DRUGS ACTING ON AUTONOMIC NERVOUS SYSTEM PART–IV: CHOLINERGIC BLOCKING AGENTS

Presented By:
Dr. Joohee Pradhan

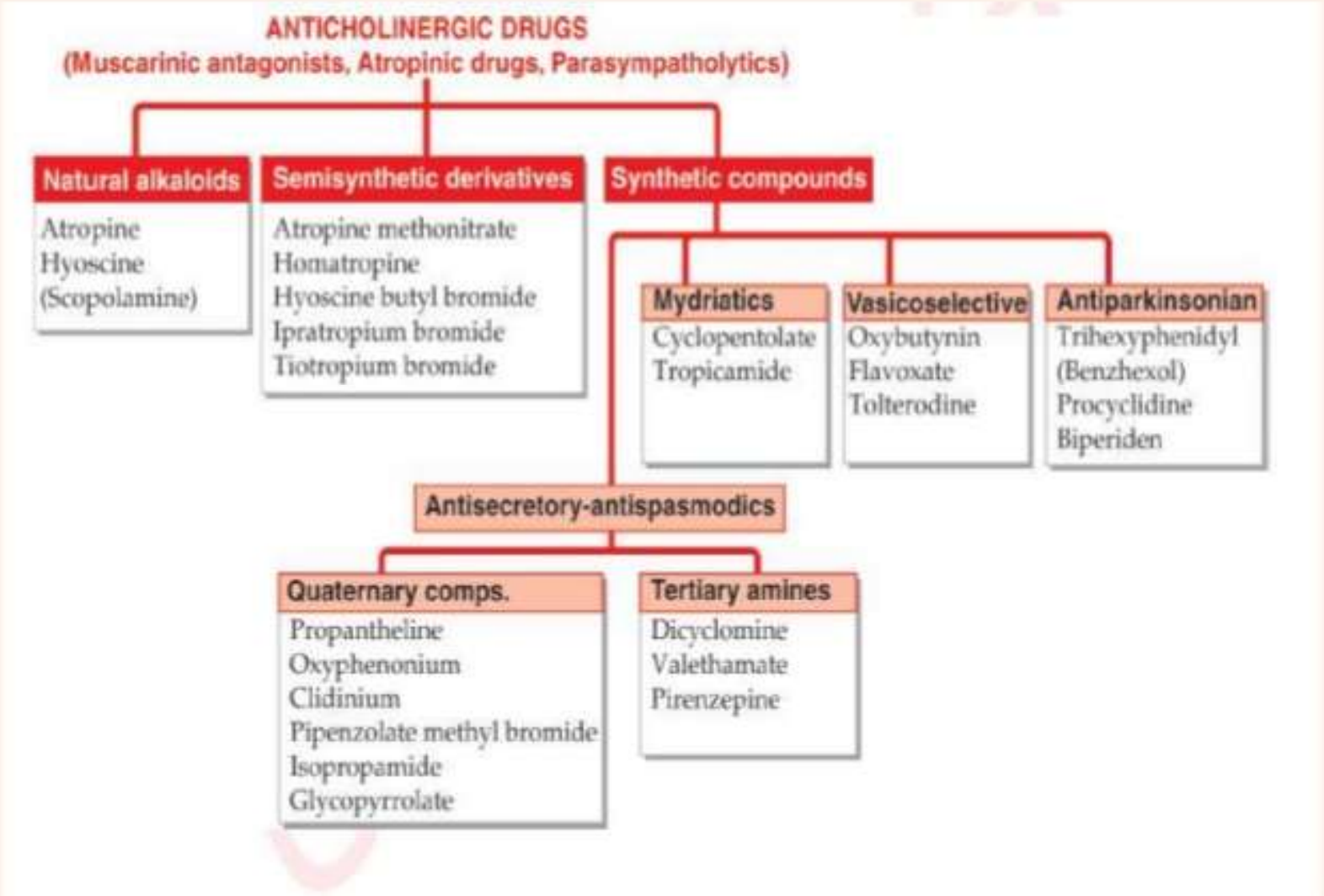
OUTLINE OF PRESENTATION

- **Cholinergic Blocking agents:** SAR of cholinolytic agents
  - **Solanaceous alkaloids and analogues:** Atropine sulphate, Hyoscyamine sulphate, Scopolamine hydrobromide, Homatropine hydrobromide, Ipratropium bromide*.
  - **Synthetic cholinergic blocking agents:** Tropicamide, Cyclopentolate hydrochloride, Clidinium bromide, Dicyclomine hydrochloride*, Glycopyrrolate, Methantheline bromide, Propantheline bromide, Benztropine mesylate, Orphenadrine citrate, Biperidine hydrochloride, Procyclidine hydrochloride*, Tridihexethyl chloride, Isopropamide iodide, Ethopropazine hydrochloride.

CHOLINERGIC BLOCKING AGENTS (ANTICHOLINERGIC DRUGS)

- **Anticholinergic/ Atropinic/ Parasympatholytic drugs/ Muscarinic receptor antagonists a**re the agents which competitively block actions of Ach on autonomic effectors and in the CNS exerted through muscarinic receptors.
- Though nicotinic receptor antagonists also block certain actions of ACh, they are generally referred to as 'ganglion blockers' and 'neuromuscular blockers'.

CLASSIFICATION
(ON THE BASIS OF PHARMACOLOGICAL ACTION)

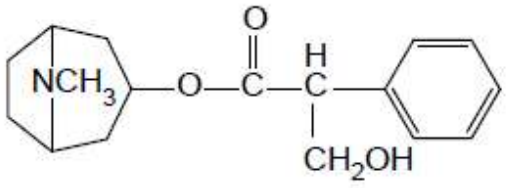


CHEMICAL CLASSIFICATION

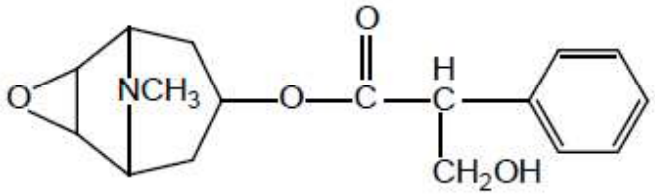
I. Solanaceous alkaloids and analogues
II. Amino alcohol esters
III. Amino ethers
IV. Amino alcohols
V. Amino amides
VI. Diamides
VII. Miscellaneous amines

I. Solanaceous alkaloids and analogues

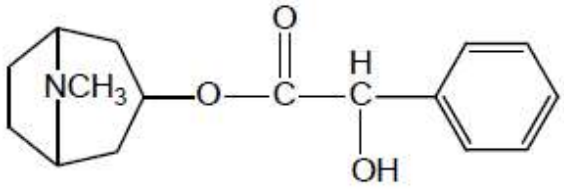
i. Atropine



ii. Scopolamine (Hyoscine)

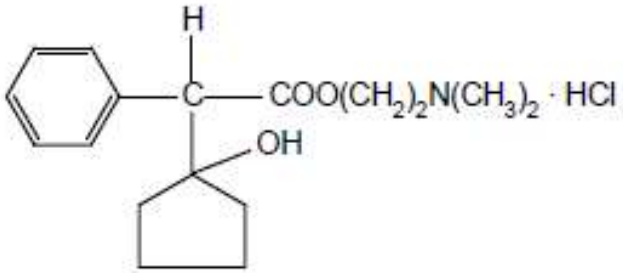


iii. Homatropine

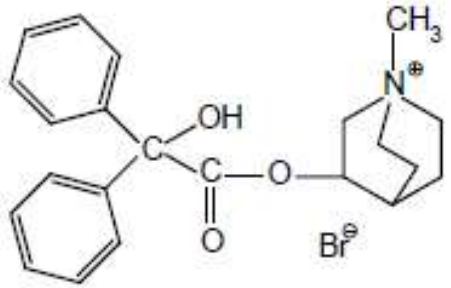


II. Amino alcohol esters

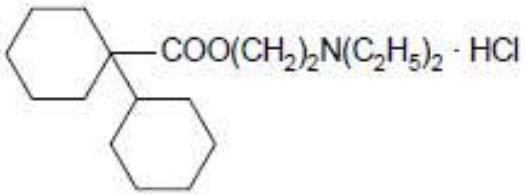
i. Cyclopentolate



ii. Clidinium

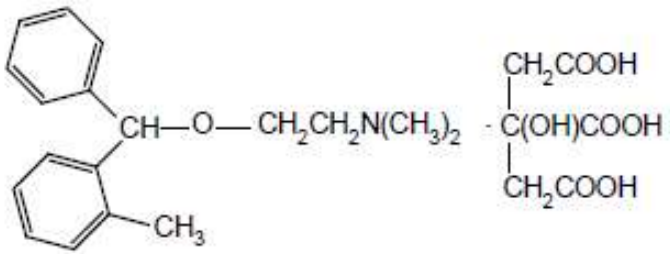


iii. Dicyclomine

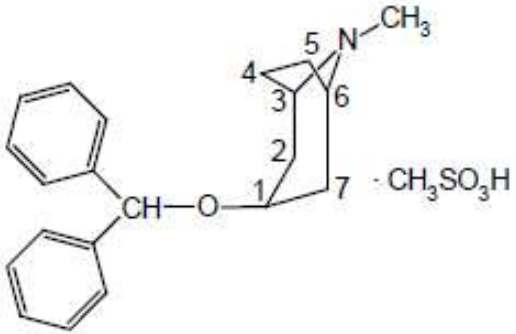


III. Amino ethers

i. Orphenadrine citrate

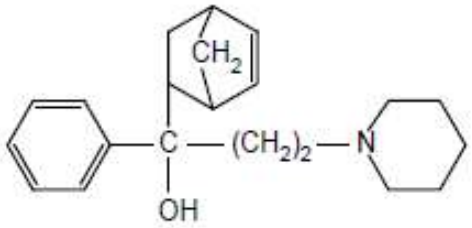


ii. Benztropine mesylate



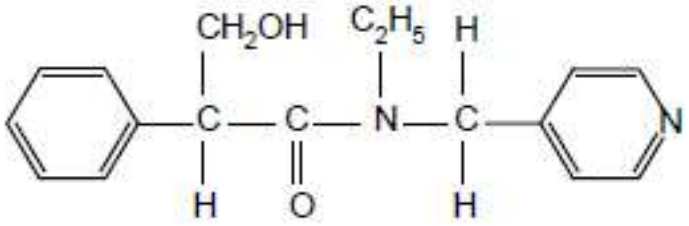
IV. Amino alcohols

i. Biperiden

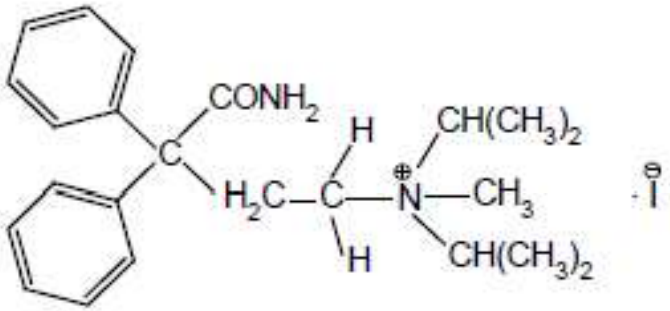


V. Amino amides

i. Tropicamide

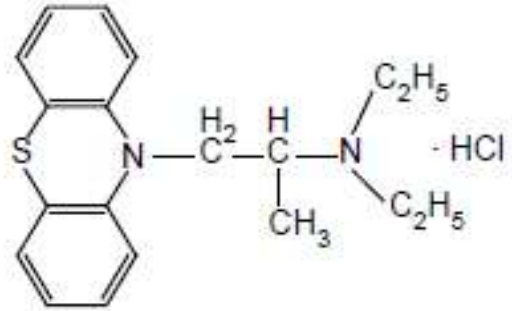


ii. Isopropamide iodide



VI. Diamides

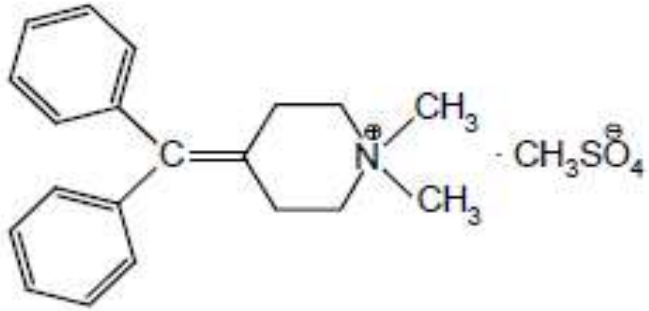
i. Ethopropazine HCl



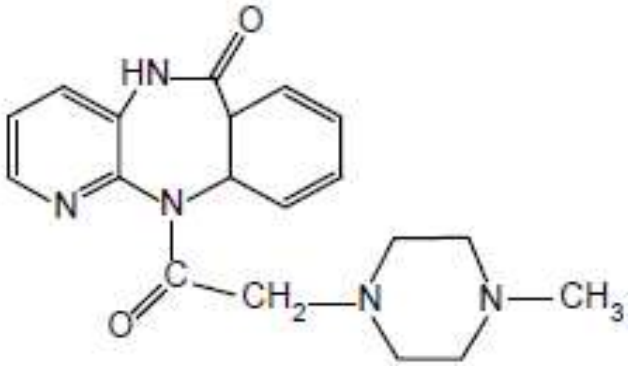
ii. Diethazine

VII. Miscellaneous amines

i. Diphenmail methyl sulphate



ii. Pirenzepine



iii. Methixene HCl

iv. Glycopyrrenium bromide

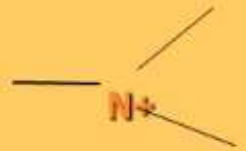
DIFFERENCE BETWEEN THE QUATERNARY AND THE TERTIARY ANTIMUSCARINICS

- **Quaternary Amines:**
  - These drugs do not pass through the blood brain barrier, and hence, lack CNS actions. Penetrate poorly into the eye from the blood stream or cornea.
  - The quaternary compounds have greater affi nity for nicotinic receptors, so that a great degree of ganglionic blockade may result.
  - These are mostly excreted unchanged into the urine.
- **Tertiary Amines:**
  - These drugs can penetrate the cell membranes in the nonionized form, and hence, can pass through the blood brain barrier. In the brain, they can exert both therapeutic and toxic actions.
  - These drugs penetrate through the cornea and cause mydriasis and cycloplegia.
  - They do not have nicotinic receptor affinity.
  - These drugs are biotransformed in the liver.

DIFFERENCE BETWEEN THE QUATERNARY AND THE TERTIARY ANTIMUSCARINICS

Synthetic atropine substitutes

Tertiary amines	Quaternary amines
Lipid soluble central actions	*Polar, water soluble No CNS effects*
Benztropine Homatropine Tropicamaide Pirenzepine Oxybutynin	Ipratropium Glycopyrrolate



Pharmacological actions of Anti cholinergic Drugs

CNS

- CNS depression
- Antiemetic effect (block vomiting center)
- antiparkinsonian effect (block ACH at basal ganglia).

Respiratory system

- Bronchial Relaxation (bronchodilator)
- ↓Bronchial secretion → ↑ viscosity

Cardiovascular system (CVS)

- Tachycardia (increase heart rate)
- AV conduction (+ ve dromotropic effect)

Urinary Tract

- Relaxation of smooth muscles of ureters.
- Sphincter contraction.
- Urinary retention (worsens prostate hypertrophy).

GIT

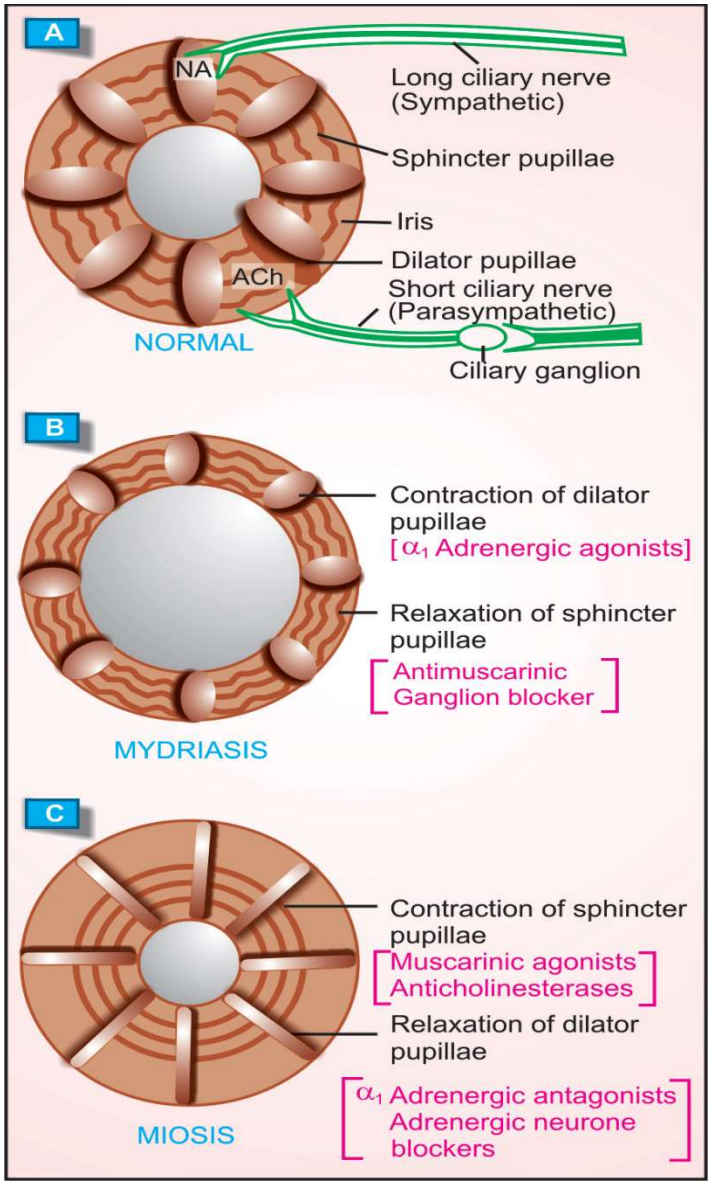
- Relaxation of smooth muscles.
- ↓ GIT motility → Antispasmodic effect.
- ↑ Sphincter contractions
- Constipation

Eye

- Passive mydriasis
  due to paralysis of circular muscle
- Cycloplegia (loss of near accommodation)
  due to paralysis of ciliary muscle.
- Loss of light reflex.
- Increase I.O.P (worsens glaucoma).
- ↓ Lacrimal secretion → sandy eye

Secretions

↓ Salivary secretion → (Dry mouth).
↓ Sweating → Dry skin → Fever in infants and children.
↓ Bronchial secretion → ↑ Viscosity
↓ Lacrimal secretion → Sandy eye



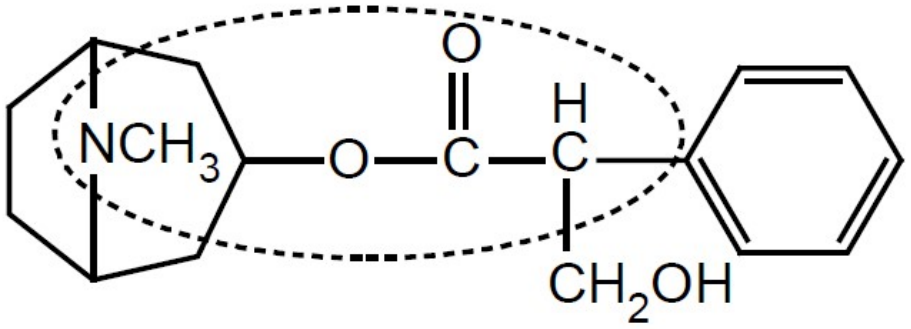
AUTONOMIC CONTROL OF PUPIL (A); AND SITE OF ACTION OF MYDRIATICS (B) AND MIOTICS (C)

GENERAL THERAPEUTIC USES OF ANTICHOLINERGIC DRUGS

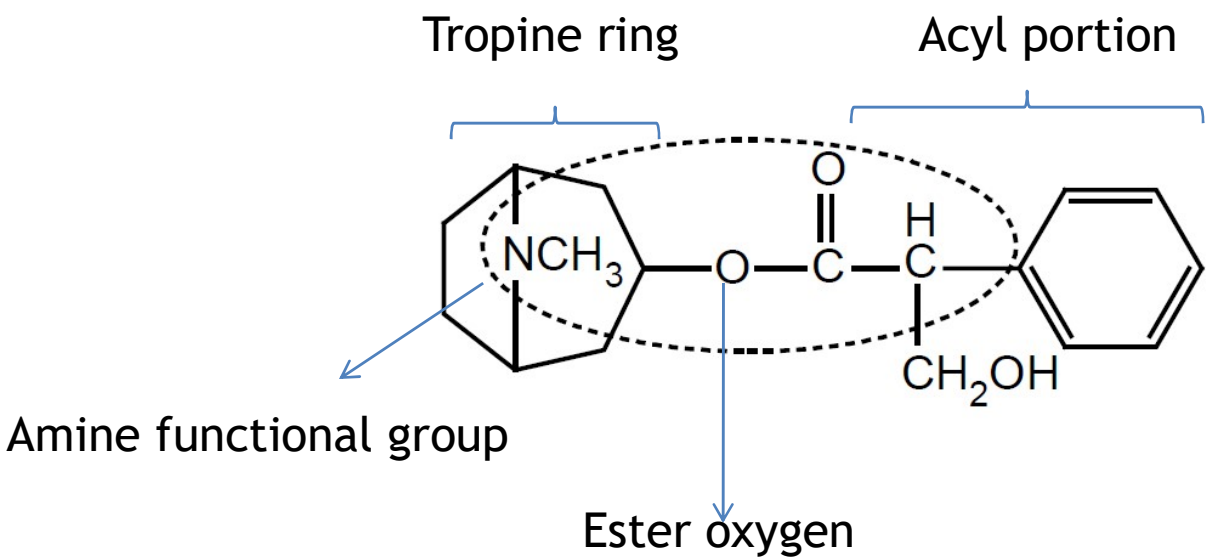
1. Used topically to dilate the pupil and paralyze accommodation.
2. Used as a preanaesthetic medication, to inhibit excessive salivary, bronchial secretions, and to prevent bronchospasm and laryngospasm.
3. The antisecretory effects are also sought in the treatment of acute coryza, hay fever, and rhinitis.
4. Used in the treatment of bronchial asthma and peptic ulcer.
5. Used in the treatment of Parkinson's disease.

SAR OF ANTICHOLINERGIC DRUGS

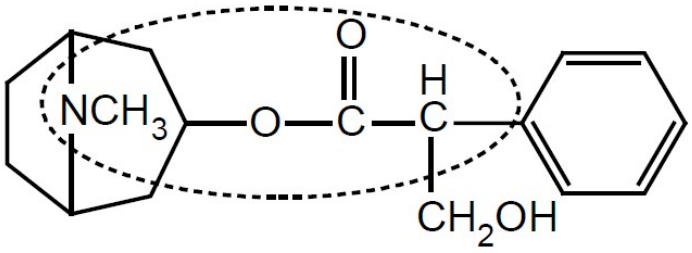
- Atropine, the prototype anticholinergic agent, provided the structural model that guided the design of many synthetic muscarinic antagonists till date. The circled portion of the atropine molecule depicts the segment resembling acetylcholine.



Atropine

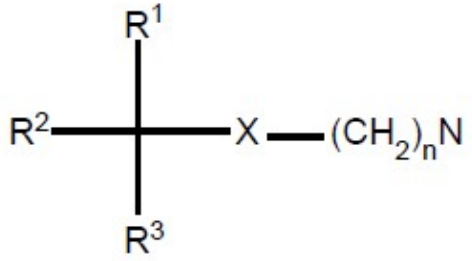


- Although the amine functional group is separated from the ester oxygen by more than two carbons, the conformation assumed by the tropine ring orients these two atoms such that the intervening distance is similar to that in acetylcholine.
- One important structural difference between atropine and acetylcholine, both of which are esters of amino alcohols, is the size of the acyl portion of the molecules.
- Based on the assumption that size was a major factor in blocking action, many substituted acetic acid esters of amino alcohols were prepared and evaluated for biologic activity.

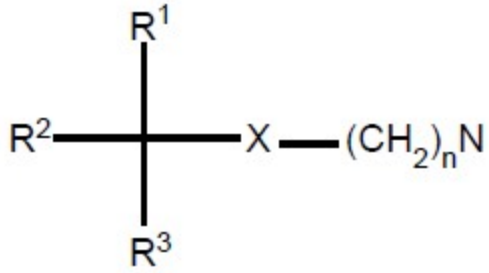


- The most potent antagonists were those that possessed two lipophilic ring substituents on the carbon α to the carbonyl of the ester moiety.

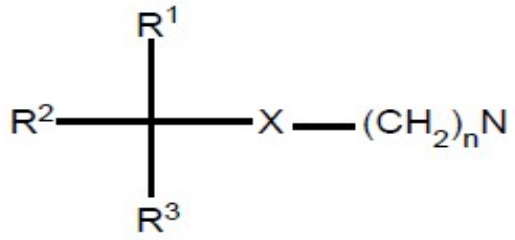
The SAR for muscarinic antagonists can be summarized as follows:



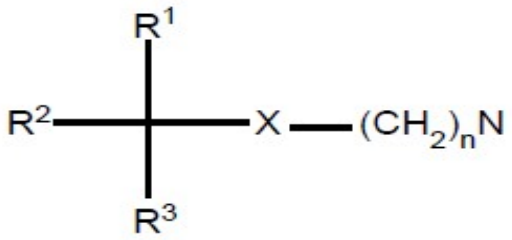
1. Substituents R1 and R2 should be carbocyclic or heterocyclic rings for maximal antagonist potency.
2. The rings can be identical, but the more potent compounds have different rings.



3. Generally, one ring is aromatic and the other saturated or possessing only one olefinic bond.
4. Substituents R1 and R2, however, can be combined into a fused aromatic tricyclic ring system, such as that found in propantheline.
5. The R3 substituent can be a hydrogen atom, a hydroxyl group, a hydroxymethyl group, or a carboxamide, or it can be a component of one of the R1 and R2 ring systems; when this substituent is either a hydroxyl group or a hydroxymethyl group, the antagonist is usually more potent than the same compound without this group.
6. The hydroxyl group increases binding strength by participating in a hydrogen bond interaction at the receptor.



7. The X substituent in the most potent anticholinergic agents is an ester, but an ester functional group is not an absolute necessity for muscarinic antagonist activity. This substituent can be an ether oxygen, or it can be absent completely.
8. The N substituent is a quaternary ammonium salt in the most potent anticholinergic agents; this is not a requirement, because tertiary amines also possess antagonist activity, possibly by binding to the receptor in the cationic (conjugate acid) form.
9. The alkyl substituents are usually methyl, ethyl, propyl, or isopropyl.

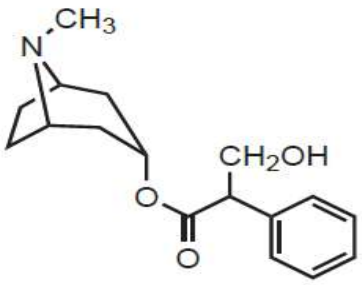


10. The distance between the ring-substituted carbon and the amine nitrogen apparently is not critical; the length of the alkyl chain connecting these can be from two to four carbons; the most potent anticholinergic agents have two methylene units in this chain.
11. Muscarinic antagonists must compete with agonists for a common receptor. This ability is because the large groups R1 and R2 enhance binding to the receptor.
12. Because antagonists are larger than agonists, this suggests that groups R1 and R2 bind outside the binding site of acetylcholine. It has been suggested that the area surrounding the binding site of acetylcholine is hydrophobic in nature. Thus in potent cholinergic antagonists, groups R1 and R2 must be hydrophobic (usually phenyl, cyclohexyl, or cyclopentyl). This concept is also supported by the current newer models for antimuscarinic agents.

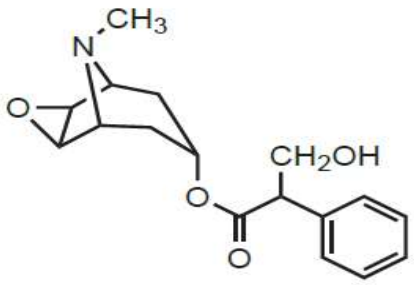
SOLANACEOUS ALKALOIDS AND ANALOGUES

•The earliest known anticholinergic agents were alkaloids found in the family Solanaceae, including *Atropa belladonna*, *Hyoscyamus niger and Datura stramonium*.

•(−)-Hyoscyamine, isolated as **atropine,** and **scopolamine** are the two alkaloids that have found the widespread clinical applications.

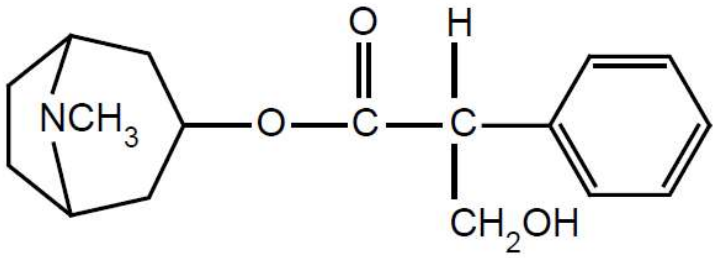


Atropine



Scopolamine

ATROPINE SULPHATE (HYOSCYAMINE SULPHATE)



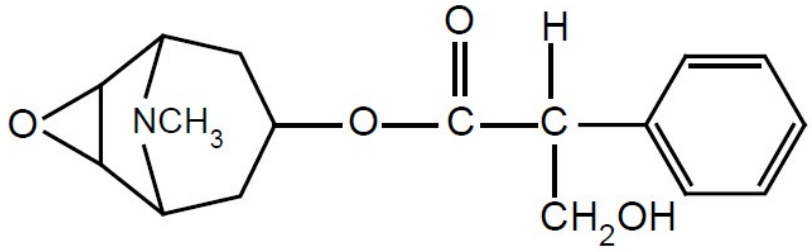
8-Methyl-8-aza-bicyclo[3.2.1]octan-3-yl 3-hydroxy-2-phenylpropanoate

Properties and Uses:

- Atropine is the tropic acid ester of tropine and is marketed as the sulfate salt.
- The naturally occurring alkaloid, (−)-hyoscyamine, undergoes base-catalyzed racemization during isolation from plants of the Solanaceae to give (±)-hyoscyamine or atropine.
- It was the first compound shown to block the effects of muscarine and electrical stimulation of the parasympathetic nervous system, hence it is the prototype of antocholinergic drugs.

- Atropine sulfate has a number of clinical uses; two of the most common are treatment of bradycardia and as a preoperative agent to reduce secretions before surgery.
- Its use for management of parkinsonism has been supplanted by newer agents with fewer peripheral side effects.
- It has been used in ophthalmology as a cycloplegic agent to paralyze the iris and ciliary muscle in treatment of iritis and uveitis and as a cycloplegic/mydriatic agent.
- Atropine is contraindicated in glaucoma due to its ability to increase intraocular pressure during mydriasis.

SCOPOLAMINE HYDROBROMIDE

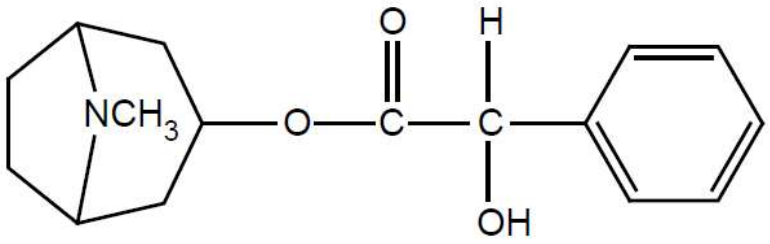


Properties and Uses:

- Scopolamine, another Solanaceous alkaloid, is chemically and pharmacologically similar to atropine.
- Scopolamine is the generic name given to (−)-hyoscine, the naturally occurring alkaloid.
- Scopolamine is marketed as the hydrobromide salt, because it is less deliquescent than some of its other salts.
- Interestingly, scopolamine is a CNS depressant at usual therapeutic doses, whereas atropine and other antimuscarinic agents are CNS stimulants.

- It has been used for the treatment of uveitis, iritis, and parkinsonism, but its most widespread use is for the treatment of motion sickness.
- For this indication, scopolamine is used in a transdermal patch applied to the skin behind the ear and is well-absorbed percutaneously following application.
- Plasma levels are observed within 4 hours and peak levels within 24 hours.

HOMATROPINE HYDROBROMIDE

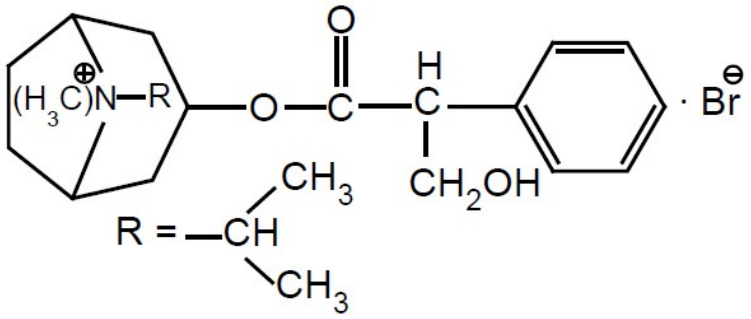


Tropane-3α-ol mandelate

Properties and uses:

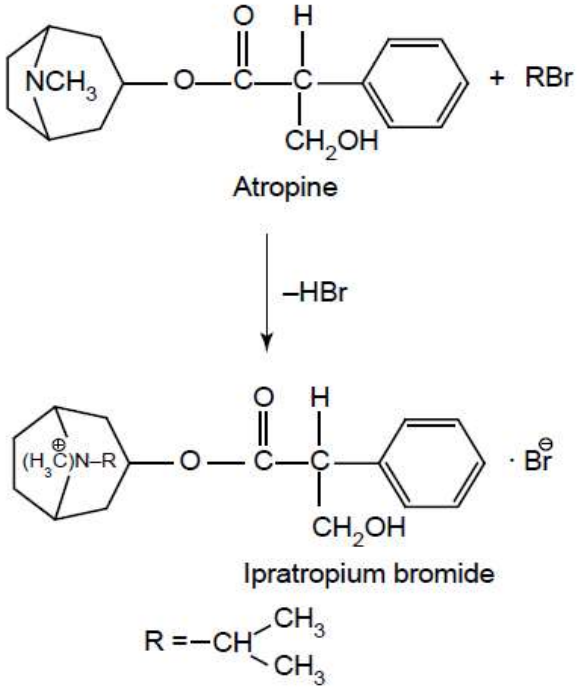
- Structurally related to atropine, It is 10 times less potent than it.
- Instilled in the eye, it acts in 45-60 min, mydriasis lasts 1-3 days while accommodation recovers in 1-2 days.
- It is used topically on the ciliary structure of the eye and to effect mydriasis.

IPRATROPIUM BROMIDE*



(±)-endo-3-(3-Hydro-1-oxo-2-phenyl propyl)-8-methyl-8-(1-methyl ethyl-8-azoniabicyclo octane bromide

Synthesis

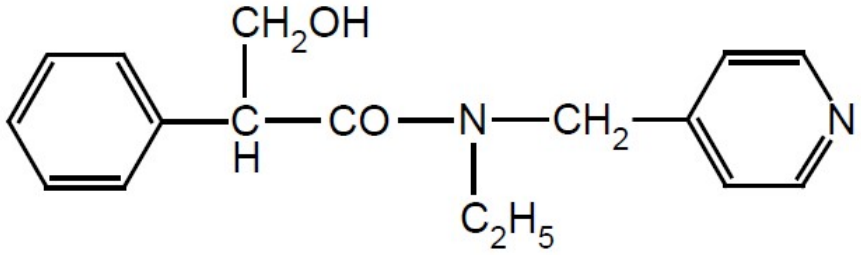


Properties and uses:

- It is a semisynthetic derivative of atropine.
- It is used in the inhalation therapy to produce dilation of bronchial smooth muscle for acute asthmatic attacks.
- It produces broncho-dilation by competitive inhibition of cholinergic receptors bound to the smooth muscles of the bronchioles.

SYNTHETIC CHOLINERGIC BLOCKING AGENTS

TROPICAMIDE

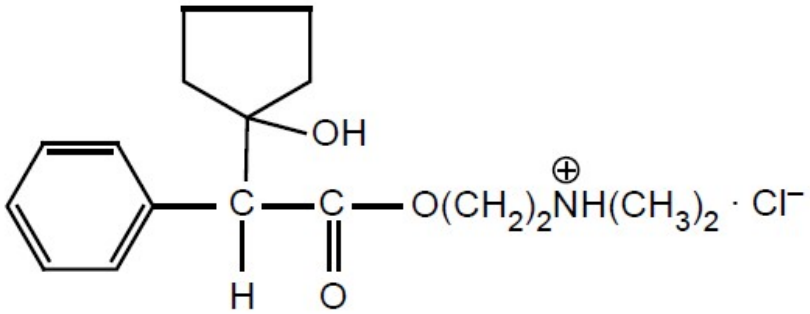


N-Ethyl-2-phenyl-N-(4-pyridylmethyl)-3-hydroxy-propionamide

Properties and uses:

- A synthetic anticholinergic agent from the class of **Amino Amides.**
- Used to induce mydriasis and cycloplegia in ophthamologic practice and it has short duration of action.

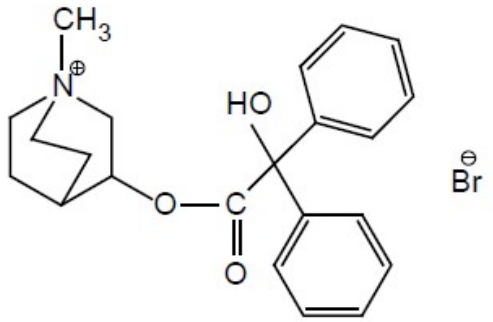
CYCLOPENTOLATE HYDROCHLORIDE



2-(Dimethylamino) ethyl-1-hydroxyl-α-phenyl cyclopentane acetate hydrochloride

- It is an Amino alcohol ester.
- It acts much faster than atropine and possesses a relatively shorter duration of action.
- Usually employed as eye drops to cause cycloplegia and mydriasis.

CLIDINIUM BROMIDE

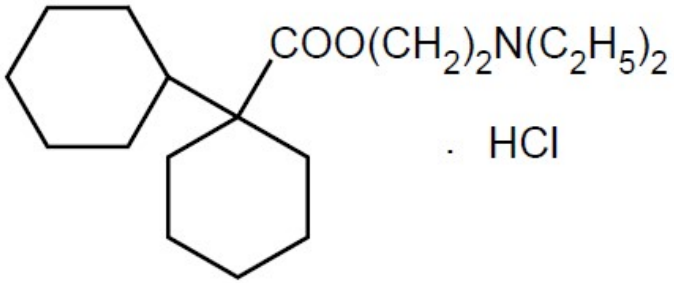


3-OH-1-Methyl quinuclidium bromide benzilate

Properties and uses:

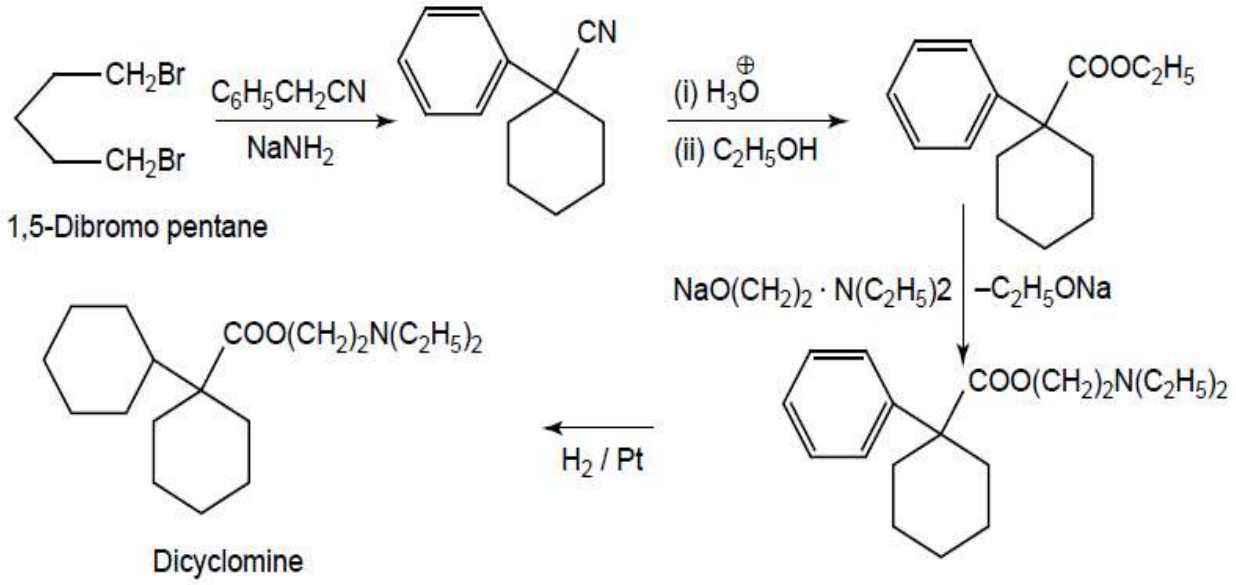
- It is an Amino alcohol ester.
- Used as a bronchodilator in asthmatic conditions. It has a longer lasting effect as compared to ß-agonists.

DICYCLOMINE HYDROCHLORIDE*

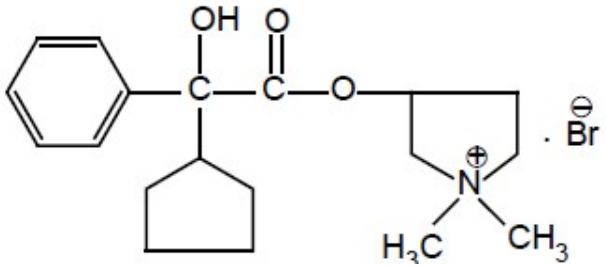


2-(Dimethylamino) ethyl bicyclohexyl-1-carboxylate HCl

Synthesis



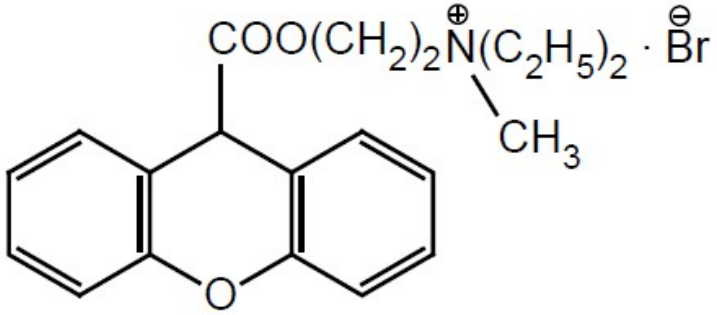
GLYCOPYRROLATE



N,N-Dimethyl pyrrolidinium bromide-3-α-cyclopentyl mandelate

- Glycopyrrolate is also an Amino alcohol ester.
- It is one of the important drugs used in the management and control of gastric secretion.
- It exerts a two-fold action, first by prolonging the gastric emptying time and secondly by decreasing the gastric acid production.
- Thus it generously favours the retention of antacids in acute cases of peptic ulcer.
- Besides, it also finds its usefulness in the treatment of colitis, biliary spasm, spastic colon, spastic duodenum.

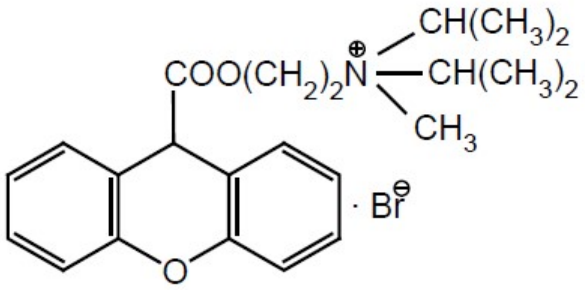
METHANTHELINE BROMIDE



diethyl-methyl-[2-(9*H*-xanthene-9-carbonyloxy)ethyl]azanium

- Methantheline is a synthetic anticholinergic antispasmodic agent. It is a member of xanthenes.
- Antispasmodics are used to relieve cramps or spasms of the stomach, intestines, and bladder. Methantheline is used to treat intestine or stomach ulcers (peptic ulcer disease), intestine problems (irritable bowel syndrome), pancreatitis, gastritis, biliary dyskinesia, pylorosplasm, or urinary problems (reflex neurogenic bladder in children).

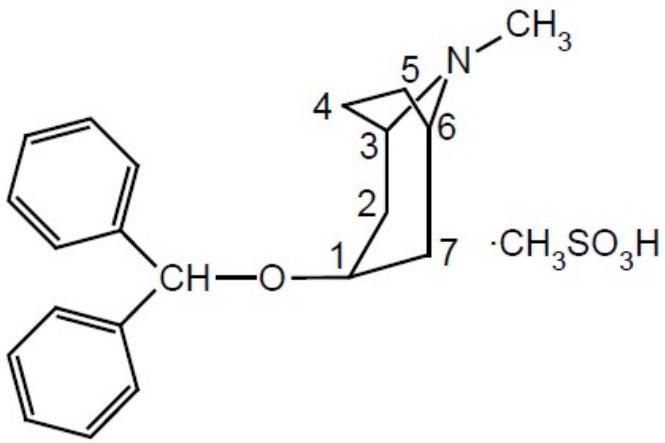
PROPANTHELINE BROMIDE



(Ethyl) di isopropyl methyl ammonium bromide xanthene-9-carboxylate

- It is a muscarinic antagonist used as an antispasmodic, in rhinitis, in urinary incontinence, and in the treatment of ulcers. At high doses it has nicotinic effects resulting in neuromuscular blocking.

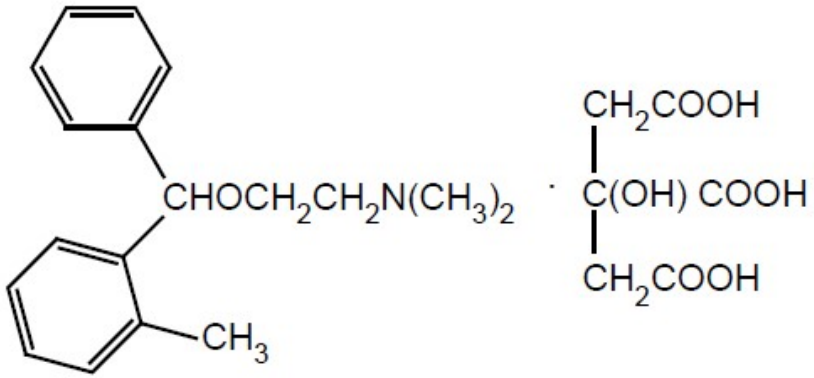
BENZTROPINE MESYLATE



3α-(Diphenyl methoxy)-1αH,5αH-tropine methansulphonate

- It is an Amino ether class of compound with anticholinergic, antihistaminic, local anaesthetic and dopamine uptake inhibitory properties.
- It is a combination molecule between a tropane ring, similar to cocaine, and a diphenyl ether from the dialkylpiperazines determined to be a dopamine uptake inhibitor.
- For this reason, used for the symptomatic treatment of Parkinson's disease.

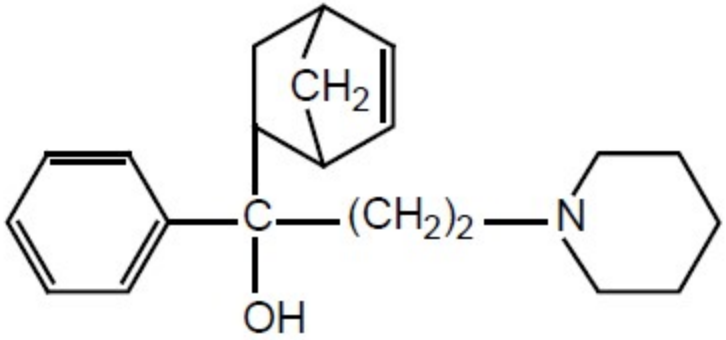
ORPHENADRINE CITRATE



N, N-Dimethyl-2-(o-methyl-α-phenyl benzyloxy) ethylamine citrate

- It is amino ether anticholinergic drug with additional dopamine reuptake inhibitory action like Benzatropine.
- It is used for the symptomatic treatment of Parkinson's disease.
- It is also used as a skeletal muscle relaxant.

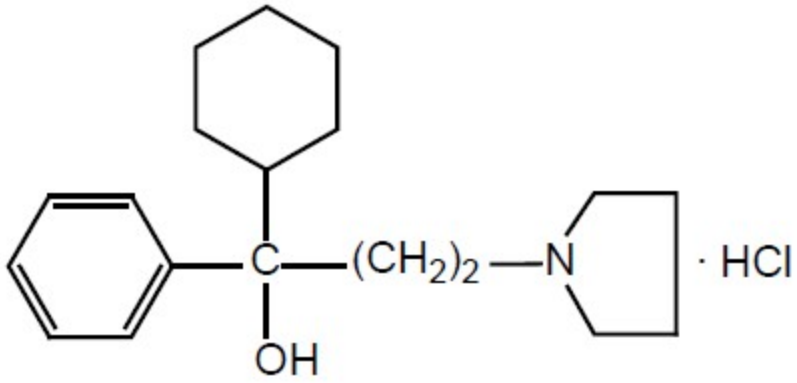
BIPERIDEN HYDROCHLORIDE



α-5-Norbornen-2-yl-α-phenyl-3-(piperidine-1-yl) propanol

- It is a muscarinic antagonist that has effects in both the central and peripheral nervous systems.
- It has been used in the treatment of al,l types (arteriosclerotic, idiopathic, and postencephalitic) parkinsonism.
- It has also been used to treat extrapyramidal symptoms induced by phenothiazine derivatives and reserpine.

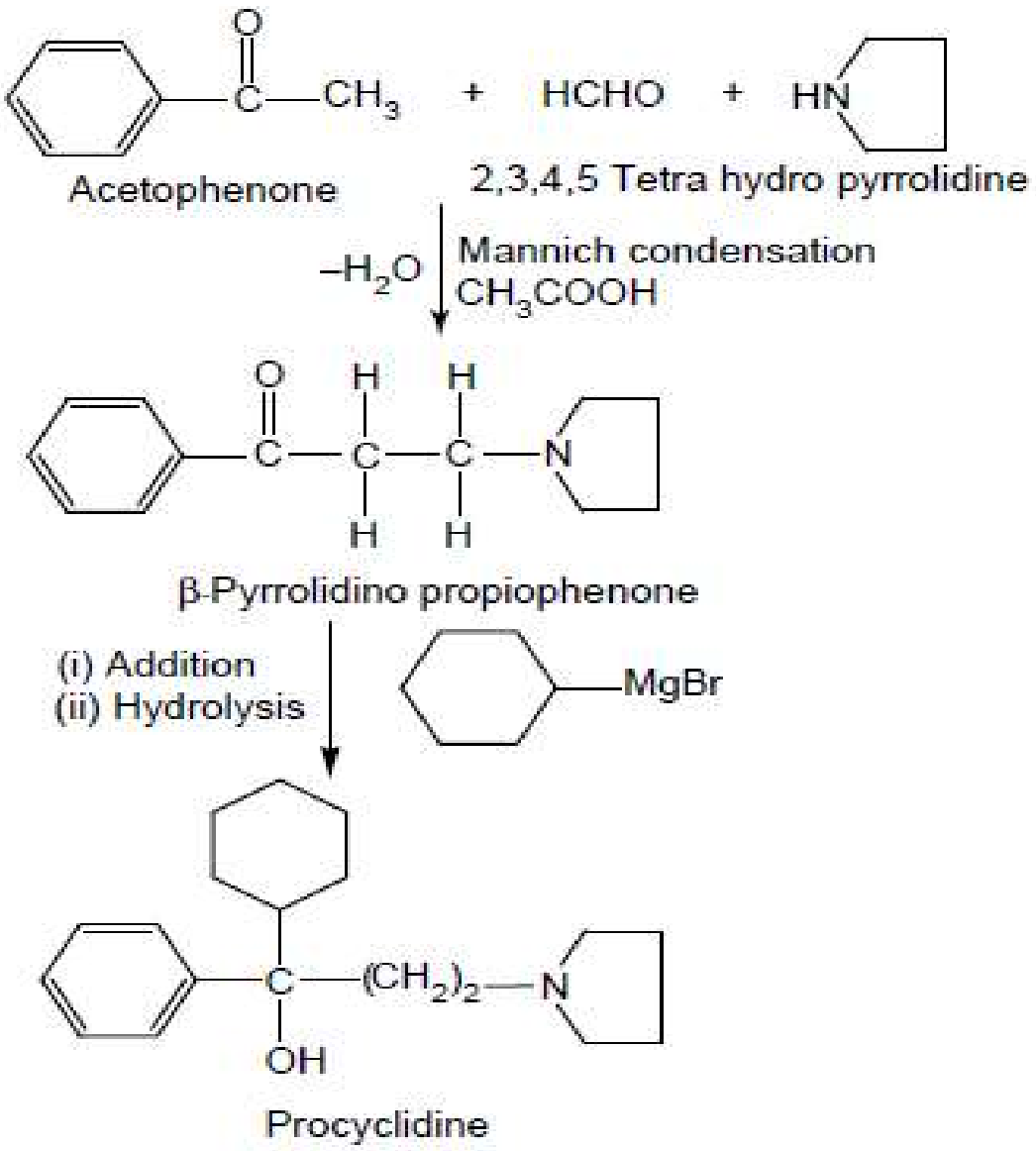
PROCYCLIDINE HYDROCHLORIDE*



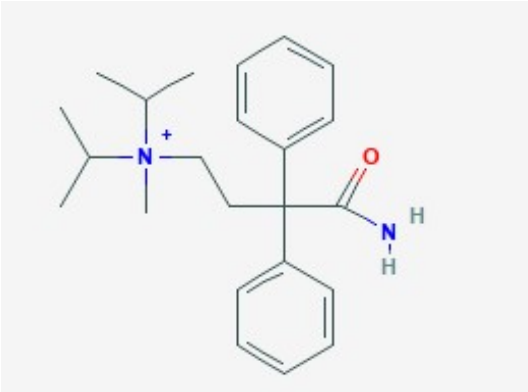
1-Cyclohexyl-1-phenyl-3-pyrrolidin-1-yl-1-propanol HCl

- An Amino Alcohol muscarinic antagonist that crosses the blood-brain barrier and is used in the treatment of drug-induced extrapyramidal disorders and in parkinsonism.

Synthesis:


Acetophenone
+ HCHO +
2,3,4,5 Tetra hydro pyrrolidine
–H2O
Mannich condensation
CH3COOH
β-Pyrrolidino propiophenone
(i) Addition
(ii) Hydrolysis
MgBr
Procyclidine

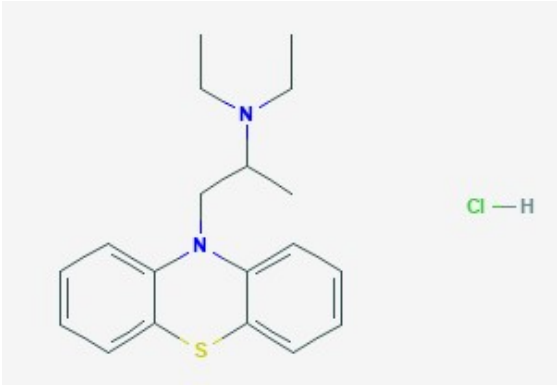
ISOPROPAMIDE IODIDE



(4-amino-4-oxo-3,3-diphenylbutyl)-methyl-di(propan-2-yl)azanium;iodide

- Isopropamide is a long-acting anticholinergic drug.
- It is used in the treatment of peptic ulcers and other gastrointestinal disorders involving hyperacidity and hypermotility.
- Chemically, it contains a quaternary ammonium group.

ETHOPROPAZINE HYDROCHLORIDE (PROFENAMINE HYDROCHLORIDE)



N,*N*-diethyl-1-phenothiazin-10-ylpropan-2-amine;hydrochloride

- Profenamine hydrochloride is the monohydrochloride salt of profenamine.
- An antimuscarinic, it is used for the symptomatic treatment of Parkinson's disease. It has a role as an adrenergic antagonist, a histamine antagonist, an antiparkinson drug and a muscarinic antagonist.

THANK YOU….