13/2/2020

Anti-Malarial Agents :- UN-2

* **Malaria** :- It is one of the most wide spread disease caused by protozoal parasite of genus plasmodium.

⇒ These parasites spend an asexual phase in man and sexual phase in female Enaphilus Mosquito.

⇒ Malaria is caused by 4 species of parasite.

1) **Plasmodium cephalceporium** :- It causes 50 % & attack 60 % patients erythrocytes.

2) **Plasmodium Vivax** :- It causes 40 %, it is chronic, it can reinfect liver cells.

3) **Plasmodium malaria** :- It causes 10 %, in this relapses are common.

4) **Plasmodium ovale** :- This is least common.

Malaria means "Bad air" in Greek Word

* Ethology of Malaria :-

Malaria is transmitted by female Enaphilus Mosquito & it is characterized by high fever with vigour anemia, profuse sweating, fever and chills.

* Life Cycle of Malaria :-

① **Hepatic / pre-erythrocytic stage** :- The Mosquito store Sporozyte stage of protozoa in its salivary glands.

⇒ Upon binding the patient, the sporozoates are injected

into patients blood. Within minutes after being injected into patients blood, the sporozoites being entering hepatocytes where they become primary schizoates & then Microzoate.

② Erythrocytic Stage :- Depending on the plasmodium species, the microzoates either rupture the infected hepatocytes & enter the systemic circulation or infect other liver cells & produces 2° schizoates.

⇒ Microzoates in systemic circulation now infect patient erythrocyte where they reside for 3-4 days reproduction.

③ Development of Sexual forms :-

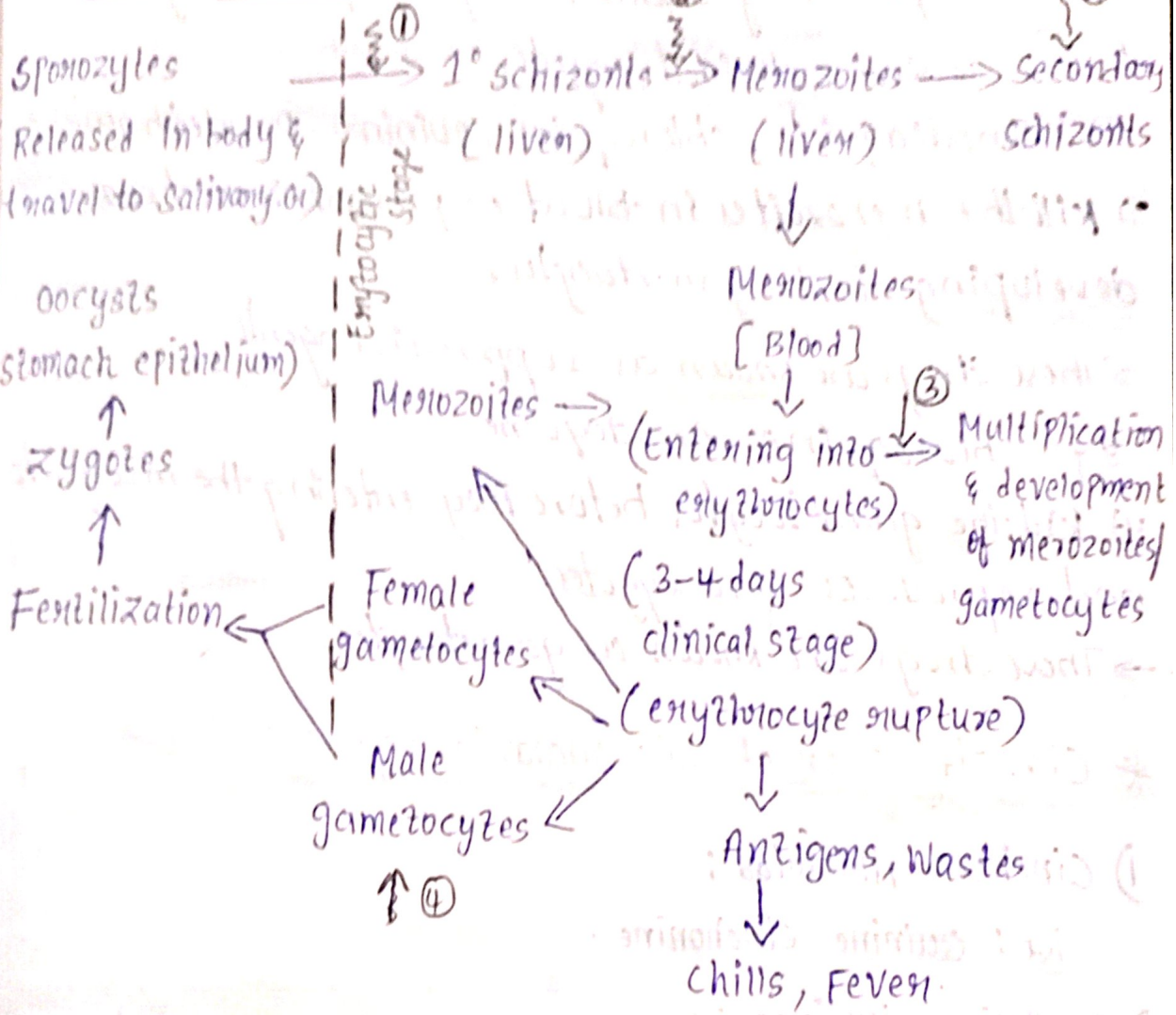
⇒ The reproduction stage in erythrocyte can produce either more microzoates & other form called "gametocytes".

⇒ The newly formed microzoates or gametocytes burst out of the infected erythrocytes.

⇒ The new microzoates infect additional erythrocytes & continue the cycle of reproducing, bursting of the erythrocyte & infecting more erythrocytes.

⇒ The debris form the destroyed erythrocytes is one of the causes of severe fever & chills.

* Female Anaphilus Mosquito :-



* Anti-Malarial agents :-

The drugs which are used to treat or prevent malaria is called "Anti malarial agents".

* Sites of Antimalarial Agents [Targets] :-

1. kills the sporozoites, injected by mosquito & prevent the sporozoite from entering the cives.

The drugs used in this state is known as prophylatic agent since no drugs is effective in this stage.

2) kill the schizoits resisting the hepatocytes or prevent them from merozoites.

The drugs acting against erythrocytic stage are known as Schizotisidal agents.

Ex:- Emodiaquine, chloroquine, quinine, Pirolethamine.

3) kill the merozoites in blood or prevent them from developing into gametocytes.

→ These drugs are known as suppressive agents.

Eg:- chloroquine, Amidoquine.

4) kill the gametocytes before they entering the mosquito and reproduces into zygotes.

→ These drugs are known as gametocytes.

* Classification of Anti-malarial agents :-

1) Cinchona Alkaloids :-

Ex :- Quinine, cinchonine.

2) 4-Aminoquinolines :-

Ex :- Chloroquine, Amodiaquine, Hydroxy Chloroquine.

3) 8-Aminoquinolines :-

Ex :- primaquine, pamaquine.

4) 9-Aminoquinolines :-

Ex :- Mepacrine or Quinacrine.

5) Biguanides :-

Ex :- Proguanil, cycloguanil. Pamoate.

6) Pyrimidine Analogues :— Pyrimethamine.

7) Polycyclics :- Doxycycline, Halofantrin

8) Miscellaneous :-

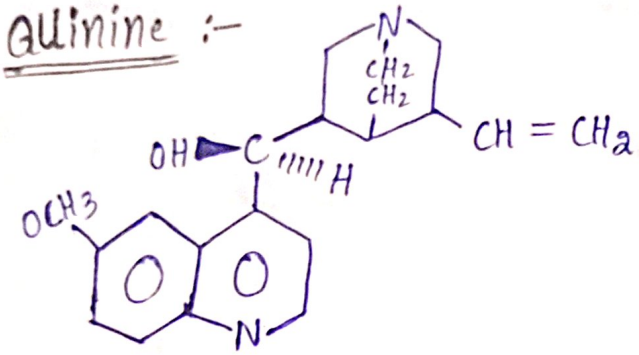
Ex :- Metalloamine, Sulfadoxine, Artemether, Mefloquine, Atovoquione, Artesunate.

9) Newer Antimalarial Drugs :-

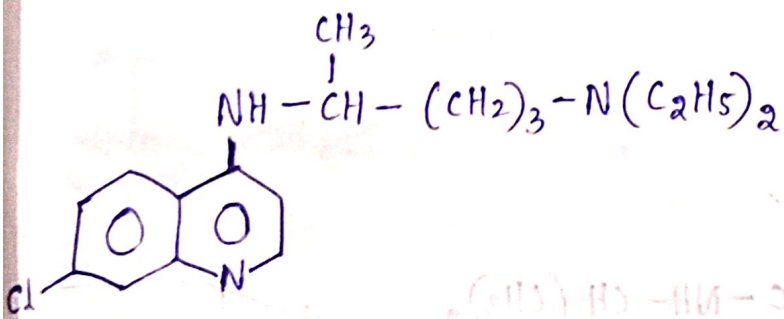
Ex :- Artemisinin, Phosmidomycin.

* Structures of Anti-Malarial agents :-

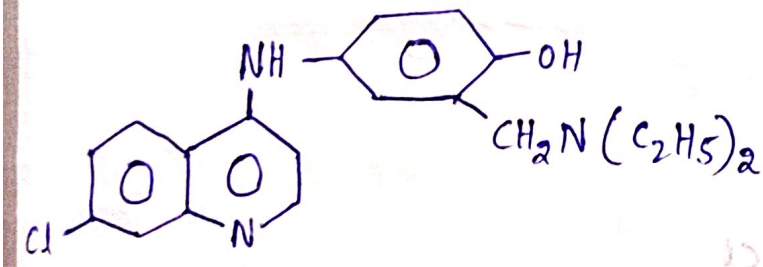
① Quinine :-



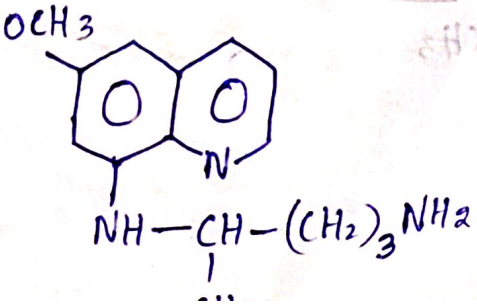
② ** Chloroquine :-



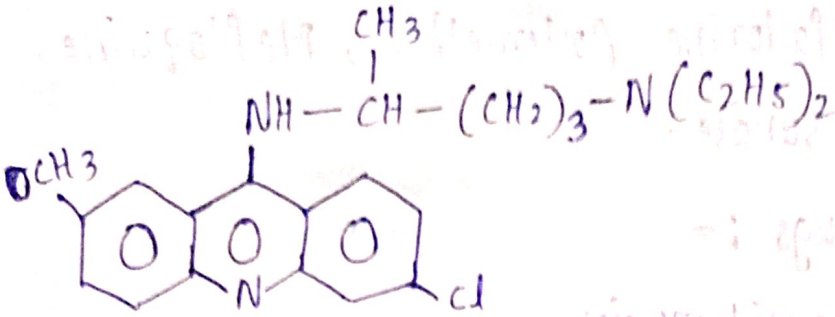
③ Amodiaquine :-



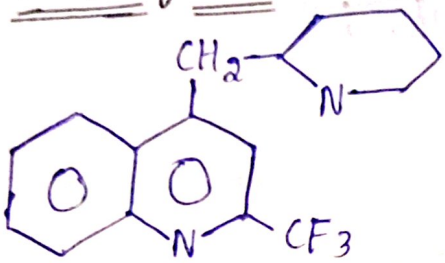
④ Primaquine :-



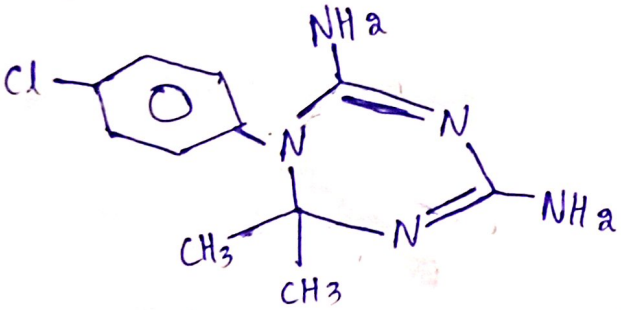
⑤ Pre Mepacrine / Quinaquine :-



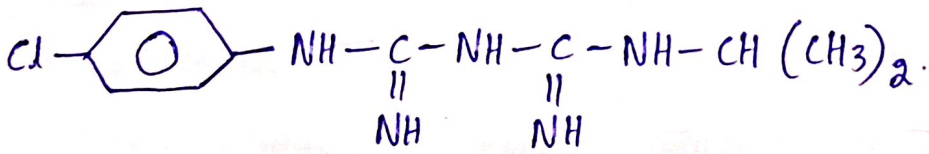
⑥ Mefloquine :-



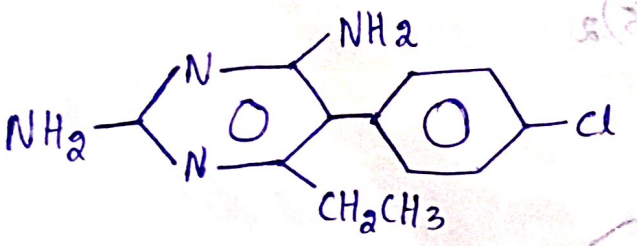
⑦ Cycloguanil :-



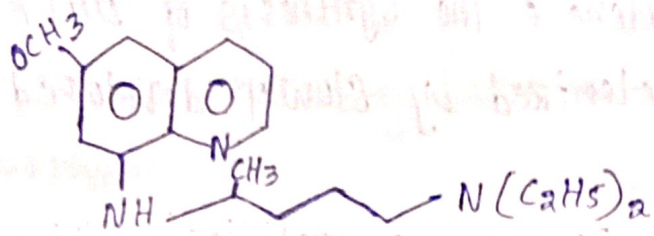
⑧ Proguanil :-



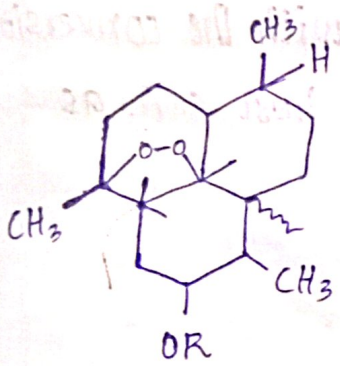
⑨ Pyrimethamine :-



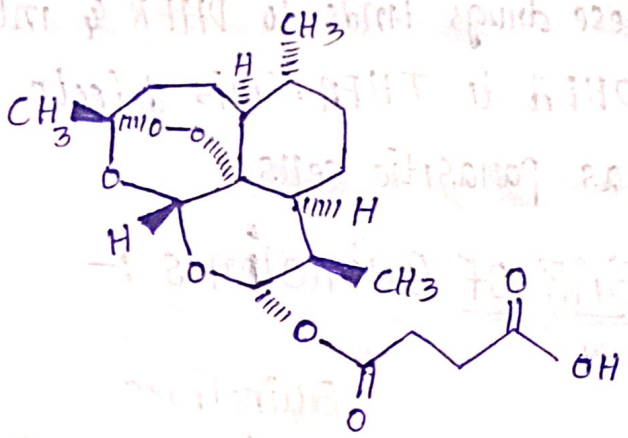
10) Pamaquine :-



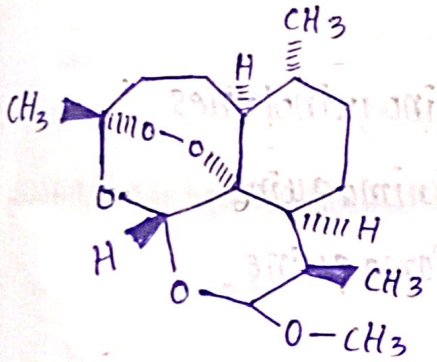
11) Artimisinin :-



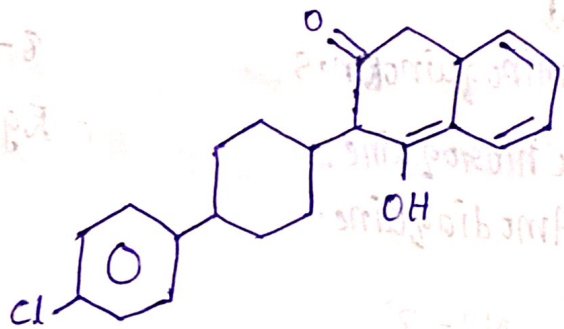
12) Artesunete :-



13) Artemether :-



14) Atovoquone :-



(*) MoA of Anti malarial agents :-

(1) Anti malarial agents involves in non-specific mechanism, in this the quinoline derivatives inhibits the Nucleic acid & Protein Syn's.

⇒ These drugs effects Protozoa cells due to the interaction b/w drug & DNA formation.

Ex :- 4- Amino quinolines — Chloroquine, Amodiaquine (84)

8- Amino quinolines — Primaquine, Pamaquine. (82)

(c) Cinchona alkaloids — Quinine, Cinchonine.

(2) Some drugs involves interfere the synthesis of DHFR. These mechanism is characterized by slowly developed in Schizoticidal action.

⇒ The pyrimidines & Biguanides are competitive inhibitors of DHFA.

⇒ These drugs binds to DHFR & interfering with the conversion of DHFA to THFA. This defects occurs in host cell as well as parasitic cells.

(*) SAR of Quinolones :-

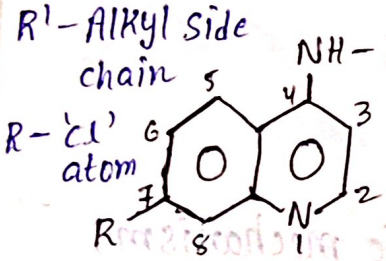
Quinolones

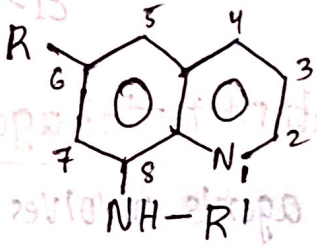
4-Aminoquinolones

Ex :- Chloroquine.
Amodiaquine.

8-Aminoquinolones

Eg :- Primaquine
Pamaquine.





* 4-Aminoquinolones :-

⇒ Diethyl amino alkyl side chain having 2-5 'c' atoms particularly 4-diethyl amino-1-methyl butyl amino side chain. It shows optical activity as chloroquine & quinacrine.

⇒ The D-isomer of chloroquine is less toxic than L-isomer.

⇒ The quinoline ring have more active than acridine ring for a side chain.

⇒ 7-chloro grp of quinoline nucleus is have optimal activity and methyl grp in 3rd psl'n will reduces the activity.

⇒ If methyl grp in 8th position will completely abolishes the activity.

⇒ If Introduction of unsaturated bonds in the side chain was not produce any harmful effects.

⇒ The 3° amine in the side chain is very much imp for the optimal activity.

⇒ Aromatic ring in the side chain in Amodiaquine reduces the activity & toxicity.

⇒ The Subst'n of hydroxyl grp on one of the ethyl grp, on the 3° amine will reduces toxicity & ↑ses the plasma concn.

* 8-Aminoquinolines :—

⇒ presence of 6-methoxy grp in quinoline nucleus is Subst'd by 'H' or 'OH' groups or low alkoxy grps, produce more active & highly. Ther. index.

⇒ 2, 4 or 6 methoxy grp analogues of 8-diethyl amino propyl amino quinoline are all active cmpnd's.

⇒ 2nd ethoxy grp at 'C' 2 & 5 will ↑se activity.

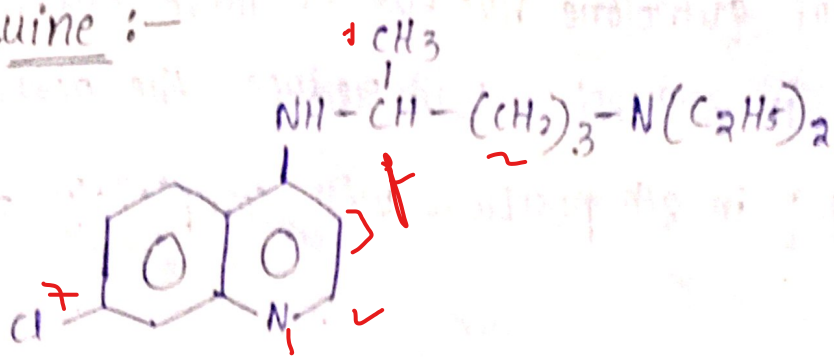
⇒ 2,6 methylene grps b/w two 'N' of side chain produces optimal activity.

⇒ Even no. of methylene grps are less active than odd no. of methylene grps.

⇒ 5-phenoxy (C_6H_5O) will ↑ses the optimal activity.

⇒ The extent of 3° Subst'n of the terminal amine may be 1°, 2° or 3°.

* Chloroquine :-

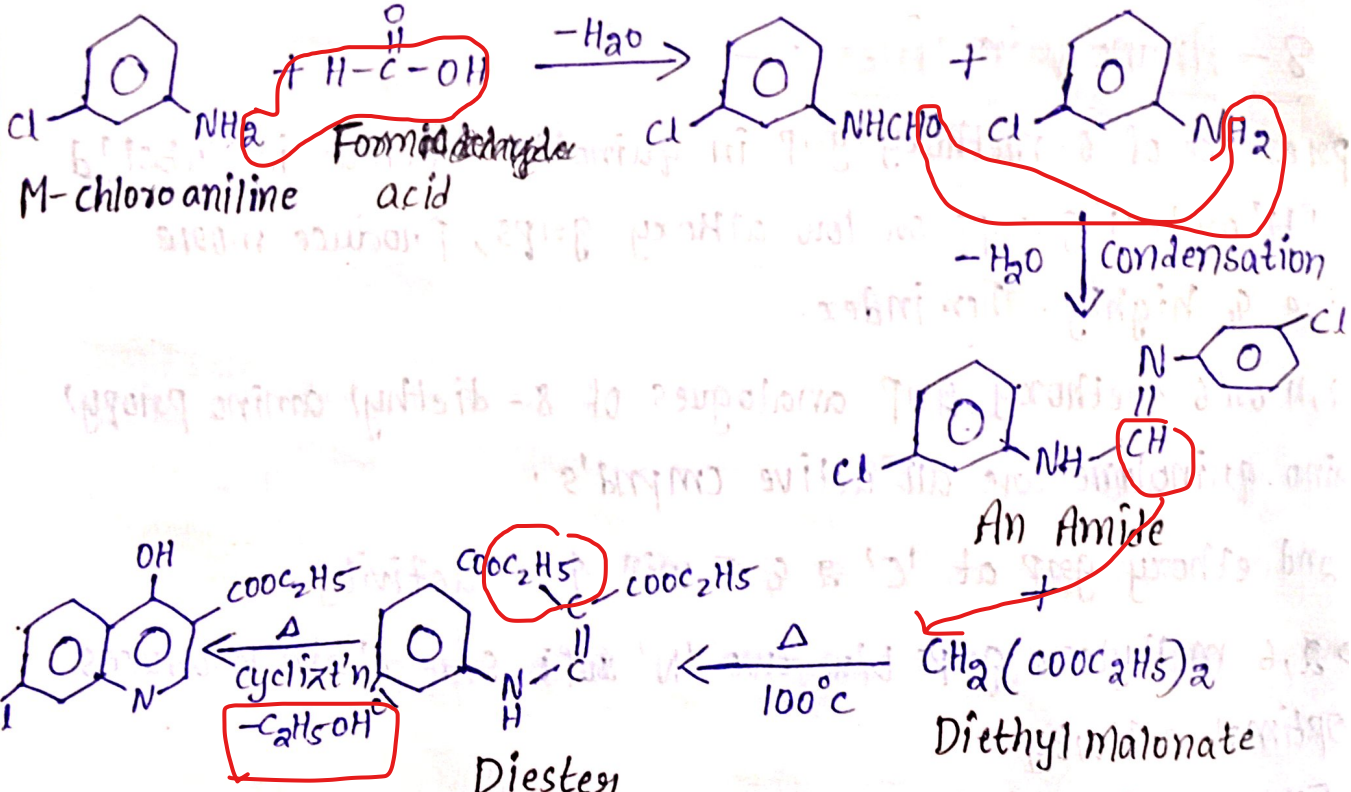


7-chloro-4-{[4-diethylamino]1-methyl butyl amino quinoline

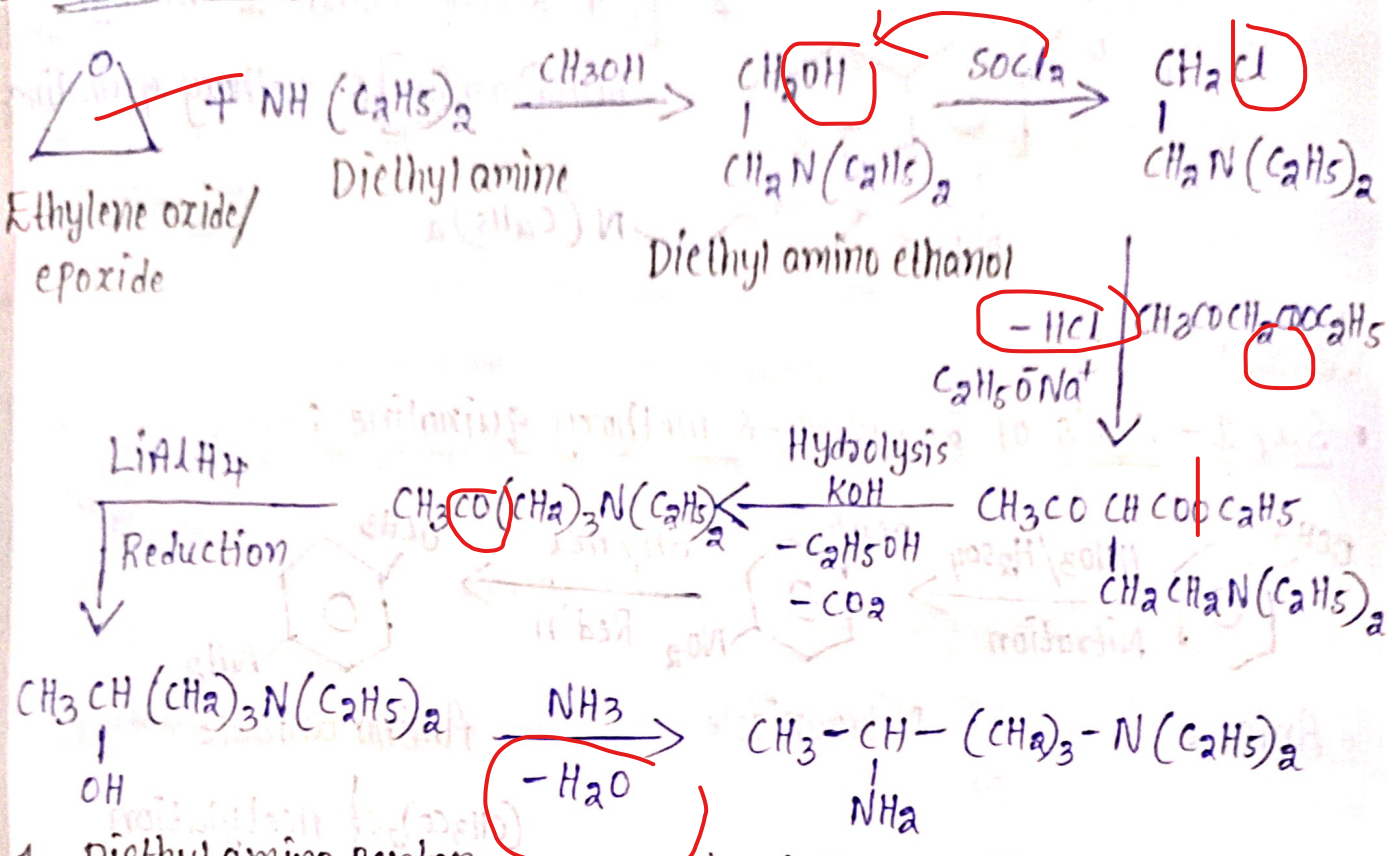
Syns :- Syn's is done by 3 methods.

1) Syn's of 4,7 - Dichloroquinoline.
2) Syn's of 4-Amino-1-diethylamino pentane.
3) condensation of Step 1 & 2.

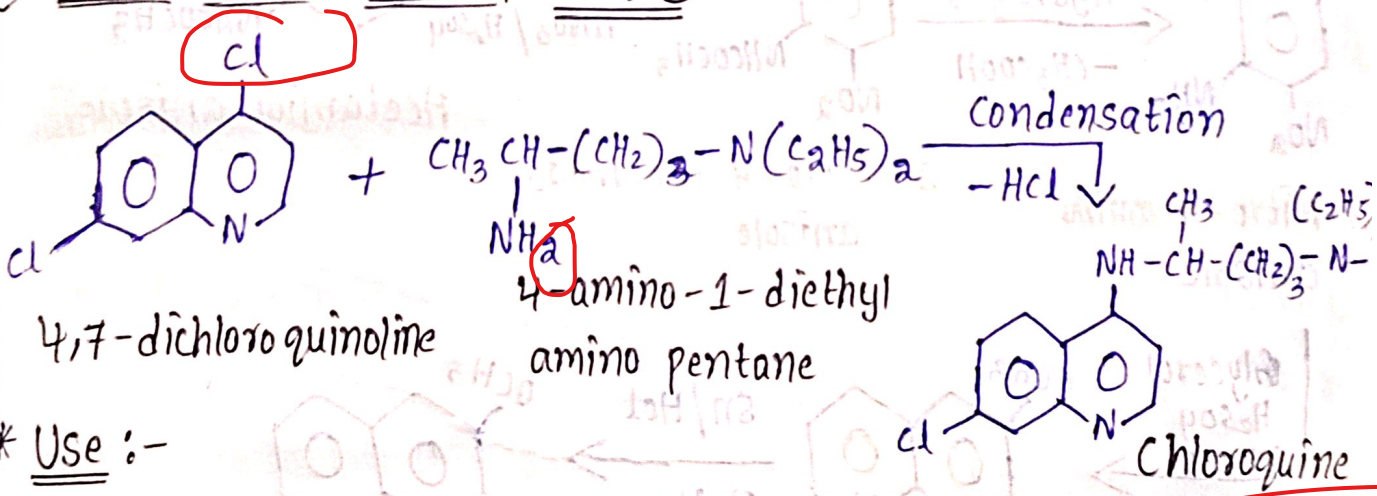
(1) Syn's of 4,7 - Dichloroquinoline :-



② Syn's of 4-Amino-1-diethylamino pentane :-



③ Condensation of Step ① & ② :-

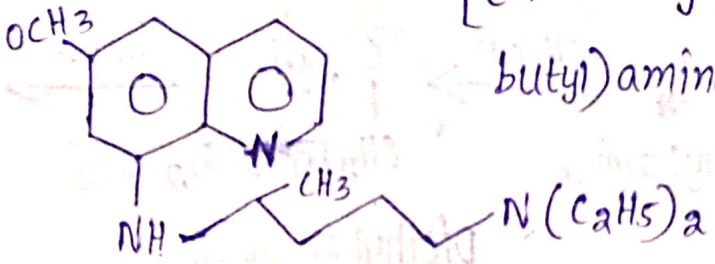


* Use :-

1) Used for both Prophylaxis & treatment of malaria.
2) It is having quick schizonticidal action.

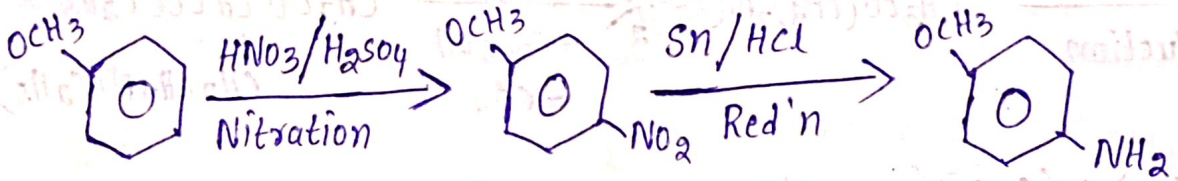
* Pamaquine :-

8-[(4-diethylamino-1-methyl butyl)amino]6-methoxy quinoli



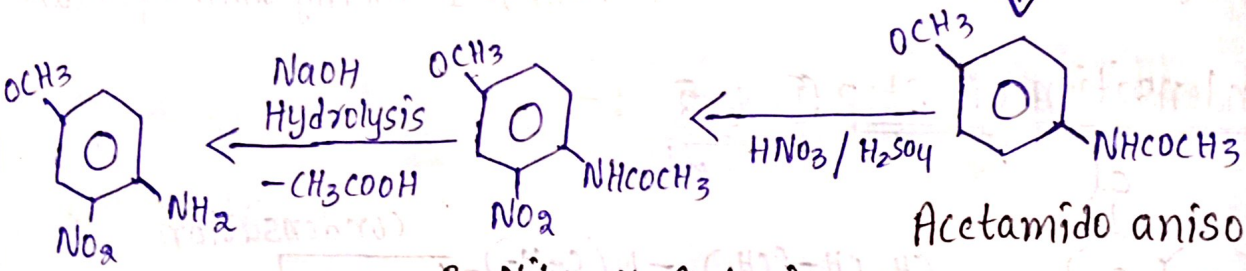
Syn's :-

- **Step 1 - Syn's of 8-Amino-6-methoxy quinoline :-**



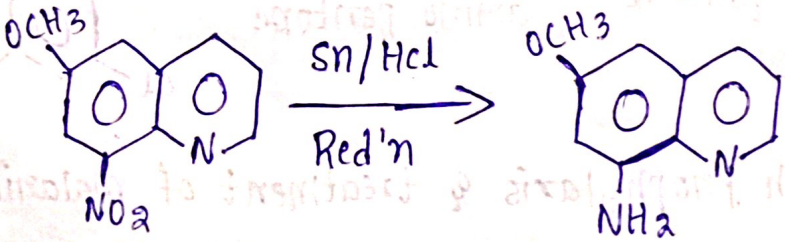
Anisole — Nitroanisole — Amino anisole

$(CH_3CO)_2O$ | Acetylation



Acetamido anisole — 3-Nitro-4-Acetamido anisole — 3-Nitro-4-amino anisole

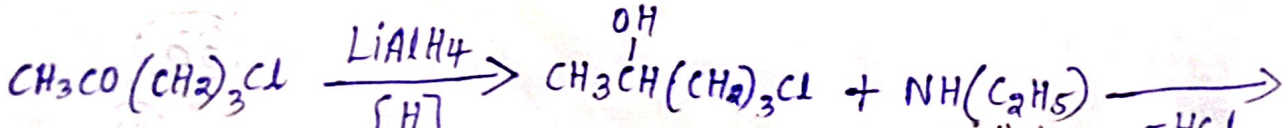
Glycerol, H_2SO_4, $C_6H_5NO_2$ → Skraup Syn's



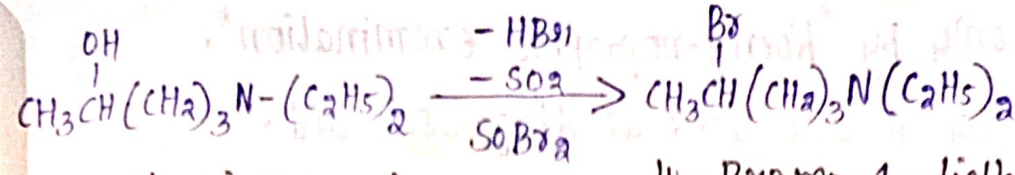
Nitromethoxy quinoline — 8-Amino-6-methoxy quinoline.

- **Step 2 :-**

- **Syn's of 4-Bromo-1-diethyl amino pentane :-**



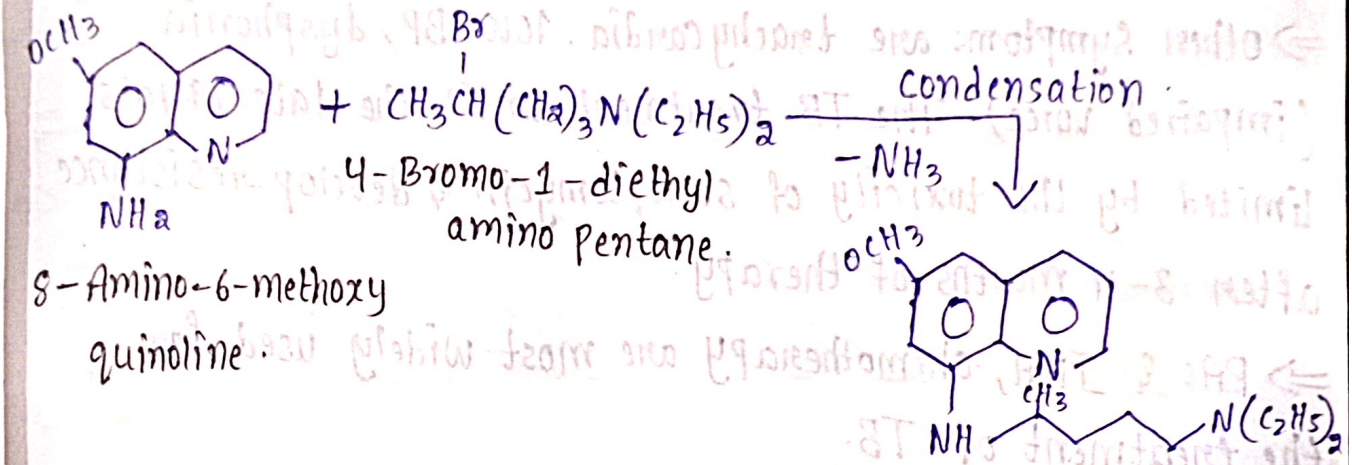
5-chloro-2-pentane — 5-chloro-2-pentanol



5-N,N'-Diethyl amino 2-pentanol

4-Bromo-1-diethyl amino pentane.

- Step 3 :- condensation of step ① & ② :-



8-Amino-6-methoxy quinoline.

Pamaquine.

* Use :- Used as Suppresive agent.

UN-3 Anti-tubercular Agents UNIT-3

* Introduction :-

⇒ Tuberculosis is a disease caused by various strains of Mycobacterium tuberculosis.

⇒ It is a chronic infectious disease

⇒ It is transmitted via the respiratory route.

⇒ The organism appears in water droplets are expelled during coughing, sneezing or talking.

⇒ It is a chronic disease that normally effects the RT, the lympathic nodes, Urogenital tract & Nervous system

⇒ This disease is a destructive process that replaces the normal tissue with TB.

⇒ The diseased symptoms are not seen in early stages and