__/__/____

Introduction

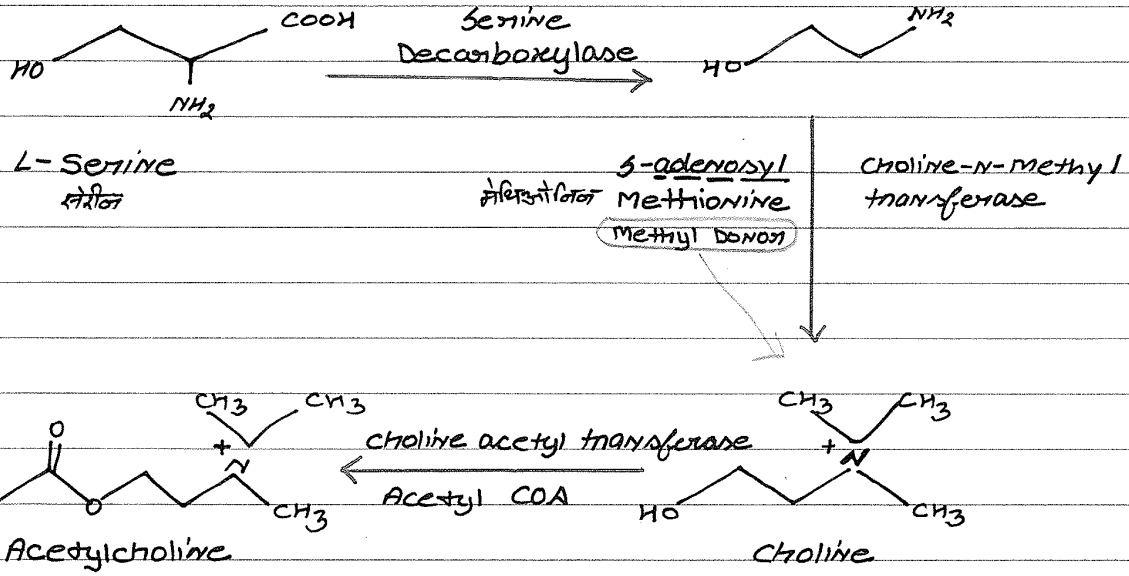
ACh is released into the synaptic vesicles of effectors junction by an impules across the neuroeffector junction.

This leads to the action potential that is due to the difference in the ionic gradients of Na^+ and K^+ Equilibrium, and in other tissues, it is mediated along with Cl ion.

ACh is synthesized locally in the cholinergic nerve ending by adenosine - triphosphate ATP dependent system.

Choline is actively taken by the axonal membrane and acetylated with the help of ATP and Co-Enzyme-A by the choline acetylase.

Biosynthesis of Acetylcholine



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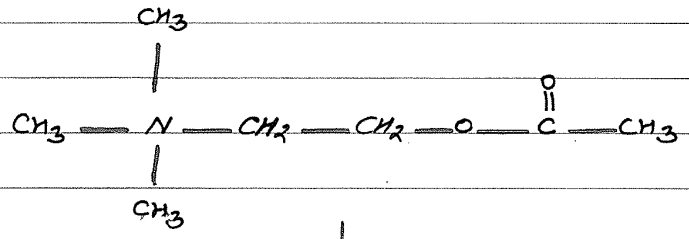
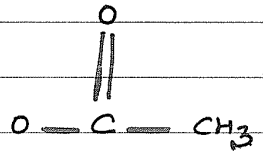
Catabolism of Acetylcholine

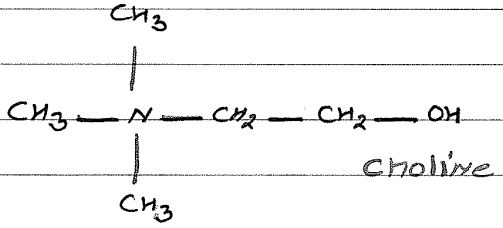


Acetylcholine

Ecetylcholine Esterase



Acetate ion



Choline

Reuptake into the terminal

__/__/____

Parasympathomimetic Agents or Cholinergic Agents.

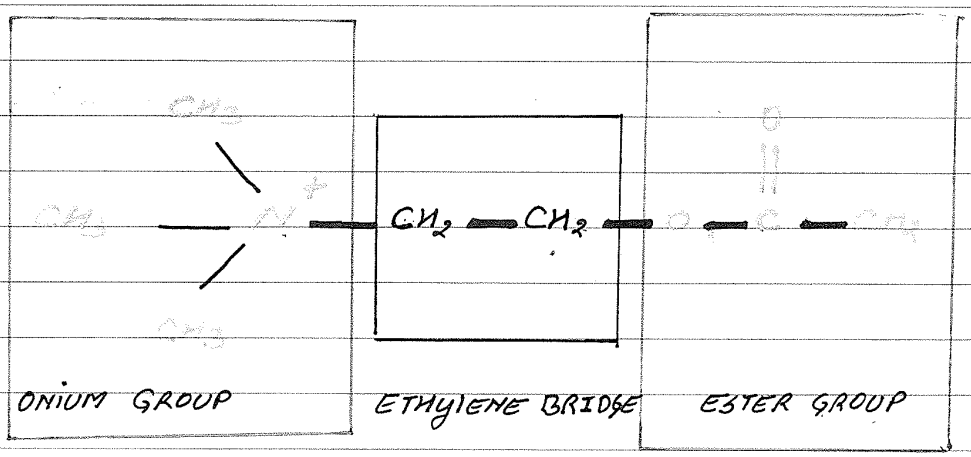
Defination

Drugs and chemicals that cause the parasympathomimetic Division ~~to~~ react.

Compounds that mimic the action of Ach at parasympathomimeti system.

Cholinergic drug + Cholinergic Receptors → Para Sympathomimetic Action

SAR



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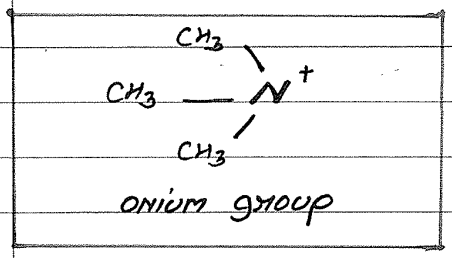
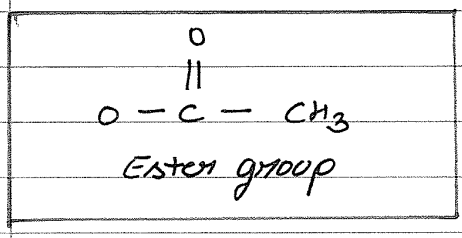


Onium group

1. Essential for affinity and intrinsic Activity.
2. It interact with the -vely charged Aspartic acid residue of the receptor.
3. Trimethylammonium group is optimal functional moiety.
4. Substitution with large alkyl gp Decrease the Activity.



Ester group

1. Essential for affinity ; from H bond with threonine and asparagine residue at the receptor site.
2. When methyl replaced by higher homologues i.e the propionyl group, the resulting ester are less potent than Ach.
3. Aromatic group possess cholinergic antagonist Activity.

__/__/____

$CH_2 — CH_2$
Ethylene bridge

1. Shortening or lengthening of Ethylene bridge Decrease M-Activity.
2. α- substitution Decrease both M and N Activity.
3. β- substitution Decrease both M and N Activity.

—X—

__/__/____

CLASSIFICATION

PSM

1) Directly Acting

(I) Choline Ester
- Ach
- Methacholine
- Carbachol
- Bethanechol

(II) Cholinomimetic alkaloids
- Arecoline
- Muscarine
- Pilocarpine

2) Indirectly Acting

Reversible Inhibitors

Carbamates
- Physostigmine
- Neostigmine
- Pyridostigmine
- Rivastigmine

4 ammonium compounds
- Edrophonium
- Demecarium
- Ambenonium

Irreversible Inhibitors
- Echothiopate
- Malathion
- Isofluorphate
- Parathion

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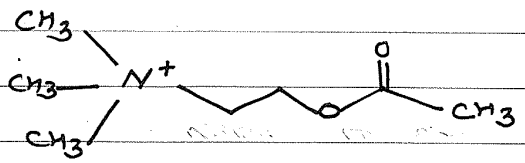
Direct Acting Agents :-

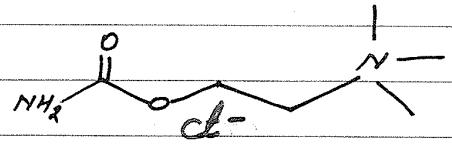
These are those Agents which Directly bind with cholinergic receptor (N & M) and produce its Action.

1. **Acetylcholine**



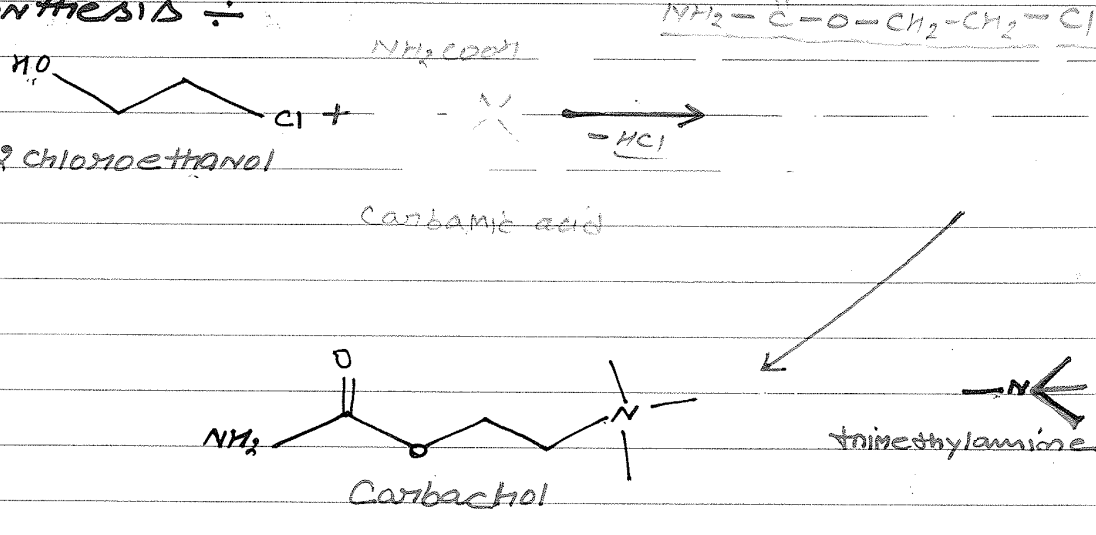
Direct Acting
Metabolized by Cholinesterase Enzyme
Used as eye drop to cause Miosis during surgery.
Used as Vasodilator & Cardiac Depressant.

2. **Carbachol**

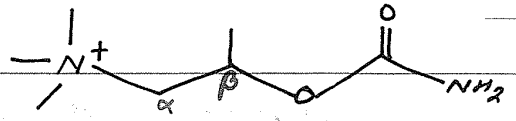


1. Bind with M & N receptor.
2. It is not inactivated by cholinesterase, thus has prolonged Action than Acetylcholine
3. Used in chronic glaucoma) intra-ocularly to produce miosis & to reduce post-operative risk.

Synthesis :-



3. Bethanechol

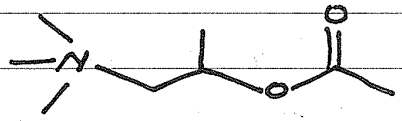


More selective on Muscarinic receptor.

More stable than Carbachol as there is methyl gp at β-carbon atom.

Used to stimulate GI Tract and Urinary bladder after surgery.

4. Methacholine

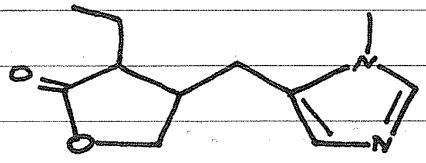


More stable on M-receptor

Prolong Action than Acetylcholine.

Used in the treatment of Reynaud's disease & glucoma. Also used in Tachycardia.

5. Pilocarpine



Directly Acting on muscrinic receptor.

Used in the treatment of glaucoma and in the treatment of dry eye and dry Mouth.

__/__/____

Indirectly Acting Cholinergic drugs

(Cholinesterase Inhibitors)

These drugs do not act on receptors Directly but inhibit the Hydrolysis of Acetyl choline by Acetyl Cholinesterase and hence increase the conc. of Acetylcholine to produce its Action.

There are two types

1. Reversible inhibitors
2. Irreversible inhibitors

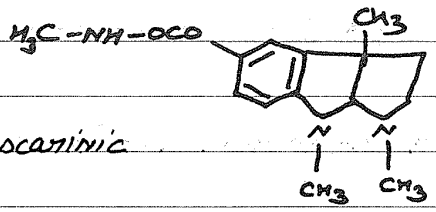
1. Reversible Inhibitors

These agents bind reversibly to the cholinesterase Enzyme and form Esters like Carbonate or phosphate and bind with Active site of Enzyme

This enzyme won't be able to Hydrolyse ACh, Hence Act as Anticholinesterase.

__/__/____

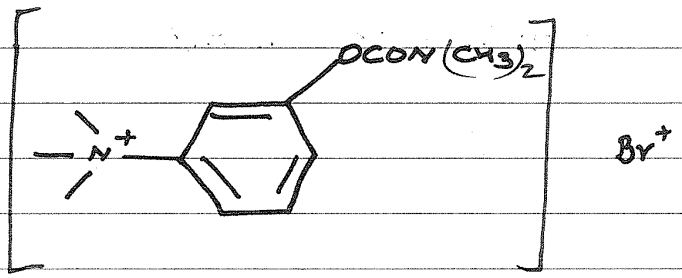
1. **Physostigmine**



Indirectly stimulate both muscarinic and nicotinic receptors.

Used to decrease the intraocular pressure in glaucoma

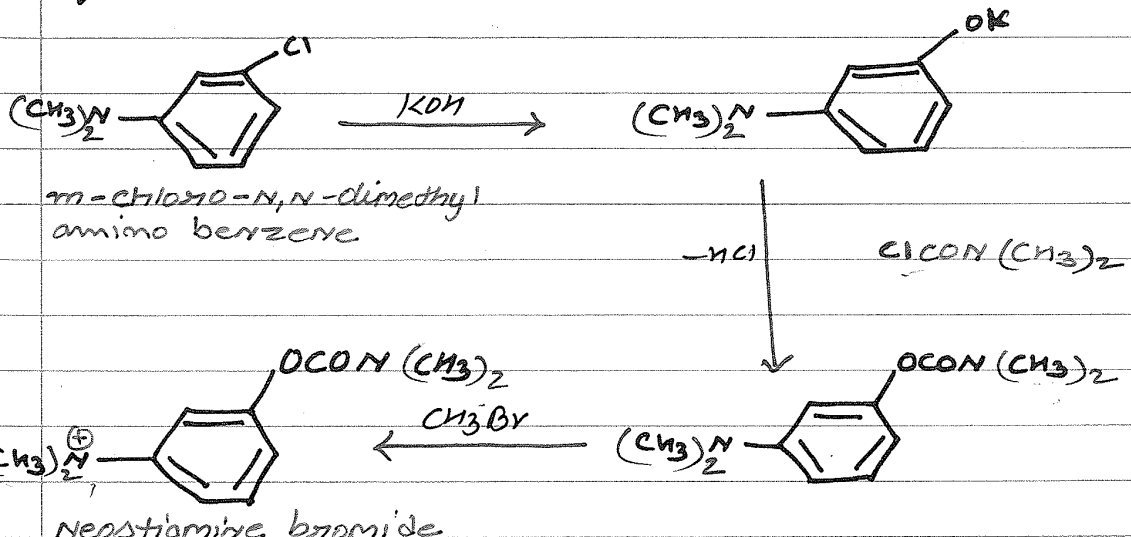
2. **Neostigmine**



Indirectly stimulate both (M + N) receptors.

It binds to anionic and Esteric site of cholinesterase and block the Activity of Acetylcholinesterase.

Synthesis



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Reversible Anticholinesterases

pyridostigmine bromide

Also helpful in nerve gas poisoning.

Edrophonium chloride

Also helpful in Snake Bite

Ambenonium chloride

Used treatment of Myasthenia gravis.

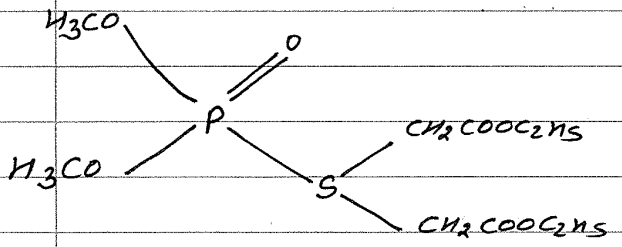
__/__/____

Irreversible Cholinesterase Inhibitor

These drugs produce irreversible inactivation of Acetylcholinesterase enzyme.

Bind irreversibly by covalent bond to the Active site of Enzyme and cause inactivation of Enzyme.

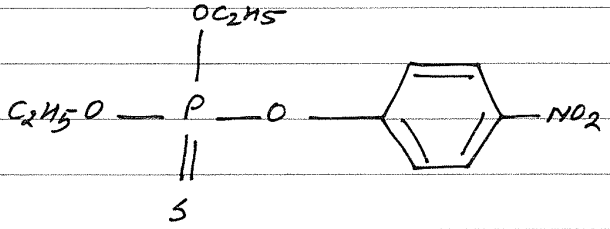
This Category include various organophosphorous Compounds



Malathion

Used as insecticide

Used in the treatment of Scabies.



Parathion

Used as insecticide in Agriculture

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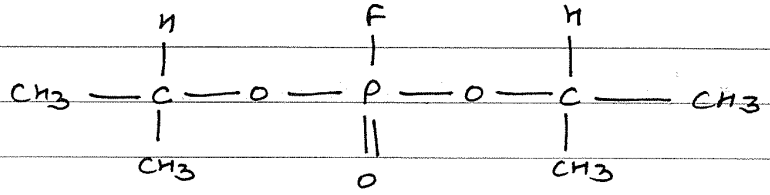
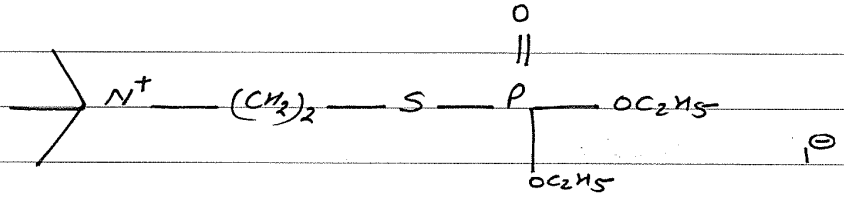


Isoflurophate



Echothiopate iodide

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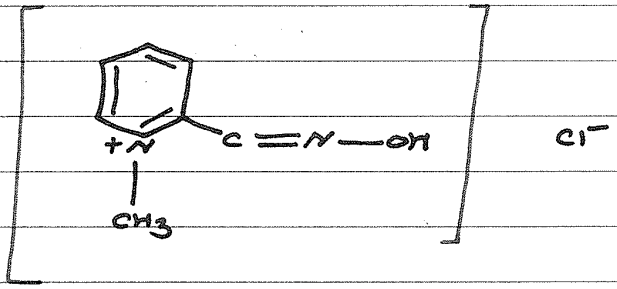
Cholinesterase Reactivators

These are drugs which cause reactivation of cholinesterase enzyme

These are mainly used in the treatment of poisoning by organophosphates, sulphonates and acetyl cholinesterase inhibitors.

Pralidoxime Chloride



The reactivites the Enzyme by Binding to the anionic site of Enzyme and displaces the phosphate from the serine residue

Used for the treatment of poisoning of Organophosphorus compounds.

__/__/____

Cholinergic Blocking Agents

Cholinergic antagonists inhibit the Actions of Endogenous acetyl choline (Ach) and Muscarinic Agonists at muscarinic receptor sites in peripheral tissues and in the CNS.

These drugs are highly specific reversible competitive antagonists for muscarinic Ach receptors. The pharmacological Effects are blockage of parasympathetic stimulation at effector organs.

They are rapidly absorbed from the GIT, slowly Absorbed when Applied locally on Eye or Skin.

The potent anticholinergics are used to.

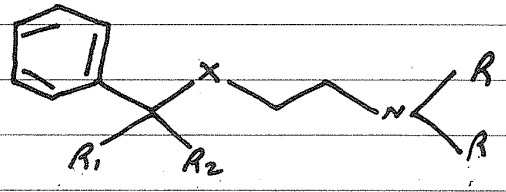
1. Control the secretion of Saliva & Gastric Acid.
2. Slow down gut motility
3. to prevent vomiting.

__/__/____

SAR of Cholinolytic Agents.

Anticholinergic agents are bulky. They combine with muscarinic receptors and shield the Binding site from ~~Acetyl~~ Acetylcholine.

The general structure of the Compounds in this Category is ;



Substituent R_1 should be Carbocyclic or Heterocyclic ring for maximal antagonist Activity.

Substituent R_2 Should be Hydrogen atom, Hydroxy gp Hydroxymethyl gp, methyl gp.

The nature of The group X Effects only the Duration of Action, physiochemical properties and the site effects of the drug molecule but... not its ~~Stability~~ to bind with the receptors.

The phenyl ring cannot tolerate any more substituent than F at the para-position, without losing Antagonist Activity.

There is a limitation for the N substitution. optimal potency is associated with 2-3 Ethyl groups.

__/__/____

Therapeutic uses of Anticholinergic drugs.

Peripheral ; Inhibition of parasympathetic transmission

* Mydriasis with Cycloplegia
* Decrease saliva production
* Decrease motility of smooth muscle.
* Inhibition of vagal transmission to heart.

Central ; Anti-parkinson & anti-motion sickness.

Side Effects

* peripheral photophobia
* Cycloplegia
* Dry mouth
* Difficult urination
* Red skin
* Increase skin temp

__/__/____

Classification.

1. Solanaceous alkaloid and Analog
   - Atropine
   - Hyoscyamine
   - Scopolamine
   - Homatropine
   - Ipratropium

2. Synthetic cholinergic blocking Agent.

(A) Aminoalcohol Esters
- Tropicamide
- Clinidium bromide
- Cyclopentolate
- Dicyclomine
- Glycopyrrolate
- Methantheline
- Propantheline

(B) Aminoalchol Ethers
- Benztropine
- Orphenadrin

(C) Aminoalcohol
- Biperidine
- Procyclidine
- Trihexethyl chloride

(D) Miscellaneous
- Isopropamide
- Ethopropazine.

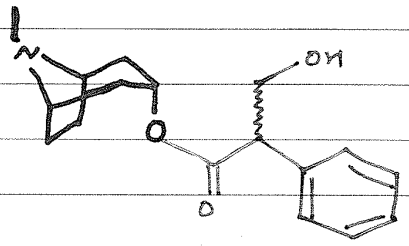
__/__/____

Solanaceous Alkaloids and Analogues.

Scopolamine is an alkaloid isolated from various members of Solanaceae. It is an optically Active Compounds and Levoform is potent.

(-) Scopolamine is slightly water miscible viscous liquid. Scopolamine occurs as scopolamine hydrobromide salt. which is a colourless, odourless, water soluble powder

Atropine



Anticholinergic, blocks. muscarinic receptors.

Alkaloid Extracted from Solanaceae plant.

It is an Ester of tropine and tropic Acid and used as a sulphate salt in racemic from.

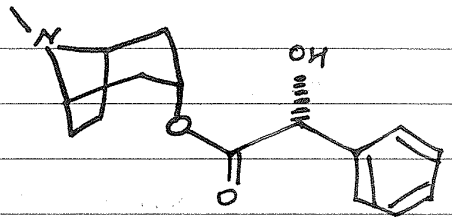
At therapeutic does it can penetrate the Brain and stimulate the CNS.

MOA:- It competitively binds to muscarinic receptor And antagonizes it thus blocking all cholinergic Effects.

USES
- Treat Bardycardia
- Reduce secretion before surgery
- Treat Initis.
- Organophosphate poisoning

__/__/____

Hyoscyamine



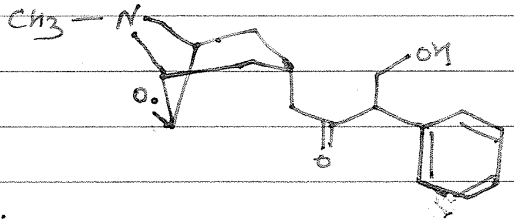
It is the levorotary isomer of atropine

Various GIT Disorders including spasms, peptic ulcers, irritable bowel syndrome, cystitis.

Used to relieve some Heart problems.

Control some of the symptoms of Parkinson's Disease.

Scopolamine



Levorotatory form is Active
Action on the Higher nerve center.
Transdermal patch of Scopolamine is available.

USES; postoperative nausea and vomitting and sea sickness, motion sickness, Irritable bowel Syndrome. Eye Inflammation.

Ipratropium Bromide

It is a Quaternary Ammonium Derivative of Atropine

Used in inhalation therapy to produce Dilation of Bronchial Smooth Muscle for acute Asthmatic Attacks.

Synthesis ;-

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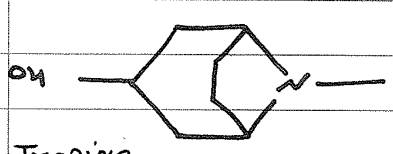
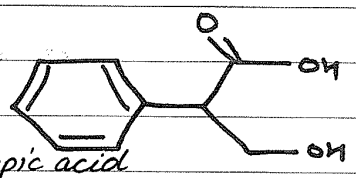
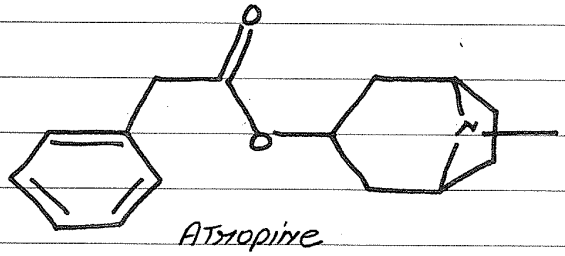


Tropine

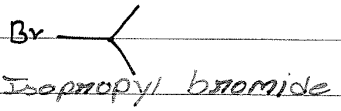


Tropic acid

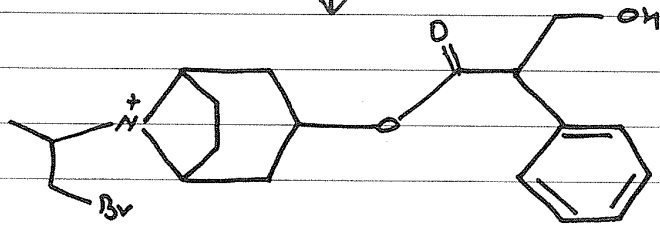
Esterification



Atropine



Isopropyl bromide



Br^-

ipratropium bromide

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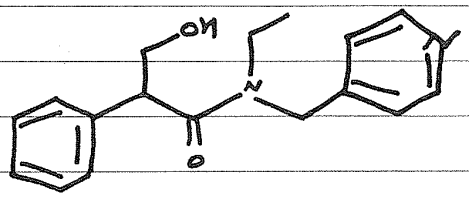
Synthetic Cholinergic Blocking Agents.

1. Tropicamide

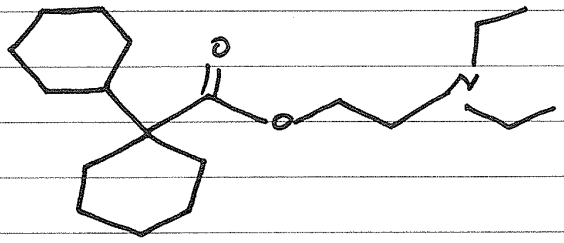


Effective anticholinergic for Ophthalmic use.

Produces short Acting Mydriasis & Cycloplegia.

Treatment of Acute iritis, iridocyclitis and keratitis

2. Dicyclomine



Used for its Spasmolytic Effect on Various smooth muscle. spasms, particularly those associated with GIT.

It is also useful in dysmenorrhea, pylorospasm and biliary dysfunction.

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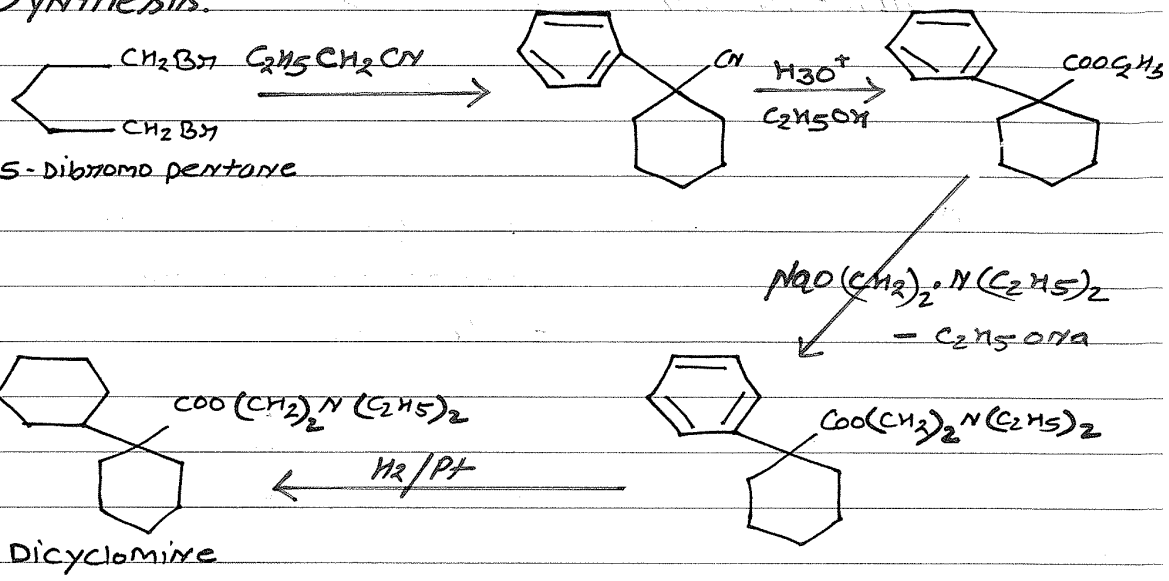
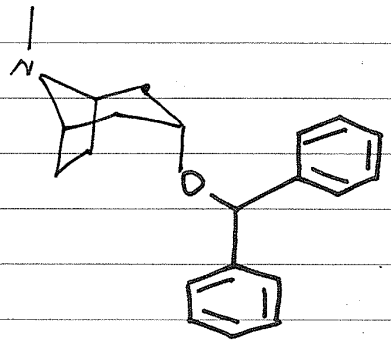
Synthesis.



1,5-Dibromo pentane

Dicyclomine

3. Benztropine



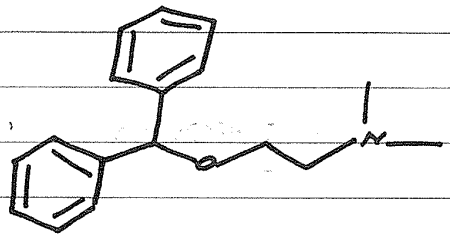
Has anticholinergic, antihistaminic and local anesthetic properties.

Its anticholinergic effect makes it Applicable as an antiparkinsonian Agent.

It is about as potent anticholinergic as atropine.

__/__/____

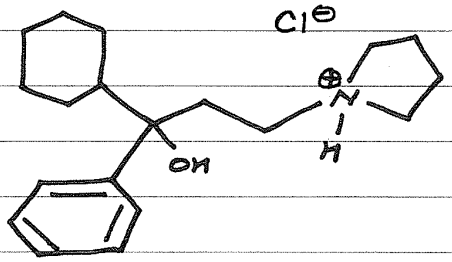
4. Orphenadrin



Closely related to diphenhydramine structurally but has much lower antihistaminic activity and much higher anticholinergic Action.

It does reduce voluntary muscle spasm, however, central inhibitory action on Cerebal motor areas.

5. Procyclidine HCl

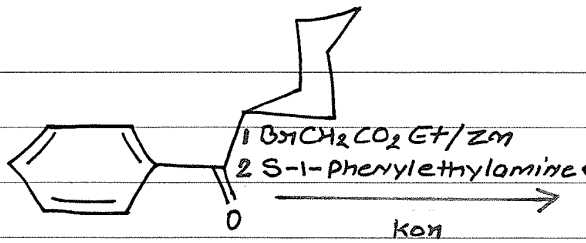


Effective peripheral anticholinergic.

Ability to relieve voluntary muscle spasticity by its central Action.

Treatment of Parkinson syndrome.

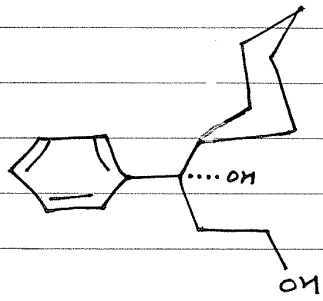
Reduce muscle rigidity in postencephalitic, arteriosclerotic, and Idiopathic type of disease.



Cyclohexyl (phenyl) Methanol

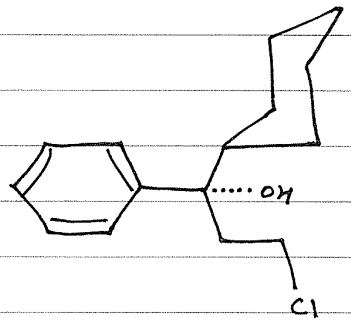
(S) 3-Cyclohexyl-3-Hydroxy 3-phenylpropanoic acid.

B_2H_6

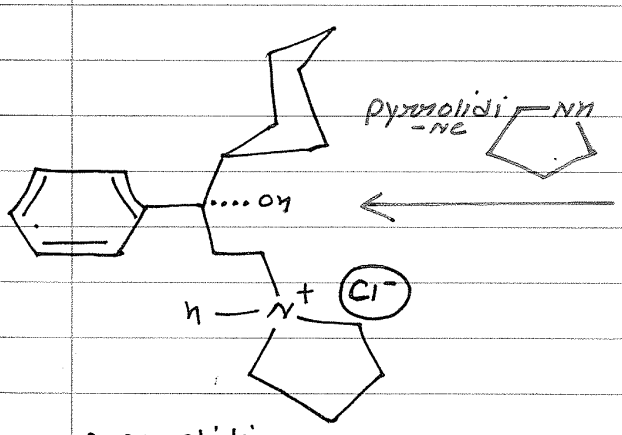


(S)-1-Cyclohexyl-1-phenylpropane-1,3-diol

CCl_4
triphenylphosphine



(S)-3-Chloro-1-Cyclohexyl 1-phenylpropane-1-ol



Procyclidine Hydrochloride