

PARASYMPATHOLYTICS

CHOLINERGIC BLOCKING AGENTS

SAR of cholinergic blockers

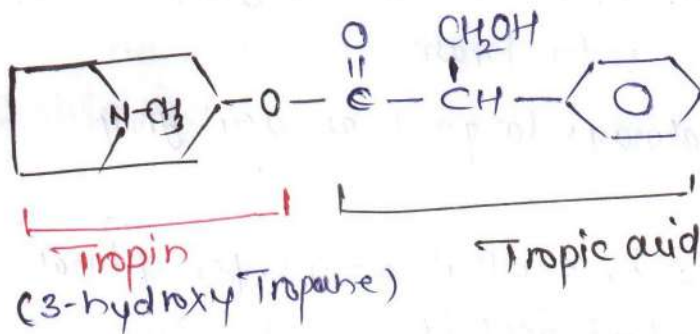
Solanaceous alkaloids & Analogues - Atropine, Hyoscyamine, Scopolamine, Homatropine, Ipratropium*

Synthetic cholinergic blockers

Tropicamide, Cyclopentolate, clidinium, Dicyclomine*, Glycopyrrolate, Methantheline, Propantheline, Benztropine, Oxphenadrine, Piperidine, procyclidine*, Tridihexethyl, Isopropamide, Ethopropazine

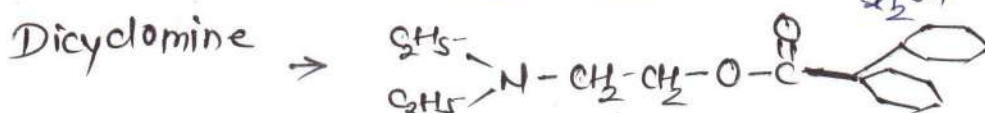
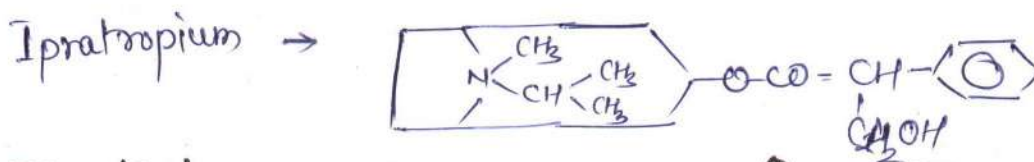
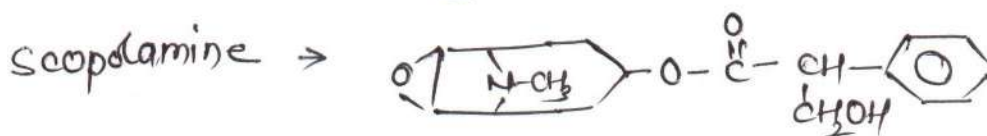
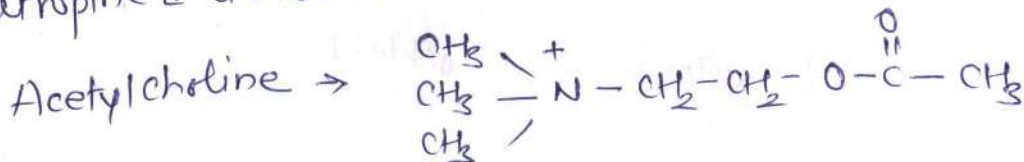
SAR OF CHOLINERGIC BLOCKERS

Atropine is the prototype drug in this category

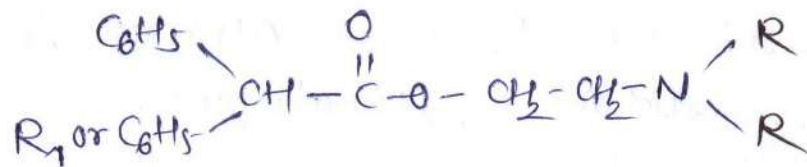


* Ester of bicyclic amino alcohol

1) Ach and atropine are acetic acid ester of amino alcohol, so many substituted acetic acid ester of amino alcohol were prepared. Unlike, Ach terminal ester carbon in atropine & derivatives had a bulky substituents.



- 2.) Ester of phenylacetic acid had little activity and ester of diphenyl acetic acid are prepared.

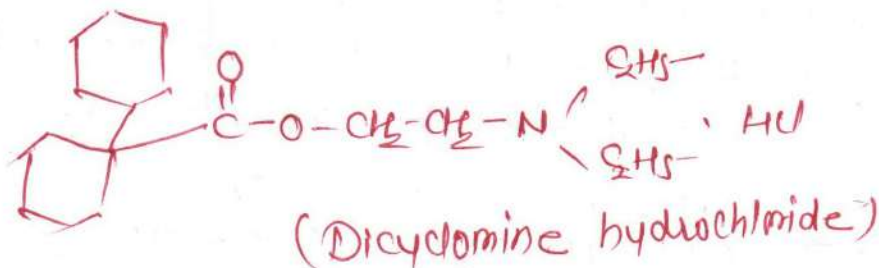


R₁ & R - must be carbocyclic or heterocyclic but if both are cyclic in nature, it will give maximum

Antagonistic potency

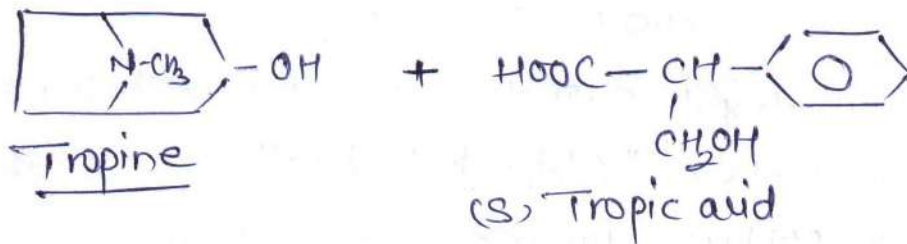
R = alkyl, R₁ = hydroxyalkyl, cycloalkyl, heterocyclic

- 3) In antagonist, N-atom ~~must be~~ need not be always quaternary (4^o) in nature. N-CH₃ (N-methyl) group on atropine & scopolamine change the activity of ligand by preventing a close interaction btw ligand and lipophilic site on receptor. & this methyl group also prevents the penetration into brain.
- 4) Acyl group in antagonist is always larger than acyl group of Ach.
- 5) N-Substitution should be 2 or 3 ethyl groups for optimal potency. (ex. - Dicyclomine hydrochloride)

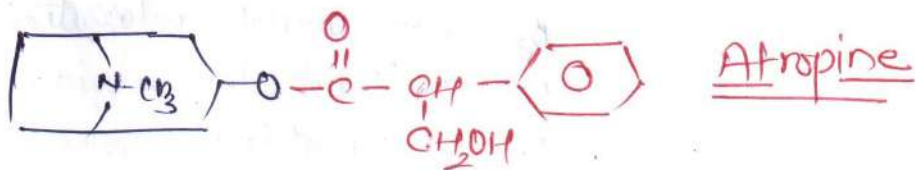


A. Solanaceous Alkaloids and Analogues

They are the Ester of tropine (bicyclo amino alcohol, 3-terpend) and tropic acid



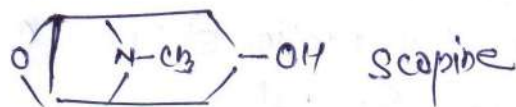
~~They~~



They are obtained from "Atropa belladonna", "Hyoscyamus niger" & "Datura stramonium"

Atropine = (+) hyoscyamine (Ester of tropine & tropic acid)

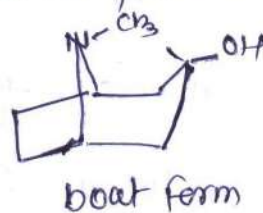
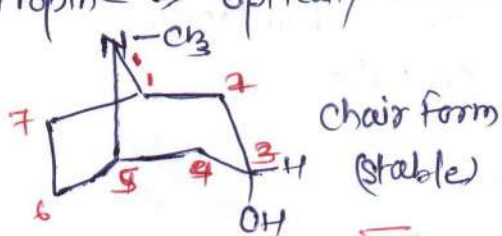
Scopolamine = (-) hyoscyine (Ester of Scopine & tropic acid)



These alkaloid contains piperidine ring system and exist both chair and boat form (Conformations)



Tropine \rightarrow optically inactive due to plane of symmetry



alkaloids are mainly occurs in chair form.

Anti muscarinic action = (-) form more active

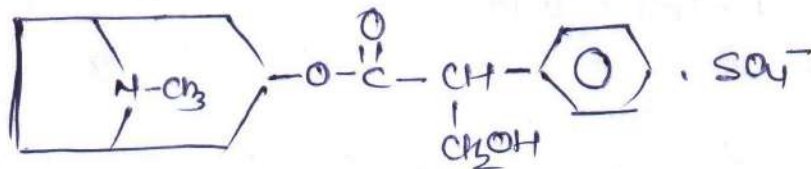
3-OH position on tropine - significant role at MR

Potency & Activity \rightarrow Scopolamine $>$ Atropine

Atropine Action \rightarrow Heart, bronchi & GI muscle

Scopolamine \rightarrow eye, secretory gland & CNS

① Atropine Sulphate



Tropane-3-yl-tropate Sulphate

- ↳ obtained from roots of "Atropa belladonna"
- ↳ Also known as (+) hyoscyamine

MOA -

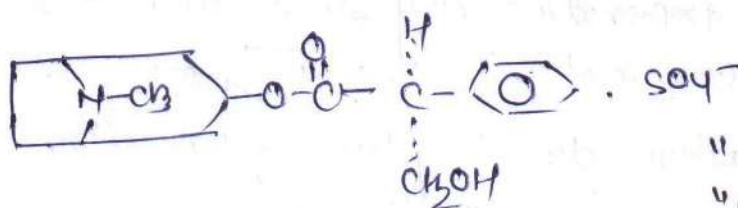
MIR blocker → ↓ GI Secretion

- ↳ Smooth muscle relaxation
- ↳ CNS depression
- ↳ ↓ GI motility

uses -

- ① Antiulcer / Antisecretory
- ② Antispasmodic
- ③ Parkinson disease
- ④ Organophosphate poisoning & Cobalt bite
- ⑤ also have cycloplegic & mydriatic action
- ⑥ ~~used~~ in motion sickness (rare)

② Hyoscyamine Sulphate



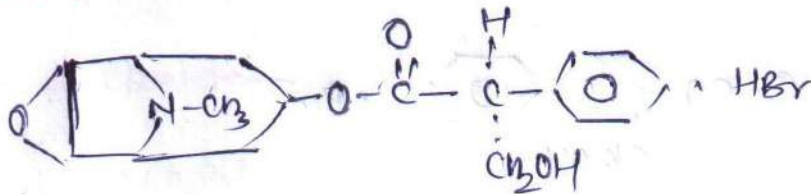
"S" enantiomer
"(-)" enantiomer

Tropane-3-yl-(S)-tropate Sulphate

MOA & uses = Similar as Atropine

- ▷ Mainly used in Motion Sickness
- ▷ more active than Atropine

③ Scopolamine hydrobromide



6,7-epoxy-tropan-3-yl-(S)-tropate hydrobromide

↳ also known as ~~(-)-hyoscyam~~ (-) hyoscyine

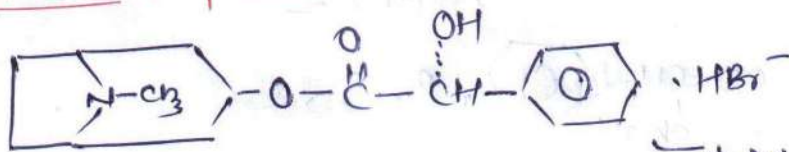
MOA - MR blocker

- ↳ More potent than Atropine
- ↳ rapid onset & shorter duration
- ↳ higher CNS activity
- ↳ More toxic

Uses -

- ① Mydriatic & Cycloplegic action
- ② Acute mania & delirium, with morphine
- ③ in Motion Sickness

④ Homatropine Hydrobromide



↳ Mandelic acid

- Mandeloyloxy-tropium bromide

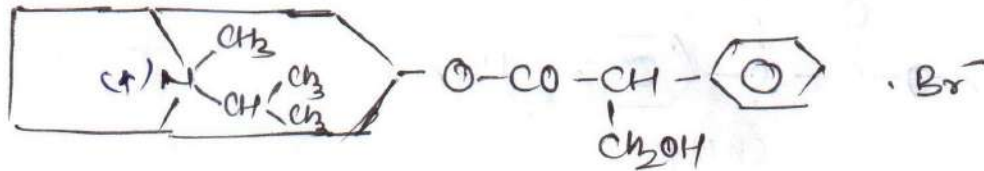
↳ Ester of mandelic acid with tropine

↳ 1/10 potency than Atropine

MIOA - MR blocker

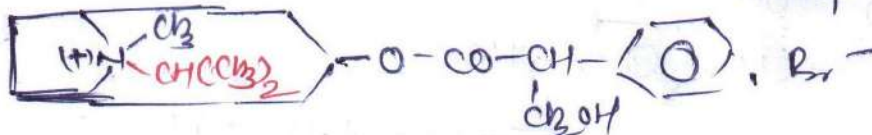
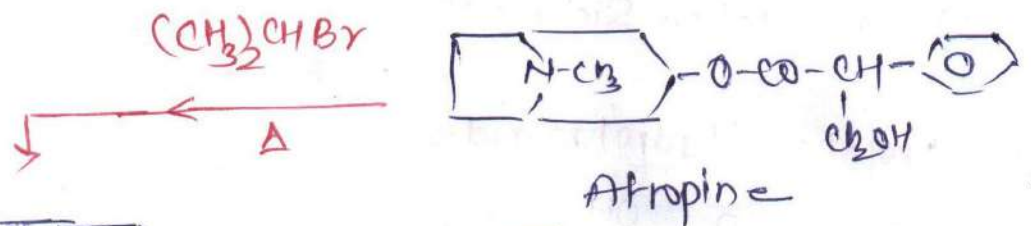
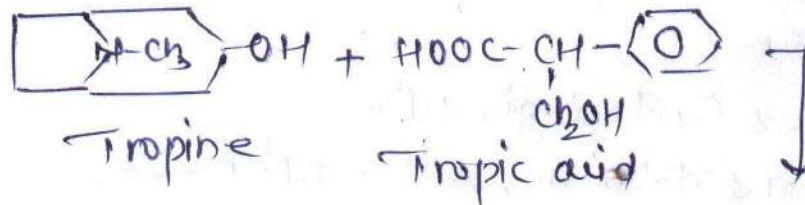
Uses - used topically as mydriatic & cycloplegic due to its rapid onset of action

⑤ Ipratropium bromide



8-methyl-8-(1-methylethyl)-8-azonia-bicyclo
[3,2,1] oct-3-yl-3-hydroxy-2-phenyl-propionate

- ↳ 4^o Ammonium analogue of Atropine
- ↳ M₃R-blocker mainly → Bronchodilator



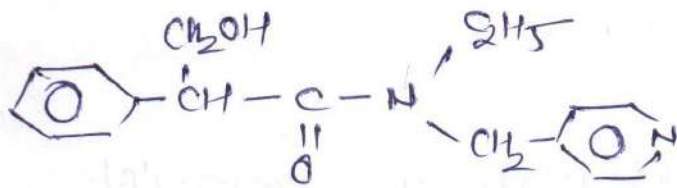
Ipratropium bromide

MOA - M₃R blocker

- Uses -
- ① Inhaled - Asthma & COPD
 - ② nasal solution - reduce rhinorrhoea
 - ③ along with β-agonist - Bronchodilator

B. Synthetic Cholinergic Blocker

① Tropicamide

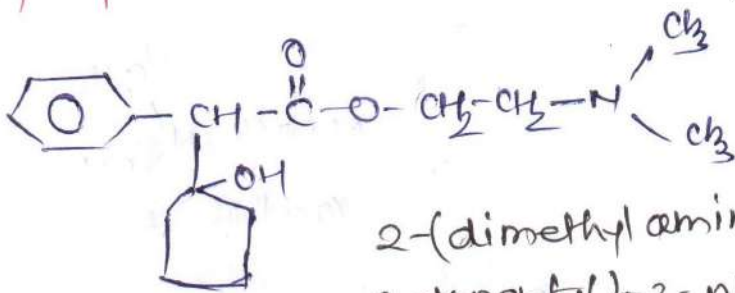


N-ethyl-N-(4-pyridyl methyl)
tropamide

MOA - MR blocker (Mainly M₃R on eye)

uses - ① Mydriatic and cycloplegic action (topically)
② eye drop - to treat anterior uveitis

② Cyclopentolate hydrochloride

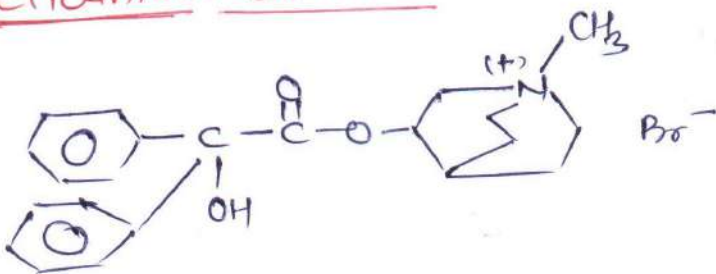


2-(dimethylamino)ethyl-2-(1-hydroxy-
cyclopentyl)-2-phenylacetate hydrochloride

MOA - MR blocker (M₃ on eye)

uses - Mydriatics & Cycloplegic

③ clidinium Bromide

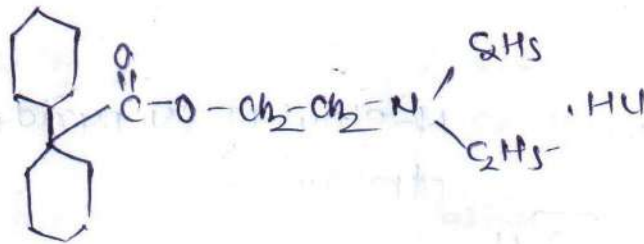


3-[2-hydroxy-2,2-diphenyl acetyl]oxy]-1-methyl-
1-azobicyclo [2,2,2] octan-1-ium bromide

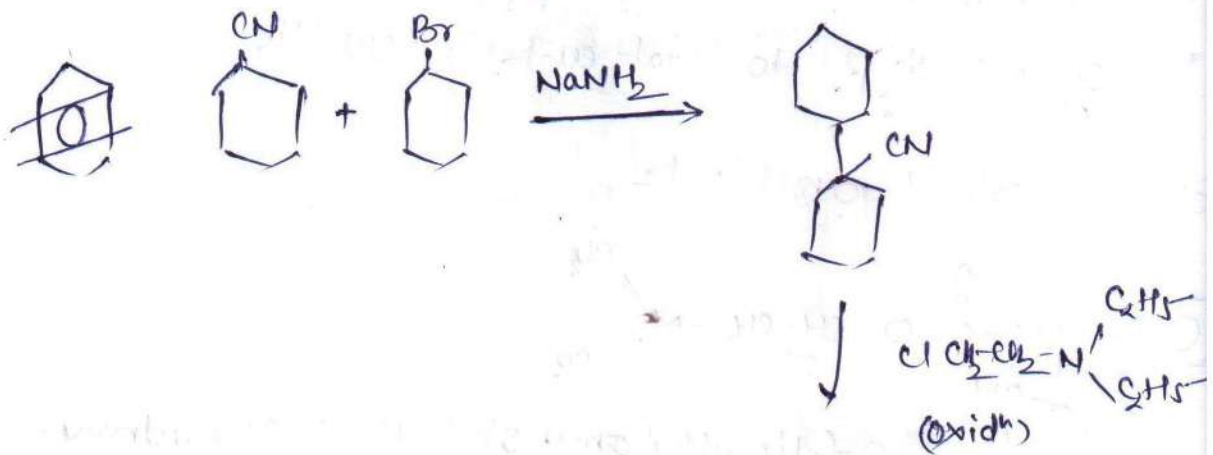
MOA - MR blocker

uses - ① antispasmodic & antiulcer
② used in irritable bowel syndrome
③ also in acute enterocolitis

④ Dicyclomine hydrochloride



2-(diethylamino ethyl)- bicyclohexyl-1- carboxylate hydrochloride



Dicyclomine

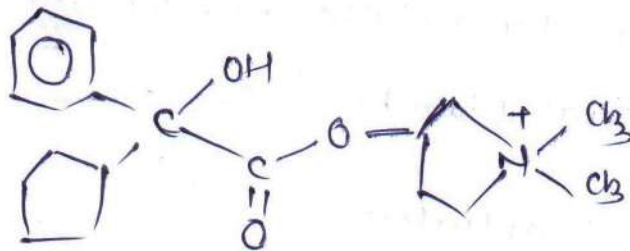
MOA - MR blocker

Uses - # anti spasmotic - treatment of irritable bowel syndrome

also used in ulcer

in motion sickness

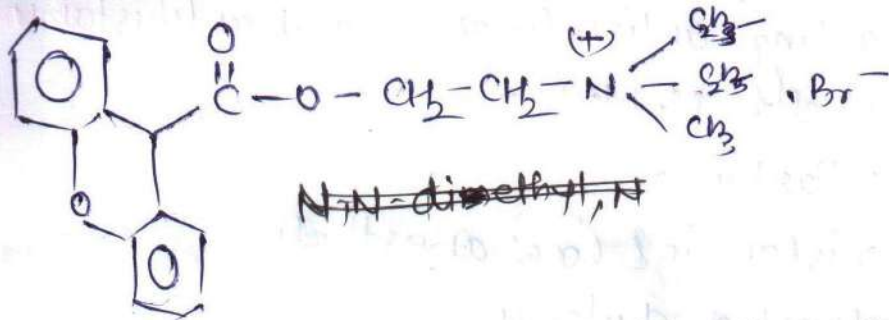
⑤ Glycopyrrolate



3 [(2-cyclopentyl-2-hydroxy-2-phenyl) acetoxy-1-(dimethyl pyrrolidinium)]

- USES - # Preanesthetic agent \rightarrow Antisecretory, Antispasmodic
 # Anticancer
 # Inhaled - COPD

⑥ Methantheline bromide

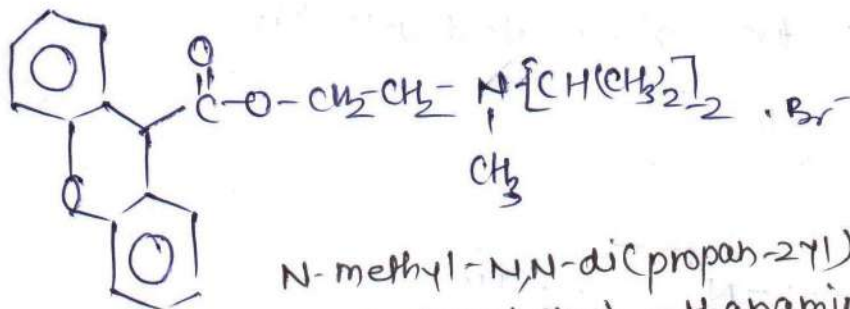


N,N-diethyl-N-methyl-2-[[9H-xanthene-9-yl carbonyl]oxy]-ethanaminium bromide

MIOA - MTR blocker

- USES - # Antispasmodic to relieve cramps or spasm of stomach, intestine & bladder
 # Anticancer along with antacids
 # also helpful in pancreatitis, gastritis, pylorospasm, reflex neurogenic bladder

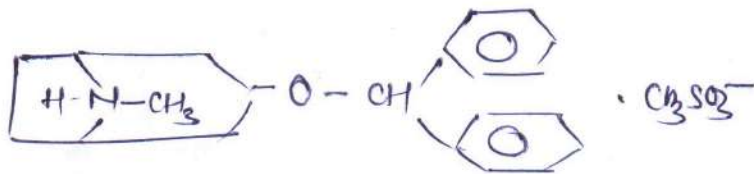
⑦ Propanteline bromide



N-methyl-N,N-di(propan-2-yl)-2-[[9H-xanthene-9-carboxyl]oxy]-ethanaminium bromide

- ① Antispasmodic
- ② treatment of excessive sweating
- ③ gastric ulcer

⑧ Benztropine mesylate

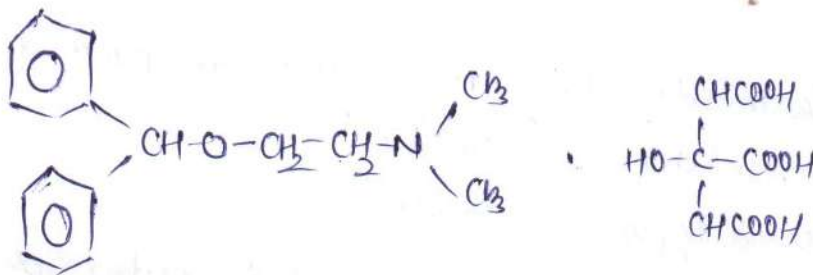


3-benzhydryloxy-tropane methane sulfate

MOA - Centrally acting anticholinergic and antihistaminic agent. Selective M₁ blocker

- uses -
- ① Anti-Parkinson
 - ② Antihistaminic & local anesthetic
 - ③ treatment of dystonia

⑨ Oxphenadrine Citrate

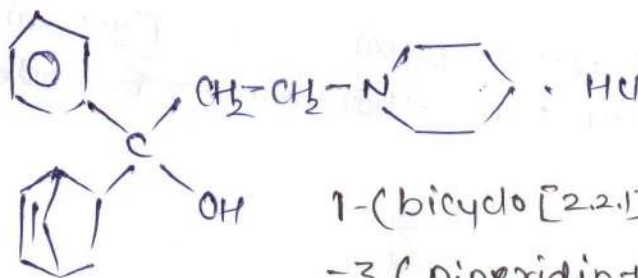


Dimethyl [2-(2-methyl benzhydryloxy ethyl)] amine citrate

MOA - M₁R blocker and also having antihistaminic action.

- uses -
- # Relief pain due to spasm of voluntary muscle
 - # used in Parkinson diseases
 - # relief pain from rheumatoid arthritis

⑩ Biperidone hydrochloride

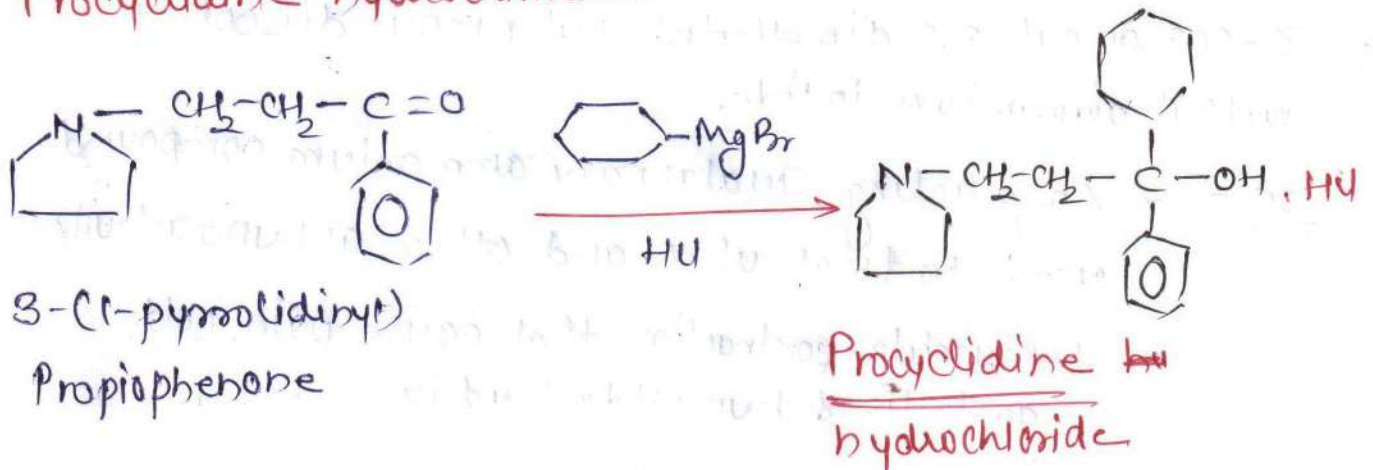


1-(bicyclo [2.2.1]-hept-5-yl)-1-phenyl
-3 (piperidin-4-yl) propan-1-ol

MOA - M₁R blocker

- use -
- ① Parkinson disease
 - ② Psychosis
 - ③ relieve muscle rigidity and reduce abnormal sweating and salivation
 - ④ **Organophosphorus toxicity**
 - ⑤ Neuroleptic malignant Syndrome

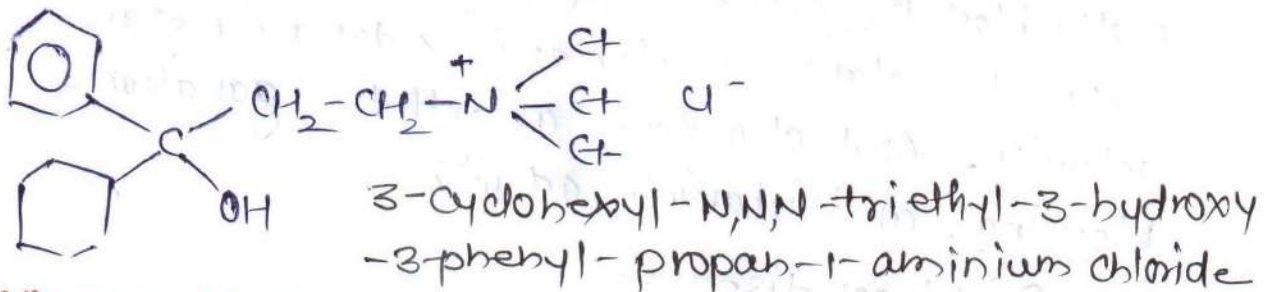
⑪ **Procyclidine hydrochloride**



α -Cyclohexyl- α -phenyl-1-pyrrolidine-propanol hydrochloride

- uses -
- ① Parkinson disease
 - ② treatment of Akathisia (movement disorder) and acute dystonia (Neurological movement)

⑫ **Tridihexethyl chloride**

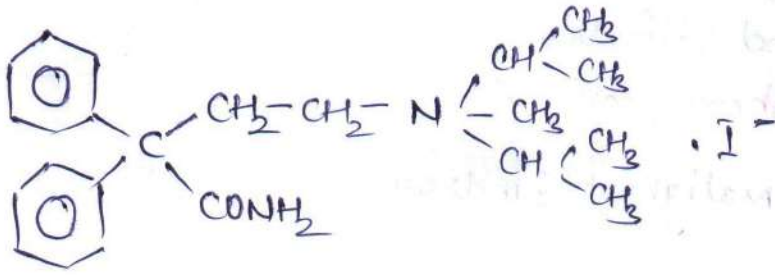


MOA - M blocker

uses - # Antispasmodic & Antiulcer

in acquired nystagmus (condition causⁿ of involuntary eye movement), **discontinue due to side effects**

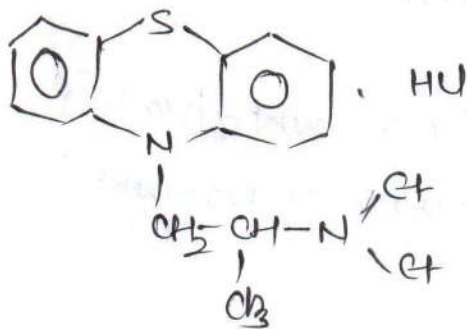
⑬ Isopropamide iodide



3-carbamoyl-3,3-dimethylphenyl propyl diisopropyl methyl ammonium iodide.

- Use -
- * Long acting quaternary ammonium compound used to treat ulcer and other GI hyperactivity
 - # ↓ muscular contraction that cause pain, cold, gastritis & hyperchlorhydria

⑭ Ethopropazine hydrochloride



10-[2-(diethyl amino)propyl]
Phenothiazine hydrochloride

MOA - partly block the centrally cholinergic receptor & helps to balance cholinergic & dopaminergic activity. And also have anesthetic, ganglionic blocking, antihistaminic activity

Use - In Parkinson disease

