Alkaloids

General properties :

1-They are alkali like ,mainly containing nitrogen in the tertiary state in heterocyclic ring

2- They are also called organic bases

3- They are mainly isolated from plant sources

4-All of them are poisonous and can be used in medicine in a very little amount , since they are physiologically active

5-They have a bitter taste

6-Most of them are colorless ,liquids , solids , insoluble in water and soluble in organic solvents such as ethanol and chloroform , but their salts such as hydrochloride and sulphate salts are soluble in water .

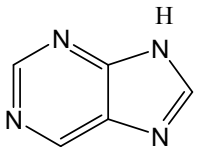
7- Alkaloids can be precipitated from their solutions using some reagents which forming salts with them , these salts are insoluble in water , these reagents such as tannic acid , picric acid , phosphomolybdic acid , phosphtungestic acid and Meyer's reagent .

Classification of alkaloids :

1-True alkaloids :These represent alkaloids containing nitrogen in heterocyclic ring and formed in nature in the plant in the form of salts , also derived from amino acids.

2-Proto alkaloids :These includes simple amino compounds , containing nitrogen not in heterocyclic ring .

3-Pseudo alkaloids :These not derived from amino acids such as steroidal alkaloids and purines.



They are classified according to the nature of the nucleus present in the molecule into :

1-β-phenylethylamine alkaloids 2-Pyrrolidine alkaloids

3-Pyridine alkaloids 4-Pyrrolidine-pyridine alkaloids

5-Piperidine alkaloids 6-Quinoline alkaloids

7-Iso quinoline alkaloids 8-Phenanthrene alkaloids

9-Indole alkaloids

Structure elucidation (confirmation , establishment) for pure alkaloid sample by:

1-Elemental analysis ; 2-Spectroscopic methods ; 3- Chemical reactions

4- Total synthesis of some alkaloids

1-Structure elucidation (confirmation , establishment) by chemical reactions on their function groups.

A-*The functional nature of oxygen in pure alkaloid sample* (specimen) such as -COOR ,-COOH, -OH, -OR , -CHO, RCOR

a-Carboxyl group (-COOH) : Can be detected by $NaHCO_3$ solution and also by estimation using acid -base titration

b-The ester group : Can be hydrolysed by excess NaOH and then back titratration for the excess NaOH

c-Hdroxyl group:The number of the hydroxyl can be estimated by reaction with PhCOCl or Ac_2O.

The aliphatic hydroxyl group give a negative test with $FeCl_3$ but the aromatic hydroxyl group give a color with $FeCl_3$ and their compounds insoluble in water and soluble in NaOH , and reprecipitated by CO_2

d-Alkoxy group : alkaloid $-OCH_3 + HI / 126\ ^0C \rightarrow CH_3I \uparrow$

$CH_3I + AgNO_3$ / ethanol $\rightarrow AgI \downarrow$ can be determined

Alkaloid $-OCH_2O-$ (dioxymetylene) + $HCl / \Delta \rightarrow CH_2O$

formaldehyde can be determined by formal titration

B- The functional nature of nitrogen in a pure alkaloid sample

a-To detect secondary and tertiary nitrogen in alkaloid

alkaloid NH (sec. *N*) reacts with PhCOCl , Ac_2O , MeI and HNO_2 to give -*N*-N=O *N*-nitros derivative

but alkaloid -*N* (tert.) not react with benzoyl chloride , acetic anhydride , MeI or nirous acid but reacts with 30 % H_2O_2 to give –NO (*N*-oxide)

b- *The nature and number of alkyl or methyl groups* attached to nitrogen by this reaction ,

alkaloid + KOH distillation →if $(CH_3)_3N$ trimethyl amine is evolved , means that the nitrogen attached to three methyl groups

if $(CH_3)_2NH$ dimethyl amine is evolved , this means that the nitrogen attached to two methyl groups

if CH_3NH_2 methyl amine is evolved , this means that the nitrogen group attached to one methyl group

if $NH_3$is evolved , this means that the nitrogen existing as amino group ($-NH_2$).

c- *To estimate the alkyl group in the alkaloid*

alkaloid-*N*-R + HI / 126-150^{o}C → RI alkyl iodide (e.g. MeI)

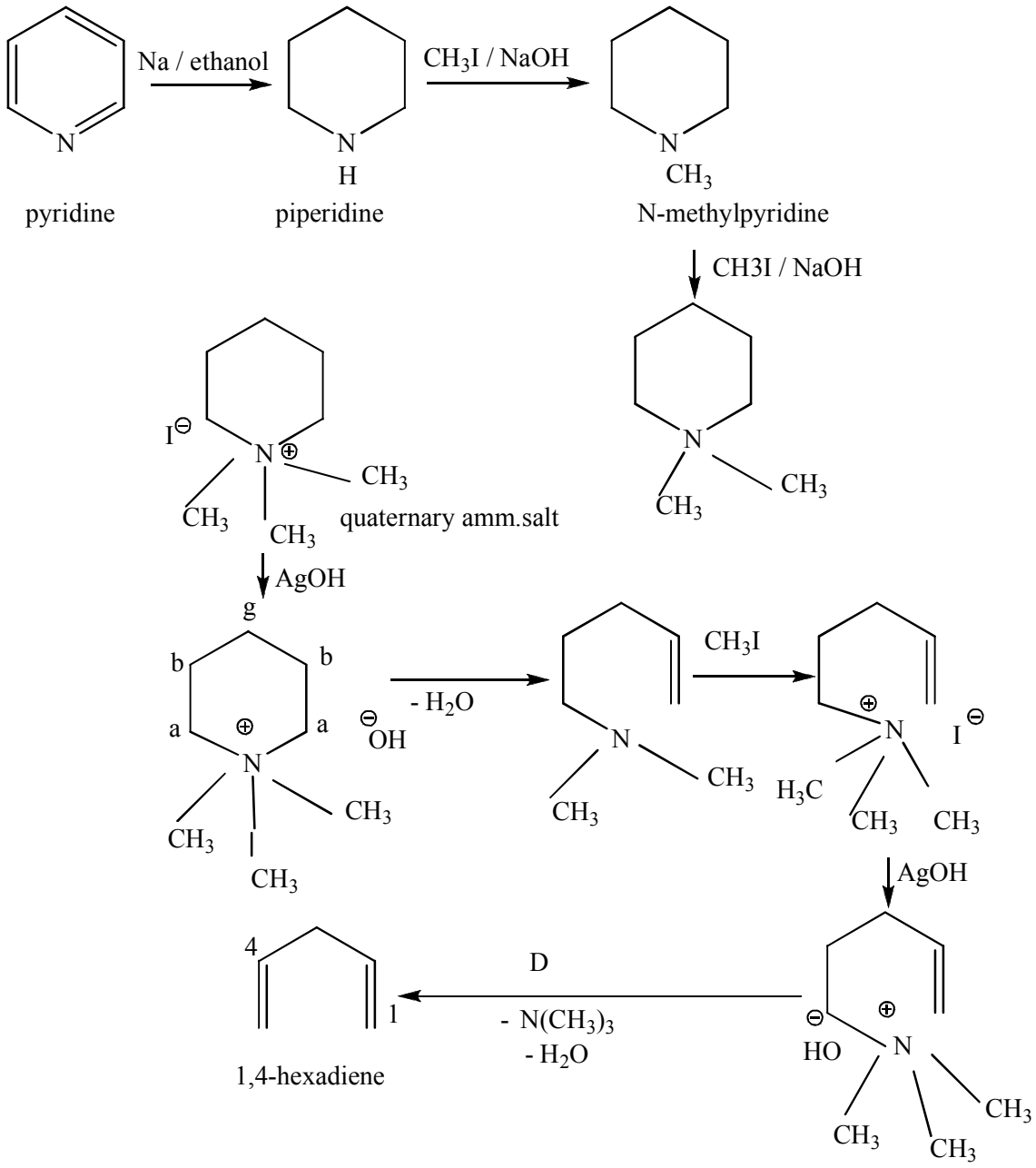
MeI + $AgNO_3$ → AgI ↓can be estimated ,

Each one mole of CH_3I = AgI

C-*For nitrogen in a heterocyclic ring* ;

1-*Hofmann exhausitive reaction* :

This reaction applied on the reduced heterocyclic ring compounds(not unsaturated rings) to determine the the carbon skeleton in it ,Thus , the reduced heterocyclic ring was alkylated till forming quaternary ammonium salt ,followed by AgOH ,then heating the hydroxyl derivative , water is removed , the hydrogen is eliminated from β-position to the nitrogen , and ring opening occurs .



c-*Reductive degradation* :

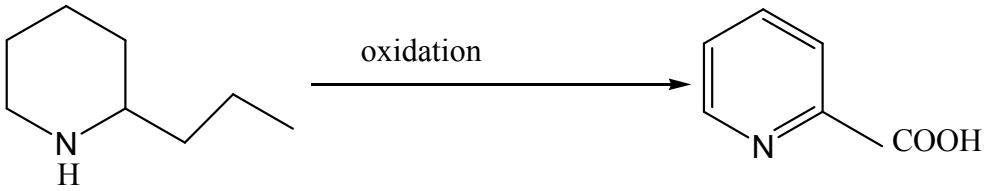
The pyridine ring or piperidine nuclei , in some cases , may be degraded giving ammonia and n-pentane by heating with HI / 300^{o}C

Pyridine or piperidine +HI / 300^{o}C → NH_3 +n-pentane

d-*Oxidation* :

Oxidation frequently gives valuable information about the undamental structure of alkaloids and the position of some of the functional groups or side chain such as C=C , CHOH , --

Example ,



coniine α–picolinic acid

This suggests that the former is α-substituted pyridine derivative .
By varying the strength of the oxidizing agent , a variety of products may be obtained as summarized below:

a-Mild oxidation : Is usually done by H_2O_2 , O_3 , I_2 / ethanol or alkaline ferricyanide

b-Vigrous oxidation : Carried out by $K_2Cr_2O_7$ / H_2SO_4 ,CrO_3/H_2SO_4 ,HNO_3 conc ., MnO_2/H_2SO_4

c-Moderate oxidation : By acid or alkaline $KMnO_4$ or CrO_3 in CH_3CO_2H

A-β-phenylethylamine alkaloids

Adrenaline $C_9H_{13}NO_3$

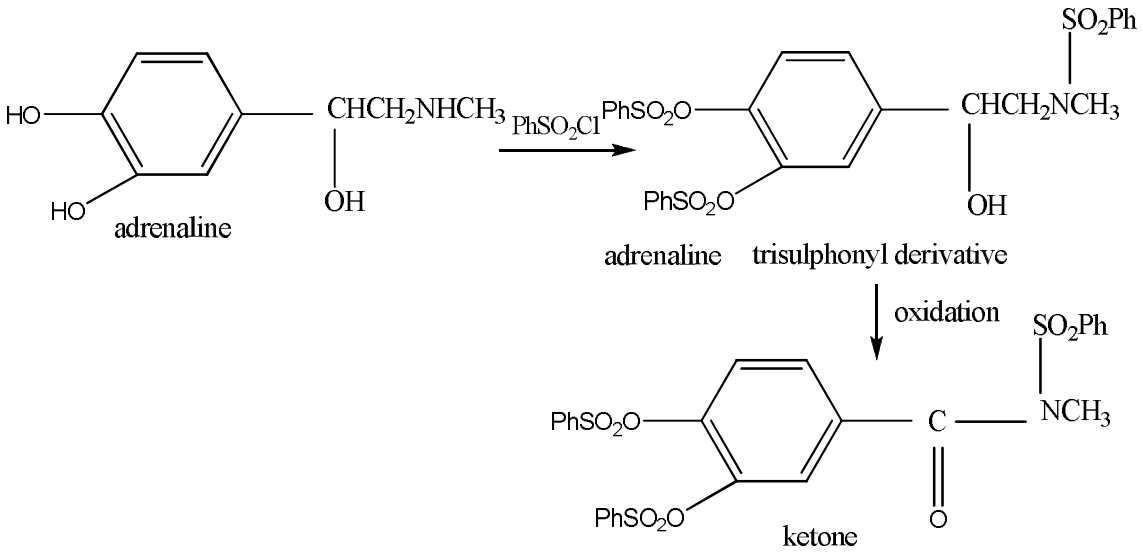
Non-steroid hormone ,the adrenal medulla is the source of the hormone adrenaline and nor-adrenaline

It dissolves in acids and alkalies and insoluble in water

The phenolic character of adrenaline is indicated by its solubility in NaOH and reprecipitated by CO_2

Since it gives a green color with $FeCl_3$, this leads to the suggestion that adrenaline is a catechol derivative (contains two adjacent phenolic hydroxyl groups)

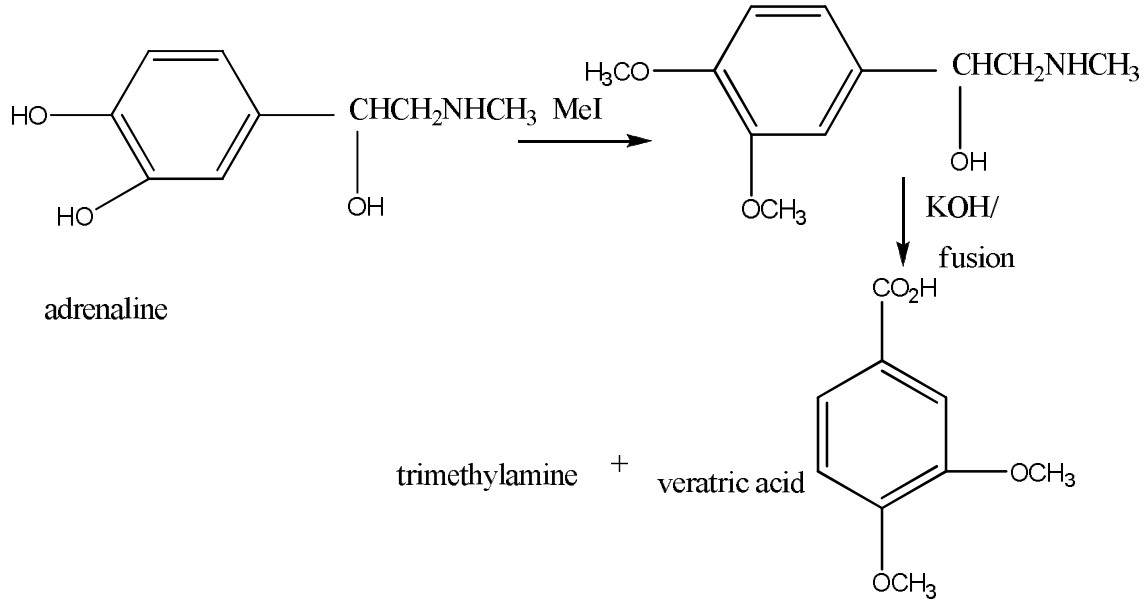
Adrenaline contains three hydroxyl groups , two of which are phenolic . The third hydroxyl group was shown to be secondary alcoholic by the fact that when adrenaline is treated with benzenesulphonyl chloride , a trisulphonyl derivative is obtained , which on oxidation give a ketone



Also,when adrenaline boiled with aqueous KOH , adrenaline evolves methylamine , thus, a methylamino group is probably present

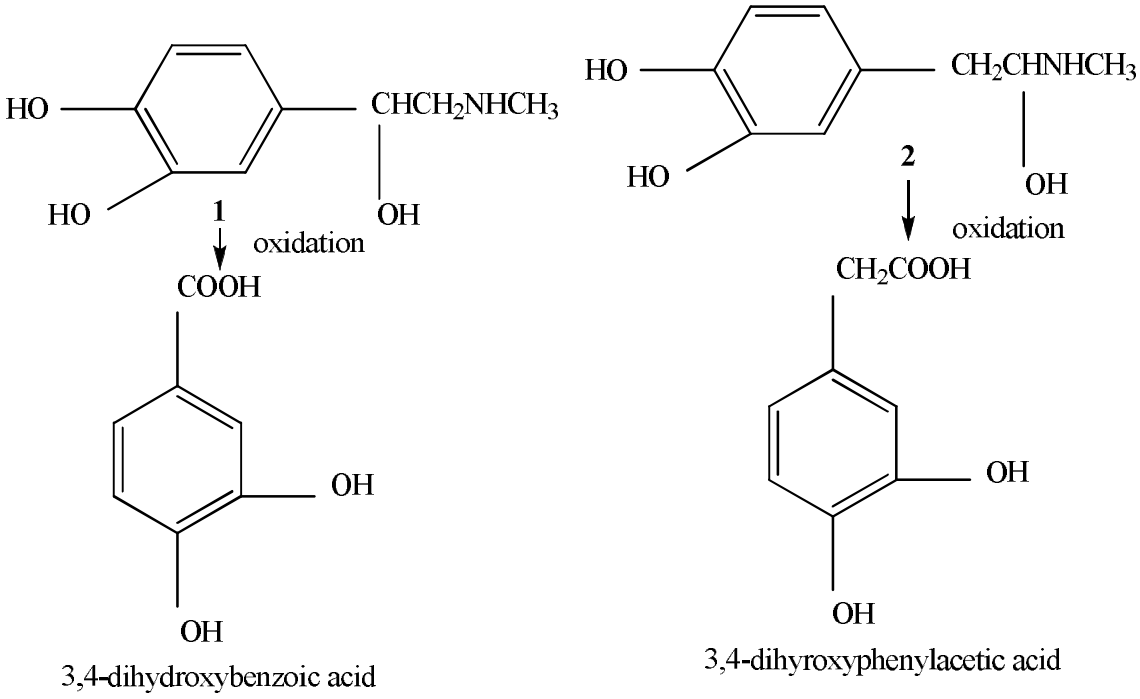
Adrenaline + KOH / boil → methyl amine

On the other hand , when adrenaline methylated and then fused with KOH , the product is veratric acid and trimethyl amine .



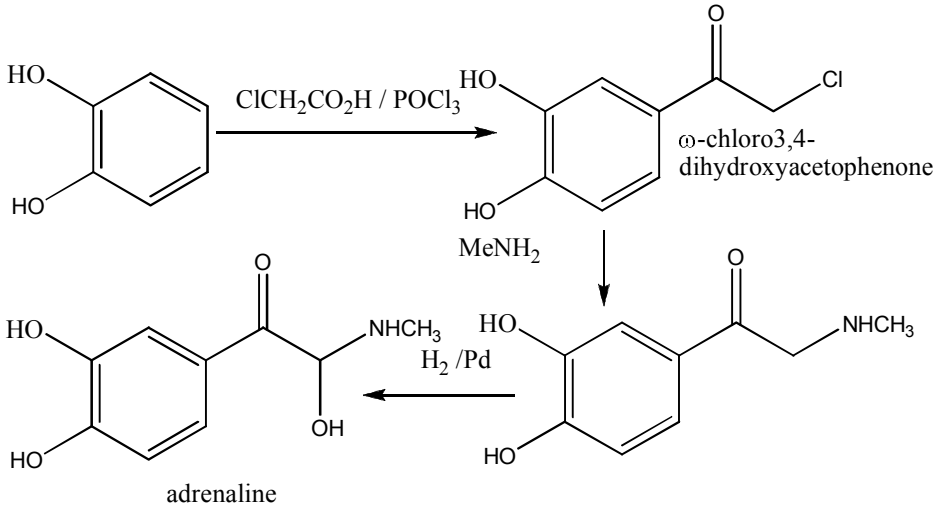
Formation of trimethylamine indicates that the nitrogen must occur at the end of the side chain .

To account for the oxidation of adrenaline to the benzoic acid derivative , the -CHOH group must be attached directly to the nucleus , had it been – CHOH , then a phenylacetic acid derivative would have been obtained .



Thus , structure 1 was confirmed for adrenaline

Confirmation of structure by synthesis ,



B-**Pyrrolidine-pyridine group**

a-Tobacco alkaloids :

Many alkaloids hve been isolated from the tobacco leaf e.g. nicotine ,nicotinimine (anabasine) ,nornicotine …….etc.

b-Coca alkaloids :

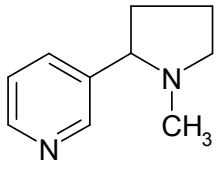
In this group occur cocaine , benzoylecgonine , tropacovaine , hygrine ,cuscohygrine ……etc.

c-Solanaceous alkaloids :

This group include atropine , hyoscymine , and scopolamine (hyoscine) .

a-Tobacco alkaloids :

Nicotine $C_{10}H_{14}N_2$

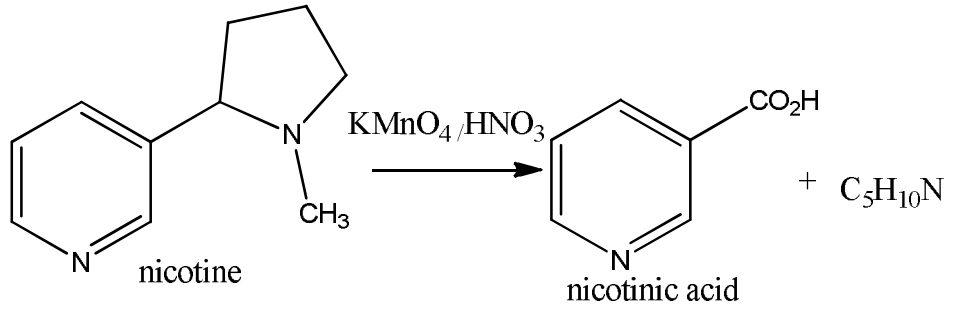


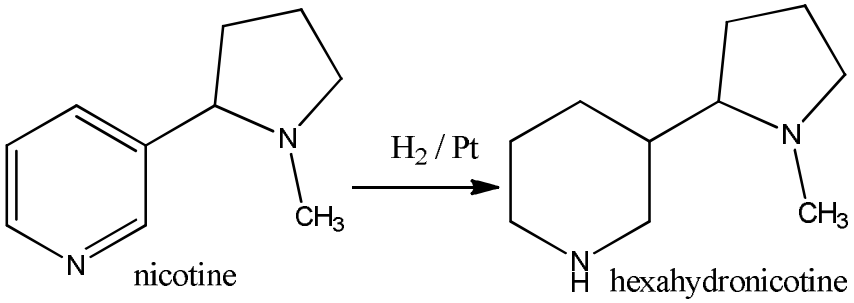
nicotine

The basic source of it is the tobacco leaves , this compound can be used as insecticide and fungicide.

When oxidized with an oxidizing agent , such as CrO_3/H_2SO_4, $KMnO_4$ / HNO_3 , $K_2Cr_2O_7/H_2SO_4$,nicotinic acid is formed ,

The alkaloid therefore , contains a pyridine nucleus with a complex side chain in the 3-position .



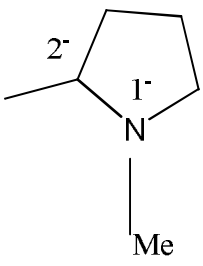


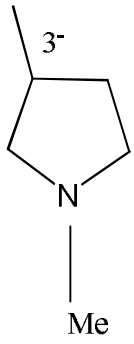
This means that nicotine contains three double bonds ,and the side chain is saturated .

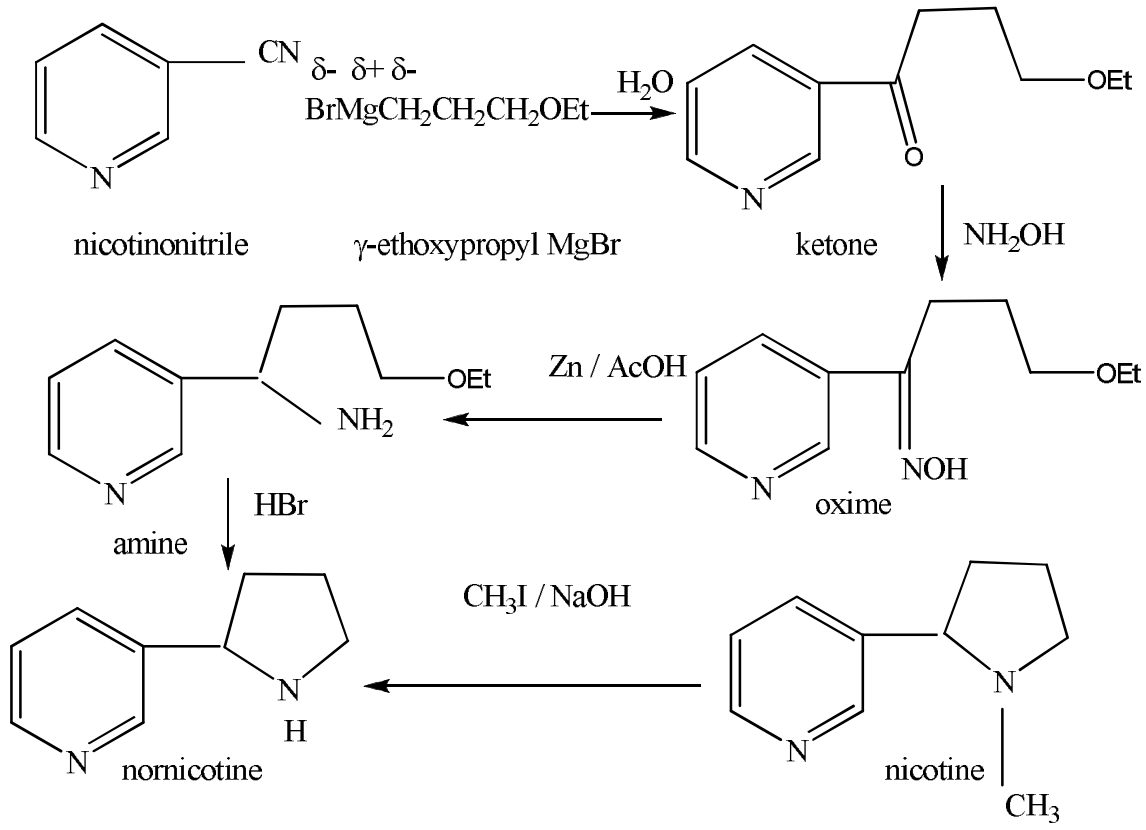
Nicotine + $ZnCl_2$ / distillation → pyridine + pyrrole + CH_3NH_2

Also, nicotine + conc. HI / 159^0C → CH_3I + other products

Therefore , the side chain of nicotine is n-methylpyrrolidine , its point of attachment to the pyridine nucleus could be either on 2^- or 3^- , this evidence based on synthesis of nicotine using one of the following methods ,






CN
δ- δ+ δ-
BrMgCH2CH2CH2OEt
H2O
OEt
O
N
nicotinonitrile
γ-ethoxypropyl MgBr
ketone
NH2OH
OEt
NH2
Zn / AcOH
OEt
NOH
N
oxime
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amine
CH3I / NaOH
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H
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nornicotine
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N
nicotine
CH3