DEPTH OF BIOLOGY

STUDY MATERIAL

YT-DEPTH OF BIOLOGY

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UNIT - IV

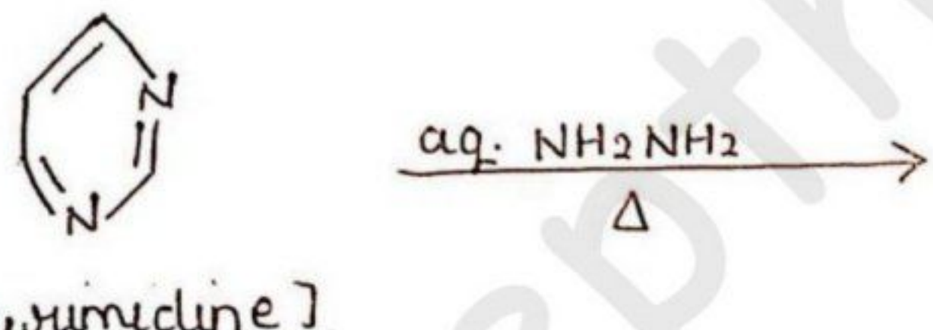
* Pyrazole

- **Structure :-**

[DEPTH OF BIOLOGY]

- **Synthesis :-**

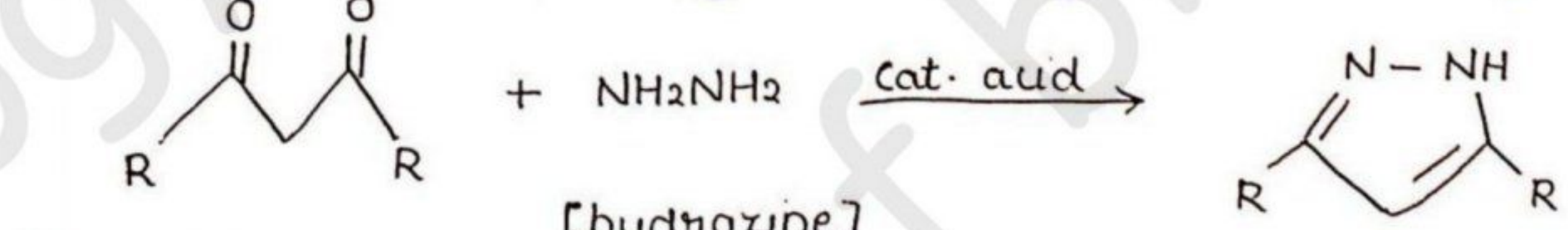
ⓘ **From pyrimidine :-** Pyrimidine react with hot hydrazine solution to give pyrazole.



[pyrimidine] → (aq. NH_2NH_2, Δ) → [Pyrazole]

[DEPTH OF BIOLOGY]

ⓘⓘ **Knorr pyrazole synthesis :-** In this reaction, hydrazine and 1,3 - dicarbonyl compound are converted into a pyrazole using an acid catalyst.



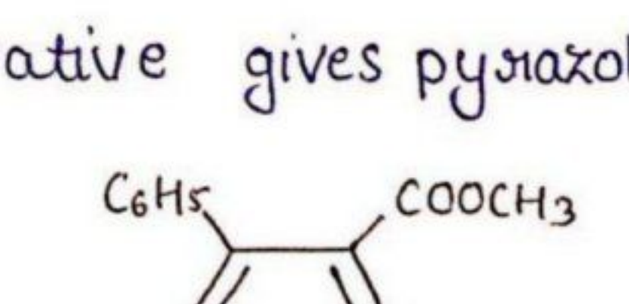
[1,3-dicarbonyl compound] + NH_2NH_2 [hydrazine] → (Cat. acid) → [pyrazole]

(iii) From Nitrile imines :- Pyrazole is produced by the dipolar cycloaddition between alkynes with nitrile amines.

(iv) From diazo Compound :- Diazo compounds adds to an acetylenic derivative gives pyrazole.

[3,5-dicarbomethoxy-4-Phenylpyrazole]

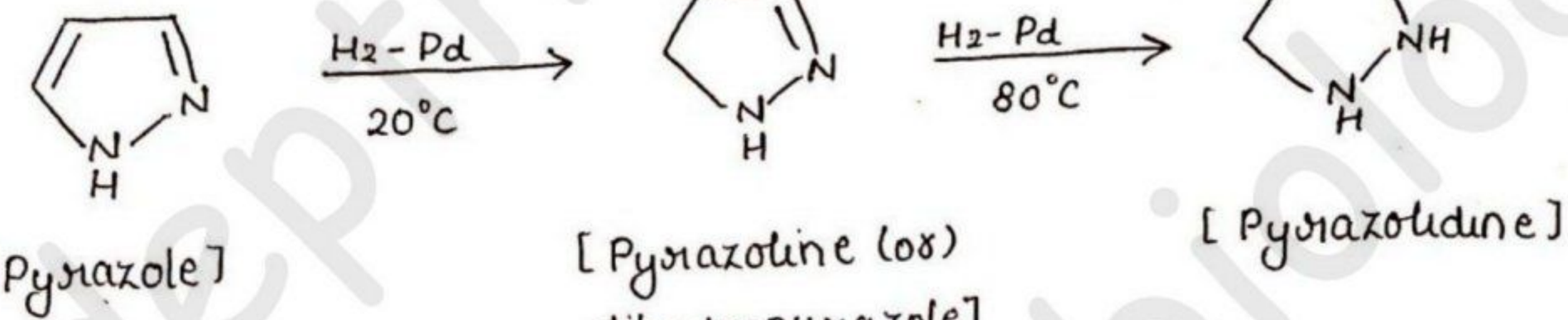
+



[4,5-dicarbomethoxy-3-phenylpyrazole]

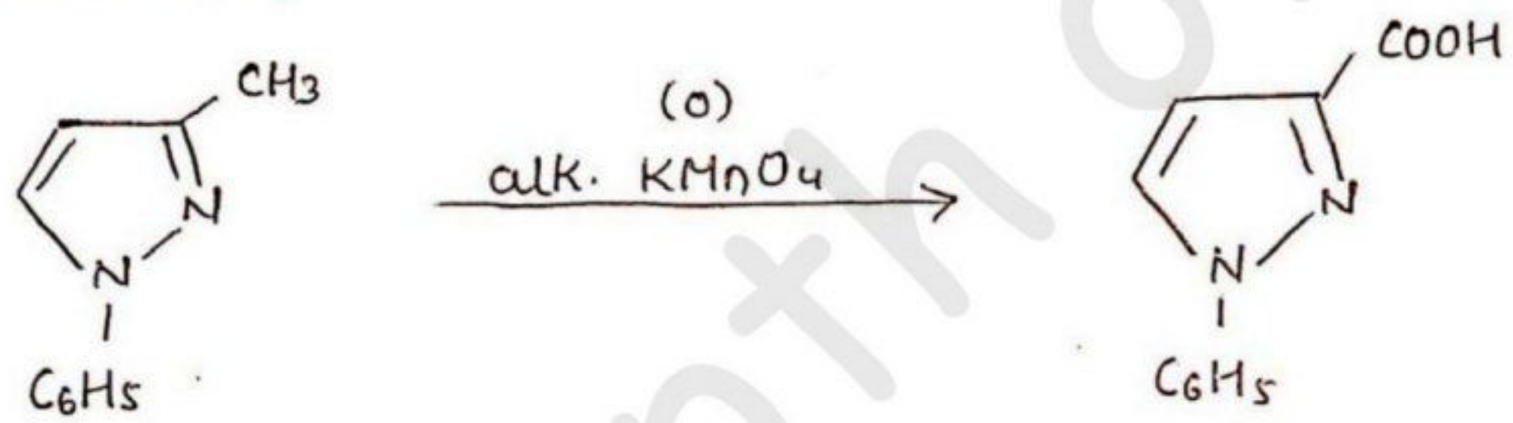
- **Reaction of Pyrazole :-**

① **Catalytic Reduction :-**



[Pyrazole] → [Pyrazoline (or) dihydropyrazole] → [Pyrazolidine]

② **Oxidation :-**

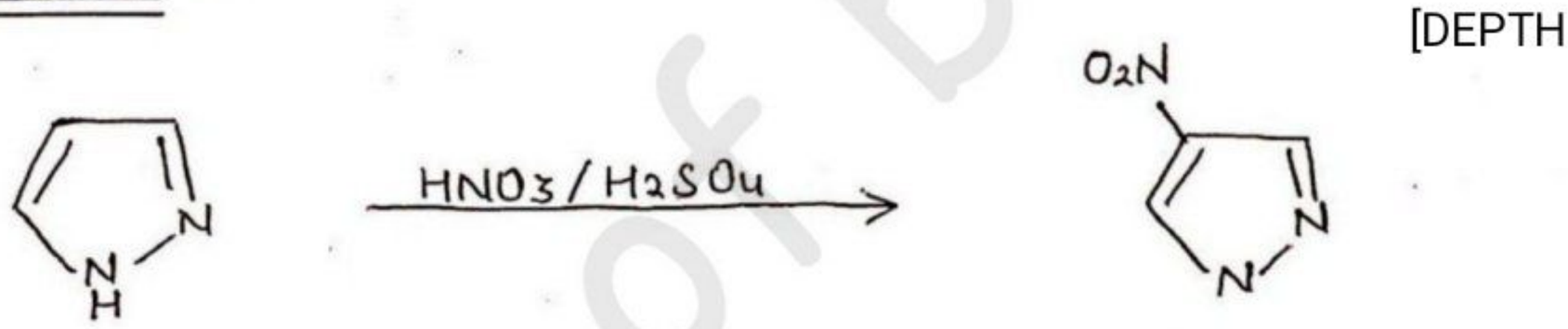


[3-methyl-1-Phenyl Pyrazole] → [1-Phenyl Pyrazole-3-Carboxylic acid]

③ **Electrophilic Substitution Reactions :-**

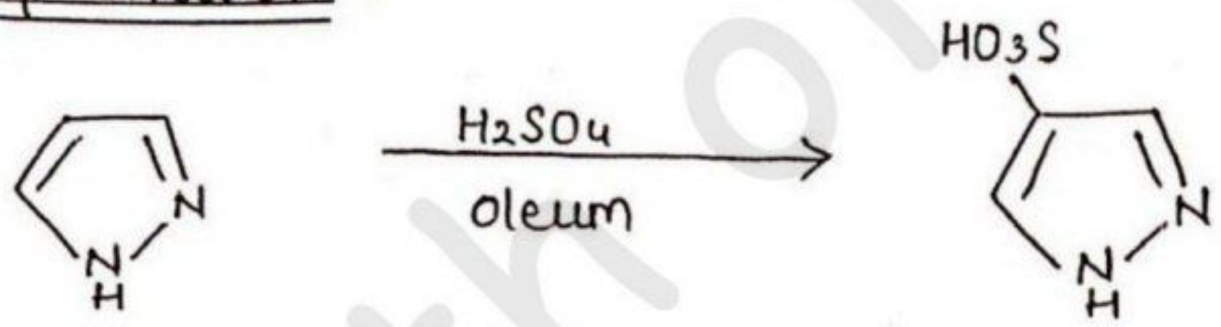
– Substitution takes place at 4th Position

ⓘ **Nitration :-**



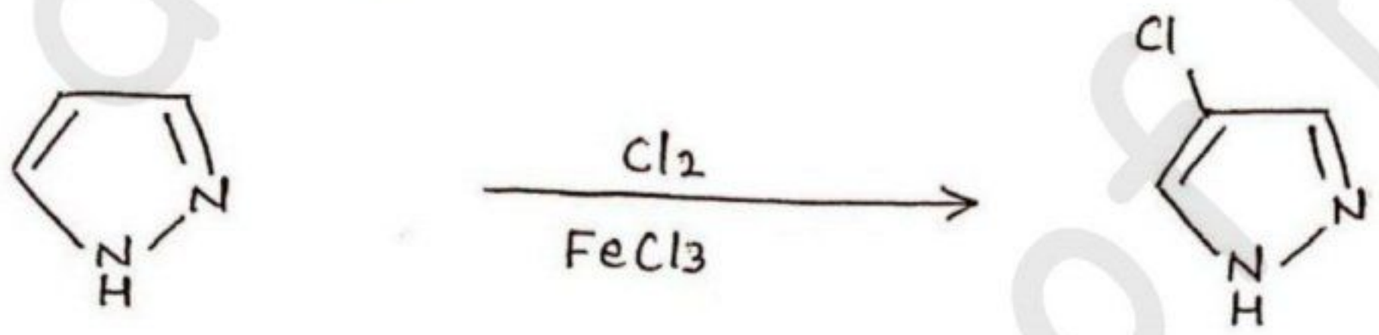
[Pyrazole] → [4-Nitro pyrazole]

(ii) Sulphonation :-



[Pyrazole] → [Pyrazole - 4- Sulphonic acid]

(iii) Halogenation :-



[Pyrazole] → [DEPTH OF BIOLOGY]

Medicinal Uses :-

- Many pyrazole compounds are used as dyes and medicines.
- Antipyrine is used as antipyretic, analgesics.
- Tetrazine is used as a yellow dye for food.
- Phenylbutazole is used as anti-inflammatory drug.
- Betazole is a H2 receptor agonist and is used clinically to test gastric secretory function.
- Ionazobic is a non-steroidal anti-inflammatory drug.

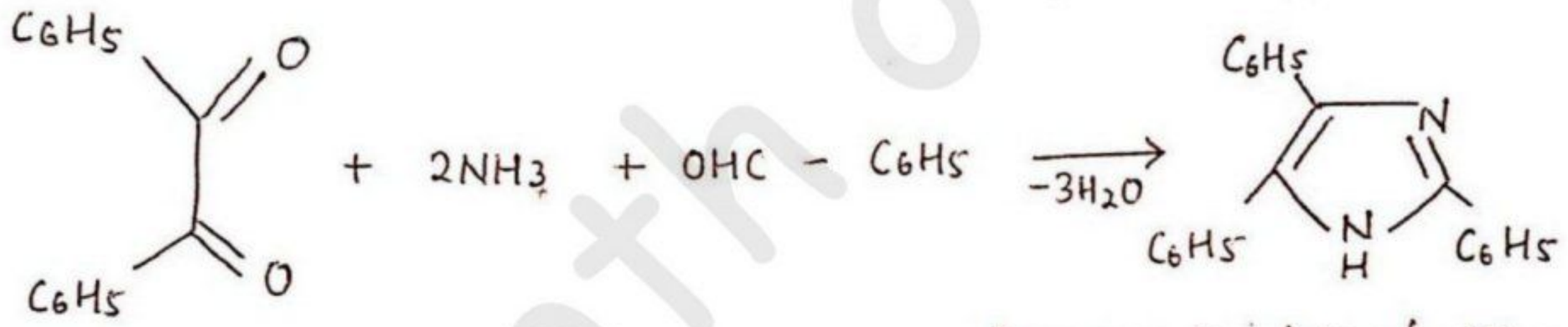
* Imidazole :-

- **Structure :-**

- **Synthesis :-**

① Radiszewski synthesis (from dicarbonyl compounds)

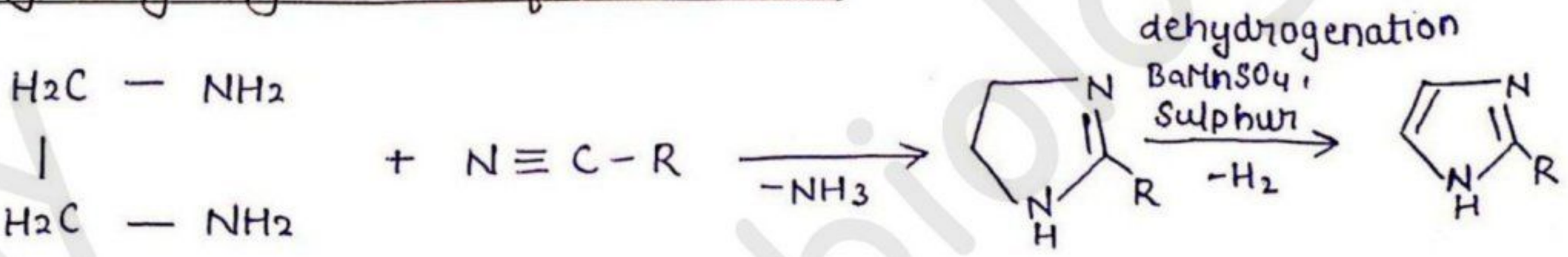
In this synthesis , dicarbonyl compounds are condensed with aldehyde in presence of ammonia.



[Benzil (dicarbonyl Compound)]

[2,4,5- triphenyl(- 1H - imidazole]

② By dehydrogenation of imidazoline :-

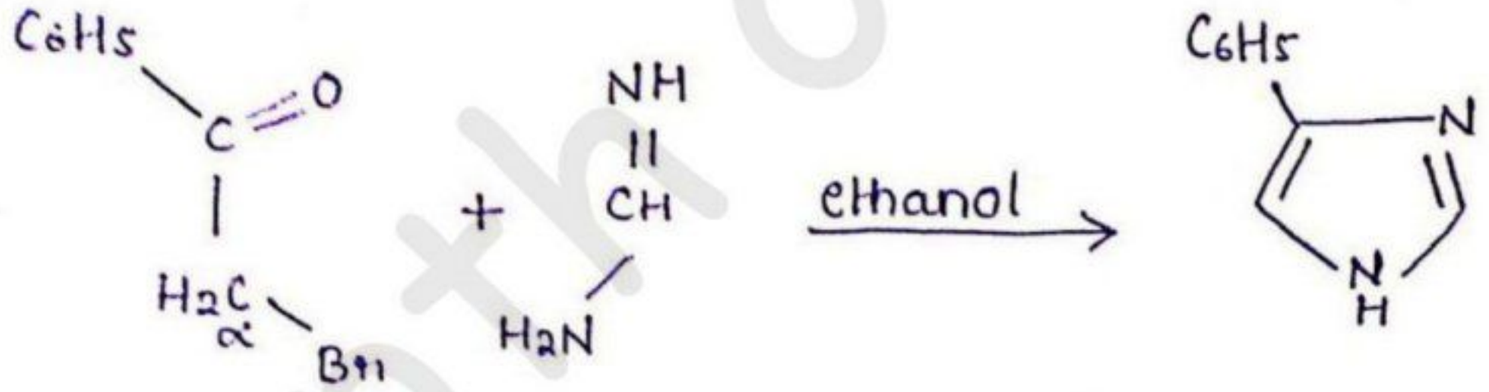


[ethylenediamine]

[2- alkyl -2 imidazoline]

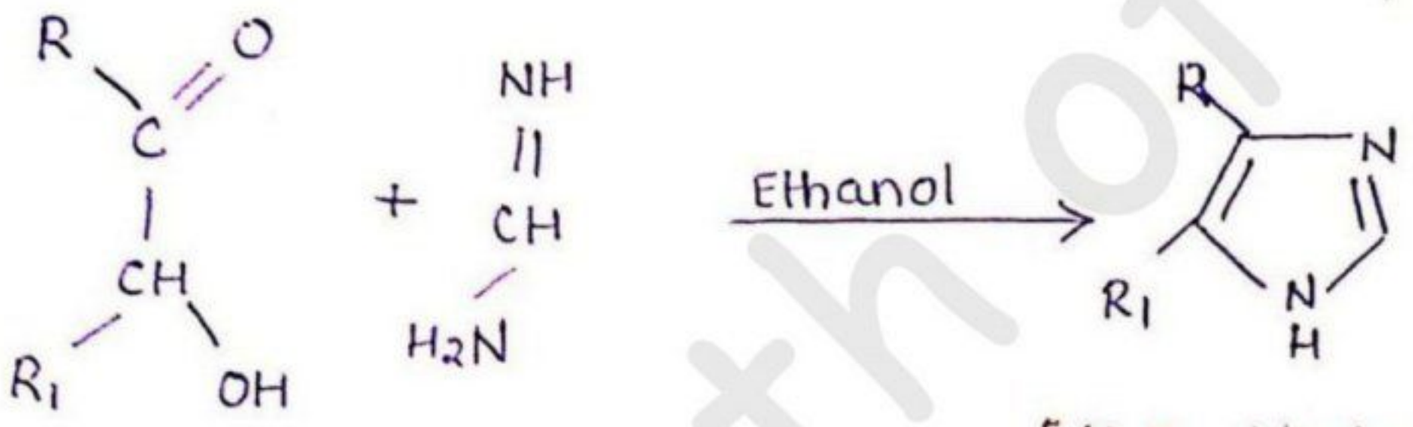
[2- alkyl imidazole]

③ From Reaction of α-haloketones and amidines



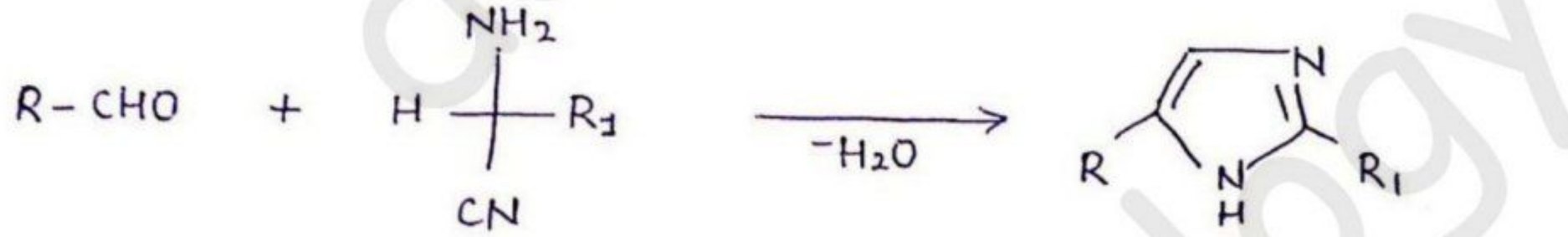
[4-phenyl-1H-imidazole]

④ From Reaction of acyloins (α-hydroxy ketones) and amidines :-



[4,5-disubstituted imidazole]

⑤ From condensation of aldehyde and aminonitrile :-

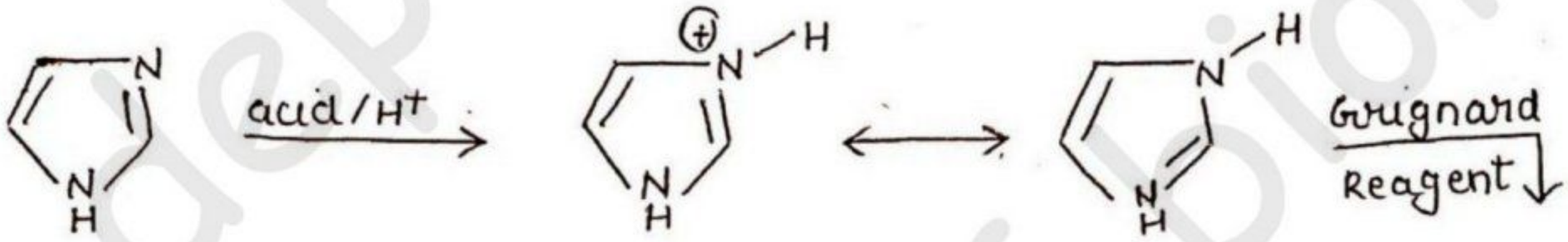


* Reaction of Imidazole :-

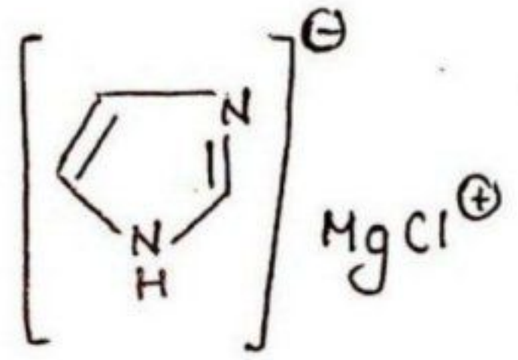
① Reaction with KOH gives potassium salt :-

② Reaction with acids (Protonation) :-

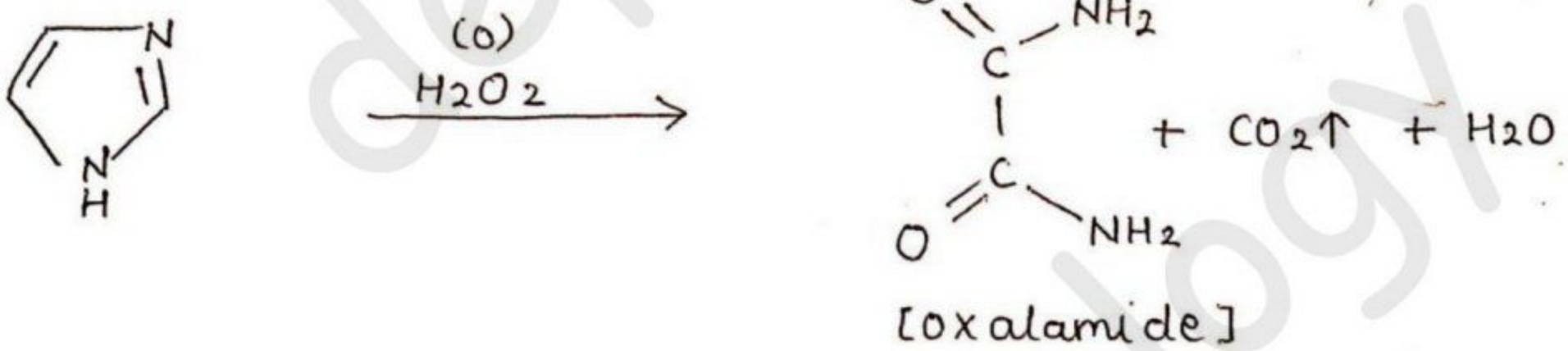
· Imidazole on reaction with acid gives imidazolium cation followed by the reaction of grignard reagent from metal ions.



[Imidazolium cation]



③ Oxidation :- Oxidation of imidazole in presence of H_2O_2 leads to ring opening.



[oxalamide]

④ Electrophilic Substitution Reaction

· Substitution takes place at 4th Position.

· If 4th Position is blocked by any substituents, substituents takes place at 5th Position.

⑤ Nitration :-

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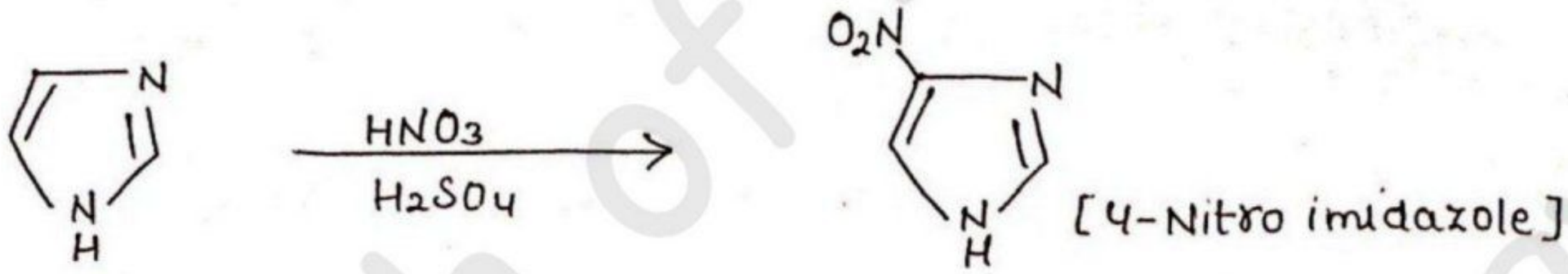
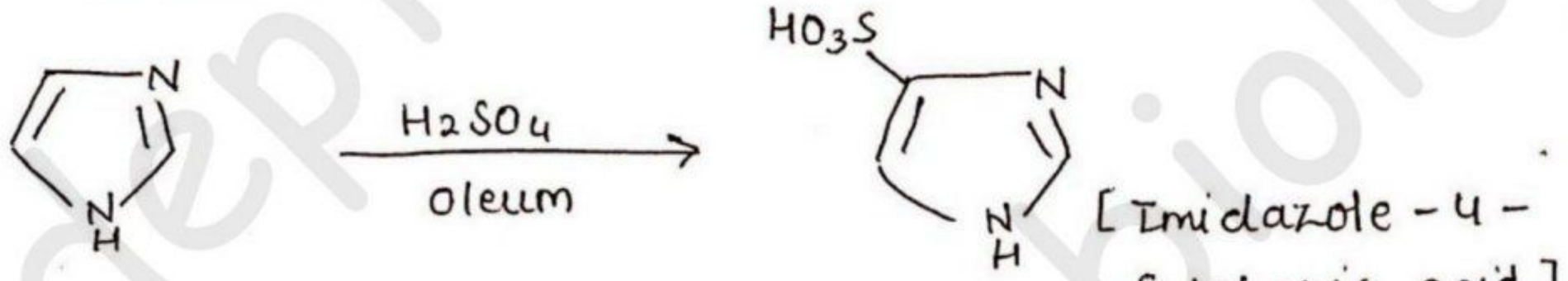
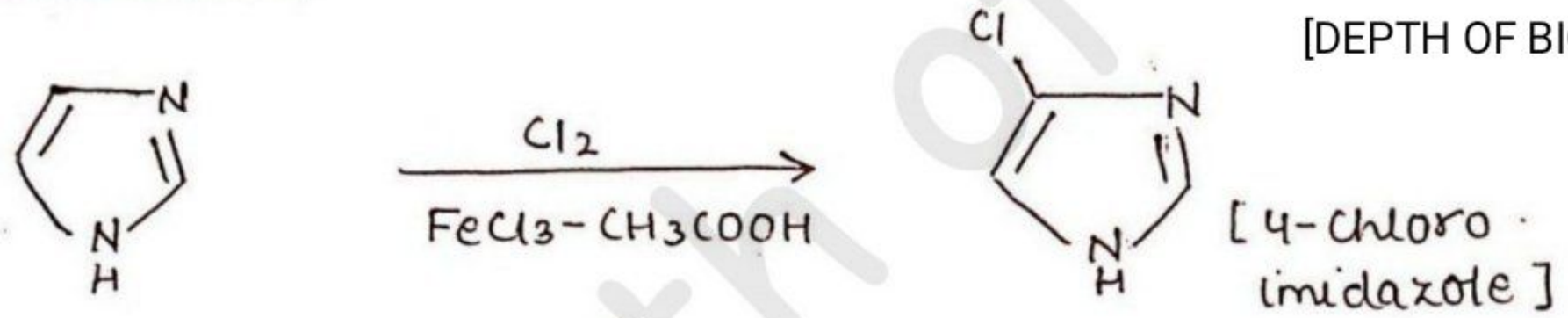


(ii) Sulphonation :-



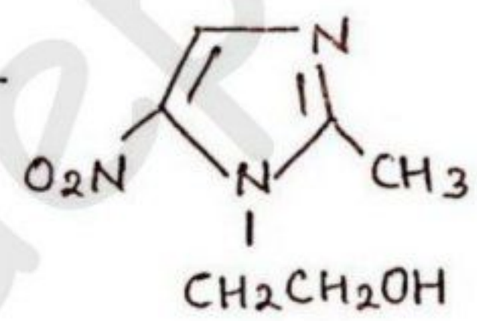
(iii) Chlorination :-

[DEPTH OF BIOLOGY]



* Medicinal Uses :-

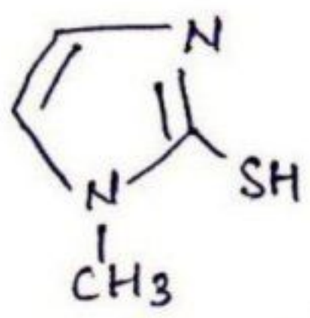
- Metronidazole -



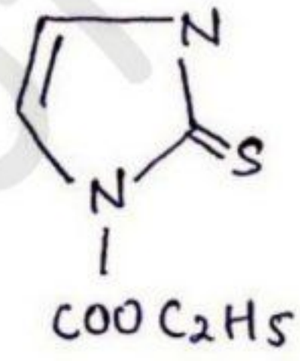
↓

It is an anti-amoebic agent used for the the treatment of amoebic dysentry.

- Methimazole and carbimazole are used as anti-thyroid drug to control hyperthyrodism.



[Methimazole]



[Carbimazole]

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- Other drug having imidazole moiety (or) its derivative are :-

ⓐ Pilocarpine → Parasympathomimetic agent used to reduce intraocular pressure in the treatment of glaucoma.

ⓑ Miconazole , Ketconazole → Antifungal drugs used to treat fungal infections.

ⓒ Albendazole , Mebendazole → Antihelmintic drug used for the treatment of helminthiasis.

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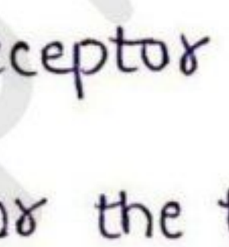
ⓓ Cimeticline → H_2 receptor antagonist - antiulcer drug for the treatment of gastric and duodenal ulcers.

* <u>Oxazole</u> :-

- <u>Structure</u> :-

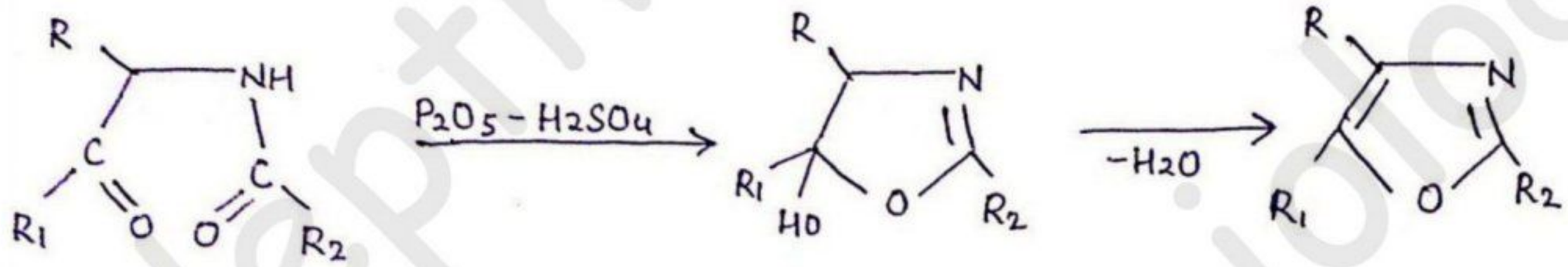


[DEPTH OF BIOLOGY]

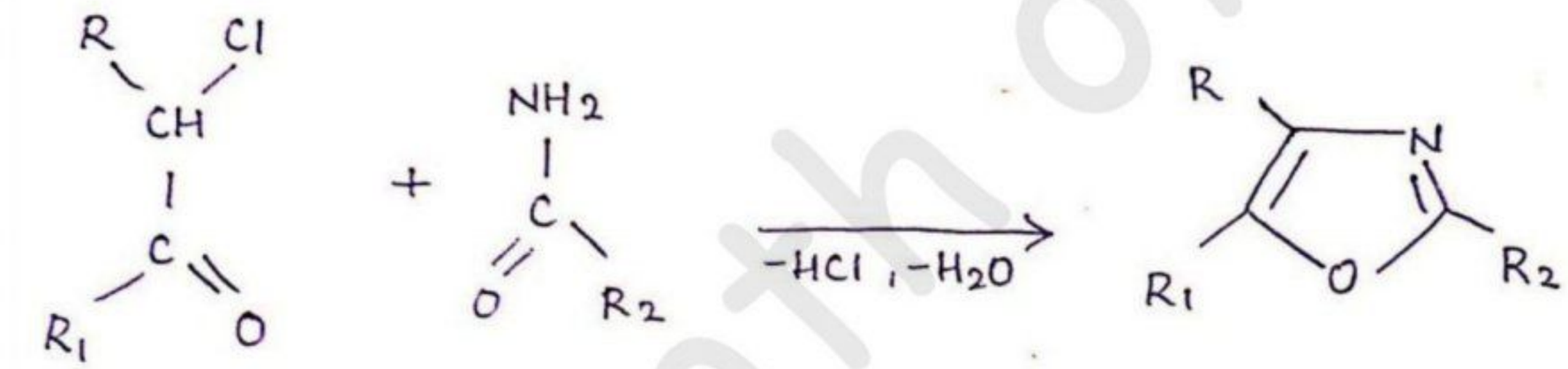
- <u>Synthesis</u> :-

ⓐ <u>Robinson - Gabriel synthesis (from α- acyl amino ketones)</u>

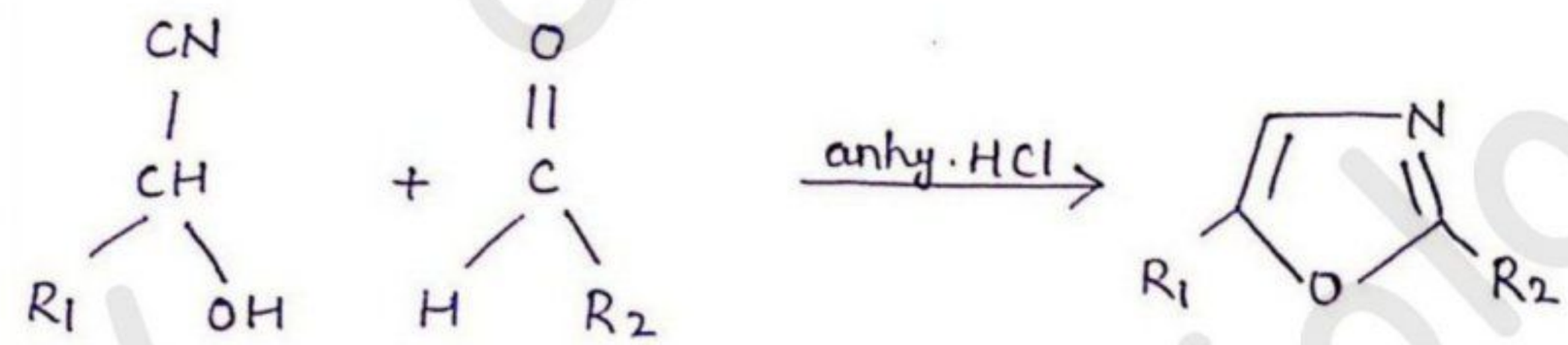
α- acyl amino ketones undergo cyclization in presence of P_2O_5 and strong mineral acid H_2SO_4 followed by dehydration.



(b) From α- haloketones and amides :-



(c) Fischer oxazole synthesis (cyanohydrins + aldehydes) :-



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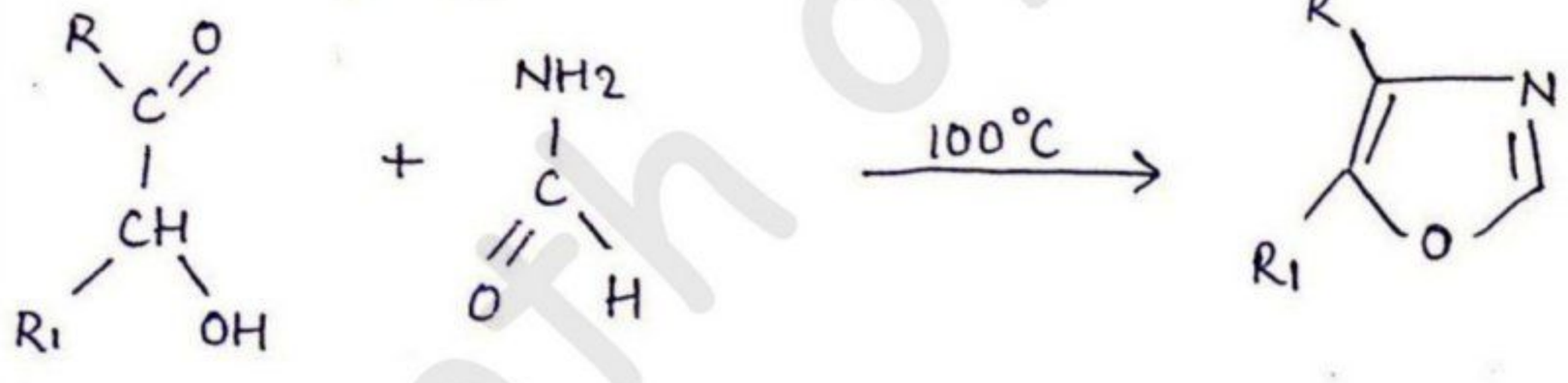
(d) From acyloins (α-hydroxy ketones)

- Reaction of acyloins with formamide



- Reaction of oxazole :-

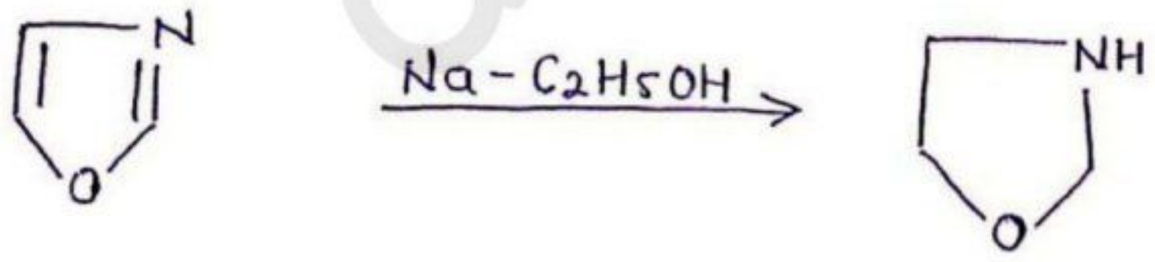
@ Reaction with acids :- (Protonation) :-

- oxazole accepts proton, acts as base and forms oxazodium cations.

[oxazole] [oxazolium cation]

ⓑ Reduction :-

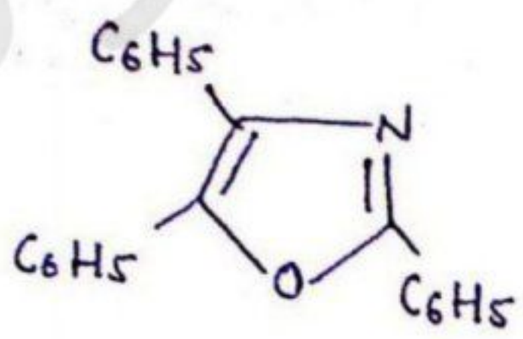
- oxazoles are stable in presence of reducing agents.
- However they can be reduced to oxazolidines with Na in ethanol.



[oxazole] [Oxazolidine]

ⓒ Oxidation :-

- oxazole ring is not stable to oxidative condition.
- Thus it is opened by the action of oxidising agent i.e. cold $KMnO_4$ / chronic acid / ozone.
- However the oxidation is stable with H_2O_2.



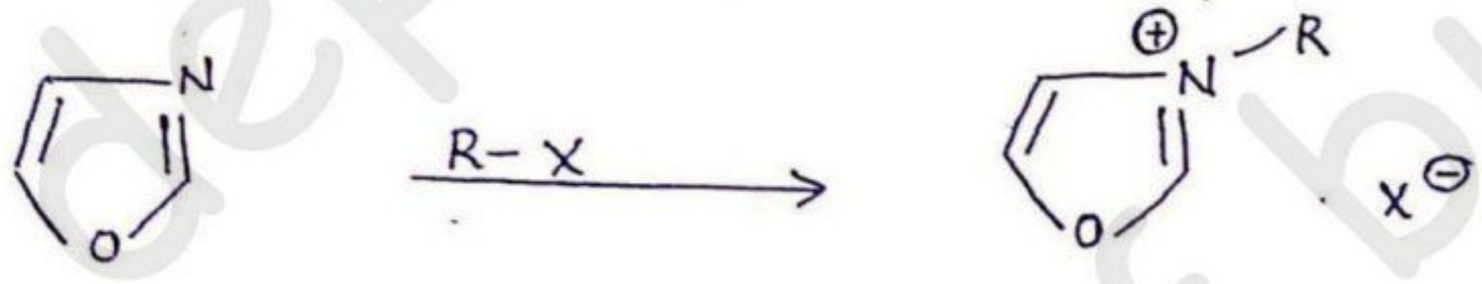
cold KMnO4 / ozone / chromic acid →

3 C_6H_5 - COOH

[triphenyloxazole]

[3 moles of benzoic acid]

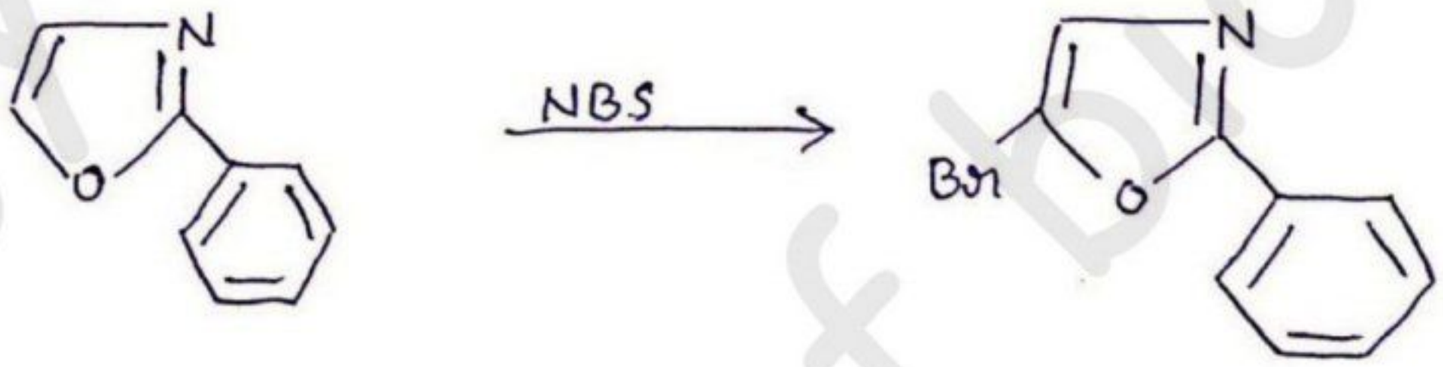
ⓓ Formation of quaternary ammonia Salts :-



ⓔ Electrophilic aromatic substitution

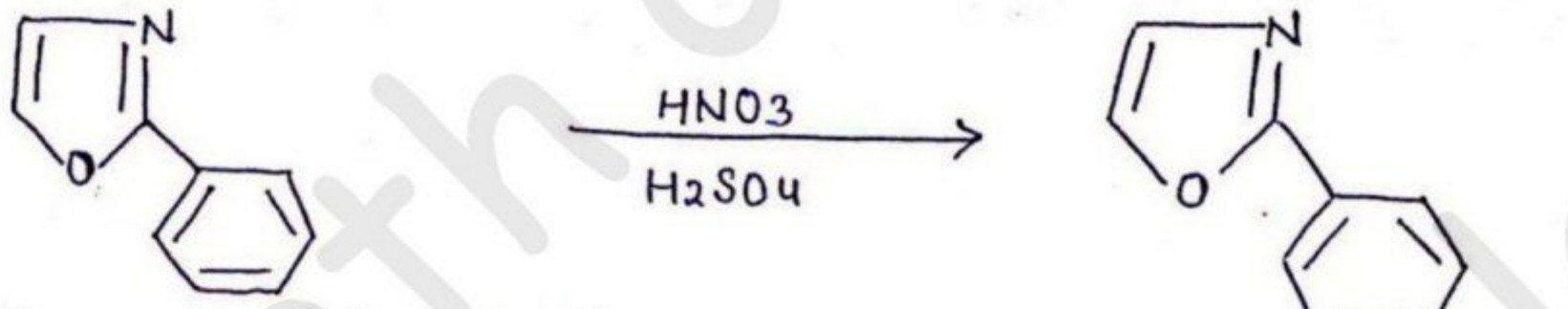
- less reactive for electrophilic substitution due to 'O' present in heterocyclic ring.
- Reaction is possible at 5th Position, if ring is activated by electron donating groups.
- Nitration and Sulphonation are more difficult.

• Bromination :-



[oxazole containing electron donating group]

- **Nitration** :-



[oxazole containing electron donating group]

- **Sulphonation** :-

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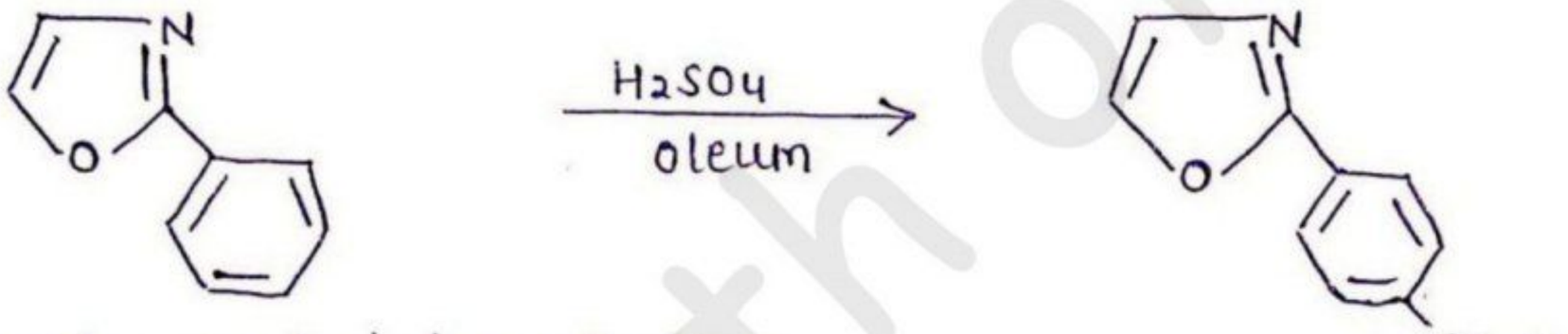
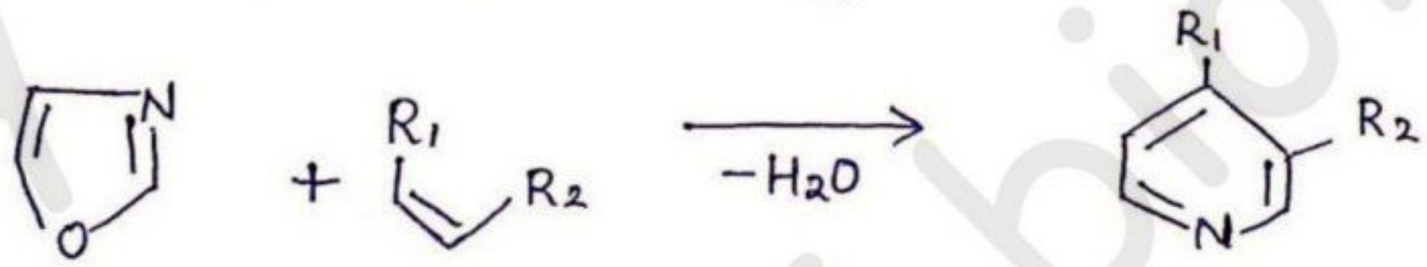


[oxazole containing electron donating group]

- **Diel's alder cycloaddition** :-

- Diel's alder cycloaddition of oxazole (conjugated diene) and dienophile produce pyridine derivatives.



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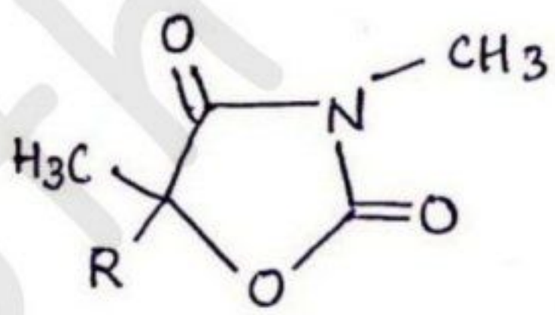
- **Medicinal Uses** :-

- Benoxaprofen, flunoxaprofen are used as analgesic, antipyretic and anti-inflammatory drugs.

- It was given to the patients with rheumatoid arthiritis and osteoarthritis because of its anti-inflammatory effect.



R = CH3

[Trimethadione]

[Paramethadione] → R = C2H5

- Trimethadione and paramethadione are used as anti-epileptic drugs, also called anticonvulsant drugs.
- It is used to treat absence seizzeris, also called 'petit mal' seizures.

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- Other drugs having oxazole moeity or its derivatives are :-

- Ditazole is a non-steroidal anti-inflammatory agent with analgesic and antipyretic. It is also act as platelet aggregation inhibitor.
- Aleglitazor used for the treatment of diabetes and cardiovascular disease.

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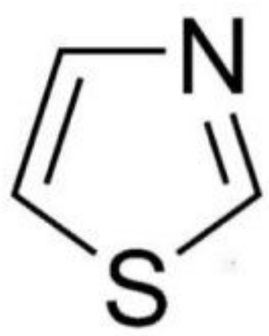
- It act by binding to both PPAR ∝ and PPAR ɣ and

decrease plasma levels of glucose , LDL , Triglycerides (TG) and increase HDL levels.

* Thiazole :-

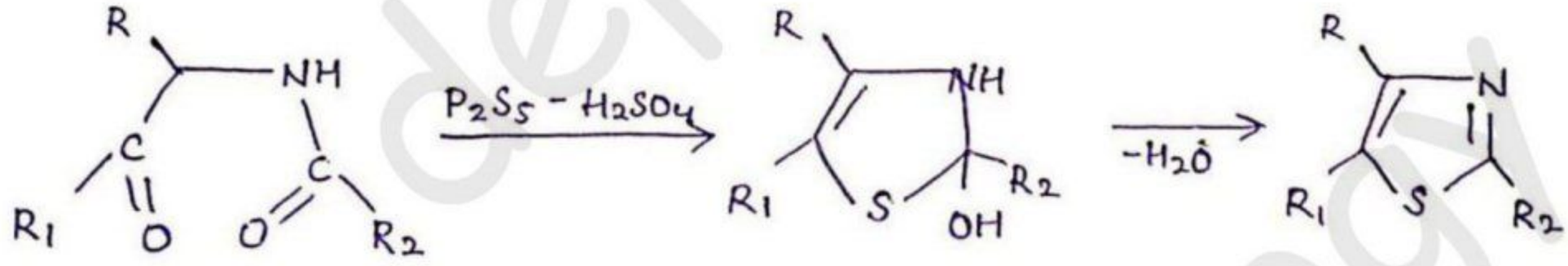
· Structure :-



· Synthesis :-

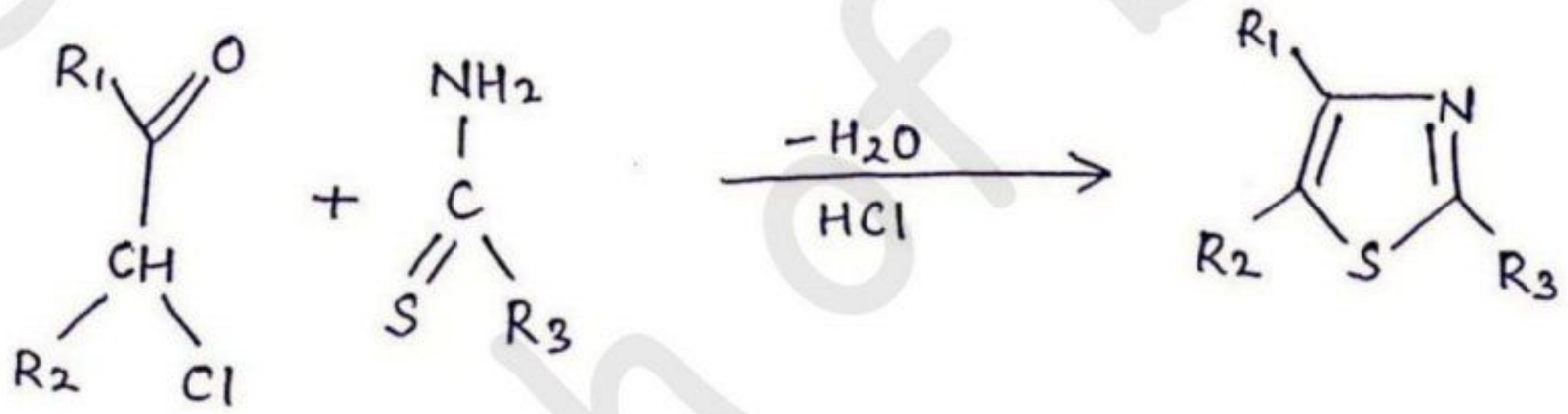
@ Gabriel synthesis (from α-acyl amino ketones)

α-acyl amino ketones undergo cyclization in presence of P_2S_5 and strong mineral acid H_2SO_4 followed by dehydration.



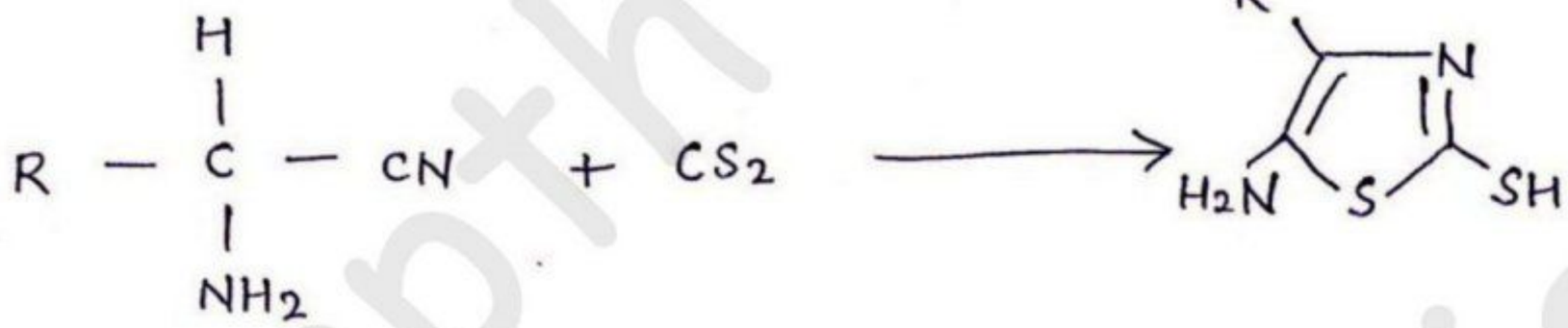
ⓑ Hantzsh thiazole synthesis :-

- Condensation of α-halo ketones with thioamides.



© Cook Helibron Synthesis :-

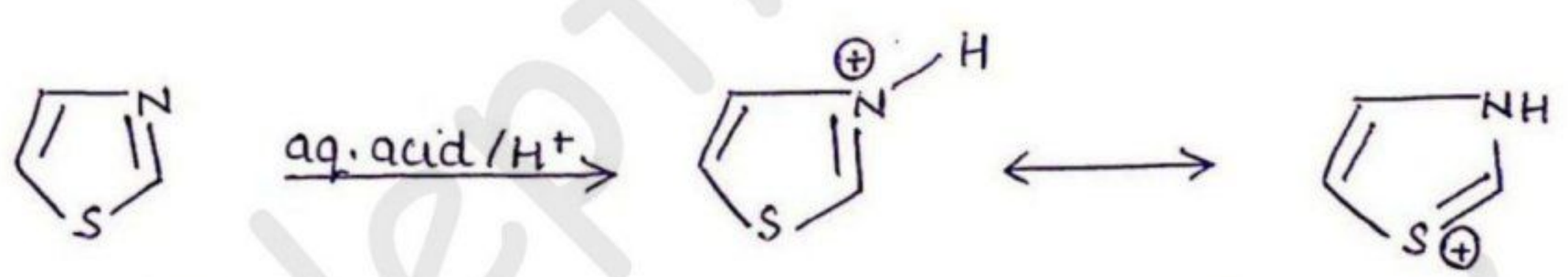
- condensation of α-aminonitrite with CS_2



* Reactions of thiazole :-

@ Reactions with acids (Protonations)

- Thiazole accepts proton act as base and forms thiazolium cation.

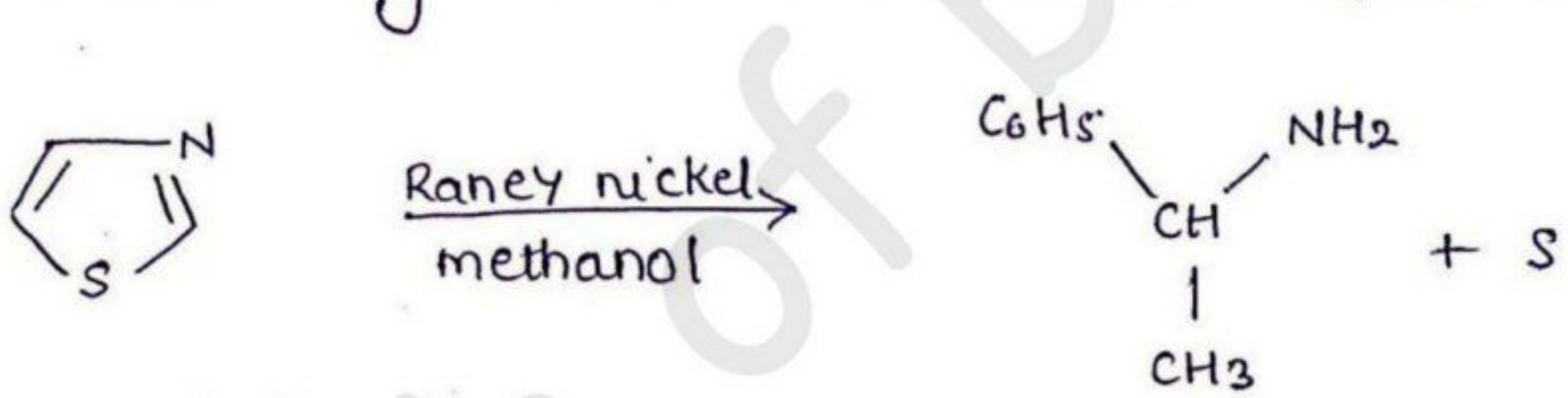


[thiazole] [thiazodium cation]

ⓑ Reduction :-

- Thiazole ring is resistant to many reducing agents.

- however, Raney nickel reduce it and opens the ring.



[4-phenylthiazole] [1-phenylethamine]

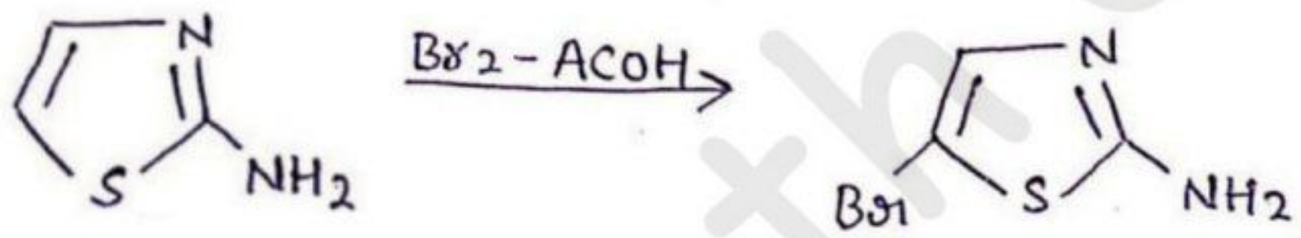
© Formation of quaternary ammonium salts :-

ⓓ Electrophilic aromatic substitution :-

- C5 is the primary site followed by C4 for electrophilic substitution in presence of electron donating group.

ⓘ Bromination :-

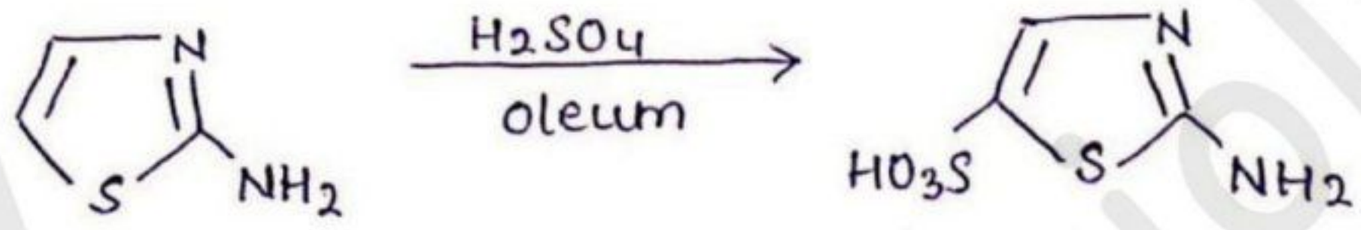
[DEPTH OF BIOLOGY]



[Thiazole containing electron donating group]

[2- amino - 5- bromo thiazole]

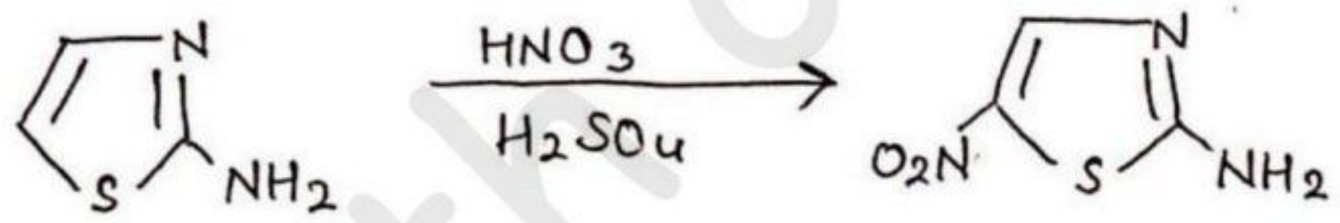
ⓘⓘ Sulphonation :-



[thiazole containing electron donating group]

[2- aminothiazole - 5- sulphonic acid]

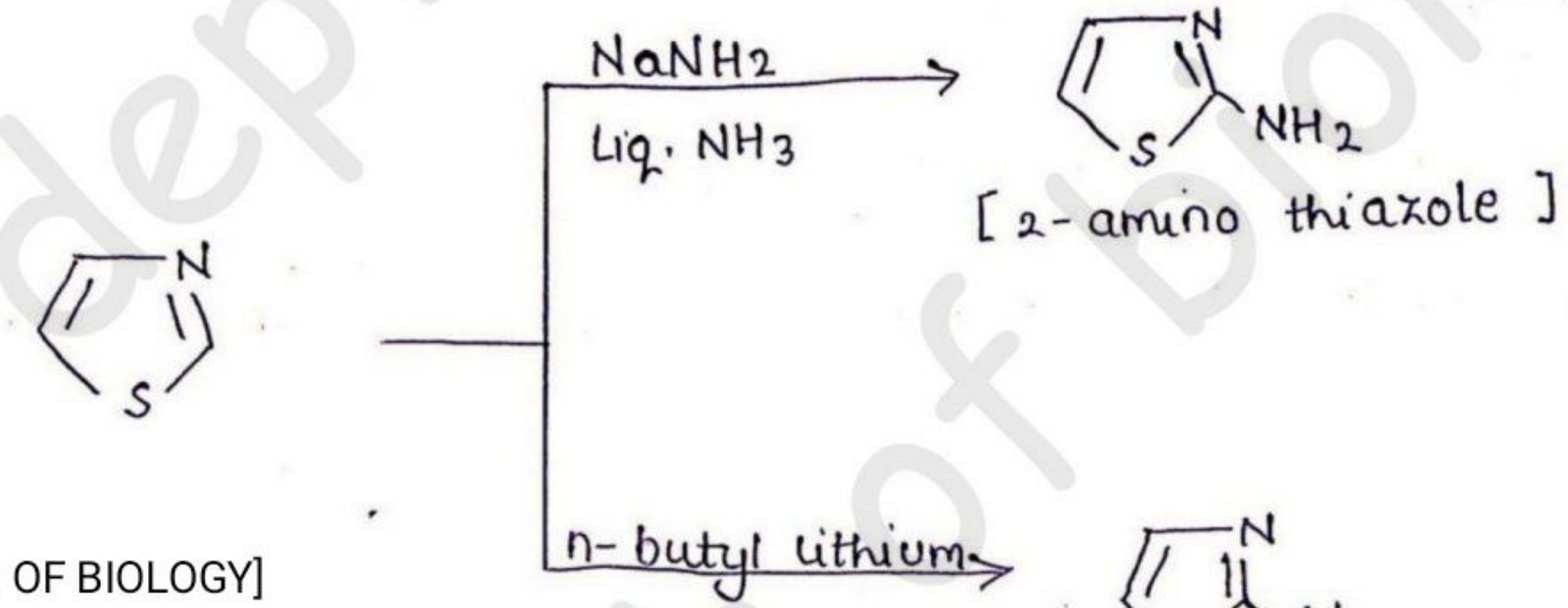
ⓘⓘⓘ Nitration :-



[2- amino - 5- nitro thiazole]

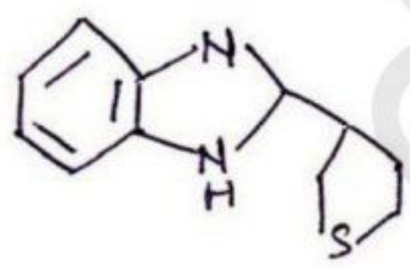
* Reaction with nucleophiles :-

- Thiazole are susceptible for nucleophilic substitution at C_2 Position.

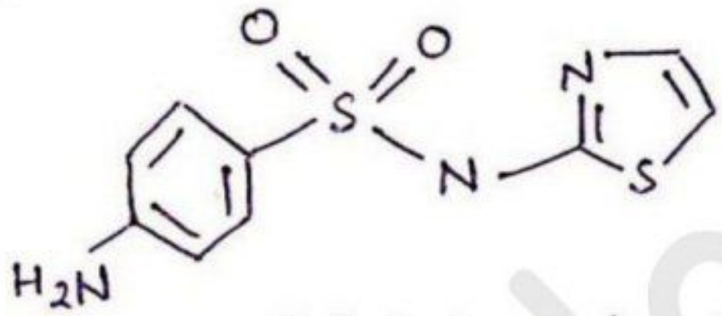


[DEPTH OF BIOLOGY]

* Medicinal Uses :-



[Thiabendazole]

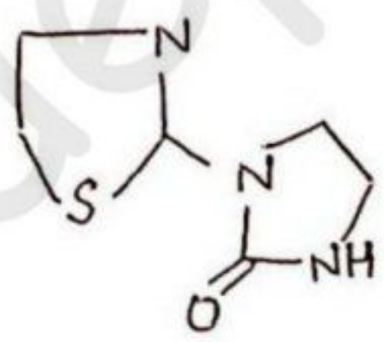


[Sulphathiazole]

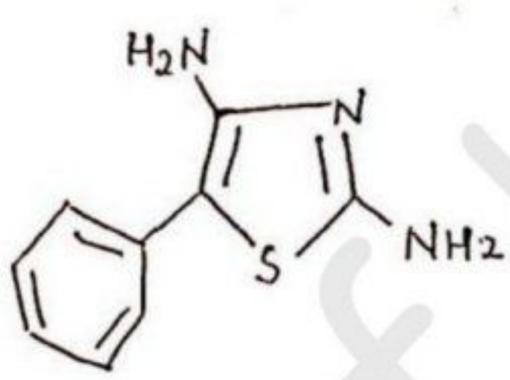
- Thiabendazole is an anthelmintic drug used to treat infection caused by worms such as threadworm.
- It may also be used to treat pinworm, hookworm, whipworm and roundworm infection.
- sulfathiazole is a short acting sulfonamide antibiotic

[DEPTH OF BIOLOGY]

- It's use has been largely replaced with less toxic alternatives but is still used in combination with sulfacetamide and sulfabenzamide for the treatment of vaginal infection and for disinfecting home aquariums.



[Nitsidazole]



[Amiphenazole]

[DEPTH OF BIOLOGY]

- Nitsidazole - anthelmintic drug used as schistosonicide
- Amiphenazole is a respiratory stimulant traditionally used as antidote for barbiturate (or) opiate overdose
- Famatidine - H_2 receptor antagonist, used to treat and prevent ulcers in the stomach and intestines.
- Vitamin B_1 or thiamine - is a water soluble vitamin, enables the body to use carbohydrate as energy.

[DEPTH OF BIOLOGY]

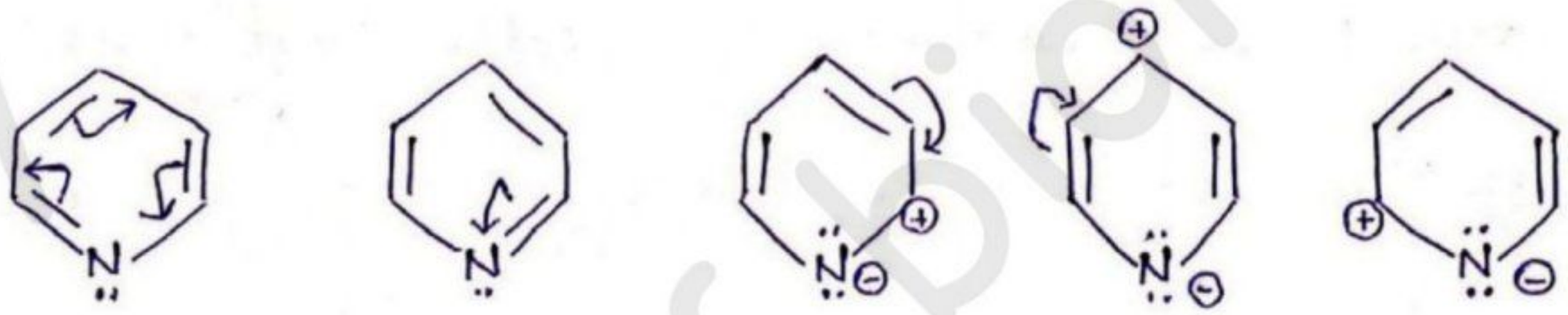
* **Pyridine :-**

- **Structure :-**

- Pyridine is an unsaturated 6 membered heterocyclic ring consists of nitrogen as heteroatom.
- It posses planar conjugated ring structure consist of six delocalised π- electrons.

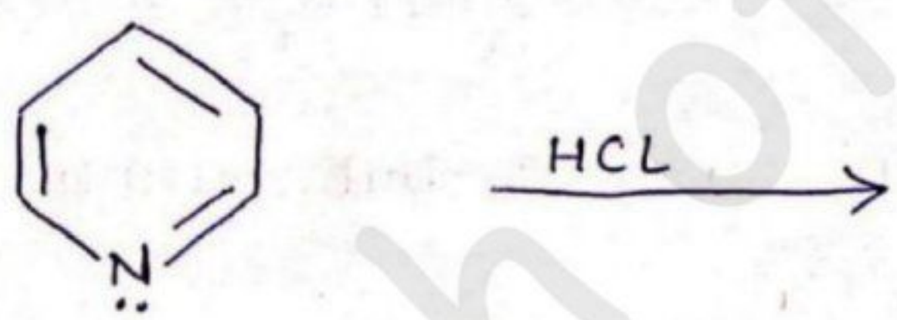
[DEPTH OF BIOLOGY]

- The aromatic nature arise from the three double bond: present in the ring as six delocalized π electrons.
- So it follows Huckle's rule hence it is aromatic compound.
- **Resonance structure of pyridine :-**



- **Basicity of pyridine :-** Pyridine is basic in nature and react with acid to form salts.

[DEPTH OF BIOLOGY]



[Pyridine]

[Pyridmium chloride]

- The basicity of pyridine is due to the readily availability of lone pair of electrons or nitrogen atom.
- Pyridine is more basic than pyrrole because the lone pair of electron of pyridine 'N' does not involve in the resonance and these lone pair 'o' electron are readily available for reactions.

- But in pyrole , the lone pair of electrons of 'N' involved in the resonance and hence that lone pair of electrons are not readily available for reactions.

[Pyridine] [Pyrrole]

- As the lone pair of electrons of the pyridine are

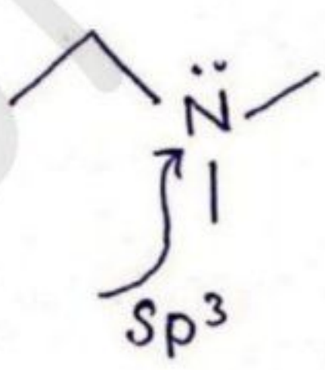
readily available for reactions than pyrolle, hence pyridine is more basic than pyrrole but pyridine is less basic than aliphatic amines.

- In pyridine the 'N' is present in sp^2 hybridised. more s character, more electronegative
- In case of aliphatic amines, the N is present in sp^3 hybridized, less s character, less electronegative.
- The lone pair of electrons on the 'N' of pyridine is more tightly held because of more s character and more electronegative, hence it is less available for reactions.
- While in case of aliphatic amines, the lone pair of electrons on the 'N' is loosely held because of less s character and less electronegative. So it is more readily available for reaction.
- Hence the aliphatic amines are more basic than pyridine.

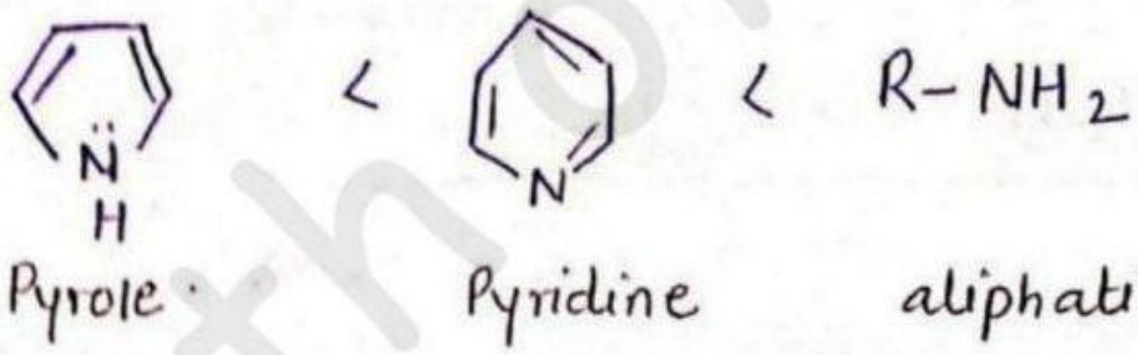
[DEPTH OF BIOLOGY]

[DEPTH OF BIOLOGY]

[More electronegative]



[less electronegative]



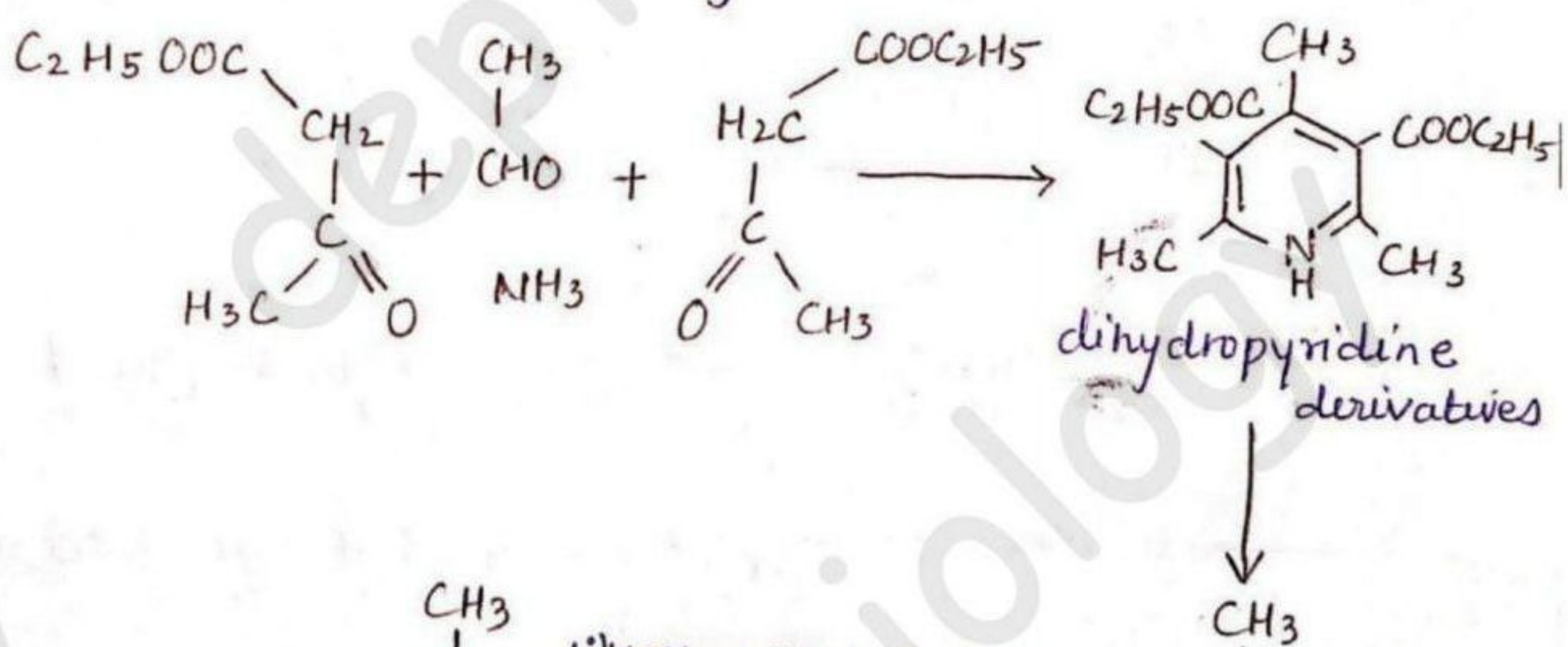
Pyrole < Pyridine < aliphatic amines.

- Synthesis of Pyridine

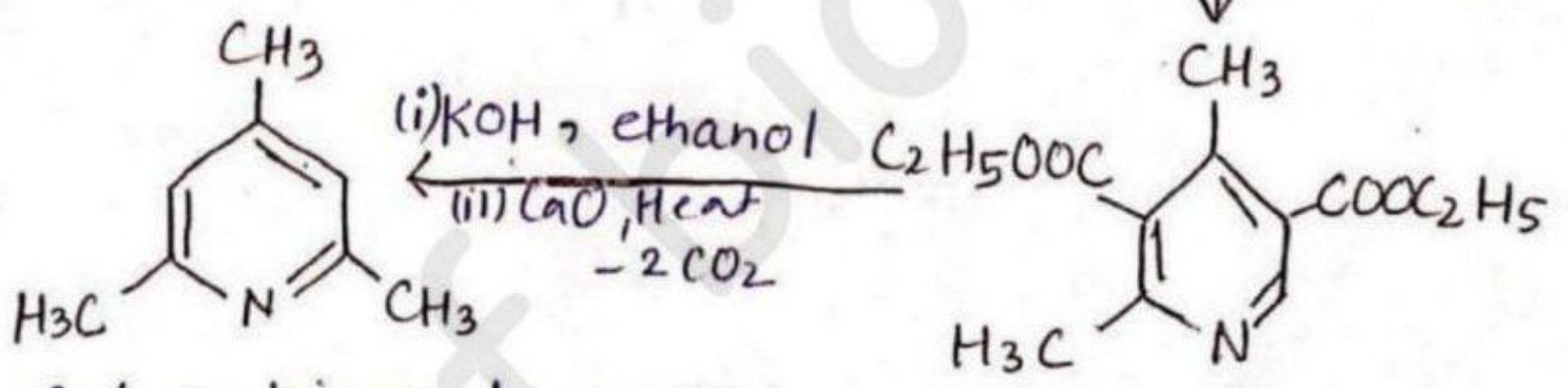
(a) Hantzach pyridine synthesis –

[DEPTH OF BIOLOGY]

Condensation of 2 moles of β-dicarbonyl compounds/ β-keto esters with aldehyde & amonia.



dihydropyridine derivatives



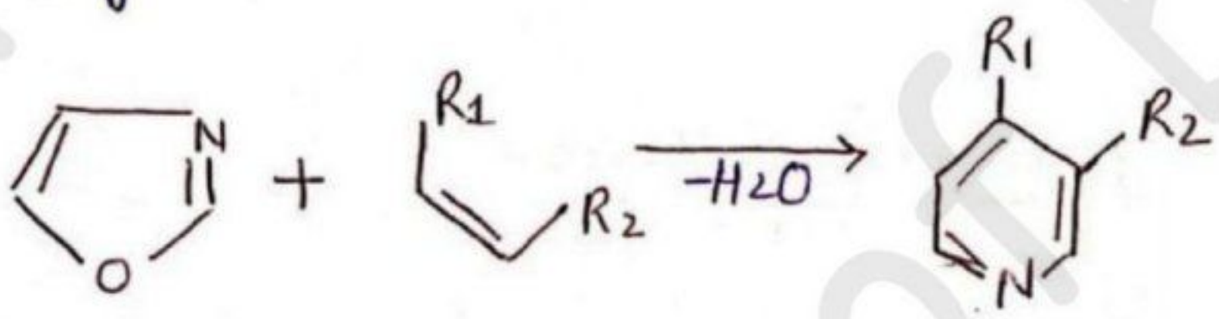
2,4,6-trimethyl pyridine

pyridine derivative

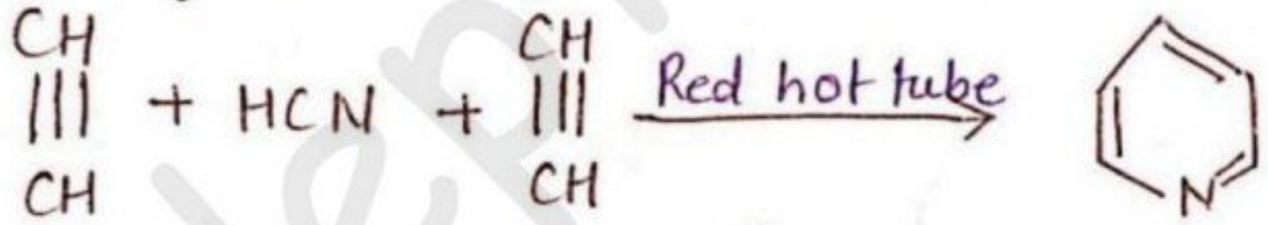
[DEPTH OF BIOLOGY]

(b) From Diel's Alder cycloaddition :-

Diel's Alder cycloaddition of oxazole and dienophile produce pyridine derivatives.

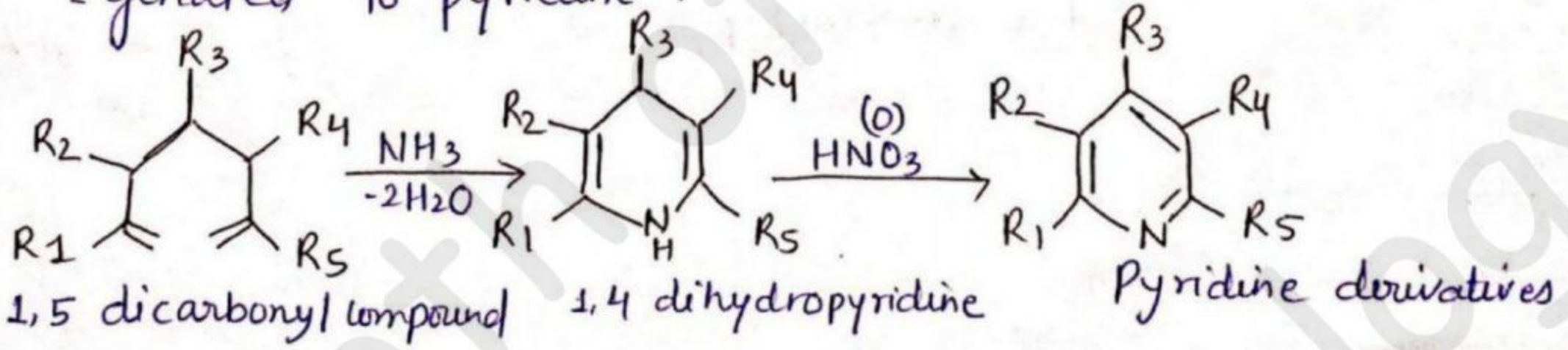


(c) From acetylene and HCN :-



(d) From 1,5-diketones/ 1,5-dicarbonyl compounds -

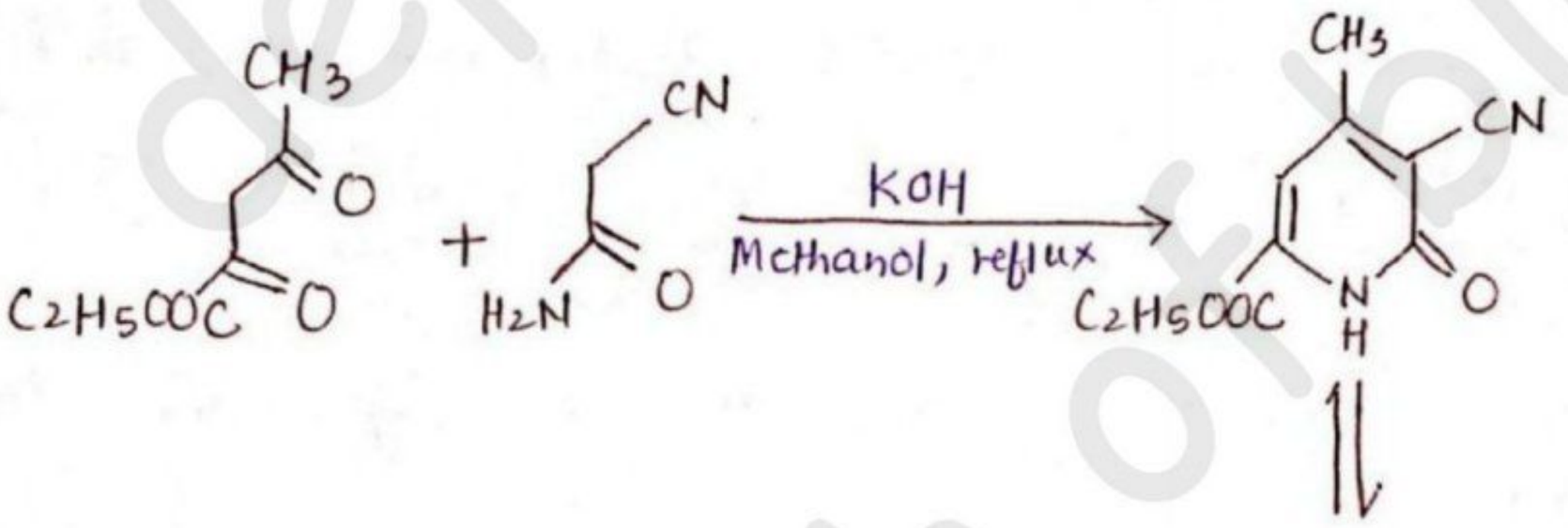
- 1,5-dicarbonyl compounds on reaction with ammonia gives 1,4-dihydropyridines, which are easily dehydro-genated to pyridine.



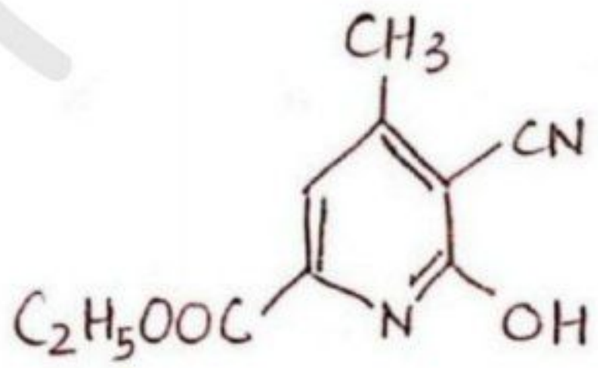
1,5 dicarbonyl compound 1,4 dihydropyridine Pyridine derivatives

(e) Guareschi pyridine Synthesis -

The preparation of pyridine derivatives by condensation of acetoacetic esters and cyanoacetamide.

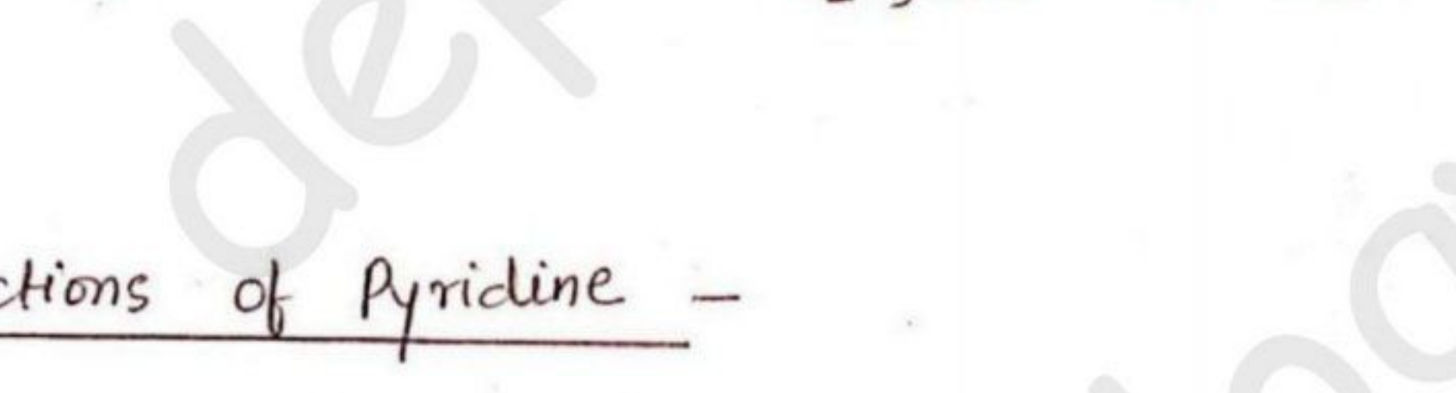


[DEPTH OF BIOLOGY]



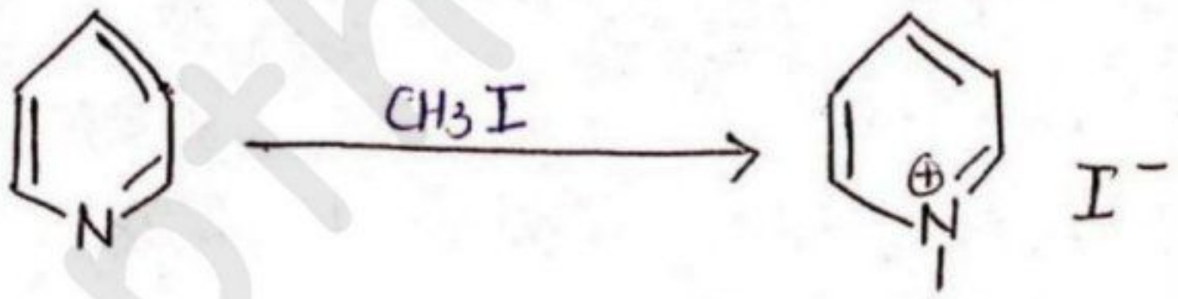
→ Reactions of Pyridine -

(a) Reaction with acid (Protonation) gives pyridinium salt -



[DEPTH OF BIOLOGY]

(b) Quarternization / N-alkylation –



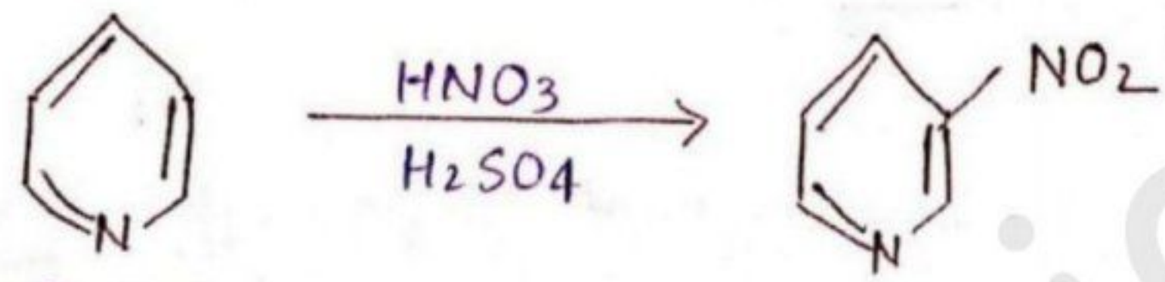
1- methyl pyridinium iodide

(c) Electrophilic aromatic Substitution Reactions –

Preferably substitution takes place at C_3 position, due to high stability of carbocations formed by the attack of electrophile at C_3 carbon atom.

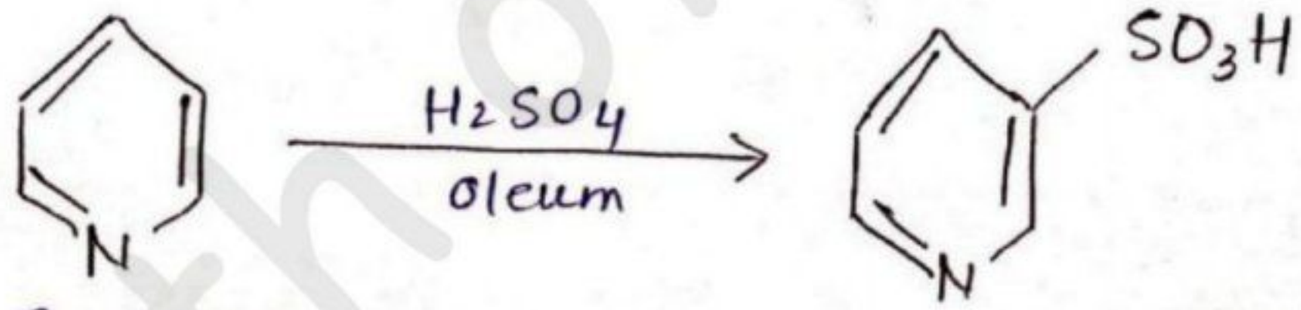
[DEPTH OF BIOLOGY]

[i] Nitration :-



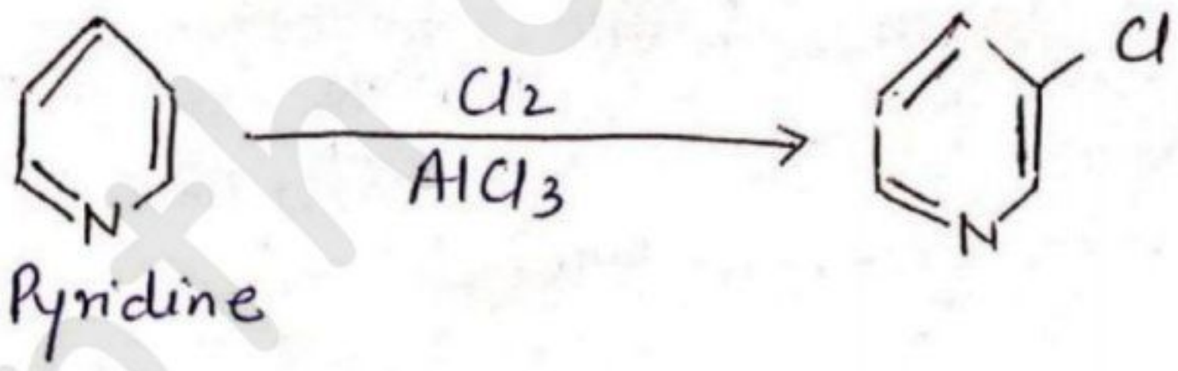
Pyridine

[ii] Sulphonation :-



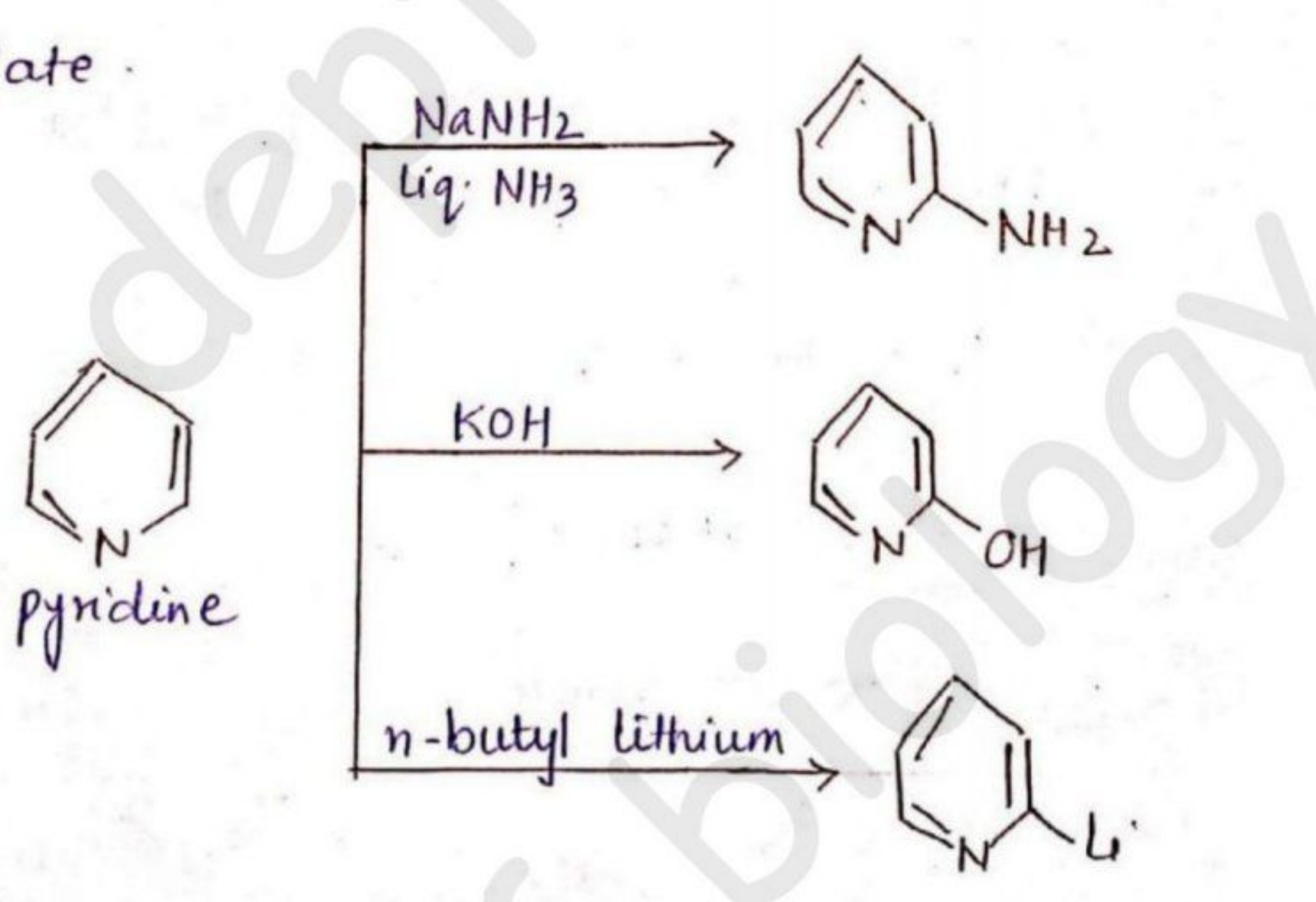
Pyridine

[iii] Halogenation :-



(d) Nucleophilic substitution reactions :-

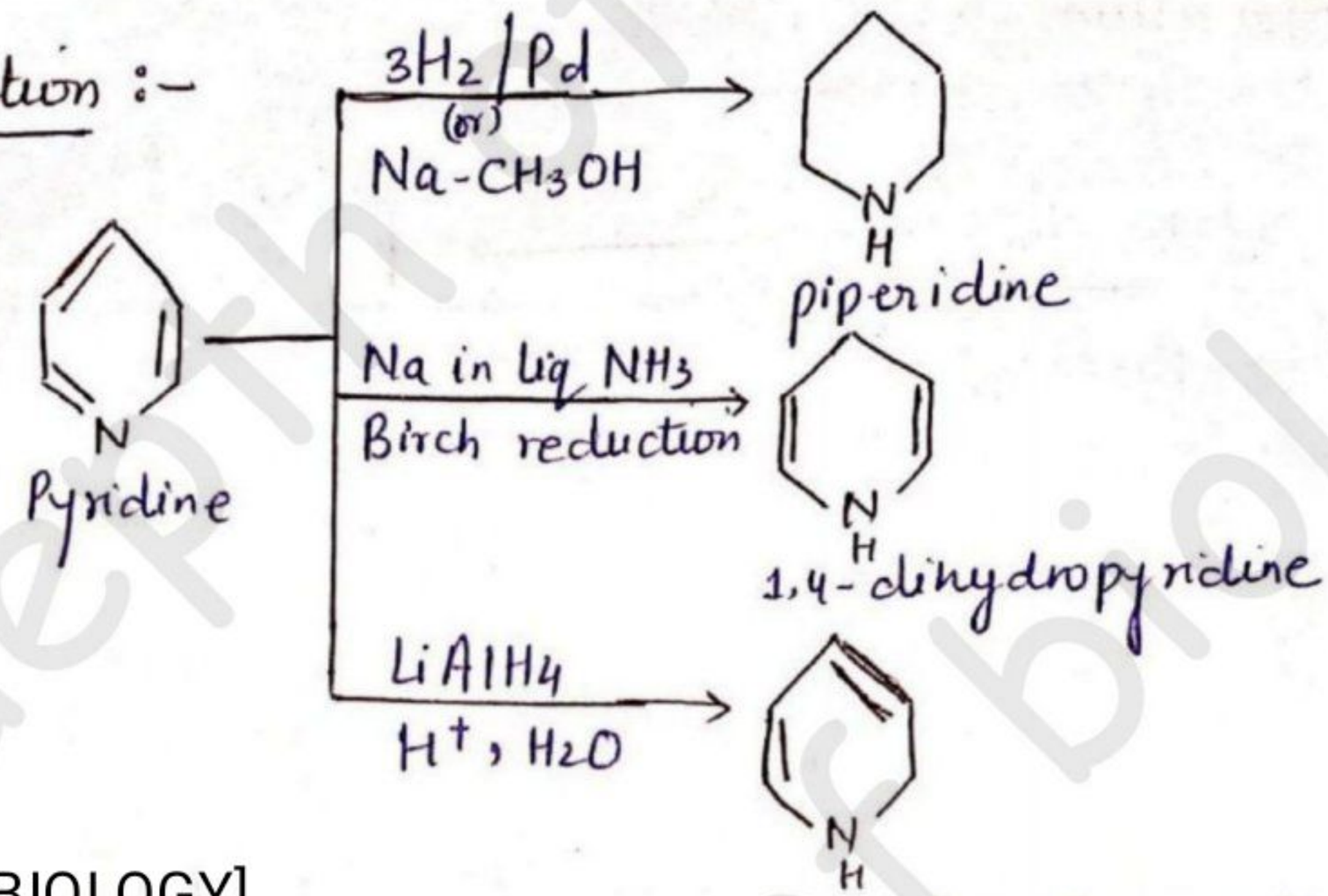
Pysidine undergoes nucleophilic substitution reaction at C_2 position. Attack on 2^{nd} position gives more stable intermediate.



[DEPTH OF BIOLOGY]

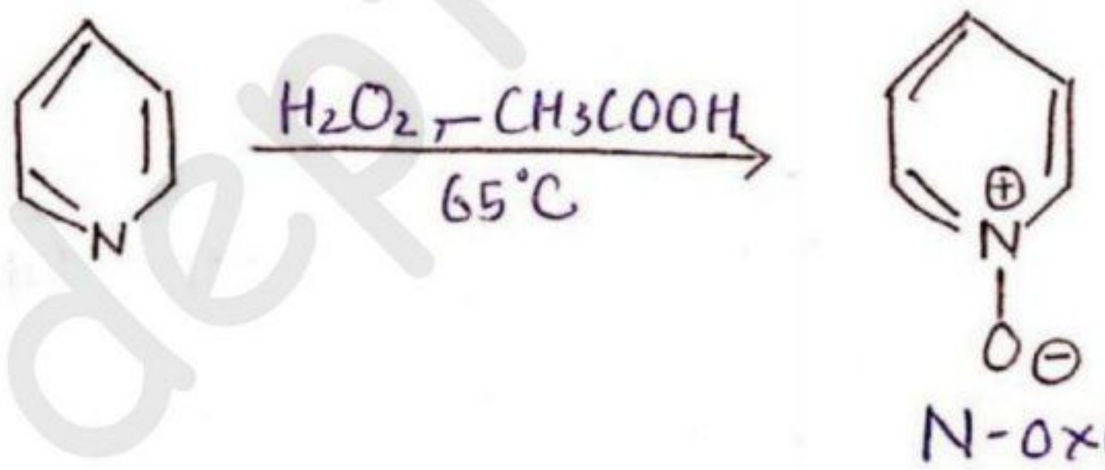
[DEPTH OF BIOLOGY]

(e) Reduction :-

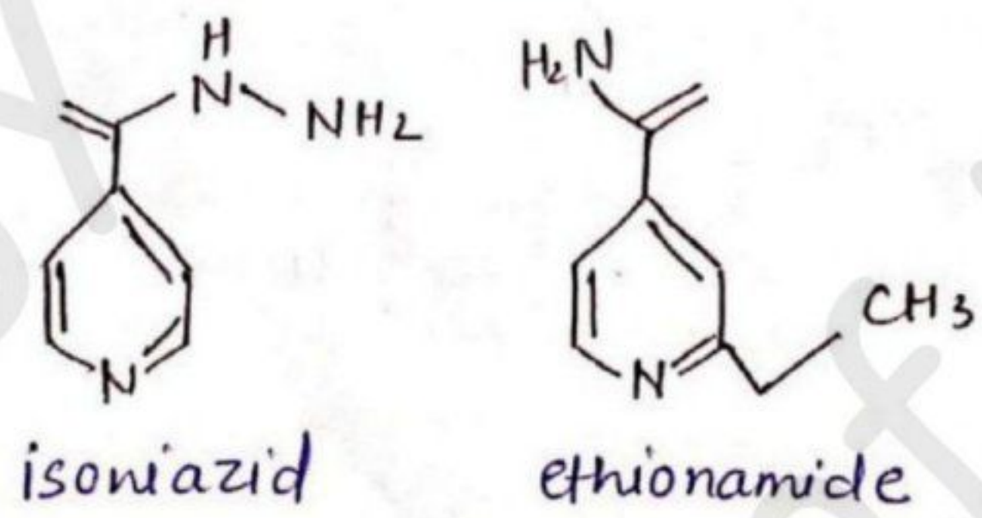


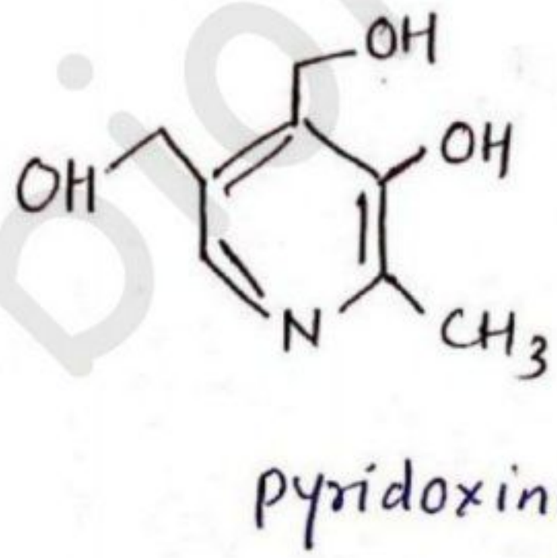
[DEPTH OF BIOLOGY]

(f) Oxidation :-



- Medicinal Uses :-





– Isoniazid is used with other medication to treat active tuberculosis (TB) infection.

[DEPTH OF BIOLOGY]

- Ethionamide is used with other medication to treat TB infections.

Pyridoxine, (Vitamin B_6) is used to maintain the health of nerves, skin and Red Blood cells (RBC)

- It has been used to prevent treat a certain nerve disorder caused by certain medication

- <u>Other drugs having pyridine moiety</u> -

(i) <u>Niacin (nicotinic acid)</u> is a Vitamin B <u>(Vit. B_3)</u>

It helps to lower cholesterol, triglycerides, in the blood and used for treatment of Pellegra.

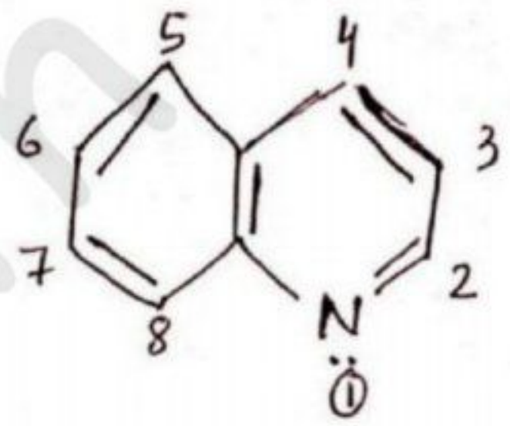
(ii) <u>Nikethamide (coramine)</u> - It is used CNS and respiratory stimulant.

[DEPTH OF BIOLOGY]

(iii) <u>Pyridostigmine</u> - It is used to treat the symptoms of myasthenia gravis.

- **Quinoline -**

→ **Structure :-**



Quinoline is fused heterocyclic compound in which benzene ring fused with pyridine.

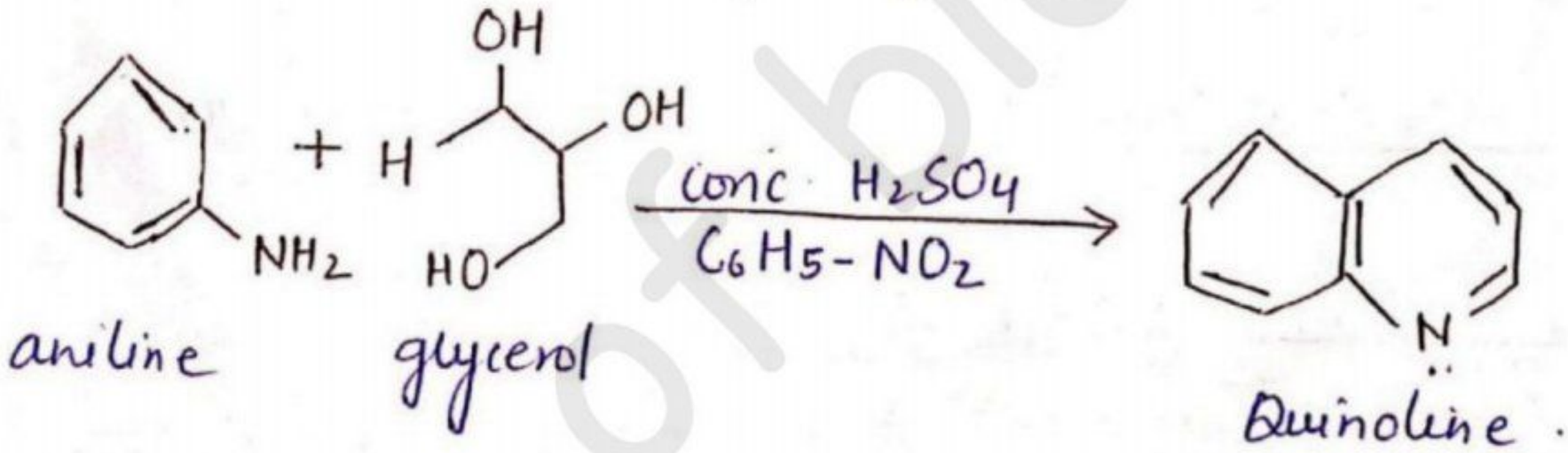
It consist of nitrogen as hetero atoms at 1st position.

Synthesis of Quinoline :-

[DEPTH OF BIOLOGY]

(a) **Skraup's Synthesis -**

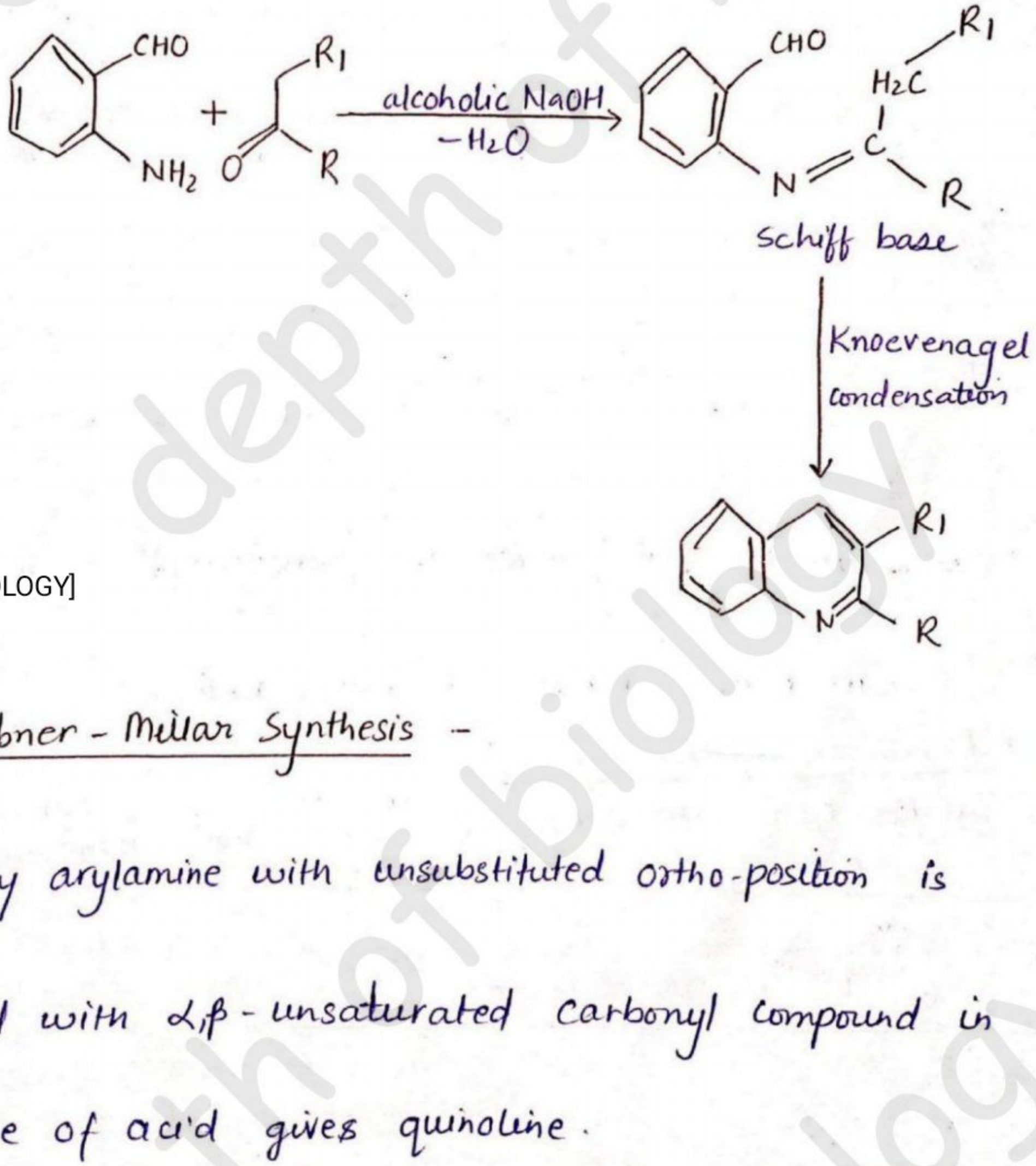
Reaction of aniline with glycerol in presence of Conc. H_2SO_4 and mild oxidising agent nitrobenzene



[DEPTH OF BIOLOGY]

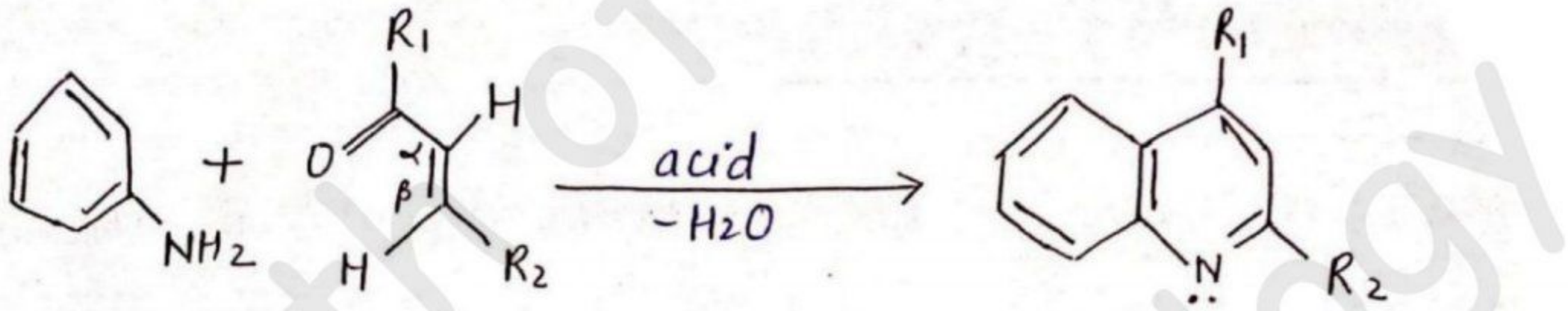
(b) Friedlander Synthesis -

Reaction of o-amino benzaldehyde with an aldehyde/ ketone containing active methylene group in Presence of alcoholic NaOH



(c) Doebner - Miller Synthesis -

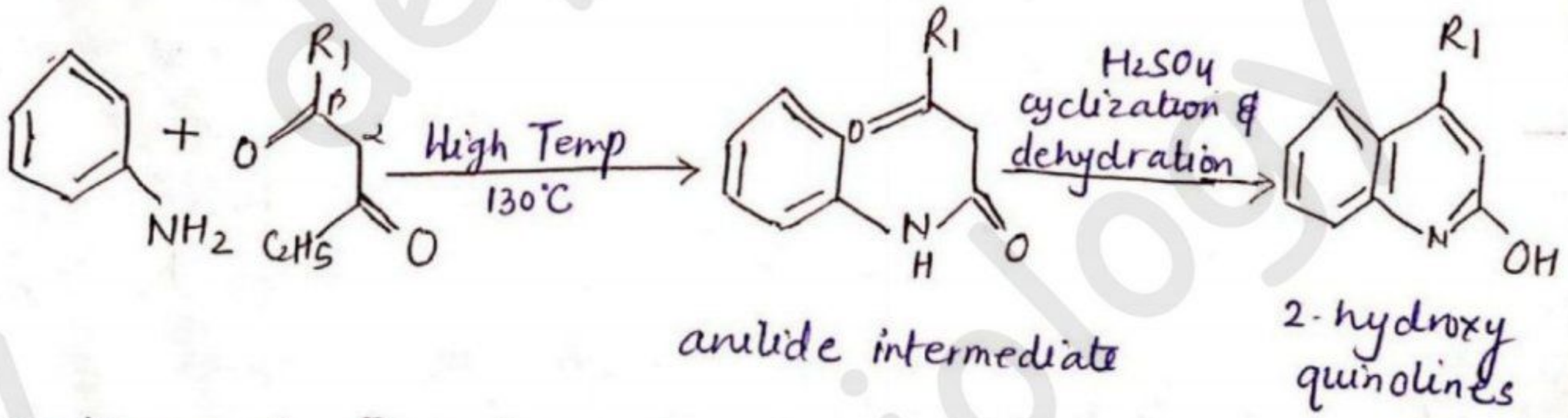
Primary arylamine with unsubstituted ortho-position is reacted with α,β - unsaturated carbonyl compound in presence of acid gives quinoline.



(d) Knorr quinoline Synthesis :-

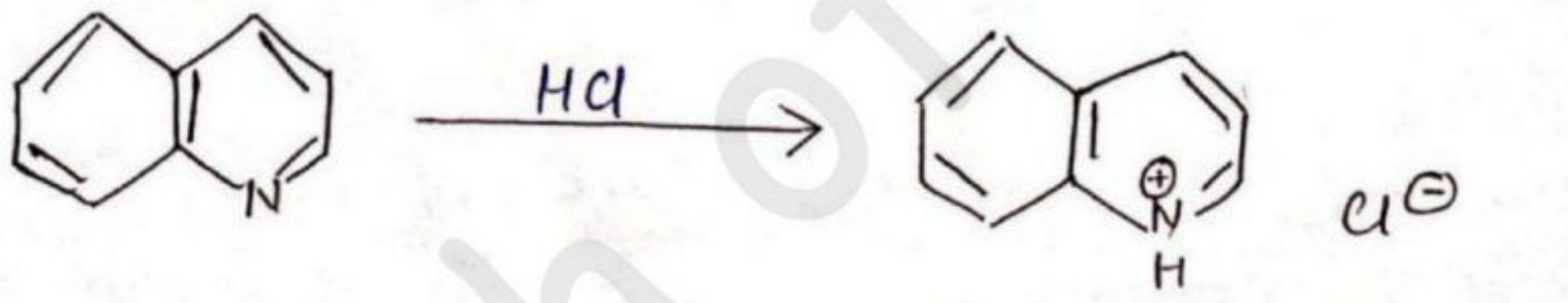
Condensation of aniline and β-Ketoester at high temperature gives an anilide intermediate, further it undergoes cyclization and dehydration in presence of Conc. H_2SO_4 produce 2-hydroxyquinolines.

[DEPTH OF BIOLOGY]



- Reactions of Quinolines :-

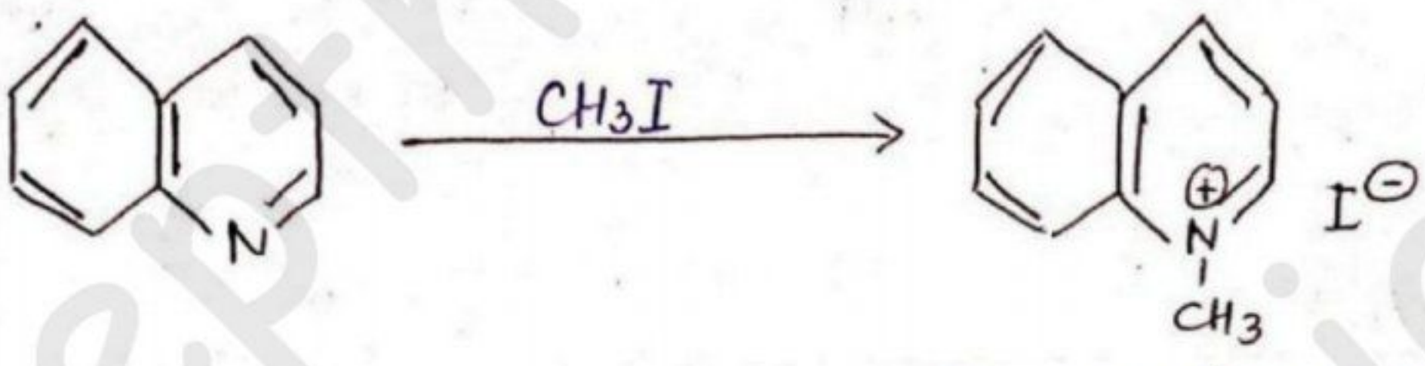
(a) Reaction with acids (Protonation) gives quinolium Chloride salt -



quinolinium Chloride.

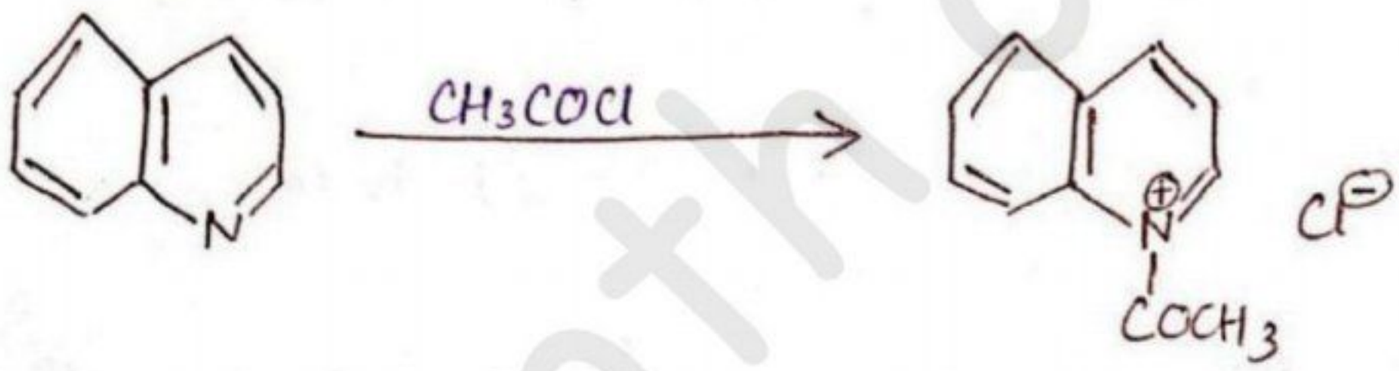
[DEPTH OF BIOLOGY]

(b) Reaction with methyl iodide (N-alkylation) gives N-methyl quinolinium iodide.



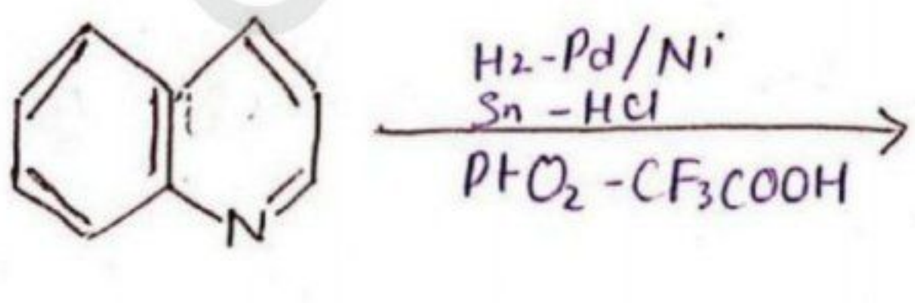
N-methyl quinolinium iodide.

(c) Reaction with acetyl chloride (N-acylation) gives N-acetyl quinolinium chloride.

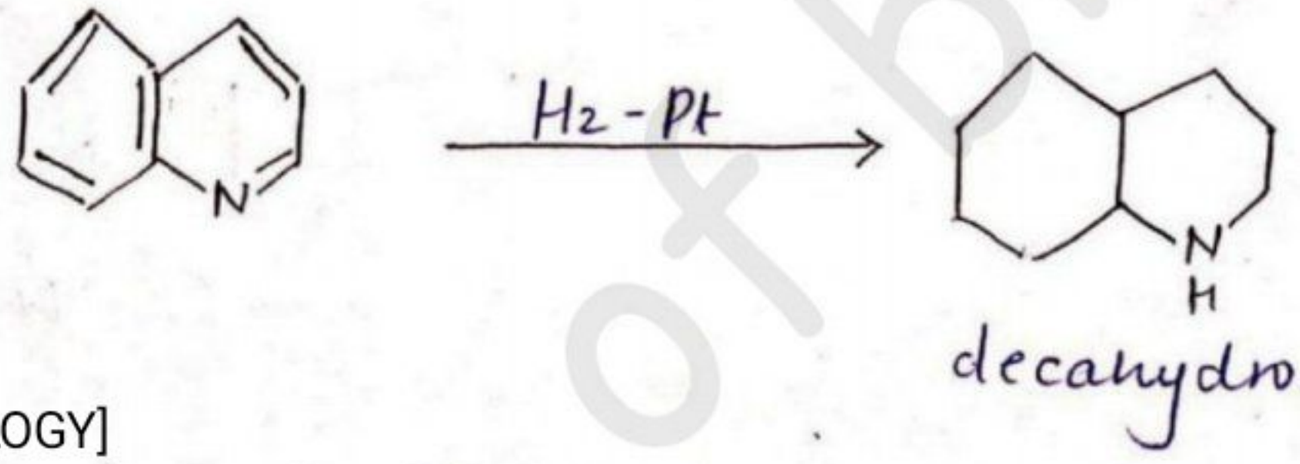


N-acetyl quinolinium chloride

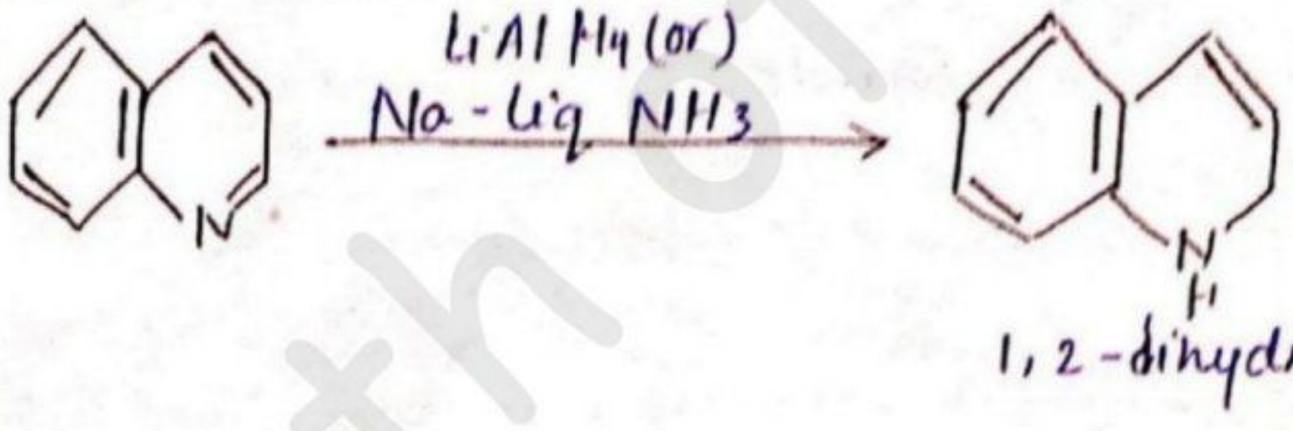
(d) Reduction -



1,2,3,4-tetrahydroquinoline

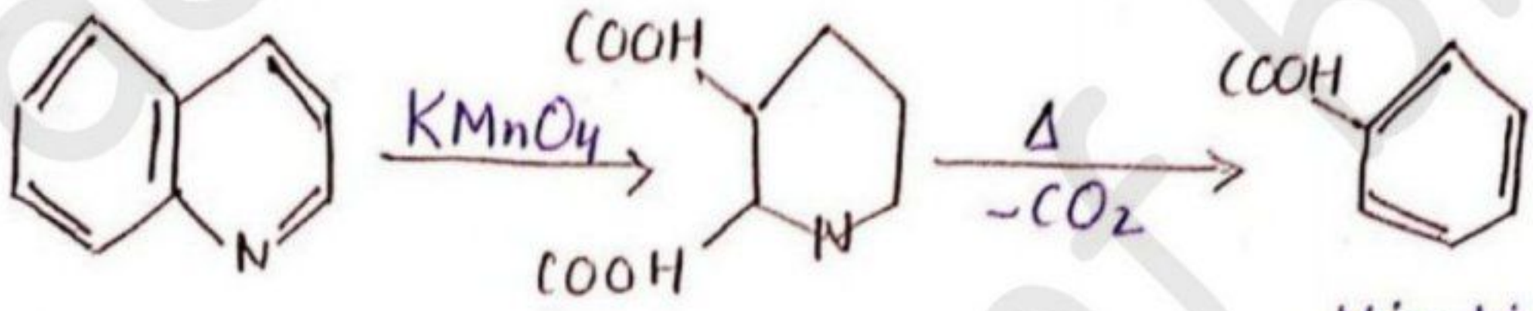


decahydroquinoline.



1, 2 - dihydroquinoline

(e) Oxidation :-

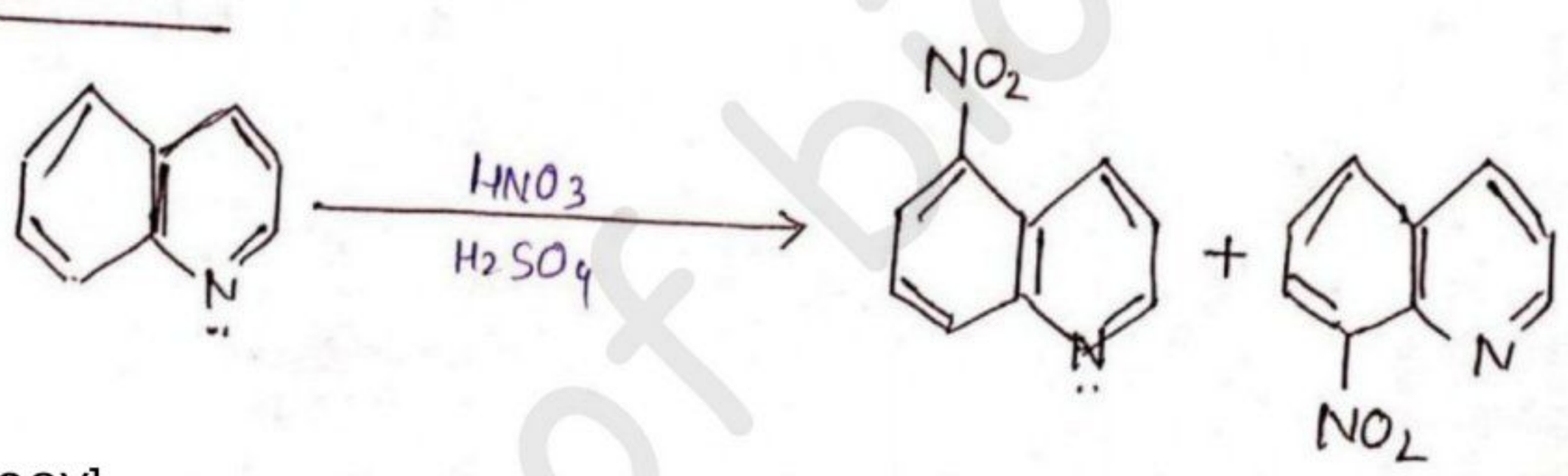


Nicotinic acid.

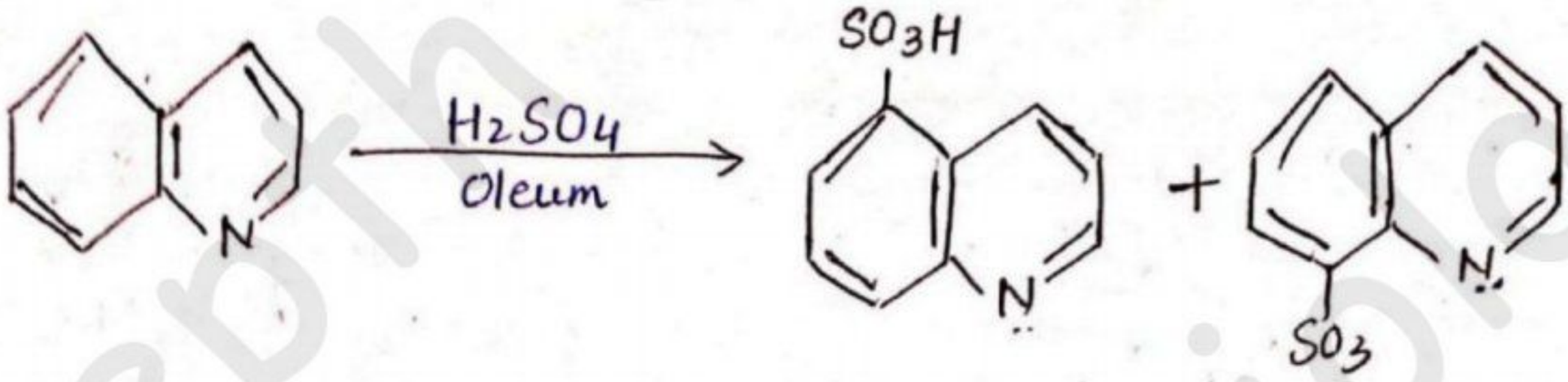
(f) Electrophilic aromatic substitution reactions :-

Substitution takes place at 5th position and 8th position Electrophilic aromatic substitution of quinoline gives mixtures of 5-substituted and 8-substituted derivatives

(i) Nitration :-

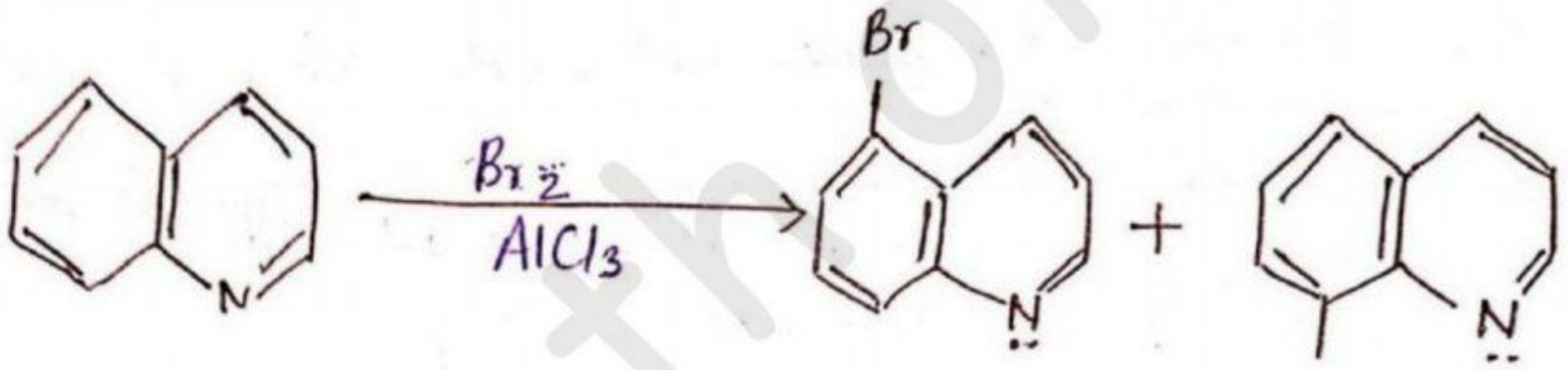


(ii) Sulphonation :-



[DEPTH OF BIOLOGY]

(iii) Bromination :-



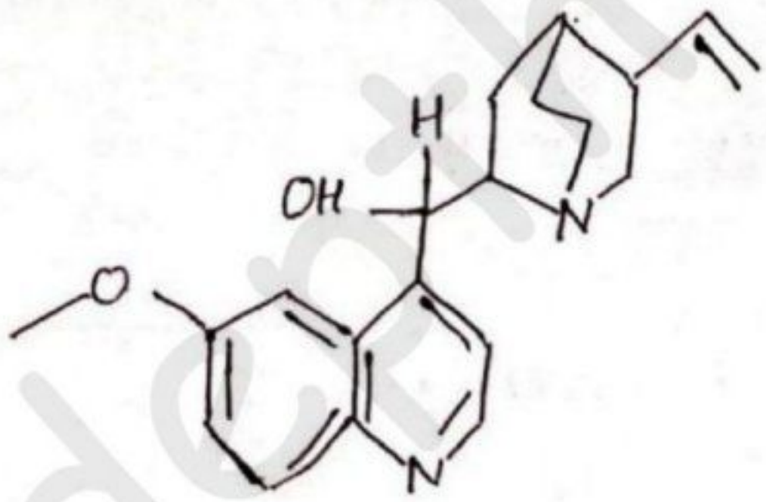
(g) Nucleophilic Substitution :-

Substitution takes place at 2nd and 4th position gives mixtures of 2- substituted and 4- substituted derivative

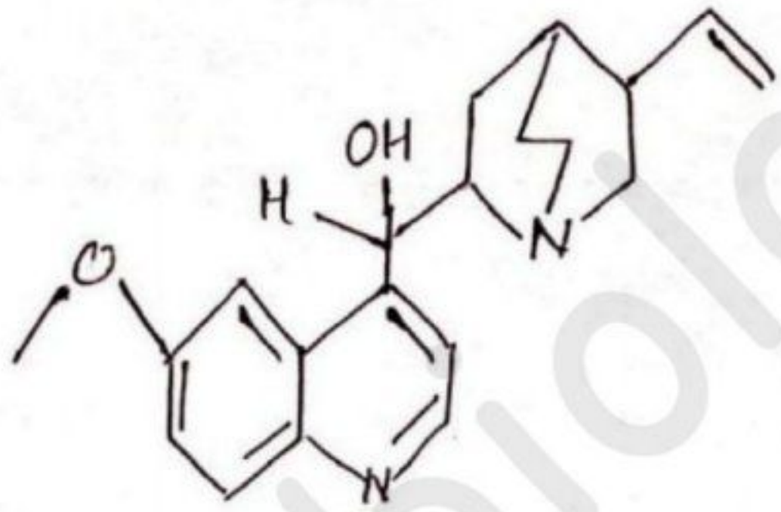
[DEPTH OF BIOLOGY]

[DEPTH OF BIOLOGY]

- Medicinal Uses :-



Quinidine



Quinine

- Quinine used as alone (or) with other medication to treat malaria.

- Quinidine is class IA antiarrhythmic drugs used to treat (or) prevent many types of irregular heartbeats

→ 4-aminoquinolines (antimalarial drugs) such as chloroquine, hydroxychloroquine, amodiaquine.

[DEPTH OF BIOLOGY]

→ 8-aminoquinolines such as primaquine, pamaquine are antimalarial drugs.

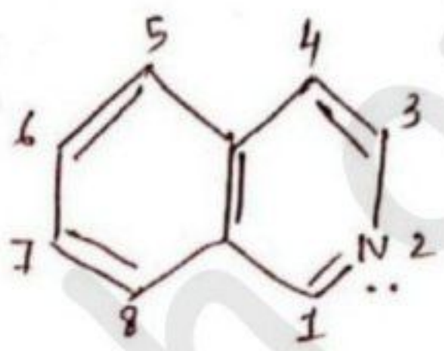
→ Norfloxacin is an antibiotic drug belong to fluroquinoline

→ Saquinavir is used in combination with Ritonavir & other medication to treat HIV infection.

→ Oxamniquine is an antihelmintic drug.

- Isoquinoline

- Structure :-



[DEPTH OF BIOLOGY]

- Isoquinoline is fused heterocyclic compound in which benzene ring fused with pyridine.

- It consist of nitrogen as hetero atom at 2nd position

- Synthesis of Isoquinoline :-

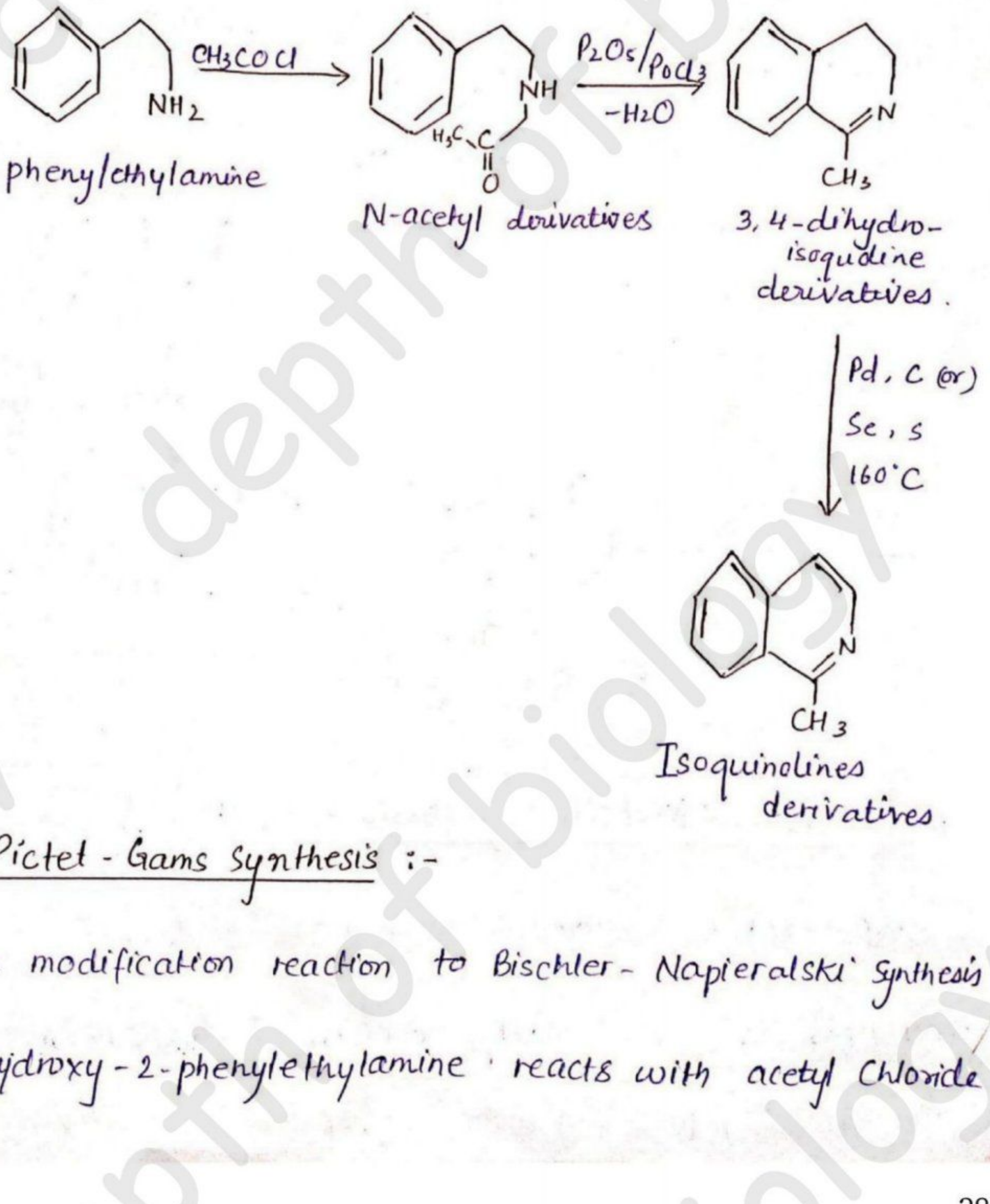
[DEPTH OF BIOLOGY]

(a) Bischler - Napieralski isoquinoline synthesis -

β-Phenylethyl amines reacts with acetyl chloride give N-acetyl derivatives, which on treatment with P_2O_5 / $POCl_3$ undergoes cyclodehydration gives

3,4-dihydroisoquinoline.

- further, on dehydration with Pd, C (or) Se, at 160°C gives Isoquinolines derivatives.



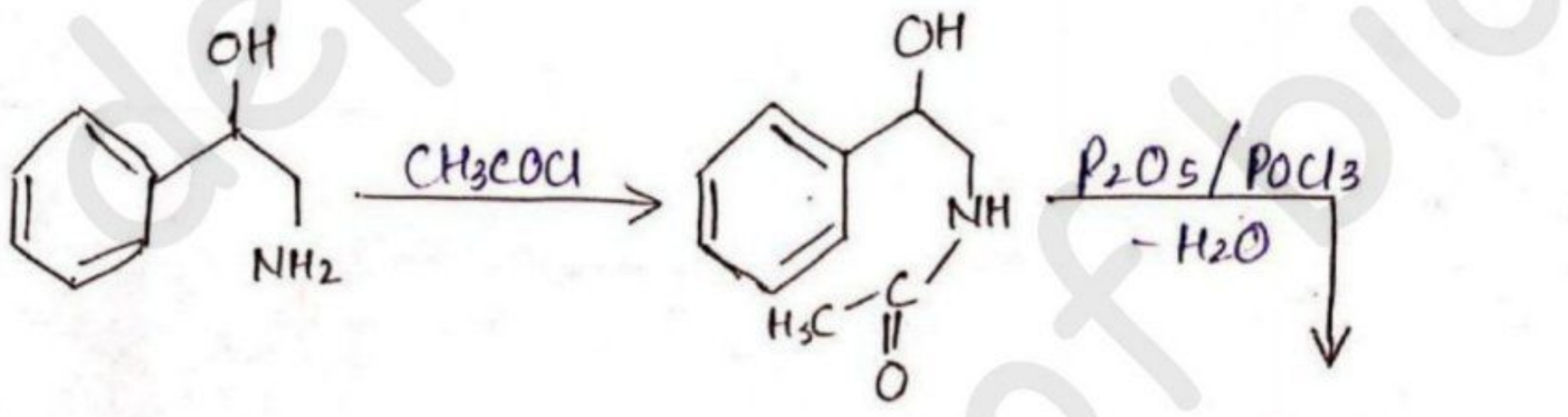
[DEPTH OF BIOLOGY]

(b) <u>Pictet-Gams Synthesis</u> :-

It is modification reaction to Bischler-Napieralski' Synthesis

- 2 hydroxy-2-phenylethylamine reacts with acetyl Chloride

gives N- acetyl derivatives, which on treatment with $P_2O_5/POCl_3$ undergoes dehydration, keto-enol tautomerism followed by cyclodehydration gives isoquinoline derivatives.



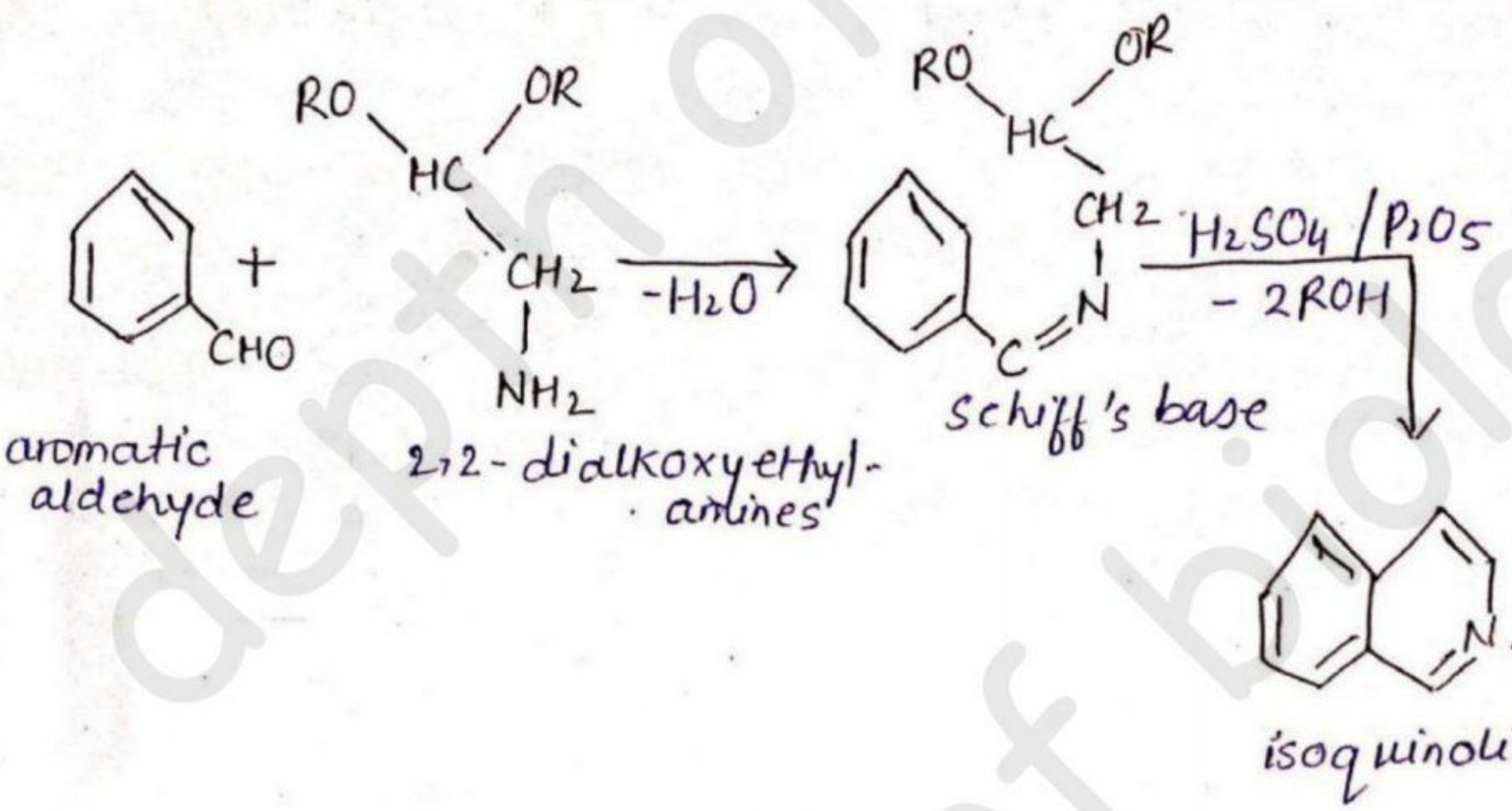
isoquinoline derivatives.

[DEPTH OF BIOLOGY]

[DEPTH OF BIOLOGY]

(c) Pomeranz - Fritsch Synthesis -

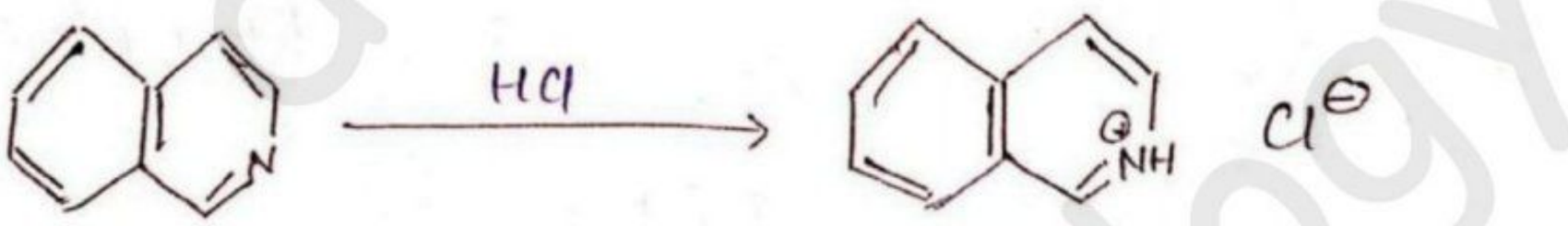
- Condensation of aromatic aldehydes with 2,2- dialkoxy ethylamines gives schiff's base, further it, on heating with H_2SO_4 / P_2O_5 gives isoquinoline derivatives.



• Reaction of Isoquinolines :-

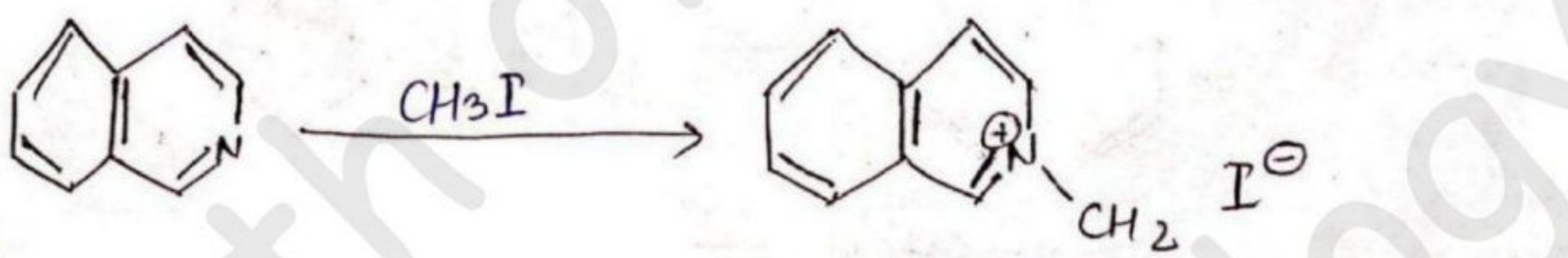
[DEPTH OF BIOLOGY]

(a) Reaction with acid (Protonation) gives isoquinolinium Chloride salt :-

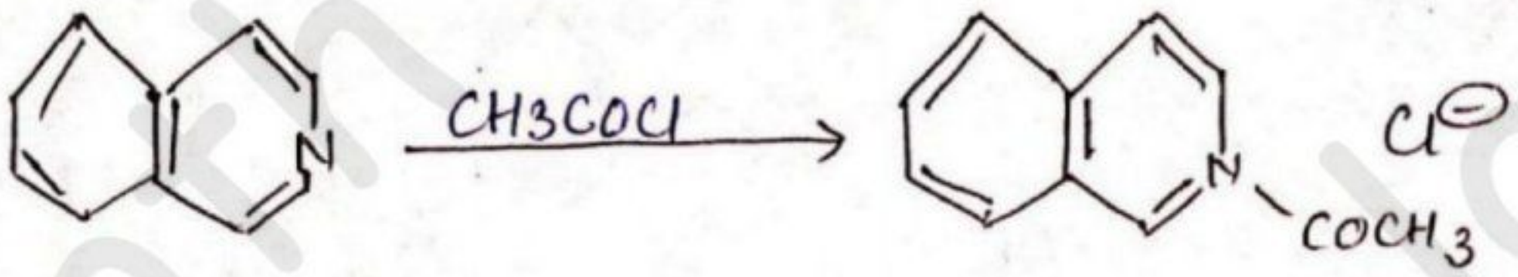


(b) Reaction with methyl iodide (N-alkylation) gives N-methyl isoquinolinium iodide :-

[DEPTH OF BIOLOGY]

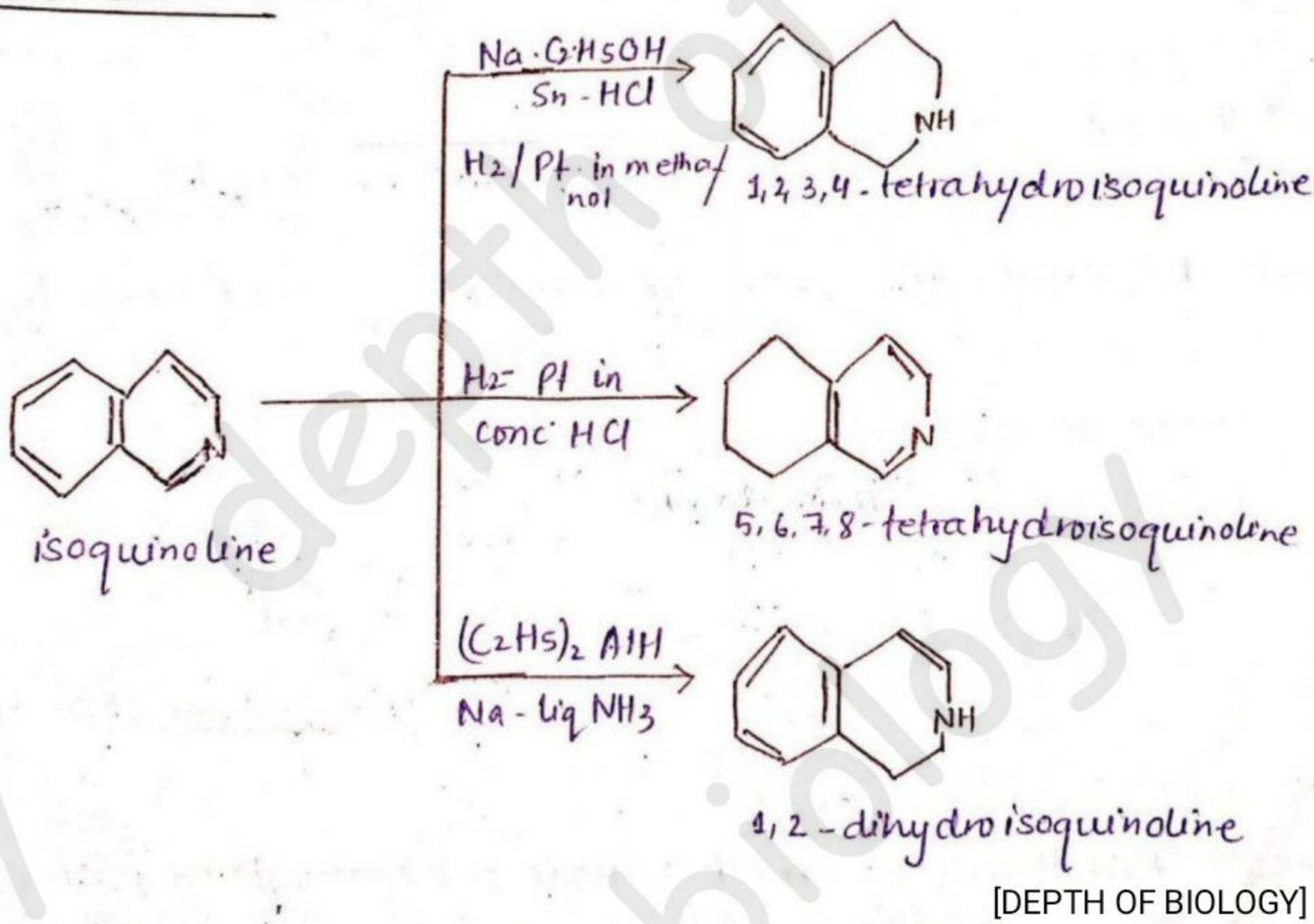


(c) Reaction with acetyl chloride (N-acylation)



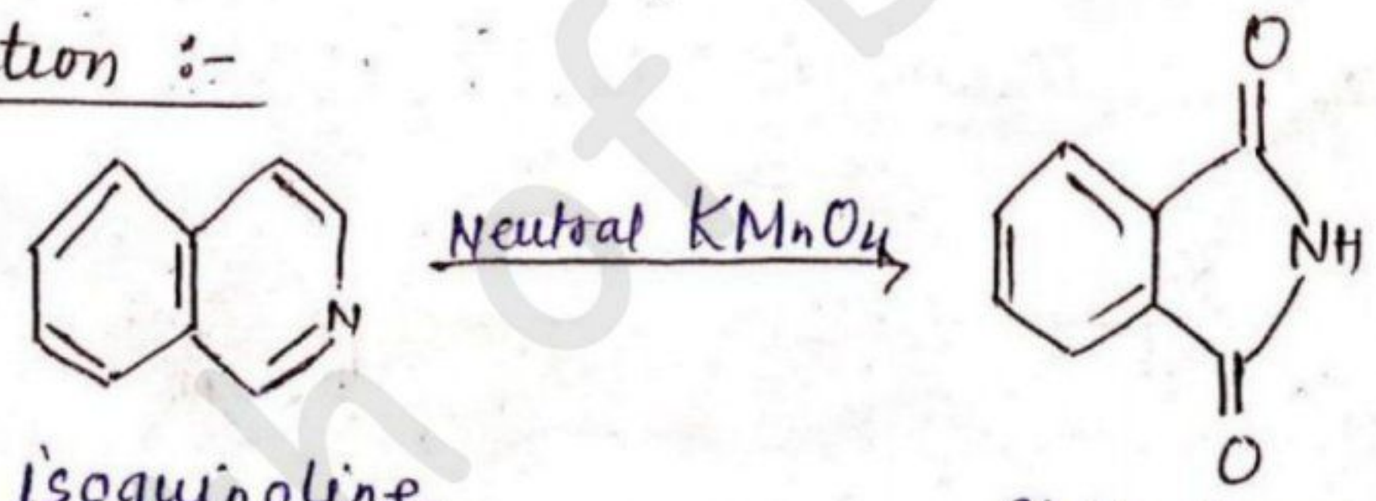
N-acetyl isoquinolinium chloride

(d) Reduction :-



isoquinoline

(e) Oxidation :-



Isoquinoline

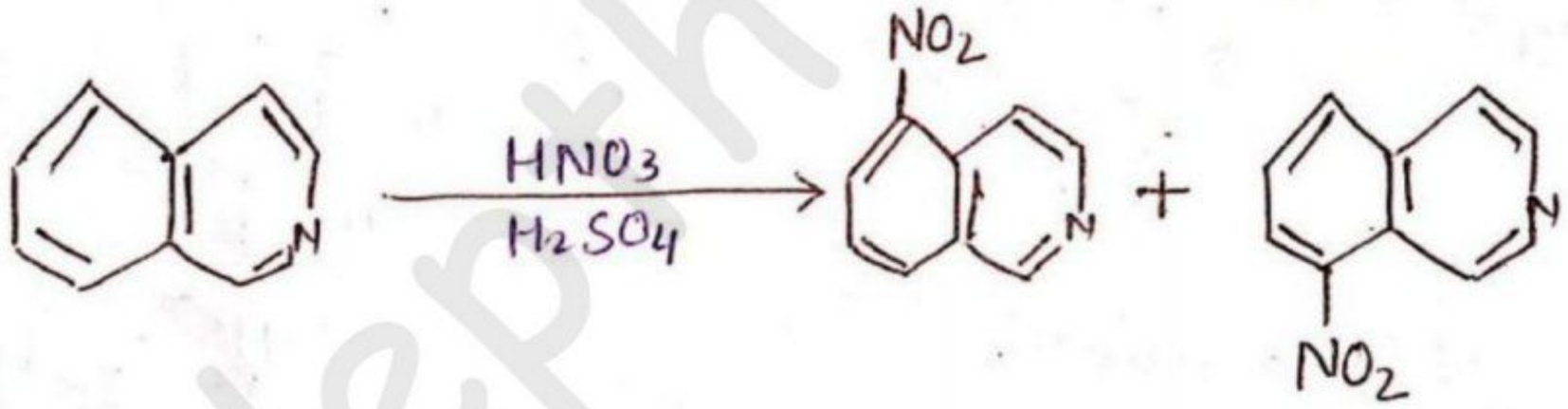
Phthalimide

(f) Electrophilic aromatic substitution reactions –

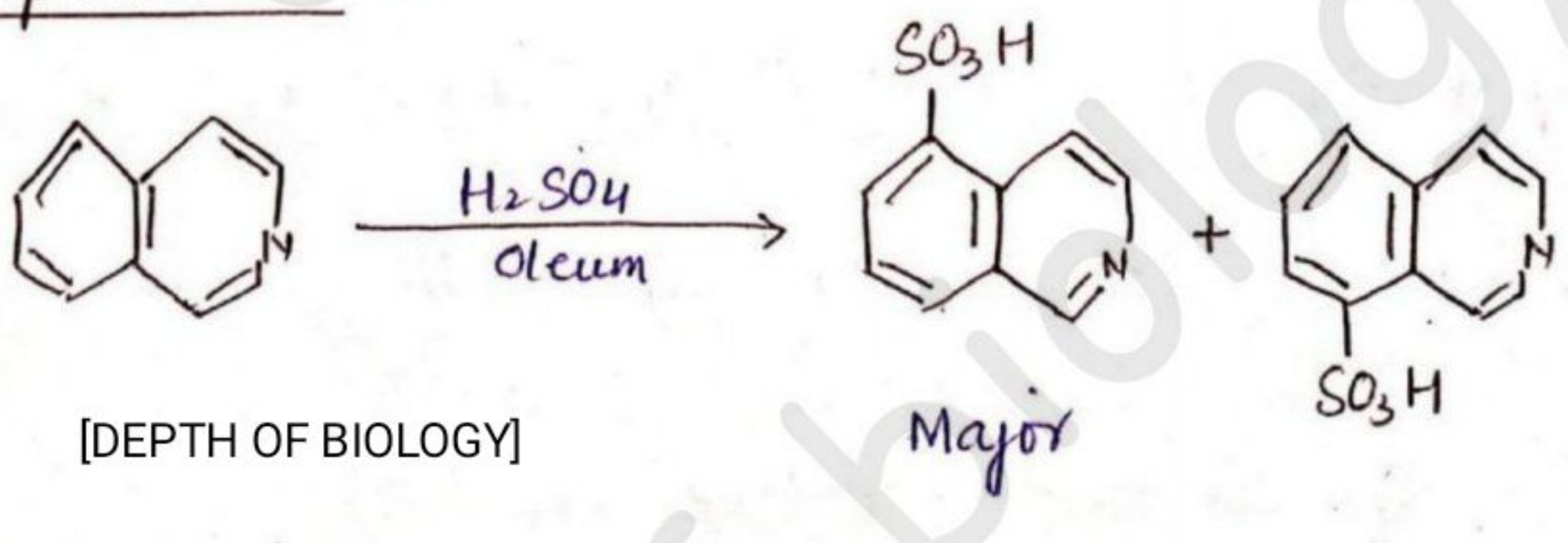
– Substitution takes place at 5th position and 8th position. Electrophilic aromatic substitution of quinoline gives mixture of 5-substituted and 8-substituted derivatives (9:10)

[DEPTH OF BIOLOGY]

(i) Nitration :-

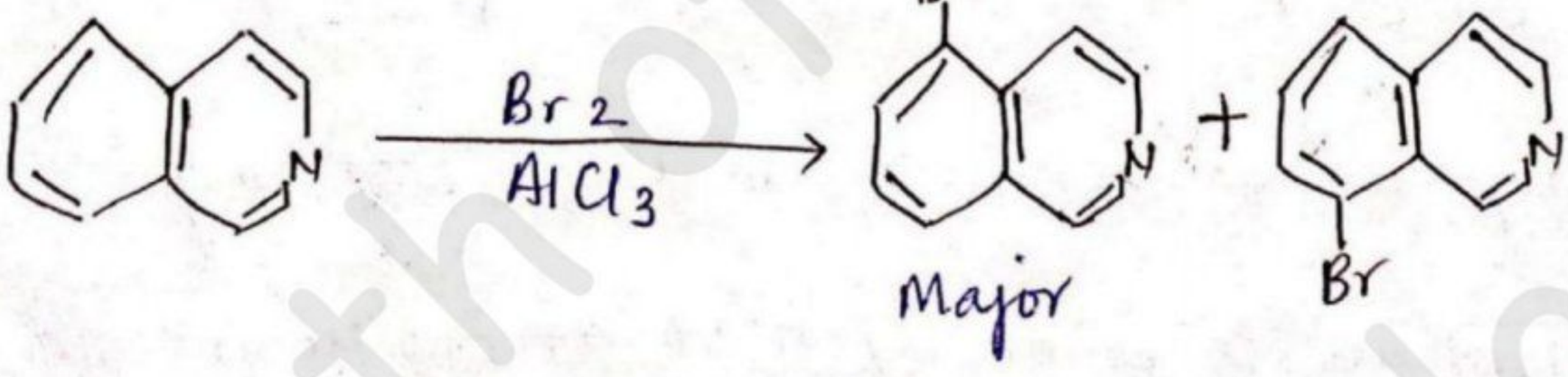


(ii) Sulphonation :-



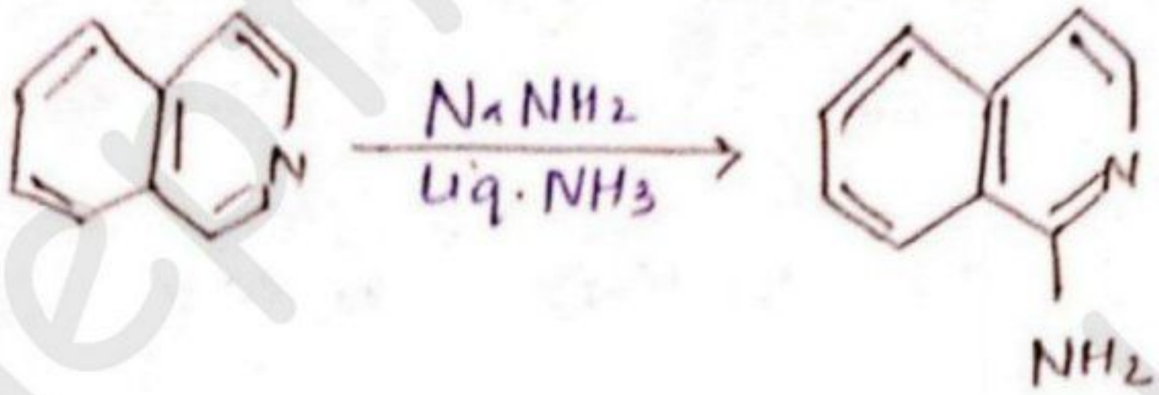
[DEPTH OF BIOLOGY]

(iii) Bromination :-

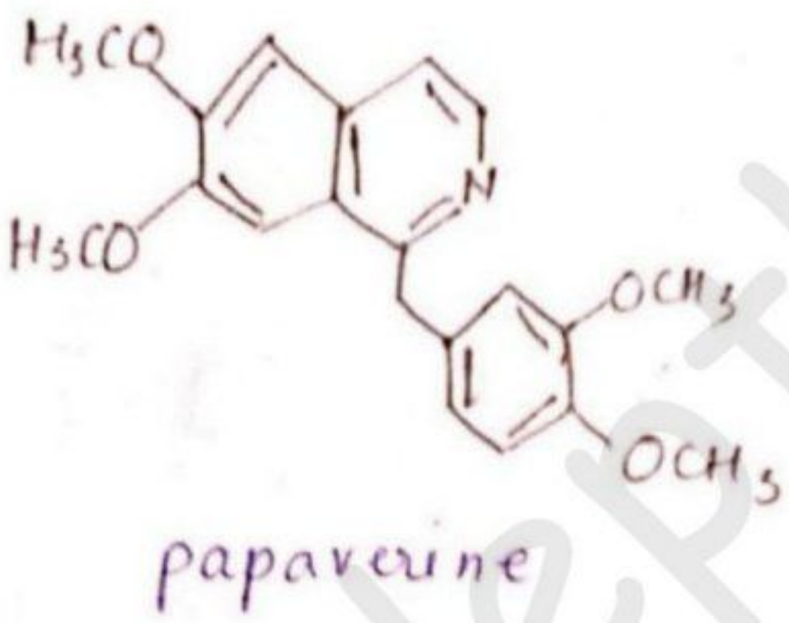


(9) Nucleophilic Substitution :-

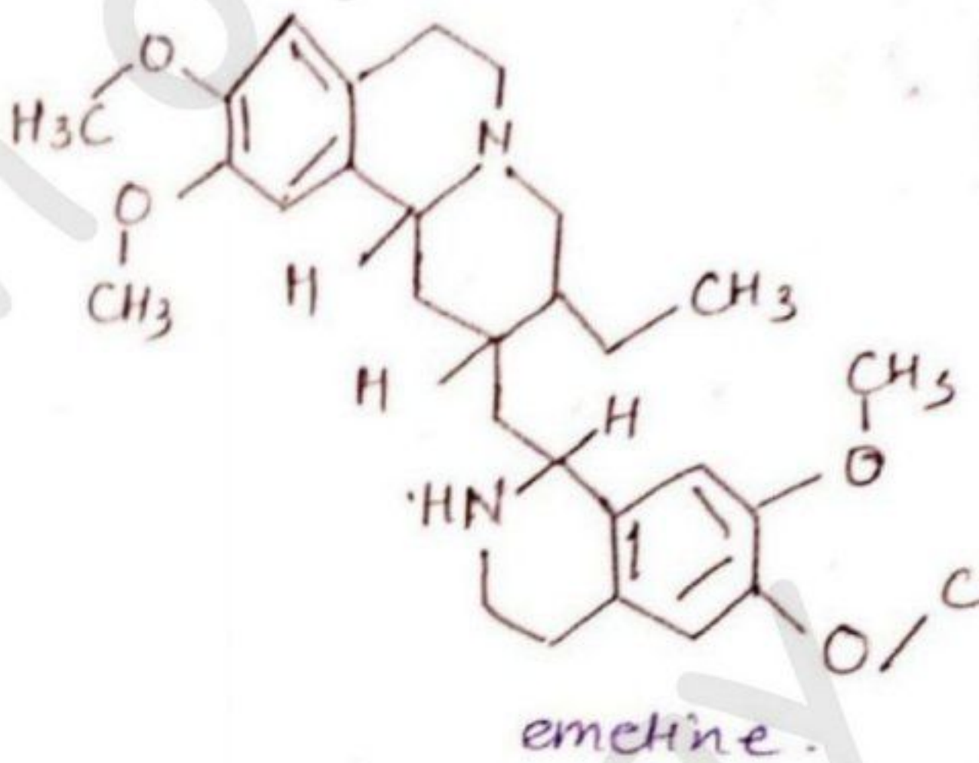
- It takes place at 1st position



- Medicinal Uses :-



papaverine



emetine.

- Papaverine is a vasodilator acts as smooth muscle relaxant used to treat many condition that cause spasm of smooth muscles.

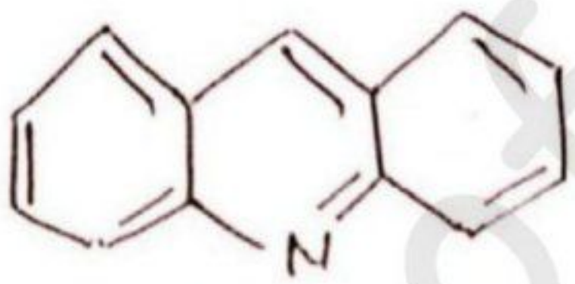
- Emetine is ipecac alkaloids used as both an antiprotozoal and to induce vomiting.

- Narcotine is primarily used as antitussive agent - (cough suppressed)

- Quinapril is ACE inhibitor used as anti-hypertensive drug. lower the high blood pressure, prevent strokes heartattack.

- **Acridine :-**

Structure :-



[DEPTH OF BIOLOGY]

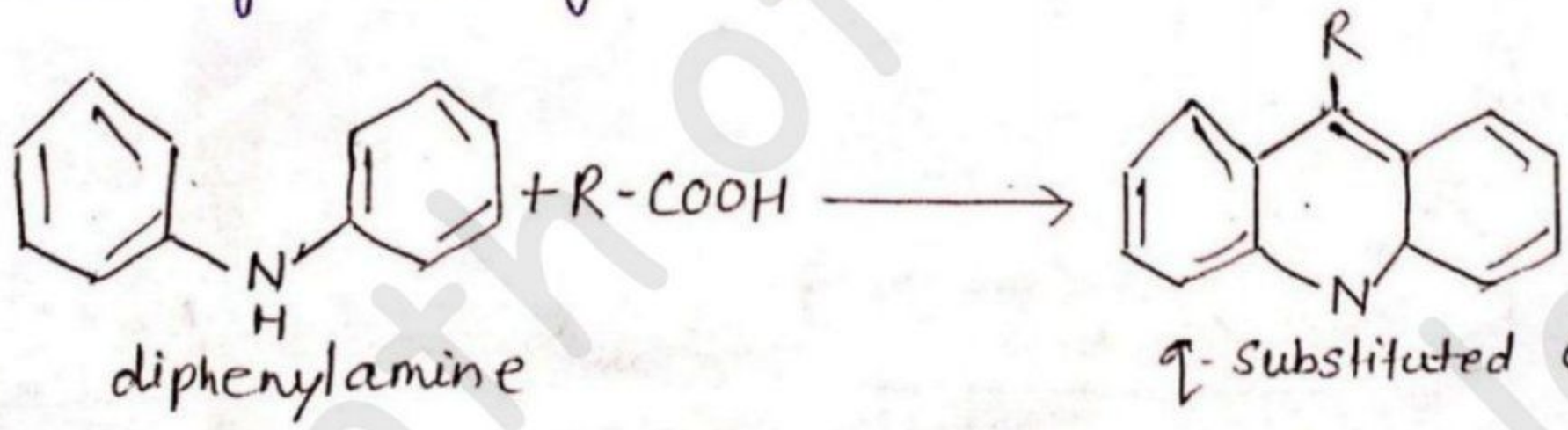
- Acridine is fused heterocyclic compound in which 2 Benzene rings fused with pyridine.

- It consist of nitrogen as hetero atom at 10^{th} Position

- **Synthesis of acridine -**

(a) **Bernthsen acridine Synthesis :-**

- Diphenylamine on heating with carboxylic acids in presence of $ZnCl_2$ gives 9-substituted acridine.

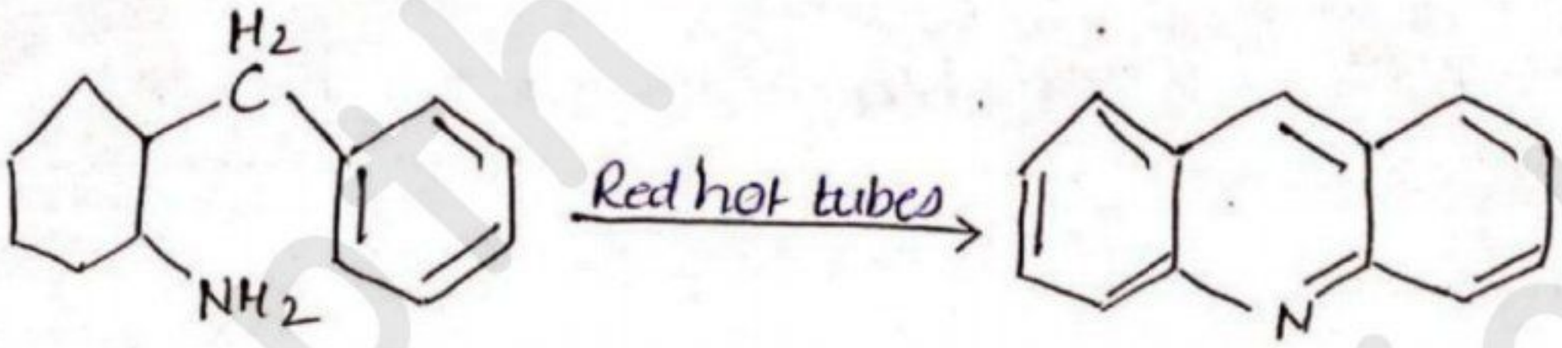


diphenylamine

9-substituted acridines

[DEPTH OF BIOLOGY]

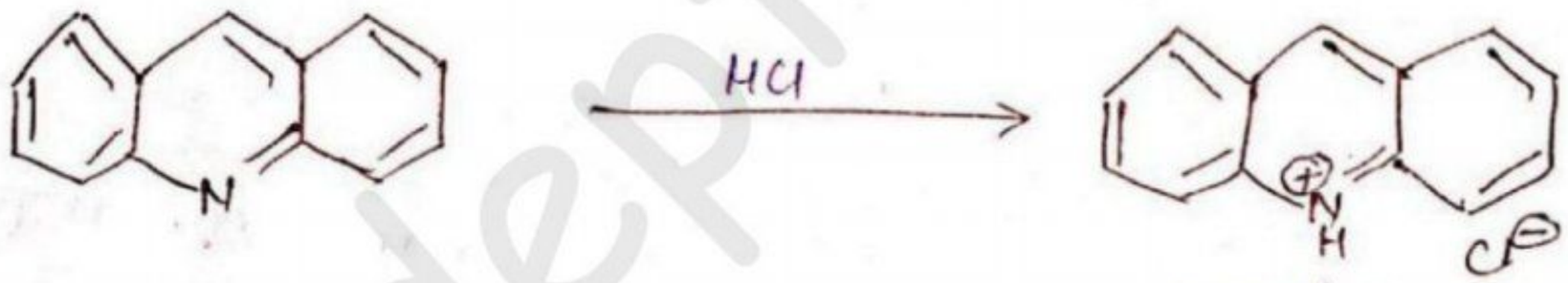
(b) From o-aminodiphenylmethane :-



o-aminodiphenylmethane — acridine

- Reactions of Acridines :-

(a) Reaction with acid (Protonation) gives acridinium salts :-

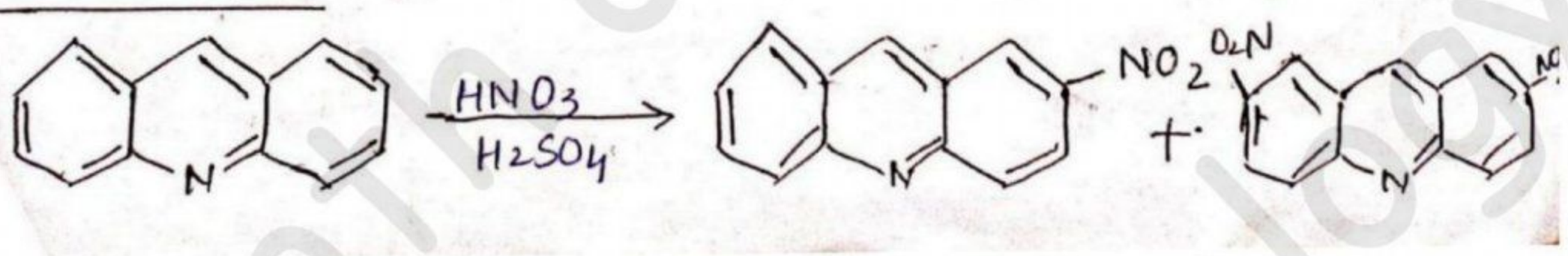


acridinium chloride.

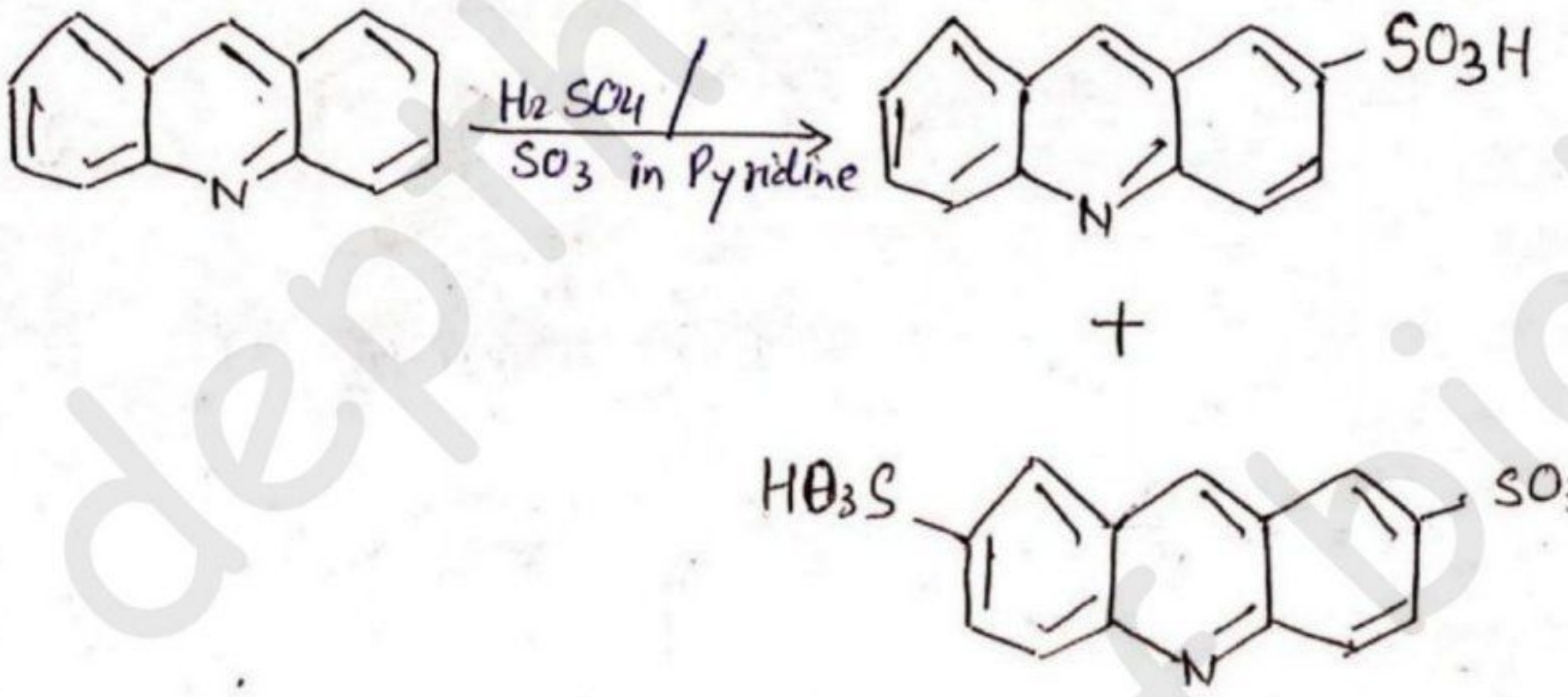
(b) Electrophilic aromatic substitution reaction -

- Electrophilic substitution Reactions of acridines gives mixtures of 2-substituted ad 2,7-disubstituted derivatives

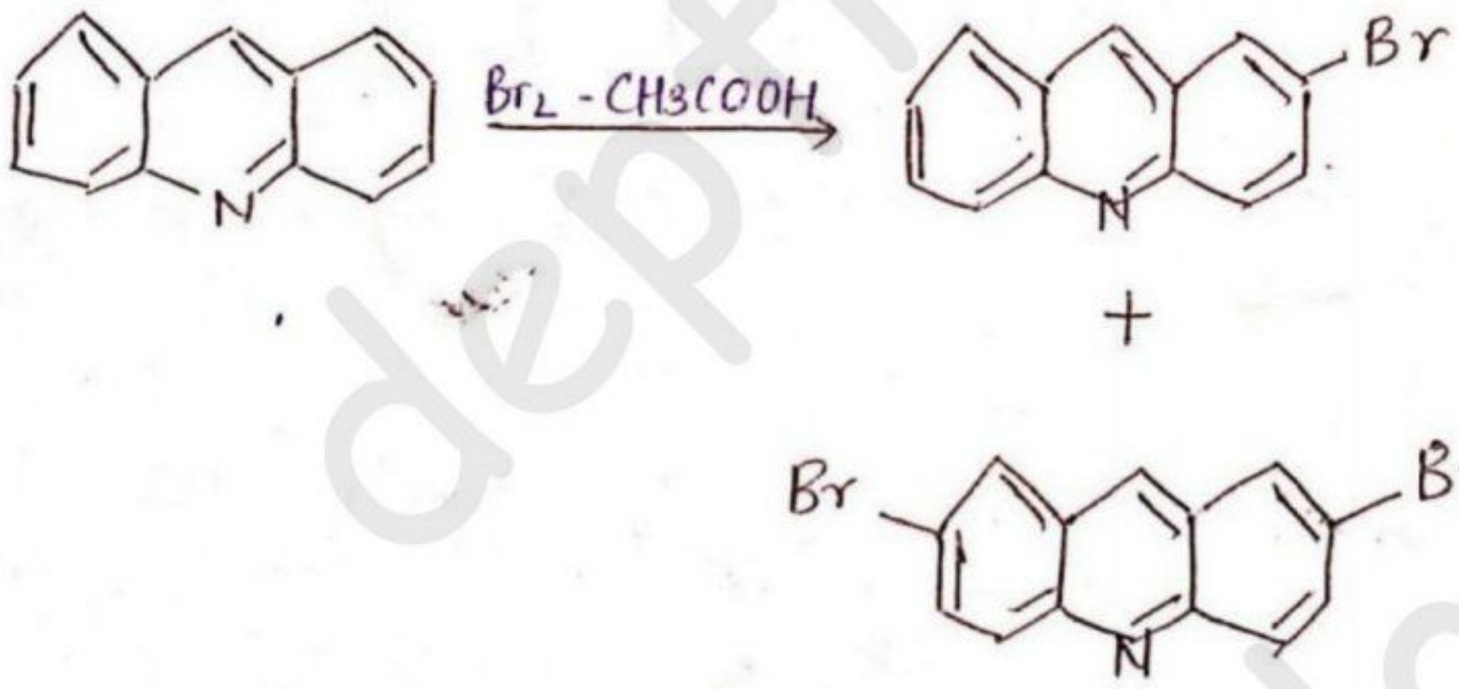
(i) Nitration :-



(ii) Sulphonation :-

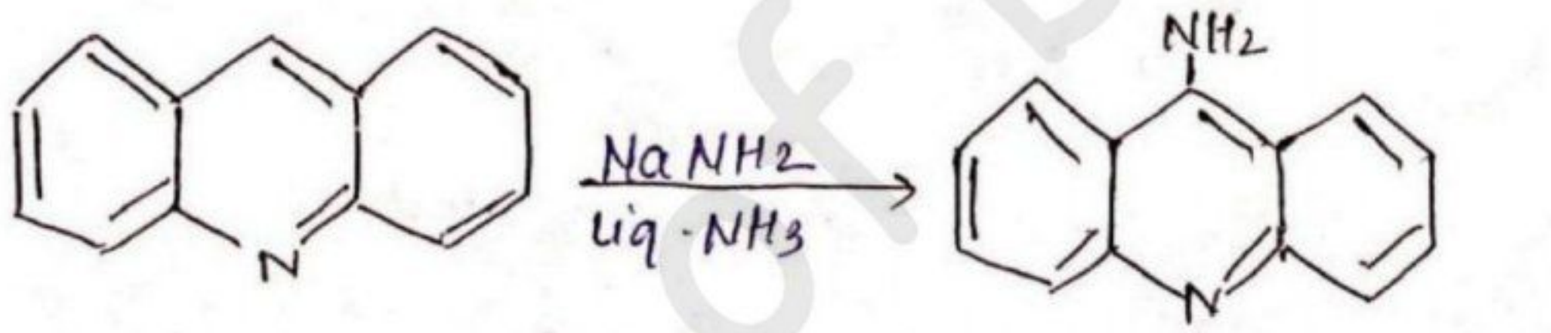


(iii) Bromination :-



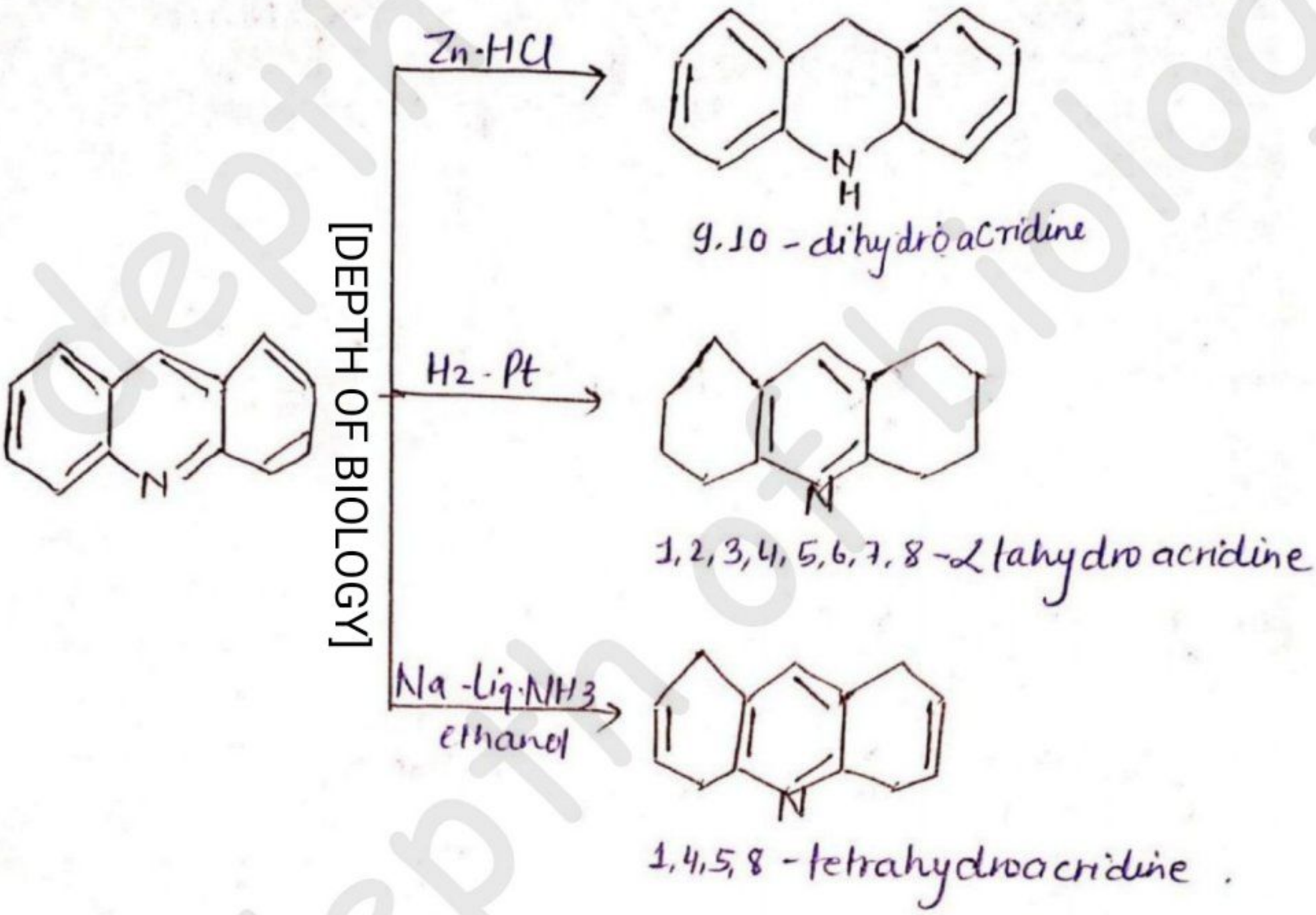
(d) Nucleophilic substitution -

This substitution takes place at 9th position

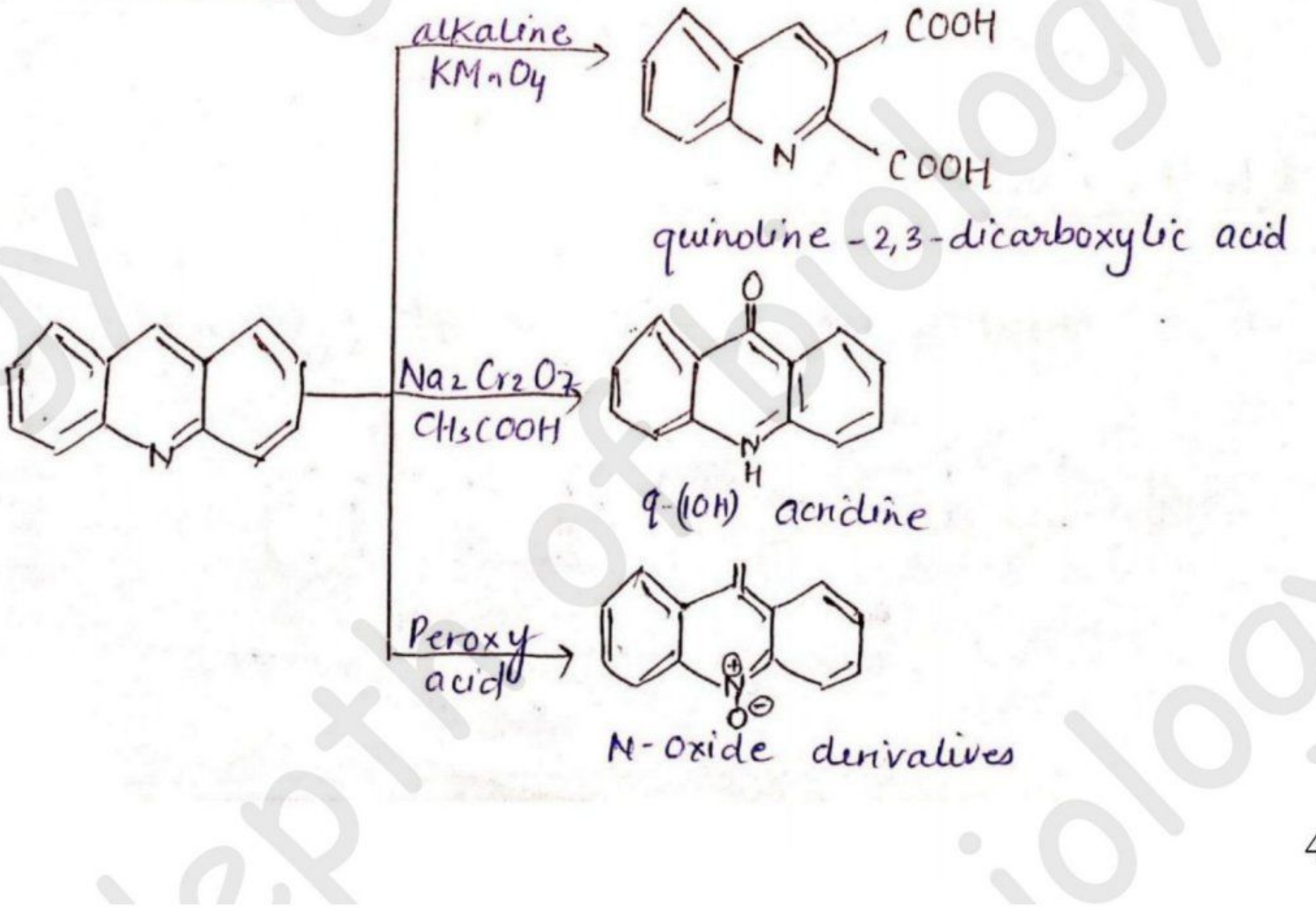


9-aminoacridine

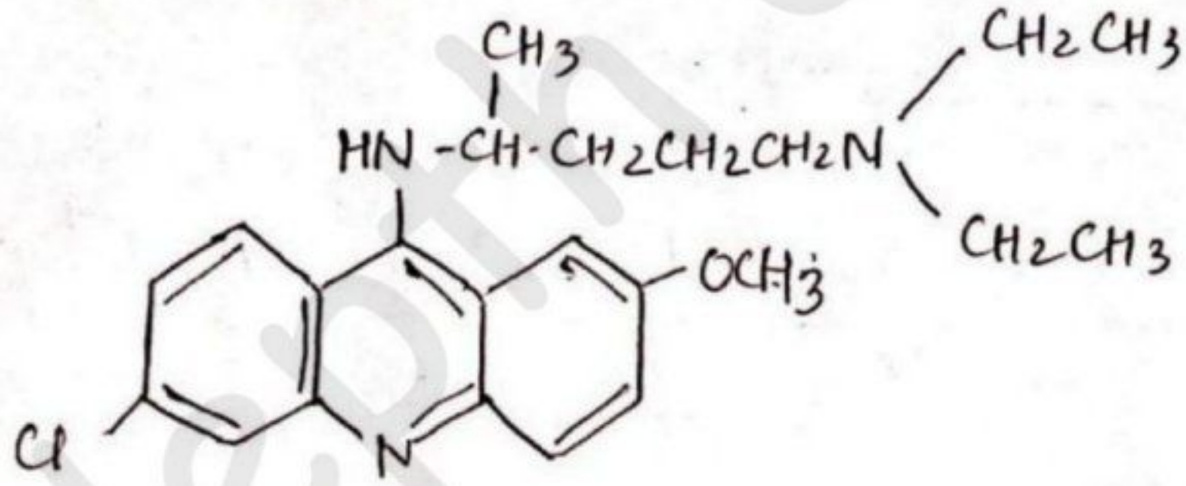
(e) Reduction :-



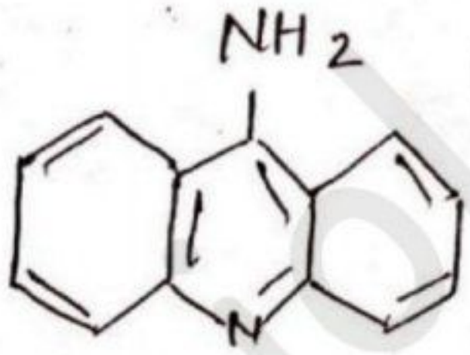
(f) Oxidation :-



- Medicinal uses :-



Quinacrine



Aminacrine

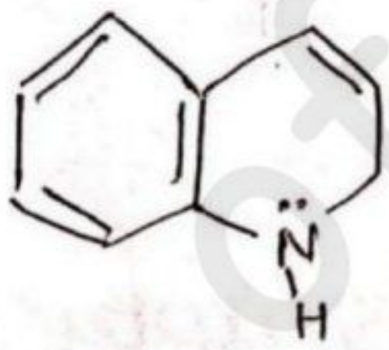
- Quinacrine is used for malaria, tapeworm, infection and giardiasis.

- Aminacrine produce germicidal actions against gram ⊕ve and gram ⊖ve bacteria against fungi and trichomonads, in the treatment of vaginal candidiasis.

- Proflavine is a disinfectant, antiseptic.

- Indole :-

- Structure :→



- Indole is a fused heterocylic compound in which benzene ring fused with pyrrole.

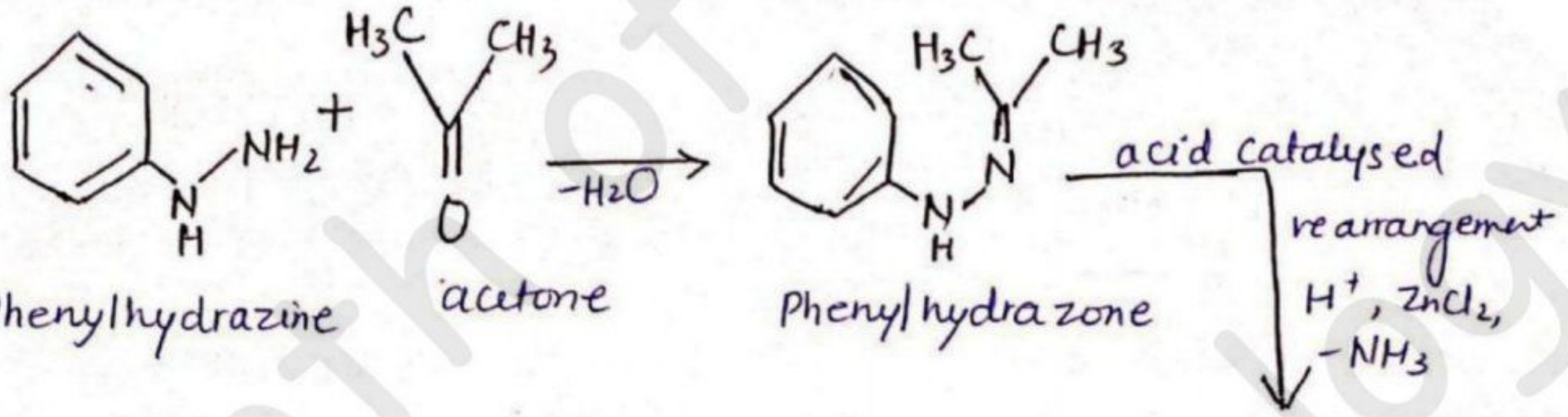
- It consist of nitrogen as heteroatom at 1st position

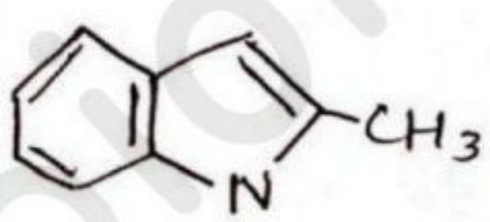
- Synthesis of Indole -

(a) Fischer indole Synthesis :-

- Reaction of arylhydrazine(phenylhydrazines with aldehyde or ketone (acetone) gives respective arylhydrazones (phenylhydrazones).

- Aryl hydrazones undergo acid-catalysed re-arrangement (in presence of acid and $ZnCl_2$) to form indole with the elimination of ammonia.

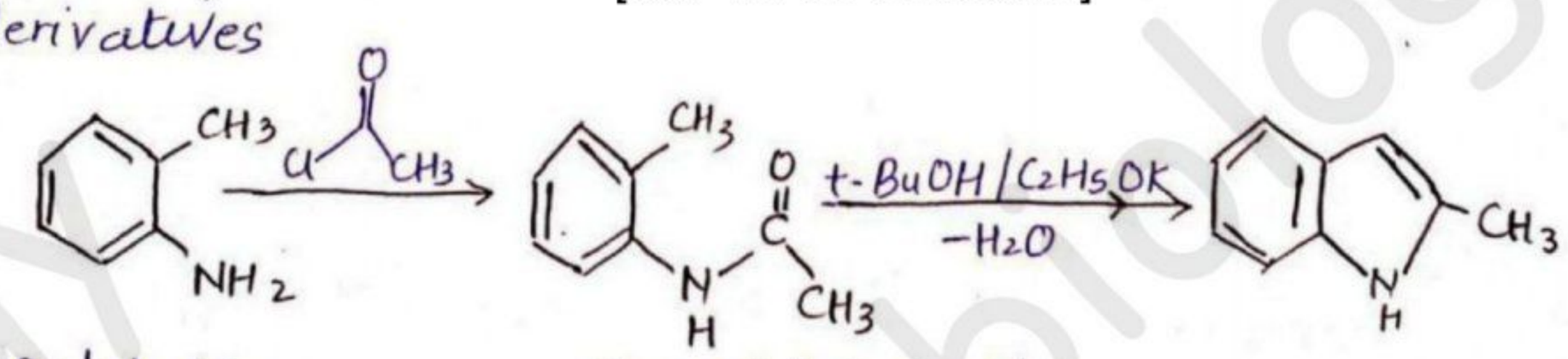




(b) Madelung indole synthesis :-

2-methyl aniline (o-toludine) reacts with acetyl chloride gives respective N-acetyl derivatives (o-methyl-N-phenylamide) derivatives. Further, it on heating with strong base (t-BuOH/ C_2H_5OK/ KOH) undergo cyclodehydration and gives indole

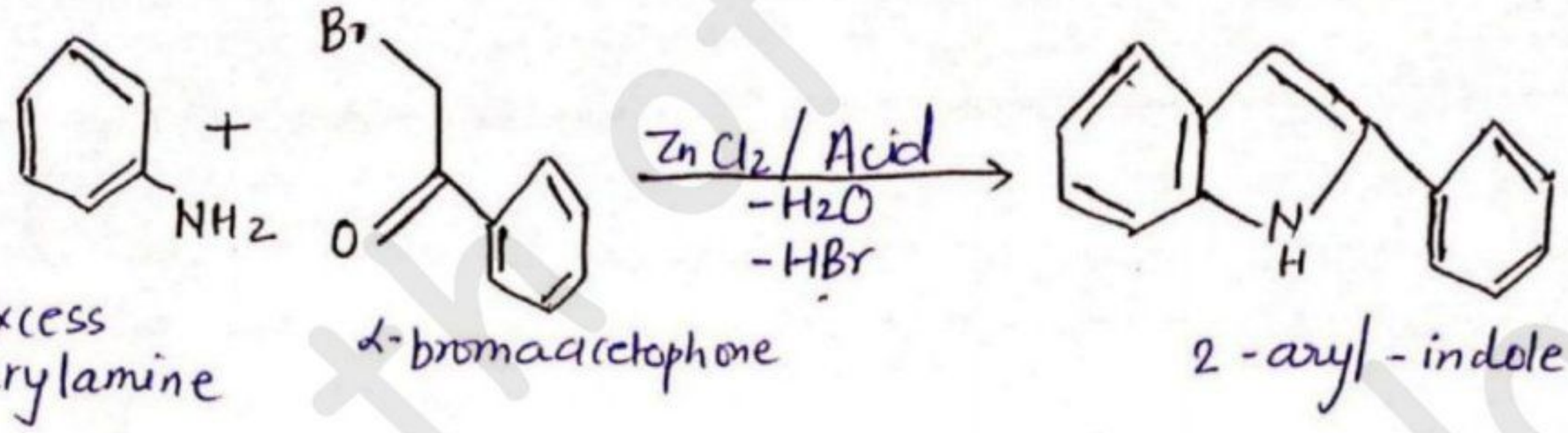
derivatives



or

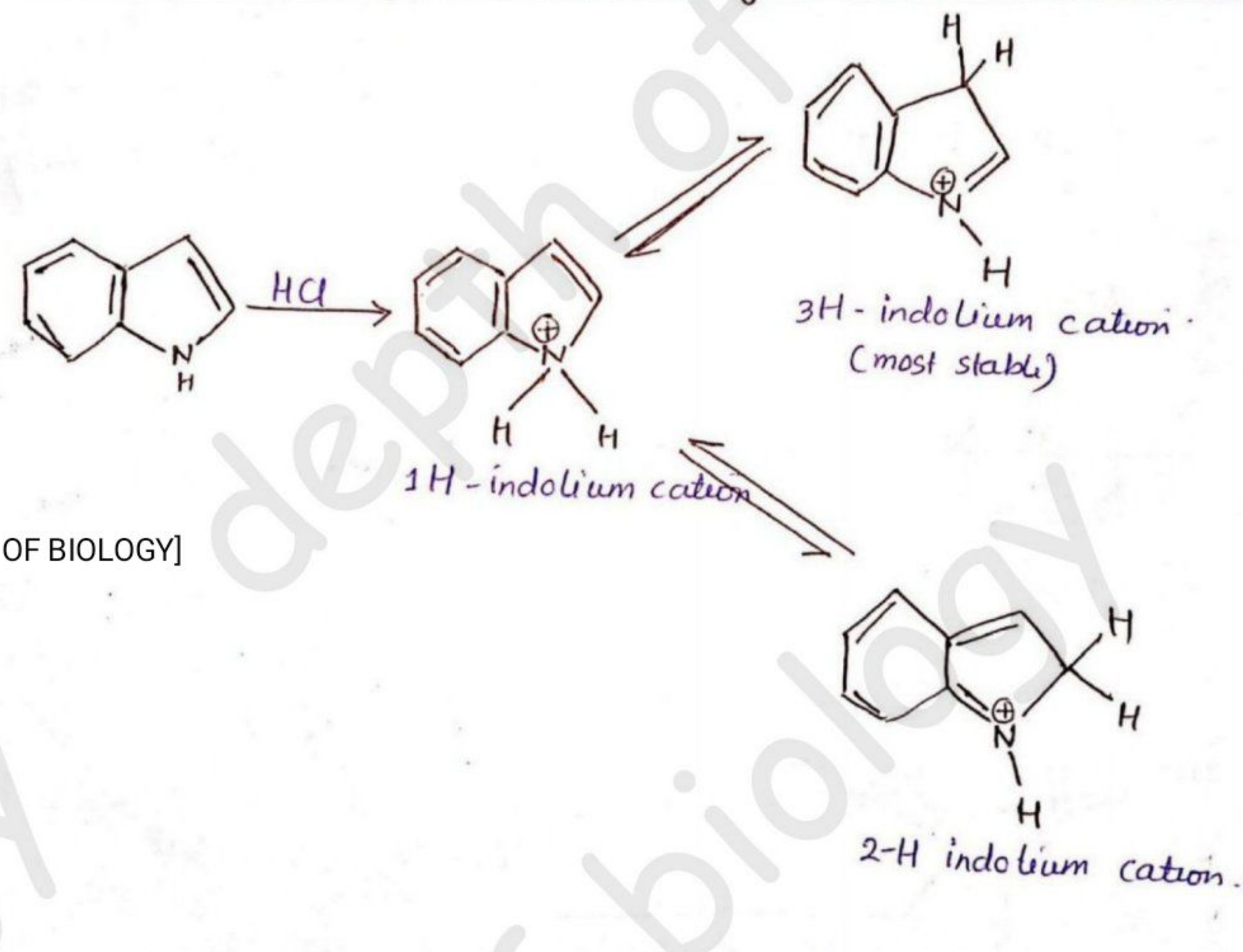
anilide derivative

(c) Bischler indole synthesis :- Reaction of α-bromo-acetophenone and excess of arylamine in presence of $ZnCl_2$ or acid forms 2 aryl-indole.



- Reactions of Indole :-

(a) Reaction with acids (Protonation) gives indolium cation -



(b) Electrophilic aromatic substitution Reaction of indole -

[DEPTH OF BIOLOGY]

- It undergoes electrophilic substitution mainly at position 3

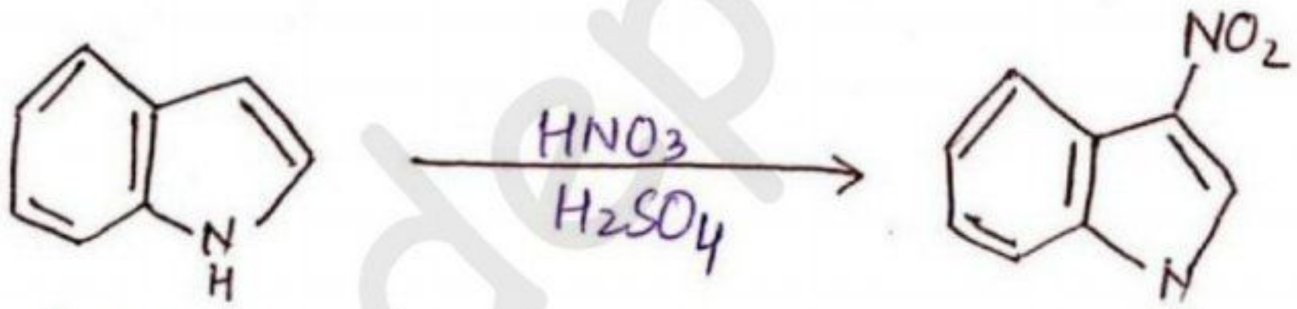
- Generally, electrophilic substitution reaction takes place at position 3 rather position 2.

- The attack of electrophile at position 3 generates carbocation which disrupts the aromatic character by delocalizing, the positive charge over benzene ring

[DEPTH OF BIOLOGY]

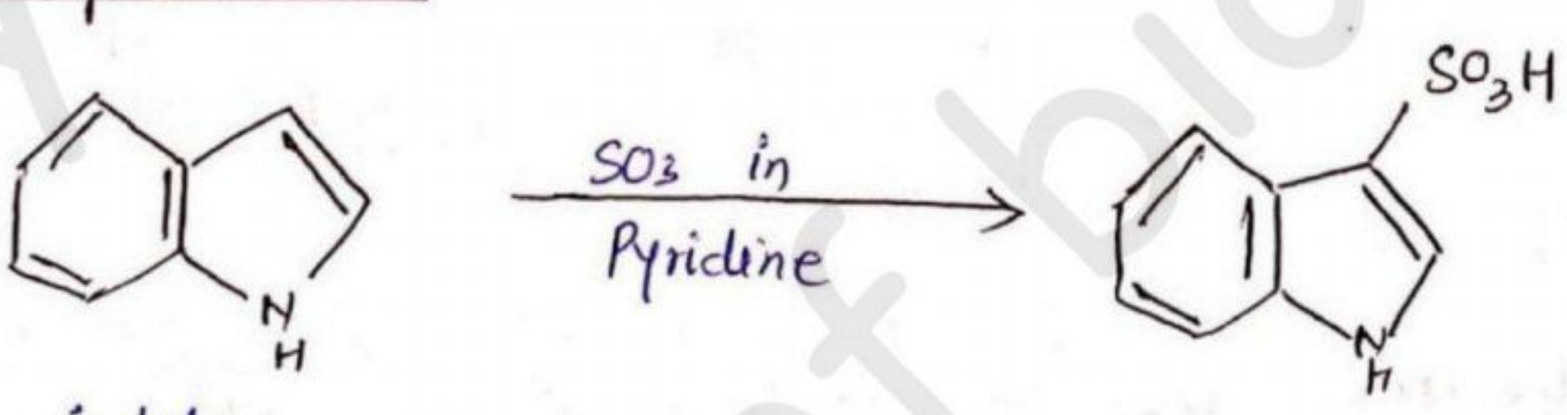
(i) Nitration :-

[DEPTH OF BIOLOGY]



indole

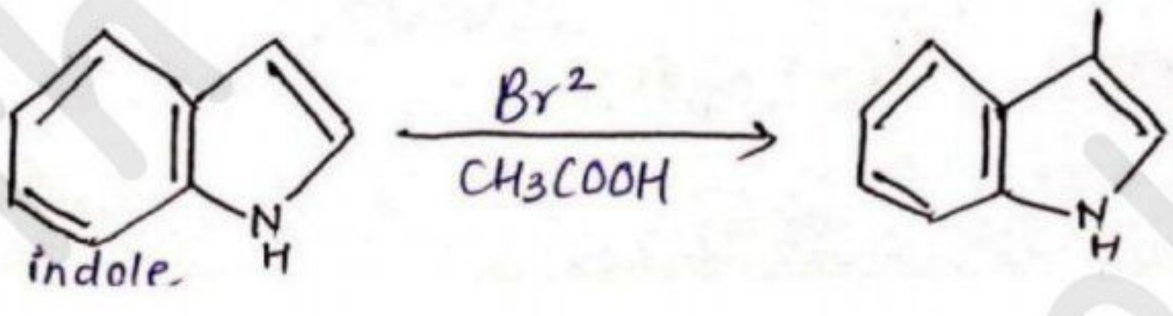
(ii) Sulphonation -



indole

[DEPTH OF BIOLOGY]

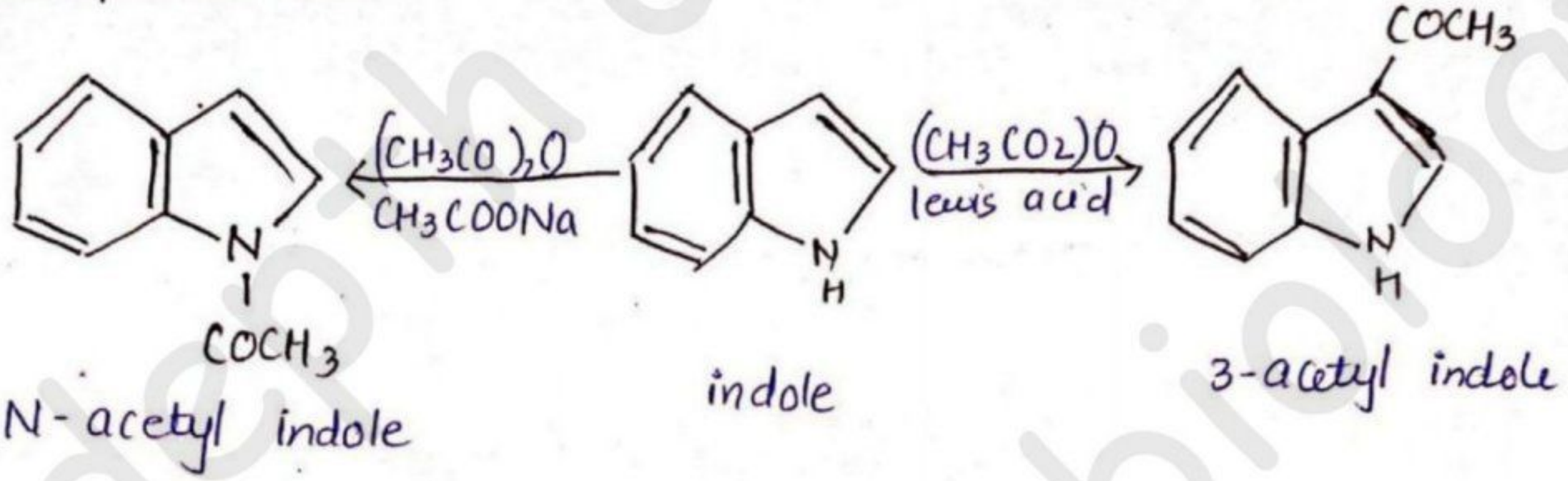
(iii) Bromination -



indole

(3.) Acetylation :-

[DEPTH OF BIOLOGY]

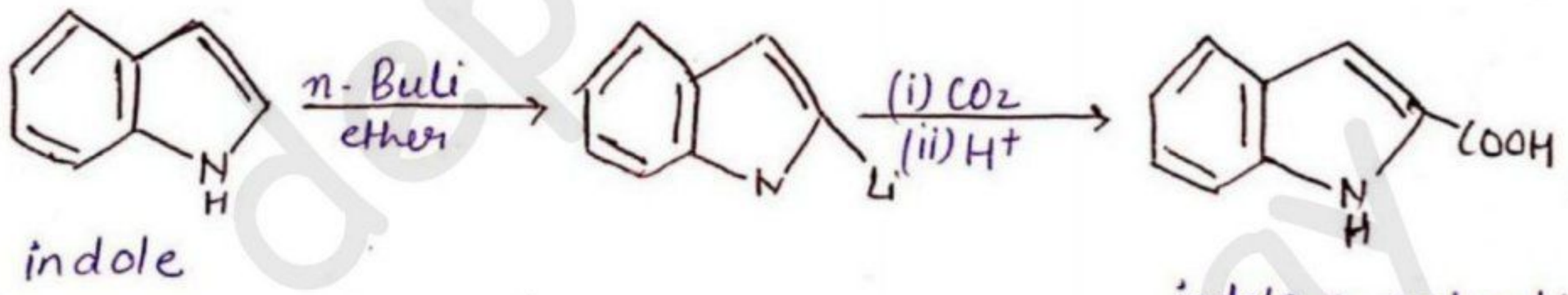


N-acetyl indole — indole — 3-acetyl indole

(d) Nucleophilic Substitution :-

[DEPTH OF BIOLOGY]

- Substitution mainly take place at 2nd position

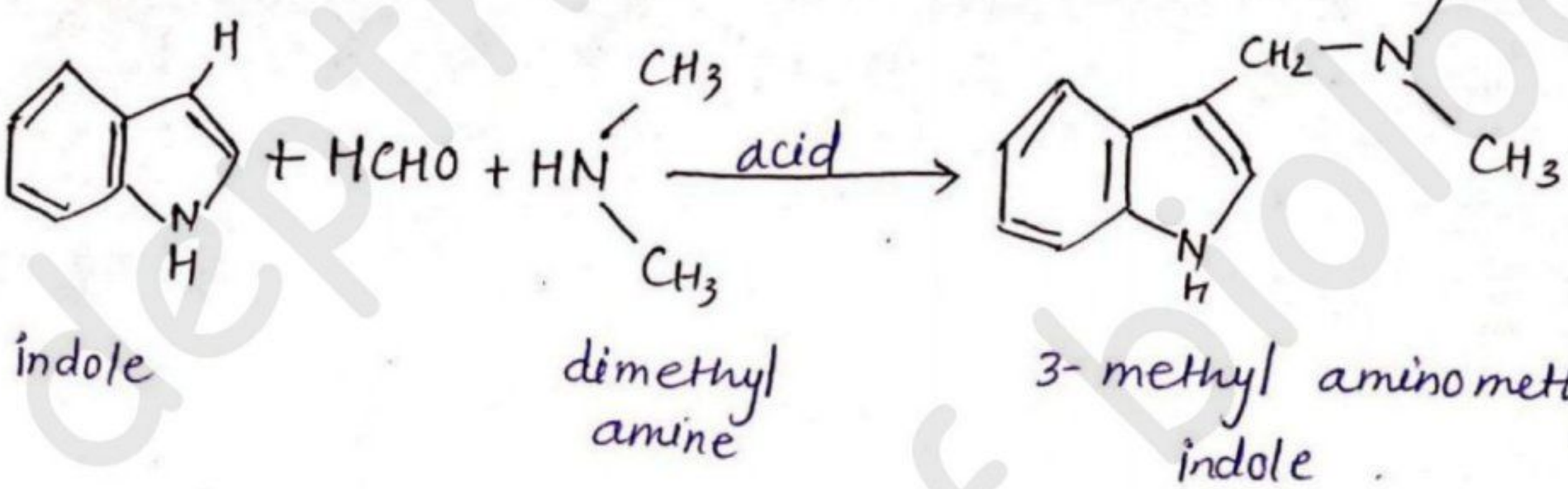


indole — indole 2-carboxylic acid.

(e) Mannich reaction of indole :-

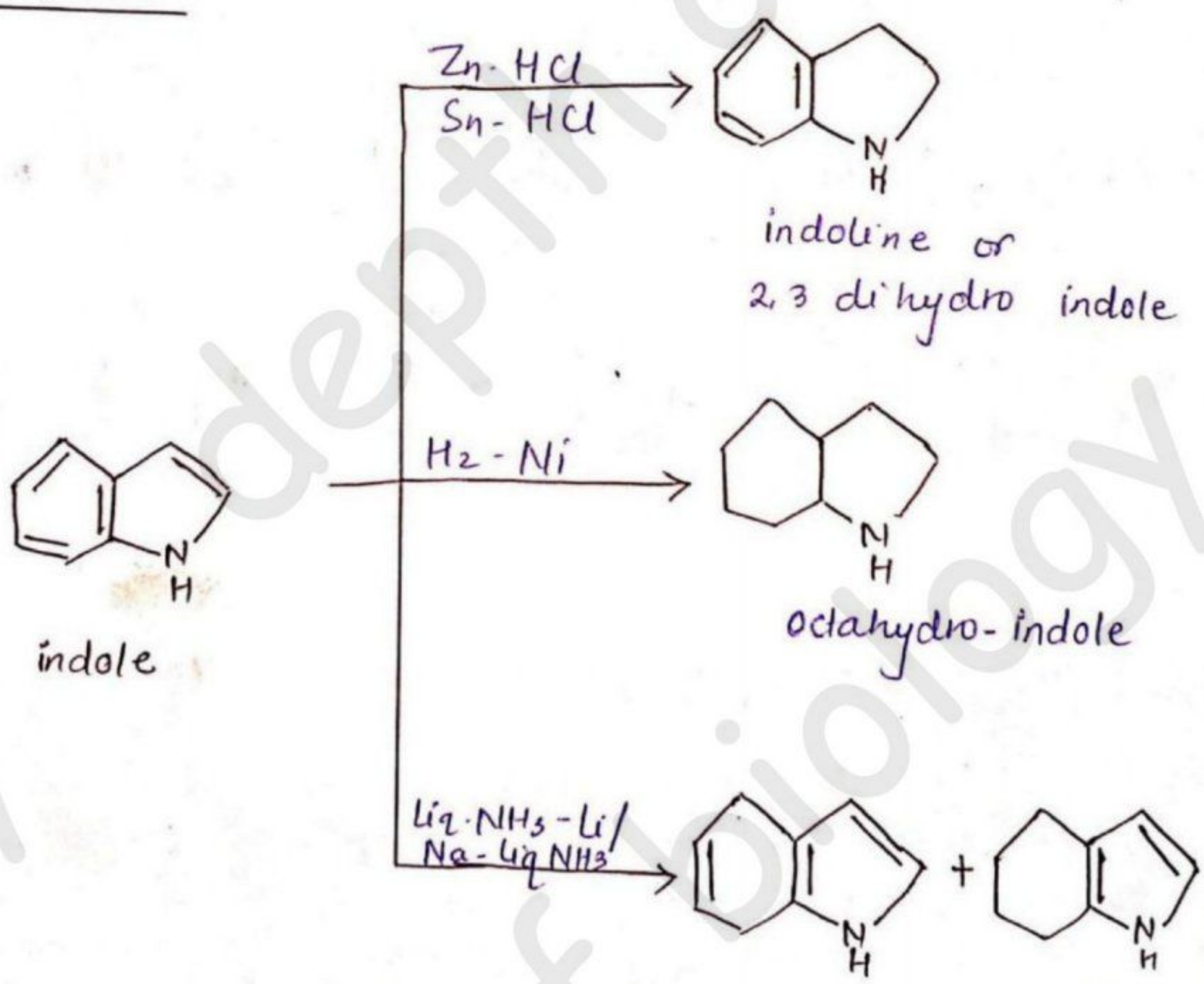
- Enolizable carbonyl compounds / compound containing active hydrogen is treated with HCHO and NH_3 / primary amine / secondary amine in presence of acid leads to replacement of hydrogen with amino alkyl chain (amino-alkylation)

-This is commonly called as Mannich reaction.



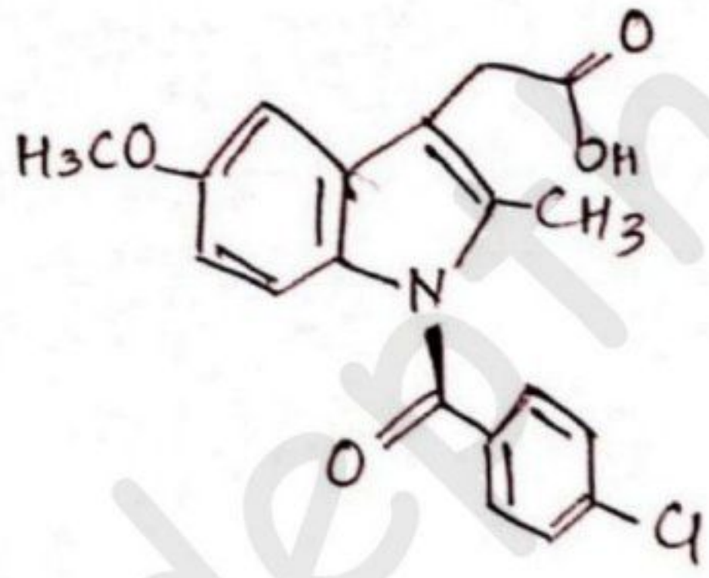
indole | dimethyl amine | 3-methyl aminomethyl indole

(f) Reduction

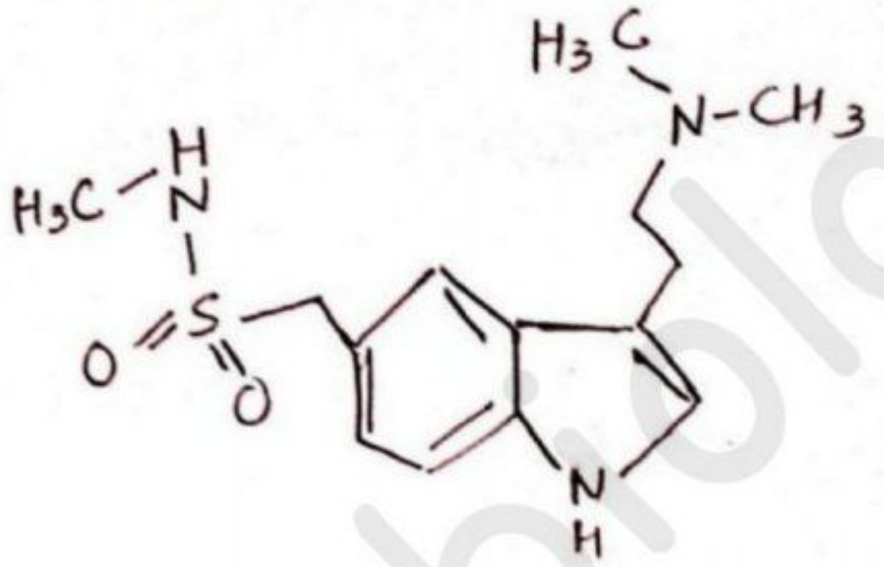


[DEPTH OF BIOLOGY]

- **Medicinal Uses**



Indomethacian



Sumatriptan

– Indomethacin is non-steroid antiflammatory drug (NSAID), used to relief pain, swelling and joint stiffness caused by arthritis gout.

[DEPTH OF BIOLOGY]

- Sumatriptan is used to treat migraine, It is used to relieve headache, pain and other migraine symptoms.

- Pindolol is non selective β-blocker used alone (or) with other medication to treat hypertension and argina pectoris

- Viaca alkoloids (vincristine, vinblastine) - anticancer drug

- Ergot alkaloids :-

(i) Ergometrine :- Used to cause contraction of uterus to treat heavy vaginal bleeding after child birth.

(ii) Ergotamine :- Used to treat migraine type headaches

- Reserpine – antihypertensive and anti-psychotic drug.

- Pyrimidine –

Structure :-

- Pyrimidine is an unsaturated 6 numered heterocyclic ring consist of 2 nitrogen as heteroatoms at 1st and 3rd position.

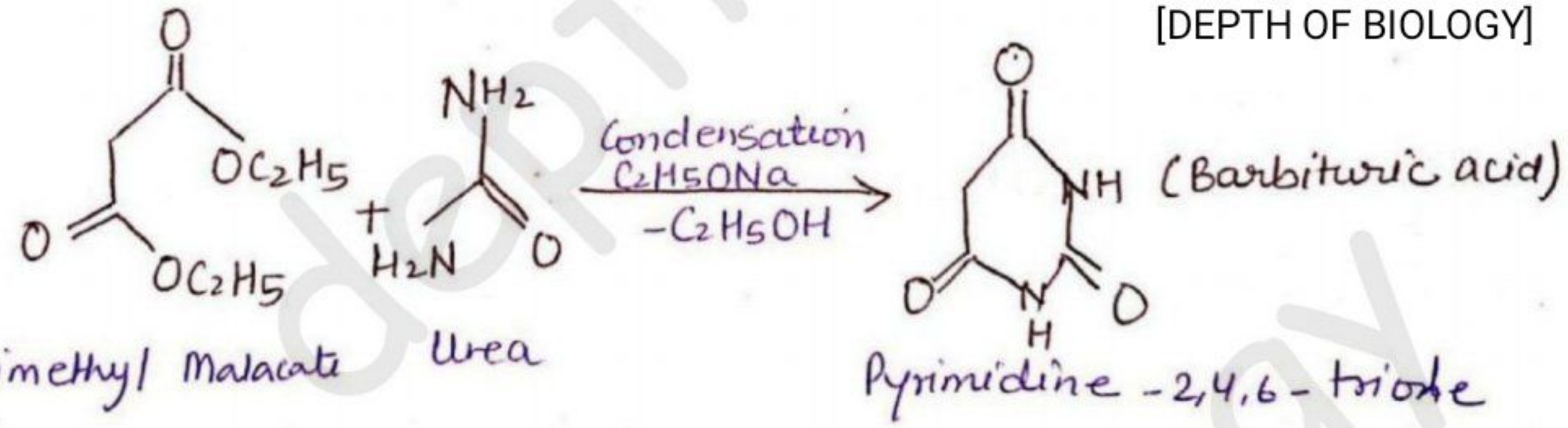
- Synthesis of Pyrimidine :

(a) From malonic esters (1,3-dicarbonyl compounds) –

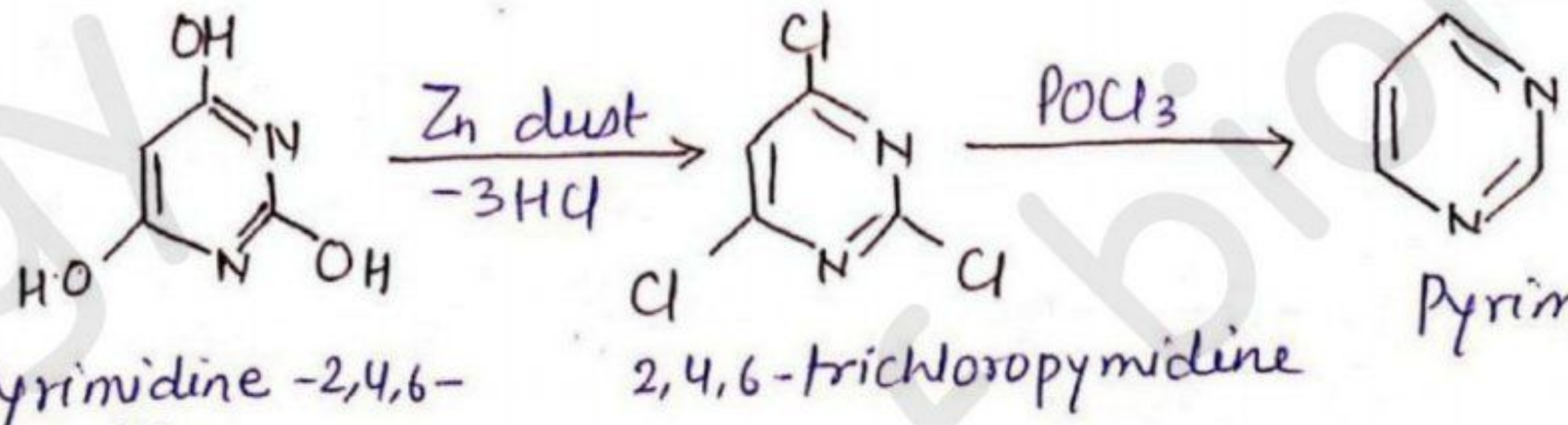
- Condensation of 1,3-dicarbonyl compound with urea in presence of C_2H_5ONa gives barbituric acid, which on Keto-enol tautomerism gives pyrimidines-2,4,6-triol.

- Further, it on treatment with $POCl_3$ followed by treatment with zinc dust gives pyrimidine.

[DEPTH OF BIOLOGY]



dimethyl Malacate Urea Pyrimidine-2,4,6-triole



Pyrimidine-2,4,6-triol. 2,4,6-trichloropymidine Pyrimidine.

(b) From α,β-unsaturated Ketones -

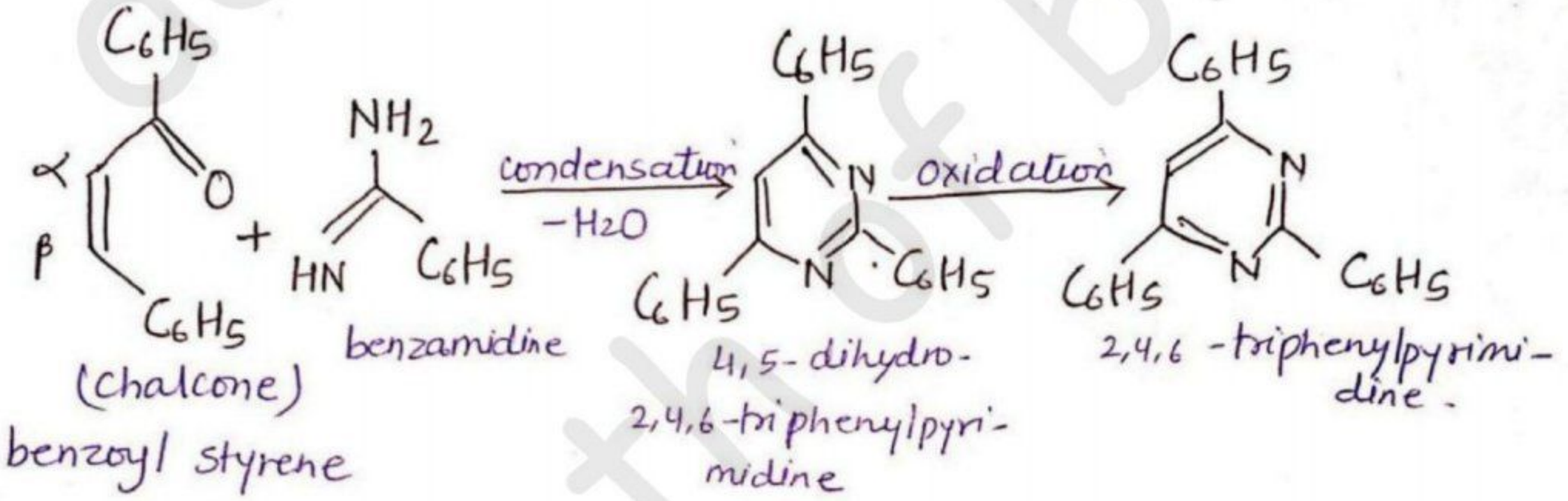
Condensation of α-β unsaturated Ketones with

[DEPTH OF BIOLOGY]

benzamidine undergo dehydration gives 4,5-dihydro-2

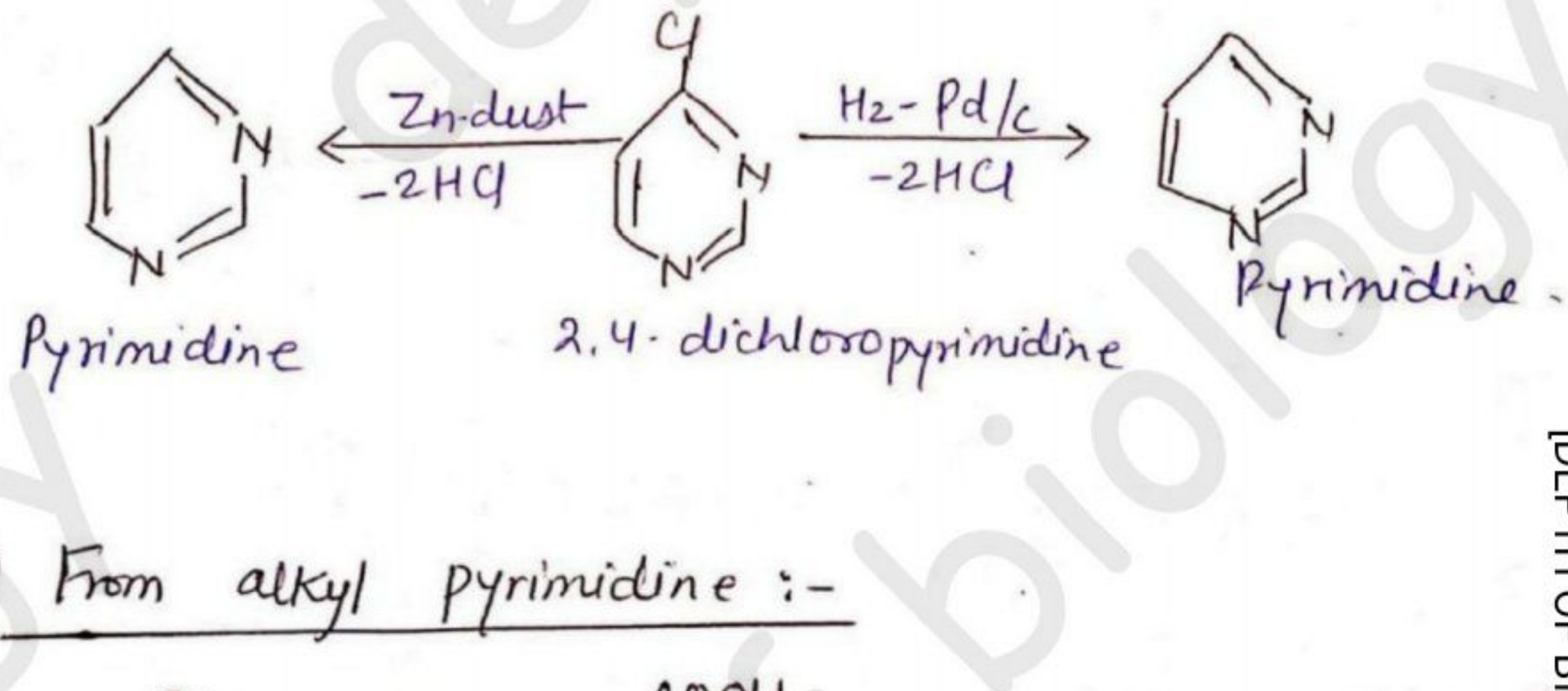
4,6-triphenylpyrimidine.

-Further, it on oxidation gives 2,4,6 triphenylpyrimidine

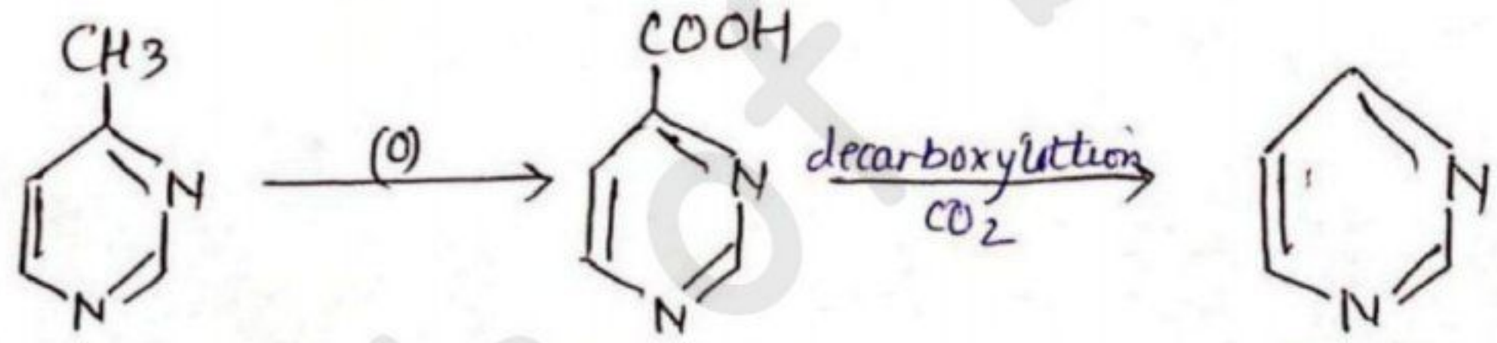


[DEPTH OF BIOLOGY]

(c) From 2,4-dichloropyrimidine –



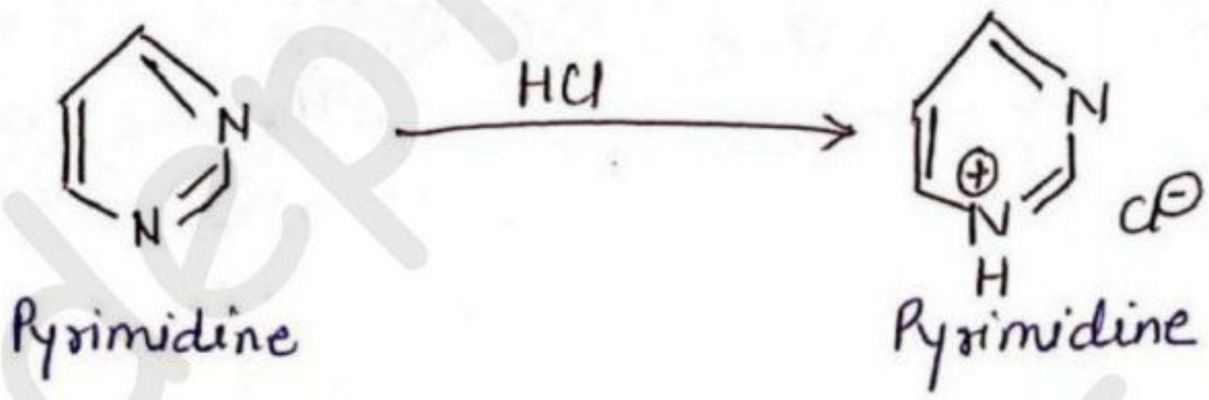
(d) From alkyl pyrimidine :-



[DEPTH OF BIOLOGY]

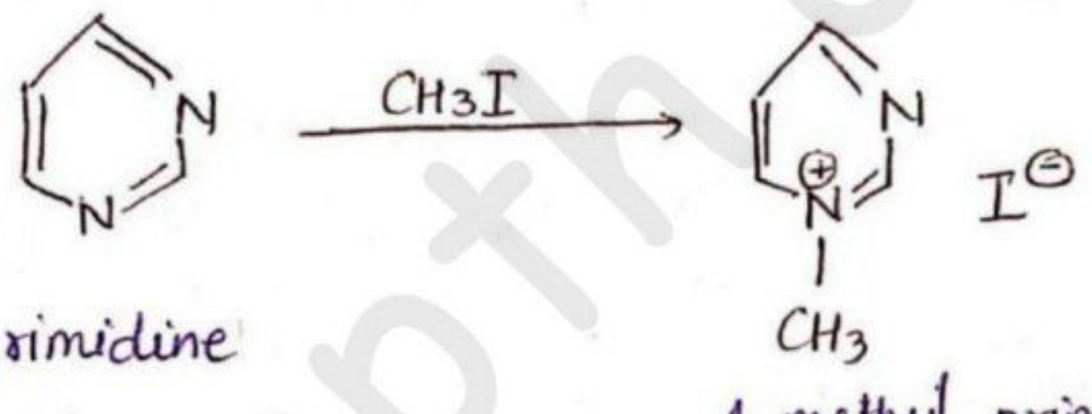
• Reaction of Pyrimide –

(a) Reaction with acid (Protonation) gives primidinium salts –



Pyrimidine — Pyrimidine Chloride.

(b) Quarternization / N-alkylation –



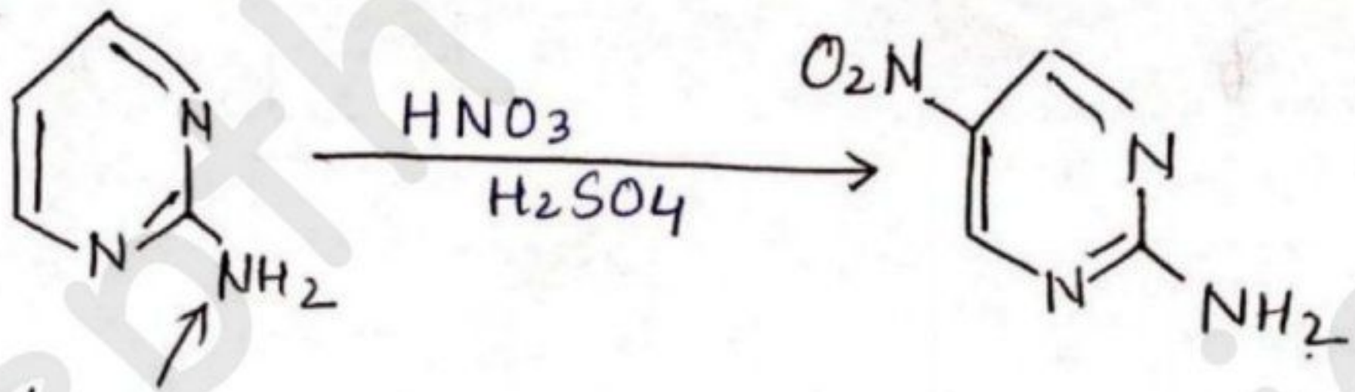
Pyrimidine — 1-methyl primidine iodide.

(c) Electrophilic aromatic substitution Reaction :–

- Less reactive due to 2 nitrogens present in the skeleton

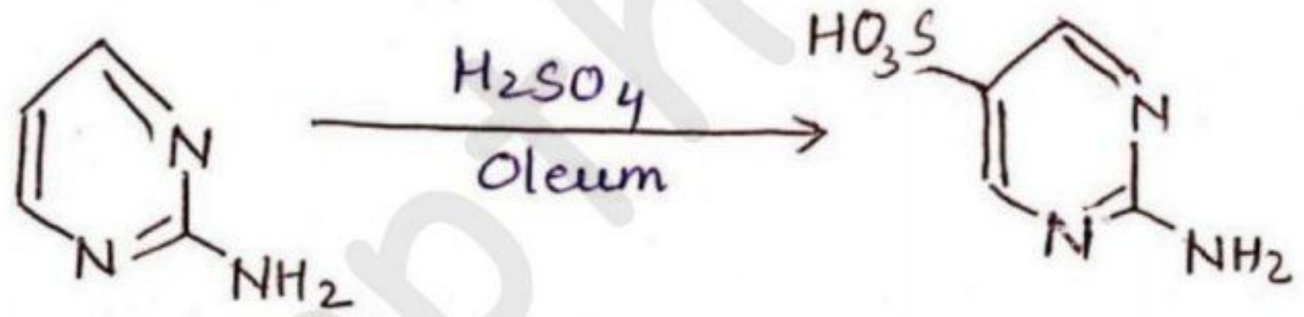
- Reaction possible in case of presence of strongly electron donating group ($-NH_2$ / $-OH$) on the ring substitution takes place at 5th position.

(i) Nitration :-

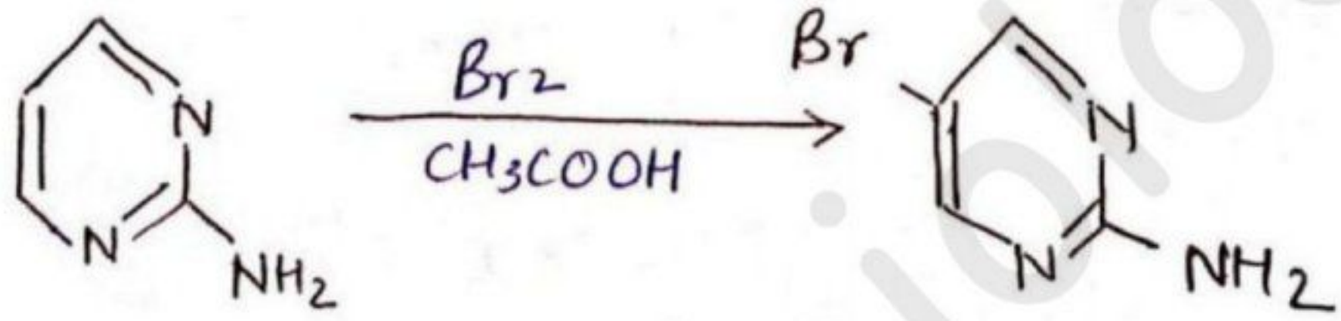


Strong electron donating group.

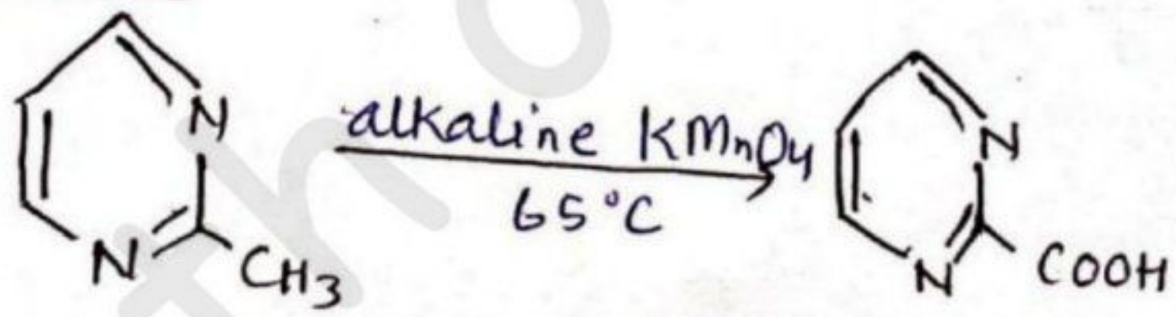
(ii) Sulphonation :-



(iii) Halogenation :-

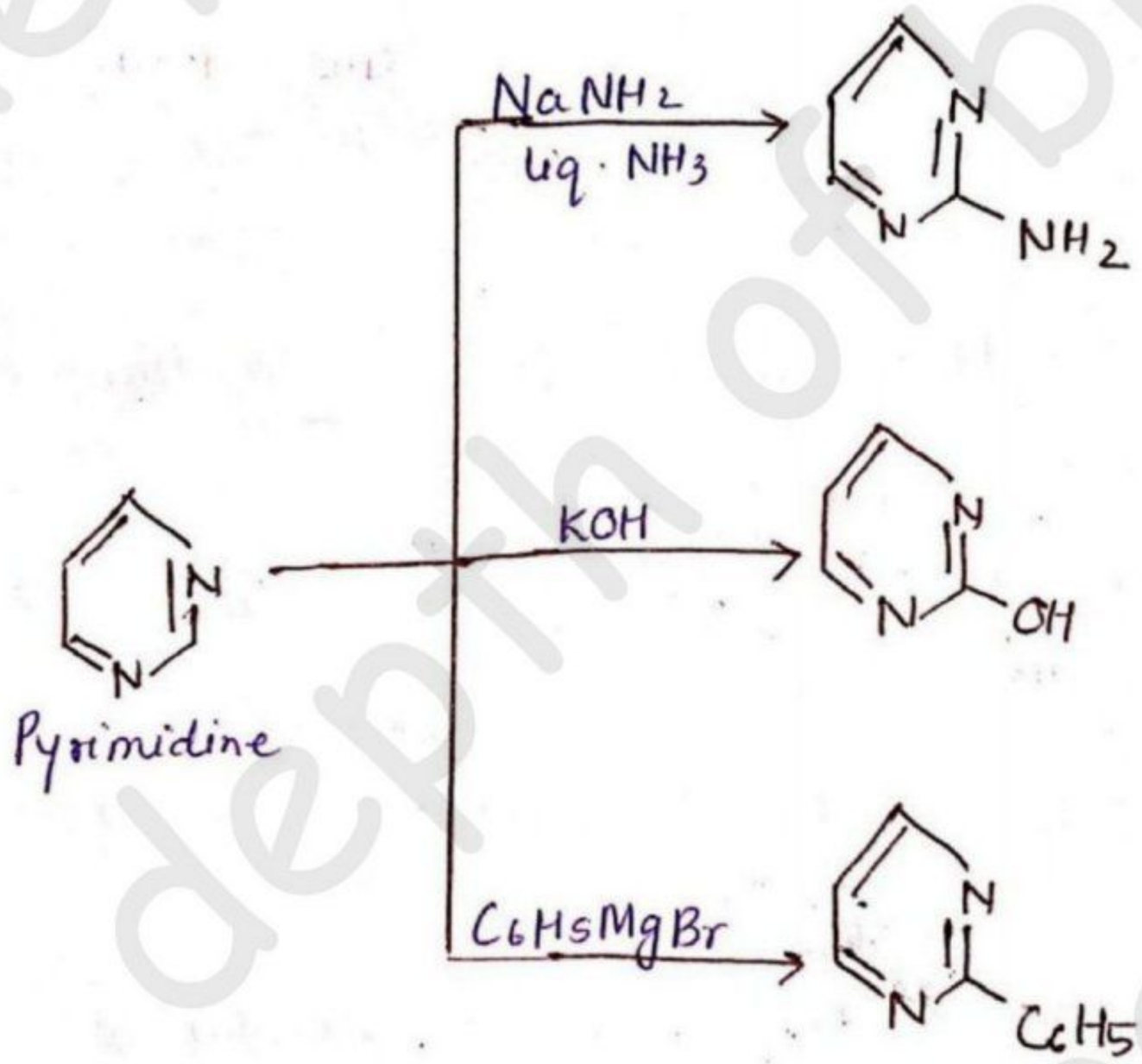


(d) Oxidation :-

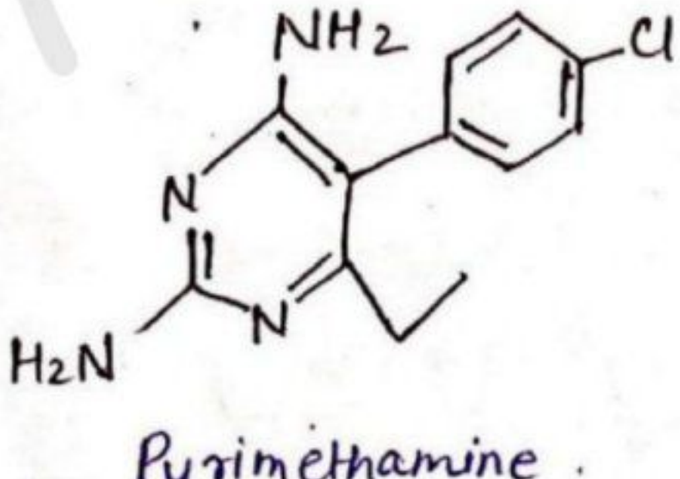


(e) Nucleophilic substitution Reaction :-

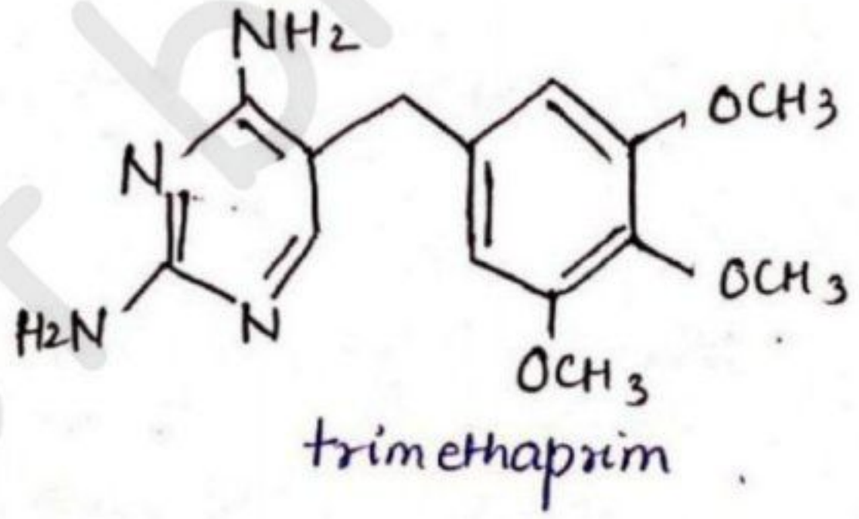
-Pyrimidines undergoes nucleophilic substitution reaction at 2nd position.



- Medical uses :-



Pyrimethamine.



trimethaprim.

- Pyrimethamine is an antiparasite medicine that helps prevent parasite from growing and reproducing in the body.

- Trimethoprim eliminates bacteria that cause urinary track infection. 5 - fluorouracil is a medication used to treat colon cancer, oesophageal cancer, stomach cancer,

pancreatic cancer, breast cancer, and cervical cancer.

- Phenobarbitone is long acting barbiturate used as sensitive and hypotonic.

- Other drugs having pyrimidine moiety.

- Sulfadiazene – sulphonamide drug commonly used to treat urinary tract infection and burns.

-Zidovidine, stavidine - nucleoside reverse transcriptase.

inhibitors (NRTIs) used as to treat human immuno-defician-

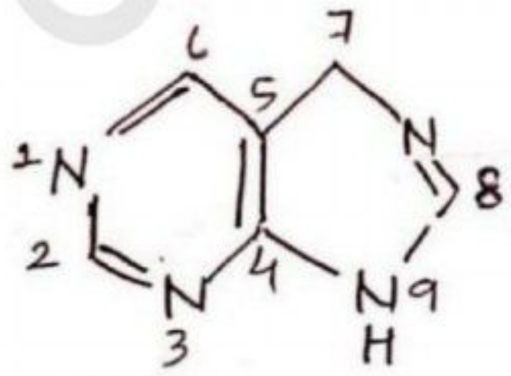
-cy (HIV) infection.

- minoxidil is a direct vasodilators used for treatment

of hypertension.

→ Purine :

• Structure :-



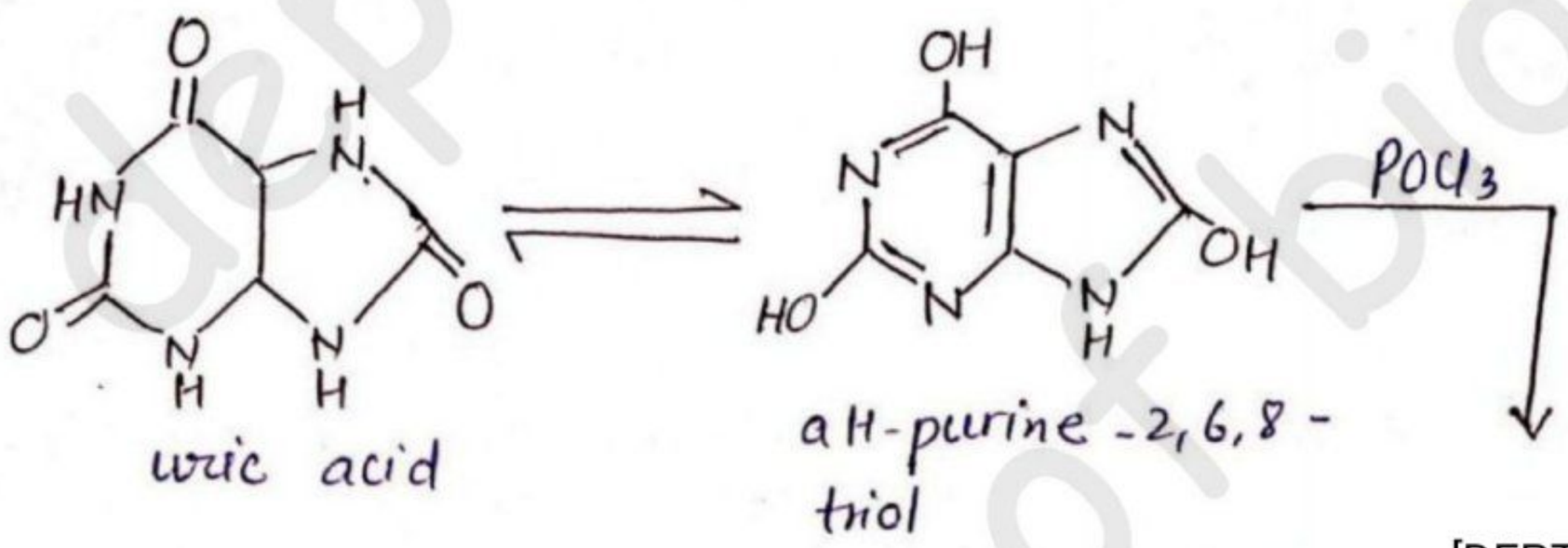
-Purine is fused heterocyclic compound in which pyrimidine

ring fused with imidozole consist of 4 nitrogens as

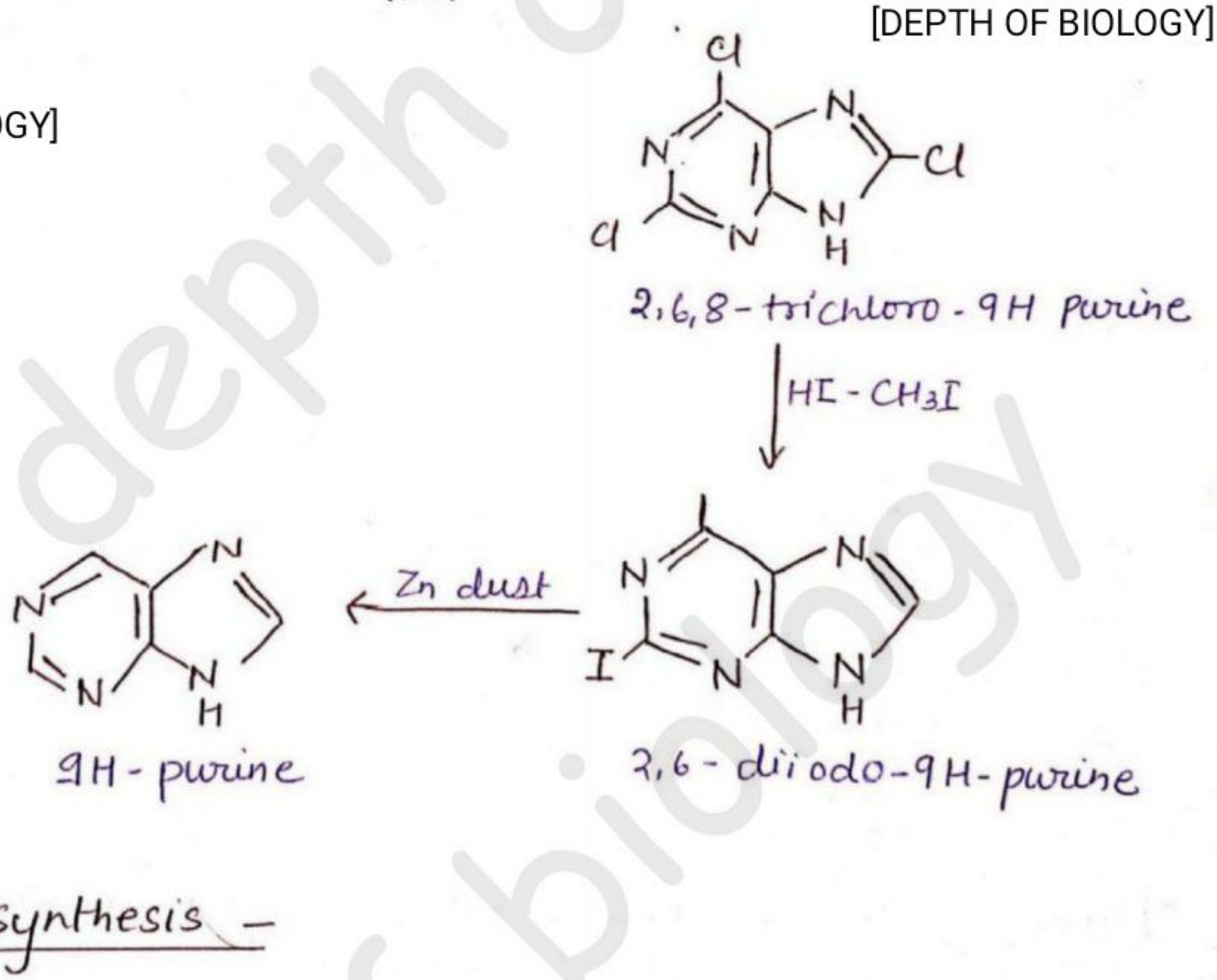
heteroatoms at 1st, 3rd, 7th and 9th position.

- Synthesis of Purine :-

(a) Fischer purine synthesis (from uric acid) -



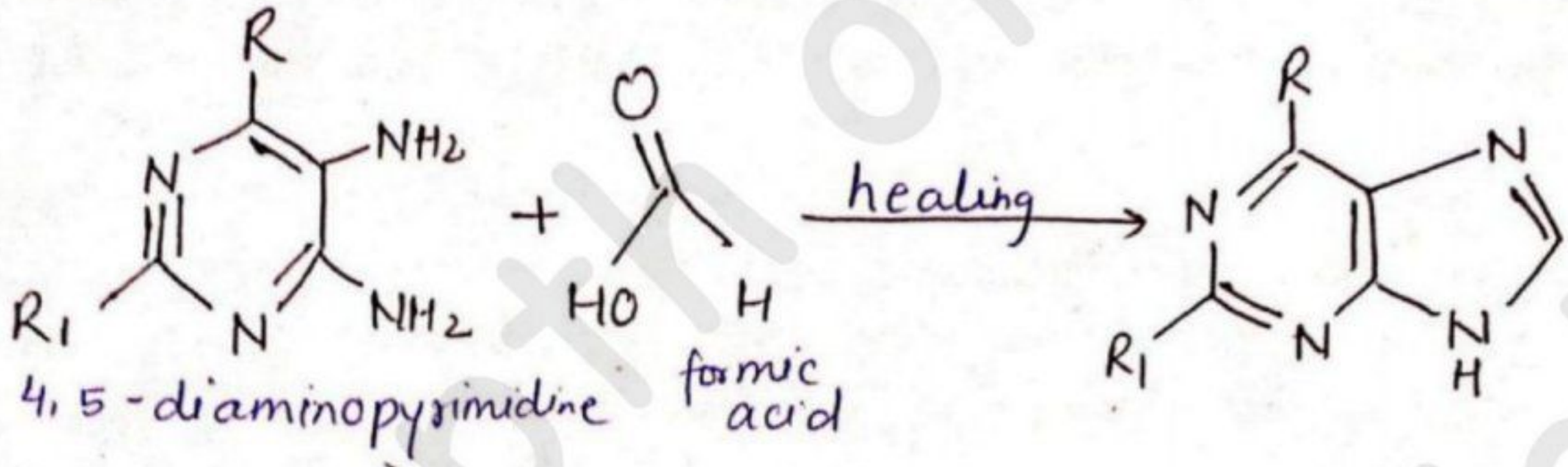
[DEPTH OF BIOLOGY]



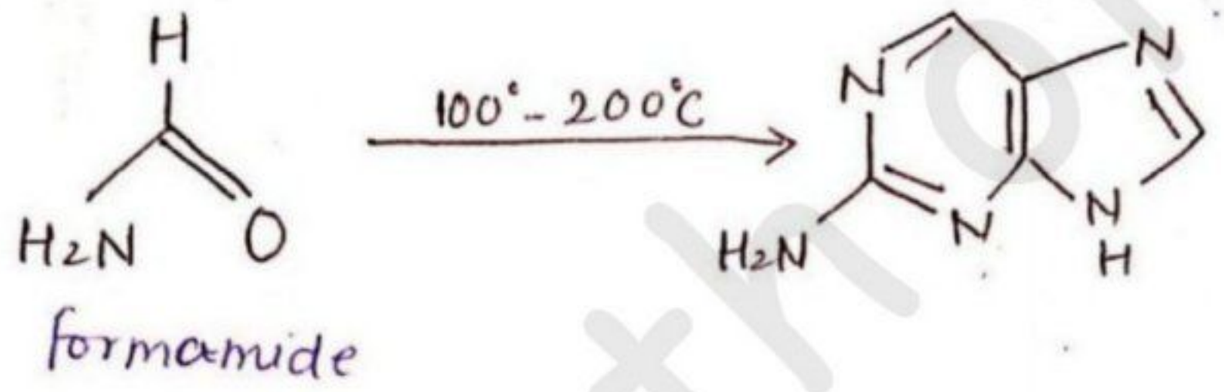
(b) Traube synthesis -

- Heating of 4-5-diamino pyrimidines with formic acid gives purines.

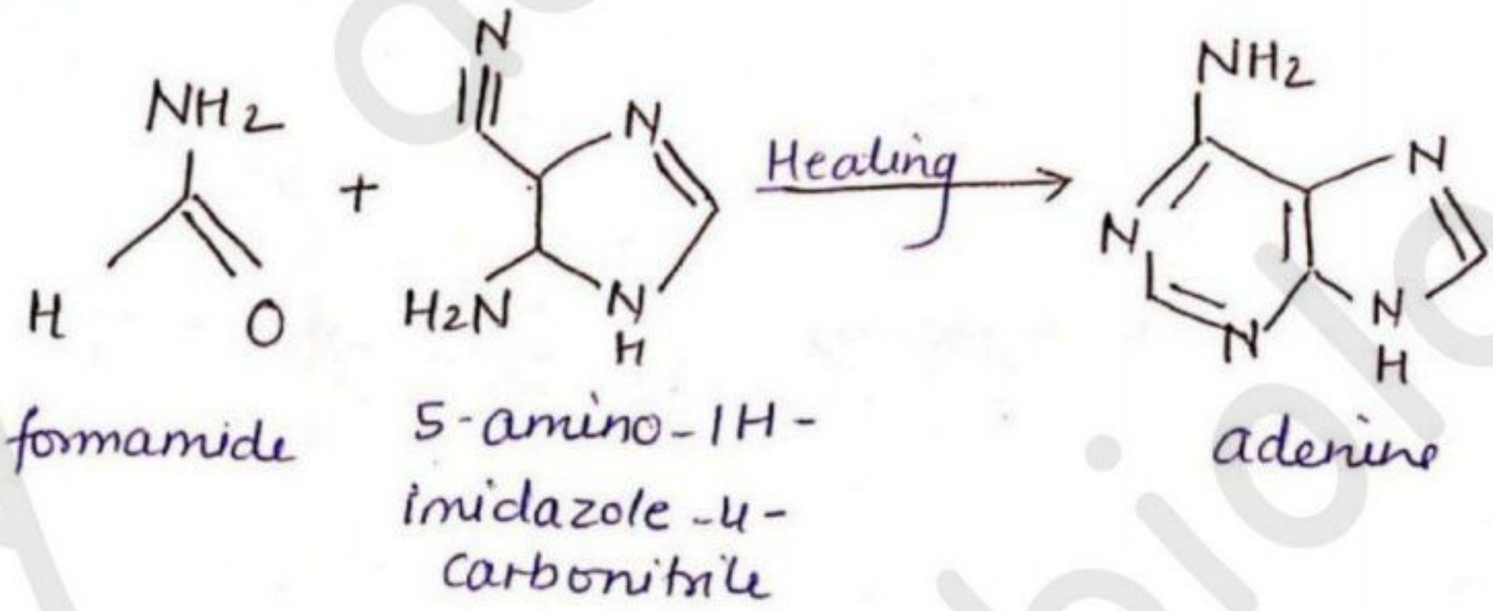
[DEPTH OF BIOLOGY]



(c) From formamide (self catalysed reaction) -



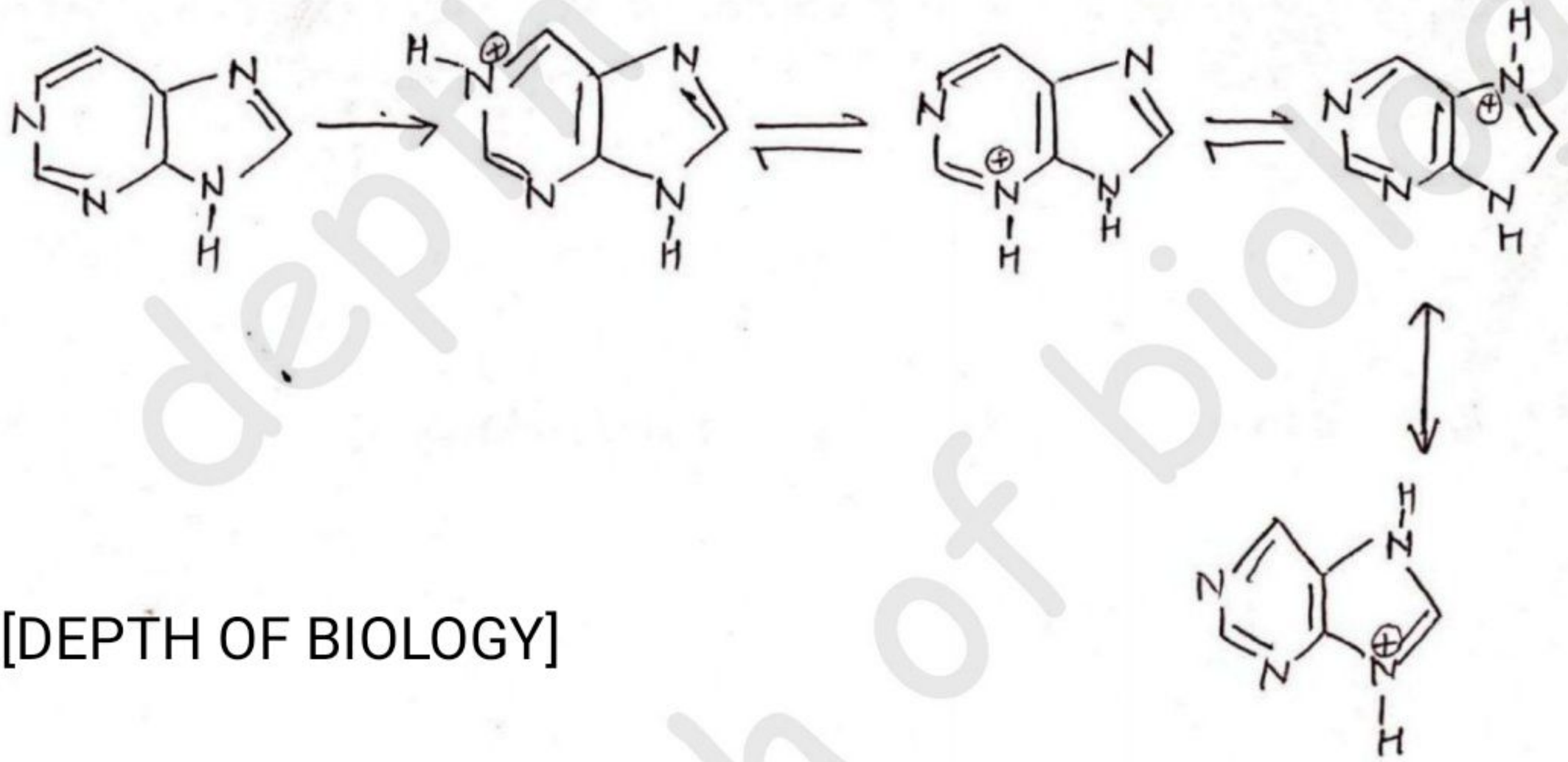
(d) From imidazoles :-



• Reactions of Purine —

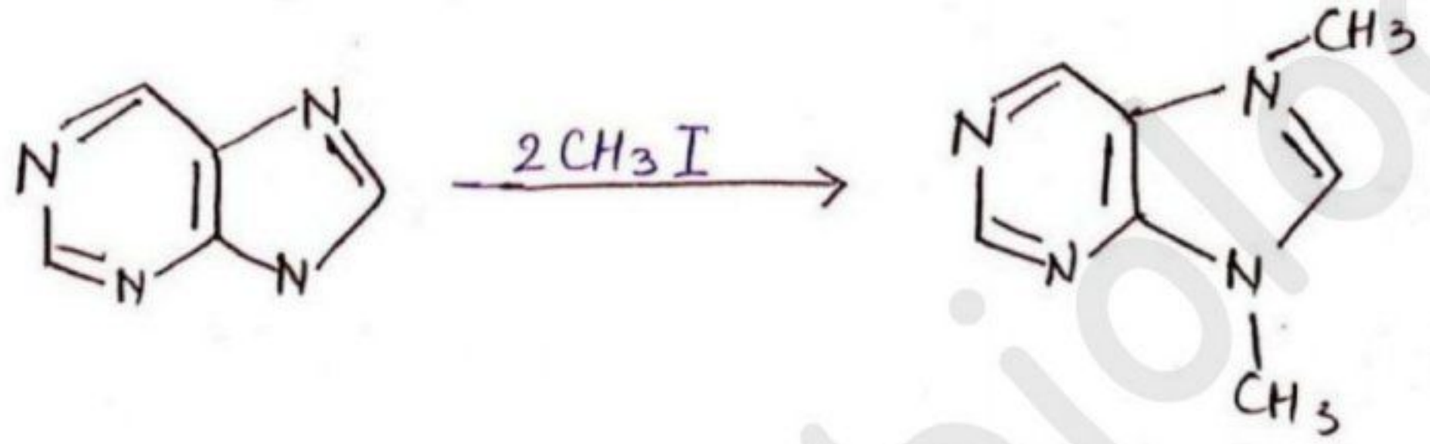
(a) Reaction with acid (Protonation) —

It gives purinum salt (N1-protonated form is predominant)



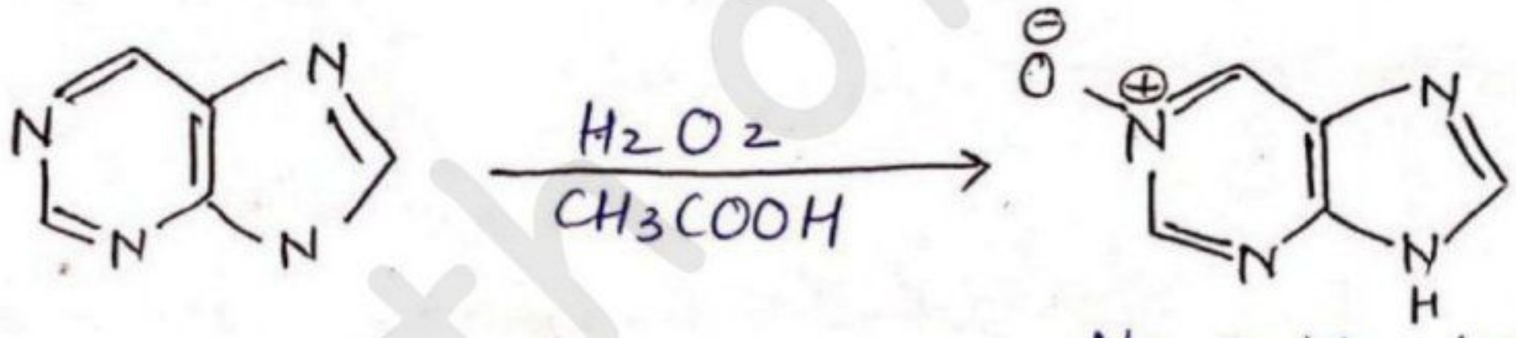
(b) Reaction with CH_3I / N-alkylation gives 7,9-dimethyl-purinium iodide.

- It gives 7,9-dimethylpurinium iodode



7,9-dimethylpurinium iodide.

(C) Reaction with H_2O_2 gives N1-oxide derivatives.

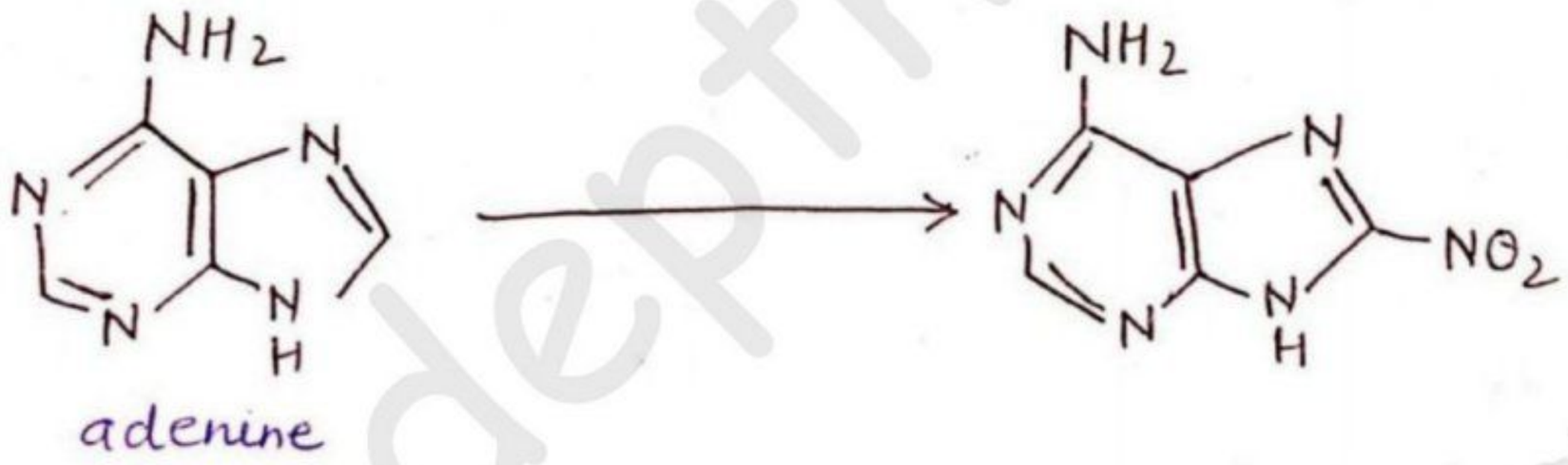


N1-Oxide derivatives

(d) Electrophilic aromatic Substitution reactions :-

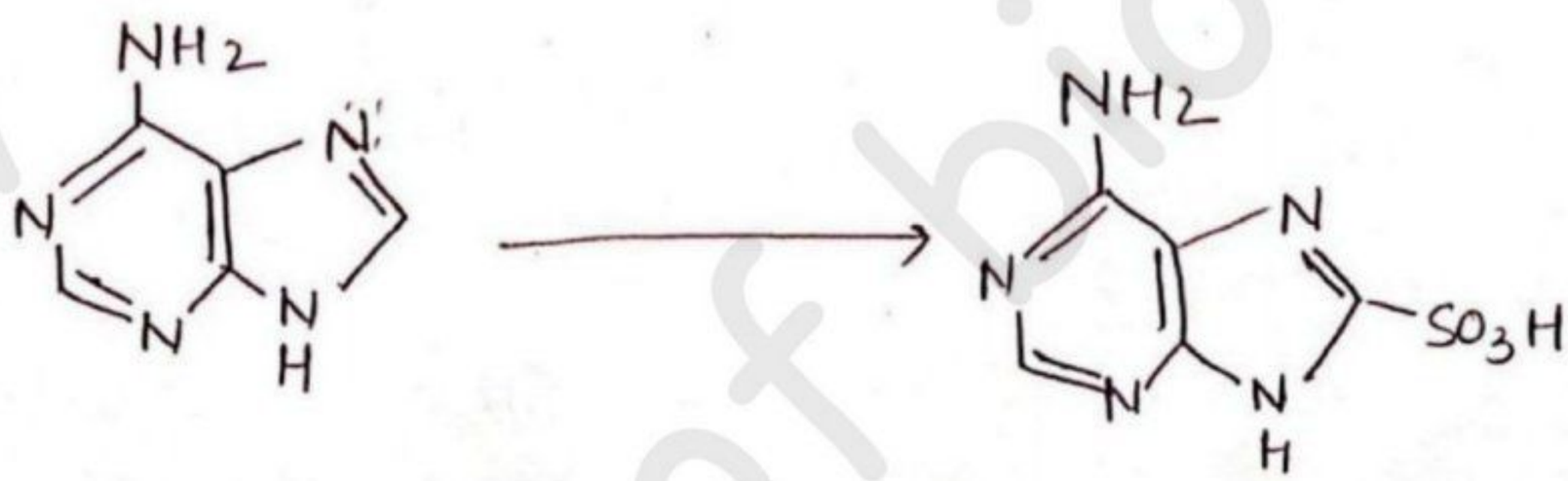
- Purine readily undergo electrophilic aromatic substitution at 8th position in presence of oxo and amino substituent than unsubstituted purines.

(i) Nitration -

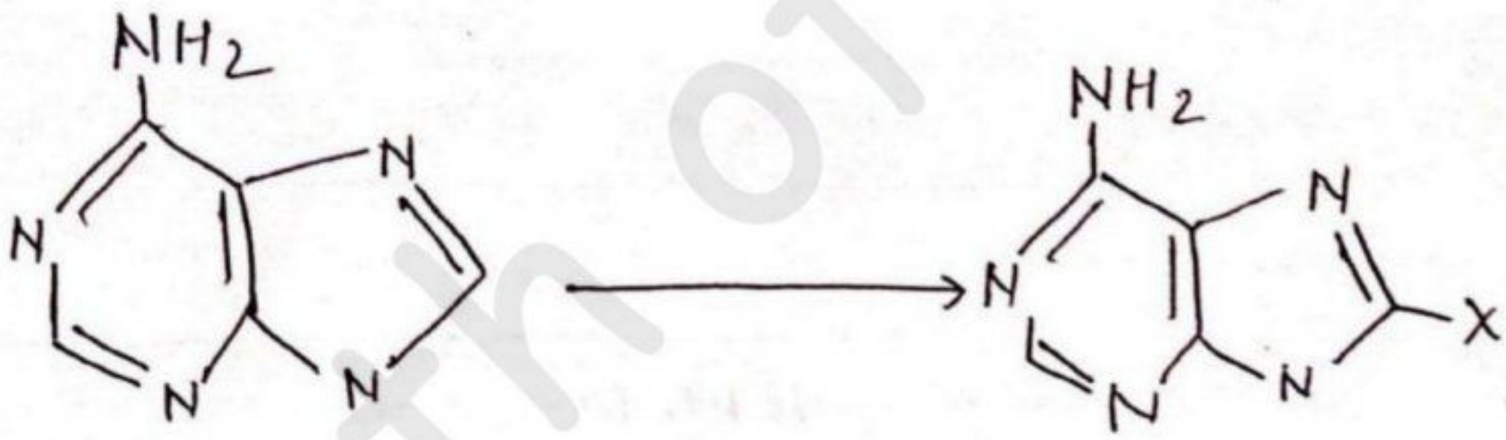


adenine

(ii) Sulphonation :-

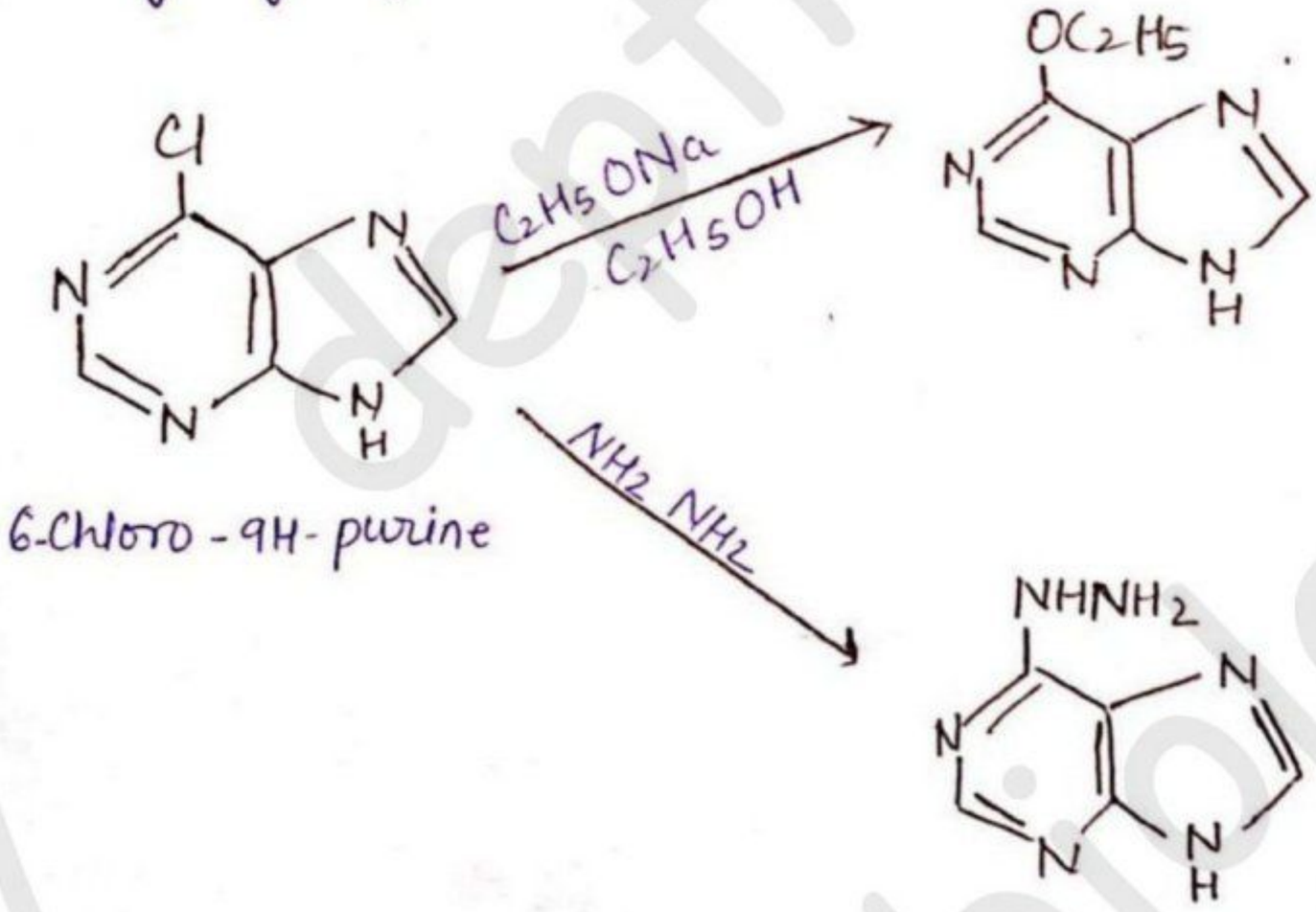


(iii) Halogenation :-



(e) Nucleophilic substitution reaction –

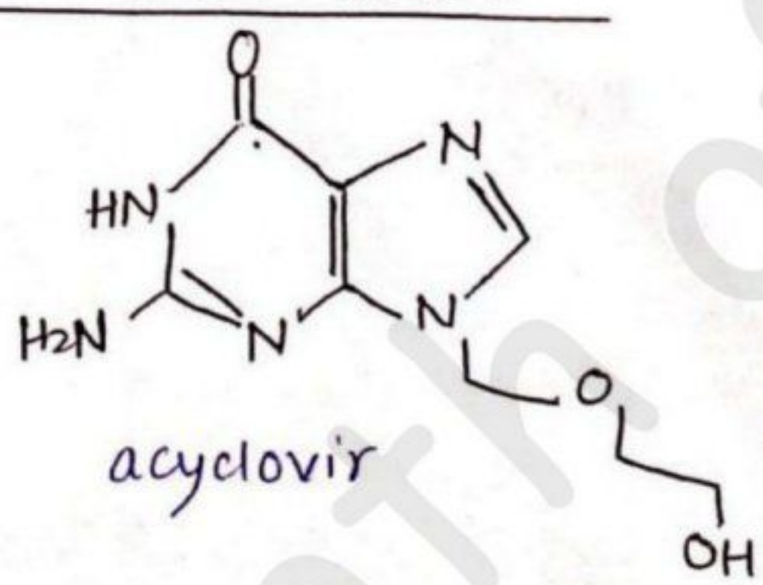
- Nucleophilic substitution takes place in presence of halide substituents, where halides are the most popular leaving groups.



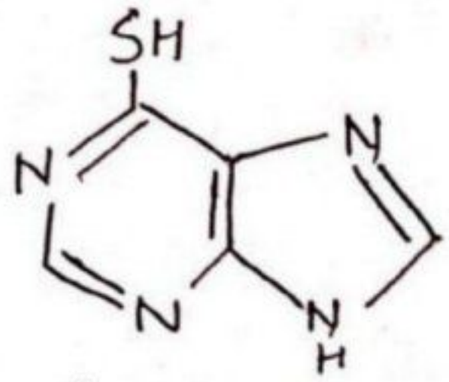
6-Chloro-9H-purine

[DEPTH OF BIOLOGY]

- Medicinal Uses :-



acyclovir



6-mercapto purine.

- Acyclovir, valacyclovir, gancyclovir, are used to treat infections caused by certain types of viruses.

- Mercapto purine (6-MP) is a medication used for cancer and autoimmune diseases.

[DEPTH OF BIOLOGY]

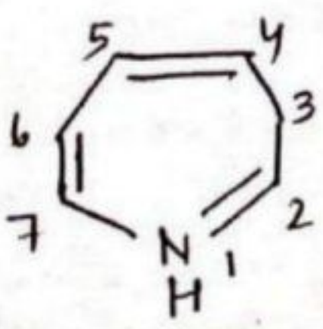
- Caffeine is a CNS stimulant used to restore mental alertness (or) wakefulness during fatigue (or) drowsiness.

- Theophyline is used to treat lung diseases such as - asthma, and bronchitis.

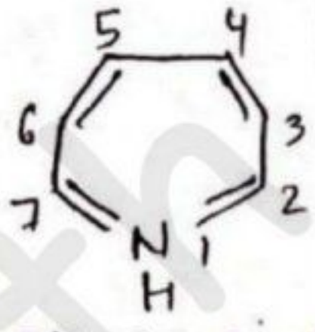
- **Azepine** -

[DEPTH OF BIOLOGY]

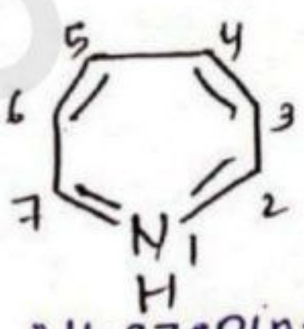
Structure :-



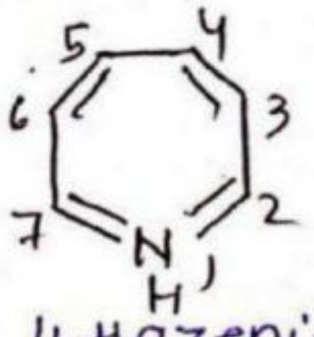
1H-azepine



2H-azepine



3H-azepine



4-H-azepine

[DEPTH OF BIOLOGY]

- Azepine is an unsaturated 7 numbered heterocyclic ring consists of nitrogen as heteroatom at 1st position.

- It does not follows huckel's rule, hence, it is non-aromatic compound.

• Synthesis of azepine -

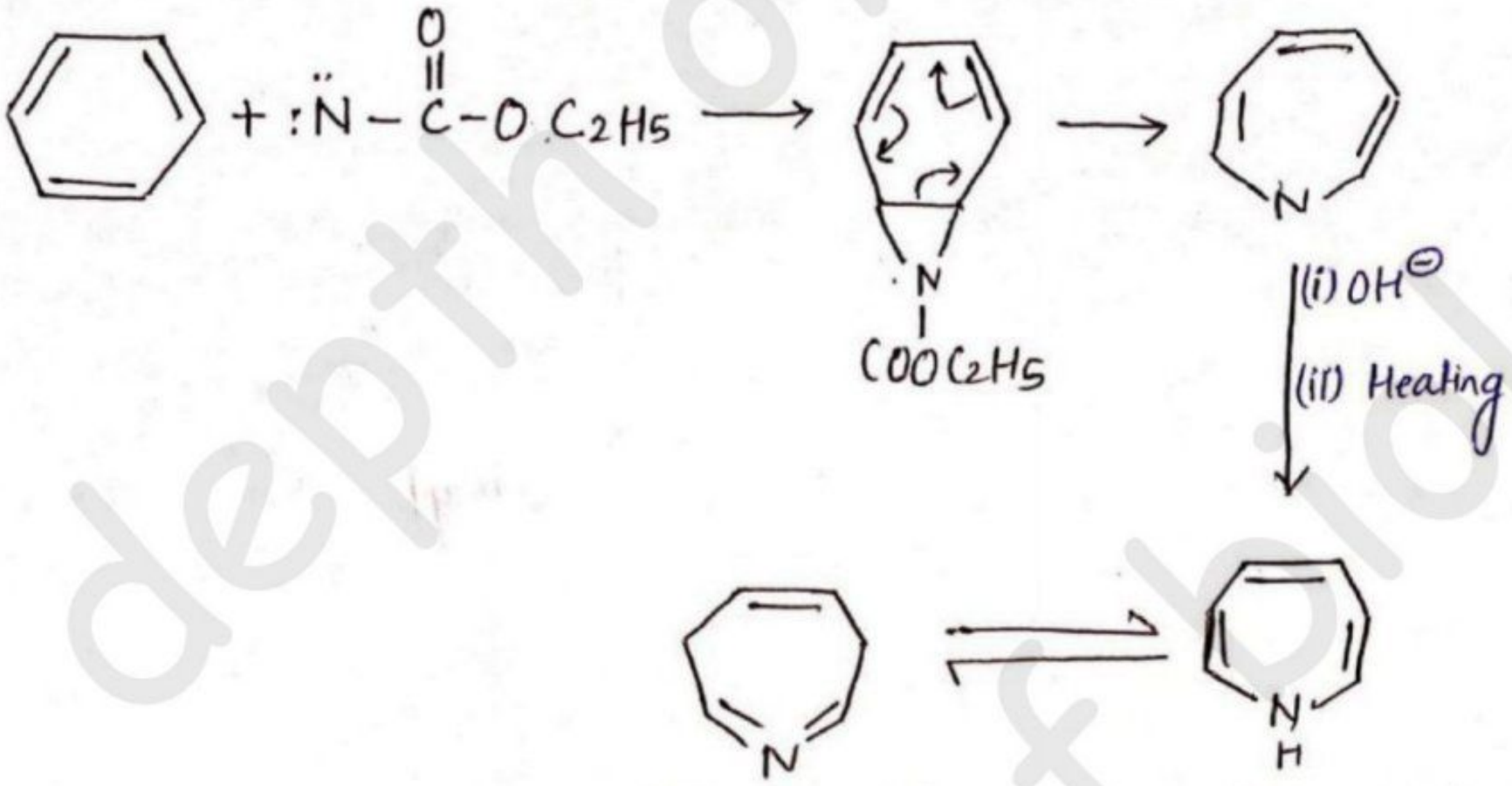
[DEPTH OF BIOLOGY]

(a) From benzene and ethoxy carbonyl nitrene -

- Benzene reacts with ethoxy carbonyl nitrene gives N-ethoxycarbonyl -1H - azepine.

- Further, it on treatment with base followed by heating gives 1H - azepine.

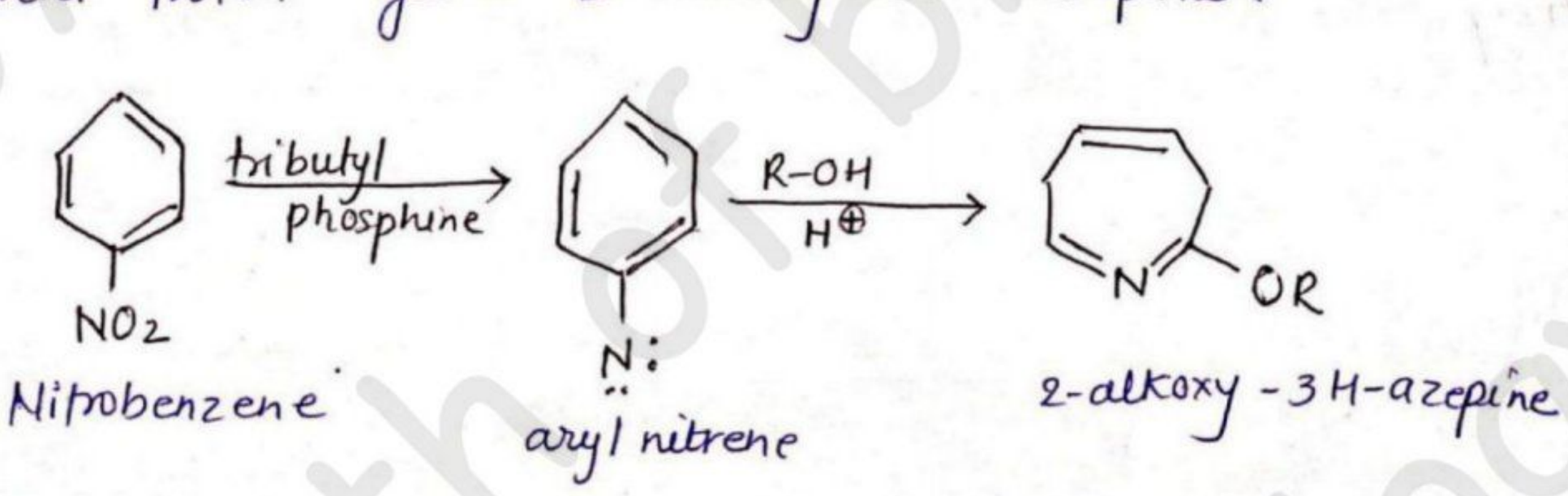
- It on isomerization gives more stable 3H - azepine.



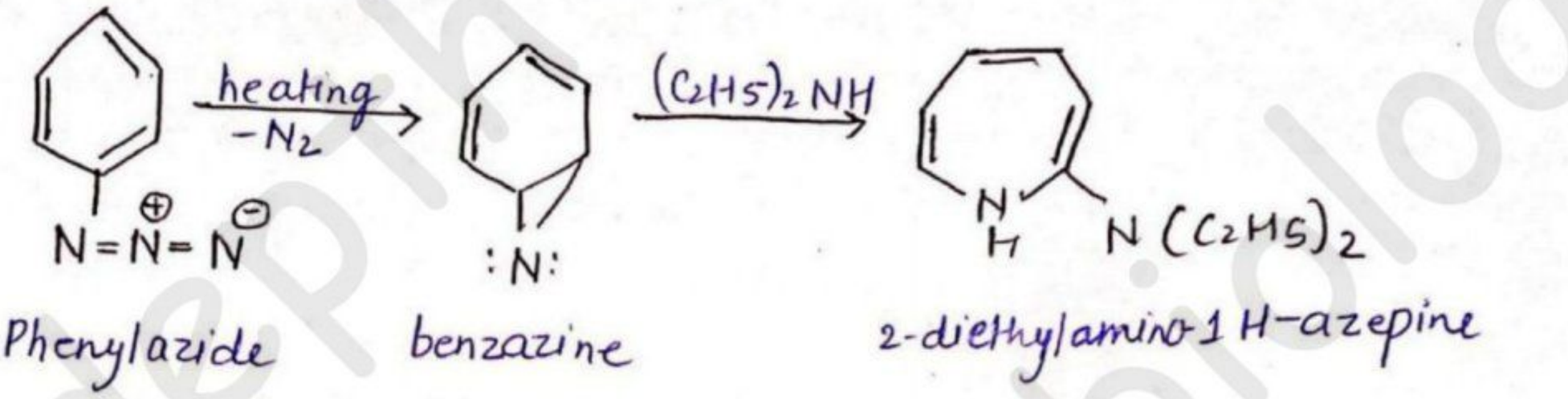
(b) From nitrobenzene :-

- Nitrobenzene on treatment with tributyl phosphine undergoes deoxygenation and gives aryl nitrene.

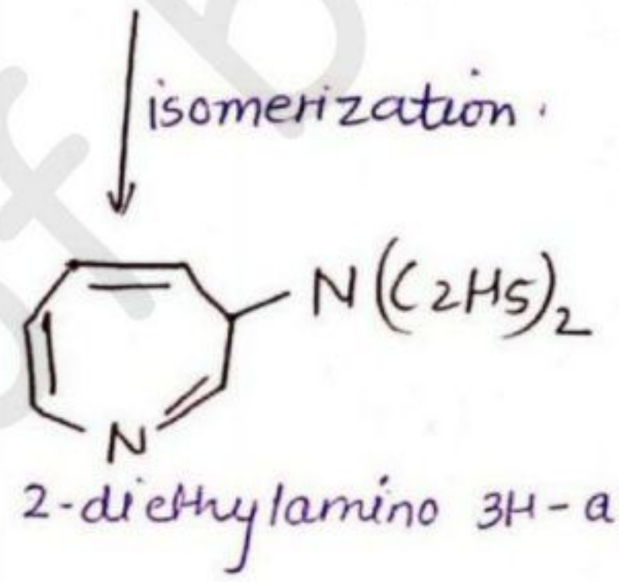
- Further, nucleophilic addition of alkoxy group to aryl nitrene followed by rearrangement and in presence of acid proton gives 2-alkoxy-3H-azepines.



(c) From phenylazide -



Phenylazide benzazine 2-diethylamino 1H-azepine



2-diethylamino 3H-azepine

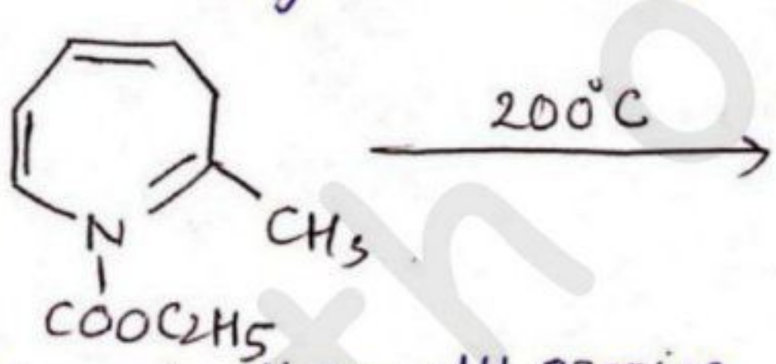
[DEPTH OF BIOLOGY]

- Reaction of azepines :-

-Azepines and their derivatives undergo interesting chemical reaction.

(a) Thermal Reaction -

-2-methyl-N-carboethoxy-1H-azepine on heating at 200°C gives 2-methyl-N-phenyl carbonate



2-methyl-N-carboethoxy-1H azepine

2-methyl-N-phenyl carbonate.

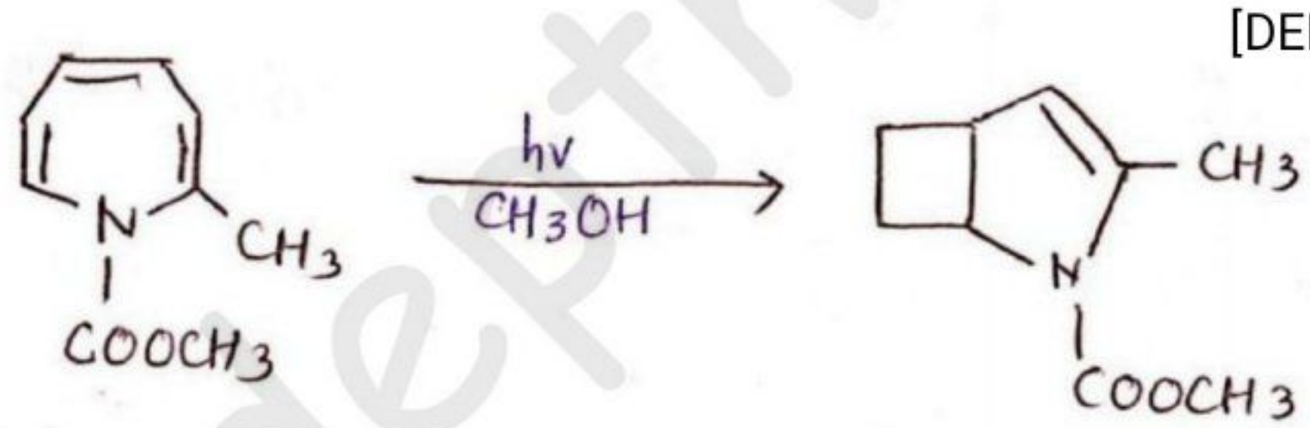
[DEPTH OF BIOLOGY]

(b) Photoring contraction :-

- Azepine undergo ring contraction on photolysis to yield bicyclic compound.

- 2-methyl-N-carbomethoxy-1H-azepine on photolysis undergo ring contraction to give 2-carbomethoxy-3 methyl-2-azabicyclo [3,2,0] hepta-3,6-diene.

[DEPTH OF BIOLOGY]



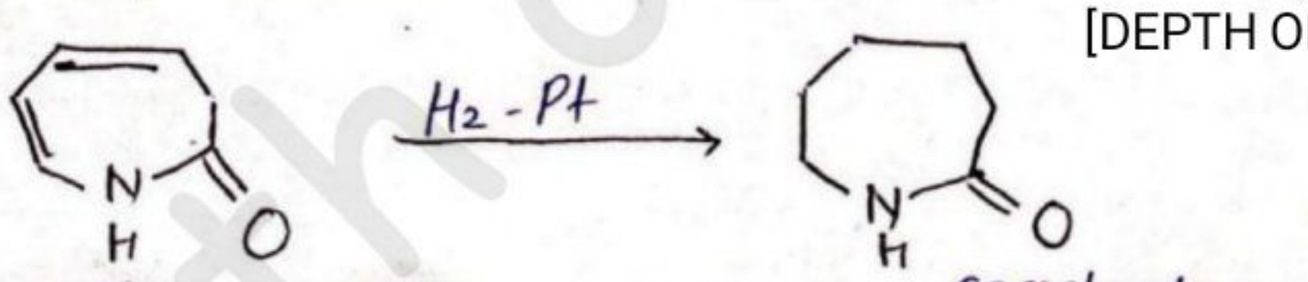
2-methyl-N-carboethoxy 1H-azepine

2-carbomthoxy-3 methyl-2 azobi--cyclo. [3,2,0] hepta-3,6,-diene

(c) Reduction :-

- 3H-azepine-2-ones undergo reaction in presence of H_2-Pt to give caprolactoms.

[DEPTH OF BIOLOGY]



3H-azepine-2-one

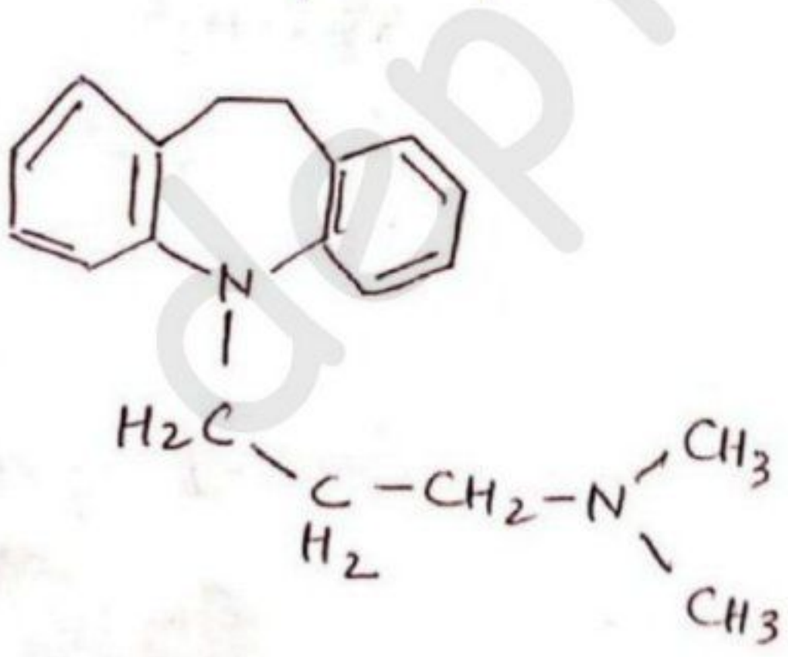
caprolactam

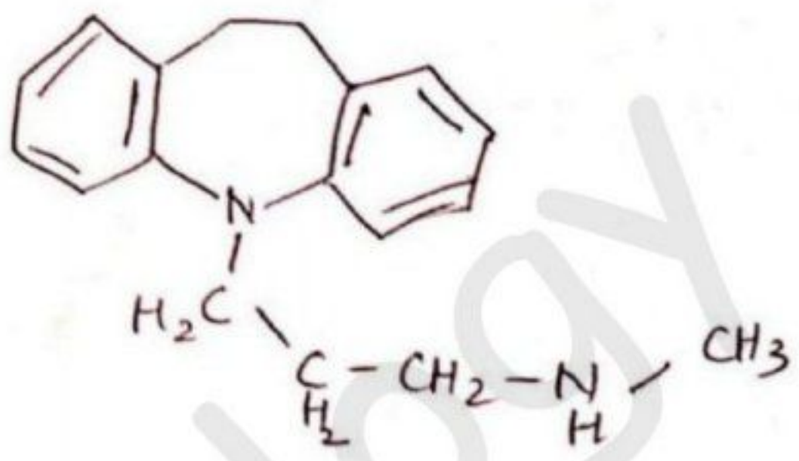
• Medicinal uses :-

Imipramine and desipramine are tricyclic anti-depressants

Imipramine is used in the treatment of depression, and certain anxiety disorder

- Desipramine is used to treat depression.
- It may improve mood, sleep, apetite and energy level., and may help restore in daily living.





- Carbamazepine is an anticonvulsant.

- Iolqramide is used in combination with other diabetes medication to control high blood sugar in people with type 2 diabetes.