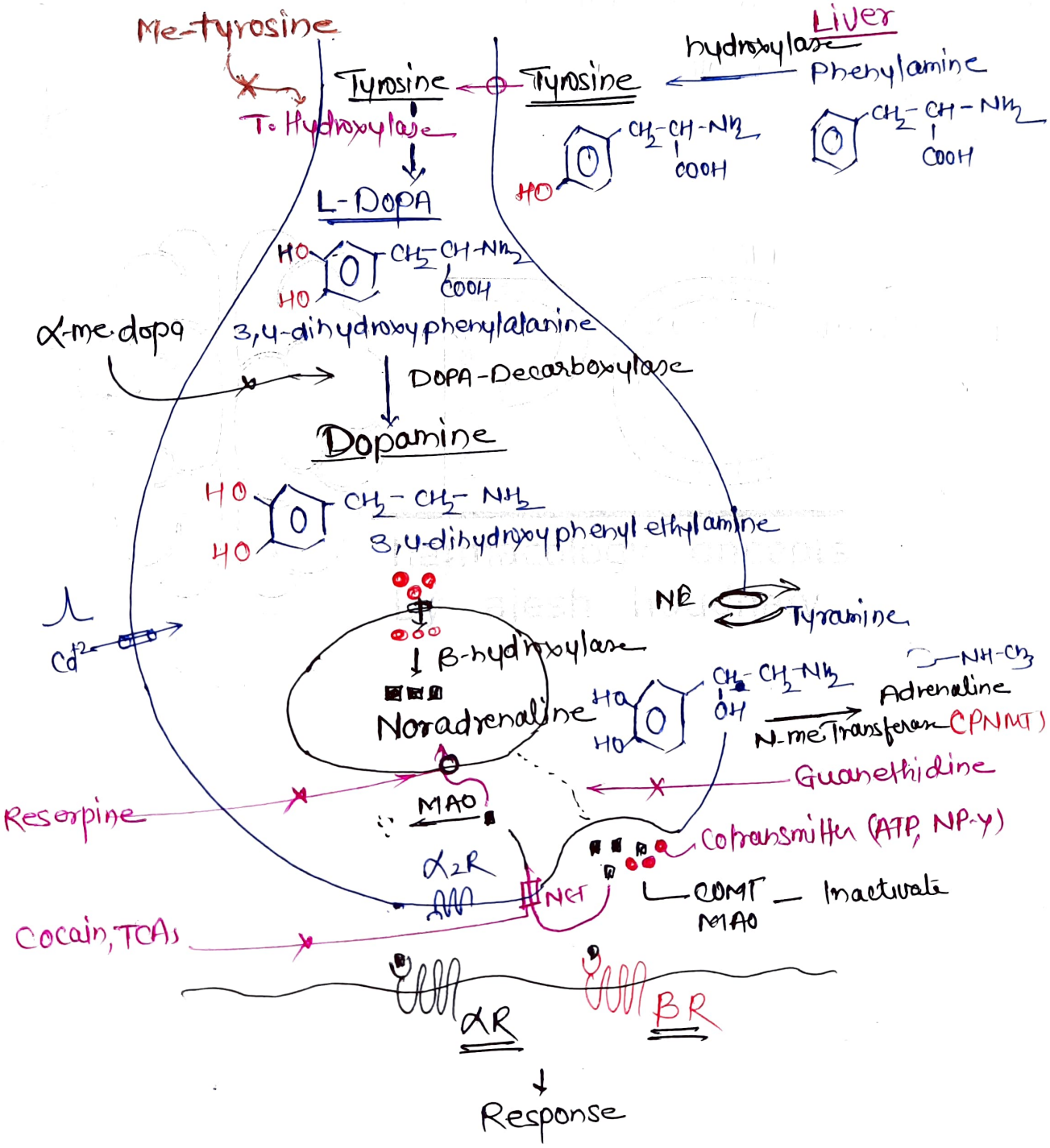
MEDICHEM-I
UNIT-II
DRUG ACTING ON ANS

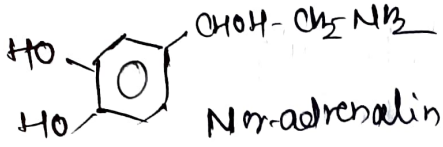
ADRENERGIC NEUROTRANSMITTER

↳ **Bio Synthesis** - 1st proposed by Blaschko in ~~193~~ 1939.

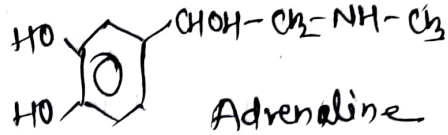
\# Take place in Adrenergic & Dopaminergic Neuron



Metabolism



Nor-adrenaline

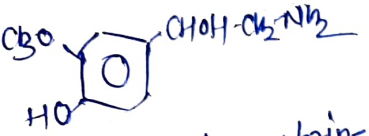


Adrenaline

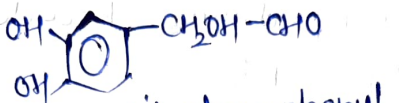
COMT

MAO

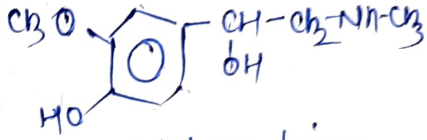
COMT



Nor-metanephrine



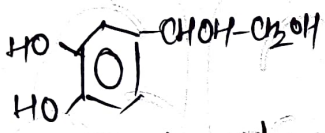
3,4-dihydroxy phenyl glycol aldehyde



Metanephrine

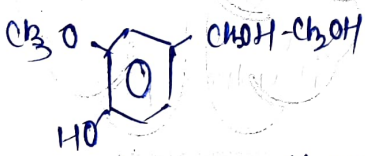
Ald Reductase

Ald DH

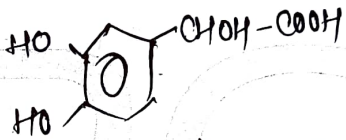


3,4-dihydroxy phenyl ethylene glycol

COMT

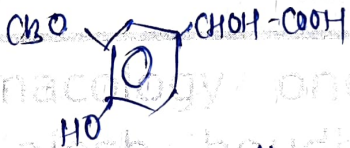


4-hydroxy, 3-methoxy phenyl ethylene glycol



3,4-dihydroxy mandelic a

COMT



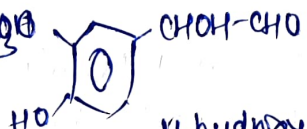
4-hydroxy 3-methoxy mandelic a

Vanillyl mandelic a

Ald Reductase

Ald dehydrogenase

MAO



4-hydroxy 3-methoxy phenyl glycol aldehyde

MAO

Sympathomimetic Agents

I. Direct Acting – Norepinephrine, Epinephrine, Phenylephrine, Dopamine, Methyl dopa, clonidine, Dobutamine, Isoproterenol, Terbutaline, Salbutamol, Bitoltarol, Nephazoline, Oxymetazoline & Xylometazoline

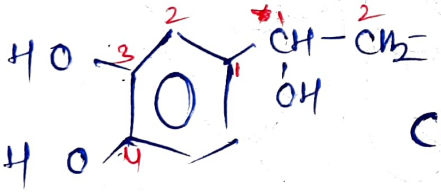
II Indirecting Acting :- Hydroxy amphetamine, Pseudoephedrine, prophyl hexidrine

III Mixed – Ephedrine, Metaraminol

STRUCTURE, NOMENCLATURE & MOA & USES

I Direct Acting :-

(1) NorAdrenaline (Nor-epinephrine)

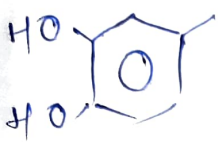


(R) 2-amino-1-(3,4-dihydroxy phenyl) - ethanol

MOA → α, & β_1 Receptor

Uses →
1. Septic shock
2. Hypotension
3. Reduce absorption and localizes effect of local anaesthesia
4. potent vasoconspictor

② Adrenaline (Epinephrine) (−) or levoform.



(R) 1-(3,4-dihydroxy phenyl)-2-methyl amino ethanol

* (−) is more active

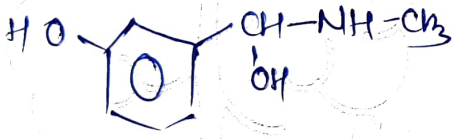
MOA = α < β Receptor

potency / Activity — α, Nor-Ad > Ad
β, Ad > Nor-ad

N-R_2 Substitution → ↑ β, activity
↓ α activity

Use =
- Hypotension,
- Anaphylaxis
- Shock (Cardiogenic & anaphylactic)
- Asthma (Inhalation)
- Allergic Rhinitis, hay fever, Sinusitis
- Glaucoma (Dipivefrine)

③ Phenylephrine*



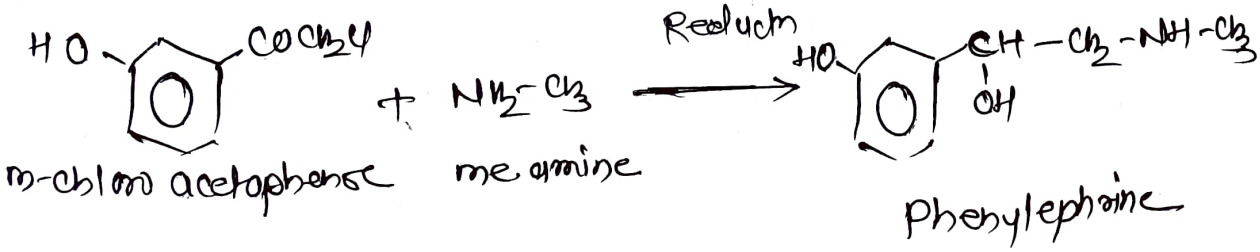
(R) 1-(3-hydroxy phenyl)-2-methyl amino-ethanol

* absent of −OH group at 3 or 4, or both → decrease the overall α < β activity • phenylephrine < Adrenaline

MOA − α, R activity, NO-β-action

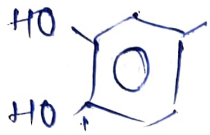
Use −
1. used as a decongestant in Rhinitis, & Sinusitis
2. eye drop for ~~dilating~~ producing mydriasis
3. pressure agent in hypotensive state like circulatory failure or hypotension
4. Supraventricular tachycardia (due to reflux vegal action)

Synthesis



m-chloro acetophenone + methamine → phenylephrine

④ Dopamine

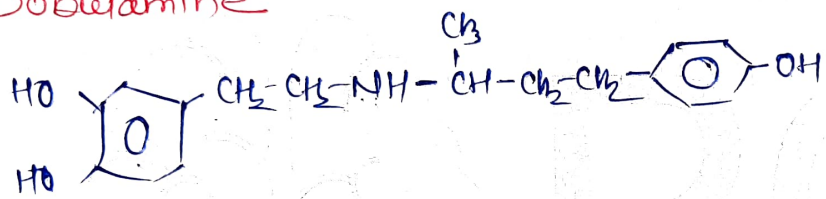


3,4-dihydroxy phenyl-ethyl amine
4-(2-aminoethyl) benzene-1,2-diol

MOA - Large dose - α_1
Medi. dose - β_1
Small dose - D_1R

Use → # Cardiogenic shock in oligouric renal failure
CHF (+inotropic), Myocardial infarction
Relax renal smooth muscle by D_1 Receptor

⑤ Dobutamine



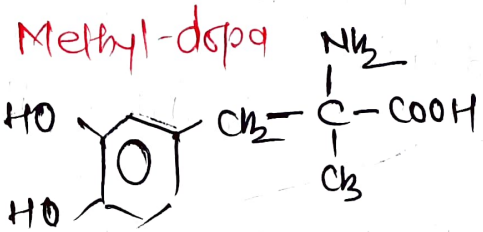
4-[2-(4-(4-hydroxyphenyl) butan-2-yl) amino ethyl] benzene-1,2-diol

MOA :- β_1 Selective & minor α_1 Agonist

Use → # CHF (+inotropic)
Cardiogenic shock
Cardiac stress testing

* only used in I.V. due to rapid first pass metabolism.

⑥ Methyl-dopa

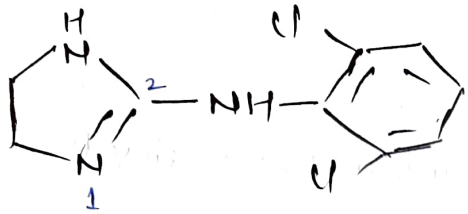


3-(3,4-dihydroxyphenyl)-2-methyl-L-alanine

MOA - ▸ α_2 Agonist (α-methyl norepinephrine)
x Competitive Inhibitor of DOPA decarboxylase

Use = In Hypertension in pregnancy

⑦ clonidine

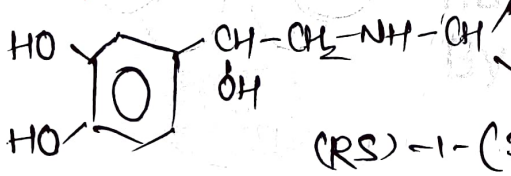


2-[(2,6-dichlorophenyl) amino]-2-Imidazoline

MOA - Centrally acting α_2R Agonist & Imidazoline Receptor Agonist → ↓ Sympathetic outflow from CNS

Use - ① Hypertension
② Attention deficit hyperactivity disorder (ADHD)
③ ↓ withdrawal symptoms associated with Alcohol, Narcotics, Nicotine, BDZ
④ Treatment of Tourette syndrome (neuropsychiatric disorder with onset in childhood)
⑤ Migraine & Restless legs Syndrome

⑧ Isoproterenol (Isoprenaline)



* Bulky alkyl group ↑ β Selectivity

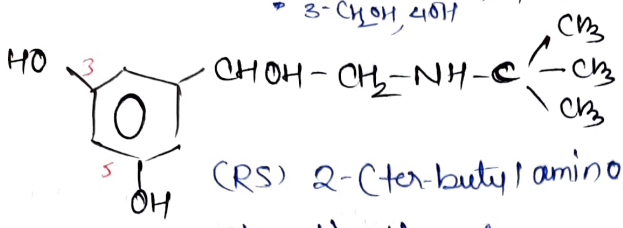
(RS)-1-(3,4-dihydroxy-phenyl)-2-isopropyl amino ethanol

MOA - β_1 & β_2 Receptor Agonist

Use : ① Cardiac Shock
② Heart block (Brady arrythmia)
③ Asthma (0.5% - 1.0% Inhalation)

(9) Terbutaline

- 3-OH = α activity
- 3,5-OH → β$_2$ activity
- 3-CH_2OH, 4OH

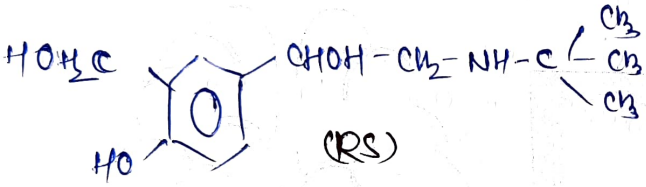


(RS) 2-(ter-butyl amino) 1-(3,5-dihydroxy phenyl) ethanol.

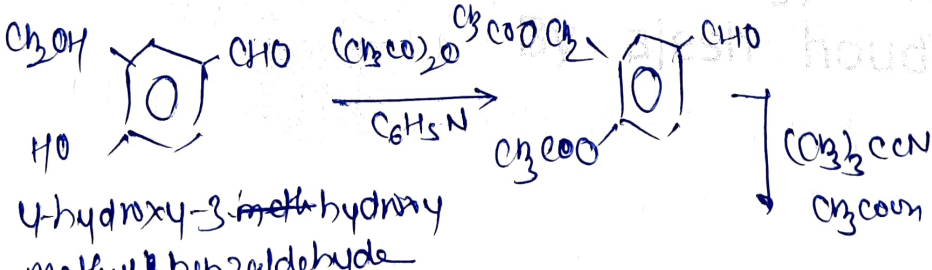
MOA = Selective β_2 Agonist

Use = ① Bronchodilator (Asthma)
② For arrest premature labour

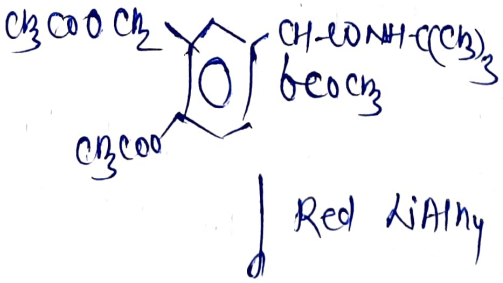
(10) Salbutamol

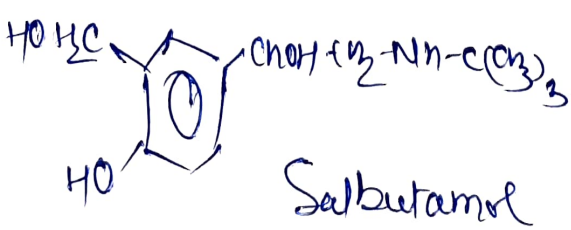


1-(4-hydroxy-3-hydroxymethyl phenyl)-2-(ter-butyl amino) ethanol



4-hydroxy-3-~~meth~~hydroxy methyl benzaldehyde



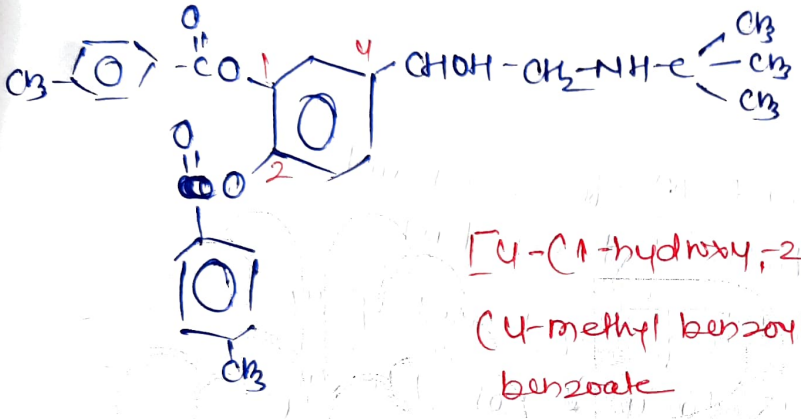


Salbutamol

MOA - Short Acting Strong β_2 Agonist → Smooth mus. Relaxation, Heart, Skmus - contracts, Liver - Glycogenolysis

Use → # Asthma (Inhalation)
bronchitis & COPD
Infusion of & Salbutamol are used to arrest premature labour

(11) Bitolterol



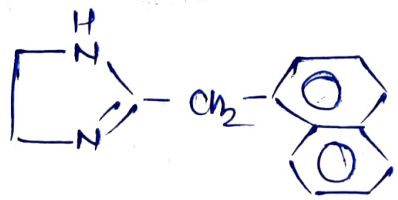
[4-(1-hydroxy-2-t butyl amino ethyl)-2-(4-methyl benzoyl) oxy-phenyl] 4-methyl benzoate

↳ β_2-Agonist (Short acting)

Uses → # Asthma
COPD

IMIDAZOLINES

(12) Naphazoline

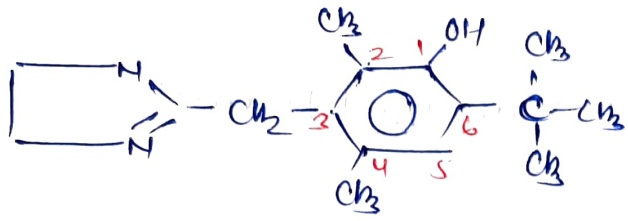


2-(1-naphthyl methyl)-2-Imidazoline

MOA - α_1 & α_2 partial Agonist

↳ Vasoconstrictor
↳ # help to reducing swelling & congestion on applicat to mucus mem. (Nasal Decongestant)
↳ # used in Rhinitis & Sinusitis
Solutn can be used conjunctival decongestant

(13) Oxymetazoline



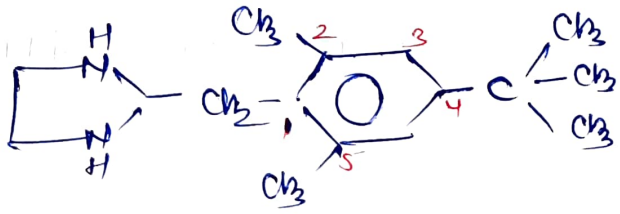
3-(4,5-dihydro-1H-imidazol-2-yl)-methyl-
6-(1,1-dimethyl ethyl)-2,4-dimethyl-Phenol

MOA → Selective α_1 Agonist
partially α_2 agonist

Use

Topical decongestant in form of nassal spray
Vasoconstrictor property to used nose bleeding & redness of eyes due to irritation
Topically used for the treatment of facial erythema

(14) Xylometazoline



2-(4-t-butyl-2,6-dimethyl benzyl)-2-Imidazoline

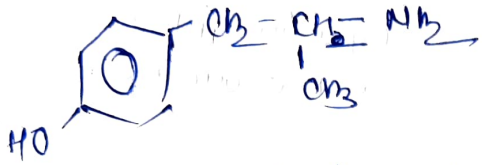
MOA - α_1 & α_2 Agonist

Use # used as Nasal Decongesant in Rhinitis, Sinusitis
Solution can be used in eye for conjunctival decongesant

II. INDIRECT ACTING DRUG

Enhance the release of Nor-Ad/Ad from storage site in sympathetic nerve to effector organ.

(1) Hydroxy amphetamine

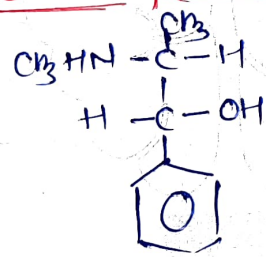


4-hydroxy-α-methyl-phenethylamine

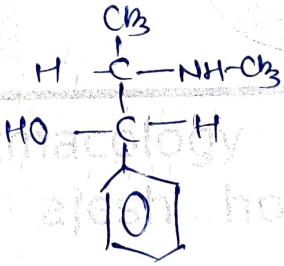
MOA → ↑ release of Nor Ad

Use : # eye-drop for pupil dilation
diagnosis for "Horner's Syndrome"

(2) Pseudoephedrine



(−) Pseudoephedrine



(+) pseudoephedrine

2-methylamino-1-phenyl-propan-1-ol

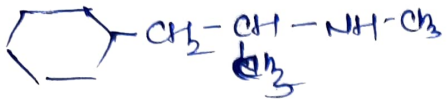
MOA : both α & β activity
(+) CNS

USES : (i) Nasal & Bronchial Decongesant
(ii) Vasoconstriction

Activity (−) ephedrine > ± Ephedrine > (+) ephedrine
> (+) pseudo > (±) pseudo > (−) pseudoephedrine

(2)

Propylhexedrine



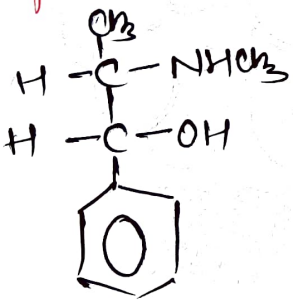
1-Cyclohexyl-N-methyl propan-2-amine

MOA :- Indirect acting
- reverses the transporter for dopamine, Noradr & 5HT which leads to release of monoamine from presynaptic vesicle

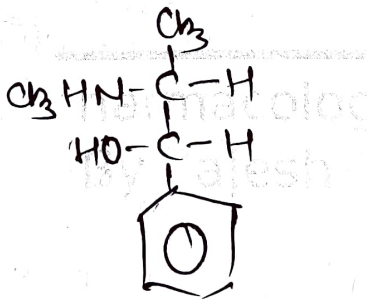
Use : Decongestant

III Mixed Action

(1) Ephedrine



(−) ephedrine



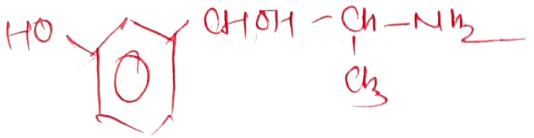
(+) Ephedrine

(1R,2S)+ 2-methylamino-1-phenyl propan-1-ol

MOA - # α and β activity
↑ release of Nor Adr (CNS)

Uses - (I) orally - Asthma
(II) CNS Stimulant in narcolepsy
(III) Spray/Inhalation - allergy - hay fever and urticaria
(IV) Nasal Decongestant
(V) Mydriatic

② Metaraminol



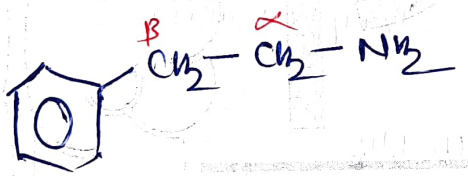
(1R2S) (-2-amino-1-(3 hydroxyphenyl) propan-1-ol

MOA - (+) α and β
↑ release

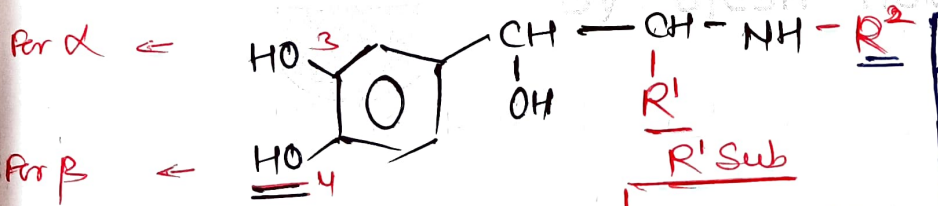
Use - ① used as pressor agent
④ anesthesia induced hypotension

SAR of Sympathetic Agent

parent ring - β-phenyl ethyl amine



Site for Substitution
↳ Aromatic ring
↳ β-carbon
↳ α-carbon
↳ Amino group



For α ←
For β ←

R² Substitution
→ # ↑ β activity
→ # ↓ α activity
→ branching alkyl chain (t-butyl)
↳ ↑ β_2
↳ ↓ MAO degradation

R' Sub
Me ↓ MAO degradation
Ethyl - ↑ β & ↓ α
- ↑ CNS

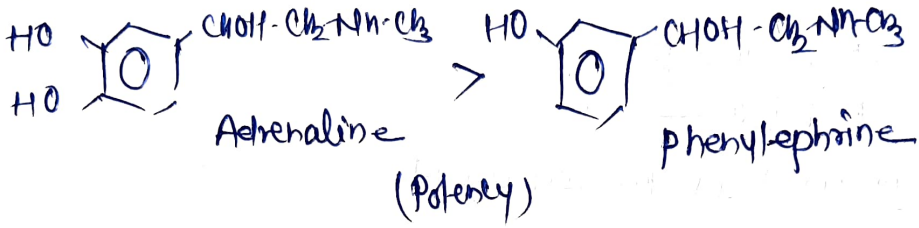
3,5-dihydroxy & 3 CH_2OH, 4 OH
↳ # ↑ β_2
↓ COMT degradn
↑ oral & duration of action

No Sub. at Aromatic ring
↳ # both -OH for α & β activity
easily metabolised by COMT
↑ CNS & oral activity, ↓ duration of action.

(A) Aromatic Ring Substitution in β-phenyl ethylamine

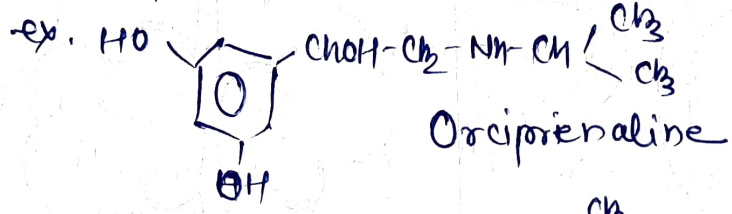
(1) 3,4-dihydroxy group for maximum α & β activity, if any of these absent overall potency get decreased.

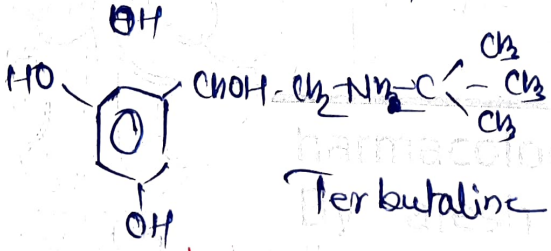
ex.



(Potency)

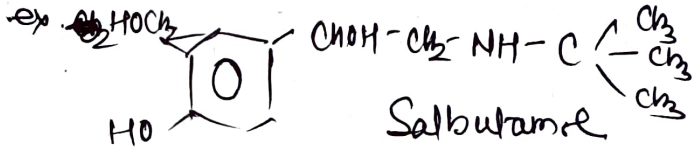
(2) 3,5-dihydroxy at aromatic ring with bulky substitution at amino group enhance the β_2 Selectivity

ex. 

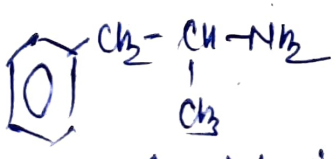


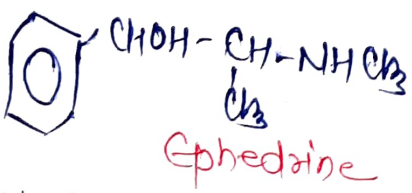
Selective β_2 Agonist

(3) Other than -OH, like $-CH_2OH$ also enhance β_2 Selectivity

ex 

(4) UnSubstituted hydroxy group- ↑ lipid Solubility and ↑ CNS activity ex Amphetamine & Ephedrine





(B) β-carbon Substitution

→ -OH Substitution at β-carbon ↓ lipid solubility and CNS activity & ↑ peripheral agonist at α & β

ex. Amphetamine > Ephedrine (CNS activity)

(C) Sub. at α-carbon

Me or Ethyl Substitution at α carbon ↓ the deamination reaction by MAO & hence ↑ duration of action

ex. Amphetamine resist degradation by MAO

(D) Sub. at amino group

Lesser Substitution – ↑ α Selectivity Norad > Ad.

bulk alkyl group → ↑ β & β_2 Selectivity

ex. Salbutamol, terbutaline – β_2

Selectivity

Isoprenaline – β_1 & β_2

Adrenaline – α & β

Noradrenaline α