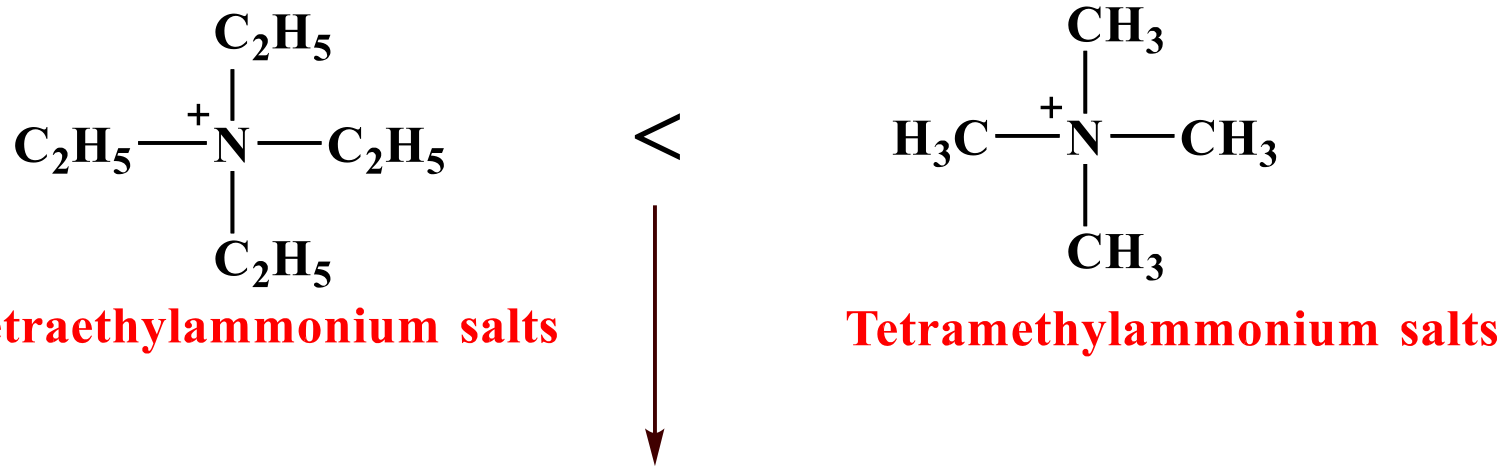
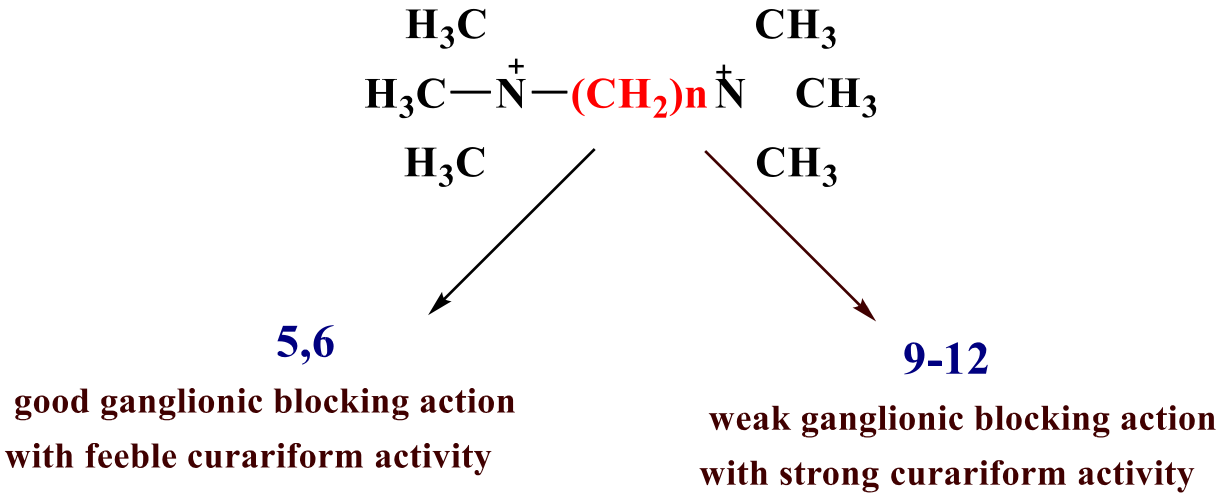
GANGUONIC BLOCKING AGENTS



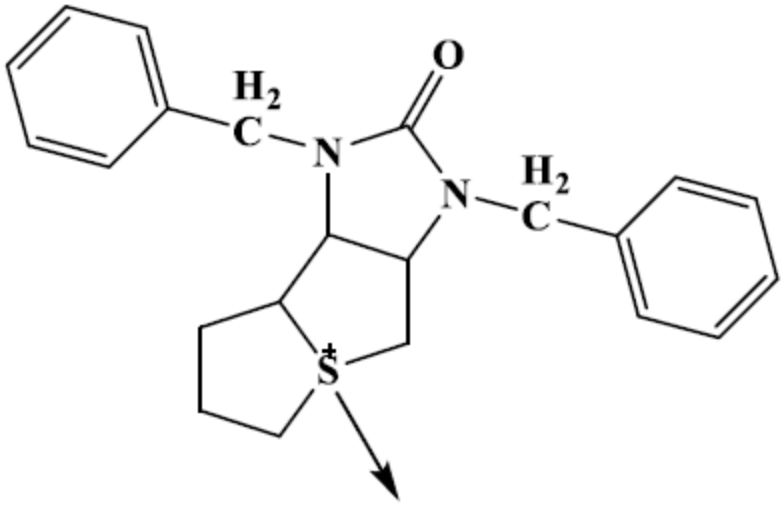
The first ganglionic blocking agents used in therapy were tetraethylammonium chloride and bromide. Although one might assume that curariform activity would be a deterrent to their use, the curariform activity of the tetraethyl compound is less than 1% of that of the corresponding tetramethylammonium compound.

Paton and Zaimis



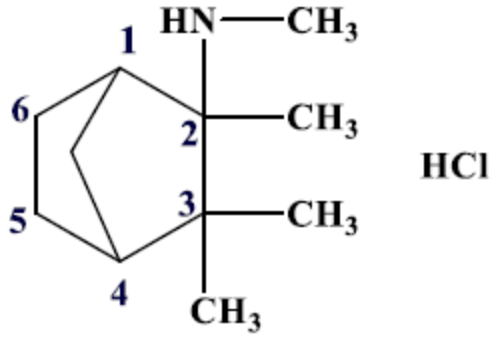
As shown, their findings indicate that there is a critical distance of about five to six carbon atoms between the onium centers for good ganglionic blocking action. Interestingly, the pentamethylene and hexamethylene compounds are effective antidotes against the curare effect of the decamethylene compound. Hexamethonium bromide and hexamethonium chloride emerged from this research as clinically useful products.

Trimethaphan Camsylate



1- completely ionic compound
2- rapid ganglion-blocking action on parenteral injection
3- its action is short
4- The drug is ineffective when given orally.
5- The usual route of administration is IV
6- Trimethaphan camsylate is indicated in the treatment of hypertensive emergencies to reduce blood pressure rapidly.

Mecamylamine



N,2.3,3-tetramethyl-2-norbornanamine hydrochlorid

1- It is 2°amine
2- well absorbed from the GIT
3- has longer duration of action
4- has a powerful ganglionic blocking effect that is almost identical to that of hexamethonium.
5- It is rarely used, however, for the treatment of moderate-to-severe hypertension because severe orthostatic hypotension occurs when sympathetic gainglia are blocked by drug.

NEUROMUSCULAR BLOCKING AGENTS

Agents that block the transmission of ACh at the motor end plate are called *neuromuscular blocking agents*.

These block the action of Ach at the end plate of NMJ, have curariform or curarmimetic action. Since the muscle is not surrounding by membrane like BBB, 4°ammonium compounds and large molecule can enter and act efficiently at NMJ, so structural variation have little influence on the activity.

The therapeutic use of these compounds includes-:

1- adjuvant in surgical anesthesia to obtain relaxation of skeletal muscle.

2- They also are used in various orthopedic procedures, such as alignment of fractures and correction of dislocations.

The neuromuscular junction consists of the axon impinging onto a specialized area of the muscle known as the muscle end plate. The axon is covered with a myelin sheath, containing the nodes of Ranvier, but is bare at the ending. The nerve terminal is separated from the end plate by a gap of 200 Å. The subsynaptic membrane of the end plate contains the cholinergic receptor, the ion-conducting channels (which are opened under the influence of ACh), and AChE.

One of the anatomical differences between the neuromuscular junction and other ACh-responsive sites is the absence in the former of a membrane barrier or sheath that envelopes the ganglia or constitutes the blood-brain barrier.
This is important in the accessibility of the site of action to drugs, particularly quaternary ammonium compounds, because they pass through living membranes with considerably greater difficulty and selectivity than do compounds that can exist in a nonionized species. The essentially bare nature (i.e., lack of lipophilic barriers) of the myoneural junction permits ready access by quaternary ammonium compounds. In addition, compounds with considerable molecular dimensions are accessible to the receptors in the myoneural junction.

As a result of this property, variations in the chemical structure of quaternaries have little influence on the potential ability of the molecule to reach the cholinergic receptor in the neuromuscular junction. Thus, the following types of neuromuscular junction blockers have been noted.

Nondepolarizing Blocking Agents

Traditionally, *nondepolarizing blocking agents* is a term applied to categorize drugs that compete with ACh for the recognition site on the nicotinic receptor by preventing depolarization of the end plate by the neurotransmitter.

Thus, by decreasing the effective ACh–receptor combinations, the end plate potential becomes too small to initiate the propagated action potential. This results in paralysis of neuromuscular transmission. The action of these drugs is quite analogous to that of atropine at the muscarinic receptor sites of ACh. Many experiments suggest that the agonist (ACh) and the antagonist compete on a one-tone basis for the end plate receptors. Drugs in this class are tubocurarine, dimethyltubocurarine, pancuronium, and gallamine.

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 (i.e., its so-called nicotinic effect), with the result that the drug, if in sufficient concentration, eventually will produce a block. Either smooth or voluntary muscle, when challenged repeatedly with a depolarizing agent, eventually becomes insensitive.

A- Depolarizing Blocking Agents

Drugs falling in this class are

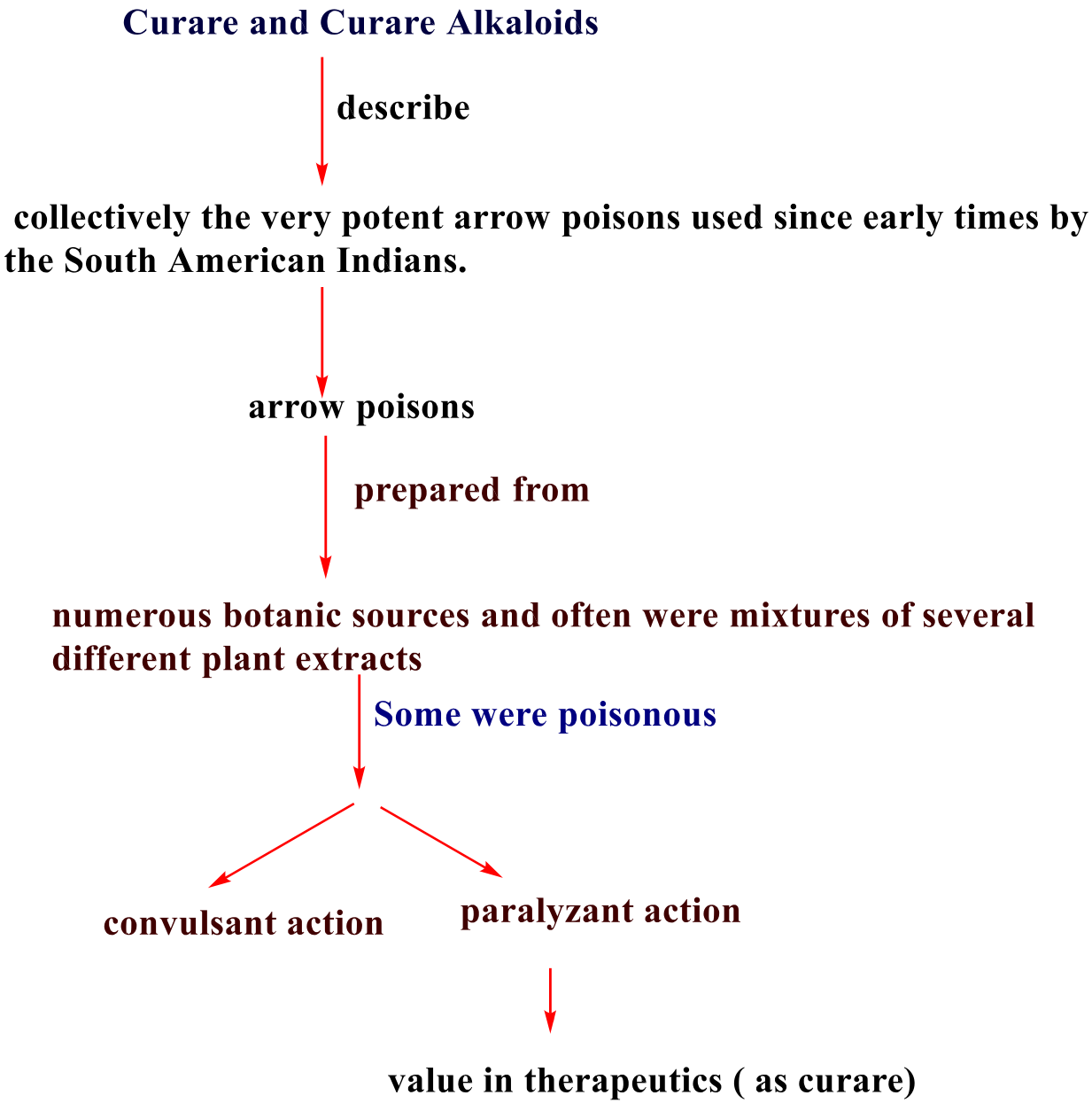
-1Decamethonium
-2Succinylcholine.

B- Non depolarizing Blocking Agents

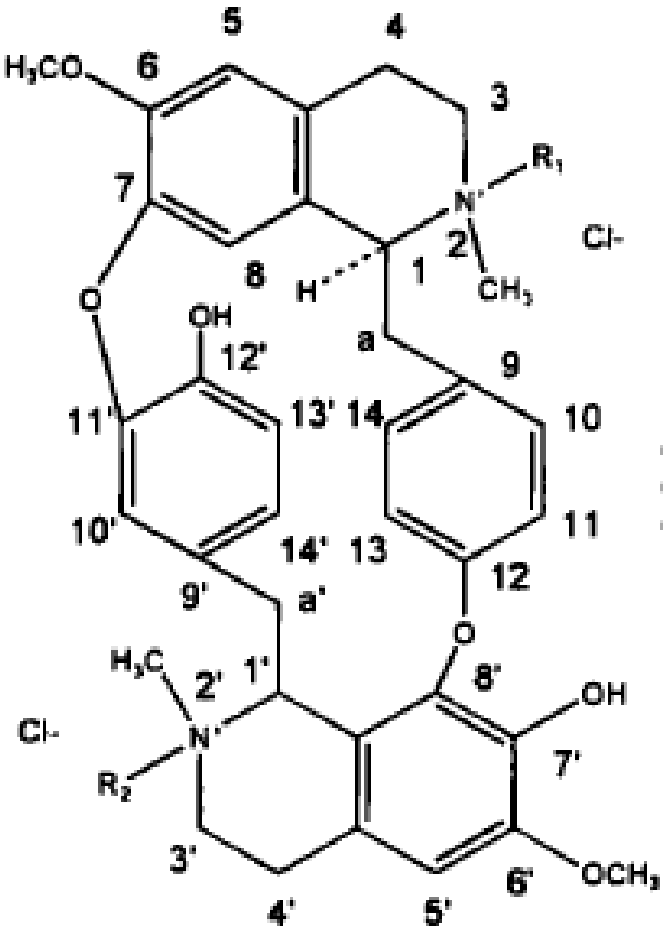
Drugs falling in this class are

-1Tubocurarine
-2Dimethyltubocurarine
-3Pancuronium
-4Gallamine.

Curare and Curare Alkaloids



•**Tubocurarine Chloride (+)-tubocurarinc chloride hydrochloride pentahydrate.**



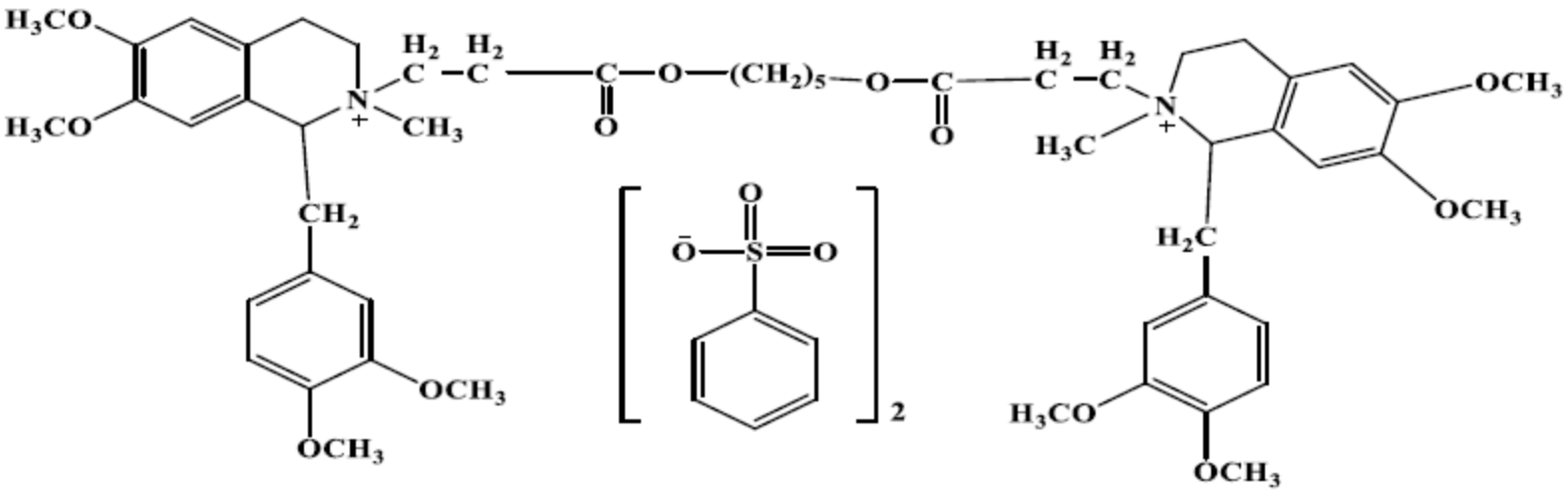
(1a) R_1=R_2= CH_3

(1b) R_1= H; R_2= CH_3

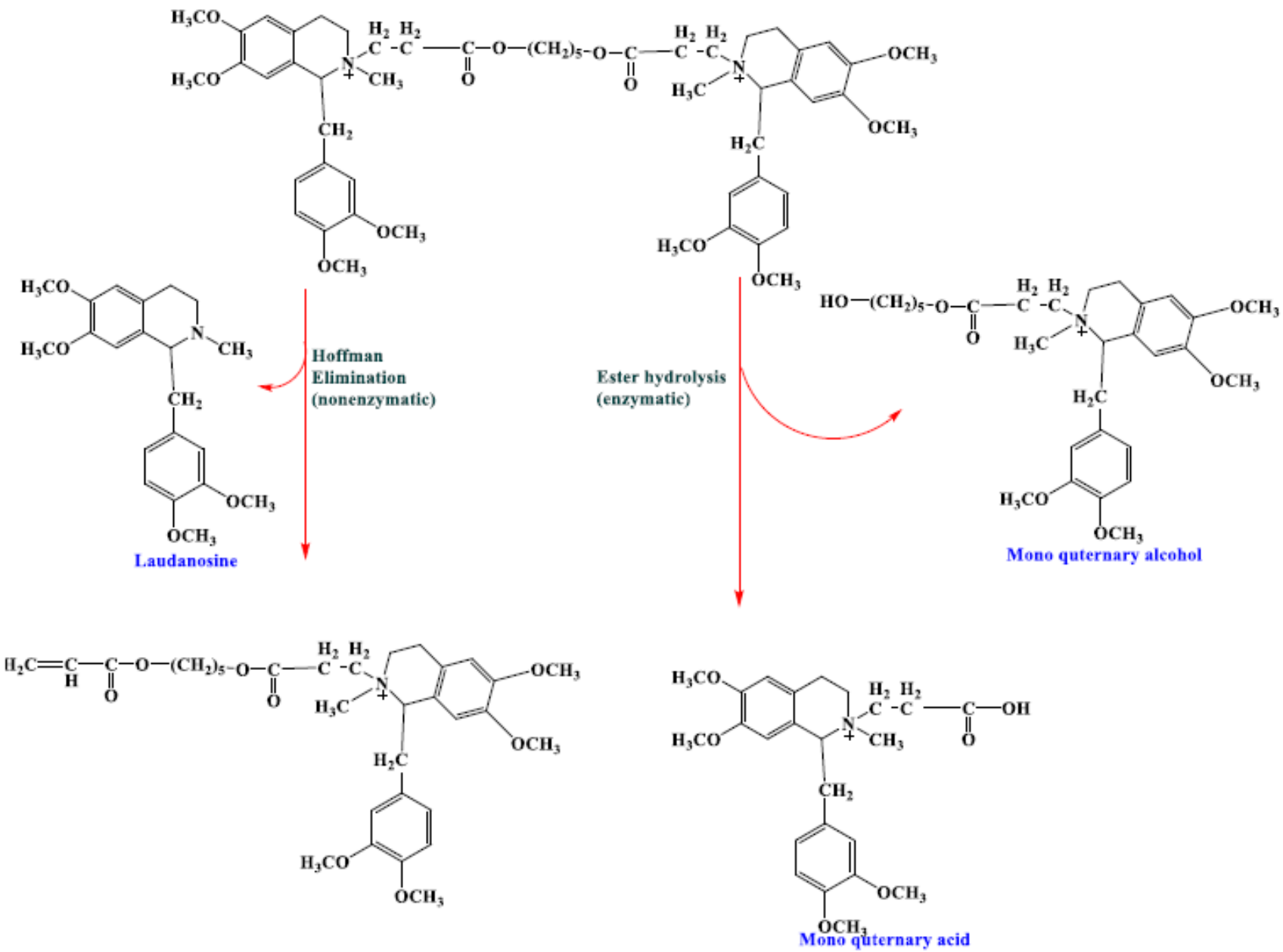
(1c) R_1= CH_3 ; R_2= H

Products

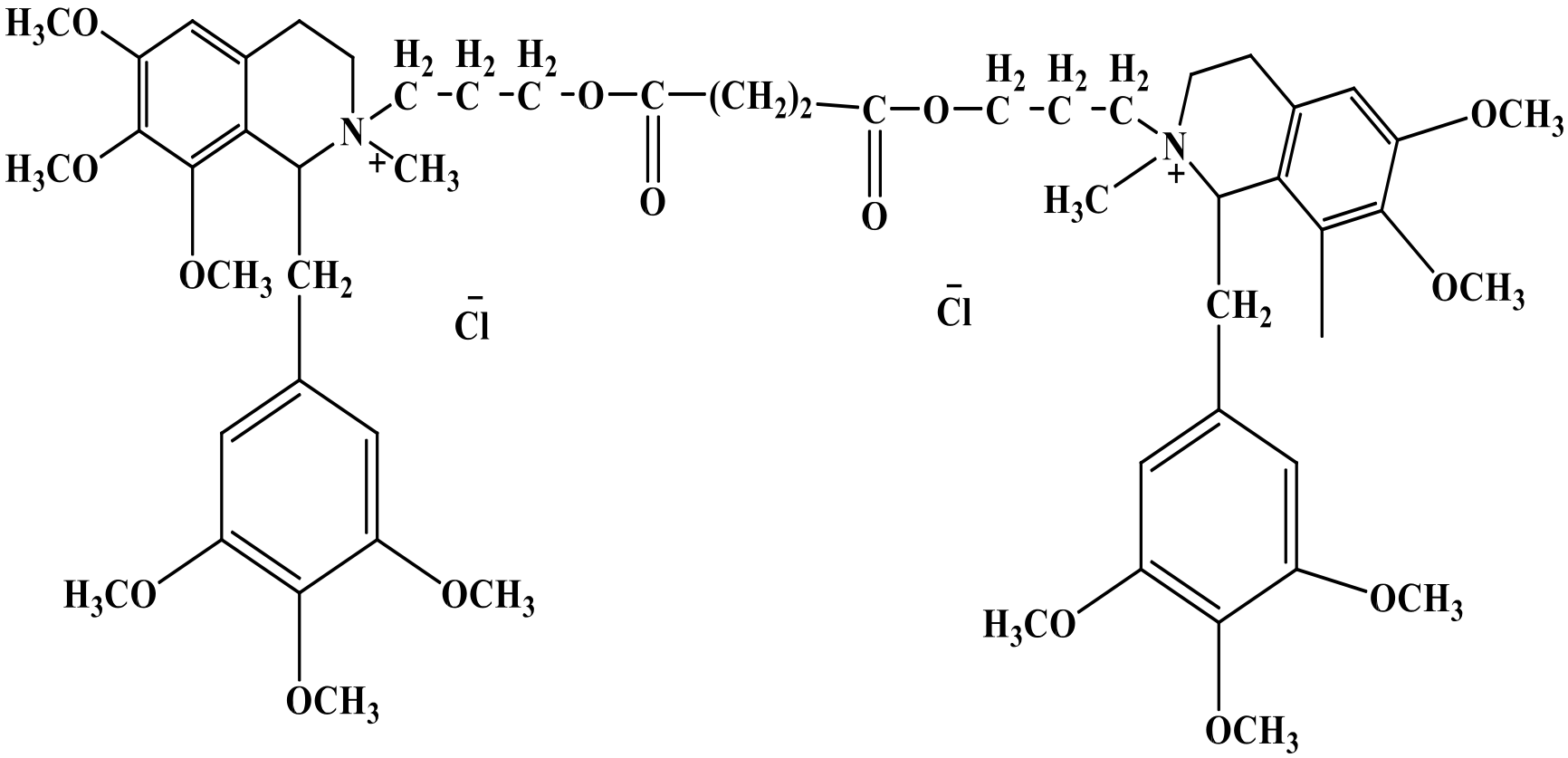
- Atracurium Besylate



2-(2-carboxyethyl)-I ,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl - 1 -veratrylisoquinolinium benzenesulfonate pentamethyleneester

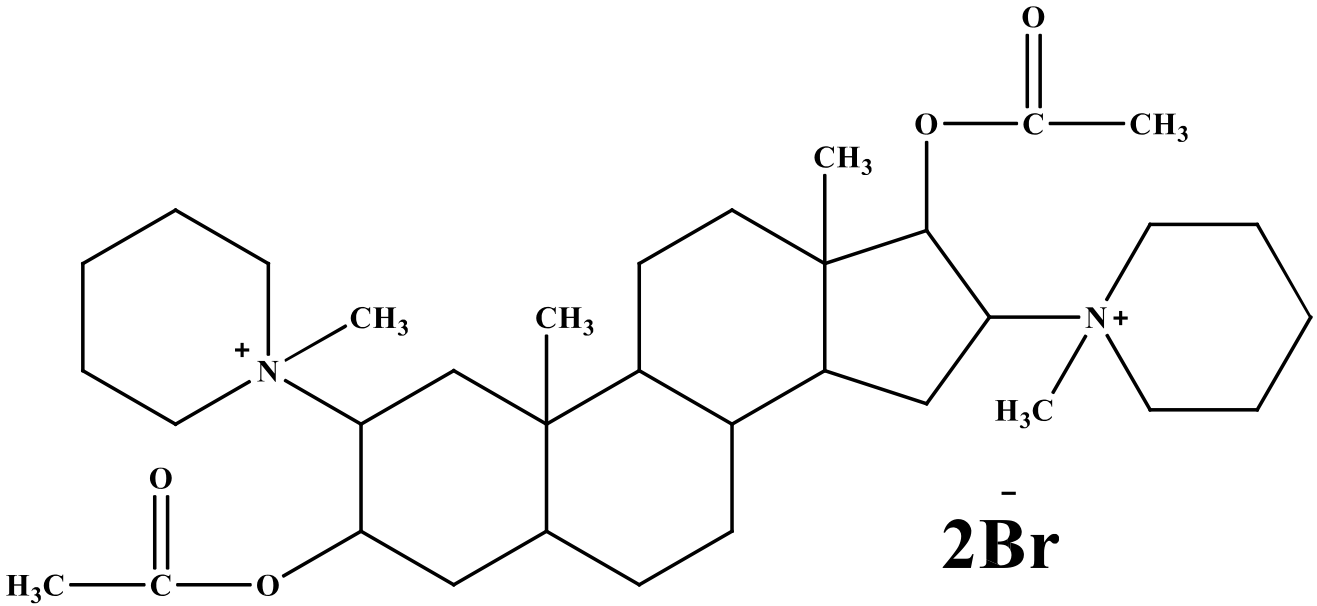

Hoffman
Elimination
(nonenzymatic)
Ester hydrolysis
(enzymatic)
Laudanosine
Mono quternary alcohol
Mono qutternary acid

•Doxacurium Chloride



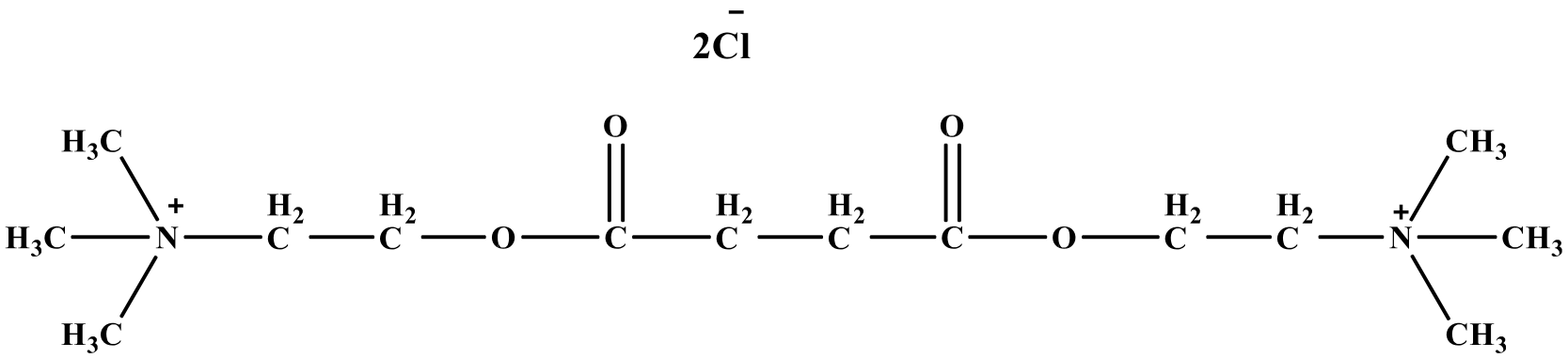
1 ,2,3,4-tetrahydro-2-(3-hydroxypropyl)-6,7,8-trimethoxy-2-methyl- 1 -(3,4,5-trimethoxybenzyl) isoquinolinium chloride succinate

•Pancuronium Bromide

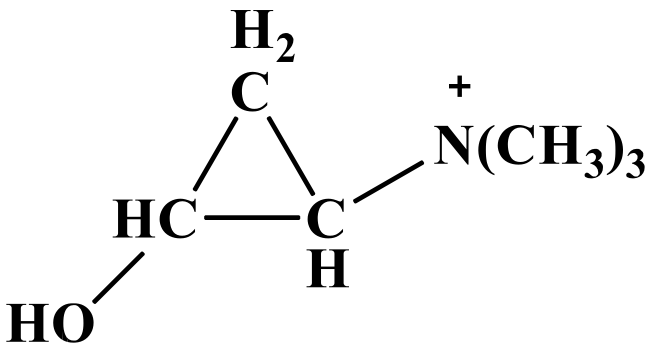


2β, 16β–dipiperidino–5α–androstane–3α,17β–diol acetate dimethobromide

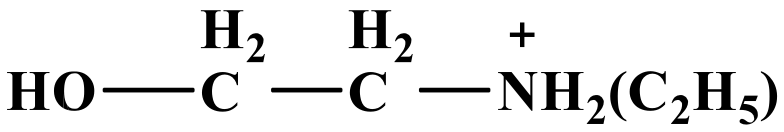
- **Succinylcholine chloride**



Q/ Both of the followijg compounds are choline analogues. Explain why compound A has stimulatory activity while compound B exhibits inhibitory action at the cholinergic synapses?



(A)



(B)

Q/ Write the chemical structures for atropine and then discuses the influence of modifications on its activity. In each case write the chemical structure and generic name for the resultant compounds

-1Replacement of tropic acid portion by mandelic acid.

-2Quaternization of the nitrogen with a methyl halid.