

Alkaloids and Terpenoids:-

Definition of alkaloids:-

Alkaloids are ^{heterocyclic} nitrogenous bases generally they are of plant origin, which possess basic properties, complex structure, physiologically active and they are generally bitter in taste.

Occurrence:-

Alkaloids occur mainly in plants. Seeds, roots, leaves and bark of the plant are the main source of plant alkaloids. They occur largely as salt of common plant acids (organic acid) such as tartaric acid, oxalic acid, lactic acid, malic acid, acetic acid, citric acid etc. In some cases they are existing as glycosides as that of sugar or as amides like piperine or as ester like atropine, cocaine etc.

General properties:-

i) Alkaloids are usually colourless, crystalline, non-volatile solid, while a few of them are log (such as conin, nicotine).

ii) Except the liquid alkaloids which are soluble in water, the rest are insoluble in water, but all of the alkaloids are soluble in ether, chloroform, benzene etc.

iii) Most of the alkaloids are optically active and majority being levorotatory.

(iv) Alkaloids are basic in properties & bitter in taste and they form crystalline salt with inorganic acid, as well as organic acid. These salts are generally soluble in water but insoluble in organic solvent (ether, chloro, alcohol etc)

(v) Most of the alkaloids have characteristic physiological activity when orally applied.

Cocaine is a violent poison. Quinine is an anti-malarian, cocaine is a local anesthetic and morphine is a pain killer.

Detection or identification of alkaloids:-

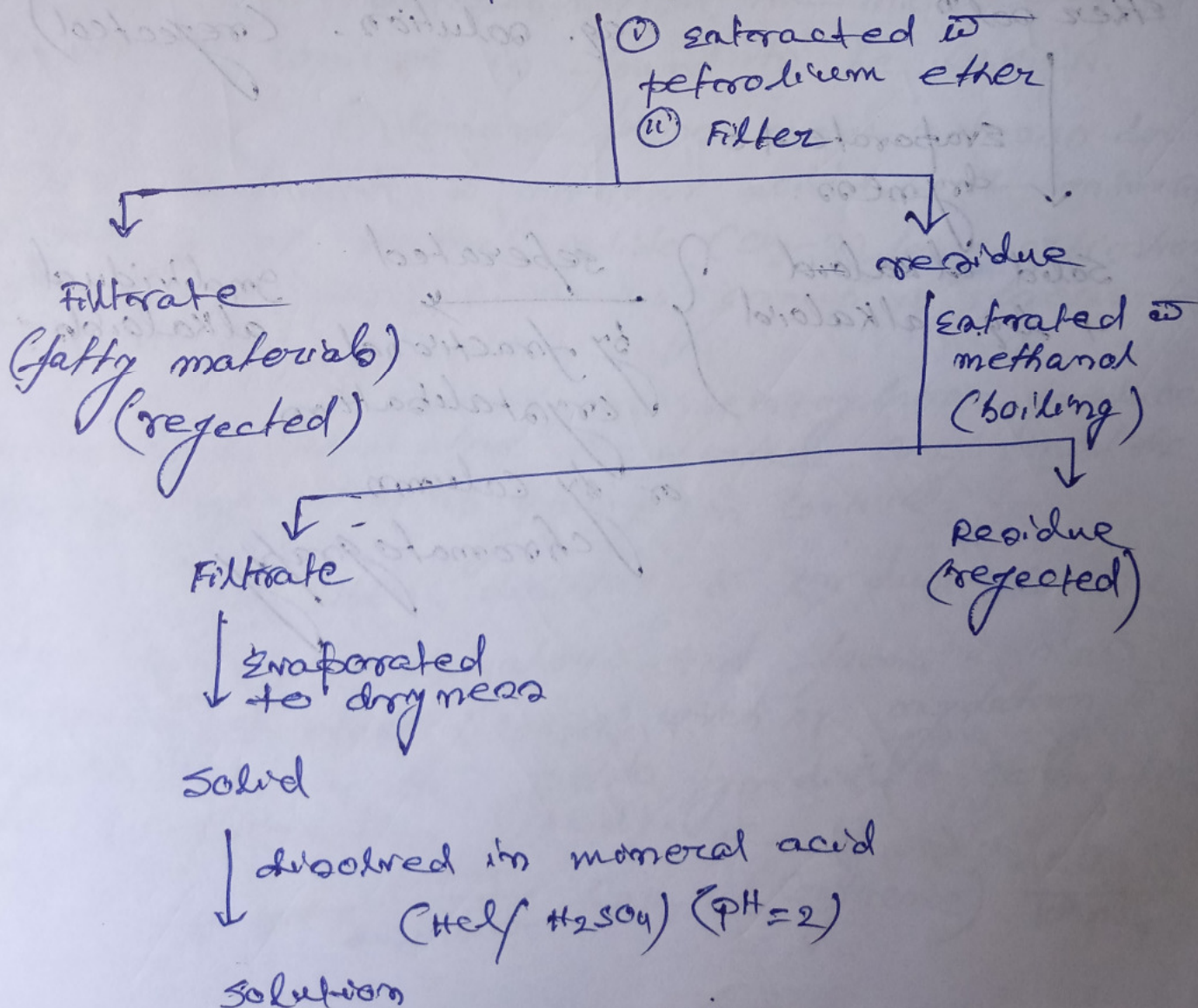
The solution of alkaloid gives ppt with certain reagent, such as picric acid, phosphotungstic acid, phosphomolybdic acid, tannic acid, potassium mercuric iodide ($K_2[HgI_4]$). Most of the ppt have definite crystalline appearance and could be used for separation and identification of alkaloids.

Isolation of alkaloids:-

Alkaloids are generally isolated from plants by first extracting the air dried powder with petroleum ether to remove fatty materials, then the plant material is extracted with boiling methanol/ethanol. Cellulose material is separated by filtration, the filtrate is evaporated to dryness and the residue is dissolved in dilute mineral acid (dil HCl/dil H_2SO_4) by maintaining pH = 2 and then water soluble nonbasic org substances

are separated by extraction w/ ether. The acid solution of the alkaloid salt are then made alkaline by the addⁿ of Na_2CO_3 and successively extracted w/ ether, CHCl_3 and CH_2Cl_2 . Now, removal of the solvent by evaporation gives a mixture of alkaloids, which are then separated into individuals, either by fractional distillation/crystallization or by column chromatography.

Air dried powder
plant material



Solution.

Extracted to ether

(Alkaloid salt)

Acid solution

$\text{Na}_2\text{CO}_3 \text{ sol}^n$

Free alkaloid

Extracted to
ether/ CHCl_3 / CH_2Cl_2

ether solⁿ

aq. solution. (rejected)

Evaporate to
dryness.

Solid alkaloid
+ liq. alkaloid

separated

by fractional
crystallization.

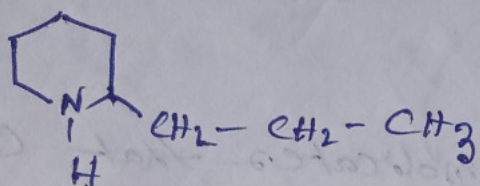
or by column

chromatography

individual
alkaloids

Coniine ($C_8H_{17}N$)

Str:-



B.P. $-168^\circ C$

Optical rotation $[\alpha]_D = +15.7^\circ$

Source:- (i) oil of hemlock tree
(ii) Conium maculatum

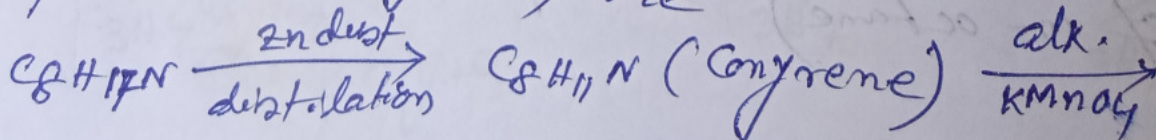
Establishment of structure of coniine:-

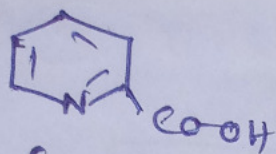
(i) From elemental analysis and molecular wt. determination, the molecular formula of coniine is found to be $C_8H_{17}N$.

(ii) Coniine forms mono-nitroso derivative on treatment to nitrous acid and it consumed two moles of methyl iodide (CH_3-I) for quaternization, which indicates the 2° amino group is present in coniine.

(iii) Coniine on benzoylation produces mono benzoyl derivative it further confirmed the presence of 2° amino group in coniine.

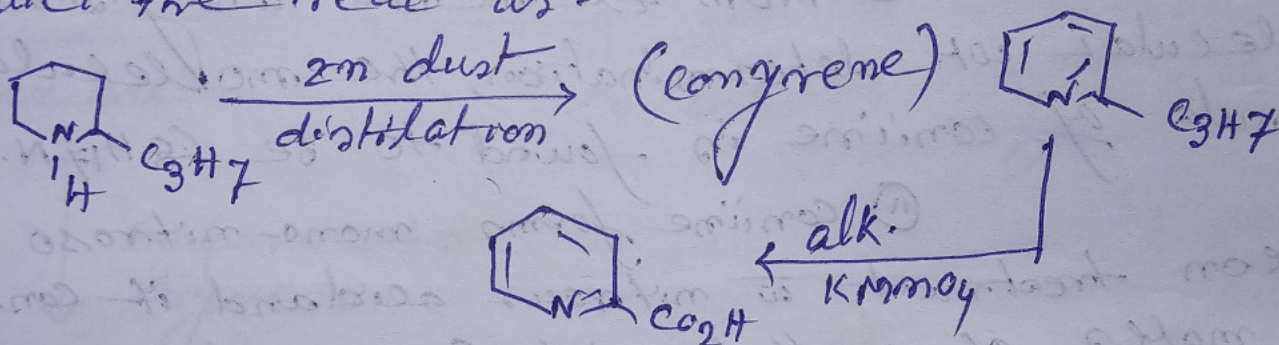
(iv) When distilled w/ Zn dust coniine loses six hydrogen atoms and forms a new compound Conyrene ($C_8H_{11}N$) which on oxidation w/ alkaline $KMnO_4$ solⁿ yields pyridine-2-carboxylic acid (α -picolinic acid) i.e.





(α -picolinic acid)

This above fact indicates that coniine is probably the pyridine derivative with a side chain at 2-position which on oxidation would be capable of giving pyridine-2-carboxylic acid. Again since conyrene is obtained from coniine by loss of six hydrogen atoms, hence coniine could be corresponding piperidine derivative with a side chain at 2-position. Thus we can predict the reaction as -



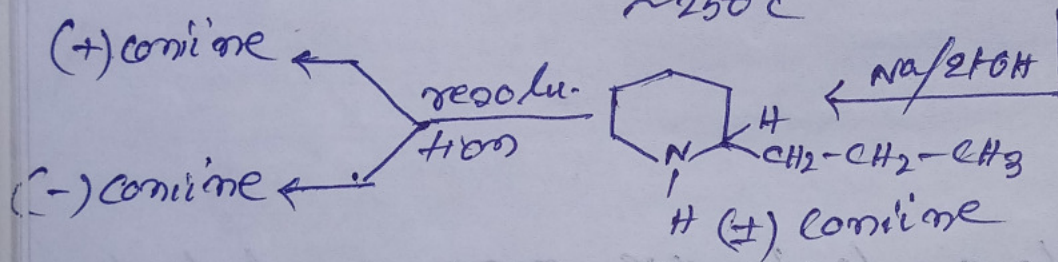
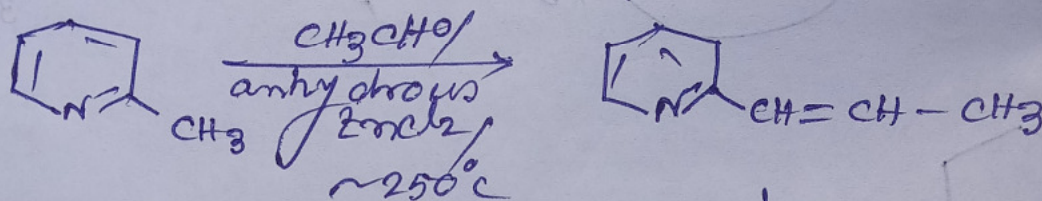
And since side chain contains three carbon atom, hence this side chain may be either n-propyl or isopropyl group.

① coniine when heated with H_2 at 300°C under pressure or in presence of red P, it forms n-octane, this expt suggests that side chain of coniine must contain n-propyl group (if this group is isopropyl, on reduction with H_2 or red P coniine produces isooctane instead of n-octane)

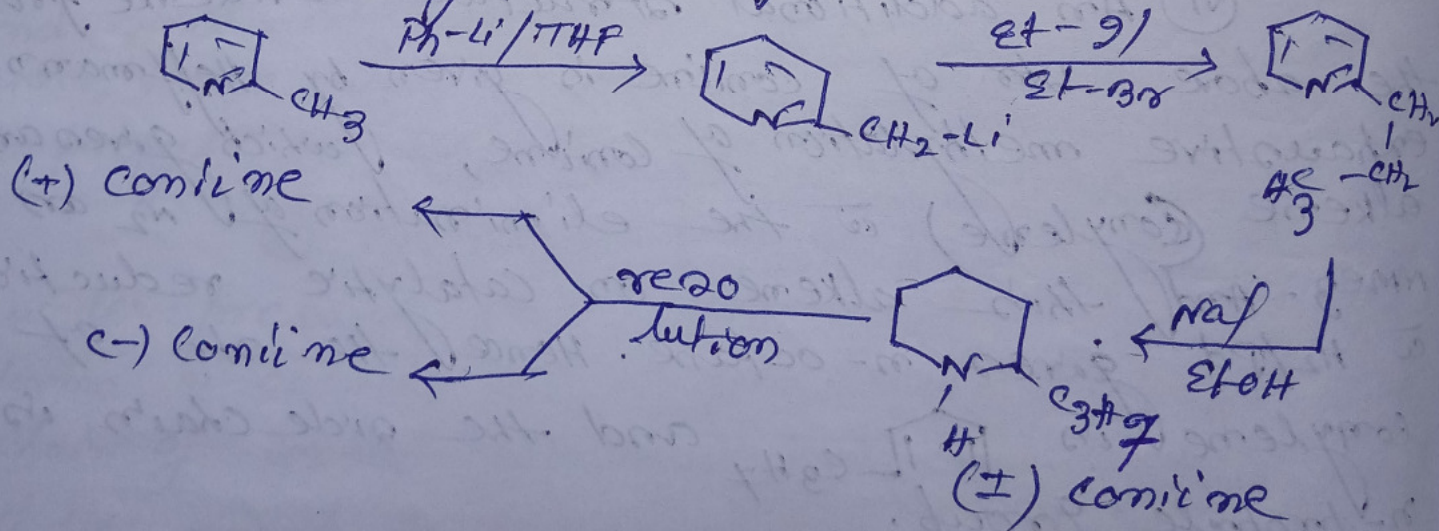
(vii) Finally the a^o was confirmed by synthesis

(a) Ladenberg's Synthesis:-

Condensation of CH_3CHO w/ 2-methyl pyridine at 250°C temp. in presence of anhydrous ZnCl_2 produces 2-propenyl pyridine which on reduction to Na in ethanol gives $\pm$ conine.

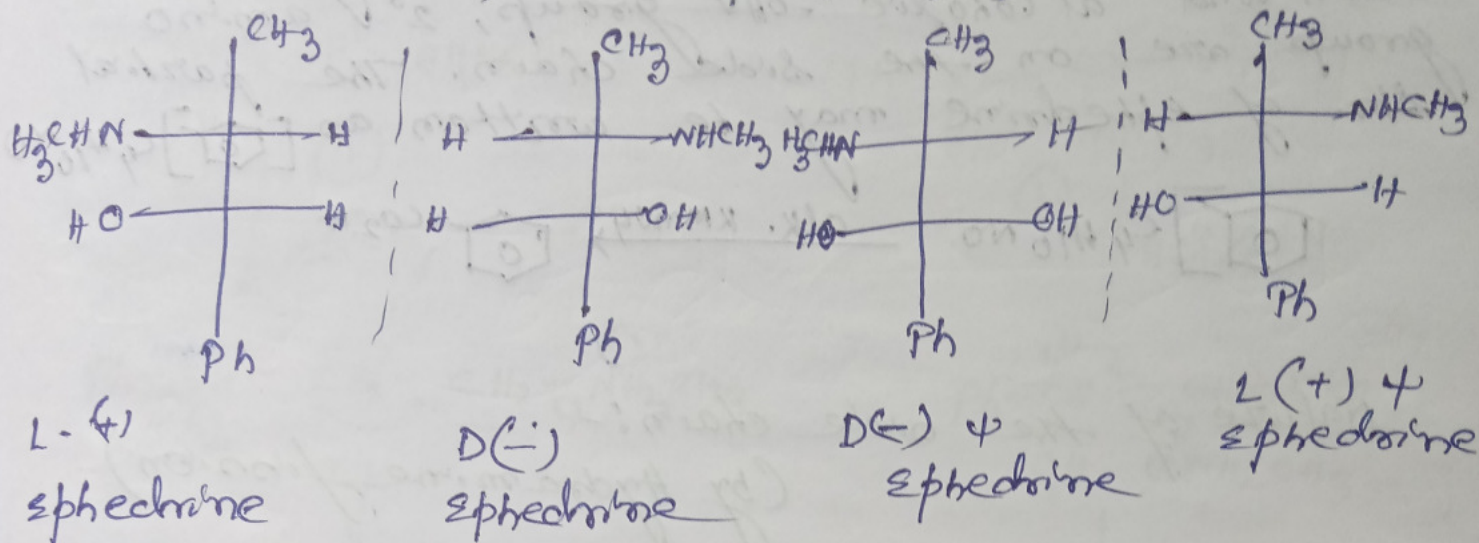


(b) Bergmann's Synthesis:-



Ephedrine (volatile)

M.F. $C_{10}H_{15}NO$, M.P. $-38^{\circ}C$, $[\alpha]_D = -6.3^{\circ}$



Source Genus *ephedra*.

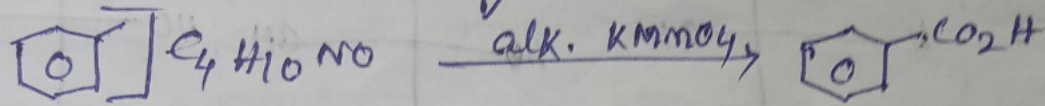
Elucidation of the str. of ephedrine:-

(i) From elemental analysis and molecular wt. determination the molecular formula of ephedrine is $C_{10}H_{15}NO$.

(ii) Ephedrine on treatment w/ $(NaNO_2 + HCl)$ nitrous acid forms mono nitroso derivative, which concluded that the 2° amino group is present in ephedrine.

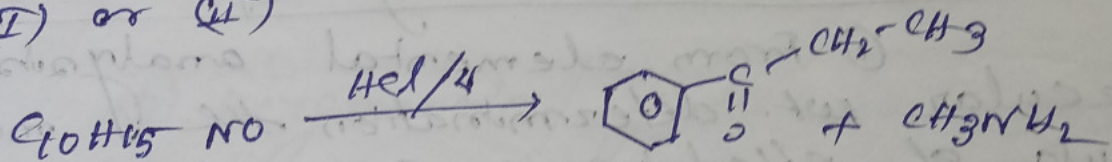
(iii) Ephedrine on benzylation produces dibenzoyl derivative which may concluded that ephedrine probably contains one 2° amino group and one alcoholic $-OH$ group. Again ephedrine on acetylation gives diacetyl derivative which further shows the presence of an alcoholic $-OH$ group and 2° amino group.

④ Ephedrine on alkaline KMnO_4 oxidation produces benzoic acid - this expt shows the ephedrine contains a benzene ring w a single side chain and alcoholic $-\text{OH}$ group, 2° amino group are on the side chain. The partial str. of ephedrine may be written as $[\text{C}_6\text{H}_5]\text{C}_4\text{H}_{10}\text{NO}$

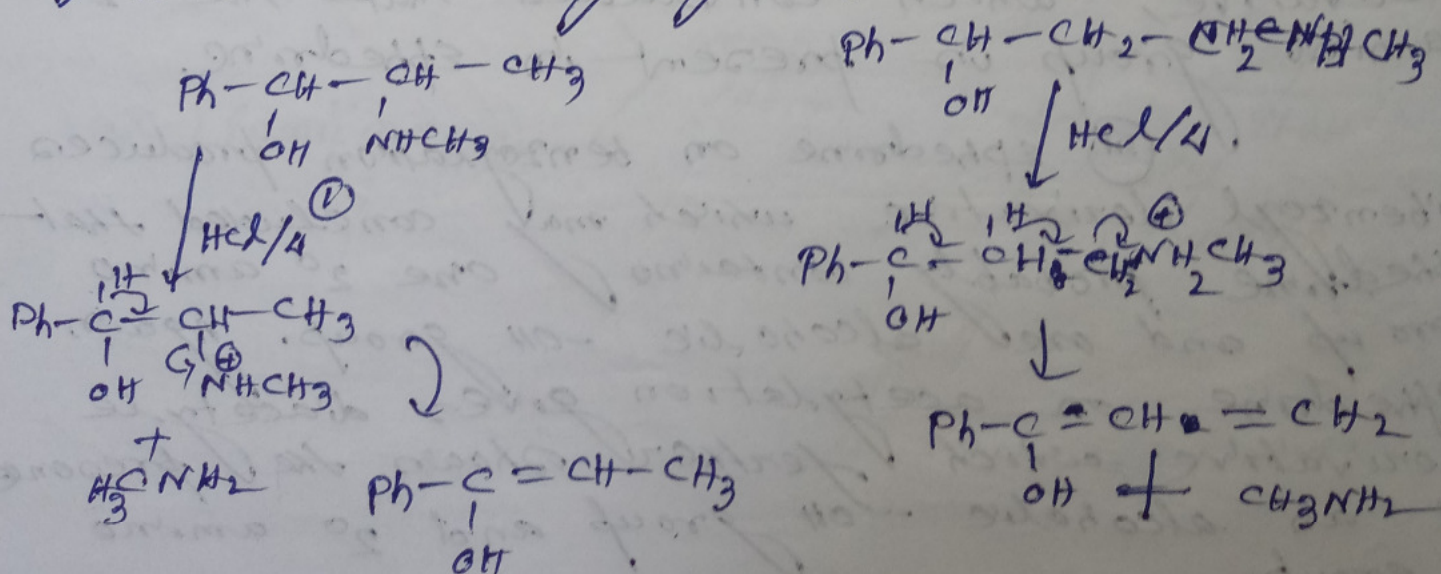


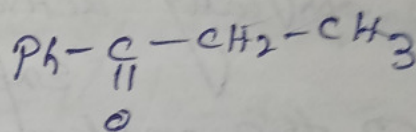
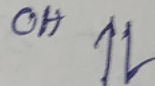
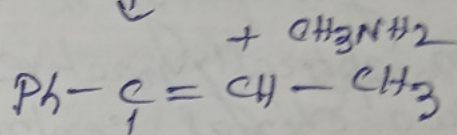
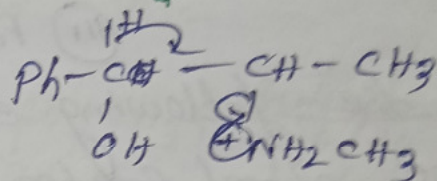
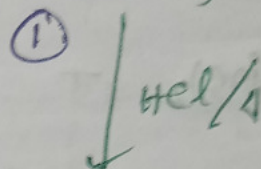
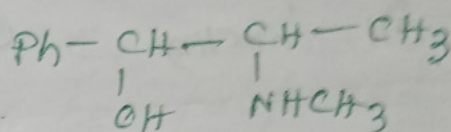
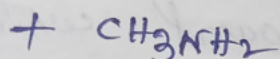
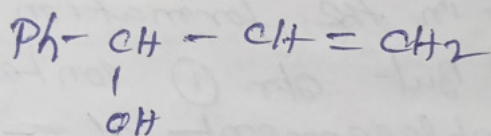
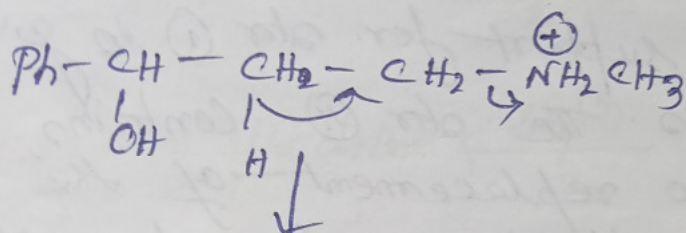
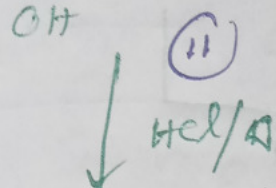
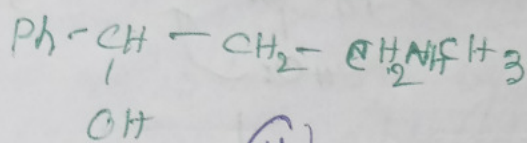
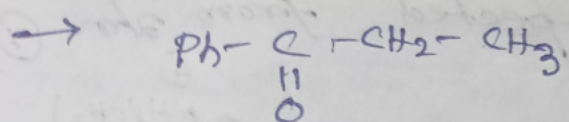
Nature of the side chain:-
(by Hydramine fission)

ephedrine when heated w HCl produces propyl phenone. By hydramine fission of ephedrine can be explained if the str. of ephedrine is either (I) or (II)



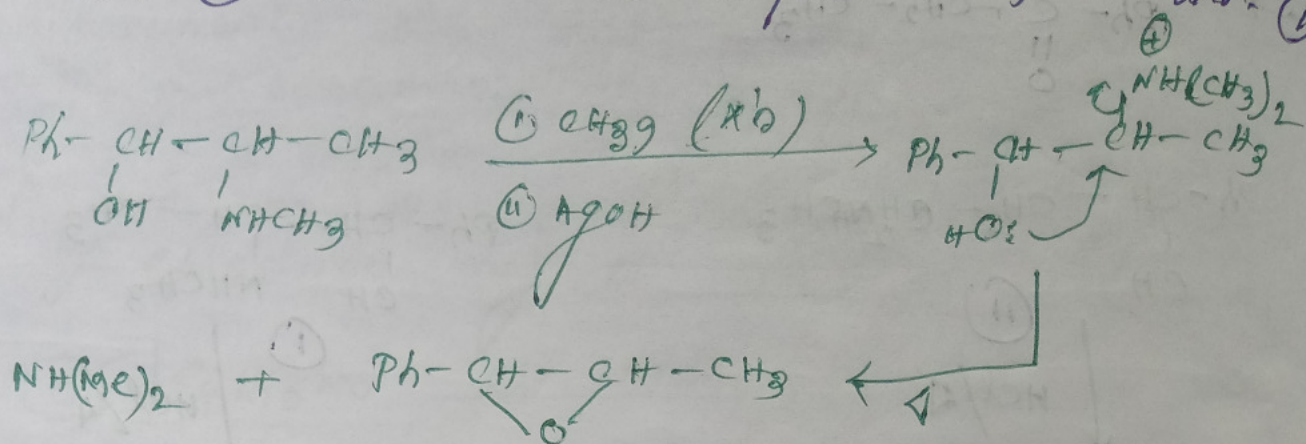
Again since methyl amine is obtained from hydramine fission then side chain must contain N -methyl group.





But it has been observed that compounds of ator (i) undergoes the hydramine fission when heated w HCl to form propiophenone and methyl amine and ator (ii) gives Ph-CH(OH)-CH=CH₂ + CH₃NH₂. And hence ator (i) is more likely the ator. of ephedrine than ator (ii).
The ator (i) is also supported by the format following method. Ephedrine when subjected to Hoffman exhaustive methylation forms 1,2-methyl-phenyl-ethylene oxide. (Ph-CH⁺-CH-CH₃), this can be not be produced

from atom (ii) but is expected from atom (i).



(iii) Further support for atom (i) is given by the following evidences. The atom (ii) contains one chiral carbon and so replacement of the $-\text{OH}$ group by H will result in the formation of an optically inactive compound. But atom (i) contains two chiral centres and so replacement of $-\text{OH}$ group by H should still give a compound which is optically active.

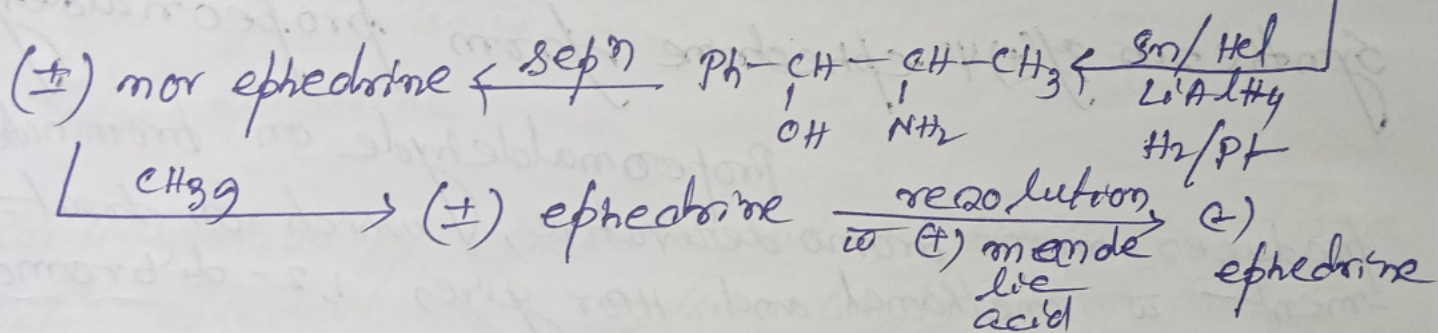
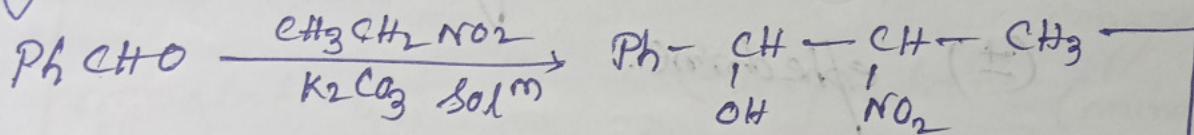
Experimentally it has been found that when this replacement is effected in (-) ephedrine (naturally occurring ephedrine) the product deoxy-ephedrine is optically active. The atom (i) agrees all the known facts. Hence the atom of ephedrine is atom (i) and this atom has been confirmed by the synthesis.

Synthesis of ephedrine:-

(i) From Benzaldehyde:-

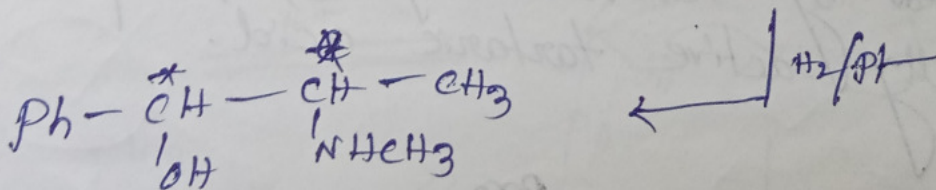
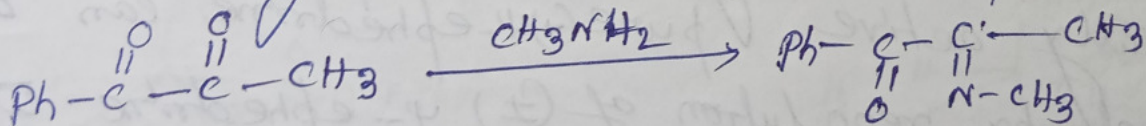
on condensation with nitro-ethane in presence of K_2CO_3 solⁿ produces a diastereomeric mixture of alcohol which on reduction with Sn/HCl

or $\text{LiAlH}_4/\text{H}_2/\text{Pt}$ gives $(\pm)$ nor-ephedrine and $(\pm)$ nor- ψ -ephedrine which are ~~substituted~~ subsequently separated and then $(\pm)$ nor-ephedrine on methylation with CH_3I produces $(\pm)$ ephedrine. This $(\pm)$ ephedrine on resolution by $(+)$ mandelic acid naturally occurring $(-)$ ephedrine can be prepared.



(ii) Synthesis of (-) ephedrine by Marke et al:-

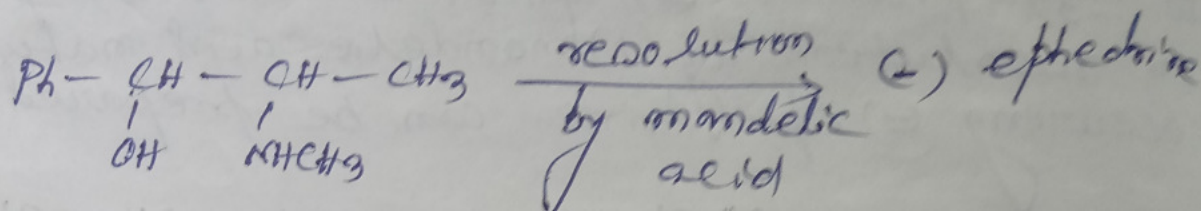
1-phenyl-propane-1,2-dione on treatment with methyl amine followed by hydro-
genated to H_2/Pt or H_2/PtO_2 produces $(\pm)$
ephedrine along to a little of $(\pm)$ ψ ephedrine.



(±) ephedrine (major)

(±) nor epinephrine (minor)

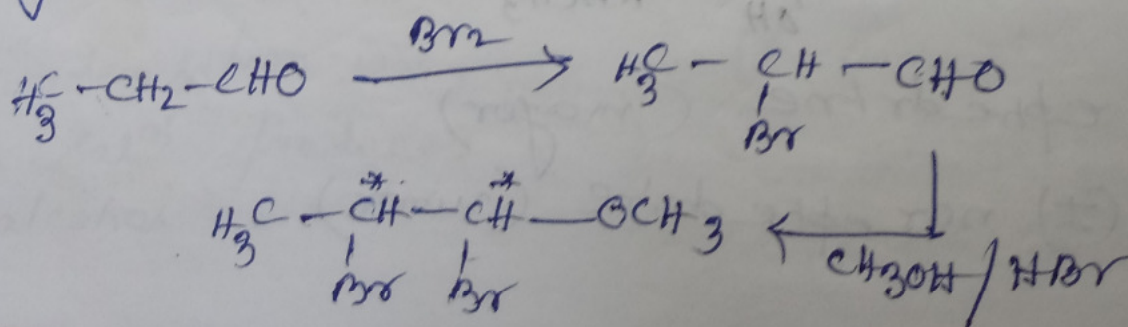
Then $(\pm)$ ephedrine is separated on a pure
 $(-)$ ephedrine can be prepared by resolution
 $(\pm)$ ephedrine w mandelic acid.

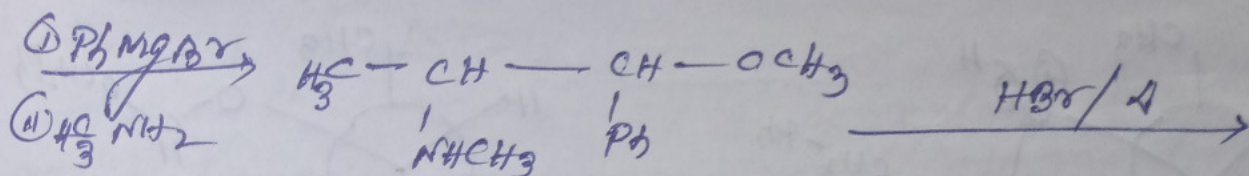


$(\pm)$ ephedrine.

Synthesis of $(+)$ ψ ephedrine from propionaldehyde.

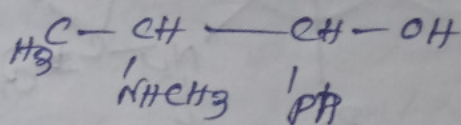
Propionaldehyde on bromination produces mono bromo derivative, which on treatment w methanol and HBr gives 1,2-dibromo-1-methoxy propane, then this on reaction w Ph-NH₂ followed by treatment w CH₃NH₂ gives 1-phenyl-1-methoxy-2-methyl amine which finally on hydrolysis by HBr gives racemic mixture of ψ ephedrine as major product along w $(\pm)$ ephedrine as minor. Then they are separated and optically active pure $(+)$ ψ ephedrine can be obtained by resolution of $(\pm)$ ψ ephedrine w optically active tartaric acid.





(±) ψ -ephedrine

$\xleftarrow{\text{deph}}$



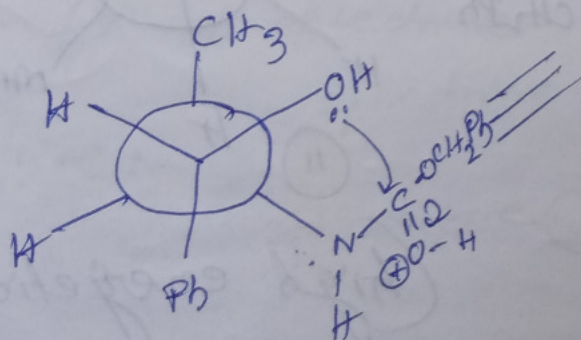
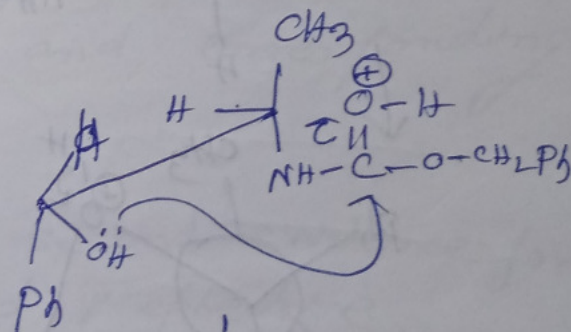
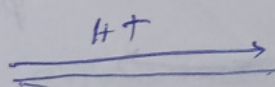
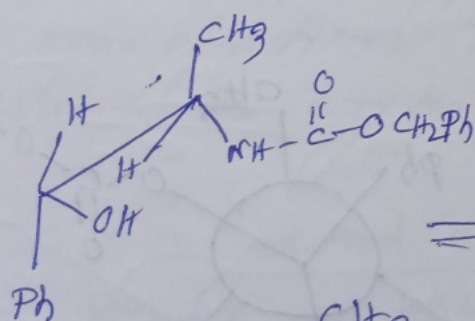
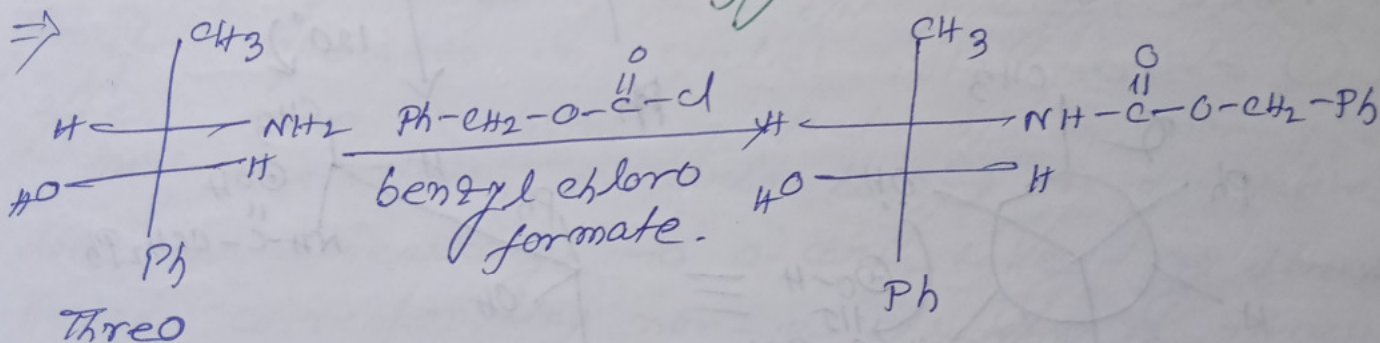
(±) ψ -ephedrine (major)

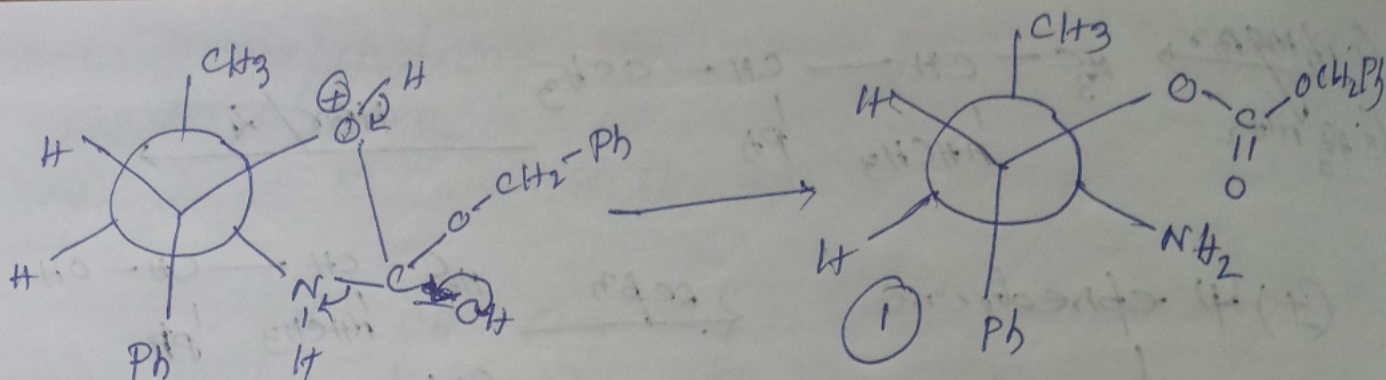
(±) ephedrine (minor)

resolution
by tartaric acid

(+)- ψ -ephedrine

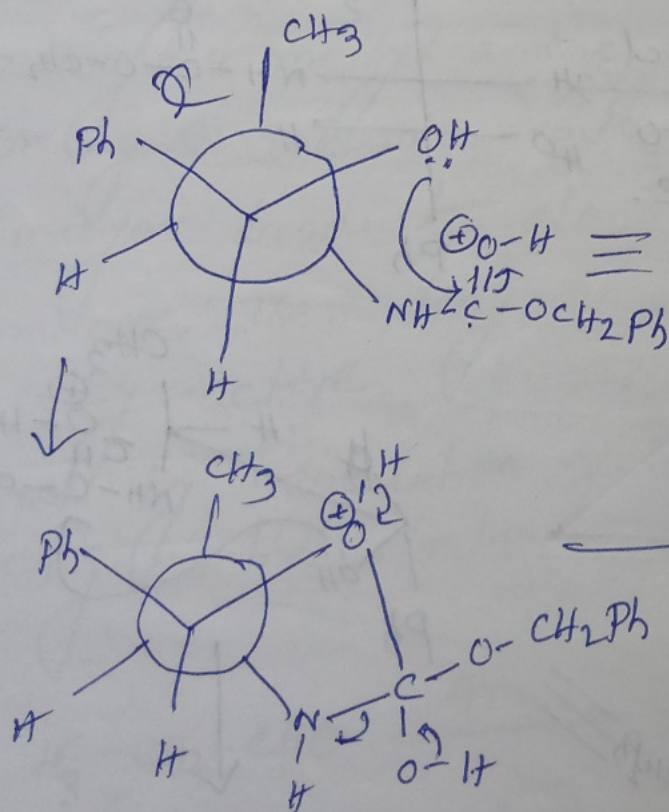
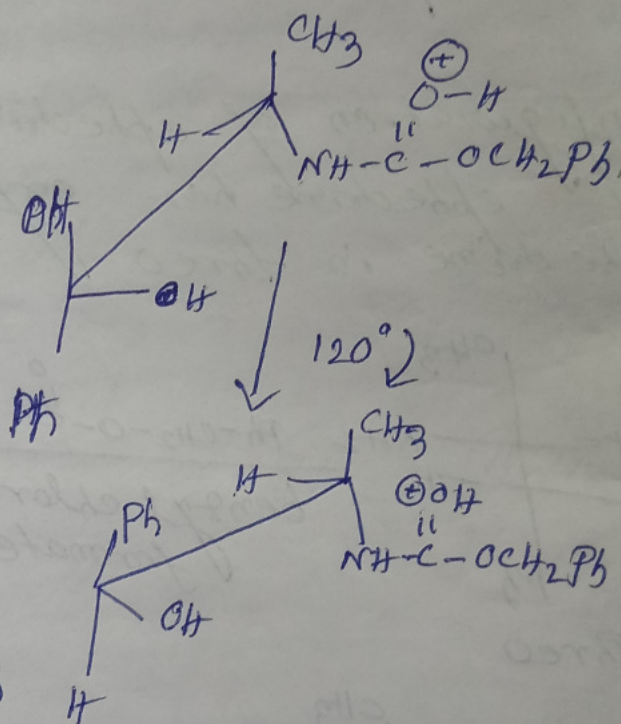
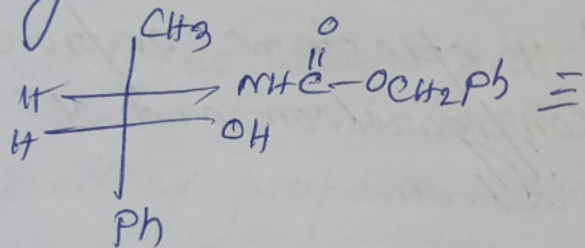
configuration of ephedrine and ψ -ephedrine or prove that ephedrine has erythro configuration and ψ -ephedrine is threo configuration.





(Here -CH₃ and -Ph are at trans to each other and hence of less energy)

Erythro



(high energetic)

observed facts:-

The *N*-carbo-benzylonyl derivative of nor- ψ -ephedrine undergoes very rapid, rearrangement from *N*-carbo-benzylonyl derivative in acid solⁿ but the same derivative of nor-ephedrine does not readily rearrange to *O*-derivative under same condition.

This above fact clearly explains if nor- ψ -ephedrine is *threo* and *confign* which leads to favourable *trans* orientation of phenyl and methyl group in the cyclic intermediate (I) where steric repulsions are minimum.

on the other hand, nor-ephedrine will therefore have *erythro* configuration where the steric repulsion b/w phenyl and methyl groups operates in cyclic intermediate (II). Hence after same condition as that of in nor- ψ -ephedrine derivative, *N*-carbo-benzylonyl derivative does not rearrange to *O*-carbo-benzylonyl derivative. Hence corresponding nor- ψ -ephedrine is *threo* and nor-ephedrine is *erythro* and corresponding ephedrine is *erythro*.

Second evidence:- second evidence for the *confign* of ephedrine and ψ -ephedrine.

ψ -ephedrine:- ψ -ephedrine is weaker base than

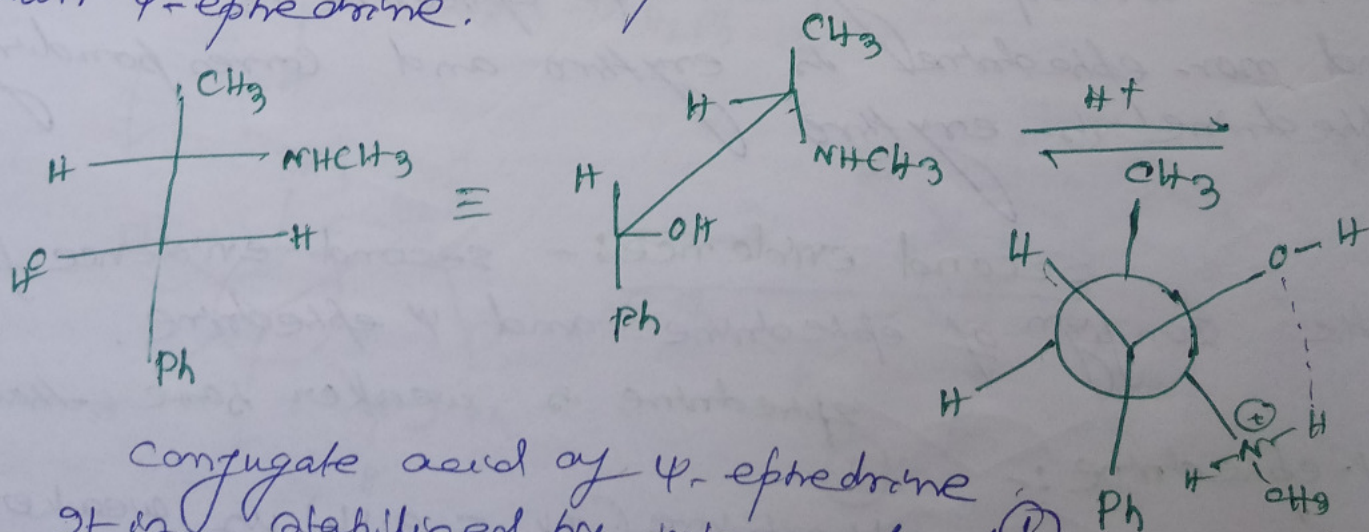
ephedrine ($pK_a = 9.14$) is weaker

base than ψ -ephedrine ($Pka = 9.22$). This can be explained by conformational analysis on the basis of stability of conjugate acid.

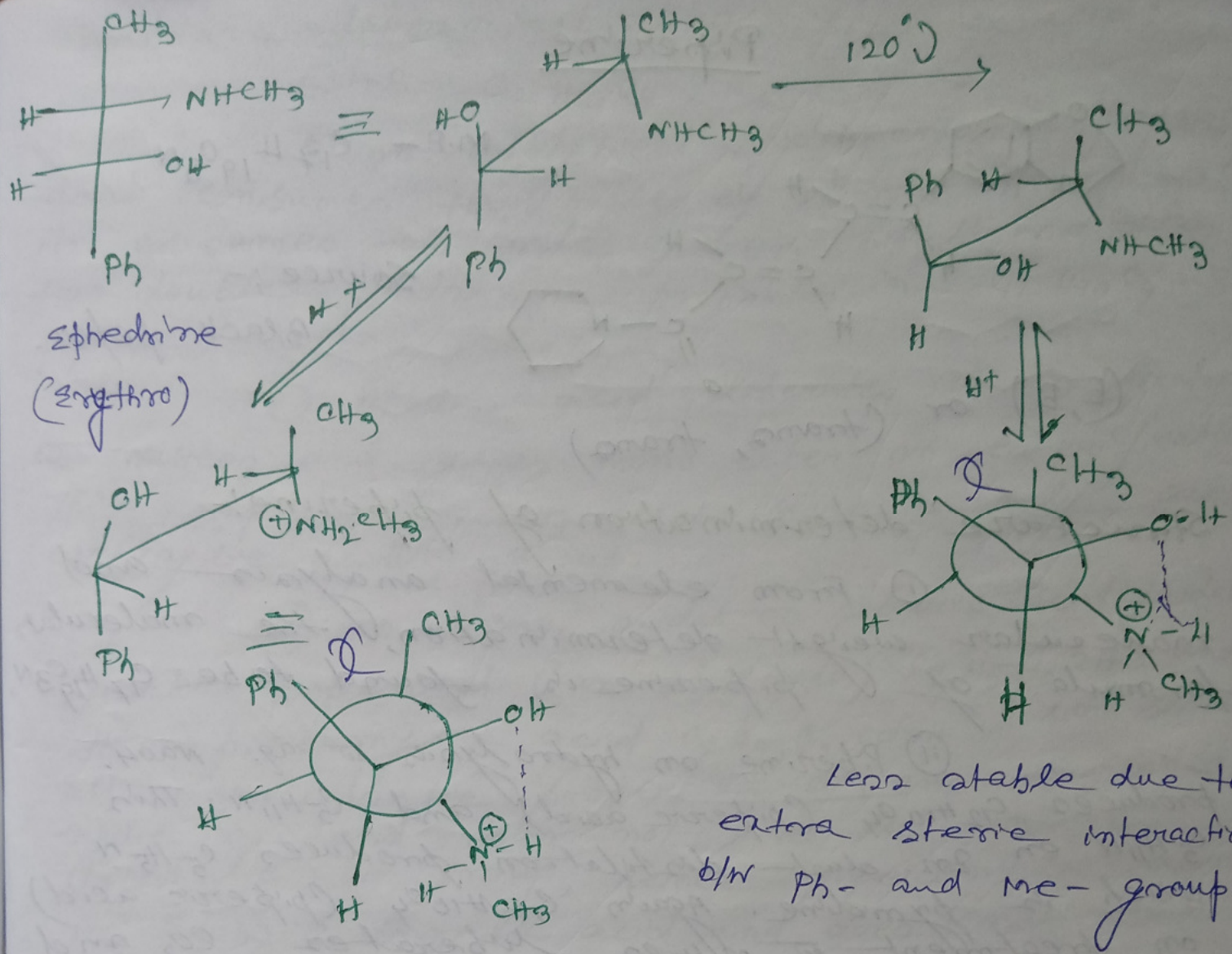
on the conjugate acid of ψ -ephedrine

① intramolecular H-bonding is possible to minimum steric interaction shown in figure ① and hence this conjugate acid is more stable than that of the conjugate acid of ephedrine where $-NH_2^+(CH_3)$ and $-OH$ groups are trans and hence for forming intramolecular H-bonding b/w them requires a conformation where $-Ph$ and $-Me$ groups are gauche interaction shown in figure (II). For these reasons the conjugate acid of ephedrine will experience high steric strain.

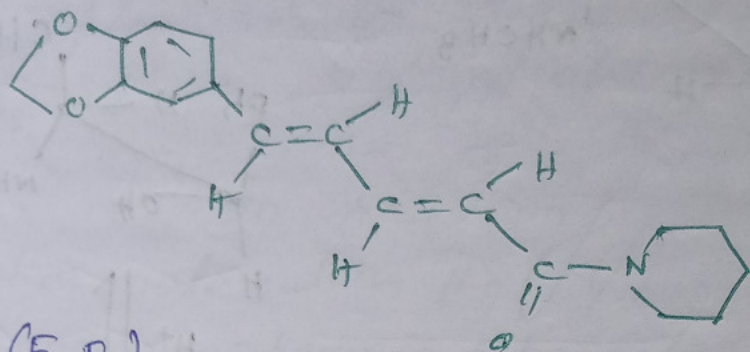
Hence conjugate acid of ψ -ephedrine is more stable than conjugate acid of ephedrine that proves that the ephedrine is weaker base than ψ -ephedrine.



Conjugate acid of ψ -ephedrine
It is stabilized by intramolecular H-bonding to minimum steric strain due to two bulkier group $-Me$ and $-Ph$ are trans to each other.



Piperine



M.P - $C_{17}H_{19}O_3N$

Source :-

Black pepper.

(E, E) or (trans, trans)

Structure determination of piperine:-

(i) From elemental analysis and molecular weight determination, the molecular formula of piperine is found to be $C_{17}H_{19}O_3N$.

(ii) Piperine on hydrolysis w aq. NaOH, produces $C_{12}H_{10}O_4$ (piperic acid) and $C_5H_{11}N$. This $C_5H_{11}N$ on Zn dust distillation produces C_5H_5N which is pyridine. Again $C_{12}H_{10}O_4$ (piperic acid) on treatment w $NaHCO_3$ liberates CO_2 and produces mono alkyl ester on esterification, hence $C_{12}H_{10}O_4$ is a carboxylic acid. As piperine ($C_{17}H_{19}O_3N$) on hydrolysis by alkali gives piperidine, a secondary amine and a carboxylic acid $C_{12}H_{10}O_4$. So piperine is piperidine amide of an organic acid $C_{12}H_{10}O_4$. Again since the str. of piperidine is well known hence by elucidation of the str. of piperic acid, we should determine the str. of piperine.

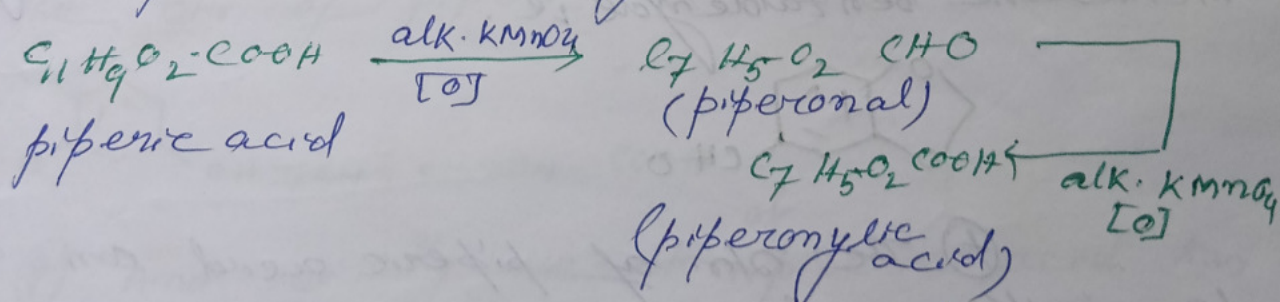
structure determination of piperic acid:-

① M.A. - $C_{12}H_{10}O_4$

② on catalytic hydrogenation piperic acid consumes two moles of H_2 , and on bromination it consumes two moles of Br_2 , which indicates two double bonds are present in $C_{12}H_{10}O_4$ i.e. piperic acid.

③ Piperic acid liberates CO_2 on treatment w/ $NaHCO_3$ and gives mono ester on esterification. This expt suggests that there is only one carboxylic acid group.

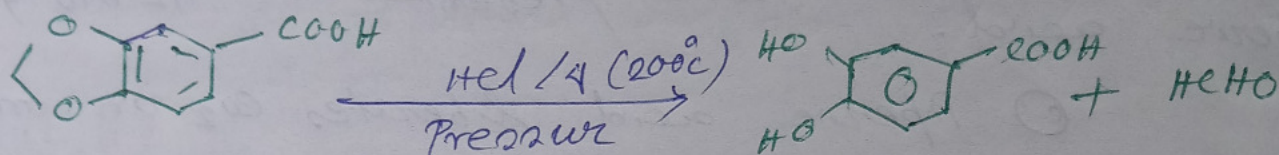
④ on $KMnO_4$ oxidation piperic acid produces first piperonal (an aldehyde) $C_7H_5O_2CHO$ and then piperonylic acid $C_7H_5O_2COOH$ which shows all characteristic properties of a monocarboxylic acid and does not give the test of phenolic -OH group, hence piperonylic acid is monocarboxylic acid and does not contain any free phenolic -OH group.



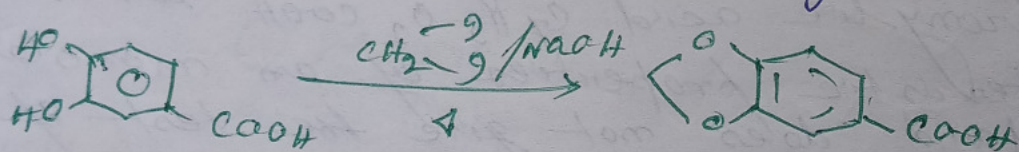
Again piperic acid on oxidation w/ alk. $KMnO_4$ loses a fragment C_4H_4 to form piperonylic acid. Therefore side chain of piperic acid contains five carbon atoms. Thus piperic acid should be written as $C_7H_5O_2-C_4H_4-COOH$.

⑤ Piperonylic acid on heating w/ HCl at $200^\circ C$ temp. under pressure forms 3,4-dihydroxy benzene

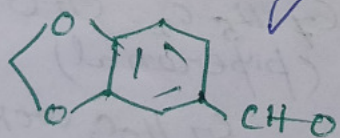
acid (proto-catechuric acid) and formaldehyde again, since piperonylic acid does not contain any free carbo phenolic -OH group, piperonylic acid must be 3,4-dimethylenedioxy benzoic acid i.e. the str. of piperonylic acid.



The str. piperonylic acid has been confirmed by the synthesis of from proto catechuric acid (3,4-dihydroxy benzoic acid) and methylene diiodide in NaOH solution by heating condition.



Since, piperonal on oxidation forms piperonylic acid, hence piperonal should be 3,4-dimethylenedioxy benzaldehyde i.e.

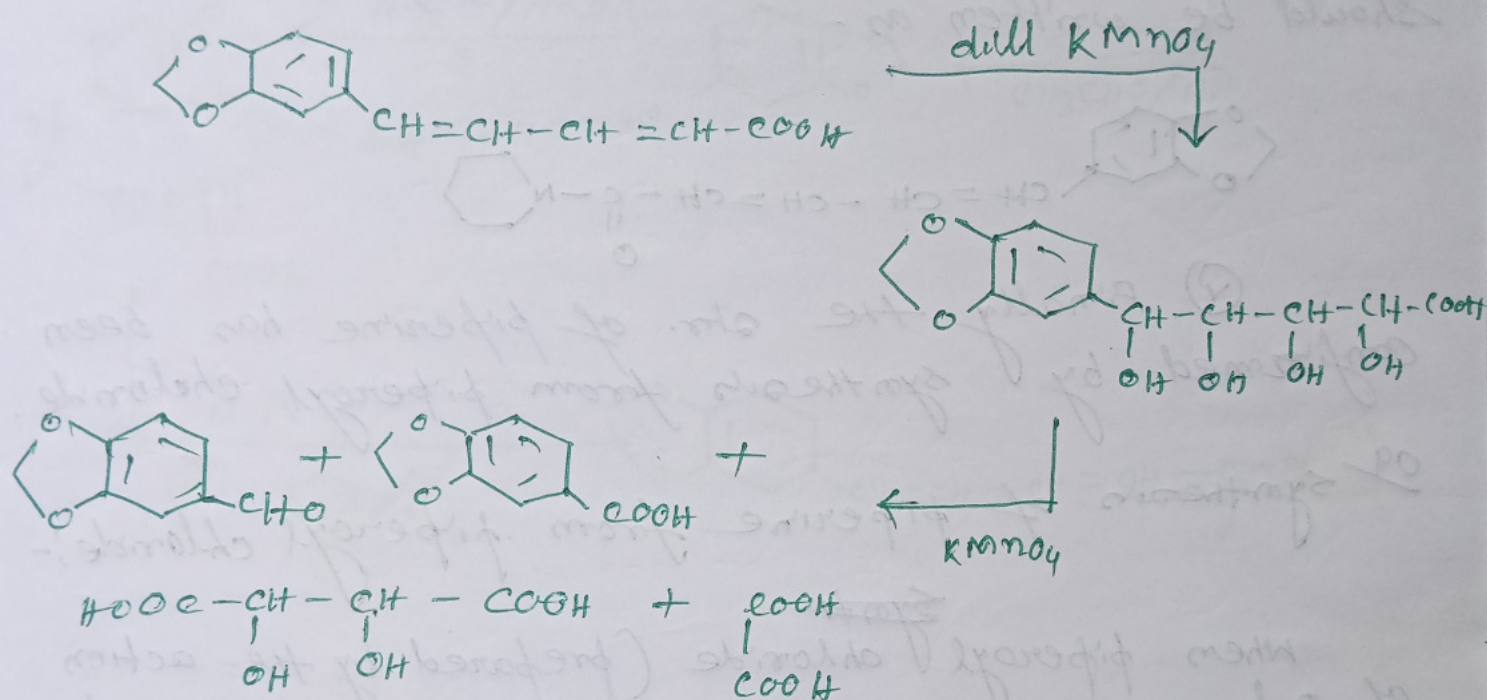


⊕ The str. of piperic acid can now be written as $\text{C}_6\text{H}_4(\text{CH}_2)_2\text{COOH}$ the nature of side chain in piperic acid becomes clear from the following experiment—

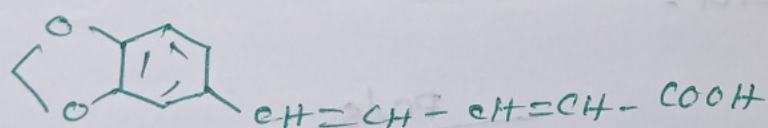
① piperic acid takes up two moles of Br_2 on bromination to give tetrabromide derivative, which indicates the presence of two

double bonds in the side chain.

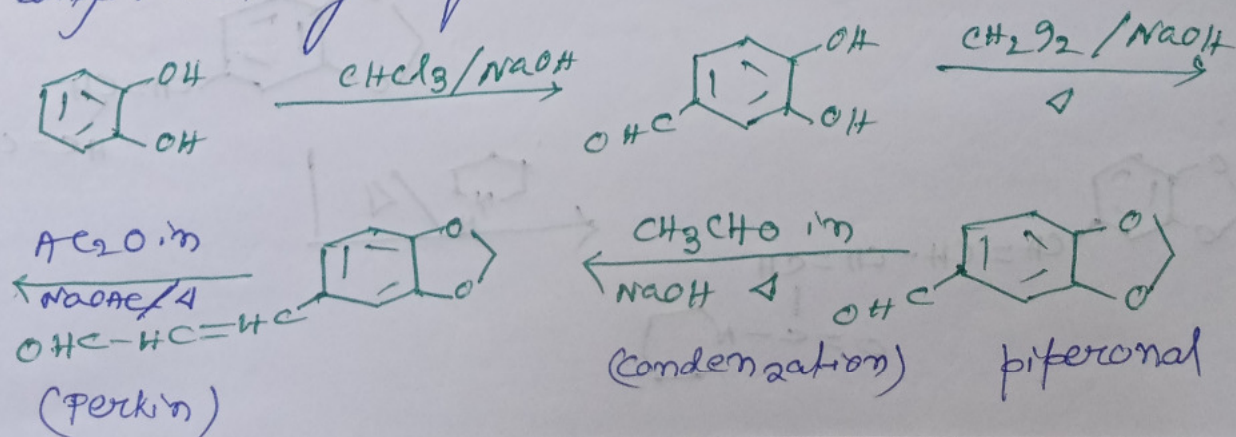
(ii) on careful oxidation with KMnO_4 , piperic acid decomposes to form a molecule of tartaric acid, oxalic acid each in addⁿ to piperonal and piperonylic acid. This expt suggests that two double bonds are located alternate positions. So, the side chain is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{COOH}$.

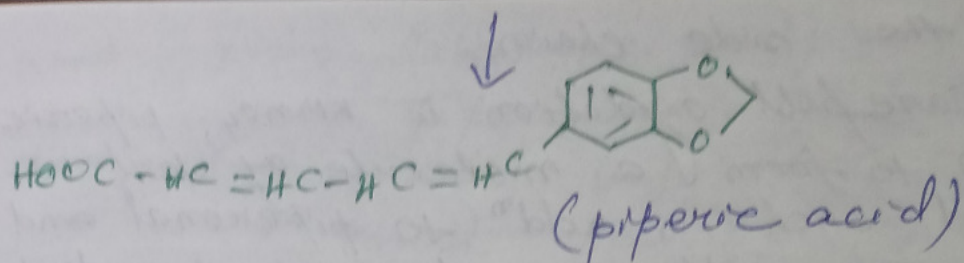


And the str. of piperic acid is,

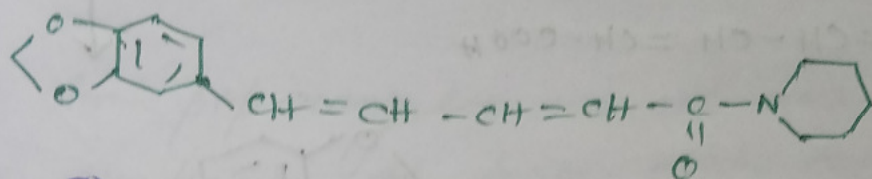


(7) And finally the str. of piperic acid has been confirmed by synthesis from catechol.





(iv) Since, piperine is the piperidine amide of piperone acid hence the str. of piperine should be written as -



(v) Finally the str. of piperine has been confirmed by synthesis from piperoyl chloride

or synthesis of piperine from piperoyl chloride:-

When piperoyl ~~chloride~~ chloride (prepared by the action of PCl_5 on piperone acid) is heated to piperidine piperine is formed. Thus piperine is the piperidine amide of piperone acid.

