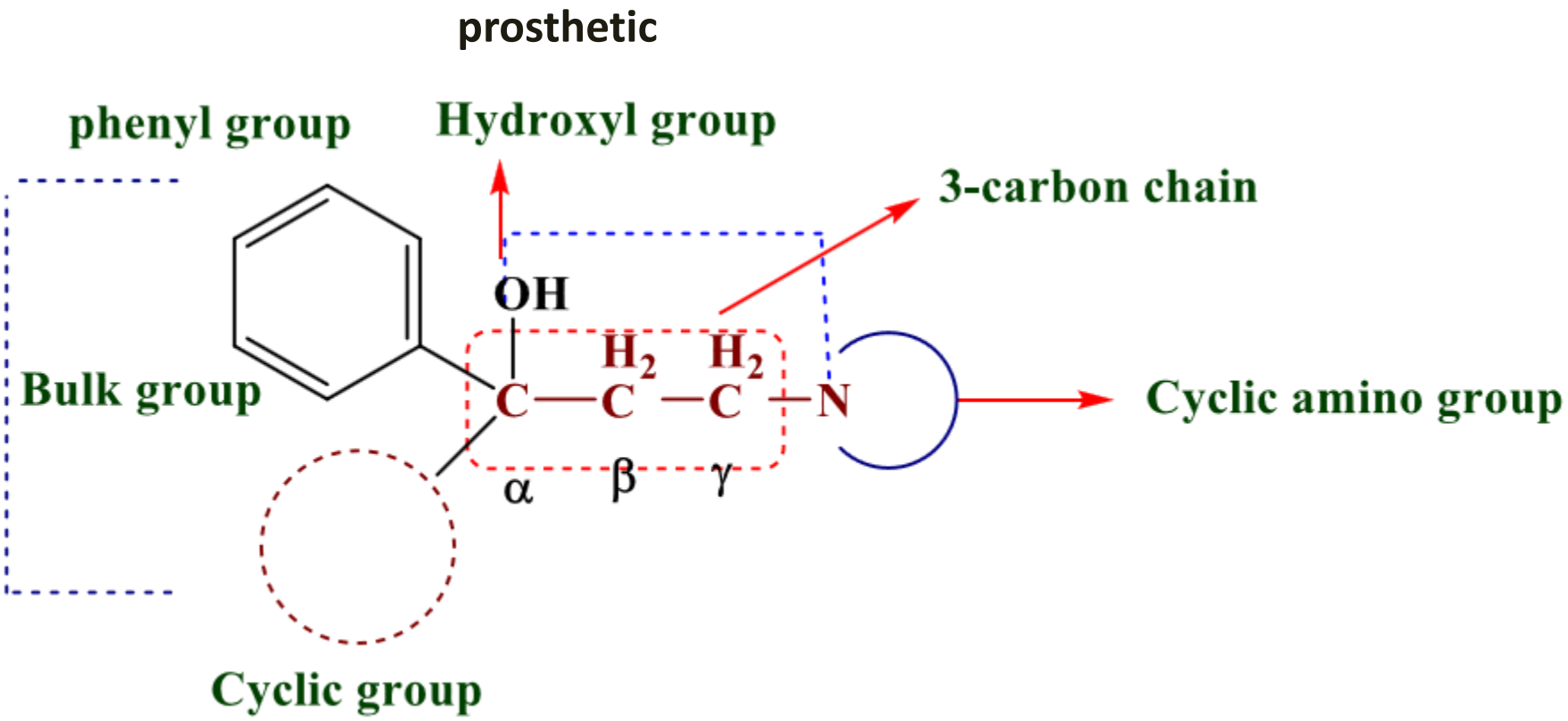
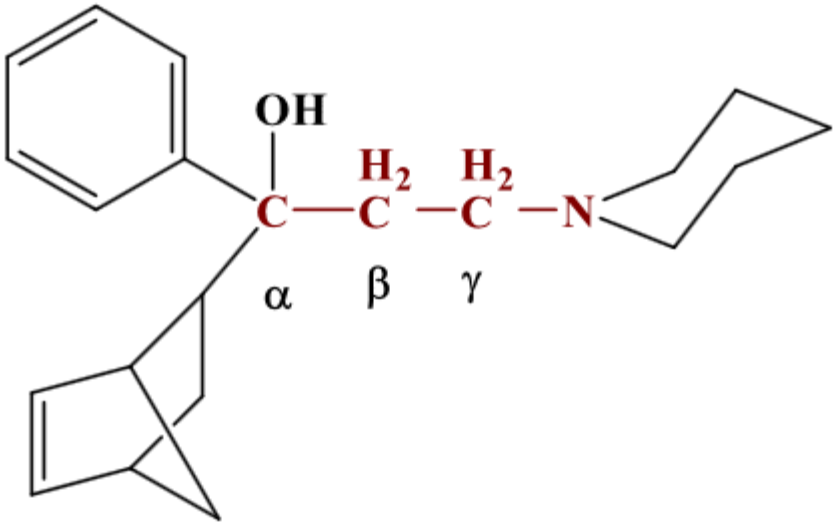
Aminoalcohols SAR



All of the aminoalcohols used for paralysis agitans are tertiary amines. Because the desired locus of action is central, formation of a quaternary ammonium moiety destroys the antiparkinsonian properties.

1-Biperiden



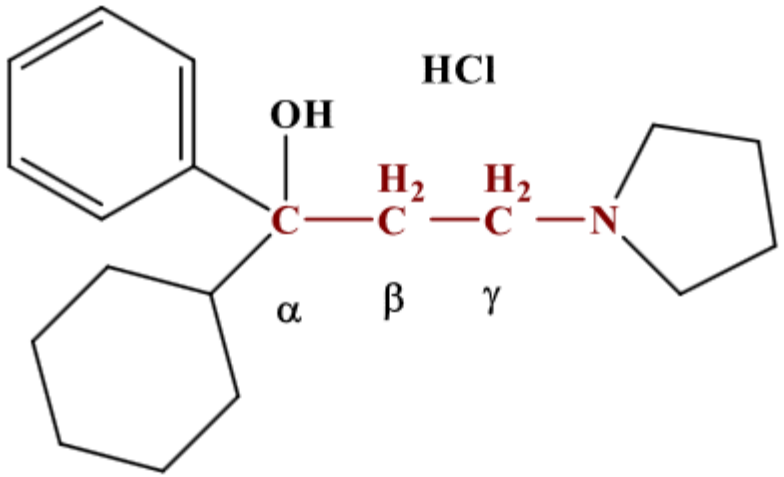
α-5-norbornen-2-yl-α-phenyl-I -piperidinepropanol

1-(bicyclo[2.2.1]hept-5-en-2-yl)-1-phenyl-3-(piperidin-1-yl) propan-1-ol

- **It has antiparkinsonian effect with minimizing side effects.**

C/I: - in epilepsy

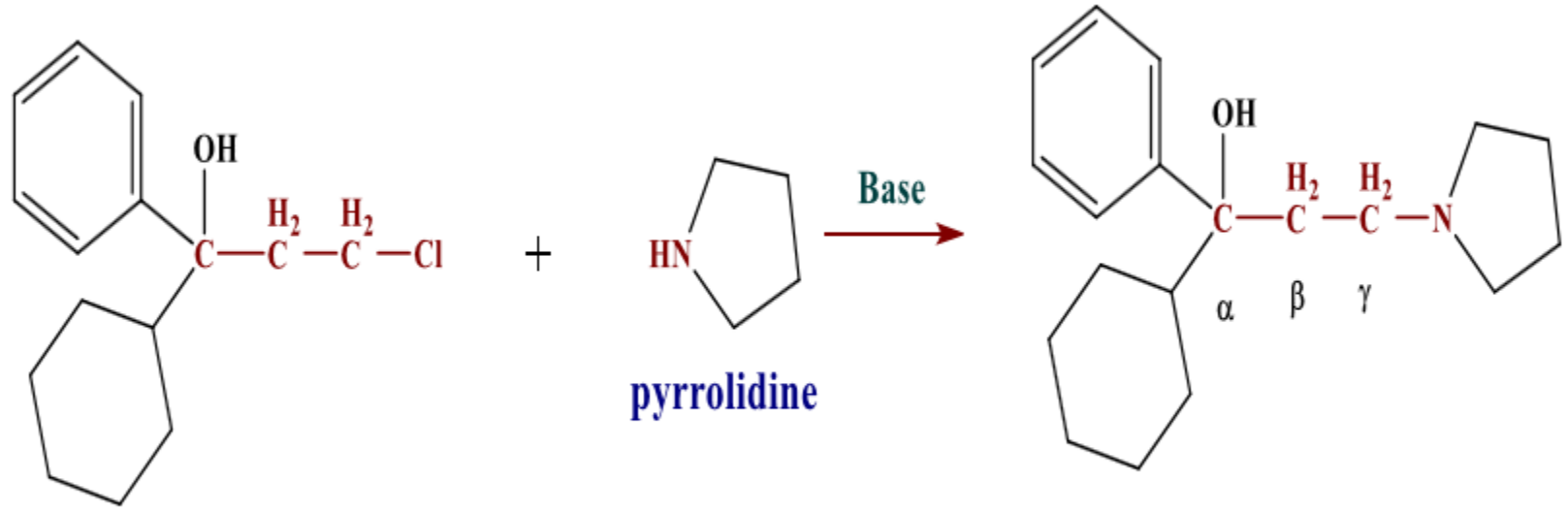
-2 Procyclidine Hydrochloride



α-cyclohexyl-α-phenyl-1 -pyrrolidinepropanol hydrochloride

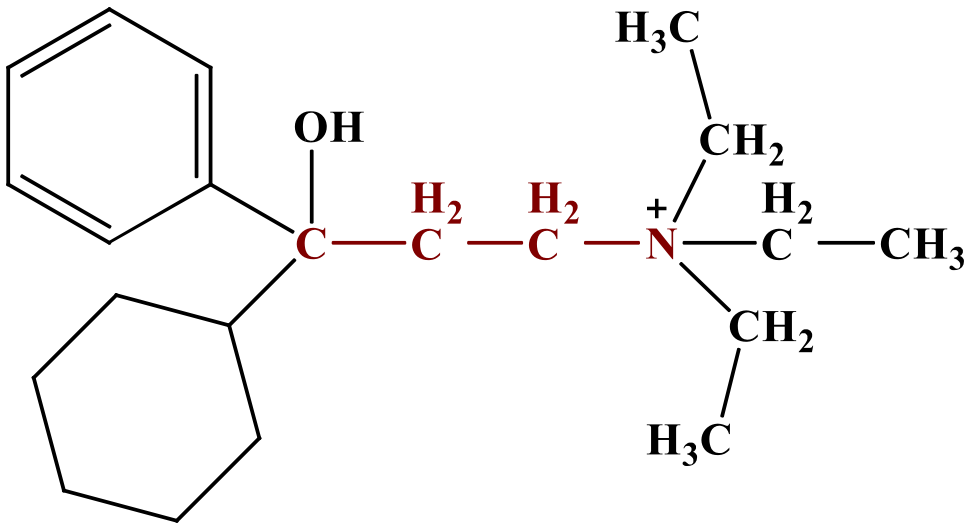
Uses :- Act both centrally and peripherally, therefore its useful in Treatment of Parkinson's syndrome and as antispasmodic. The toxicity of the drug is low, but when the dosage of the drug is high S/E are noticeable.

Preparation



3-chloro-1-cyclohexyl-1-phenylpropan-1-ol

-3 Tridihexethyl chloride



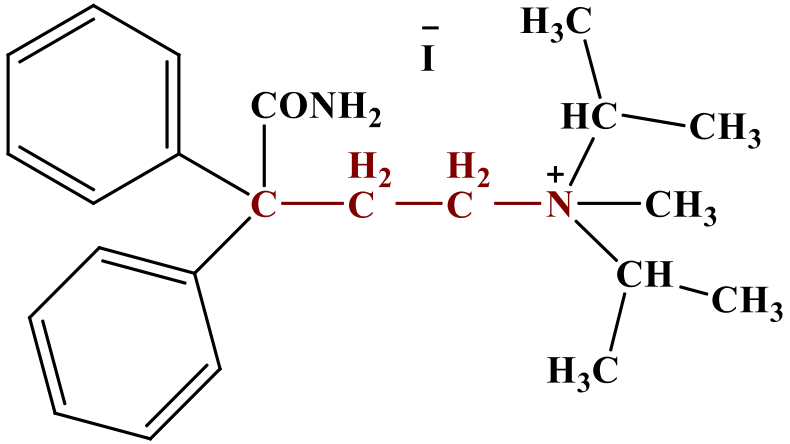
(3–hydroxy-3-cyclohexyl-3-phenylpropyl)triethylammonium chloride

Uses: - Antispasmodic and antisecretory

It has no effect in reliving the Parkinson syndrome because of 4°N character.

Aminoamides

-1 Isopropamide



(3–carbamoyl-3,3-diphenylpropyl)diisopropylmethylammonium iodide

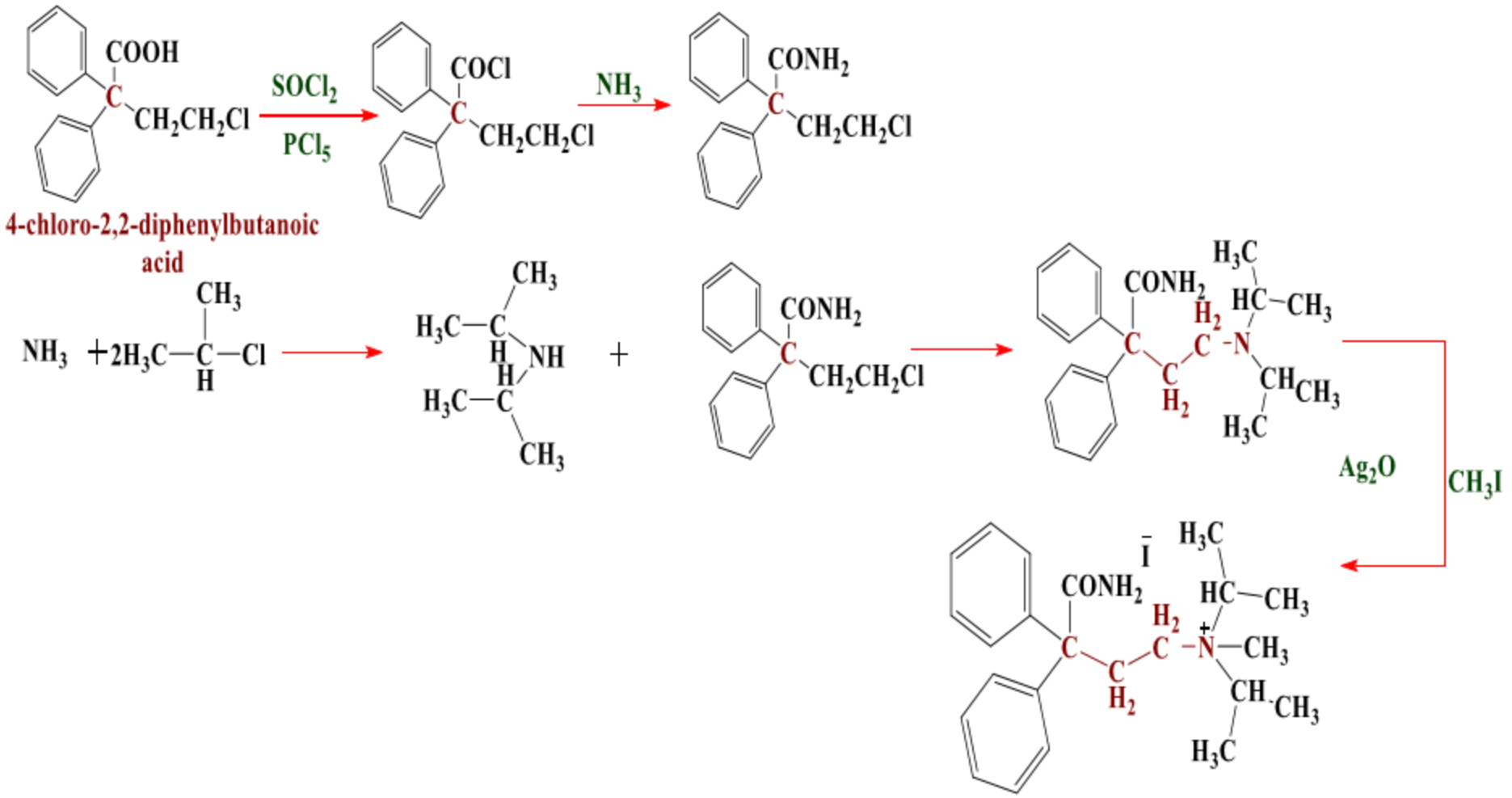
Uses :- **Isopropamide is a long-acting anticholinergic and antimuscarinic drug of quaternary ammonium structure. It is used in the form of the iodide, (also bromide or chloride) to treat peptic ulcer and to suppress gastric secretion and other gastrointestinal disorders.**

- **Antispasmodic**
- **Antisecretory**

S/E :- dryness of mouth, mydraisis,

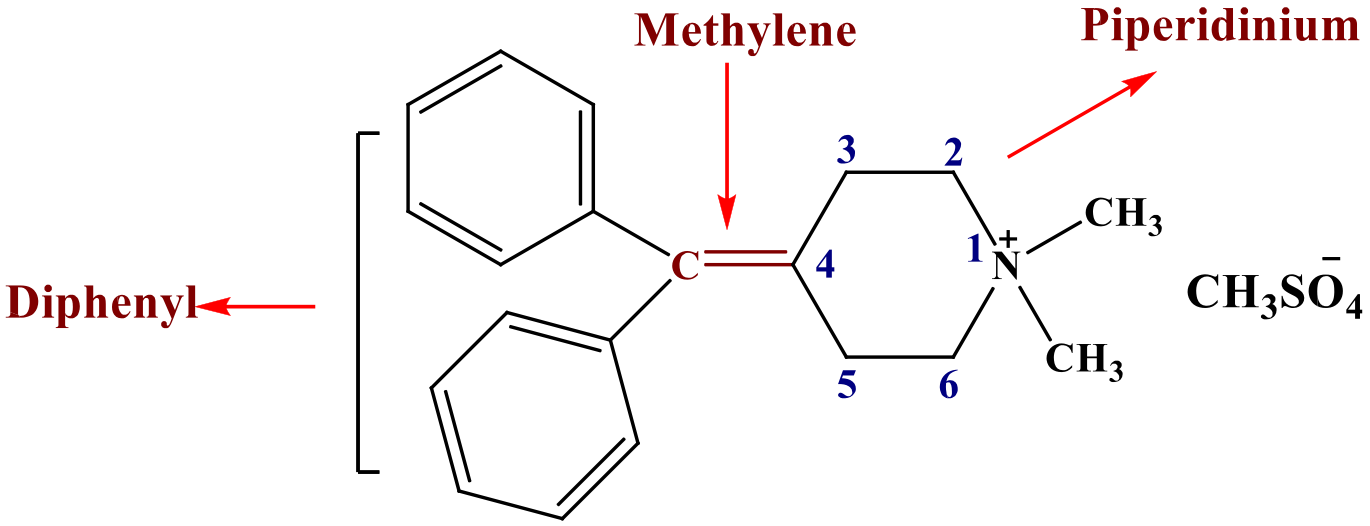
C/I:- glaucoma, prostatic hypertrophy.

Preparation



Miscellaneous

-1 Diphemanil Methylsulfate

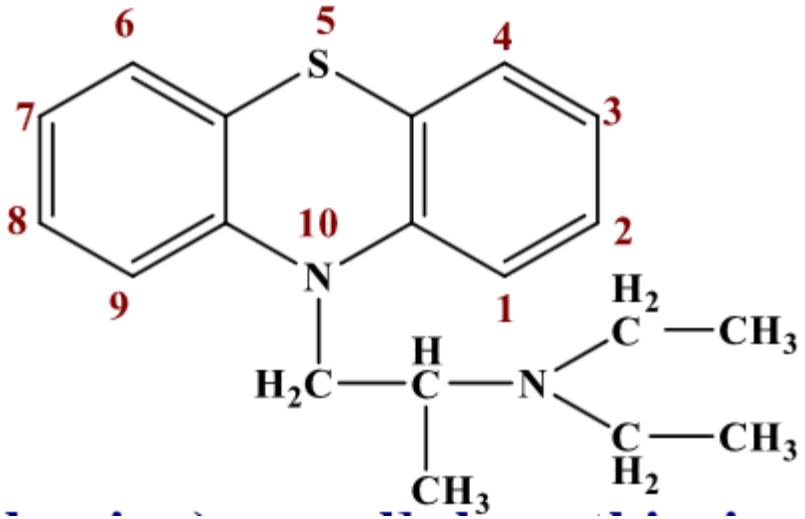


4-(diphenylmethylene)-1,1-dimethylpiperidinum methylsulfate

The methylsulfate salt was chosen as the best because the chloride is hygroscopic and the bromide and iodide ions have exhibited toxic manifestations in clinical use.

Uses :- Diphemanil Methylsulfate is a quaternary ammonium anticholinergic. It binds muscarinic acetycholine receptors and thereby decreases secretory excretion of stomach acids as well as saliva and sweat. The drug is not well absorbed from the GIT, particularly in the presence of food, and should be administration between meals.

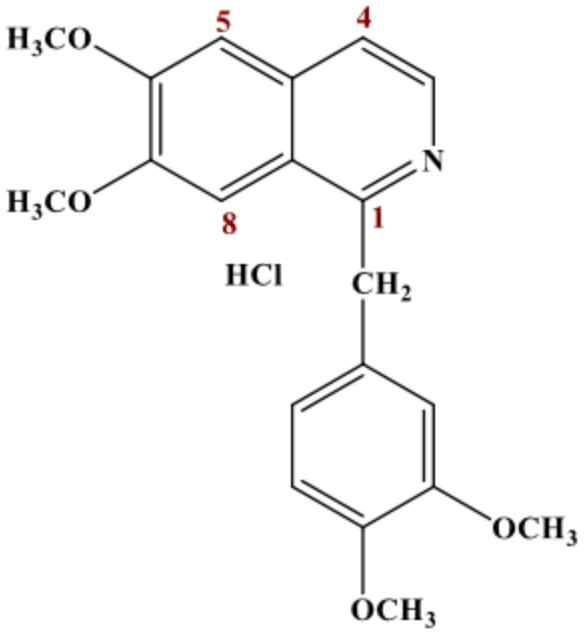
-2 Ethopropazine Hydrochloride



10-[2-(diethylamino)propyl]phenothiazine monohydrochloride

Uses:-It is a phenothiazine derivative used as an antiparkinsonian agent that has anticholinergic, antihistamine, and antiadrenergic actions.

***Papaveraceous*)Papaverine Hydrochloride(**



6,7-dimethoxy-1-veratrylisoquinoline hydrochloride

Uses :- Its main effect is as a spasmolytic on smooth muscle, acting as a direct, nonspecific relaxant on vascular, cardiac, and other smooth muscle. (produce musculotropic effect which is differ from the neurotropic action of atropine

GANGUONIC BLOCKING AGENTS

Impulse transmission through the ganglion occurs when ACh is released from preganglionic fibers and activates the N2 nicotinic receptors of the neuronal membrane. This triggers an increase in sodium and potassium conductances of a subsynaptic membrane, resulting in an initial excitatory postsynaptic potential (EPSP) with a latency of 1 ms, followed by an inhibitory postsynaptic potential (IPSP) with a latency of 35 ms, and, finally, a slowly generating EPSP with a latency of several hundred milliseconds.

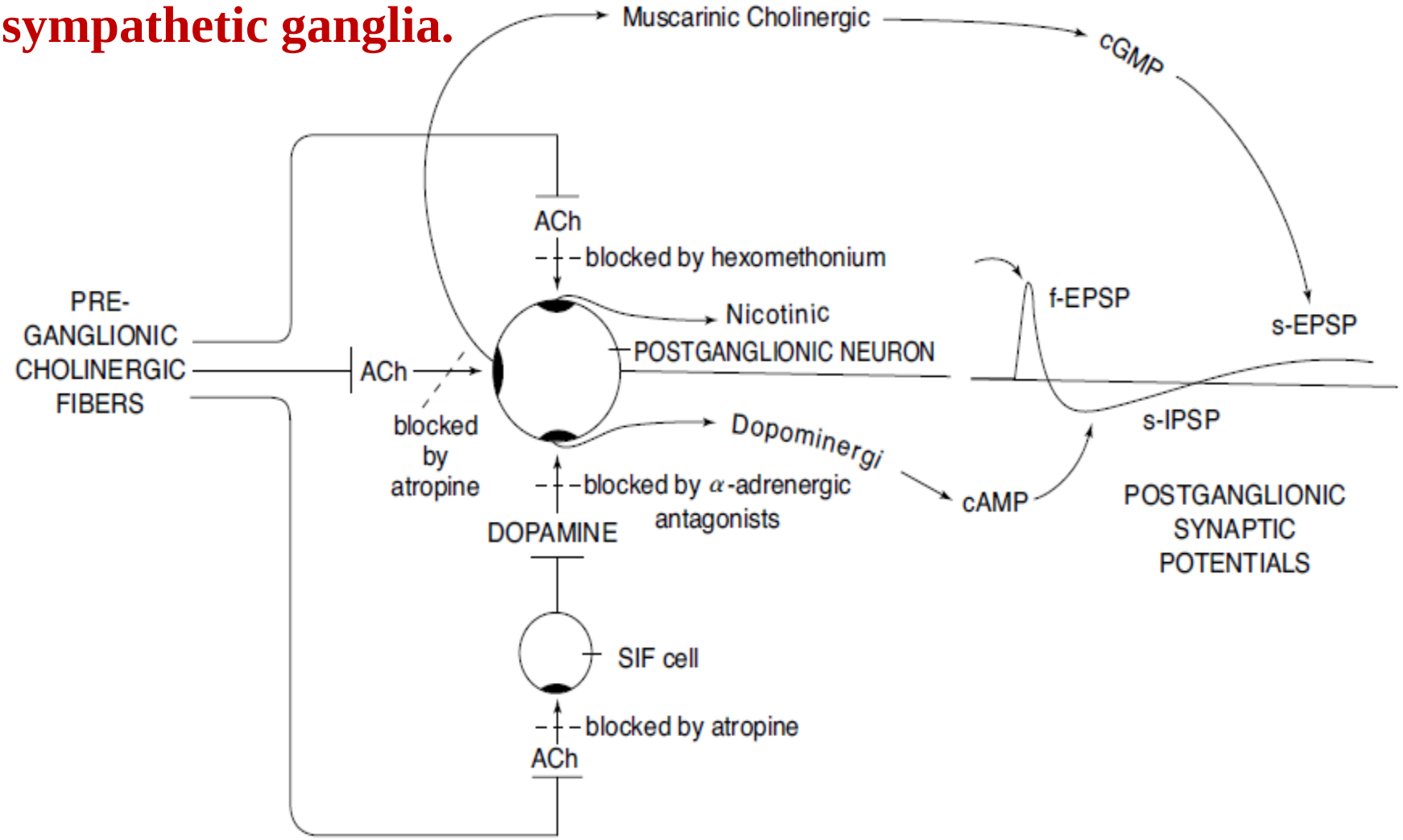
The ACh released by preganglionic fibers also activates M1 muscarinic receptors of the ganglion and probably of the smallintensity fluorescent (SIF) cell. This results in the appearance of a slow IPSP and a slow EPSP in the neurons of the ganglion. The initial EPSP is blocked by conventional competitive nondepolarizing ganglionic blocking agents, such as hexamethonium, and is considered the primary

pathway for ganglionic transmission. The slowly generating or late EPSP is blocked by atropine but not by the traditional ganglionic blocking agents. This receptor has muscarinic properties because methacholine causes generation of the late EPSP without causing the initial spike characteristic of ACh. Atropine also blocks the late EPSP produced by methacholine.

There may be more than one type of muscarinic receptor in sympathetic ganglia. Atropine blocks both high-affinity (M1) and low-affinity (M2) muscarinic receptors in the ganglion. In addition to the cholinergic pathways, the cervical sympathetic ganglion has a neuron that contains a catecholamine. These neuronal cells, identified initially by fluorescence histochemical studies and shown to be smaller than the postganglionic neurons, are now referred to as SIF cells. Dopamine has been identified as the fluorescent catecholamine in the SIF cells that are common to many other sympathetic ganglia. Dopamine apparently mediates an increase in cAMP, which causes hyperpolarization of postganglionic neurons (Fig. 17.19). The IPSP phase of the transmission of sympathetic ganglia following Ach administration can be blocked by both atropine and - adrenergic blocking agents

GANGUONIC BLOCKING AGENTS

Stimulation of autonomic ganglia by ACh produces a triphasic in sympathetic ganglia.



Neurotransmission at the sympathetic cervical ganglion.

There are two types of ganglionic blockers

-1Depolarizing Ganglionic Blocking Agents.

Depolarizing blocking agents are actually ganglionic stimulants. Thus, for nicotine, small doses give an action similar to that of the natural neuroeffector ACh, an action known as the "nicotinic effect of ACh." Larger amounts of nicotine, however, bring about a ganglionic block characterized initially by depolarization, followed by a typical competitive antagonism.

To conduct nerve impulses, the cell must be able to carry out a polarization and depolarization process, and if the depolarized condition is maintained without repolarization, obviously no conduction occurs. ACh itself, in high concentration, will bring about an autoinhibition. Chemicals that cause this type of ganglionic block are not of therapeutic significance.

2-Nondepolarizing Competitive Ganglionic Blocking Agents

Compounds in the class of nondepolarizing competitive ganglionic blocking agents possess the necessary affinity to attach to the nicotinic receptor sites that are specific for ACh, but they lack the intrinsic activity necessary for impulse transmission (i.e., they cannot effect depolarization of the cell).

such blocking agents are "competitive" with Ach for the specific receptors involved and that either the agonist or the antagonist, if present in sufficient concentration, can displace the other.

Drugs falling into this class are tetraethylammonium salts, hexamethonium, and trimethaphan. Mecamylamine possesses a competitive component in its action but is also noncompetitive, a socalled dual antagonist.

3-Nondepolarizing Noncompetitive Ganglionic Blocking Agents

Nondepolarizing noncompetitive ganglionic blocking agents produce their effect not at the specific ACh receptor site but at some point farther along the chain of events that is necessary for transmission of the nerve impulse. When the block has been imposed, increasing the concentration of ACh has no effect; thus, apparently, ACh does not act competitively with the blocking agent at the same receptors.

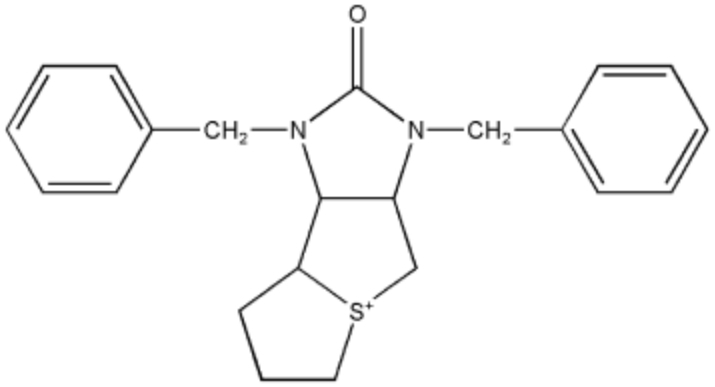
Theoretically, a pure noncompetitive blocker should have a high-specific affinity for the noncompetitive receptors in the ganglia and a very low affinity for other cholinergic synapses, together with no intrinsic activity.

there is a critical distance of about five to six carbon atoms between the onium centers for good ganglionic blocking action.

The principal therapeutic application has been in the treatment of hypertension through blockade of the sympathetic pathways. Unfortunately, the action is nonspecific, and the parasympathetic ganglia, unavoidably, are blocked simultaneously to a greater or lesser extent, causing visual disturbances, dryness of the mouth, impotence, urinary retention, and constipation.

Trimethaphan Camsylate, USP.

Trimethaphan camsylate, ()-1,3-dibenzyldecahydro2-oxoimidazo[4,5-c] thieno[1,2-]-thiolium 2-oxo-10-bornanesulfonate (1:1) (Arfonad), consists of white crystals or a crystalline powder with a bitter taste and a slight odor. It is soluble in water and alcohol but only slightly soluble in acetone and ether. The pH of a 1% aqueous solution is 5.0 to 6.0.

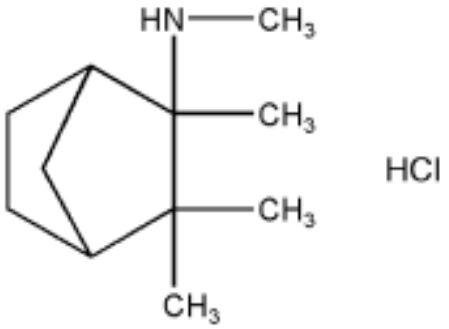


Trimethaphan Camsylate

This ganglionic blocking agent is short acting and the action of the drug is direct vasodilation, indicated in the treatment of hypertensive emergencies to reduce blood pressure rapidly.

Mecamylamine Hydrochloride.

The secondary amine mecamylamine hydrochloride, N,2,3,3-tetramethyl-2-norbornanamine hydrochloride (Inversine), has a powerful ganglionic blocking effect that is almost identical to that of hexamethonium. It has an advantage over most of the ganglionic blocking agents in being absorbed readily and smoothly from the GI tract.



Mecamylamine Hydrochloride

-2Nondepolarizing Ganglionic Blocking Agents.

A- Nondepolarizing Competitive Ganglionic Blocking Agents

B- Nondepolarizing Noncompetitive Ganglionic Blocking Agents

•Depolarizing Ganglionic Blocking Agents

-1 Nondepolarizing Competitive Ganglionic Blocking Agents

Drugs falling into this class are-:

A- Tetraethylammonium salts.

B- Hexamethonium.

C- Trimethaphan.

D- Mecamylamine possesses a competitive component in its action but is also noncompetitive, a so-called dual antagonist.

-2Nondepolarizing Noncompetitive Ganglionic Blocking Agents

Drugs falling in this class are:-

A- Mecamylamine.

B- Succinylcholine.