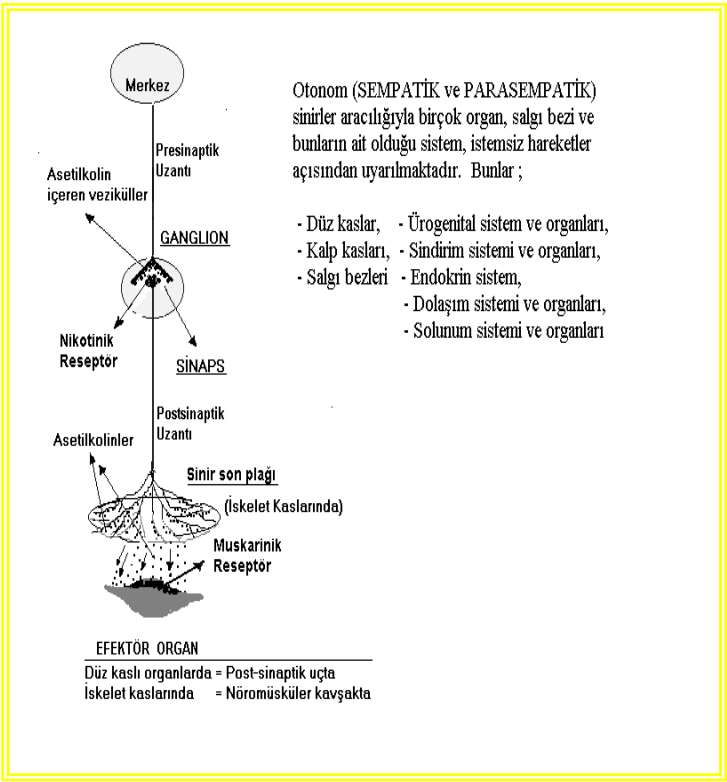
B. Nicotinic antagonists

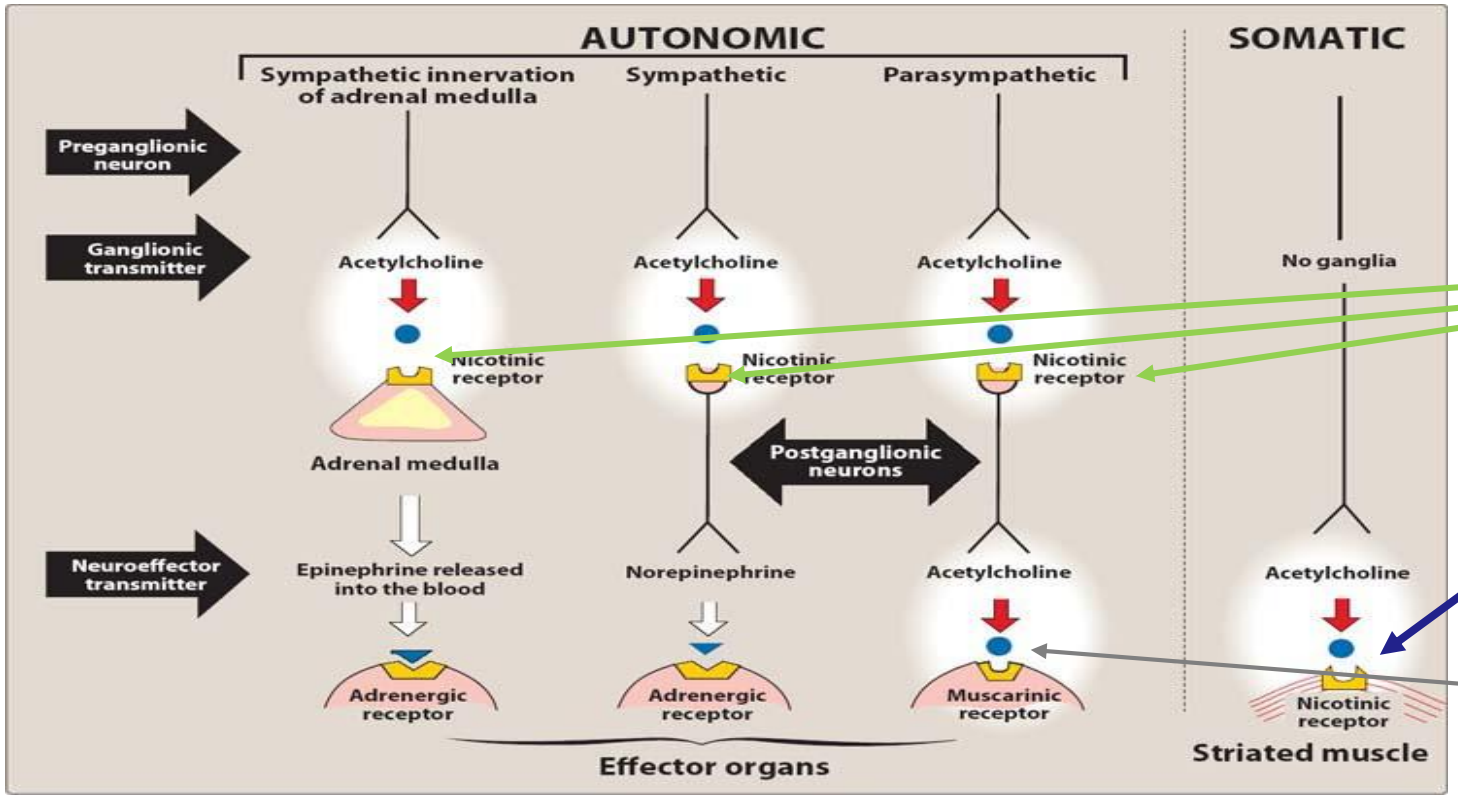
B1. Ganglionic Blocking agents

B2. Neuromuscular blocking agents

B2A. Nondepolarizing Blocking Agents (Competitif)

B2B. Depolarizing Blocking Agents (Non-Competitif)





Ganglionic blockers

Neuromuscular blockers

Antimuscarinic drugs

Nicotinic Antagonists

- **Nicotinic antagonists competitively bind to nicotinic receptors and block nicotinic response which results in blockade of skeletal muscle contraction ie paralysis**

- **There are two types:**

  - ✓ **Neuromuscular blockers (not the same as skeletal muscle relaxant that work by CNS depression)**
  - ✓ **Ganlionic blockers**

Nicotinic Antagonists

- **Normally used as muscle relaxant.**

- **Clinical uses:**

  - ✓ **Neuromuscular blocker for surgical operations**
  - ✓ **Permits lower and safer levels of general anaesthetic**

B. Nicotinic antagonists

B1. Ganglionic Blocking Agents

Ganglion blockers block nicotinic receptors in both sympathetic and parasympathetic autonomic ganglia. They are not selective and do not act as neuromuscular antagonists.

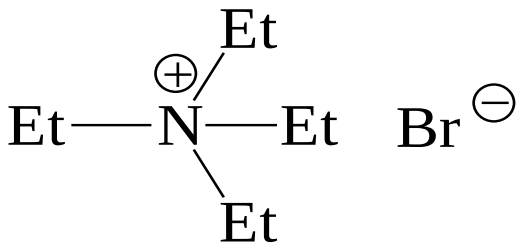
Ganglion blocking drugs are particularly effective in lowering blood pressure as they loosen vascular smooth muscles, and are used to minimize bleeding in haemorrhagic patients.

Because the effects are short-term [metabolism is very fast], the blood pressure returns to normal as soon as the drug is discontinued.

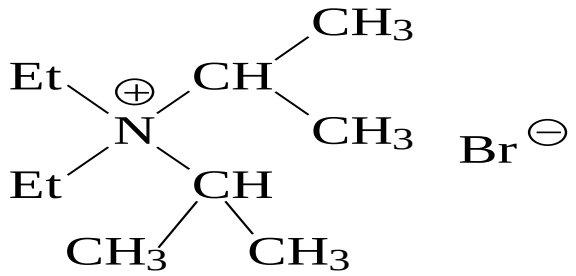
Tetraethylammonium-Br (**TEA**) and **Hexamethonium-Br.**

They compete with ACh for nicotinic receptors in synapses in ganglia and adrenal medulla. They are especially used in the treatment of hypertension and peripheral vascular diseases. They were divided into 4 subgroups based on their chemical structure.

a) Mono quaternary ammonium compounds



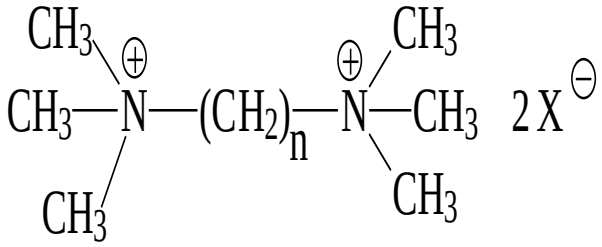
Tetraethyl ammonium bromide (TEA)



Diethyl diisopropyl ammonium bromide

b) Bis quaternary ammonium compounds

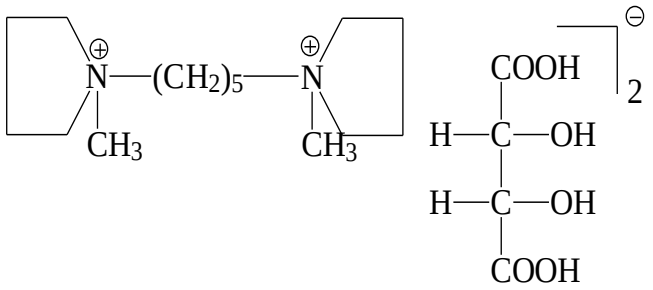
n - count: 5 or 6, active as ganglionic blockers
n - count: 9 to 12, weak ganglionic blockers



[Pentamethonium, Hexamethonium]

Quaternary nitrogens [Piperidine, Pyrrolidine] may be in the ring.

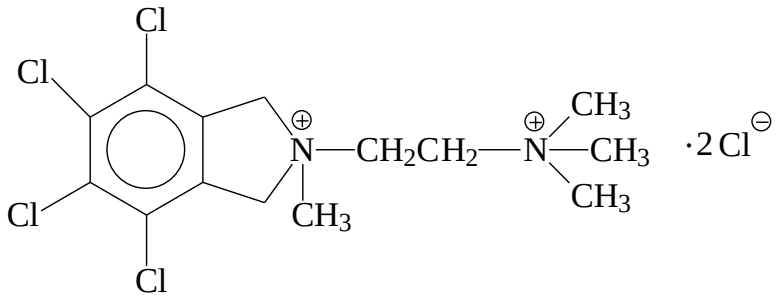
Pentolinum tartrate



Nitrogen is quaternized in the pyrrolidine ring.

There are also bis-derivatives in asymmetric structure.

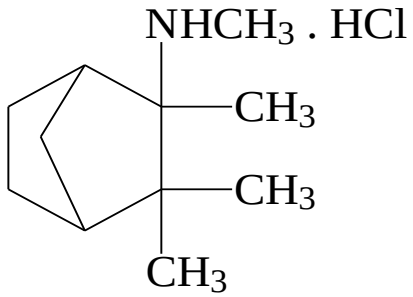
Chlorisondamine



There is no advantage from others. However, water and oil solubility of it are more balanced.

c. Secondary and tertiary amines

Mecamylamine HCl



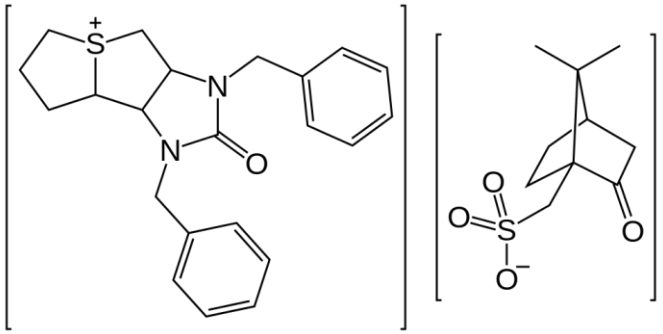
2-methylamino-2,3,3-trimethylnorbornan

It is a secondary amine designed to improve the oral bioavailability of ganglionic blockers.

Used to Reduce Nicotine Dependence in Smokers.

d. Quaternary Sulphonium Compounds

Trimethaphan camphorsulfonate (Trimetaphan CamsylateARFONAD



Trimetaphan camphorosulfonate, a monosulfonium compound, bears some similarity to the quaternary ammonium types because it, too, is a completely ionic compound. Although it produces a prompt ganglion-blocking action on parenteral injection, its action is short, and it is used only for controlled hypotension during surgery. May cause histamine release.

It can not cross the BBB owing to the positive charge of its sulphonium ion. It does not show any effect on the CNS.

B2. Neuromuscular Blocking Agents

B2A. Competitive (Nondepolarizing) Blockings

B2B. Non-Competitive (Depolarizing) Blockings

Agents that block the transmission of ACh at the motor end plate are called neuromuscular blocking agents. The therapeutic use of these compounds is primarily as adjuvants in surgical anesthesia to obtain relaxation of skeletal muscle. Additionally, they are used in various orthopedic procedures, such as alignment of freactures and correction of dislocations.

These neuromuscular blockers are structural analogues of acetylcholine. They act as either antagonists (non-depolarizing) or agonists (depolarizing) at the receptors on the final plate at the neuromuscular junction.

The compounds in this group sometimes are referred to as possessing **curariform** or **curarimimetic** activity in reference to the original representatives of the class, which were obtained from curare.

The antagonists of the ganglionic nicotinic receptor sites cannot be used for treatment because they cannot differentiate the parapathy nervous system ganglia and the parasympathetic nervous system ganglia (both carry nicotinic receptors). After all, you may have side effects.

However, antagonists of the neuromuscular junction are useful in the treatment and are known as neuromuscular blocking agents.

B2A. Competitive (Nondepolarizing) Blocking Agents

•They compete with ACh for the recognition site on the nicotinic receptor by preventing depolarization of the end plate by the neurotransmitter.

•The concentration of this drugs determines the degree of blockade.

•Their activities can be eliminated by acetylcholinesterase inhibitors.
- [Mostly Neostigmine is used for this purpose].

Tubocurarine-like Drugs

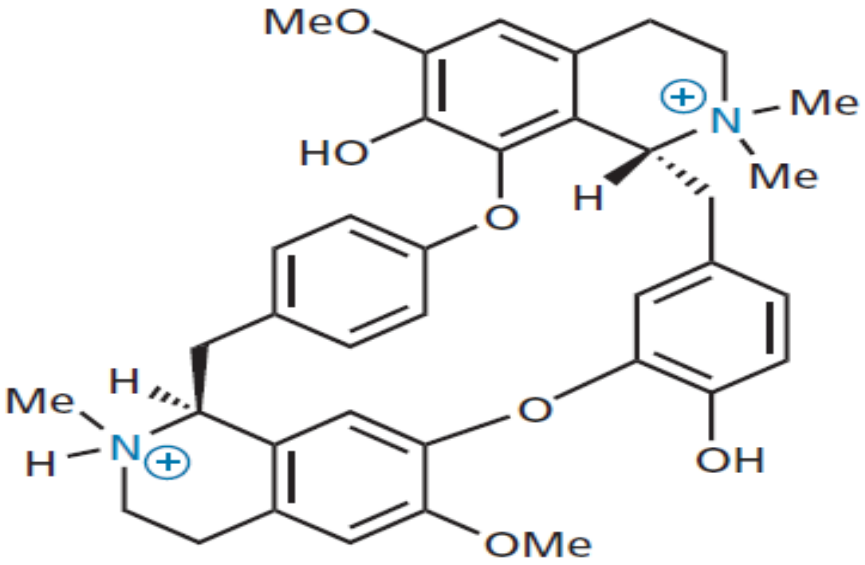
Curare ve D-Tubocurarine

CURARIN-Asta®

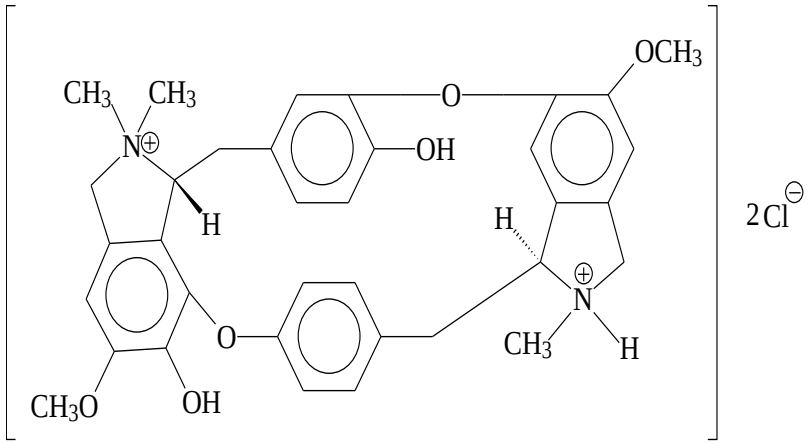
Curare was a term used to describe collectively the very potent **arrow poisons** used since early times by the South American İndians and extracted from curare plant (*Chondodendron tomentosum*).

Curare extracts contain several alkoloids, the most potent of which is **D-Tubocurarine.**

It has a complex structure with two amine functions, one being quaternary and the other tertiary, and both are thought to be involved in the mechanism of the action of tubocurarine.



Tubocurarine.



Tubocurarine-like Drugs

Curare ve D-Tubocurarine

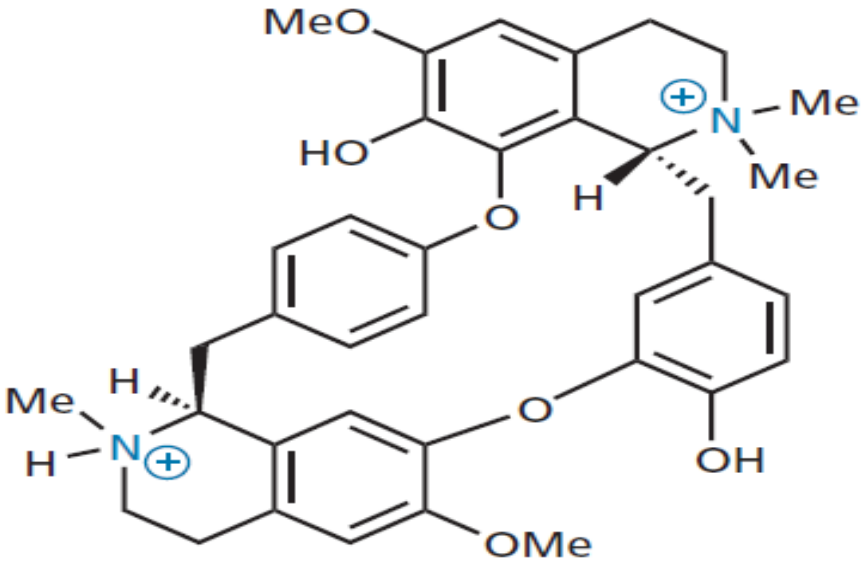
CURARIN-Asta®

Tubocurarine causes a hypotension due to a moderate release of histamine and blocks the autonomic ganglionic nicotine receptors, producing a vagolytic effects (tachycardia).

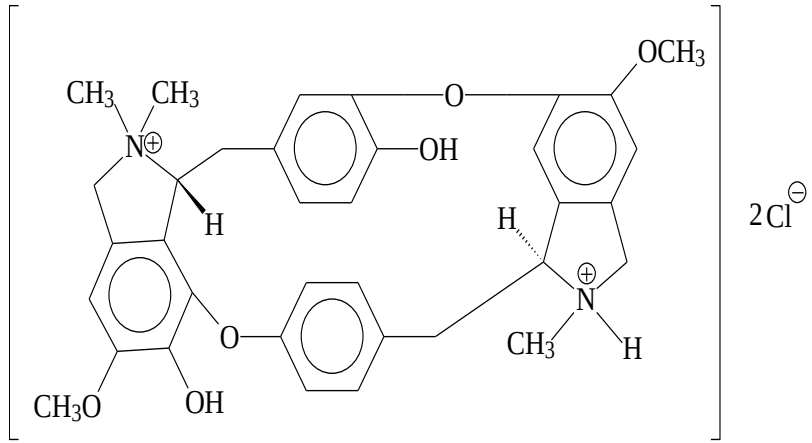
It is still employed in doses of 0.12-0.4 mg/kg and its action lasts for 60-90 minutes.

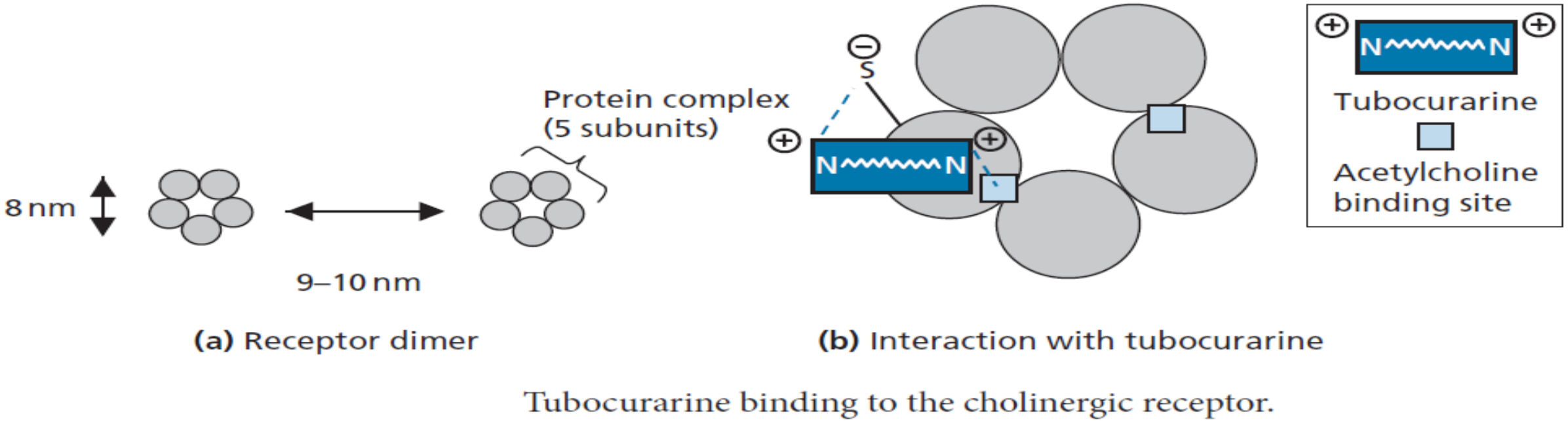
It causes paralysis (blocks ACh signals to muscles)

The paralysis of the muscles develops sequentially and due to the increase of the dose, the inter-costal muscles and diaphragm may be paralyzed and the respiration may stop. An oxygen mask may be required at any time during the administration of such medicines.



Tubocurarine.

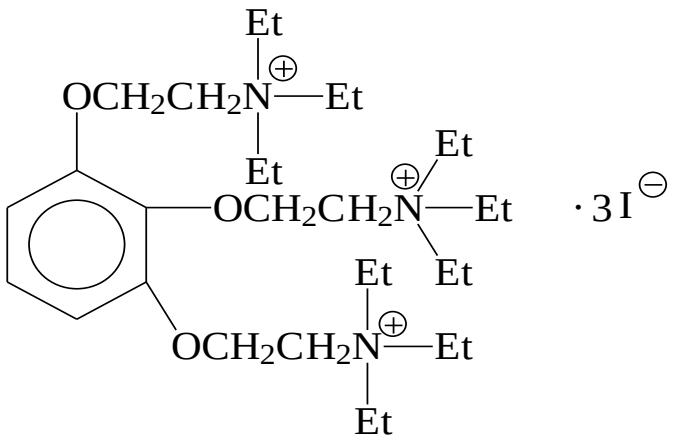




Tubocurarine binding to the cholinergic receptor.

One of the charged nitrogen is bound to the cholinergic binding site; the other interacts with a nucleophilic group adjacent to the binding site.

Gallamine Triethiodide FLAXEDIL

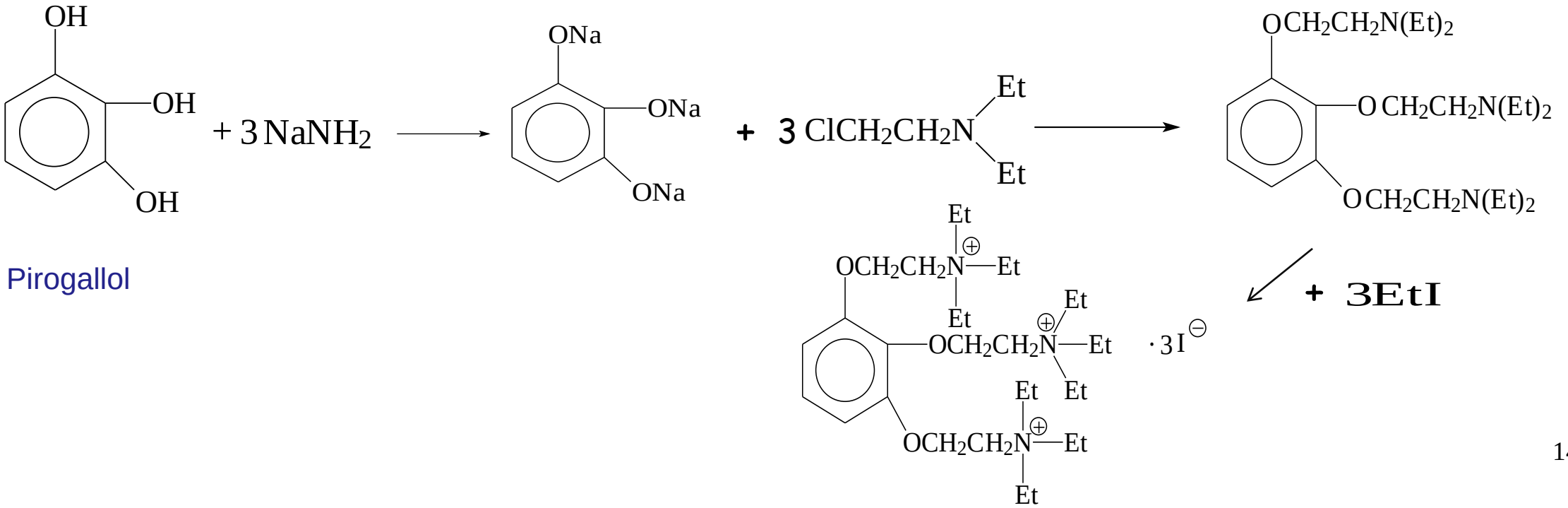


1,2,3-tri(2-diethylaminoethoxy) benzen tri ethyl iodide

- ✓ Synthetic compound with curariform activity.
- ✓ It is a skeletal muscle relaxant. It has a strong vagolytic effect.
- ✓ It is used in general anesthesia by IV.
- ✓ It does not make histamine releasig like D-Tubocurarine

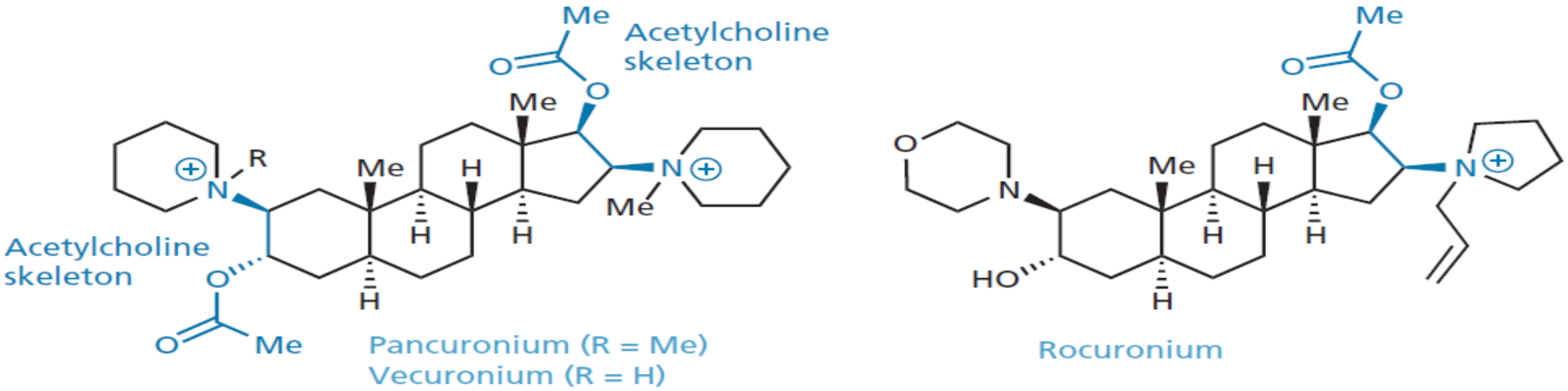
- ✓ **Contraindicated:** Myestenia gravis

Sentezi



Pirogallol

Steroidal [Androstan] Neuromuscular Blocking Agents

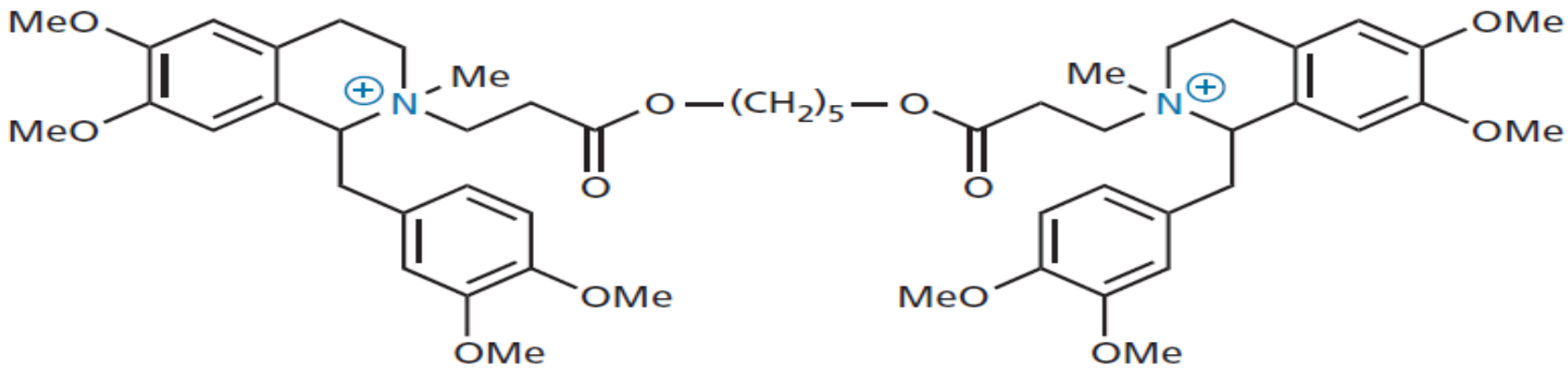


Steroidal neuromuscular blocking agents.

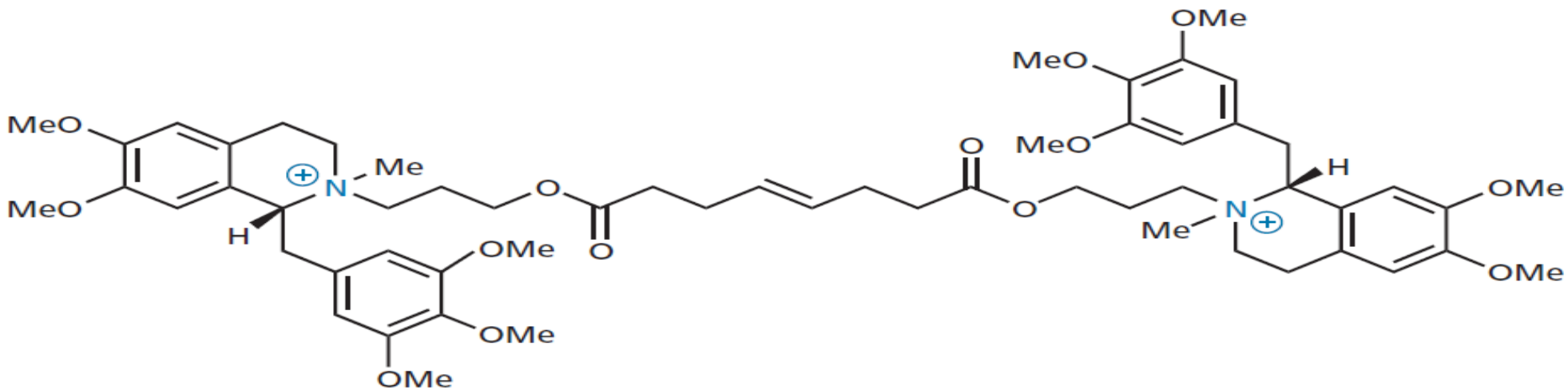
Pancuronium Br PAVULON ®

- It was first steroid-like neuromuscular blocking agent employed in clinical use. It is composed of two acetylcholine motifs seperated by a rigid steroid-like structure. The acetylcholine motifs use parts of the steroid as the two carbon separator bridge, and the quaternary ammonium groups are incorporated into a piperidenium ring.
- It is more potent than D-Tubocurarine.
- It has little or no histamine-releasing potential or ganglion-blocking activity.
- It is used in the anesthetic procedure to relax the skeletal muscle.

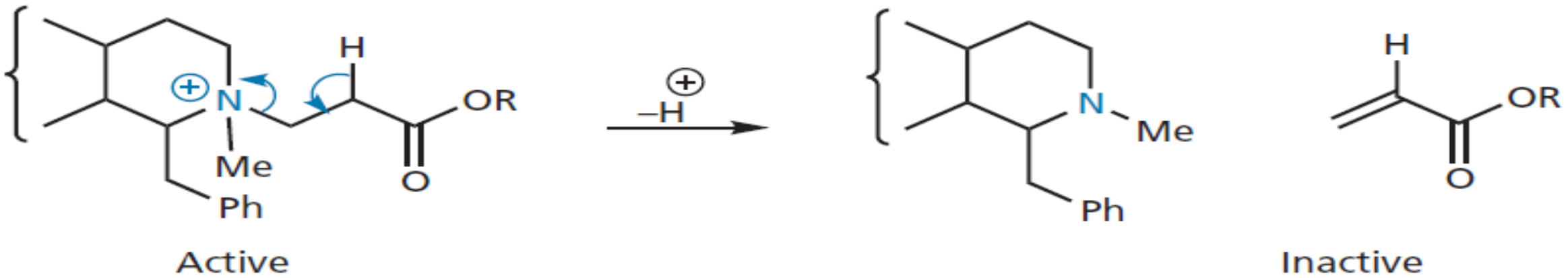
İsoquinoline derivatives as neuromuscular blocking agents



Atracurium.



Mivacurium.



Active

Inactive

Hofmann elimination of atracurium.

B2B. Non-Competitif (Depolarizing) Blocking Agents

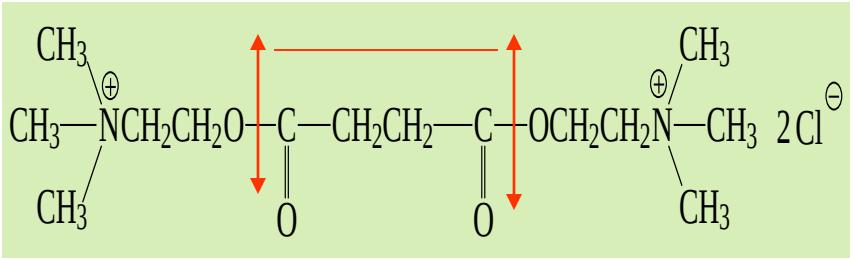
Drugs in the category of depolarizing blocking agents depolarize the membrane of the muscle end plate. This depolarization is quite similar to that produced by ACh itself at ganglia and neuromuscular junctions (its so-called nicotinic effect), with the result that the drug, if in sufficient concentration, eventually will produce a block.

The effects of these drugs on neuromuscular junction are similar to acetylcholine. They affect cholinergic receptors and make depolarization like ACh. However, the depolarization performed by this group of drugs takes longer time.

The effect of this group of compounds is the accumulation of ACh at the NM junction. Therefore, striated muscle paralysis develops because of continuous depolarization.

Succinylcholine (Suxamethonium®) Cl LYSTENON

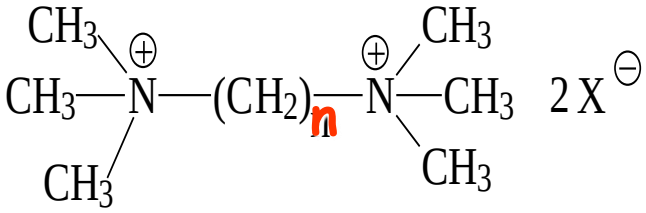
Choline and succinic acid form the ester



- Succinylcholine is characterized by a very short duration of action and a quick recovery because of its rapid hydrolysis (by pseudocholinesterases) after injection.
- It is used with saline in long-term anesthesia applications.
- The effect starts at 1 min and continues till 4-5 min.
- Like ACh , it's is rapidly metabolized in blood and thus has short duration of action of about 6 to 8 mins.
- It should not be used with thiopental sodium because of the high alkalinity of the latter. If used together, they should be administered immediately after mixing; However, separete injection is preferable.

Bis-Quaternary Ammonium Derivatives

They contain lots of methyl groups. Therefore they called as Methonium Derivatives. [n number determines activity].

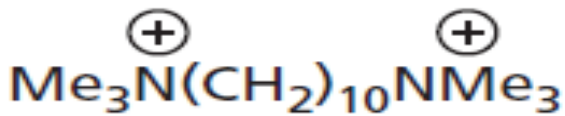


(n) number = **3** or **4** no curar-like activity

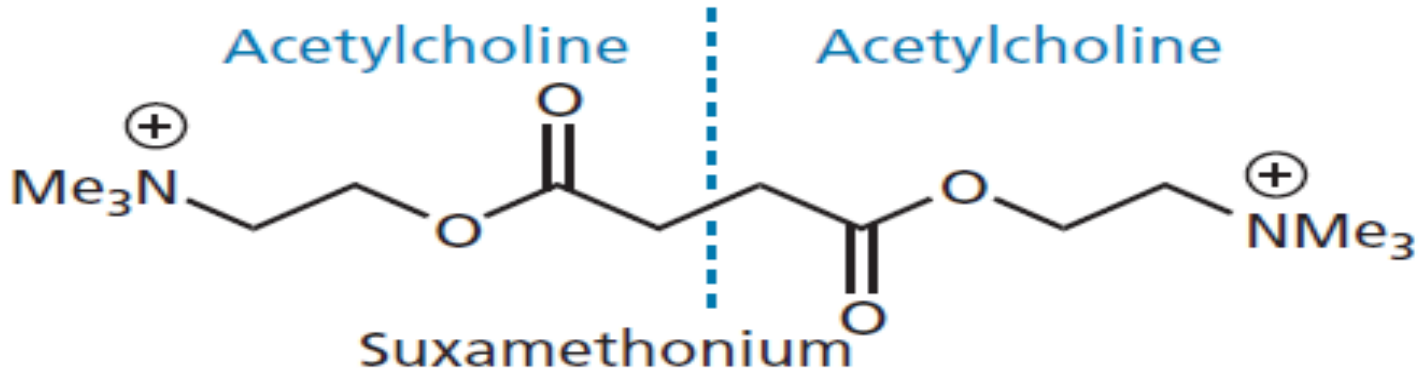
= **5** or **6** little curar-like activity , and ganglionic blocker activity

= **10**, curar-like aktivity is optimum.

= If greater than **10** the curar-like activity starts to decrease

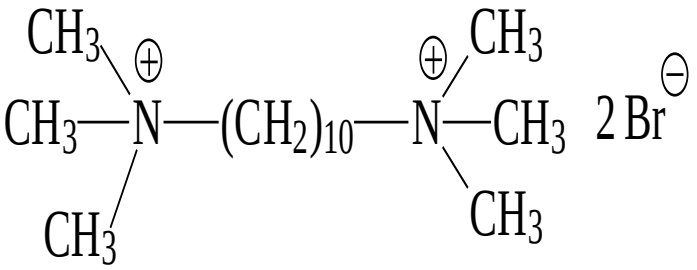


Decamethonium



Decamethonium and suxamethonium.

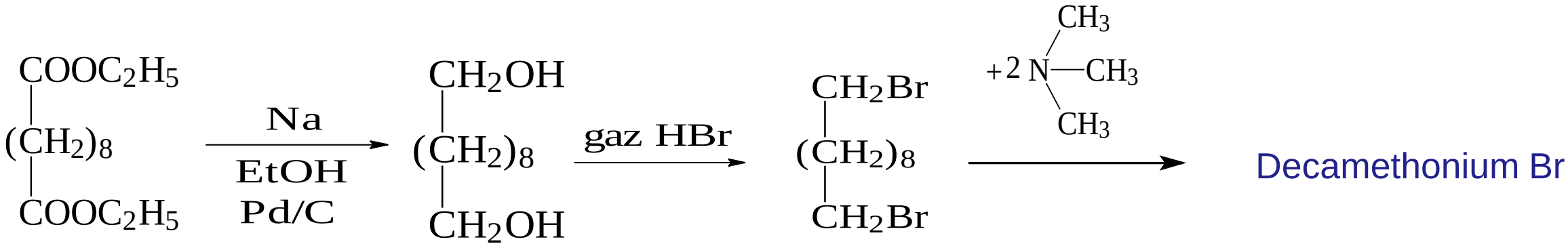
Decamethonium Br



Bis(trimethylammonium)decamethylen dibromide

- Relax the skeletal muscles at the desired dose.
- If the dose increases, the duration of the effect is long, so paralysis can develop.
- Does not cause histamine release.
- Pseudocholinesterases do not disrupt the structure.
- It is a controlled and infrequently used compound.

Synthesis ;



Decandioic acide