Structure-Activity Relationships

The development of anticholinergic agents has been depends on atropine as the prototype .

The following classification delineates the major chemical types:-

- **-1 Solanaceous alkaloids and synthetic analogues**
- **-2 Synthetic amninoalcohol esters.**
- **-3 Aminoalcohol ethers.**
- **-4 Aminoalcohols.**
- **-5 Aminoamides.**
- **-6 Miscellaneous.**
- **-7 Papaveraccous.**

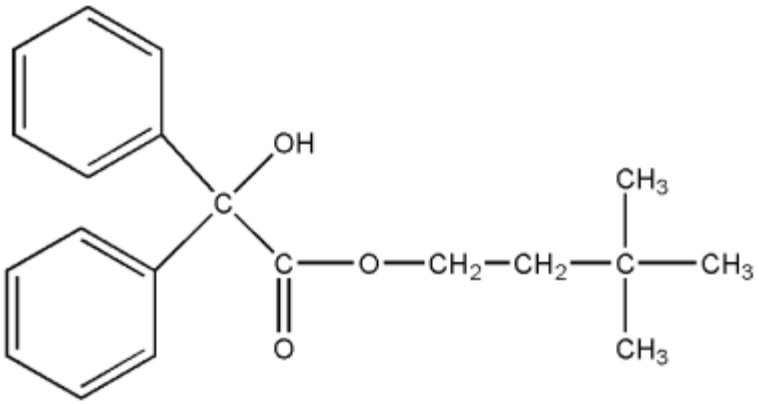
Nevertheless, structural permutations have resulted in compounds that do not have obvious relationships to the parent molecule.

The chemical classification of anticholinergics acting on parasympathetic postganglionic nerve endings is complicated somewhat because some agents, especially the quaternary ammonium derivatives, act on the ganglia that have a muscarinic component to their stimulation pattern and, at high doses, at the neuromuscular junction in skeletal muscle.

The relationship could be considered, depends on the considerations of Long et al, who based their postulations on the 1 -hyoscyamine molecule.

– 1hyoscyamine is the most active anlicholinergics and have an optimal arrangement of groups for maximal activity.

Anticholinergic compounds have similar structure to ACh but contain additional substituents that enhance their binding to the cholinergic receptor.

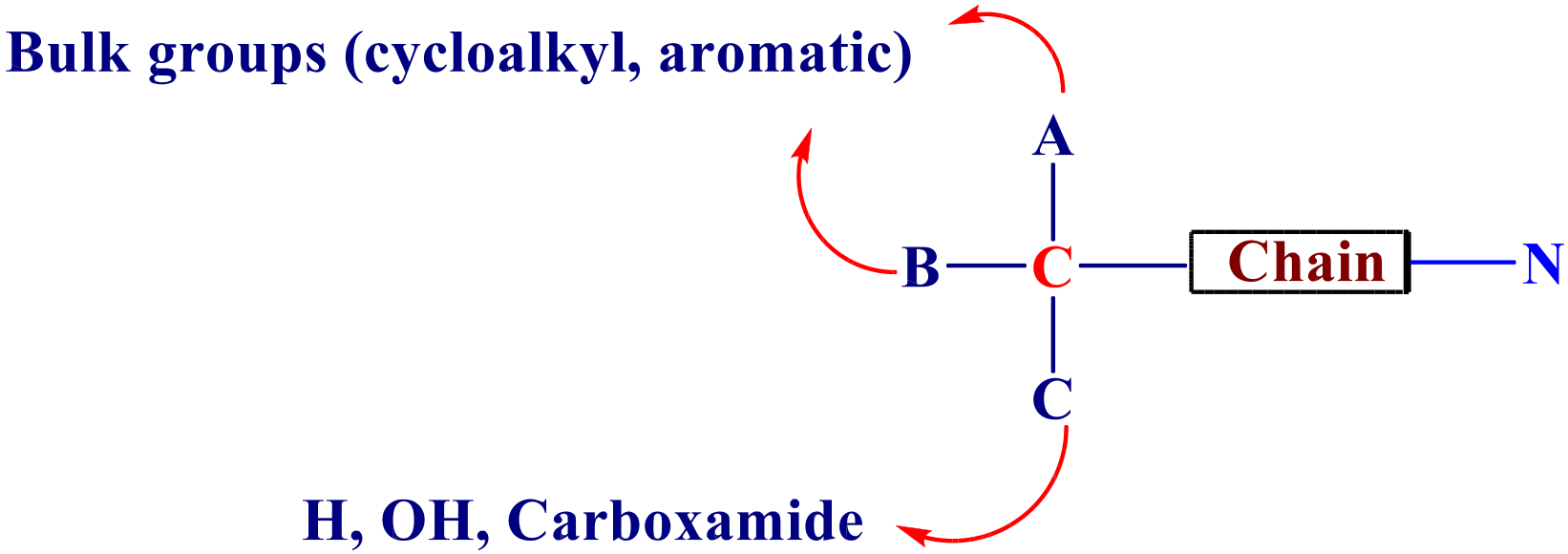


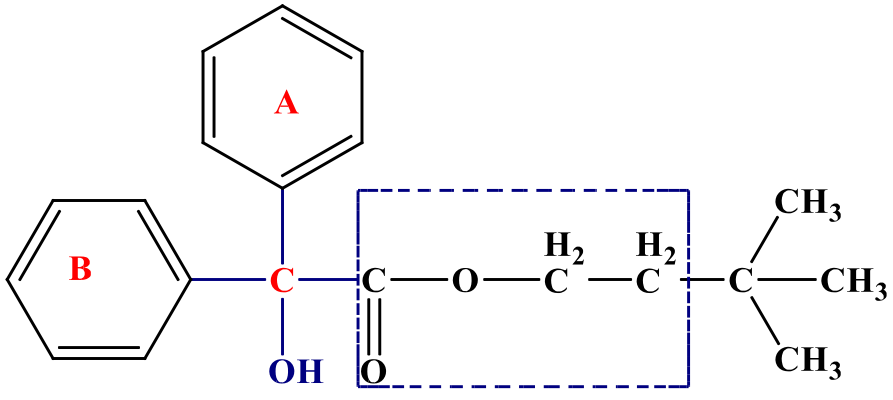
Benzilylcarbocholine

As depicted above, an anticholinergic agent may contain a quaternary ammonium function or a tertiary amine that is protonated in the biophase to form a cationic species. The nitrogen is separated from a pivotal carbon atom by a chain that may include an ester, ether, or hydrocarbon moiety.

The substituent groups *A* and *B* contain at least one aromatic moiety capable of van der Waals interactions to the receptor surface and one cycloaliphatic or other hydrocarbon moiety for hydrophobic bonding interactions. *C* may be hydroxyl or carboxamide to undergo hydrogen bonding with the receptor.

General structure





(C)

Benzilylcarbocholine

1-THE CATIONIC HEAD-:

For quaternary ammonium compounds, there is no question of what is implied, but for tertiary amines, one assumes, with good reason, that the cationic head is achieved by protonation of the amine at physiological pH.

Steric factors that cause diffusion of the onium charge or produce a less-than-optimal drug–receptor interaction result in a decrease of parasympathomimetic properties and allow the drug to act as an antagonist because of other bonding interactions.

Ariens has shown that carbocholines (e.g., benzilylcarbocholine) engage in a typical competitive action with ACh, although they are less effective than the corresponding compounds possessing a cationic head, suggesting that hydrophobic bonding may play an important role in these drug–receptor interactions.

-2 THE HYDROXYL GROUP-:

Although not requisite for activity, a suitably placed alcoholic hydroxyl group enhances antimuscarinic activity over that of a similar compound without the hydroxyl group.

It is assumed that the hydroxyl group contributes to the strength of binding, probably by hydrogen bonding to an electron-rich portion of the receptor surface.

-3 THE ESTERATIC GROUP-:

Many of the highly potent antimuscarinic compounds possess an ester grouping, and this may be a contributing feature for effective binding. This is reasonable because the agonist (i.e., ACh) possesses a similar function for binding to the same site. An esteratic function is not necessary for activity, because several types of compounds do not possess such a group (e.g., ethers, aminoalcohols).

-4 CYCLIC SUBSTITUTION (A and B(

in the following sections reveals that at least one cyclic substituent (phenyl, thienyl, or other) is a common feature in almost all anticholinergic molecules. Use of aromatic acids leads to low activity of these compounds as anticholinergics but potential activity as local anesthetics.

Ariens points out that the "mimetic" molecules, richly endowed with polar groups, undoubtedly require a complementary polar receptor area for effective binding. As a consequence, it is implied that a relatively nonpolar area surrounds such sites. Thus, increasing the binding of the molecule in this peripheral area by introducing flat, nonpolar groups (e.g., aromatic rings) should achieve compounds with excellent affinity but without intrinsic activity. This postulate is consistent with most antimuscarinic drugs, whether they possess an ester group or not.

PARASYMPATHETIC POSTGANGLIONIC BLOCKING AGENTS

Parasympathetic postganglionic blocking agents are also known as antimuscarinic, anticholinergic, parasympatholytic, or cholinolytic drugs. Antimuscarinic drugs act by competitive antagonism of ACh binding to muscarinic receptors.

Ariens noted that competitive reversible antagonists generally are larger molecules capable of additional binding to the receptor surface. The most potent anticholinergic drugs are derived from muscarinic agonists that contain one or sometimes two large or bulky groups.

Ariens suggested that molecules that act as competitive reversible antagonists generally are capable of binding to the active site of the receptor but have an additional binding interaction that increases receptor affinity but does not contribute to the intrinsic activity (efficacy) of the drug.

Therapeutic Actions

Organs controlled by the autonomic nervous system usually are innervated by both the sympathetic and the parasympathetic systems. There is a continual state of dynamic balance between the two systems. Theoretically, one should achieve the same end result by either stimulation of one of the systems or blockade of the other. Unfortunately, there is usually a limitation to this type of generalization.

Therapeutic actions

There are three predictable and clinically useful results from blocking the muscarinic effects of ACh.

1-Mydriatic effect: dilation of the pupil of the eye; and cycloplegia. (paralysis of the ciliary structure of the eye, resulting in a paralysis of accommodation for near vision.

2- Antispasmodic effect: Lowered tone and motility of the GI tract and the genitourinary tract.

3-Antisecretory effect: reduced salivation (antisialagogue), reduced perspiration (anhidrotic), and redaced acid and gastric secretion.

S/E: - for anticholinergic drug used orally in the usual doses (mydriases, dryness of the mouth,

urinary retention)

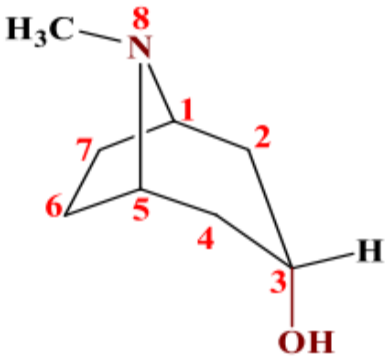
Atropine is used widely as an antispasmodic because of its marked depressant effect on parasympathetically innervated smooth muscle. It appears to block all muscarinic receptor subtypes. Atropine is, however, the standard by which other similar drugs are measured. Also, atropine has a blocking action on the transmission of the nerve impulse, rather than a depressant effect directly on the musculature. This action is termed neurotropic, in contrast with the action of an antispasmodic such as papaverine, which appears to act by depression of the muscle cells and is termed musculotropic.

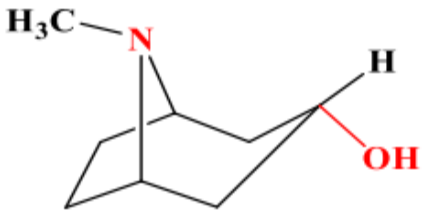
The Solanaceous alkaloids and analogues

The solanaceous alkaloids, represented by:-

1- (-) hyoscyamine
2- Atropine [(±)]hyoscyamine
3-Scopolamin(hyoscine)

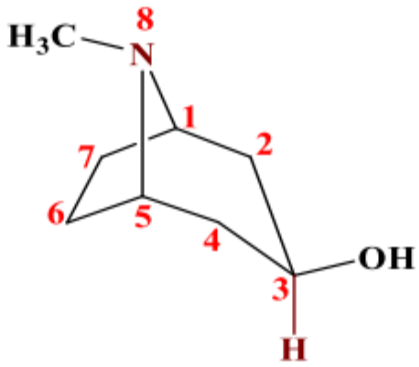
Structural Considerations (SAR(

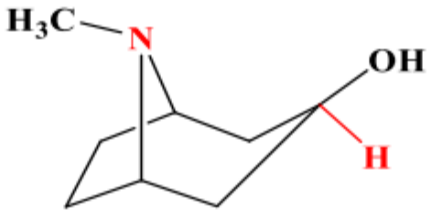




Boat(less stable)

Tropine (Chair)
3α- hydraoxytropane
3α-tropanol
Axial structure (OH trans to the N- briadg)

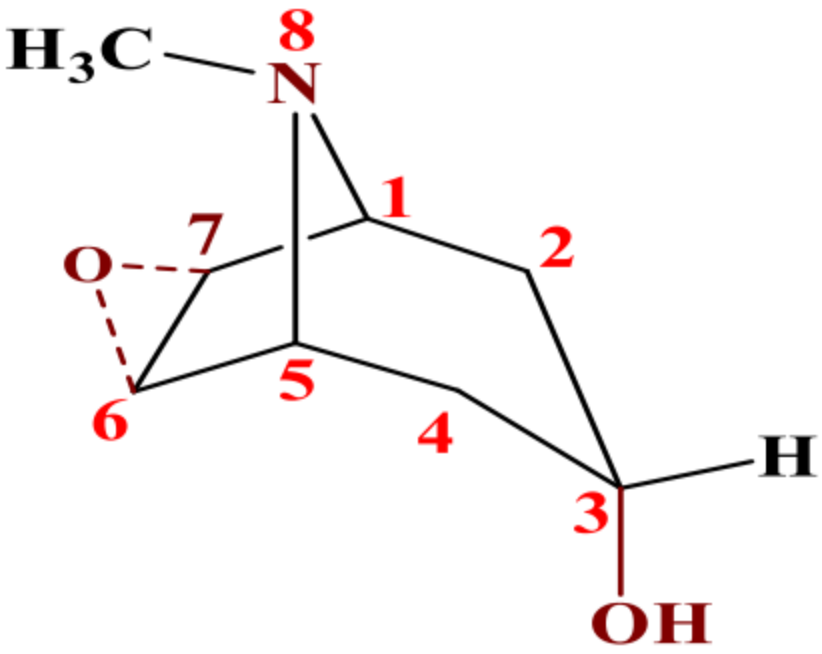




Boat(less stable)

PseudoTropine (Chair)
3β- hydraoxytropane
3β-tropanol
Equatorial structure (OH Cis to the N- bridge)

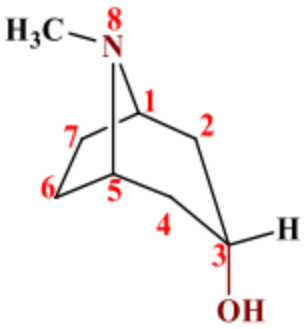
the 3-hydroxytropane formula also indicates that even though there is no optical activity because of the plane of symmetry, two stereoisomeric forms (tropine and pseudotropine) can exist because of the rigidity imparted to the molecule through the ethylene chain across the 1,5 positions.



Scopine(Chair)

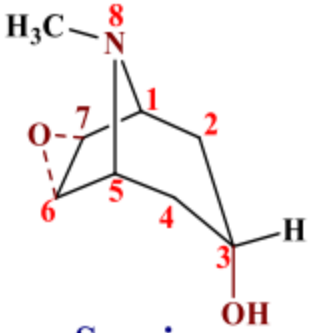
6,7β-epoxy-3α- hydraoxytropane

6,7β-epoxy-3α- tropanol

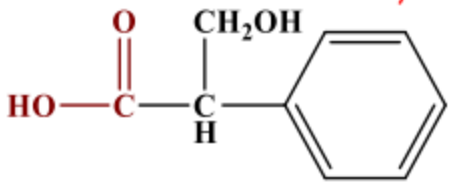


Tropine

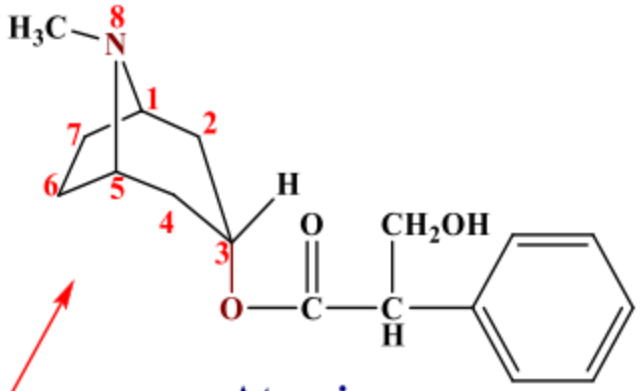
+



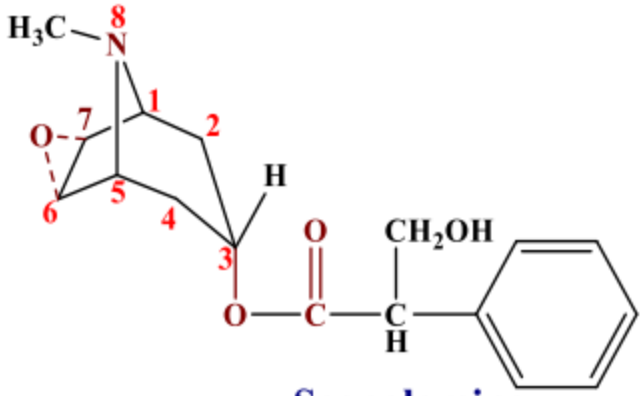
Scopine



Tropic acid

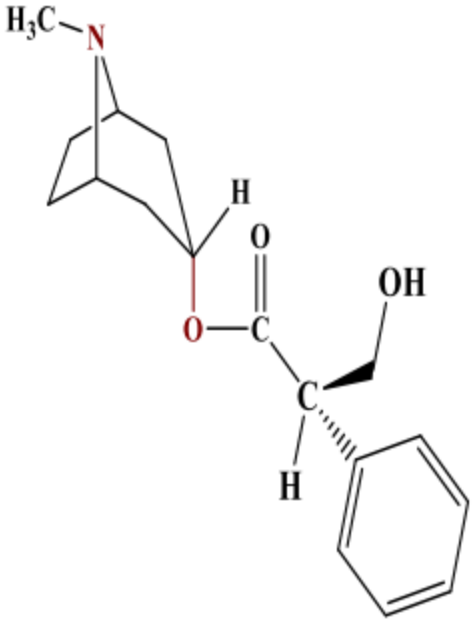


Atropine
Hyoscyamine

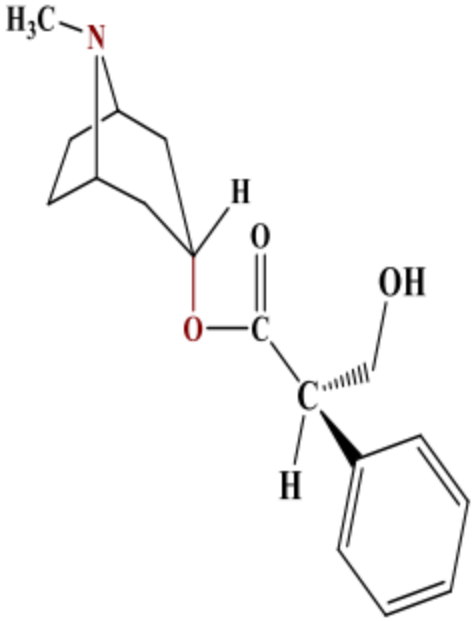


Scopolamine
Hyoscine

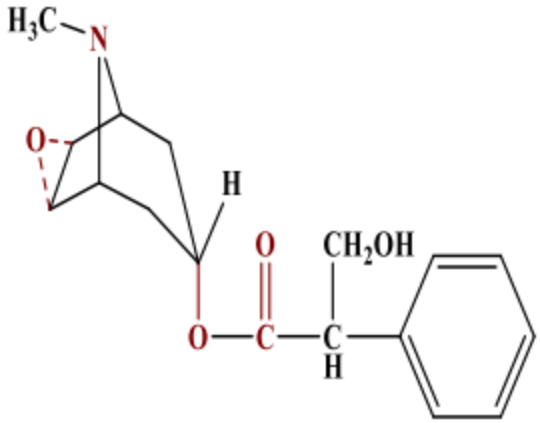
SAR



L-hyoscyamine

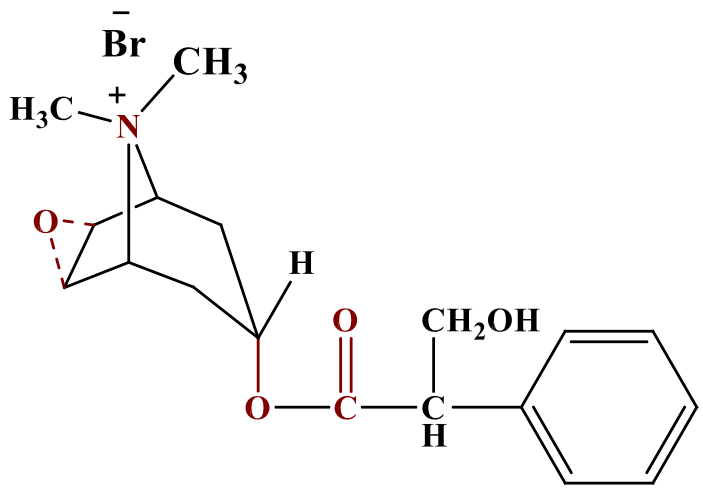


D-hyoscyamine

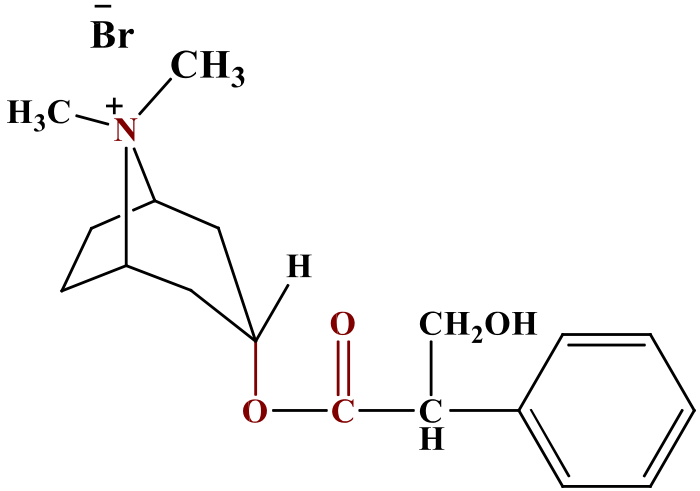


Scopolamine
Hyoscine

•Quaternization of the nitrogen with a methyl halid.



MethyScopolamine bromide



methylatropine

Quaternization of the tertiary amine produces variable effects in terms of increasing potency. Decreases in activity are apparent in comparing atropine with methylatropine (no longer used) and scopolamine with methscopolamine.

ascribed decreased activity, especially when the groups attached to nitrogen are larger than methyl, to a possible decrease in affinity for the anionic site on the cholinergic receptor. They attributed this decreased affinity to a combination of greater electron repulsion by such groups and greater steric interference to the approach of the cationic head to the anionic site.

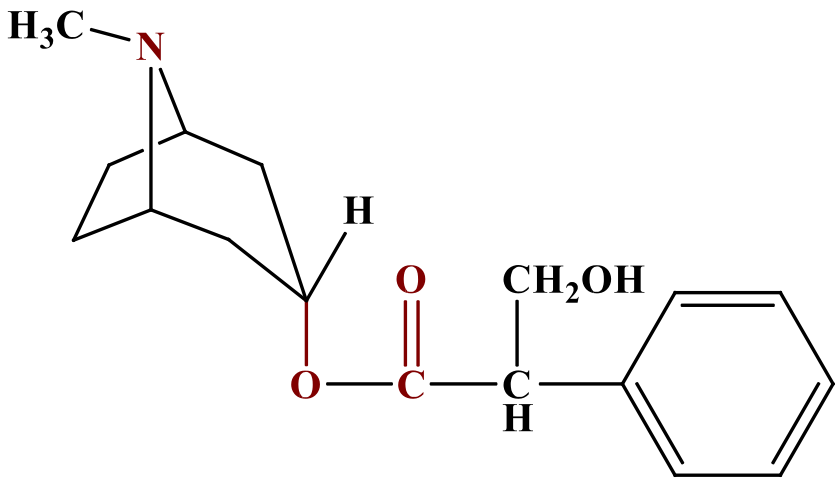
In general, quaternization reduces parasympathomimetic action much more than parasympatholytic action.

quaternization increases the curariform activity of these alkaloids and aminoesters, a usual consequence of quaternizing alkaloids. Another disadvantage in converting an alkaloidal base to the quaternary form is that the quaternized base is absorbed more poorly through the intestinal wall, so that the activity becomes erratic and, in some instances, unpredictable.

Bases (such as alkaloids) are absorbed through the lipoidal gut wall only in the dissociated form, which can be expected to exist for a tertiary base, in the small intestine. Quaternary nitrogen bases cannot revert to an undissociated form, even in basic media and, presumably, may have difficulty passing through the gut wall. Since quaternary compounds can be absorbed, other less efficient mechanisms for absorption probably prevail. Quaternary ammonium compounds combine reversibly with endogenous substances in the gut, such as mucin, to form neutral ionpair complexes. These complexes penetrate the lipid membrane
by passive diffusion.

Products

1- Atropine



8-methyl-8-azabicyclo [3.2.1]oct-3-yl) 3-hydroxy-2-phenylpropanoate

Atropine is the tropine ester of racemic tropic acid and is optically inactive.

Uses:- the action of atropine or its salts is the same

1- mydriatic effect by paralyzing the iris and the ciliary muscles so used in iritis and corneal inflammations and lesions.

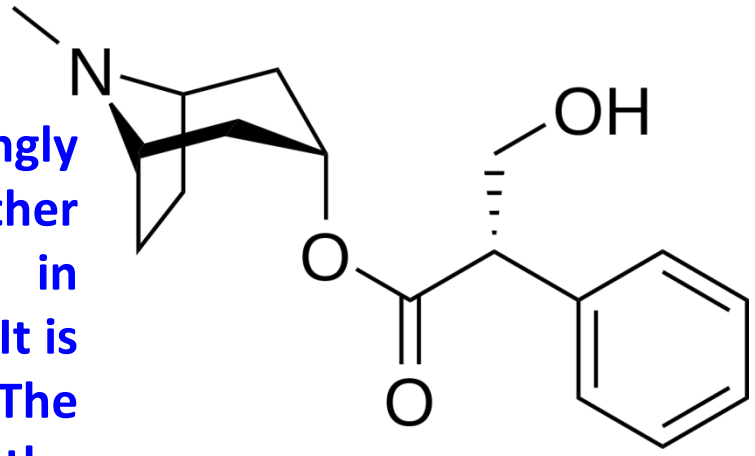
2- Used to reduce the respiratory secretion in surgical procedure

3- **Used to treat some types of arrhythmias. (bradyarrhythmias)**

4- Used as antidote for organophosphorous compounds, by blocking the muscarinic effect of Ach.

5- Its used also for several GIT complains by its antispasmodic action.

•Hyoscyamine



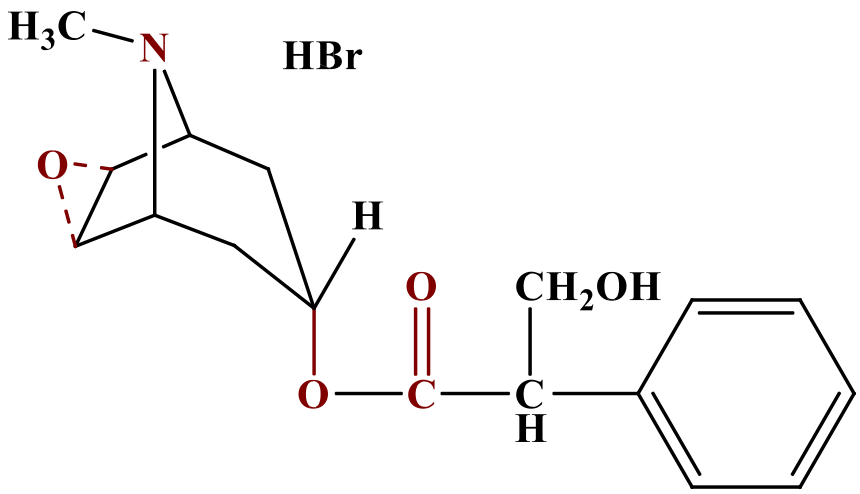
It occurs as white needles that are sparingly soluble in water (1:281), more soluble in ether (1:69) or benzene (1:150), very soluble in chloroform (1:1), and freely soluble in alcohol. It is used as the sulfate and hydrobromide. The principal reason for the popularity of the hydrobromide has been its nondeliquescent nature. The salts have the advantage over the free base in being quite water soluble.

Uses-:

- **It is used to treat spasms of the bladder (urinary Stimulant)**
- **It is used together with a narcotic to counteract the spasm produced by the narcotic when the latter is used to relieve the pain of urethral colic.**
- **Hyoscyamine preparations are also used as antispasmodics in the therapy of peptic ulcers.**

•Scopolamine (hyoscine)

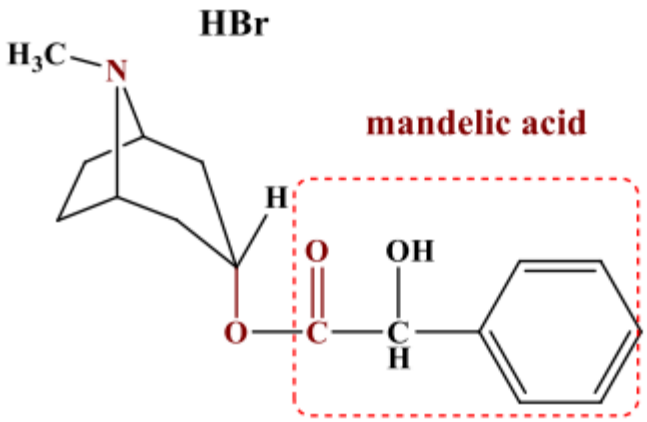
Hyoscine is the older name for this alkaloid, though scopolamine is the accepted name in the United States. Scopolamine is the levo component of the racemie mixture that is known as atroscine . The alkaloid is racemized readily in the presence of dilute alkali. Its available as hydrobromide salt, (scopolamine hydrobromide)



occurs as white or colorless crystals or as a white, granular powder. It is odorless and tends to effloresce in dry air. It is freely soluble in water (1:1.5), soluble in alcohol (1:20), only slightly soluble in chloroform, and insoluble in ether.

Uses:- scopolamine usually acts us CNS depressant.

•Homatropine hydrobromide



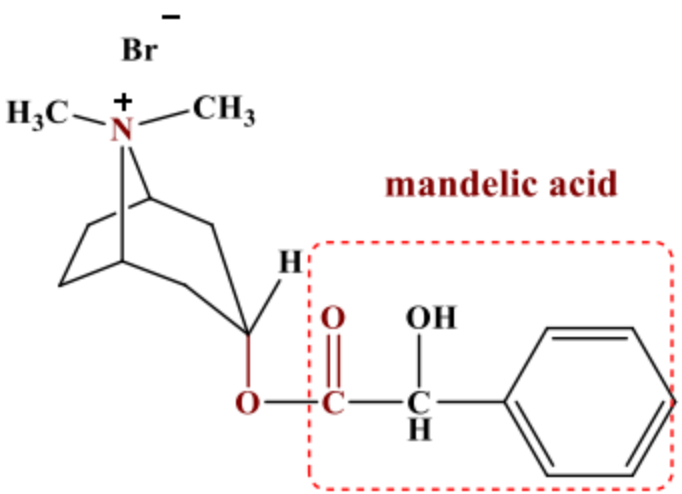
I αH.5αH–tropan–3α–ol mandelate hydrobromide

occurs as white crystals or as a white, crystalline powder that is affected by light. It is soluble in water (1:6) and alcohol (1:40), less soluble in chloroform (1:420), and insoluble in ether. Solutions are incompatible with alkaline substances, which precipitate the free base, and with the common reagents that precipitate alkaloids.

Uses:- **Is used topically to paralyze the ciliary structure of the eye (cycloplegia) and to effect mydriasis.**

It behaves very much like atropine but is weaker and less toxic. In the eyes. It has rapid onset and shorter duration of action than atropine.

•Homatropine Methylbromide



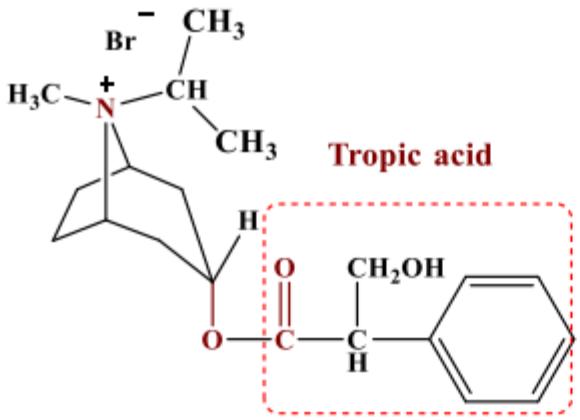
3 α–Hydroxy–8–methyl–1αH–5αH–tropanium bromide mandelate

occurs as a bitter, white, odorless powder and is affected by light. The compound is readily soluble in water and alcohol but insoluble in ether. The pH of a 1% solution is 5.9 and that of a 10% solution is 4.5.

Homatropine methylbromide is transported poorly across the blood—brain barrier because of its quaternary ammonium group and, therefore, has far fewer stimulant properties than atropine.

Uses: - It is used to reduce oversecretion and to relieve GI spasm.

•Ipratropium Bromide



It is freely soluble in water and ethanol but insoluble in chloroform and ether. The salt is stable in neutral and acidic solutions but rapidly hydrolyzed in alkaline solutions.

3-(3-hydroxy-l-oxo-2-phenylpropoxy)-8-methyl-8-(l-methylethy-8-azoniabicyclo[3.2. I]octane bromide

Ipratropium bromide, is a quaternary ammonium derivative of atropine.

Uses:-Ipratropium bromide is used in inhalation therapy to produce dilation of bronchial smooth muscle for acute asthmatic attacks. The drug produces bronchodilation by competitive inhibition of cholinergic receptors bound to smooth muscle of the bronchioles. Ipratropium may also act on the surface of mast cells to inhibit ACh-enhanced release of chemical mediators.

The drug has a slow onset of action, within 5 to 15 minutes after being administered by inhalation, and should not be used alone for acute asthmatic attacks.

Give the mechanism of Regeneration of phosphorylated AChE by -2PAM (-2 pyridinealdoximemethyl iodide(.)support your answer with chemical structure and example(