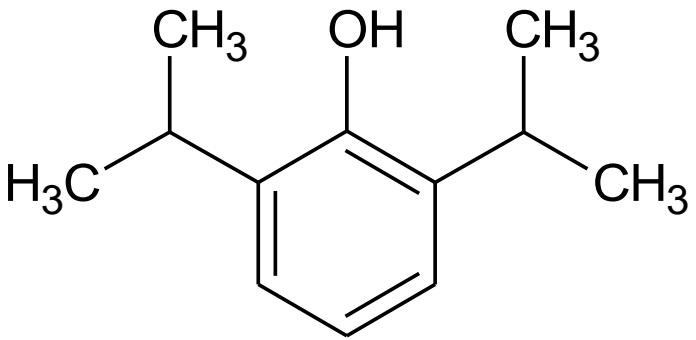
(R)-(+)-**etomidate**

•neuroleptic and strongly pain relieving effects
•short surgical procedures
•stunning (narcotization) projectiles for catching wild animals
Narkamon Spofa ® 1%

•ultrashortly acting narcotic

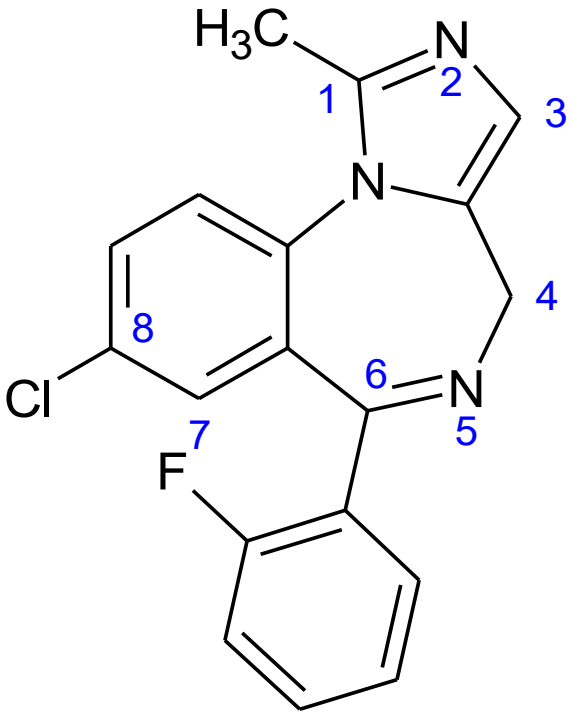
•used as hydrochlorides

Intravenous general anaesthetics



propofol

•poor solubility in water ⇒ use in emulsions
•very fast onset of action and very fast awakeing after finishing of infusion also (in several minutes)
•anticonvulsive and antiemetic effects
Diprivan®



midazolam

•derivative of 4*H*-imidazo[1,5-a][1,4]benzodiazepine
•for both onset and keeping of anaesthesia
•combined with ketamine
•hydrochloride
Dormicum® inj. sol.