Muscle relaxants

•cause relaxation of striated (voluntary skeletal) musculature (in contrast to spasmolytics which relax unstriped musculature)

Classification of myorelaxants

1. Neuromuscular blocking drugs

•periferial (direct) myorelaxants: interact with acetylcholine nicotinic (N) receptors of skeletal musculature

a) stabilizing myorelaxants – N-receptors antagonists

b) depolarizing myorelaxants – N-receptors agonists

•continuous N-receptors stimulation $\Rightarrow$ depolarization of cells $\Rightarrow$ functional antagonism: further leading of impulses imposible, no muscle contraction

c) indirect myorelaxants: botulinum toxin

•irreversibly inhibits acetycholine releasing

2. Central muscle relaxants

•acts in CNS

•structurally heterogenic group

•compounds with various mechanisms of action

Stabilizing myorelaxants

- N-receptors antagonists in skeletal muscle cells
- usage: surgical operative measures (often as a part of some form of anaesthesia)
- structures derived from curare alkaloids

Curare: arrow poison of South American Indians

- preparation from various plants
- contained a complex mixture of alkaloids

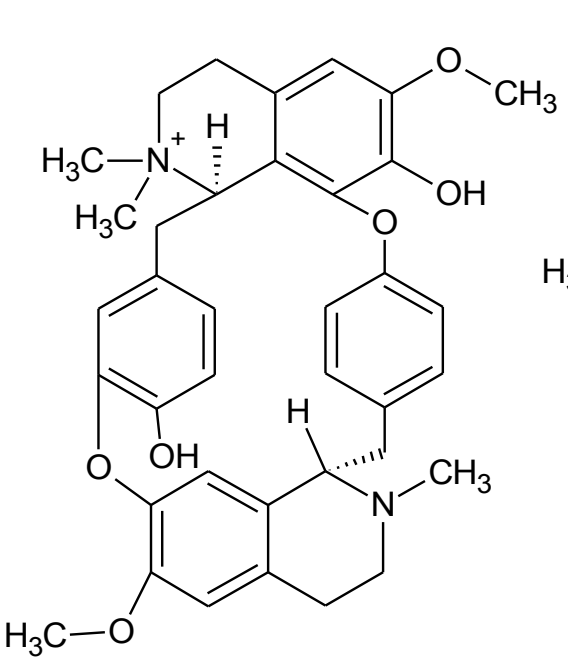
Curare classification: according to preparation and package in which it was shipped to Europe

1. Tubocurare: in hollow bamboo rods
2. Calebase curare: in bottle-shaped cucurbits (gourds, calabashes - from plants of genus *Strychnos*)
3. Pot curare: in ceramic vessels

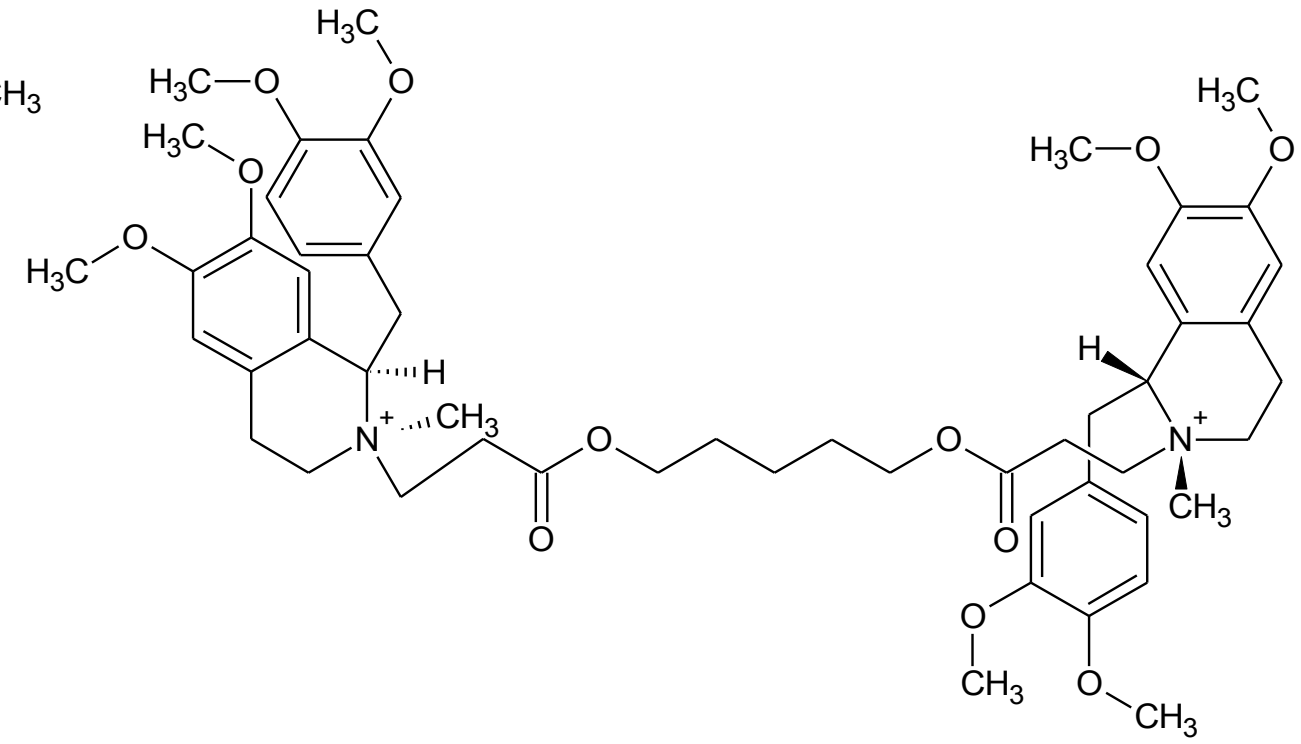
Structural types:

1. Benzyltetrahydroisoquinolines:	tubocurarine (from tubocurare) atracurium besylate (synthetic) mivacurium besylate (synthetic) etc.
2. Indole derivatives:	toxiferine C alcuronium chloride
3. Steroids with basic substituents:	vecuronium bromide pancuronium bromide rocuronium bromide

1. Benzyltetrahydroisoquinolines

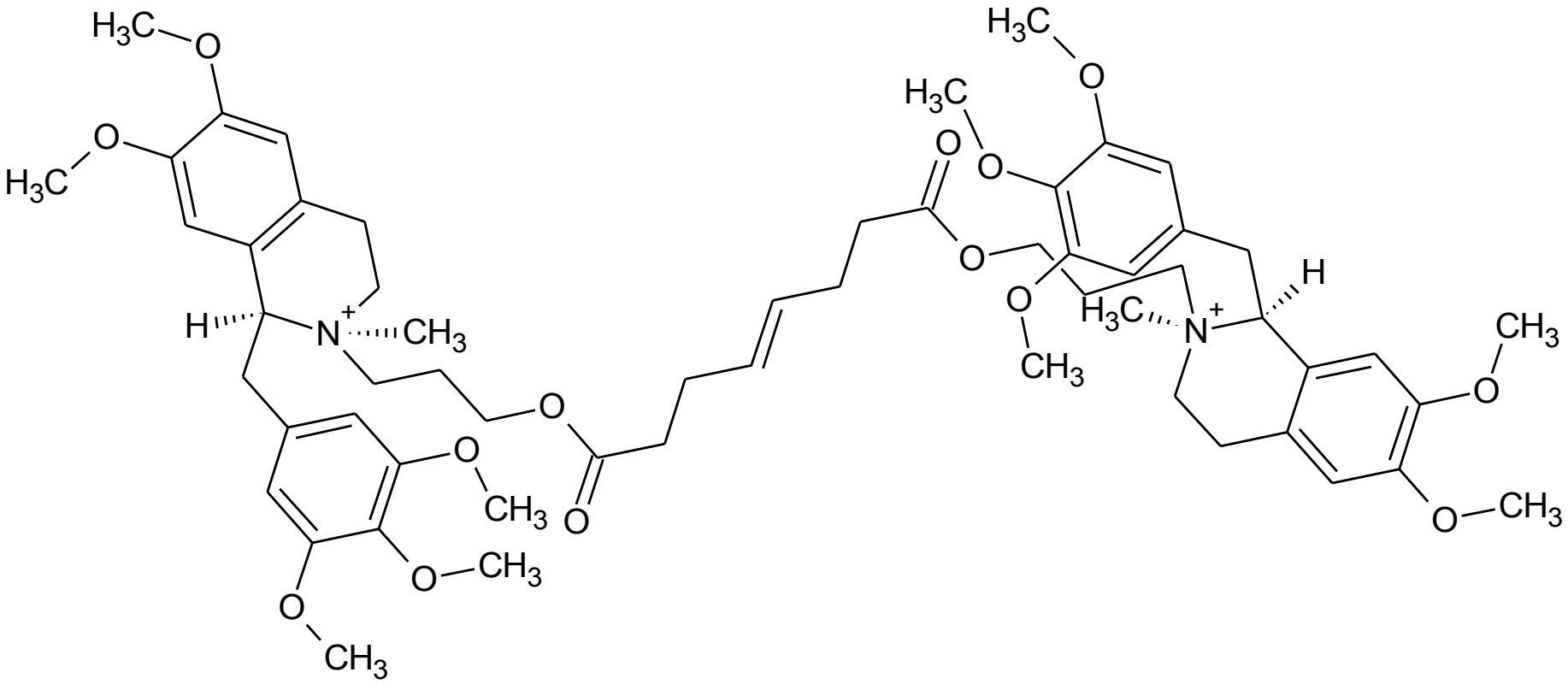


tubocurarine



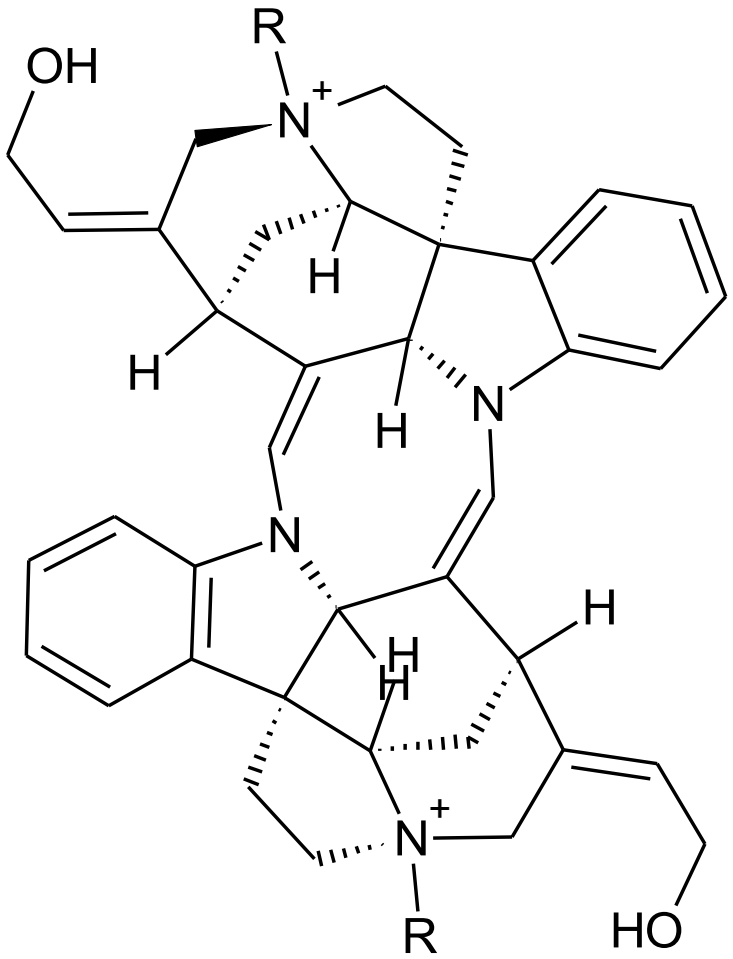
atracurium
•used as besylate
Tracrium ® inj. sol.

1. Benzyltetrahydroisoquinolines (continued)



mivacurium
•used as besylate
Mivacron ® inj. sol.

2. Indole derivatives

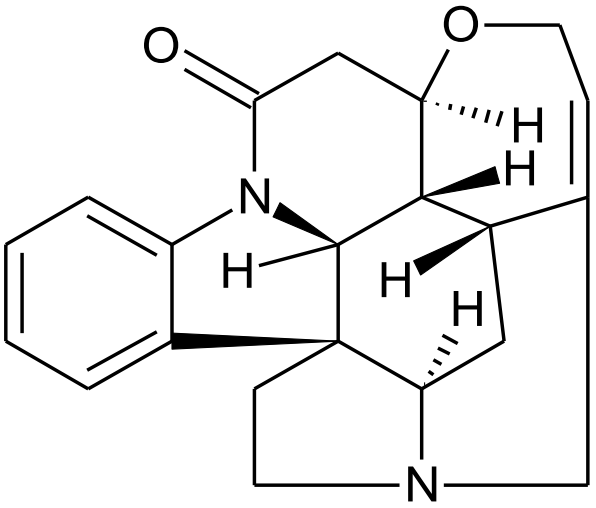


R = -CH_3 **toxiferine C**

•natural

R = -$CH_2CH{=}CH_2$ **alcuronium**

•as chloride

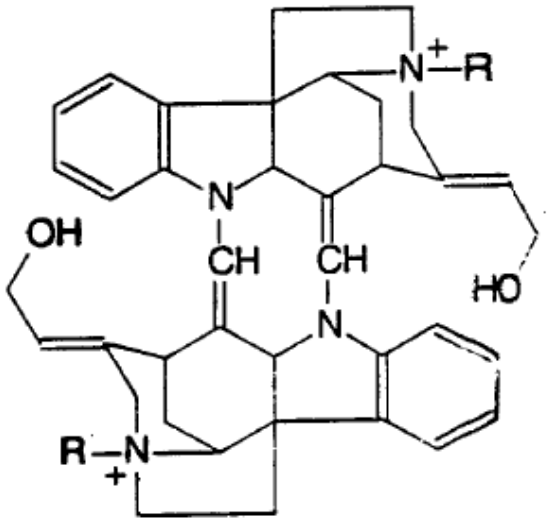


•for comparison: **strychnine**

•from *Strychnos nux vomica*

•in small amounts as central analeptic (obsolete)

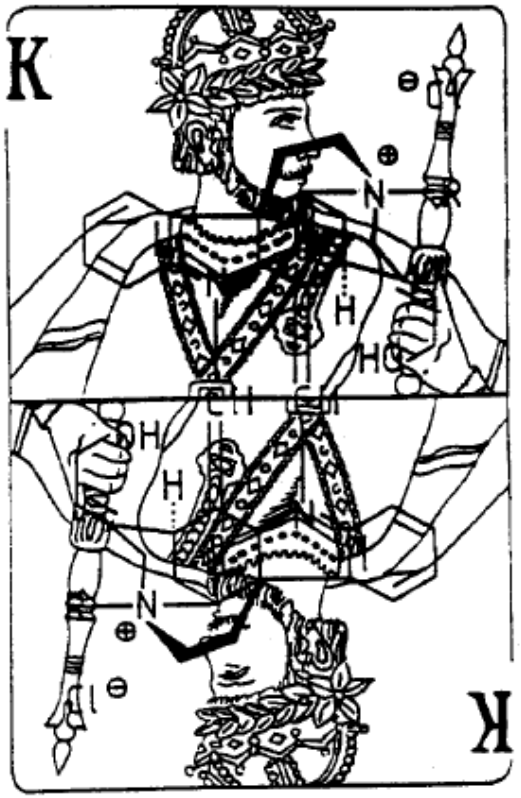
Stereochemistry: „playing cards symmetry“



2 Cl⁻

R = CH_3 C - Toxiferin I

R = CH_2–CH=CH_2 Alcuroniumchlorid



toxiferin C
alcuronium chloride

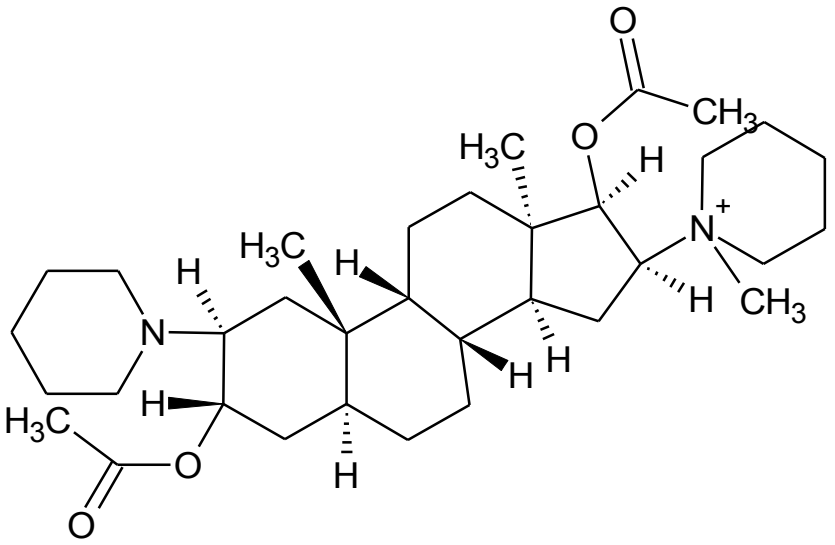
•structure similarity with strychnine, both indole alcaloids
•dimer
•2x pentacyclic system
•2 quarternary ammonium moieties

Stereochemistry:
•chiral
•contain C2 symmetry axis: „playing cards symmetry“

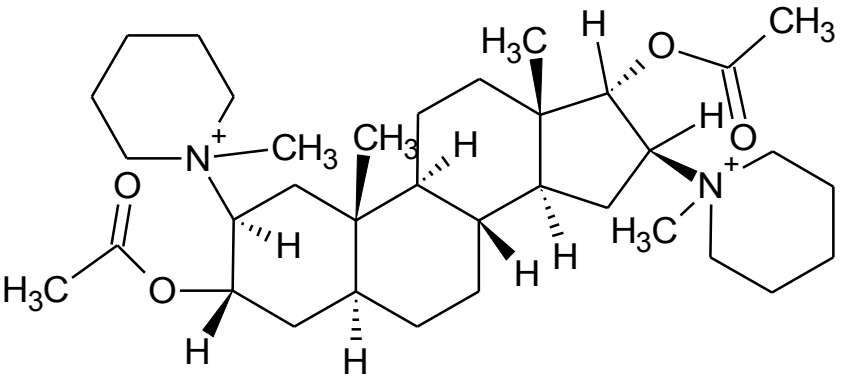
Effects of alcuronium chloride
•more active than tubocurarine
•relatively short time of action
•not absorbed from GIT
•very stable, excreted in unchanged form

Preparation:
•partial synthesis from strychnine

3. Steroids with basic substituents



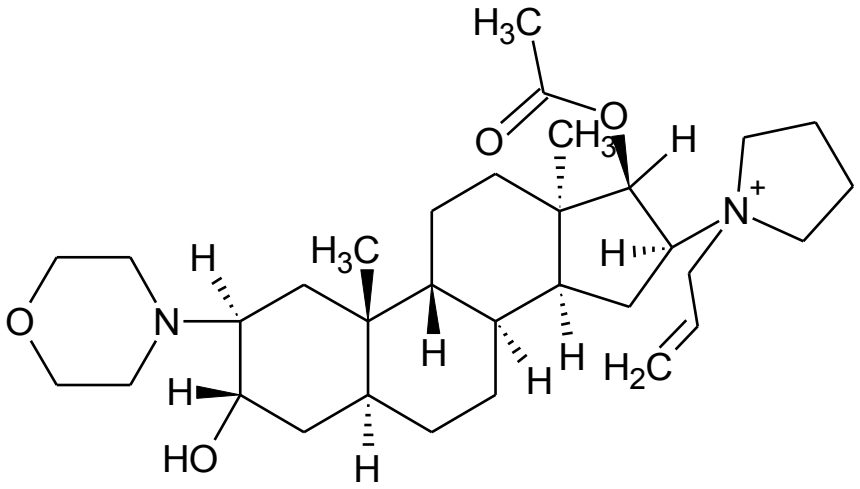
vecuronium
Norcuron ® inj.



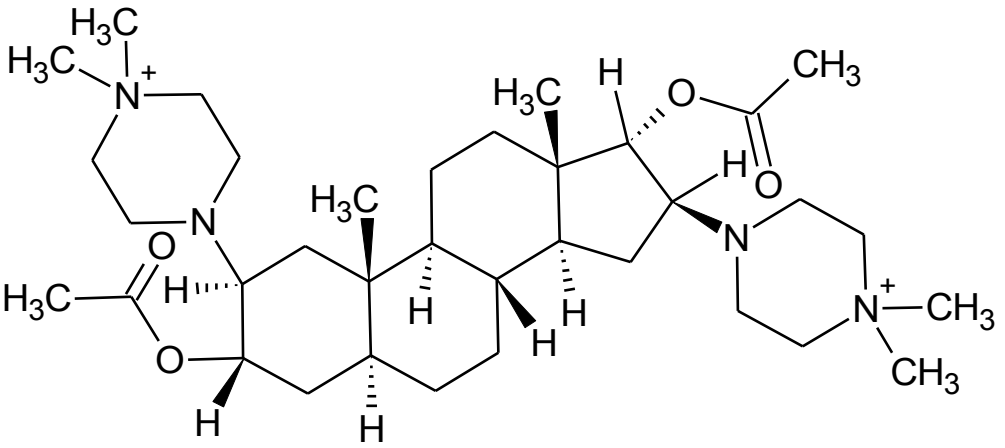
pancuronium
Pavulon ® inj. sol.

•as bromides

3. Steroids with basic substituents (continued)



rocuronium
Esmeron ® inj. sol.
•facilitation of tracheal intubation



pipecuronium
Arduan ® inj. sicc. + solv.

Depolarizing myorelaxants

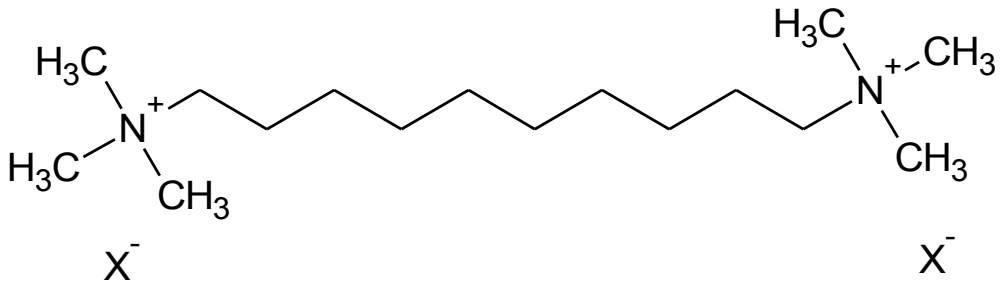
•agonist of N-receptor

•continuous depolarization leads to muscules slack

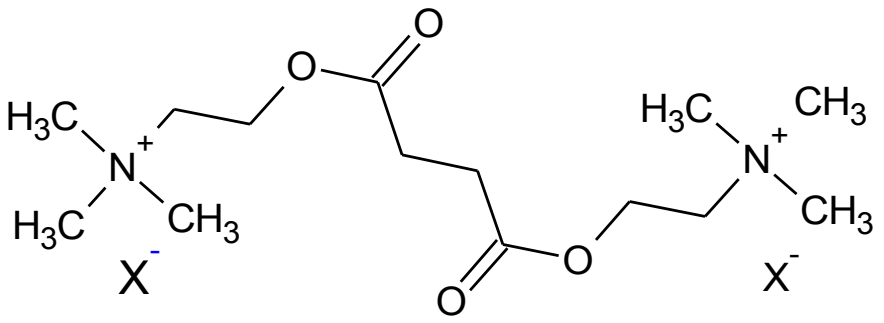
Usage: introduction into general anaesthesia (intubation)

Compounds: synthetic bis-quarternary ammonium salts

•originated by simplifying of tubocurarine structure

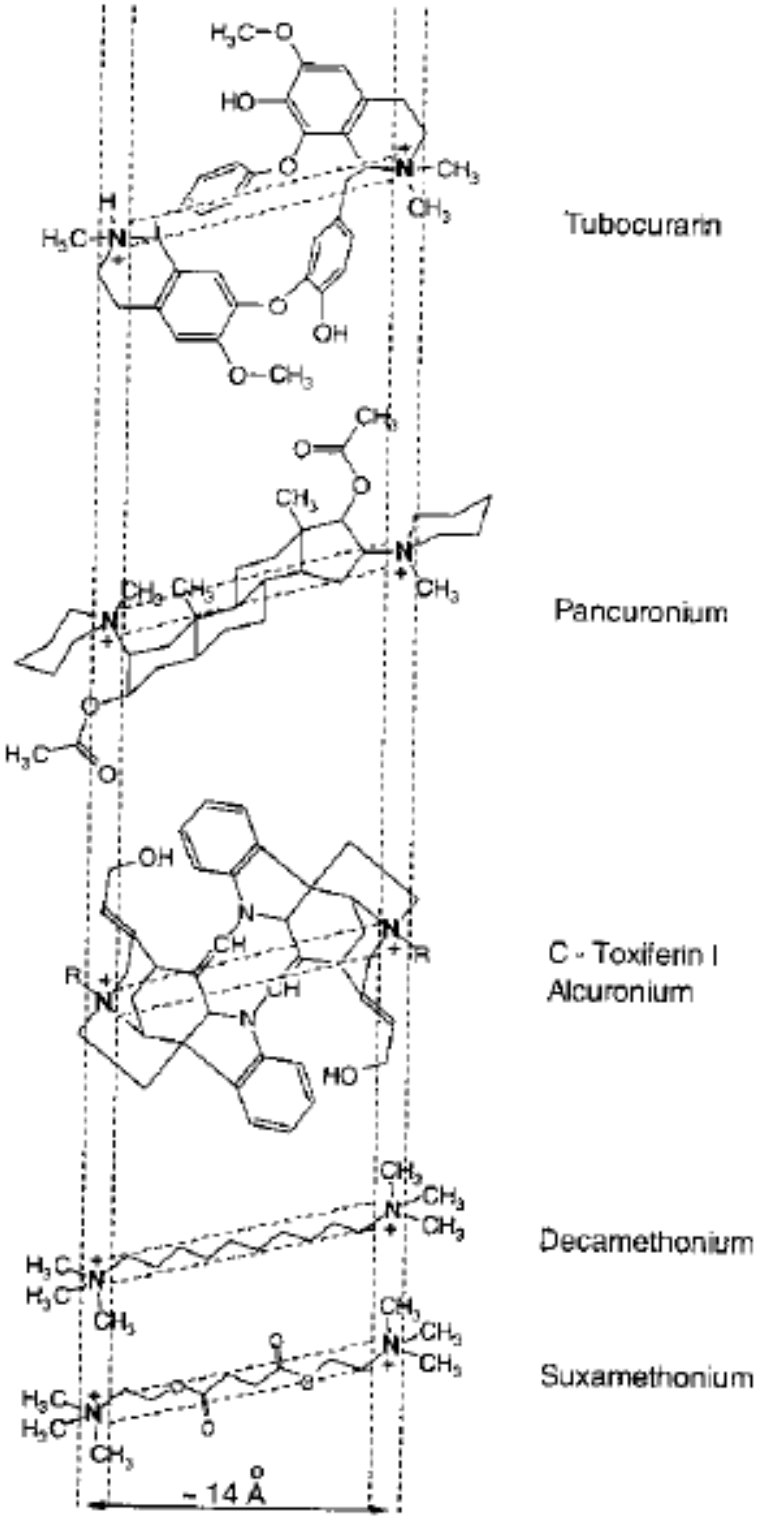


dekamethonium (halide)
•non-hydrolyzable
•comparatively toxic
•long effect



suxamethonium (halide)
syn. succinylcholine (halide)
•hydrolyzable
•fast cleft by esterases ⇒ short effect
Succinylcholinjodid Valeant ® inj. plv. sol.

Comparison of molecule sizes of direct muscule relaxants



Indirect myorelaxants

Botulinum toxin

- protein with M_r about 150, 000
- product of anaerobic bacterium *Clostridium botulinum* (serotypes A – G: A – Botox infusion; B - Neurobloc infusion)
- extremely toxic (food poisoning, potential biologic weapons)

Indications: cervical dystonia, facial spasms, writer's cramp and other spasms

- in cosmetics for smoothing of wrinkles – very hazardous

- irreversibly inhibits acetylcholin release
- local injection into the particular muscle
- blocks transfer of impulse by means of acetylcholine to the muscle
- muscle paralysis
- to hands of qualified physicians only
- by no means can reach bloodstream
- new injection is possible after 3 – 4 months (the effect is poorly estimable in shorter intervals due to possible formation of antibodies)

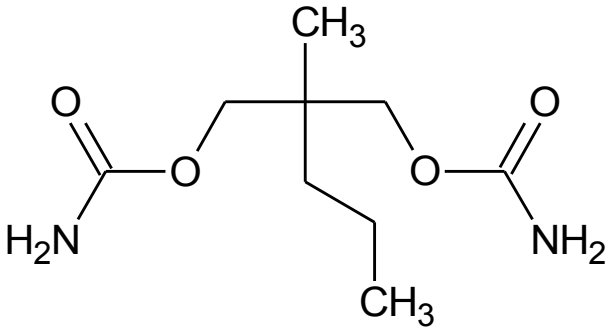
Central muscle relaxants (myotonolytics)

Using: painful spasms of skeletal muscles (not in surgical measures)

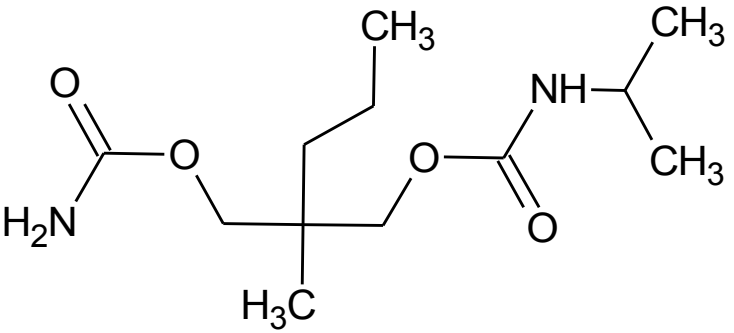
Structures: heterogenic group
Mechanisms of action: various, not perfectly known in every case
•im most they act sedatively in high doses

Central muscle relaxants (myotonolytics)

Carbamates derived from diols



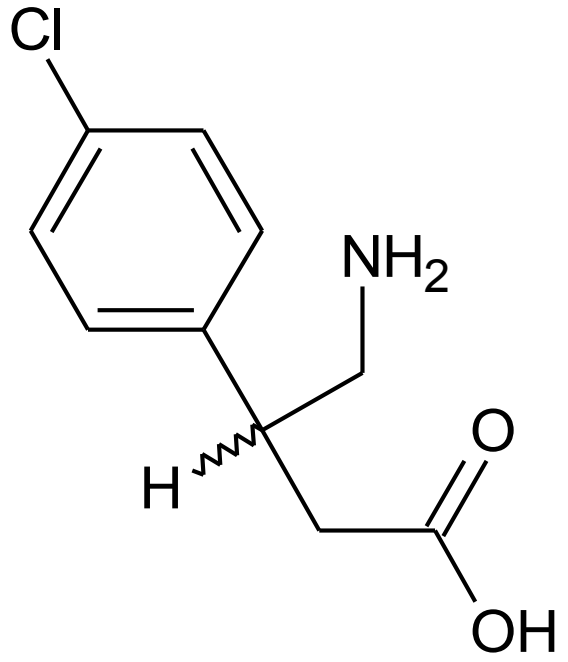
meprobamate



carisoprodol

•myorelaxant, sedative, anxiolytic

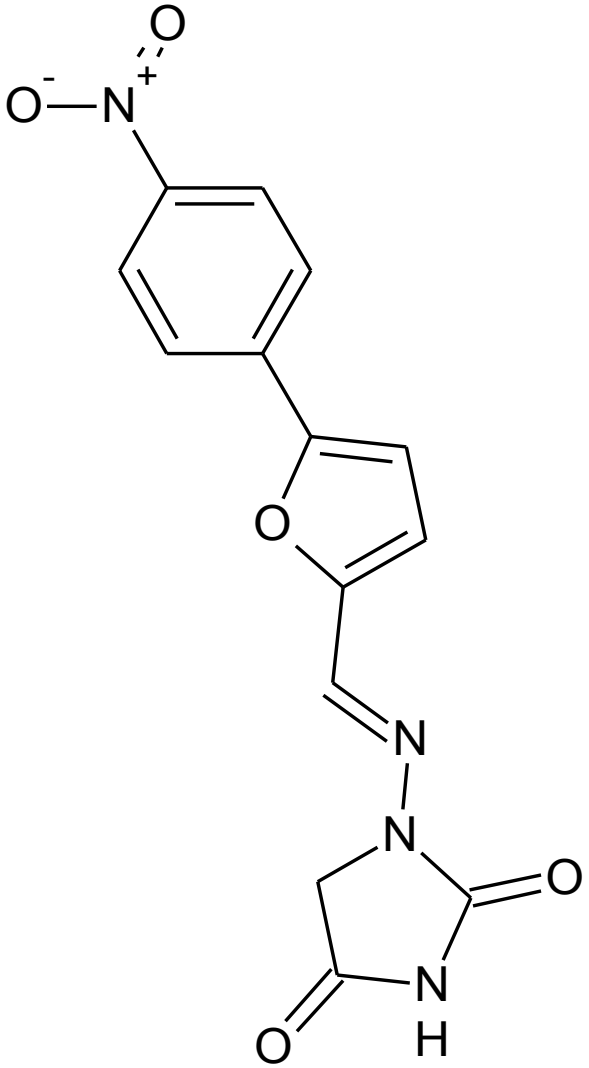
•effectiveness unsure



baclophene

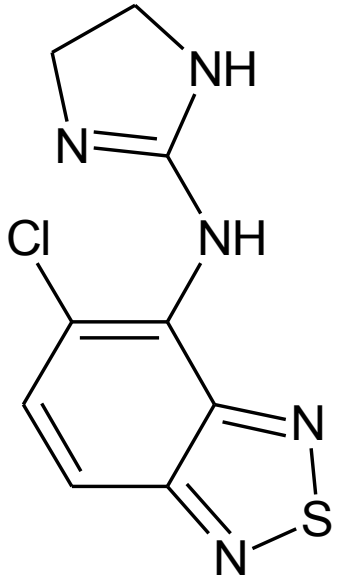
- GABA derivative
- $GABA_B$ receptor agonist
- blocks voltage-gated input of Ca^{2+} into CNS neurons

Usage: spasmodic conditions (sclerosis multiplex, cramps in crucial region etc.)



dantrolene

- hydantoine derivative
- myorelaxant
- Mode of action: directly to skeletal muscles; lowers Ca^{2+} release



thizanidine

- myorelaxant, analgesic, antihypertensive
- probably α_2 receptors agonist
- blocks release of excitation transmitters (glutamate, aspartate)
- usage: eg. *sclerosis multiplex*, ischias