Unit – III

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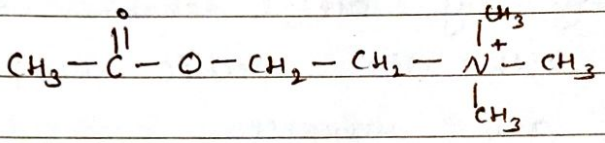
Cholinergic neurotransmitters

Cholinergic agent :-

These are the drug and agent that either directly or indirectly produce effect similar to those elicited by acetyl choline (ACh).



Acetyl choline

Biosynthesis and catabolism of acetyl choline

ACh is the acetic acid ester of choline.

It is synthesized within the nerve terminal from Choline, most of which is taken up into the nerve terminal by a choline transport system (CTS).

Free choline is acetylated by a cytosolic enzyme CAT (choline acetyl transferase). It is the source of the acetyl groups being acetyl coA.

CoA is widely distributed in the body and choline is an essential dietry constituent belonging to the B-complex group of vitamins.

Acetyl choline is produce throughout the neuron and is stored in the synaptic vesicles which are mainly accumulated at the nerve ending.

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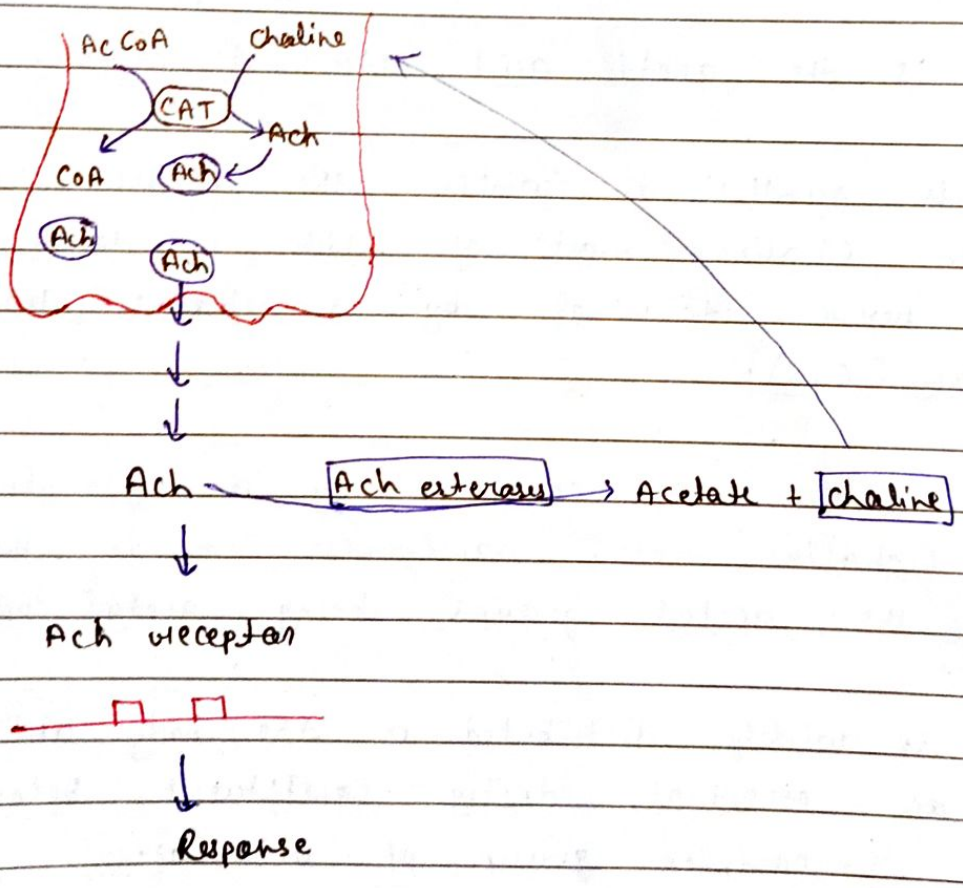
Within the vesicle acetyl choline is protected from hydrolysis.

On the receipt of a stimulase they combine within the membrane of the nerve ending and discharge their content of acetyl choline.

When sufficient quantity of acetyl choline are released, it combine with the specific receptors so that it can reduce any response



Ach degredation :-

As soon as the nerve impulse is generated the ach is broken down by the enzyme acetyl choline esterase (Ach - esterase).

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Ach $\xrightarrow{\text{Ach-E}}$ Choline + Acetate

It breaks down (hydrolysis) acetylcholine into the inactive metabolites choline and acetate.

Ach-E is abundant in the synaptic clapt. For proper muscles function. The ach-E should rapidly clear the ach present in the post-synaptic membrane as soon as the impulse is generated.

Chalinergic receptor :-

There are two main types of chalinergic receptor which are as following —

1- Nicotinic.
2- Muscarinic.

Nicotinic receptor are mainly found in neuro muscular junction (skeleton muscle) (mainly N_m). and also in autonomic ganglia and adrenal medulla (N_n).

SAR of chalinergic drugs

Chalinergic agents are also k/as chalinomimetic and parasympatho mimetic agent.

SAR of these drug can be summerised according to the structure and modifications of the Ach.

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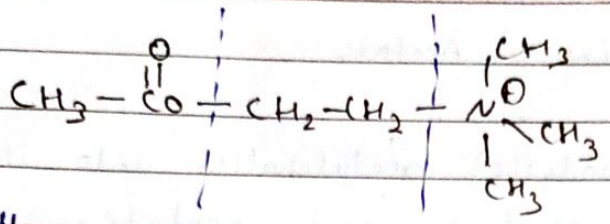


Aceloxy group — Ethylene linkage — Quarternary Ammonium group.

For the better understanding of the SAR of the cholinergic drug, the structure of Ach is divided into 3 parts —

(i) Aceloxy group.
(ii) Ethylene linkage.
(iii) Quarternary ammonium group.

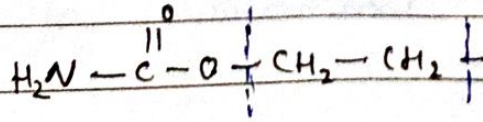
(i) The aceloxy group :-

(a) If we replace the methyl group from it's higher homologs.

Ex :- Propyl or butyl etc, the compound produced will be less active than Ach so methyl is the optimum substitution.

(b) The methyl ester is rapidly hydrolysed by the choline esterase. To reduce this hydrolysis acetyl group was replaced with a functional group which is resistent to hydrolysis.

Ex :-

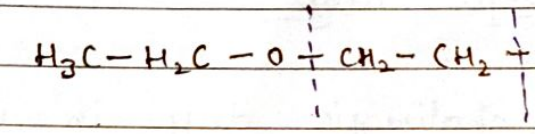


Carbachol

Date: _____ Page: _____

(c) Replacement of ester group with ether or ketone produces chemically stable and potent compound so they are better substitute of Ach.

Ex-



Choline ethyl ether.

(ii) Ethylene linkage -:

(a) On ↑ing the chain length from two carbon more than two carbon the activity is rapidly reduced.

(b) Replacement of hydrogen atoms of the ethylene bridge by methyl groups leads to equal or slightly greater activity but the groups larger than methyl groups leads to ↓ in activity.

(iii) Quarternary ammonium group -:

Quarternary ammonium group is essential for activity.

Replacement of nitrogen with sulfur, arsenic or selinium, results in less active compound.

Primary, secondary or tertiary amines are less active than acety choline.

Date: _____ Page: _____

Replacement of methyl group by ethyl or larger alkyl groups produces inactive compound.

Classification of cholinergic drugs

The various recognized cholinergic drug in variably mimic the actions of acetylcholine (Ach) in the specific parasympathetic system and are usually their metabolism of action.

- Cholinergic drugs
  - Directing acting CDs
    - Cholin ester
    - Cholinomimetic alkaloids
  - Indirectly acting CDs
    - Reversible cholinesterase drugs
    - Irreversible cholinesterase drugs

1- Directly acting cholinergic drugs :-

The so-called directly acting cholinergic agents usually exert their effects by causing specific stimulation of the muscarinic / nicotinic receptor.

They are further subdivided into 2 heads as follows —

① Choline ester :-

The important members of this class of compounds are —

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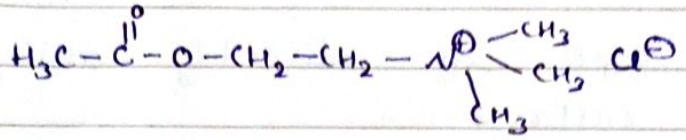
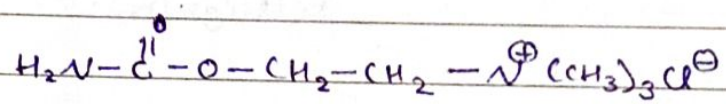
(a) Acetylcholine –



(b) Methacholine –

(c) Carbachol –



(d) Bethanechol –

(ii) – Cholinomimetic alkaloids –

Important members are as follows –

(a) Muscarine –

(b) Pilocarpin –

(c) Arecoline –

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2- Indirectly acting cholinergic drug :-

There are two types of indirectly acting cholinergic drugs are as follows—

(I) Reversible cholinesterase inhibitors :-

These are also k/as the reversible blockers.

eg → Physostigmine (Eserine, synaptan)
Neostigmine bromide (Prostigmine, myestigmin, tilstigmin).

(II) Irreversible cholinesterase inhibitors :-

Eg :- Pralidoxime chloride.
Ecothiophate iodide
Isofluorphate.

$COCl_2$ → Phosgene gas / phosphene gas

Date: _____ Page _____

Carbachol

$[H_2NCOO \cdot CH_2CH_2 \, N^+(CH_3)_3]Cl^-$

Synthesis -:

$HO CH_2CH_2 N^+(CH_3)_3 \cdot Cl^- \xrightarrow{COCl_2} ClCOOCH_2CH_2 N^+(CH_3)_3 Cl^-$

Choline chloride

$\downarrow NH_3$

$H_2NCOOCH_2CH_2 N^+(CH_3)_3 Cl^-$

Uses -:

- It is used in the treatment of glaucoma.
- It is used in the eyedrop to ↓ intraocular pressure.
- It is used to constrict pupil after the eye surgery.

Acetyl choline

- It is used for the constraction of the skeletal muscle.
- For the activation of granular muscle.
- To ↑ sweating, salivation, lacrimation.

- For the dilation of blood vessels of face skin, neck, salivary gland etc.
- It ↑es GIT peristalsis.
- Contraction of the eye.
- Used for bronchospasm.

Bethanechol

It is mainly used for the action on urinary bladder.

Methacholine

It's mainly used to depress heart rate.

Pilocarpine

It's mainly used in eye drops as 0.5 - 4% concentration in open angle glaucoma.

It's used to constrict the pupil.

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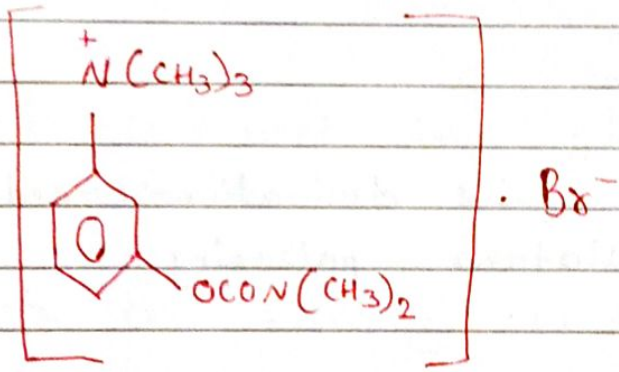
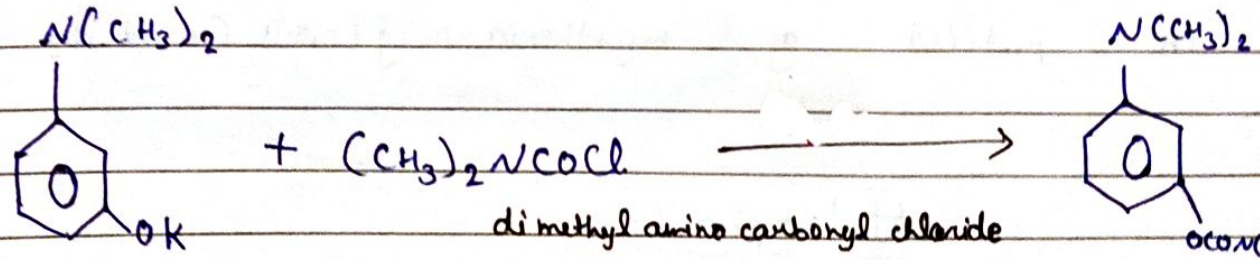
Indirectly acting cholinergics drug (cholinesterase inhibitor)

These are the drugs which inhibit the choline esterase enzyme and preserve the Ach by preventing the breakdown of acetyl choline so ultimately gives the cholinergic actions.

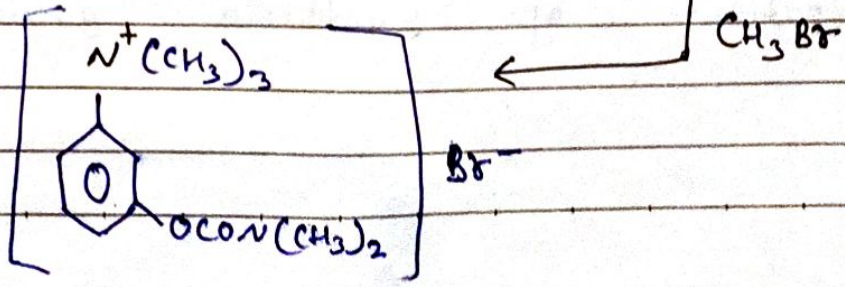
Neostigmine Bromide



Synthesis :-



m- potasium (dimethyl amino phenolate)



Date: _____ Page: _____

Uses -

- It is used in preventing intestinal, skeletal ↓ spasm. and bladder

- It is used in mysthenia gravis.

- It is a quarternary ammonium compound basically used in curare poisoning.

Physostigmine

It is a tertiary amine derivative used in glaucoma and balladona poisoning

Pyridostigmine

It is used to improve the muscles strength in patient of mysthenia gravis (weak the muscle).

Edrophonium

It is a suitable diagnostic agent for the patient of mysthenia gravis.

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Tacrine · HCl

It is the drug of chaice for alzheimer's disease but it is not preffered now becoz of hepatotoxicity and diarrhoea.

Ambenonium Cl⁻

Same as physostigmine

Isofluorphate Iodide

It is used for glaucoma and other eye infection.

It is basically used in the form of eye drop.

Echothiophate iodide

Same as isofluorphate iodide.

Parathione and Malathion

It is basically insecticide and not therapeuti-cally used.

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Cholinesterase reactivators

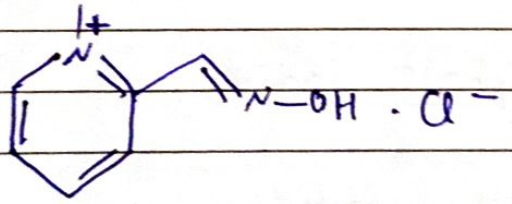
* These are the agents which reactivate the cholinesterase enzyme.

* These are used as antidote in organophosphorous insecticides poisoning. that is a state of Ach excess becoz of cholinesterase inhibition.

* They are the important component of therapy in agreecultural, industrial and military poisoning by organophosphate and sulphonate.

Ex-: Pralidoxime Cl^-

It is also k/as 2-PAM (2-pyridine aldoxime methyl chloride).



It is used for the treatment of poisoning due to pestiside or chemicals of organophosphate class.

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Cholinergic blocking agent (Anticholinergic agent)

* These are the agent which act by preventing the normal effect of Ach on the receptor cells.

* They reduce the production of bronchial, lacrimal, gastric, nasal, intestinal, sweat and salivary secretion. together with a reduction in intestinal motality.

Anticholinergic drug

- Natural alkaloids
  - Atropine
  - Hyoscine (Scopolamine)
- Semi synthetic derivatives
  - Atropine methonitrate
  - Homatropine
  - Hyoscine butyl bromide
  - Ipratropium bromide
  - Tiotropium bromide
- Synthetic compounds
  - Antiparkinsonian
    - Trihexyphenidyl
    - Procyclidine
    - Biperiden
  - Mydriatics
    - Cyclopentolate
    - Tropicamide
  - Vesicoselective
    - Oxybutynin
    - Flavoxate
    - Tolterodine
  - Antisecretory - antispasmodics
    - Quaternary comps.
      - Propanthiline
      - Oxyphenonium
      - Clindinium
      - Isopropamide
      - Glycopyrrolate
    - Tertiary amines
      - Dicyclomine
      - Valethamate
      - Pirenzepine

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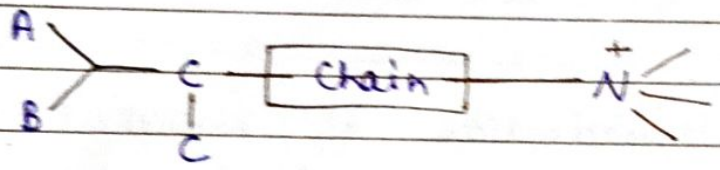
SAR of anticholinergic agent

SAR of anticholinergic drug can be summarised into into following step —



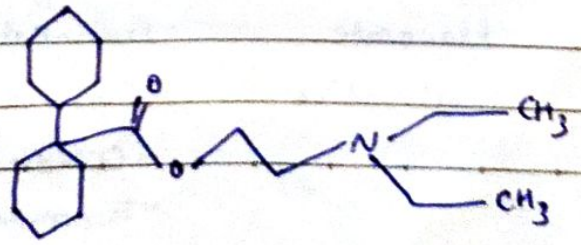
Quaternary ammonium group is essential for the activity due to the poor penetration in brain is responsible for their lack of CNS activity which is also very important for the anti-cholinergic activity.

For showing anticholinergic activity aryl group like phenyl is substituted in place of A. and cycloaliphatic group like cycloalkane is substituted in place of B for better anti-cholinergic activity.

Ex :- Dicyclomine.

Both the groups of A and B can be aromatic or aliphatic, both will show good anticholinergic activity.

Dicyclomine →



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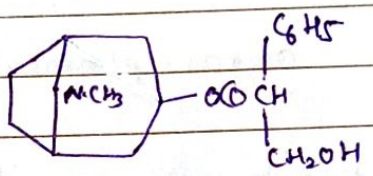
Ester grp is very important for the anticholinergic activity.

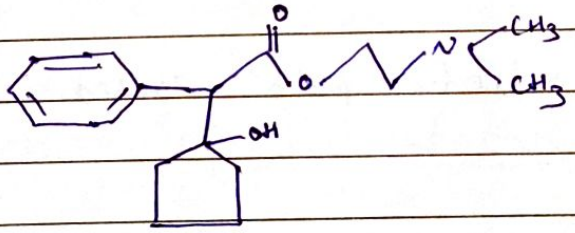
Three function group if attached with the carbon chain, the anticholinergic activity will ↑.

Atropine :-



The presence of a free hydroxyl group is important for hydrogen bonding with the receptor so important for anticholinergic activity.

Ex :- Cyclopentolate –



The levo- isomer of the anticholinergic drug are more active than the dextro isomer.

The difference b/w the free hydroxyl group and quarternary N group should be minimum of 2-3 carbon atom for the maximum anticholinergic activity.

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Atropine sulphate

It is used in mydriasis, traveller's diarrhoea

Used in the mushroom poisoning.

Also used in organophosphate poisoning.

Used in treatment of arrhythmia.

Also used as pre anesthetic medication.

Hyoscyamine sulphate

It is used in stomach or intestinal problems like cramps or spasm.

It is used to relief pain caused by kidney and gall stones.

Used in parkinson's disease, mysthenia gravis and also as insecticide.

Scopolamine HBr

Used in motion seekness, stomach pain, post operative nausea, and before surgery to reduce saliva and also as an anaesthetic.

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Homatropine HBr

It is used before and after certain eyes surgery. and eye disorders.

It acts by dilating the eyes.

Ipratropium Br^-

Used in asthma by inhaler or nebulizer

Tropicamide

It is used to dilate the pupil of eye, used in eyedrop to produce mydriasis.

Cyclopentolate HCl

Same as tropicamide

Clidinium Br^-

Used in stomach ulcer.

Dicyclomine hydrochloride

Worked by slowing the natural movement of gut.

It reduce the stomach and intestinal cramping by relaxing muscles.

Glycopyrrolate

It is used in the form of injection before surgery to reduce salivery, bronchial and gastric secretion.

Methantheline Br^-

Used to reduce excessive sweating.

Cramps or spasm of stomach and also in invaluntery urination.

Propantheline Br^-

Same as methantheline Br^-

Benztropine mesylate

Used in parkinson's disease.

Orphenadrine citrate

Used to releaf pain caused by intestinal cramp.

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Biperidine HCl

Used in parkinson's disease.

Procyclidine HCl⁻

Parkinson's and dystonia (involuntary muscle contraction or

Ethopropazine HCl

Used in parkinson

Isopropamide I⁻

Peptic ulcer to reduce hyperacidity.

Tridihexethyl Cl⁻

Used as antispasmatic and peptic ulcer.

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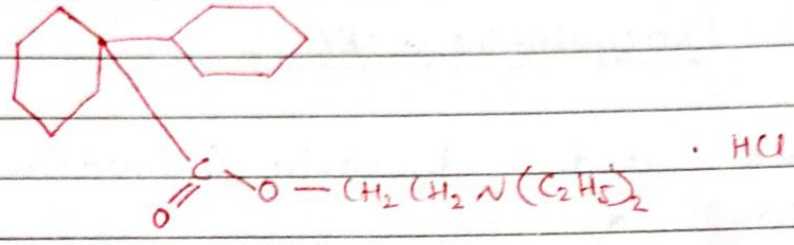
Dicyclomine hydrochloride

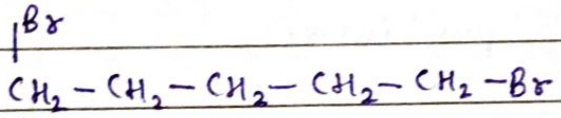
Structure :-



Synthesis :-

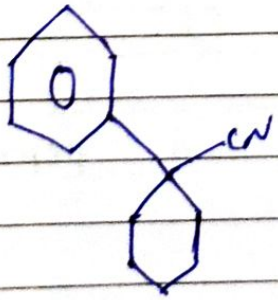
Benzyl cyanide

+

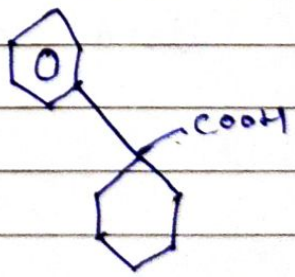


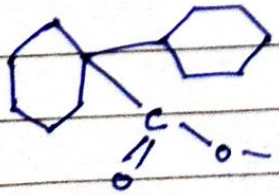
1,5 di bromo pentane

— 2 HBr

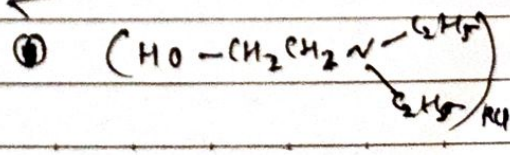


Saponification / oxidation





① Reduction



N,N di ethyl ethanol amine hydrochloride

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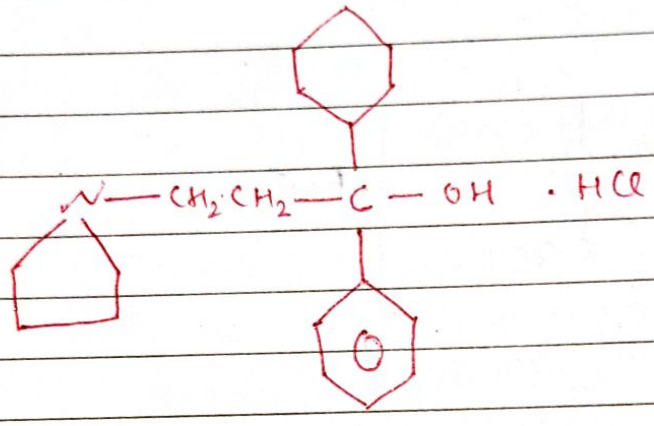
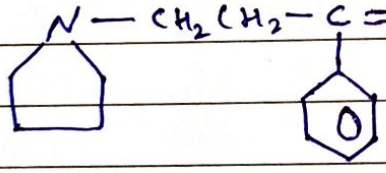
Procyclidine hydrochloride

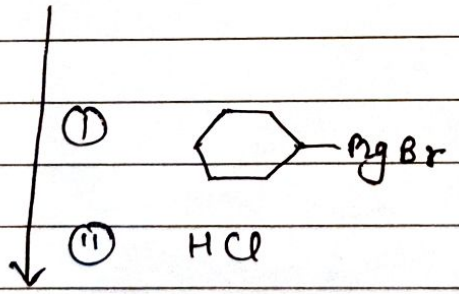
Structure →

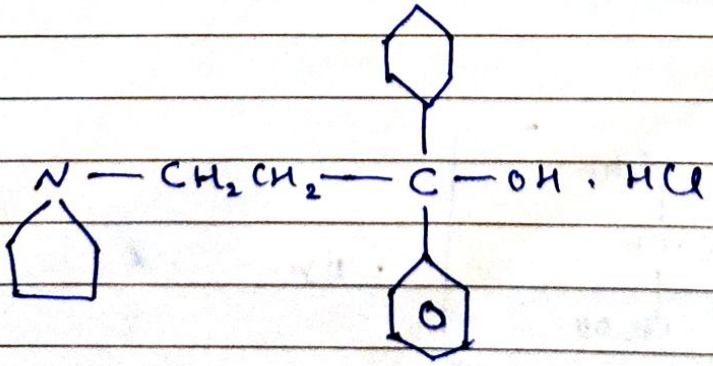


Synthesis →



3-(1-pyrrolidinyl) propiophenone





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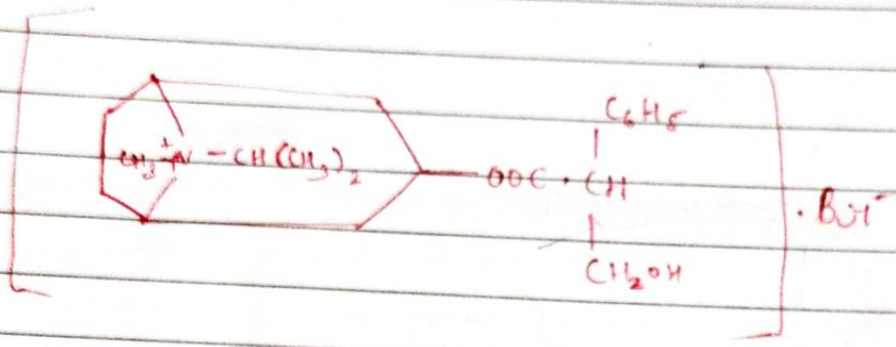
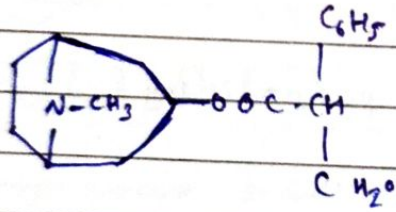
Ipratropium Bromide

Structure →



Synthesis →



Atropine

$(CH_3)_2CHBr$