Unit - 2

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Sympathetic (Adrenergic) Nervous System

I. The Autonomic nervous system ANS or visceral nervous system is a part of peripheral nervous system that acts as control system.

II. It is responsible for control of "involuntary" or visceral body function ; like Cardiovascular, Respiratory, digestive, Urinary Reproductive functions.

III. It play a key role in the Bodies respones to Excitement and stress.

	Sympathetic Nervous System	Para-sympathetic nervous system.
1	Allow Body to function under stress	Maintenance Function
2	Flight + Fright	Rest and digest.
3.	Primes Body for intense muscular Activity	Counterbalances Sympathetic function

Sympathetic Nervous System.

1. Regulate involuntary movements
2. Allow body to function under stress
3. Prime Body for intense skeletal muscle Activity
4. Sympathetic work requires in quick Action
5. Act as accelerators, produce alertness

__/__/____

Action on Sympathetic Nervous System

1. Dilate pupil
2. Increases heart rate
3. Constrict arteries
4. Dilate Bronchi
5. Directs blood flow to arms & legs away from body internal organ & Digestion
6. Inhibit stomach motility & secretion, Inhibit pancreas secretion.
7. Inhibit Intestinal Motility
8. Relaxes Bladder
9. Stimulate Ejaculation

__/__/____

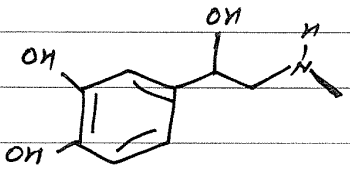
Adrenergic Neurotransmitters

Neurotransmitters are the chemicals which transmit signals from a neuron to a target cell across the synapses

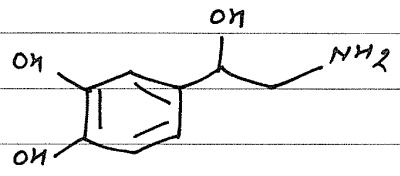
Neurotransmitter secreted by Adrenergic Nervous System belongs to the chemical class of Catecholamines.

They are named due to the presence of Catecholamine nucleus.

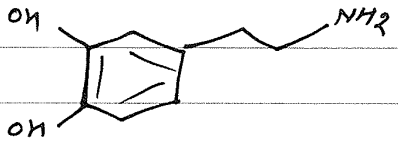
Neurotransmitter from adrenergic nervous system



Adrenaline
(Epinephrine)



Non-adrenaline
(Norepinephrine)



Dopamine

__/__/____

Biosynthesis of Catecholamine

Biosynthesis of CAs (Dopamine, Epinephrine) involves sequence of Enzymatic reactions

CAs Synthesized in adrenergic & Dopaminergic neurons in the CNS, in Sympathetic neurons of ANS and adrenal medulla.

The Amino acid and L-Tyrosin is the precursor for the Biosynthesis of Catecholamines.

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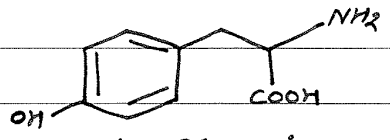
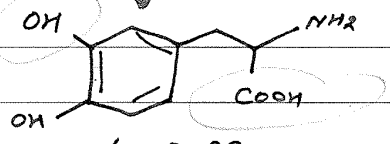


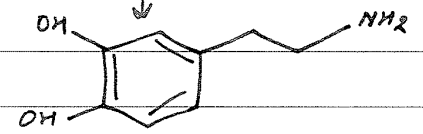
L- Tyrosine

Step-I — Tyrosine hydroxylase



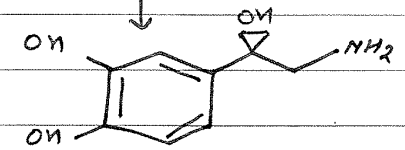
L- DOPA

Step-II — L- Aromatic amino acid



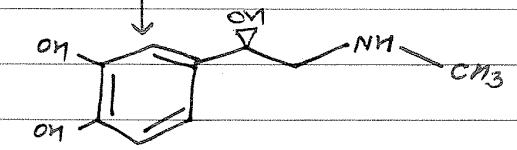
Dopamine

Step-III — β- Hydroxylase (Hydration)



Norepinephrine

Step-IV — Phenylethanolamine N-Methyl transferase



Epinephrine

Biosynthesis of Catecholamines.

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Catablism of Catecholamines

Two principal Enzymes involved in the Biotransformation of Catacholamines

1. Monoaminoxidase (MAO) मोनो
   Present in outer membrane of mitochondria

2. Catechol-o-methyl transferase (COMT)
   found in the nearly all cells, including erythrocytes, thus, the enzyme act on extraneuronal Catecholamines.

Both are distributed widely throughout the Body. including the Brain. The higest concentration of Each are found in the liver & kidney.

Steps Involved in Catecholamines are -

MAO Oxidatively deaminates Norepinephrine to give 3,4-dihydroxy phenylglycoaldehyde.

↓ reduced to

Dihydroxyphenylethyleneglycol
by the Action of
Aldehyde reductase

__/__/____

3 This glycol metabolite released into the circulation and undergoes methylation by the COMT that results in the formation of 3-methoxy-4-hydroxy phenyl ethylene glycol.

↓ oxidised by Aldehyde dehydrogenase - give

3-methoxy-4-hydroxy mendelic acid

This metabolite is commonly known as Vanilyl Mandelic Acid.

5 In Extraneuronal sites such as liver, Norepinephrine and epinephrine undergo oxidative deamination by MAO to give Aldehyde, which is oxidized by Aldehyde dehydrogena to give 3,4-dihydroxy mandelic acid

Norepinephrine and Epinephrine also undergo Methylation by COMT on the meta-OH gp of the Catechol this results in the formation of Normetanephrine.

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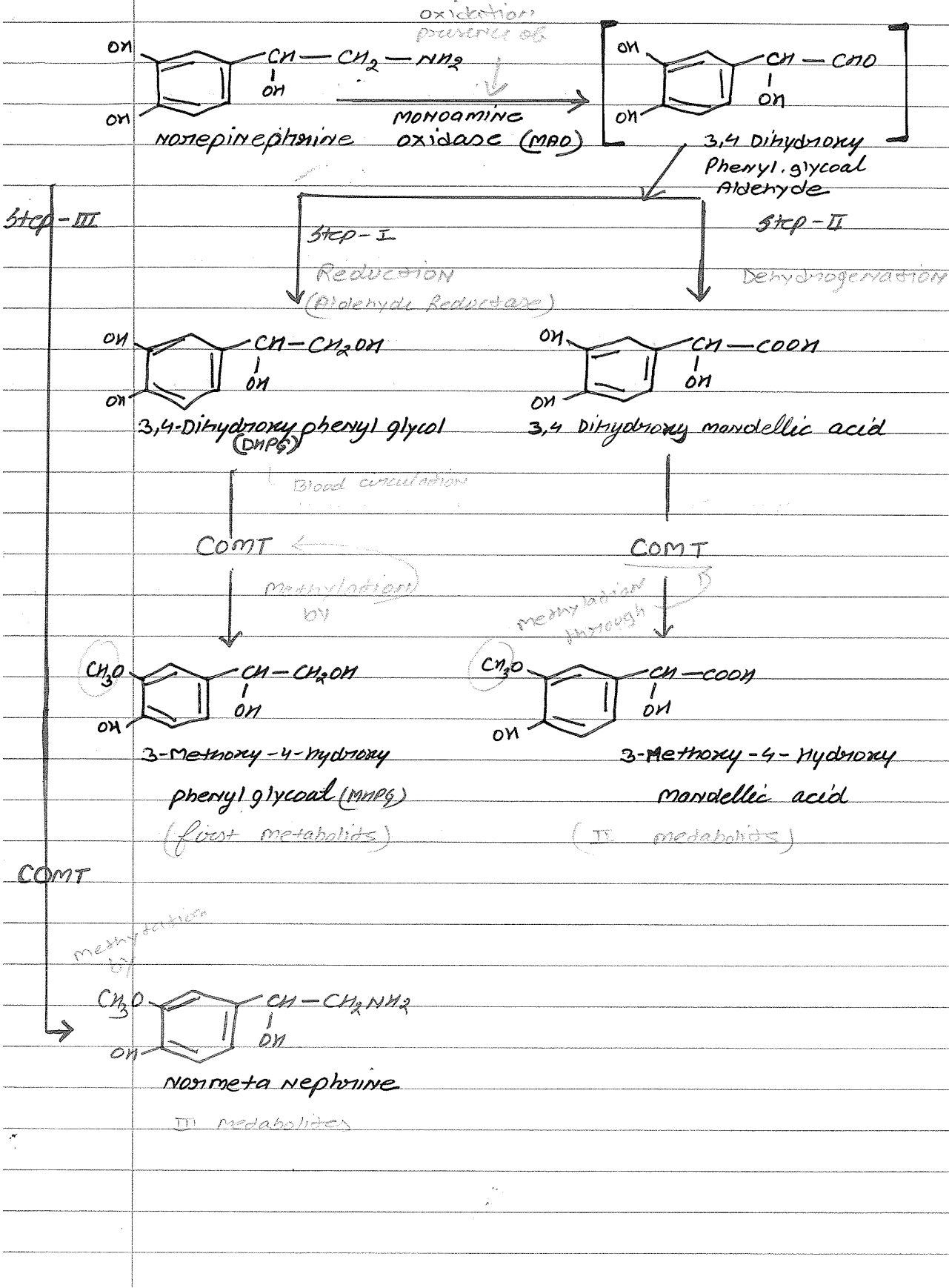
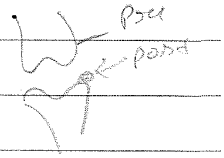

oxidation in presence of
Monoamine oxidase (MAO)
Norepinephrine
3,4 Dihydroxy Phenyl glycoal Aldehyde
Step-I
Reduction
(Aldehyde Reductase)
Step-II
Dehydrogenation
Step-III
3,4-Dihydroxy phenyl glycol (DHPG)
3,4 Dihydroxy mandellic acid
Blood circulation
COMT
Methylation by
3-Methoxy-4-hydroxy phenyl glycoal (MHPG)
(first metabolite)
3-Methoxy-4-hydroxy Mandellic acid
(II metabolite)
COMT
Normeta nephrine
III metabolites

__/__/____

Neurotransmitter work on

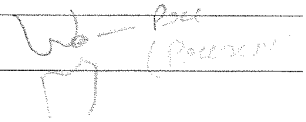
Adrenergic Receptor Types / Adreno-Receptors

α- receptors	β- Receptors
Receptor subtype are	Receptor subtype are
α_1- Adrenergic receptor	β_1 - Adrenergic receptor
α_2- Adrenergic receptor	β_2 "
	β_3 "



Distribution of α and β Receptors.

α_1 - Adrenergic receptors postsynaptic receptor found in the smooth muscles of Iris, arteries, arterioles, veins stimulation causes smooth muscle contraction & Vasoconstriction.



α_2 - Adrenergic receptors
Found in Brain.
They mediate the inhibition of Adrenergic neurotransmitter release.

β_1 Adrenergic receptors Found in myocardium (heart) where they stimulation increases the force and rate of Myocardial Contraction.

β_2 Adrenergic receptors found Bronchial & Vascular smooth muscles, where their stimulation cause smooth muscle Dilation & Relaxation

β_3 Adrenergic receptors These receptors are expressed on fat cells and their stimulation cause lipolysis

__/__/____

Sympathomimetic Agents.

Drugs that partially or Completely mimic the Action of Epinephrine (Epi)
Non-Epinephrine (NE)

They produce Effects Similar to the Effects of Sympathetic Nerve fibers.

Agonist - that activates receptor to produce Biological Action or response.

Anta-Agonist - In Medicine, Substance that stop the Action or Effect of another substance.

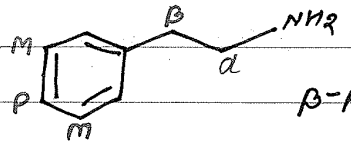
__/__/____

SAR of Sympathomimetic Agents

SAR It is defined as the relationship b/w the chemical structure of molecule & its Biological Activity

This allow modification, of the effect or potency of a Bioactive compound by changing its chemical structure

Many of the sympathomimetic Drugs contain β- phenyl Ethylamine in parent structure



β-phenyl Ethylamine

Structurally, substitution or modification occurs on.

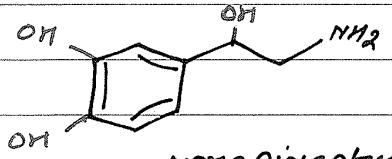
Catechol
β-carbon
α-Carbon
Amino gp
Meta / para position of Aromatic ring

__/__/____

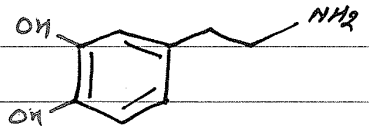
Substitution on meta & para position of Aromatic ring.

maximum activity is seen in β-phenyl ethyl amine Derivatives containing -OH gp in the meta & para positions of aromatic ring.

Ex



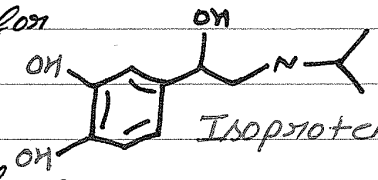
Norepinephrine



Dopamine

Substitution on amino group of the Side Chain

presence of $-NH_2$ group is imp for Direct agonistic Activity.



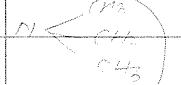
Isoproterenol

$-NH_2$ gp should be separated from aromatic ring by two carbon atom for optimum Activity

Both 1°, 2° amines are potent direct acting Agonist where as 3°, 4° amines tends to be poor Direct Agonist.

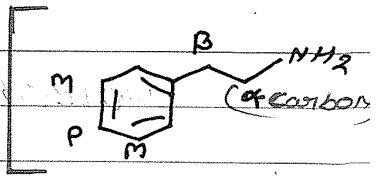
Bulky nitrogenous substituent Decreases α-receptor Agonistic Activity and increases β receptor Agonistic Activity.

Large substituents on the $-NH_2$, gp also protect from undergoing oxidative Deamination by MAO.

 ——> Not orally active / Low Duration of Action

__/__/__

α-Carbon of Ethylamine Side Chain.



Methyl or ethyl substitution on Alpha Carbon of Ethylamine side chain reduces Direct receptor Agonist activity at Both α and β receptors

Substitution on α-carbon increases Duration of Action by causing metabolic resistance of MAO.

Such Compounds shows oral effectiveness and greater CNS Activity as compared to compounds not having alkyl substitution at α-carbon of Ethylamine side chain.

α-carbon substitution with methyl or ethyl group also has effect on receptor selectivity towards receptor binding, They have β_2 and α_2 receptor selectivity.

β-Carbon of Ethylamine Side Chain

β-Hydroxy group of Correct Stereo-chemical Configuration in the Ethylamine side chain

R-Configuration is 100 times more potent than S-enantiomer.

R-enantiomer provides 3-point attachment with the receptor as compared to S-enantiomer which provides only 2-point attachment

__/__/____

Catechol Nucleus $C_6H_4(OH)_2$

Catechol Nucleus is imp for significant Agonistic Activity.

Replacement of Catechol with resorcinol in Isoproterenol gives metaproterenol which is selective β_2-receptor Agonist.

Resorcinol is resistant toward COMT Metabolism
Hence, have better Absorption & Long Duration of Action as compared to catechol.

__/__/____

Adrenergic Drugs / Sympathomimetics

Adrenergic drugs are the chemical Agents that exert their principal pharmacological & therapeutic Effects by Either enhancing or reducing the Activity of the various compounds of the sympathetic Division of the ANS (autonomic nervous system).

Adrenergic Drugs stimulate the Adrenergic Nerves Directly by mimicking the Action of Norepinephrine or indirectly by Stimulating the release of Norepinephrine

Classification of Adrenomimetics / Sympathomimetics.

Direct Acting - Directly Stimulate the receptor for the release of Epinephrine or norepinephrine Norepinephrine, Epinephrine
Indirect Acting - Stimulate release of norepinephrine from terminal nerve Ending. Hydroxyamphetamine, Pseudoephedrine
Mixed Acting - Stimulate the receptor site & release of norepinephrine from the nerves Ending Ephedrine, Metaraminol

__/__/____

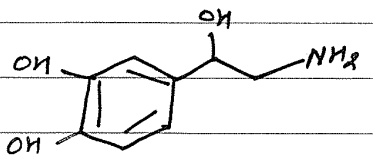
Direct Acting Drugs

These are those Drugs and Agents which Directly bind with Adrenergic Receptors, both α & β and gives its pharmacological Action.

The action produced are of rapid onset and of short Action.

__/__/____

1. Norepinephrine (noradrenaline)



It is not effective through oral route Due to Metabolism by MAO and COMT. It is given by Intravenous infusion.

MOA

a. It is Direct Acting Nonselective sympathetic Agonist, predominantly Stimulates α_1 and α_2 receptors that Causes peripheral Vasoconstriction & increases Blood pressure.

b. It also stimulates β_1 adrenergic receptors the Effect is increase in heart rate and Cardiac output

Uses

a) used treatment of Hypotension.
b) Reduced the Absorption and to localize the Effect of. local Anastetics.
c) Strong Vasoconstriction properties, So it is used in local anastetics solution for dental use.

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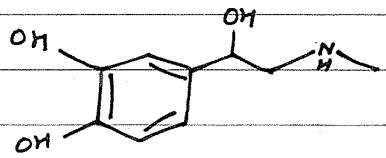
2. Epinephrine (Adrenaline)



* It is not Effective orally as it is metabolized by MOA. or COMT.

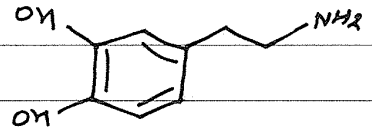
MOA

* It stimulates Both α and β Adrenergic receptors.

USES

It is more widely used clinically than norepinephrine
It is used as constrictor in hemorrhage.
It also used treatment of Asthma.
It used to enhance Activity of local Anesthetic

3. Dopamine



* It is D_1 and D_2 receptor Agonist.
* It is ineffective orally as large pat metabolized by MAO and COMT, HENCE Administered intravenous infusion.

MOA

* It act by Binding to the D_1 and D_2 receptors present on the cell surface, by Activating these receptors.
* It cause vasodilation of renal Vasculature and promotes renal blood flow.
* Dopamine also stimulates β_1 receptor on the Heart

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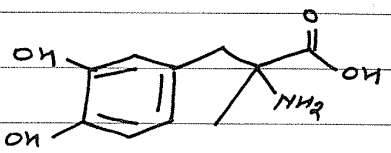
Uses

Most commonly used Drug in the treatment of low severe Blood pressure, Slow heart rate and cardiac arrest specially in infants.

4. Methyldopa



It is a phenylethylamine derivative having Selective α_2- receptors Adrenergic Agonistic Activity.

MOA

a) It is centrally acting sympathomimetic.
b) Methyldopa is transported across the Blood Brain Barrier (BBB)
c) where it converted into Active metabolite.
d) This metabolite is selective α_2- receptor Agonist and act as an antihypertensive Agent.
e) That lower the sympathetic neuronal output from CNS
f) That result Lowering the Blood pressure.

Uses

* Used in Higher B.P treatment.
* one of the prefferred treament for High, B.P in pregnancy.

__/__/____

5. Phenylephrine.

It is selective direct acting α_1-receptor Agonist.
It is potent vasoconstrictor.
Due to α_1 selectivity it has minimal Cardiac Stimulation.

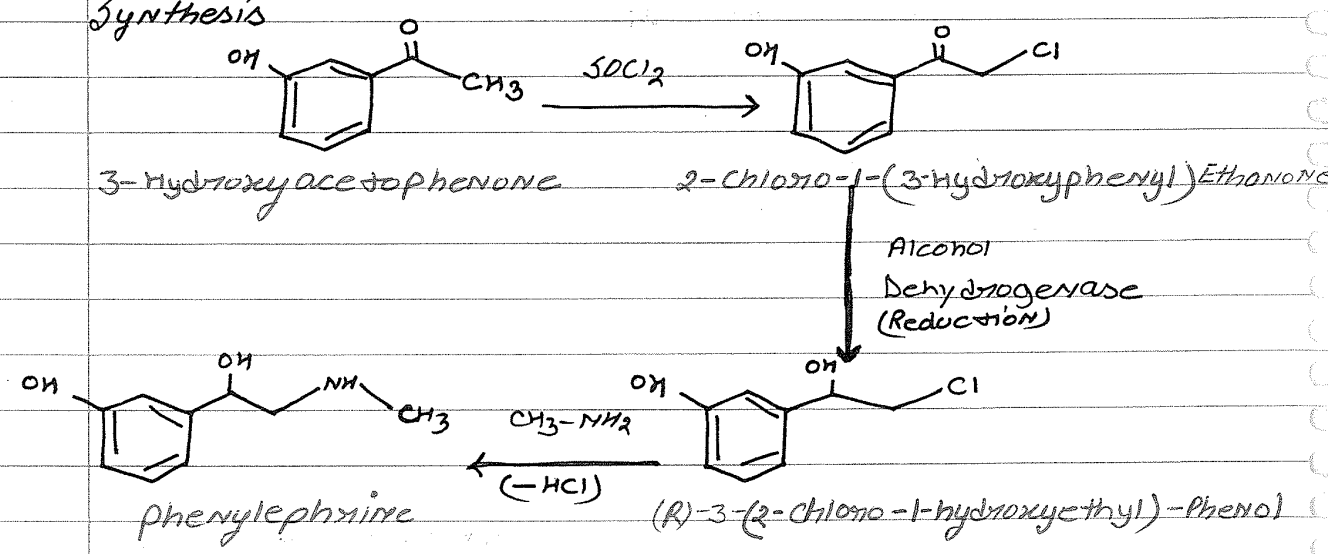
It is used in the relief of nasal Congestion by Constricting the Blood Vessels of the nasal membrane.

It is used to Dilate pupil and to treat open-angle glaucoma.

It is used in spinal anesthesia to prolong the anesthesia and to prevent the Blood pressure During the procedure.

It is used in the treatment of severe Hypotension resulting from either shock or drug administration or during Surgery.

Synthesis



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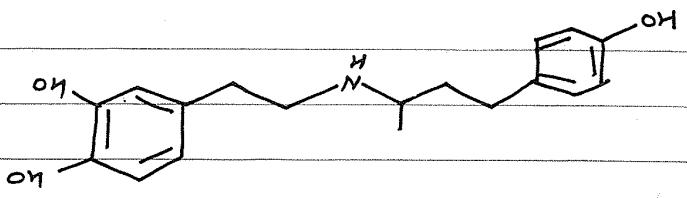
6. Dobutamine

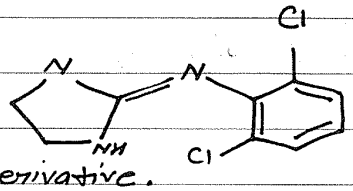


It is Direct acting non selective α and β Adrenergic receptor Agonist.

It is Analog of Dopamine. Dobutamine possesses an asymmetric Carbon that results in a pair of Enantiomers. (+)-enantiomer is a potent full Agonist at both β_1 and β_2 receptors, where as (−)-enantiomer is a potent Agonist at α_1 receptors.

Recemic Dobutamine increases the inotropic Activity of the Heart to a greater Extent as compared to increase in Chronotropic Activity that used in Congestive Heart failure.

7. Clonidine



It is a phenyl iminoimidazoline Derivative.
It is selective α_2-receptor Adrenergic Agonist.

Clonidine enters the CNS and stimulate α_2-receptors located in the regions of Brain. Stimulation of α_2 receptors brings Decrease in Neurotransmitter that results in Decrease in peripheral Vascular resistance and blood pressure.

It has been used in to treat Attention-Deficit Hyperactivity Disorder.

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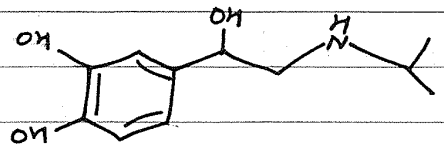
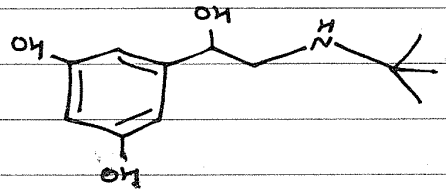
8. Isoproterenol



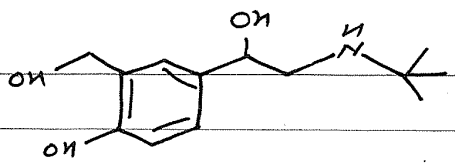
* It is a β-adrenergic receptor Agonist.
* It Act on Both β_1 and β_2 receptors.
* It produces an increase in Cardic output by stimulating β_1-receptor and Cause bronchodilation of β_2 receptors in the respiratory tract.
* It is available by inhalation and injection and mainly used for the relief of Bronchospasm associated with bronchial Asthma. It is one of the most potent Bronchodilator Available
* Due to non Selectivity towards beta receptors it Causes cardic stimulation as a Dangerous side Effect. Hence its use become limitted in Asthma patients.

9. Terbutaline



* It is a Selective β_2 receptor Agonist.
* Wheen given orally it has longer Duration of Action and more Effective as compared to Isoproterenol Bec it is not metabolized by MAO and COMT.
* It is available in oral Dosage forms as well as Inhalers and Injections.
* It is used primarily as Bronchodilators in Asthma and other Constrictive Pulmonary Conditions

10. Salbutamol



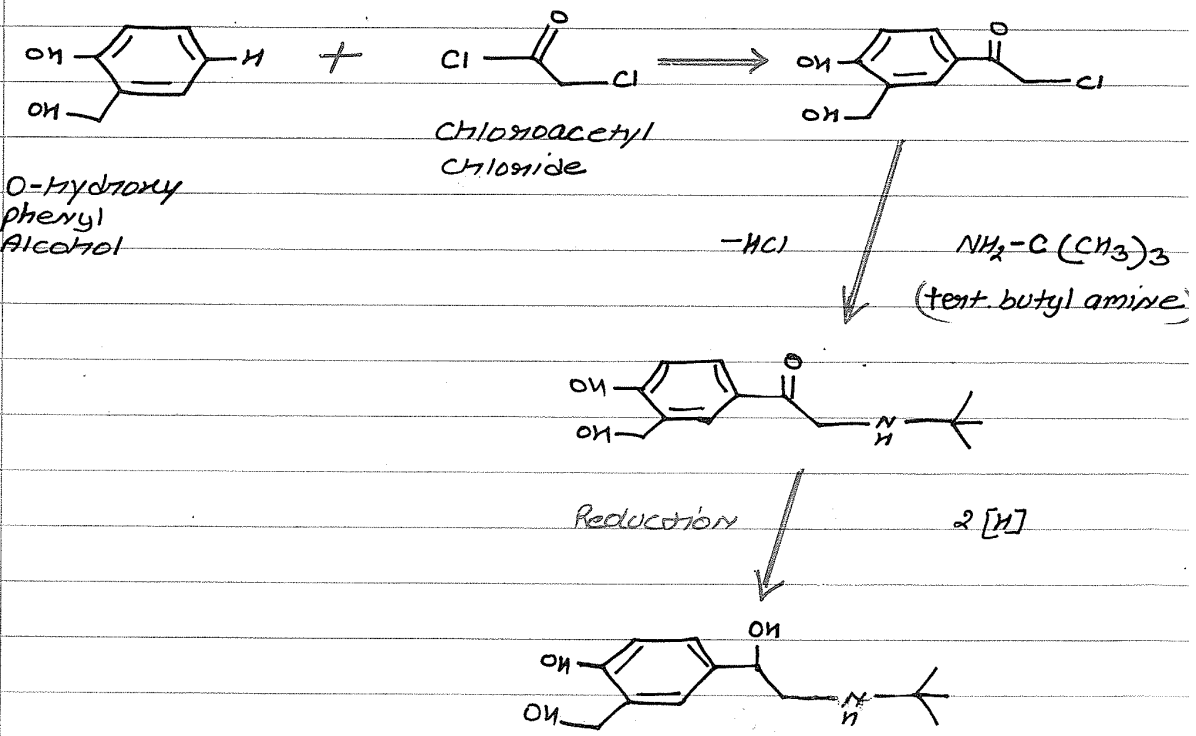
It is also known as Albutarol.
It is noncatechol selective β_2-receptor Agonist.

It is resistant to metabolism by MAO and COMT has orally Effective. Onset of Action is within 5 min, when Inhaled with a Duration of Action of 4-8 hours.

Mechanism Binding with β_2 receptor results in relaxation of smooth muscles of airway.

Uses It is a drug of choice for relief of acute bronchospas of Asthmatic attack and COPD.
It has been used to treat Hyperkalemia.

Synthesis;



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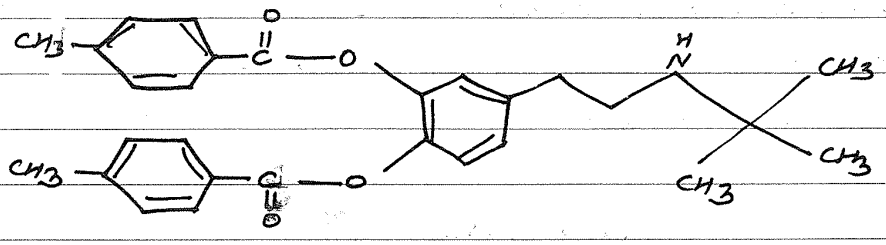
11. # Bitolterol

It is a prodrug of selective β_2 receptor Agonist.

It Contains two p-toluic acid Esters this makes it more lipophilic than colterol. It has long Duration of Action.

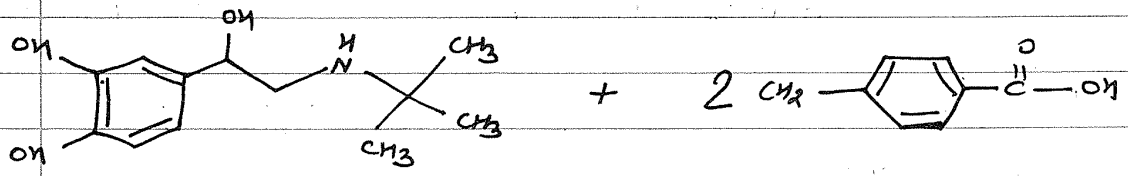
It is Administered by inhalation for Asthma and reversible bronchospasm.

Structure;-



Bitolterol (prodrug)

Esterases



colterol + 2 p-Toluic Acid.

12. 13 14.

Naphazoline, Xylometazoline, Oxymetazoline

Similar Action / and Basic Structure

These are 2-aroalkylimidazolines.

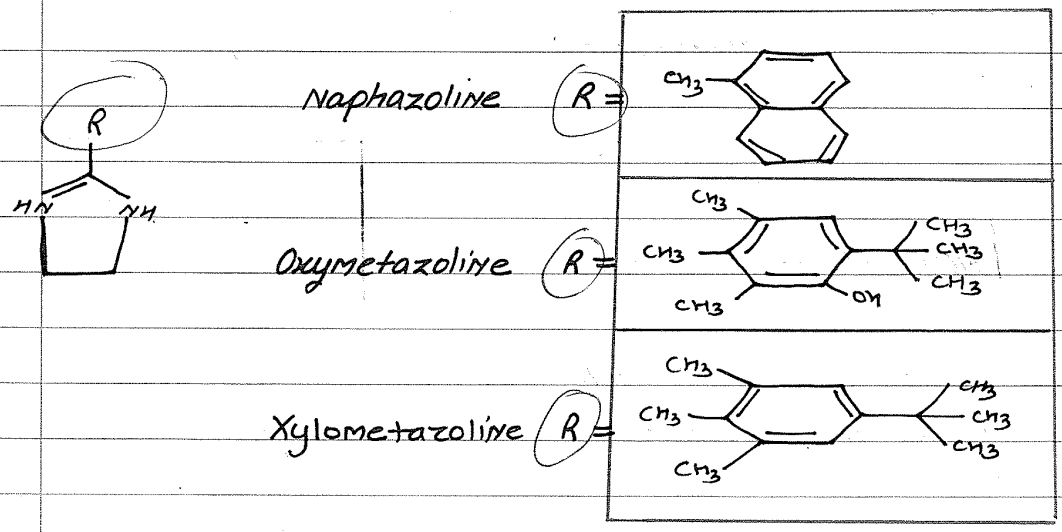
These are α_1 and α_2- receptor Agonist.

These Agents used for their Vasoconstrictive Effects as nasal and ophthalmic decongestants.

Oxymetazoline and Xylometazoline work by stimulating Adrenergic receptors of Blood Vessels in the nose.

The Decongestant Effects Duto constriction of large veins in the nose, which swell up during the inflammation of any infection of allergy of the nose.

Naphazoline is a decongestant used to relieve redness, puffiness and watering eyes Duto colds, Allergies, or eye irritations.



Naphazoline 2-(Naphthalen-1-ylmethyl)-4,5-Dihydro-1H-imidazol

Oxymetazolin 6-tert-butyl-3-(4,5-dihydro-1H-imidazol-2-ylmethyl -2,4 Dimethylphenol.

Xylometazoline 2-[(4-tert-butyl-2,6-Dimethylphenyl) Methyl1]- 4,5-dihydro-1H-imidazole.

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Indirect Acting Drugs

Mechanism

- Act by releasing endogenous norepinephrine
- Inhibit MAO-A
- Inhibition of norepinephrine metabolism

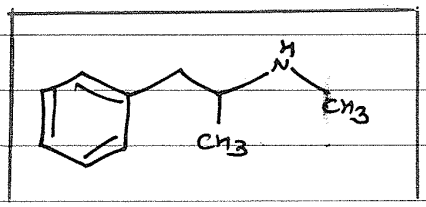
Study of 3 Drugs in this class.

Hydroxyamphetamine

Pseudoephedrine

Propylhexedrine

3. Propylhexedrine



It is an analogus of amphetamine in which aromatic ring has been replaced with a cyclohexane ring.

Mechanism It bind & Activates α-Adrenergic receptors in the mucosa of Respiratory tract thus mimic the Action of norepinephrine. It also act indirectly by Blocking the reuptake of norepinephrine neurotransmitters.

Uses - Drug produces Vasoconstriction and Decongestant effect on the nasal Membrane.

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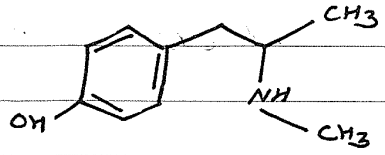
1. Hydroxyamphetamine



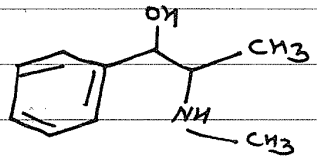
a. It causes (NON-Selective stimulation of α and β Adrenergic receptor.)

b. It is an Effective indirect acting Sympathomimetic Drugs.

c. It is used to Dilate pupil for Diagnostic eye Examination and for Suragical procedures on the eyes.

d. It is used Sometimes like cholinergic blocking Agents to produce Mydriadic Effect which is more pronounced than produced by any drug i Alone.

2. Pseudoephedrine



a. It is Diastereoisomer of Ephedrine.

b. It principle Action is the stimulation of Adrenergic receptor It act on α and β receptor to cause vasoconstriction. and smooth muscle relaxation. It also cause release of norepinephrine in synaptic nerve terminals.

c. It is used in many nasal Decongestants and cold Medicines

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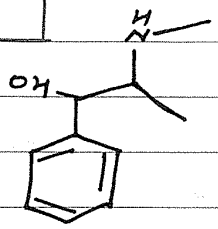
Mixed Action

Drug Acting by Both – Direct and Indirect Action

1. Ephedrine



- It is a mixed action Sympathomimetic.
- The Drug acts on Both α and β adrenergic receptors. It has Action similar to Epinephrine But less potent. It Causes more CNS Stimulation than Epinephrine.
- Ephedrine has two asymmetric carbon atoms. The Erythro racemate called Ephedrine and threo racemate called pseudoephedrine.

Uses

It is used locally to Constrict nasal mucosa Causes Decongestion and Dilate Bronchi.

It can also used intravenously, intramuscularly and topically in variety of conditions such as allergic Disorders, cold, narcolepsy.

over sleepyness in day time

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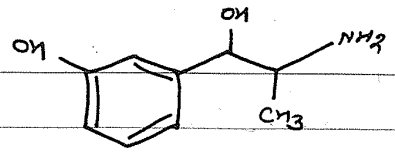
2 Metaraminol



It is structurally similar to phenylephrine

In Metaraminol stu 1° Amine is present in place of 2° Amine of phenylephrine.

It is mixed Action Sympathomimetic with Direct Action Mainly on α- Adrenergic receptors.

Uses It is used parenterally as vasopressor in the treatment and prevention of Acute Hypotensive state occurring with spinal anesthesia.

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Adrenergic Antagonist

Drugs that inhibit the function of Adrenergic receptors. These are also called Blockers or Sympatholytic Agents.

Classification of Adrenergic Blockers.

Non selective α-antagonist phenoxybenzamine, Tolazoline

selective α_1-antagonist prazosin, Terazosin

selective α_1-antagonist yohimbine

β-Adrenergic antagonist propranolol, Atenolol.

Mixed α/β adrenergic antagonist Labetalol, Carvedilol

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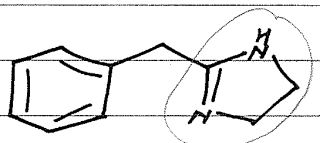
α- Adrenergic Blockers.

> Drugs that inhibit the interaction of norepinephrine epinephrine and other sympathomimetic Drugs and thus inhibit the function of Alpha receptor.

1. Tolazoline



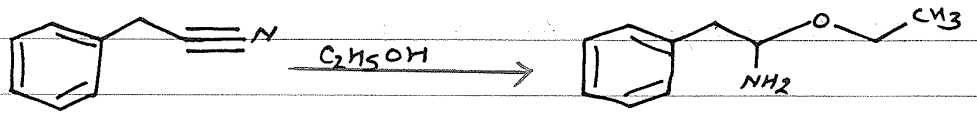
It is a non-selective imidazoline α-antagonist also having antihypertensive Activity.

Antagonistic action of tolazoline at presynaptic α_2 receptor lead to its Cardic Stimulant Effect By Increasing release of norepinephrine.
It has vasodilatory action on vascular smooth muscle which is more promient than α-receptor Antagonistic Effects

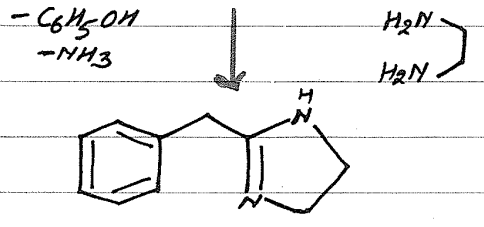
Tolazoline has been used to treat Raynaud's syndrome and other conditions involving peripheral Vasospasm.

It is indicated in persistent pulmonary hypertension of the new born when supportive measure are not useful

Synthesis



2-phenyl acetonitrile — Ethyl ester of iminophenzylic Acid



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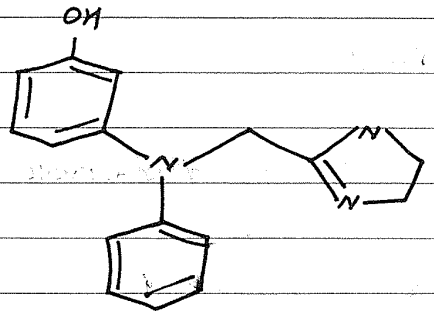
2. Phentolamine



It is "Non-selective imidazoline α-antagonist."

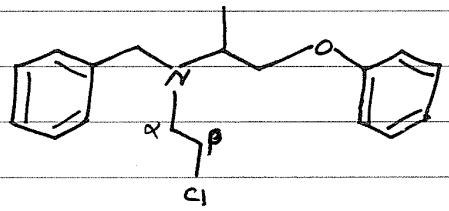
It is competitive (reversible) blocking Agent for α_1 and α_2 receptor.

It is used to prevent or control Hypertensive Episodes of pheochromocytoma patient.

It can be used as an aid in the Dignosis of pheochromocytoma.

It has been used in Combination with papaverine to treat impotence.

3. Phenoxybenzamine



Chemically it is β-haloalkylamine.

It is nonselective, noncompetitive irreversible blocker of α-Adrenergic receptors

It produces a long lasting irreversible blockade of α-adrenergic receptors it binds covalently with the receptor.

Oral phenoxybenzamine is used for the preoperative management of patient with phenochromocytoma and in chronic management of patient cotrose tumors

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4. Dihydroergotamine

It is an ergot alkaloid, Derivative of Ergotamine.

Dihydroergotamine (DHE) has antimigraine Activity due to its Action as an Agonist at the serotonin, 5-HT, adrenergic and dopamine receptors.

It used treatment of Severe migraines.

5. Methylsergide

It is an ergot alkaloid. It is a congener of lysergic Acid and diethylamide.

It is an antagonist of 5HT, receptors. It antagonizes the Effect of serotonin in CNS leading to Vasoconstriction This Narrowing the Blood Vessels in Brain relieves Headaches.
It metabolized to methylergonovine which is responsible for the antimigraine Effict of Methylsergide.

Used treatment of Migraine and cluster Headache

Used to treat Episodic and chronic migraines

Also used to treat Carcinoid Syndrome.

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β- Adrenergic Blockers

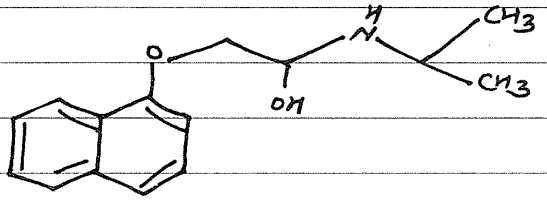
Also known as beta blockers.

These are the substances that block the action of epinephrine (adrenaline).

They lowers the blood pressure by relaxing and dilating blood vessels.

Beta blockers also reduce force of contraction of heart

SAR



1. Basic structural unit of β- antagonist is aryloxypropanolamine

2. Nature of aromatic ring & its substituents are responsible for β- antagonistic Activity.

3. Aromatic ring.

- ✡ phenyl gp also Effect the absorption, Excretion, Metabolism of β- Blocker.
- ✡ Nature of aromatic ring is Determinat factor for β_1- selectivity.
- ✡ presence of para substituents of sufficient size on aromatic ring is common feature of many Cardio Selective antagonist.

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4. Amino functional gp.
gt must be secondary amine for optimum Activity.

5. Substitution on Amino functional gp
Bulky Aliphatic gp such as tertiary butyl and Isopropyl on amino functional group of aryloxypropanolamine are imp for β- receptor antagonist.