Chapter

20 Antimalarials

1. INTRODUCTION

Antimalarials are chemotherapeutic agents which are used for the prevention and treatment of malaria.

Malaria is still one of the most dreadful protozoal diseases affecting man. Until recently it was of a world-wide spread. However, the disease occurs now mainly in tropical countries of the world. It is quite painful and distressing to know that more than one million people die of malaria each year and most of these people belong to the third world countries. Malaria has been eradicated from the developed countries as a result of the **Malaria Eradication Programme** of the **World Health Organization (WHO).** This was achieved through improved living conditions, use of insecticides, destruction of breeding places for mosquitoes and use of antimalarials as prophylactic agents. Similar efforts in developing countries have not yielded good results.

The causal organisms responsible for malaria belong to the genus *plasmodium* which is of the class of protozoa known as **sporozoa.** There are four different species which are accepted as being responsible for human malaria. These are *Plasmodium malariae,* the parasite of *quartan malaria ; Plasmodium vivax,* the parasite of benign *tertian malaria, Plasmodium falciparum,* the parasite of *malignant* or *subtertian malaria,* and *Plasmodium ovale,* the parasite that causes a mild type of *tertian malaria.*

These protozoa have complex life cycles embodying both the female anopheles mosquito and the liver and the erythrocyte of the human host. Hence, an ideal antimalarial must be able to exert an effect on two fronts simultaneously, namely : to eradicate the microzoan from the blood and also from the tissues, in order to produce an effectife **'radical cure'.** It has been established beyond reasonable doubt that the various **antimalarials** differ essentially in their point of interruption of the cycle of the parasite and, therefore, the stages of the infection that is effected.

In actual practice, there are *three* well recognized and predominant manners to control malaria effectively, namely ;

(*a*) Elimination of the vector*,

(*b*) Drug therapy, and

(*c*) Vaccination.

*A carrier, usually an insect or other arthropod, that transmits the causative organisms of disease from infected to non infected individuals, especially one in which the organism goes through one or more stages in its life-cycle.

Elimination of the Vector. Currently, the elimination of the vector is considered to be one of the easiest and most cost-effective measure adopted across the globe.

In fact, there are *two* different ways to control the **'mosquito carrier'.** *First,* being check and prevent the usual contact usually taking place between the insect and the human beings. It is, however, pertinent to observe here that the **Anopheles mosquito** happens to be a **nocturnal feeder** ; and, therefore, it is relatively much easier to control than the corresponding **Aedes aegypti mosquito** which is a *day feeder* and is responsible solely for carrying **dengue** as well as **yellow fever** (prevalent in the African continent). Simply by installing nylon or iron screens on widows and using mosquito netting (at night while sleeping) in bed-rooms may provide an effective measure of prevention. *Secondly,* the elimination of the **Anopheles mosquito**, normally by total erradication by the application of *insecticide* and drastically destroying the breeding hide-outs, is believed to be one of the most practical ways to eliminate (as opposed to control) malaria.

Examples : Dichloro diphenyl trichloroethane (DDT) an insecticide discovered by the Nobel laureate Dr. Muller (1948), almost kills the malaria-carrying **Anopheles mosquito** completely. Though its *long lasting* effect is eventually very much beneficial from the standpoint of Anopheles mosquito control, but it gets accumulated in the environment unfortunately that may ultimately gain entry into the **food chain** and can affect both **humans** and **animals** equally. Hence, the use of **DDT** has been banned completely by **FDA, WHO** and other law enforcing authorities ; and duly replaced by other **'safer insecticides'.**

DDT

Drug Therapy. A host of **'drug substances'** either isolated from the **plant sources,** such as : **quinine ; quinidine, cinchonine, cinchonidine, artimisinine ;** or **synthetic compounds** for instance : **chloroquine, paludrine, pamaquine** etc., are being used profusely in topical countries to fight the menace of malaria as the *'life-saving drugs'*. It is worth noting at this juncture that the currently employed **'antimalarials',** while being effective against certain species, also exhibit certain adverse reactions, and noticeable resistance is enhancing also progressively.

Vaccination. Inspite of the tremendous impetus and thrust instituted legitimately by **WHO,** the dream of developing an effective, safer, economically viable **'antimalarial vaccine'** is yet to be discovered to combat the human sufferings, more specifically the rate of infant mortality in economically less privileged and developed countries of the world.

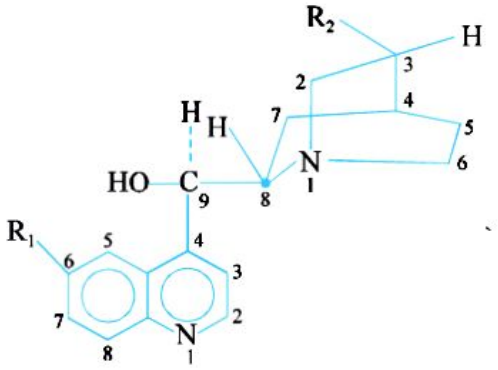
It has been duly observed that the **malaria parasite** does elicit obviously an immune-response, demonstrated by virtue of the fact that usually the children, in particular, having an initial exposure are more prone to die than the adults who have since experienced/exposed to several recurring attacks.

Besides, a **T-cell response** which essentially comprise of both **$CD4^+$ and $CD8^+$ T-cells,** production of **interferon gamma,** and **nitric oxide synthase** induction serves as an additional proof of evidence that the **human-immune system** is *able to detect the parasite and hence responds accordingly.**

A plethora of chemotherapeutic agents having divergent chemical structures have been introduced clinically since the mid-twenties, *e.g.,* **pamaquine (1926), quinacrine (1930).** Although historical evidence of **cinchona** dates back to 1638 when it was used to treat **Countess of Cinchona,** wife of the

*Pombo DJ *et al. Lancet,* **360** : 610, 2002.

then governor of Peru, and hence the name. Later on, in 1820, Polletier and Caventou succeeded in the isolation of quinine from the circhona bark. Now, more than twenty-five alkaloids from the circhona bark have been characterized, out of which only a few are useful clinically, *viz.*, **quinine, quinidine, cinchonine, cinchonidine.**



Quinine : $R_1 = OCH_3$; $R_2 = -CH = CH_2$; (–) 8S : 9R isomer

Quinidine : $R_1 = OCH_3$: $R_2 = -CH = CH_2$; (+) 8R : 9S isomer

Cinchonine : $R_1 = H$; $R_2 = -CH = CH_2$; (+) 8R : 9S isomer

Cinchonidine : $R_1 = H$; $R_2 = -CH = CH_2$; (–) 8S : 9R isomer

All these alkaloids bearing the same substitution at R_1 and R_2 are essentially **diastereoisomers,** only having different configuration at the *third and fourth chiral centres (C-8 and C-9).*

Soon after the Second World War (1943), a large number of compounds were synthesized and tested for **antimalarial** actions, and these eventually gave birth to a host of potent drugs like, **chloroquine, proguanil, comoquine and amodiaquine,** etc.

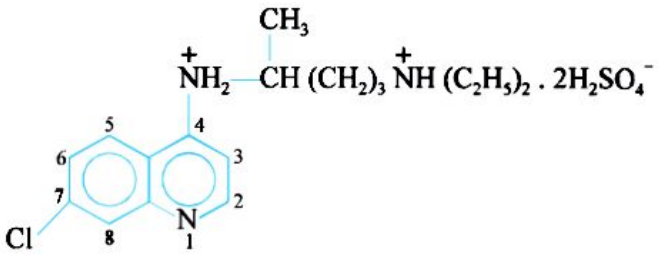
2. CLASSIFICATION

The **antimalarials** may be classified on the basis of their basic chemical nucleus as stated below and some representative examples belonging to each class are given.

2.1. 4-Aminoquinoline Analogues

In 1942, a group of German researchers first reported that 4-, 6- and 8-aminoquinolines when duly substituted produced **antimalarial agents**. An extensive research in East and West was augmented due to the acute shortage of cinchona bark during the Second World War. These drugs are found to be active against the erythrocytic form of most malarial parasites ultimately affecting a clinical cure. They do not cause prevention of the disease, and they are inactive against the liver-infecting forms.

A. Chloroquine Phosphate BAN, USAN, Chloroquine INN,



7-Chloro-4-[[4-(diethylamino)-1-methyl] butyl] amino]-quinoline phosphate (1:2) ; 1, 4-Pentanediamine, N^4-(7-chloro-4-quinolinyl)-N^1, N^1-diethyl-, phosphate (1:2) ; Resochin ; BP ; USP ; Int. P., Ind. P. ;

Aralen$^{(R)}$ (Winthrop).

Synthesis

It is prepared by adopting the following *four* steps *viz.*,

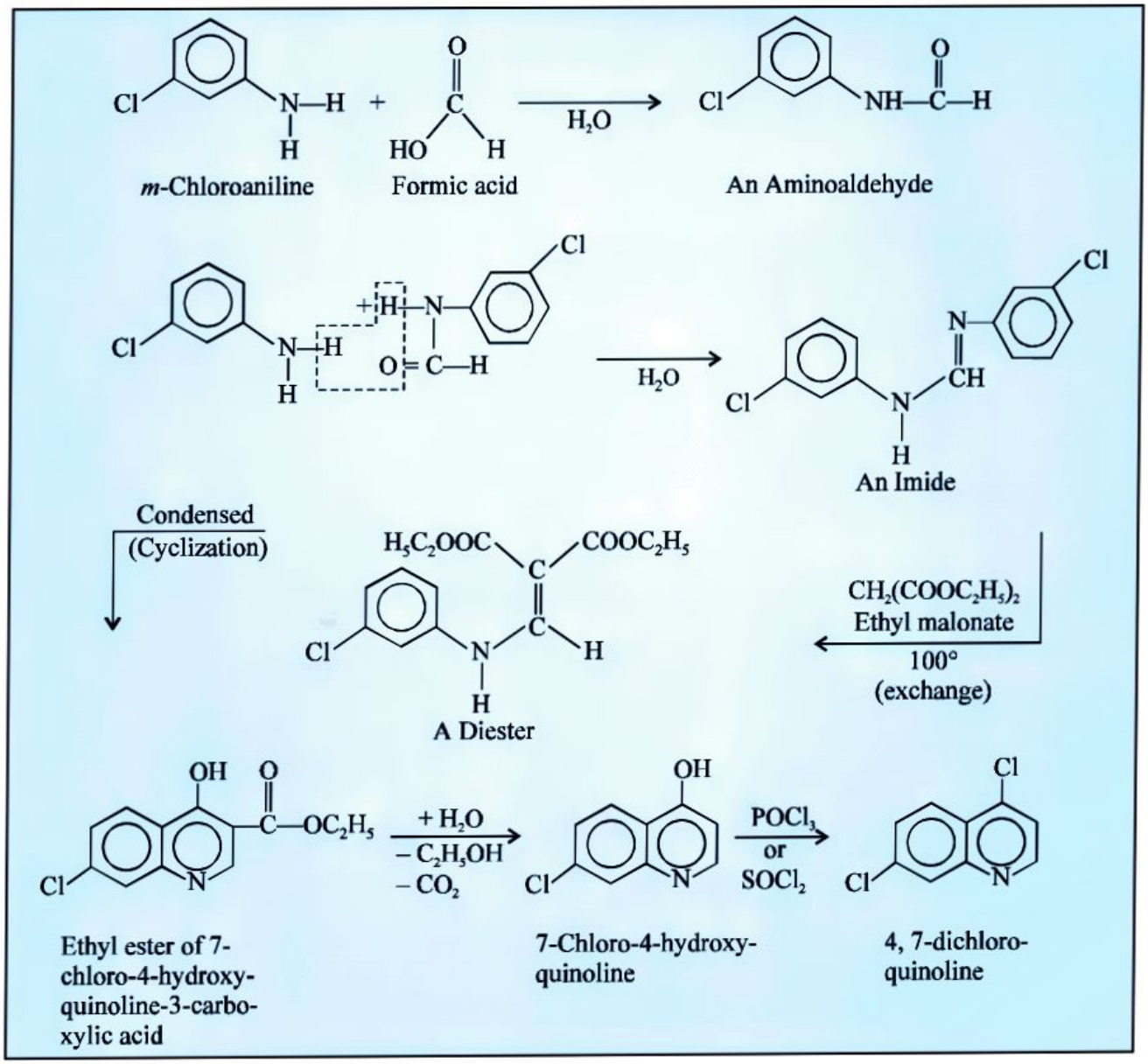
(*a*) Preparation of 4, 7-Dichloroquinoline (*i.e.*, the nucleus)

(*b*) Preparation of 2-amino-5-diethyl amino pentane, or 1-diethylamino-4-amino pentane (*i.e.*, the side chain).

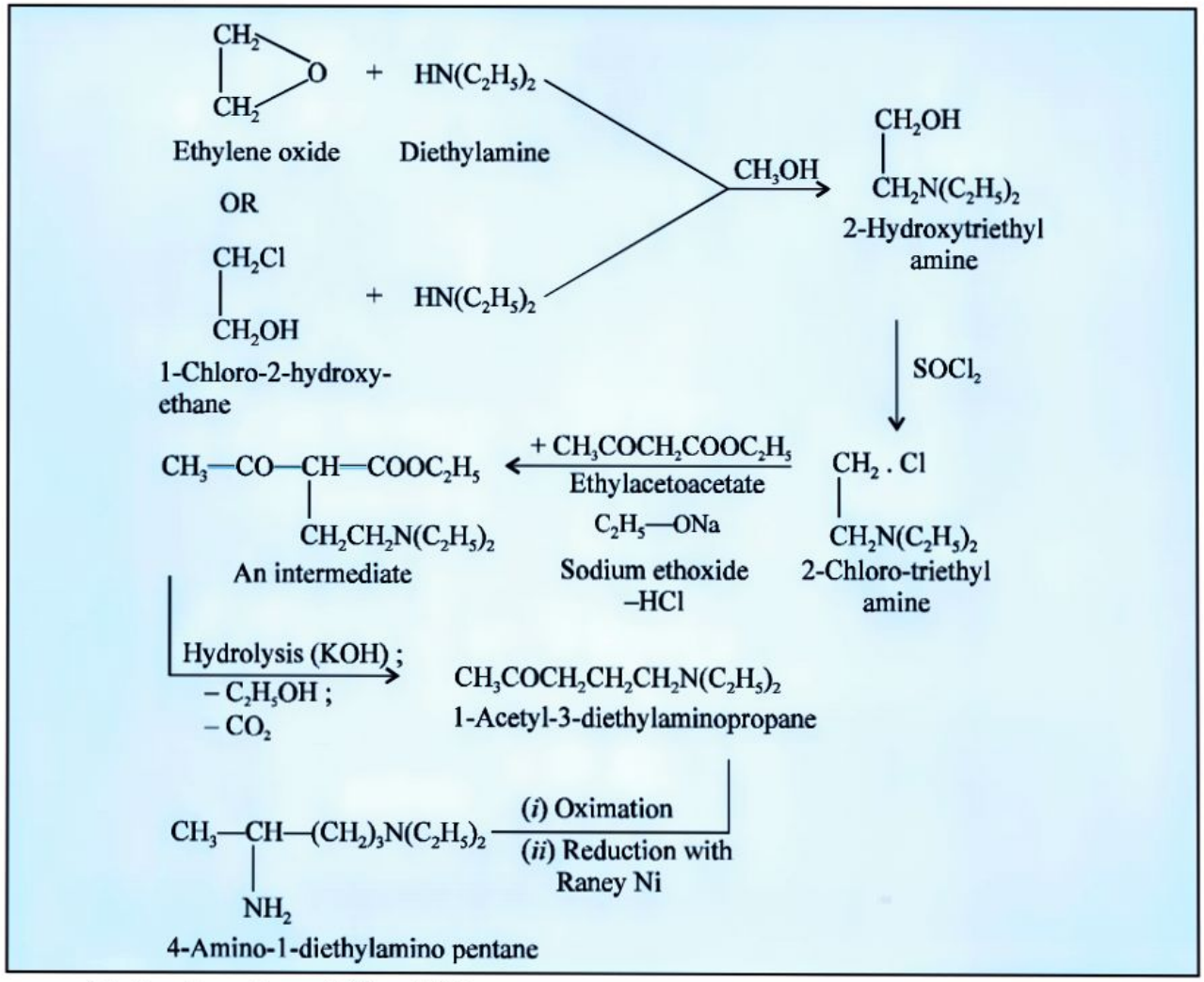
(*c*) Condensation of '*a*' and '*b*'.

(*d*) Addition of concentrated phosphoric acid to a hot ethanolic solution of the condensed product.

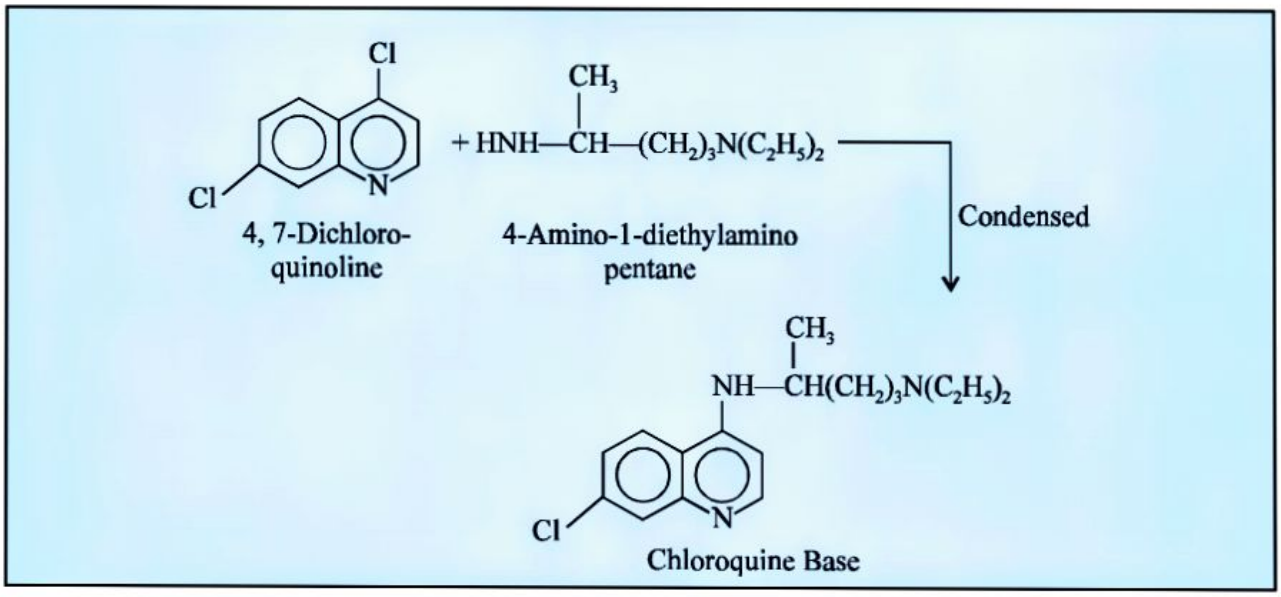
(*a*) Preparation of Nucleus



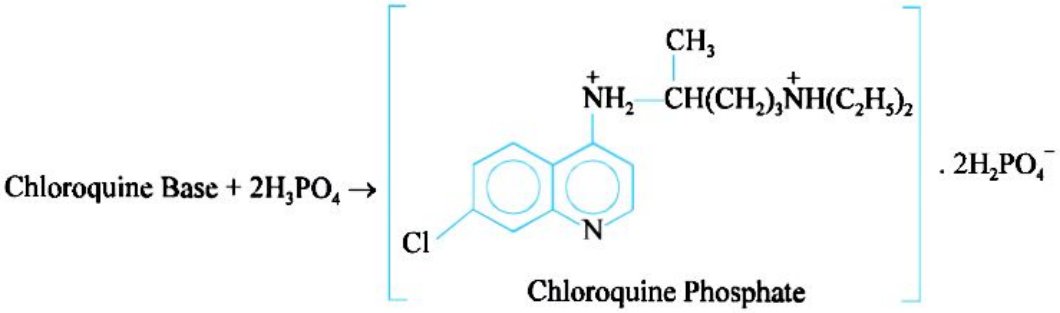
(*b*) **Preparation of Side Chain**



(*c*) **Condensation of (*a*) and (*b*)**



(*d*) Preparation of Phosphate Salt



Chloroquine Phosphate

Reaction between two moles of *m*-chloroaniline and a mole of formic acid yields an imidine which on treatment with ethyl malonate at 100° undergoes exchange and results into a diester. This further undergoes cyclization through condensation to yield the corresponding ethyl ester of 7-chloro-4-hydroxy-quinoline-3-carboxylic acid which on hydrolysis gives 7-chloro-4-hydroxy quinoline. Finally, on chlorination with either phosphorus oxychloride or thionyl chloride yields the nucleus 4, 7-dichloro quinoline.

The side chain is prepared by the interaction between either ethylene oxide or 1-chloro-2-hydroxy ethane with diethyl amine in methanol yields 2-hydroxy-triethyl hydrochloride. This on chlorination with thionyl chloride yields 2-chloro-triethyl amine which on treatment with ethyl aceto-acetate in the presence of sodium ethoxide gives an intermediate compound. Alkaline hydrolysis produces 1-acetyl-3-diethylamino propane which on reduction with **Raney Nickel** followed by oximation yields 4-amino-1-diethylamino pentane.

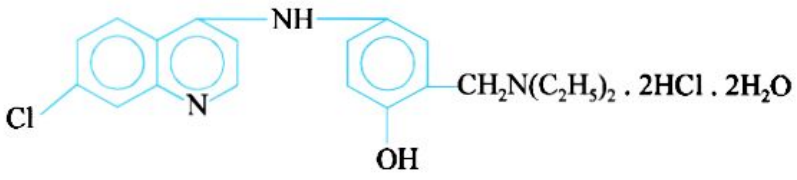
Condensation of the nucleus and the side chain gives rise to the **chloroquine base** which on treatment with hot phosphoric acid in an ethanolic solution yields the official compound.

Chloroquine is extensively employed for the suppression and treatment of malaria. *It has been found to exert a quick schizonticidal effect and seems to affect cell growth by interfering with DNA.*The overall activity of chloroquine appears to be partially dependent on the preferential accumulation in the infected erythrocyte. It has been observed that *it specifically kills the erythrocytic forms of all malaria parasites at all states of development, but has no effect on the malaria parasite in the human liver cells. Hence, chloroquine produces complete cure of malaria caused by P. falciparum.* It fails to check the relapse caused by the secondary exoerythrocytic phase of *P. malariae, P. ovale and P. vivax.*

Dose : *As prophylactic, suppressive, 500 mg once per week ; therapeutic, initially, 1 g, followed by 500 mg in 6 hours, and 500 mg on the 2nd and 3rd days.*

Chloroquine sulphate is another salt of **chloroquine [Nivaquin(R), May & Baker]** which possesses almost similar actions to those of **resochin.**

B. Amodiaquine Hydrochloride BAN, USAN, Amodiaquine INN,



4-[(7-Chloro-4-quinolyl) amino]-α-(diethylamino)-*o*-cresol dihydrochloride dihydrate ; Phenol, 4-[(7-Chloro-4-quinolyl)-amino]-2-[(diethylamino) methyl]-dihydrochloride, dihydrate, Amodiachin Hydrochloride ; BP ; USP ; Int. P ; Ind. P ;

Camoquin(R) (Parke-Davis).

Synthesis

It consists of the preparation of :

(*i*) 4, 7-Dichloroquinoline (*i.e.*, nucleus),

(*ii*) 4-Amino-2-diethylaminomethyl phenol,

(*iii*) Condensation of (*i*) and (*ii*),

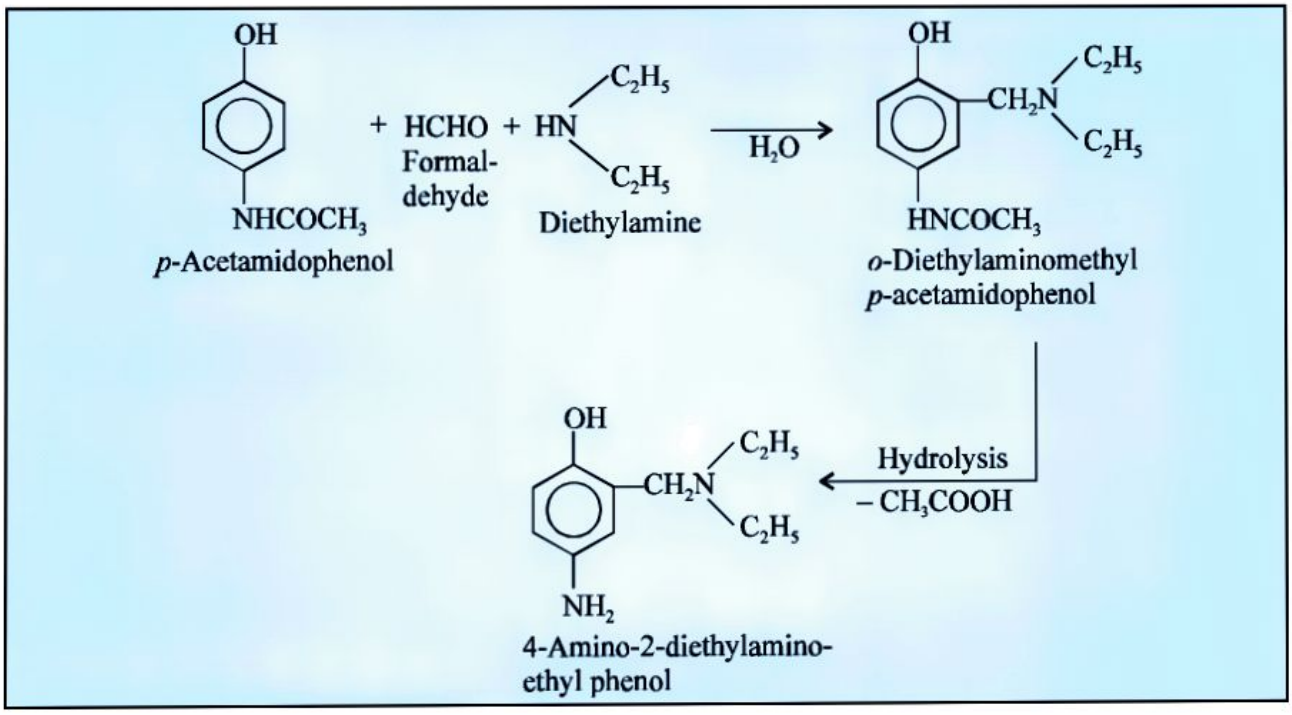
(*iv*) Formation of hydrochloride salt.

(*a*) *Preparation of 4, 7-dichloroquinoline nucleus.* It is prepared as described under chloroquine phosphate earlier.

(*b*) *Preparation of the side chain 4-amino-2-diethylamino-ethyl phenol* : It may be prepared by two methods as described below :

Method-I : From p-Acetamido phenol

o-Diethylaminomethyl-*p*-acetamidophenol is prepared by the interaction of *p*-acetamidophenol, formaldehyde and diethyl amine with the elimination of a molecule of water. Hydrolysis of this product yields 4-amino-2-diethylamino ethyl phenol with the elimination of a mole of acetic acid.

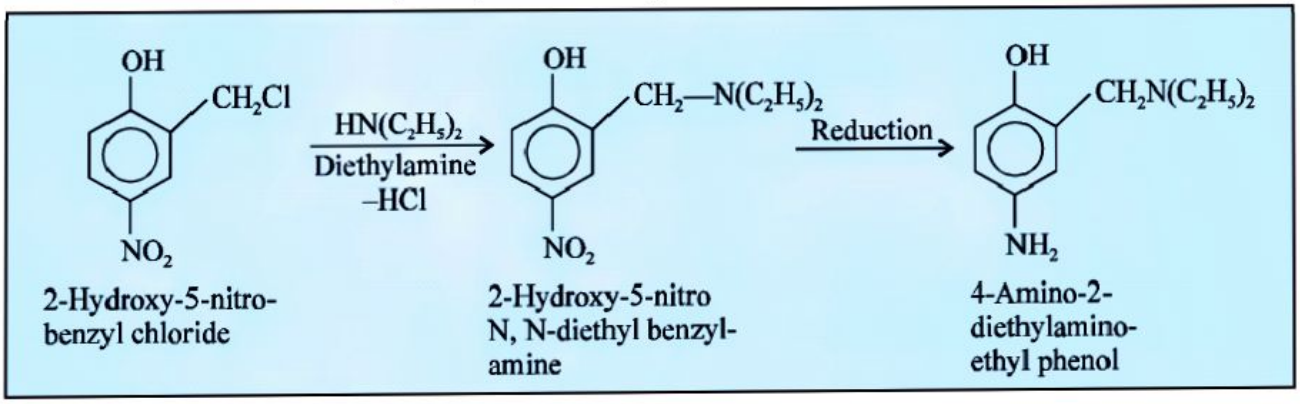


p-Acetamidophenol

o-Diethylaminomethyl *p*-acetamidophenol

4-Amino-2-diethylamino-ethyl phenol

Method-II : From 2-Hydroxy-5-nitrobenzyl chloride



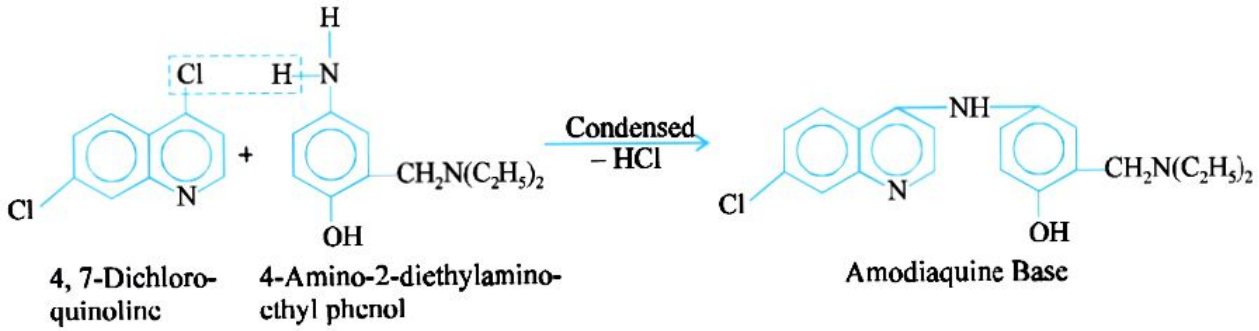
2-Hydroxy-5-nitro-benzyl chloride

2-Hydroxy-5-nitro N, N-diethyl benzyl-amine

4-Amino-2-diethylamino-ethyl phenol

The reaction between 2-hydroxy-5-nitro-benzyl chloride with diethylamine yields 2-hydroxy-5-nitro-N, N, diethyl benzyl amine, which on reduction gives 5-amino-2-diethylamino ethyl phenol.

(*c*) **Condensation of (*a*) and (*b*), we have :**



4, 7-Dichloro-quinoline

4-Amino-2-diethylamino-ethyl phenol

Amodiaquine Base

(*d*) **Preparation of Hydrochloride Salt :**

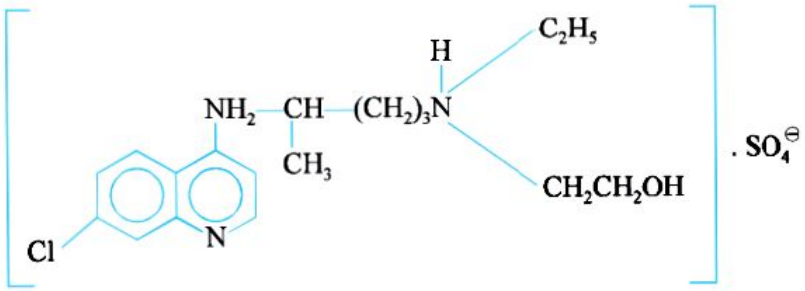
$$\text{Amodiaquine Base} \xrightarrow{\text{HCl}} \text{Amodiaquine Hydrochloride}$$

The condensation of the nucleus and the side chain prepared above in (*a*) and (*b*) gives the amodiaquine base which on neutralization with hydrochloric acid yields the official compound.

Its antimalarial action is very much similar to that of chloroquine and hence may be used alternatively for the same purpose.

Dose : *Initially, 600 mg of base followed by 300 mg doses 6, 24, 48 hours later.*

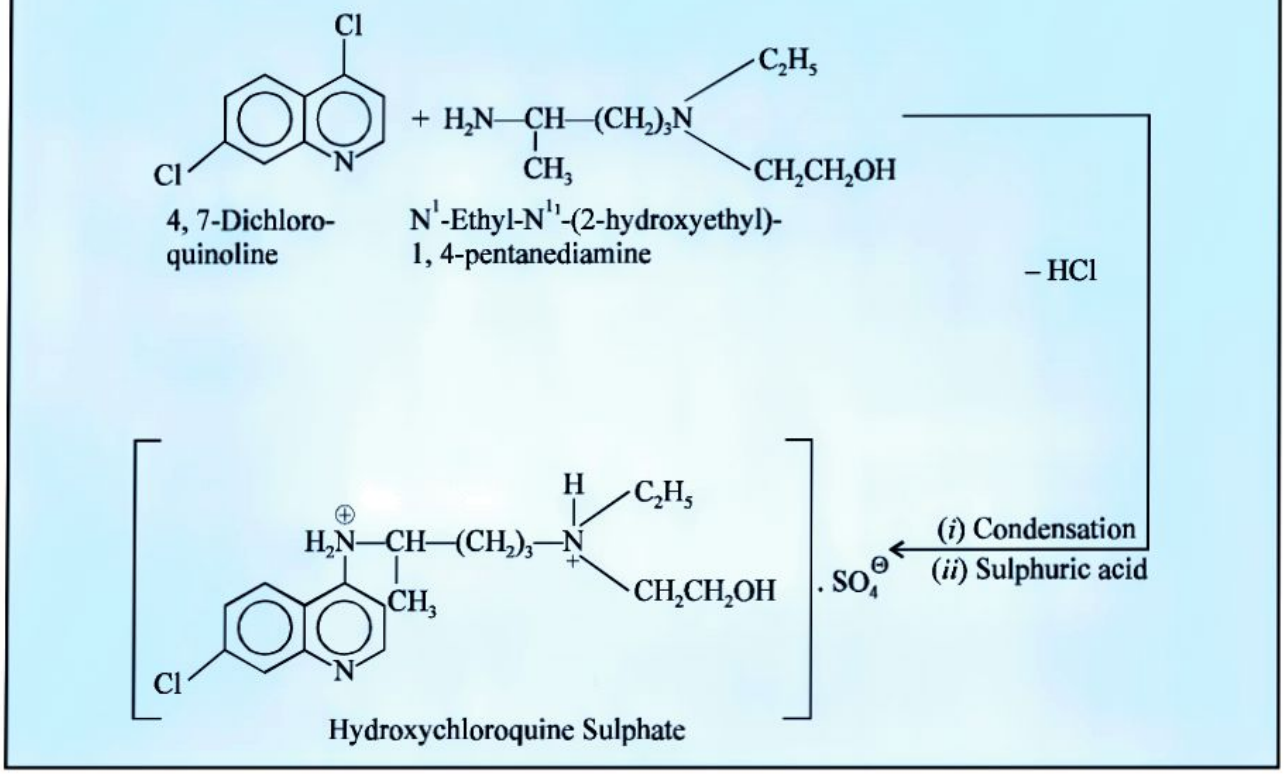
C. Hydroxychloroquine Sulphate BAN, Hydroxychloroquine Sulfate USAN,



2-[[4-(7-Chloro-4-quinolyl] amino] pentyl] ethylamino] ethanol sulphate (1:1) (salt) ; Ethanol, 2-[[4-(7-chloro-4-quinolyl) amino]-pentyl] ethylamino]-, sulphate (1:1) salt ; Oxichlorochin Sulphate ; Hydrochloroquine Sulphate BP ; Hydroxychloroquine Sulfate USP ;

Plaquenil Sulfate(R) (Winthrop).

Synthesis

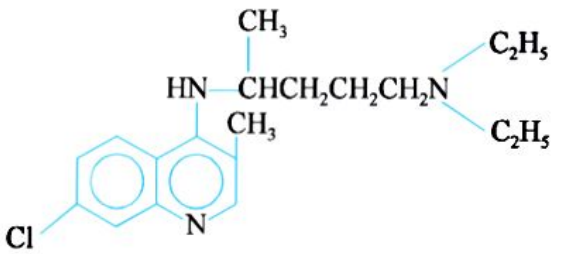


It may be prepared by the condensation of 4, 7-dichloro quinoline and N^1-ethyl-N^1-(2-hydroxyethyl)-1, 4-pentanediamine and dissolving the resulting **hydroxychloroquine base** in absolute ethanol. The coversion to the corresponding sulphate is achieved by treating with an equimolar portion of sulphuric acid.

Its actions and uses are similar to those of **chloroquine**. Owing to its specific action on the erythrocytic phase of the malaria parasite it fails to serve as a 'radical cure' for *P. vivax* infections. *It also finds its clinical usefulness in the treatment of rheumatoid arthritis and lupus erythematosus.*

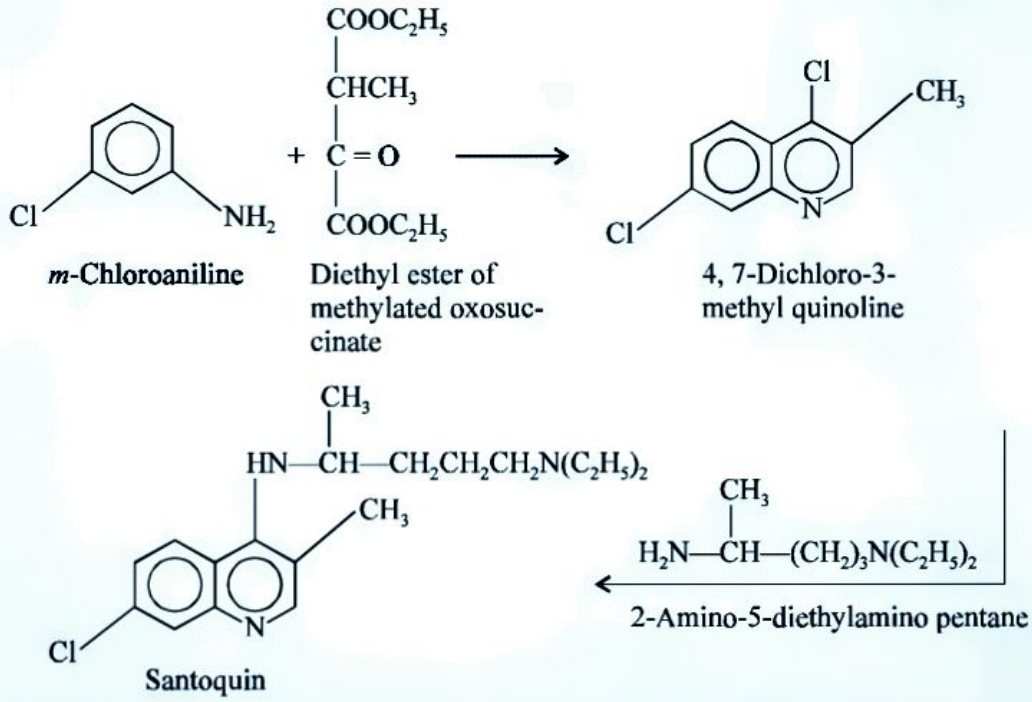
Dose : *In P. falciparum infections, 1.25 g in a single dose or in 2 divided doses at 6-hour intervals ; in rheumatoid arthritis, 400 mg daily ; in lupus erythematosus, 200 to 400 mg 1 or 2 times daily.*

D. Santoquin



7-Chloro-4-{[4-(diethylamino)-1-methylbutyl]-amino}-3-methylquinoline.

Synthesis



4, 7-Dichloro-3-methylquinoline is prepared by the interaction of *m*-chloroaniline and diethyl ester of methylated oxosuccinate which on treatment with 2-amino-5-diethyl-amino pentane affords santoquin.

It has an additional methyl group at C-3 in the quinoline nucleus of **chloroquine**. It is found to be less reactive than **chloroquine**.

2.1.1. Mechanism of Action

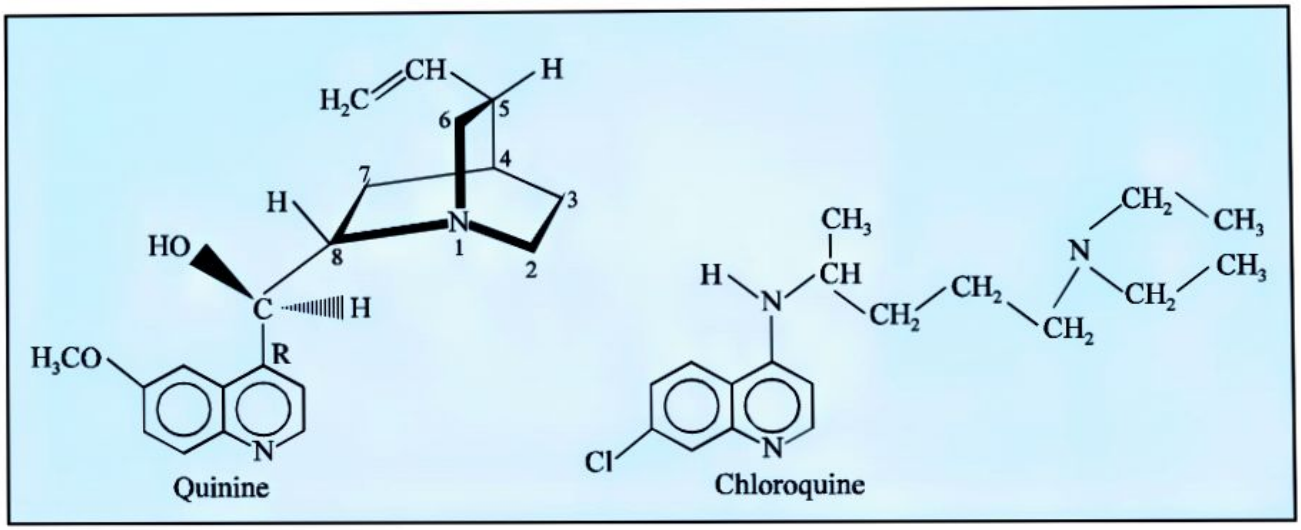
The mechanism of action of the four compounds described under Section 20.2.1 shall be dealt with individually in the sections that follows :

2.1.1.1. Chloroquine Phosphate

The **'drug'** particularly causes significant dysfunction of the *acid phagosomes in plasmodia* and also in human leukocytes and macrophages. It is neither a prophylactic nor a radical curative agent in vivax malaria. Interestingly, in regions wherein *Plasmodium falciparum* is invariably sensitive to chloroquine, it is specifically and predominantly effective in terminating acute attacks of **non-resistant falciparum malaria ;** and, therefore, normally affords total cure in this type of malaria. As **chloroquine** is well tolerated, it has been recommended to be used rountinely in **amebiasis** *without any demonstrable hepatic involvement.*

The **'drug'** usually gets absorbed almost completely from the GI tract when administered orally. The parenteral IM administraction is usually given with its HCl-salt. It has also been observed that the tissues bind the drug, but not to the same extent as that of **quinacrine**. It gets degraded in tissues to unknown products.

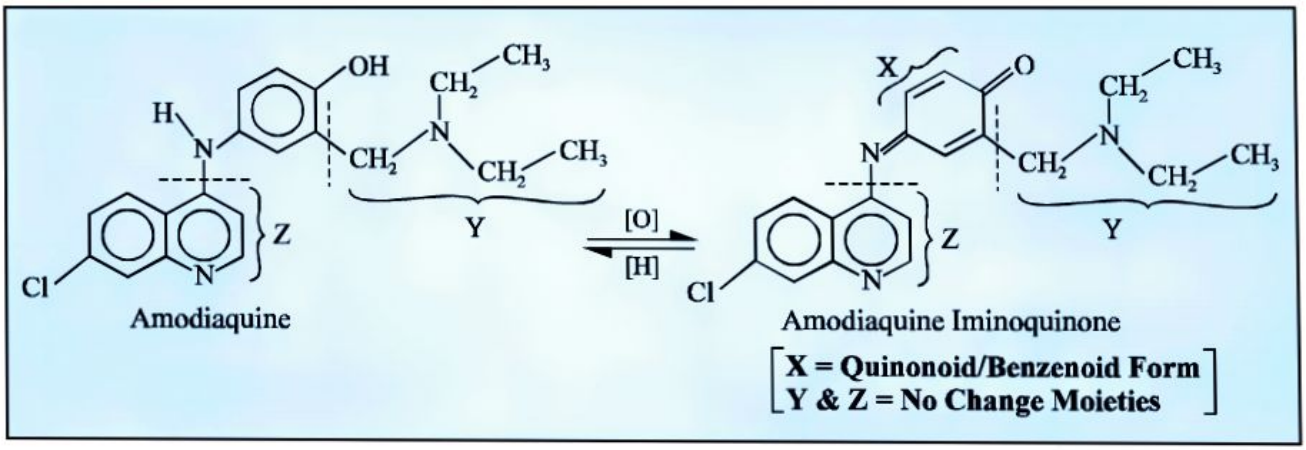
SAR of chloroquine. It may be regarded as the **prototypical** structure which overwhelmingly succeeded **'quinine'** and recognized as a potential **'synthetic antimalarial drug'** since the mid-1940s, as shown below :



2.1.1.2. Amodiaquine Hydrochloride

The **'drug'** resembles very similar to **chloroquine** mechanistically ; and it does not possess any added advantages over the other **4-aminoquinoline drugs**. It has been demonstrated amply that the **hydroquinone (phenol) amine system** rapidly gets oxidized to a corresponding **quinone-imine system,** either accomplished *via* **antioxidatively** and/or **metabolically ;** and the resulting product may be solely responsible for the ensuing **amodiaquine toxicity.**

Note : The quinine-imine system is almost identical to the acetaminophen (paracetamol) toxic metabolite.



In other words, **amodiaquine** upon oxidation gets converted to its *ketone-form* termed as **amodiaquine iminoquinone** which essentially embodies in it a quinonoid/benzenoid moiety.

2.1.1.3. Hydroxychloroquine Sulfate

The **'drug'** exerts its action exclusively in the *suppressive treatment* of **autoimmune inflammatory** diseases, for instance : *rheumatoid arthritis* (RA) and *systemic lupus erythromatosus* (SLS). Just like **chloroquine (CQ),** this **'drug' (HCQ)** is found to remain in the body for over a month and the prophylactic dosage is once-*a*-week only. It is somewhat less toxic than **CQ**.

SAR of HCQ. Structurally, it essentially differs exclusively in having an additional hydroxy (OH) moiety strategically attached to one of the terminal N-ethyl functions which eventually renders it less toxic than **CQ** perhaps due to H-bonding *in vivo.*

2.1.1.4. Sontoquine

The **'drug'** is found to be effective against **amaebic hepatitis** in *man* as well as *hamsters*. Unfortunately, the drug fails to show any specifically promising activity against the intestinal infections, most probably by virtue of the fact that it gets rapidly absorbed and do not reach the *lower intesine zone* in an effective therapeutic concentrations.

2.2. 8-Aminoquinoline Analogues

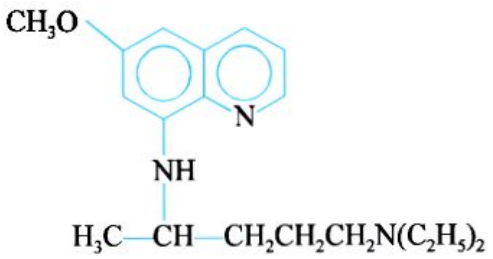
These structural analogues, unlike **4-aminoquinolines** offer a rather more significant derivative from the basic quinine moiety. From the structural aspect these drugs seem to be optimally substituted as evidenced by the presence of a side-chain consisting of 4 to 6-carbon atoms as well as the location of methoxy group at C-6. In general, the **8-aminoquinoline analogues** are relatively more toxic than the **4-aminoquinoline counterparts**.

They are active against the pre- or exoerythrocytic form of the malarial parasite, but lack activity against the erythrocytic forms. The 8-amino-quinolines possess gametocidal activity. They are used mainly for the radical cure of relapsing malaria like vivax malaria.

A few classical examples belonging to this category are discussed below :

Pamaquine ; Primaquine phosphate ; Pentaquine phosphate ; Isopentaquine and Quinocide hydrochloride.

A. Pamaquine INN, Pamaquin BAN, Pamaquine Naphthoate USAN,



8-(4-Diethylamino-1-methylbutylamino)-6-methoxyquinoline ; Pamachin ; Pamaquine Embonate ; Plasmoquinum ; BP ; 1953, NF IX.

Synthesis

It consists of the preparation of :

(*a*) 4-amino-diethylamino pentane, *i.e.*, side-chain,

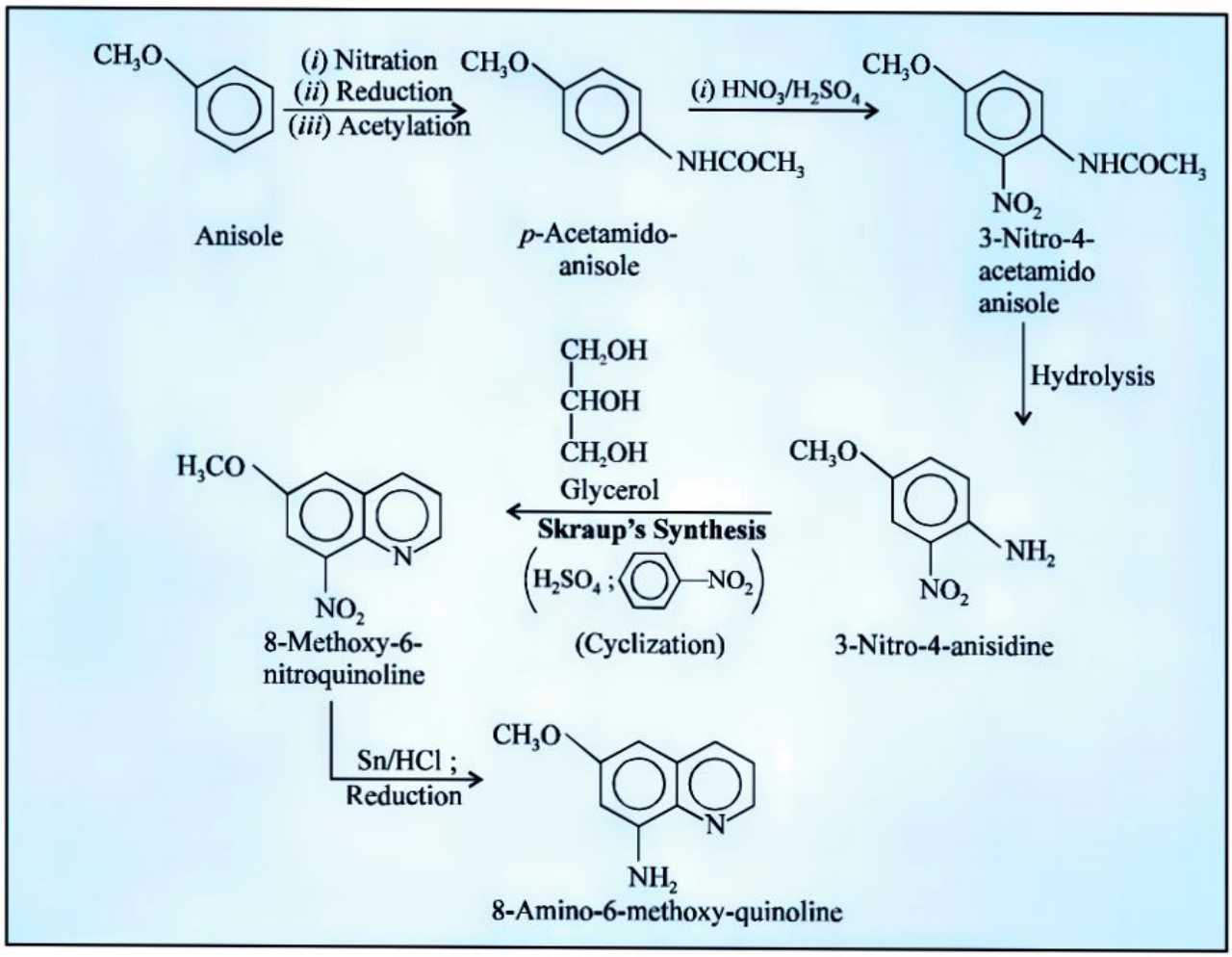
(*b*) 8-amino-6-methoxy quinoline, *i.e.*, quinoline nucleus,

(*c*) Condensation of (*a*) and (*b*).

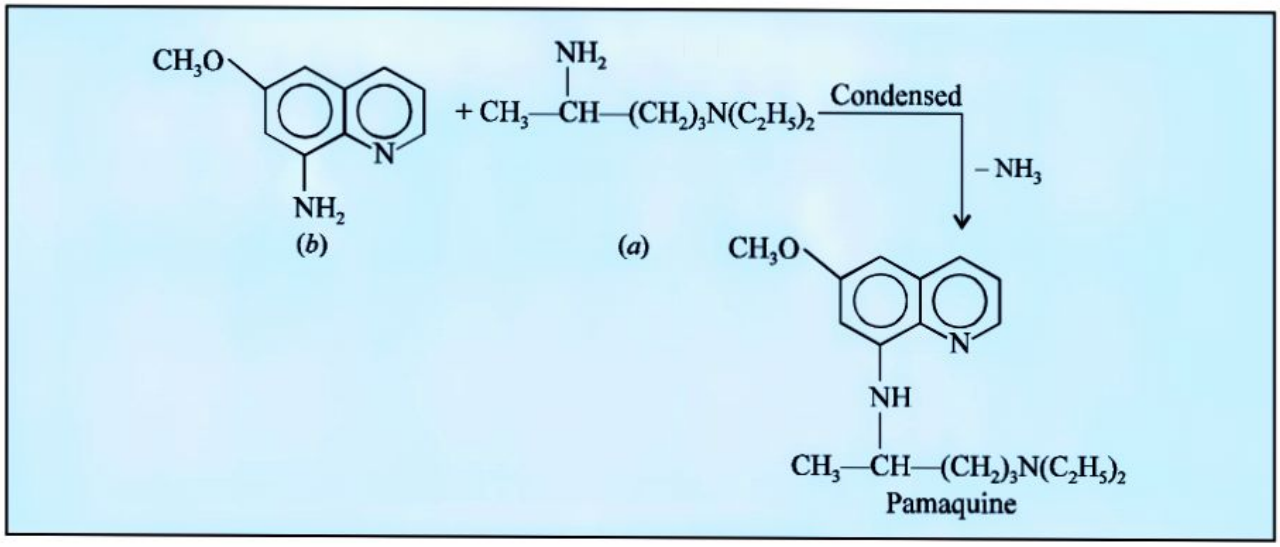
(*a*) *Preparation of Side-Chain*

It has been described earlier under chloroquine phosphate.

(*b*) **Preparation of Quinoline Nucleus**

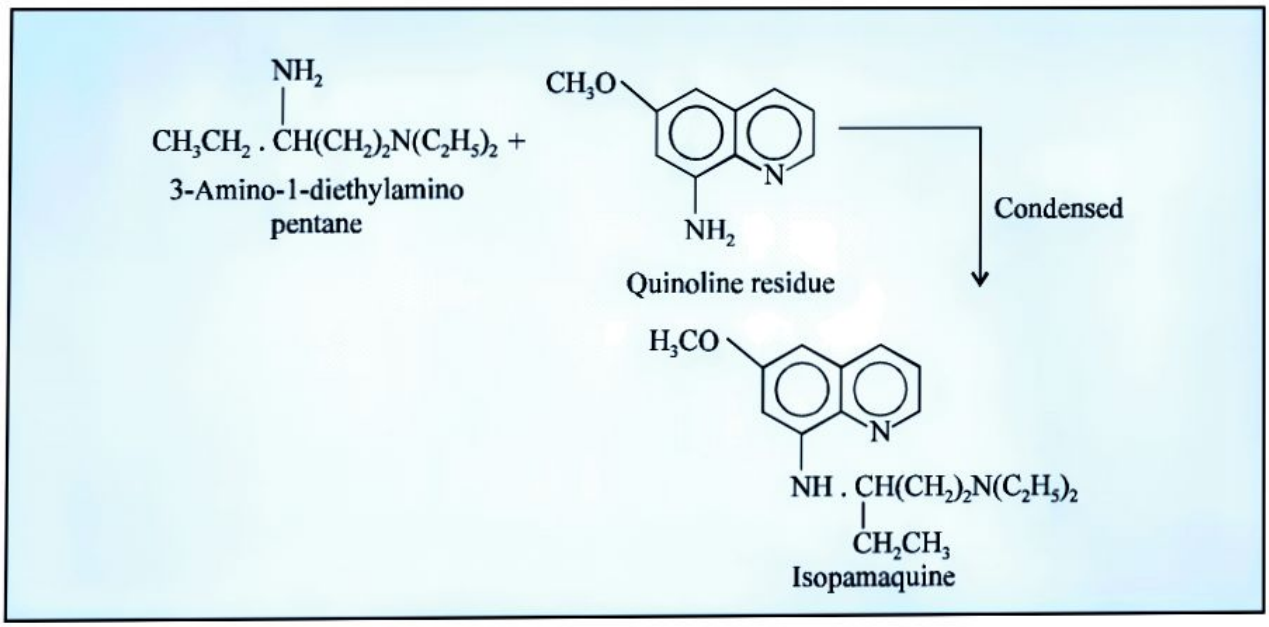


(*c*) **Condensation of (*a*) and (*b*)**



p-Acetamido anisole may be prepared by the sequential nitration, reduction and acetylation of anisole which on further nitration yields 3-nitro-4-acetamido anisole. This on hydrolysis gives 3-nitro-4-anisidine which on treatment with glycerol in the presence of concentrated sulphuric acid and nitrobenzene undergoes cyclization through **Skraup's synthesis** to yield 8-methoxy-6-nitro quinoline. Reduction of the resulting product gives rise to 8-amino-6-methoxy quinoline. Condensation of this quinoline residue with 4-amino-1-diethylamino pentane forms **pamaquine**.

Craig (1944) first discovered the presence of an isomeric form of pamaquine known as **isopamaquine,** in the commercial sample of pamaquine. The evolution of isopamaquine may be logically explained on the basis of the fact that the oximation of the amino alcohol obtained from the reduction of 1-acetyl-3-diethylamino propane actually gives rise to 4-amino-1-diethylamino pentane as major product together with 3-amino-1-diethylamino pentane as minor product. The latter product then condenses with 8-amino-6-methoxy quinoline to yield **isopamaquine** as given below :



The antimalarial activity of **isopamaquine** and **pamaquine** are fairly identical.

Toptchiev and Braude, in 1947, put forward a modified synthesis for **pamaquine** which consists of the following steps, namely :

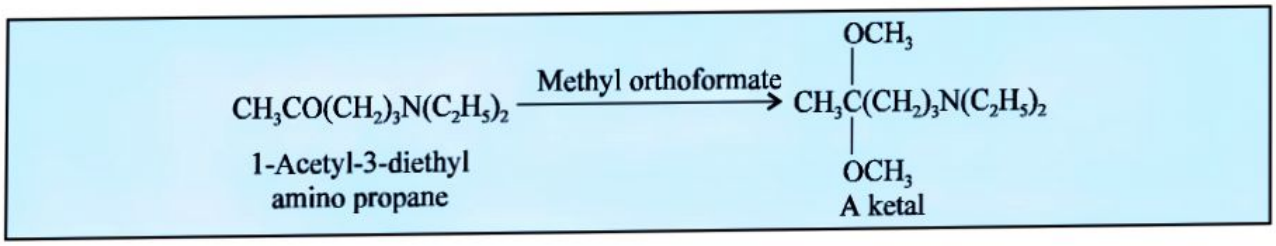
(*a*) Preparation of a ketal from 1-acetyl-3-diethyl amino propane

(*b*) Preparation of 8-amino-6-methoxy quinoline

(*c*) Condensation of (*a*) and (*b*)

(*d*) Reduction of the condensed product.

(*a*) Preparation of a Ketal

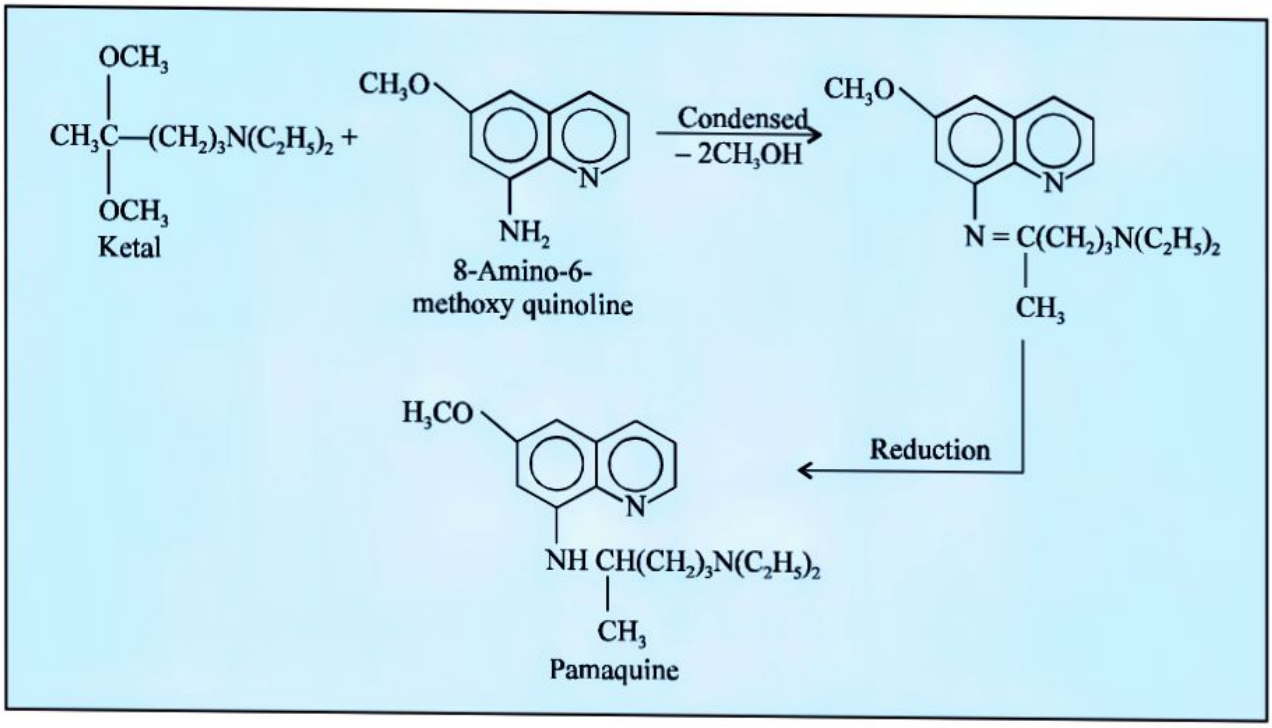


The starting compound is prepared by the method described earlier for the preparation of the side chain, which on treatment with methyl orthoformate yields a ketal.

(*b*) **Preparation of quinoline residue**

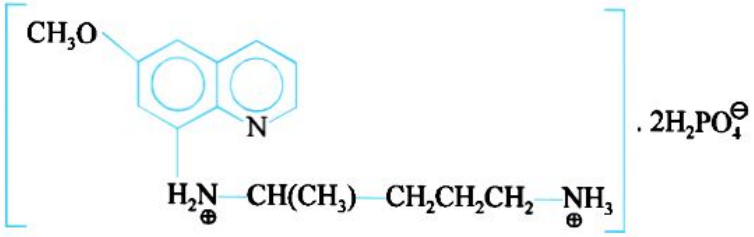
It is same as described under pamaquine.

(*c*) **Condensation of (*a*) and (*b*) ; and (*d*) Reduction.**



Pamaquine was initially employed for the treatment of malaria but has since been superseded by primaquine phosphate.

B. Primaquine Phosphate, BAN, USAN, Primaquine INN,

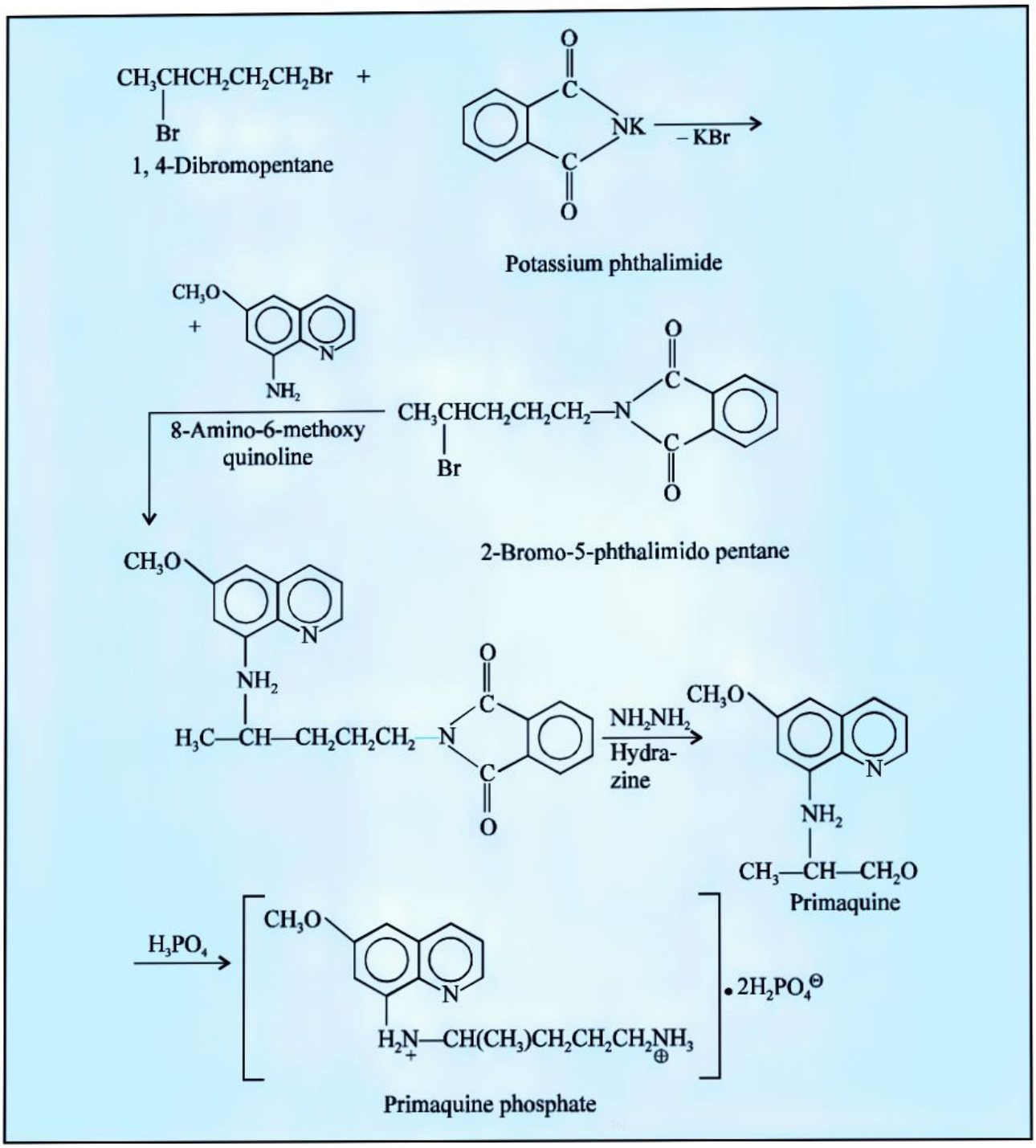


8-[(4-Amino-1-methylbutyl) amino]-6-methoxy quinoline phosphate (1:2) ; 1, 4-Pentanediamine, N^4-(6-methoxy-8-quinolyl)-, phosphate (1:2) ; Primachin phosphate ; BP ; USP ; Int. P. ; Primaquine Phosphate(R) (ICI Pharmaceuticals, U.K.)

Synthesis

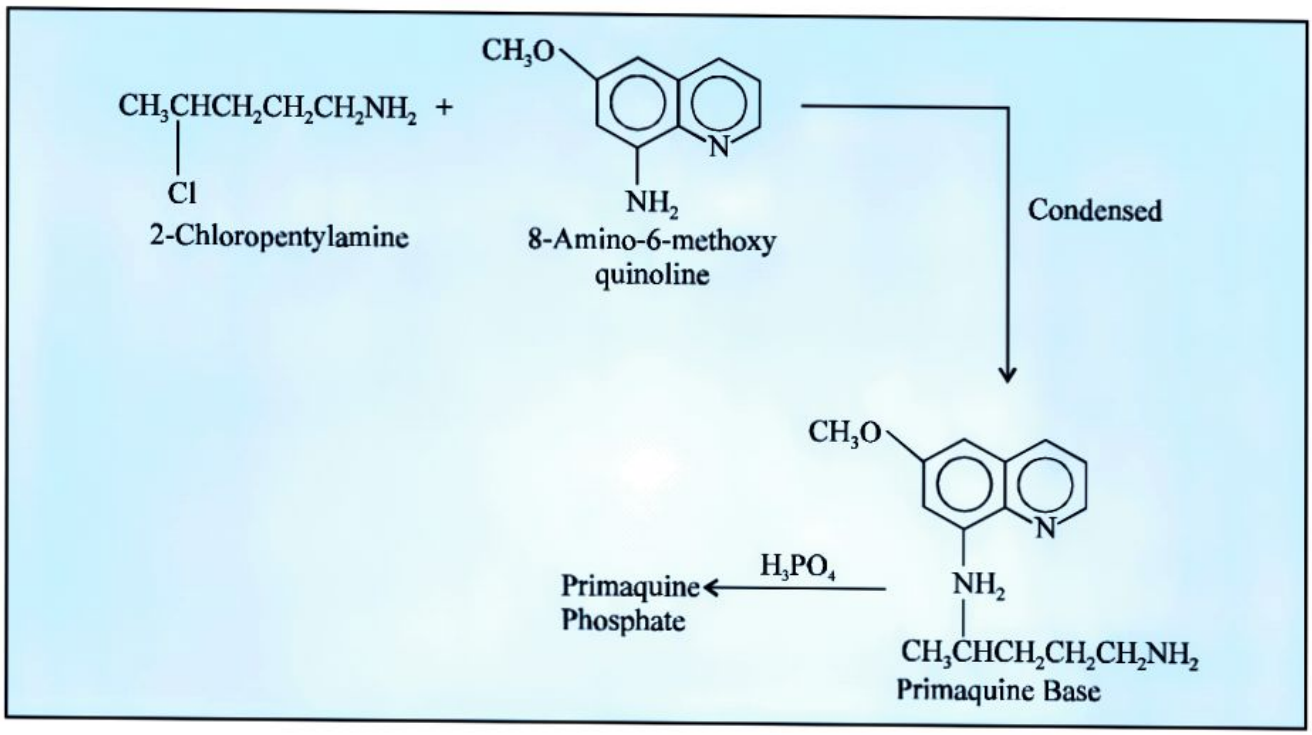
The synthesis of **primaquine phosphate** may be accomplished by either of the *two* following methods :

Method-I ; Elderfield's Method from 1, 4-Dibromopentane



2-Bromo-5-phthalimido pentane is prepared by the interaction of 1, 4-dibromopentane with potassium phthalimide, which on reaction with 8-amino-6-methoxy quinoline yields the condensed product. Further treatment with hydrazine eliminates the phthalimido residue and yields the **primaquine base** which on reaction with a double molar quantity of phosphoric acid forms the official compound.

Method-II. From 2-Chloropentylamine

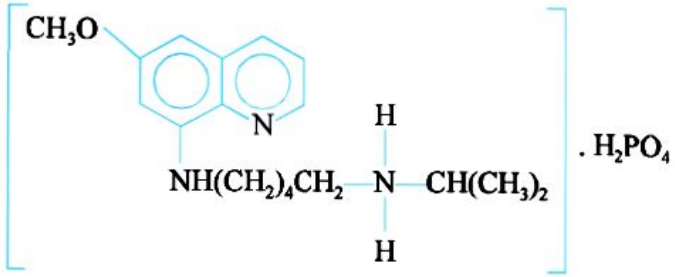


It may also be prepared by the condensation of 2-chloro-pentylamine with 8-amino-6-methoxy quinoline to obtain primaquine base which on treatment with bimolar quantity of phosphoric acid yields **primaquine phosphate**.

It is an **antimalarial drug** which *specifically kills the primary exoerythrocytic stages of P. vivax, P. falciparum, P. malariae and P. ovale, and the secondary exoerythrocytic form of all except P. falciparum,* which has no secondary forms. It is extensively used for the radical cure of relapsing vivax malaria, but is not normally employed either for arresting the severe attacks of the disease or for suppressive therapy. It invariably kills gametocytes of all species, or inhibits their growth and development in the mosquito. *It fails to produce any significant effect on other erythrocytic stages and hence it must not be employed alone for the treatment of malaria.*

Dose : *17.5 to 26.3 mg (10 to 15 mg of base) once daily for 14 days.*

C. Pentaquine Phosphate BAN, USAN, Pentaquine INN,



8-(5-Isopropylaminoamylamino)-6-methoxy quinoline phosphate ; 8-(5-Isopropylaminopentyl-amino)-6-methoxyquinoline phosphate. USP ; XIV.

Synthesis :

It consists of the preparation of :

(*a*) 8-Amino-6-methoxy quinoline

(*b*) 1-Chloro-5-isopropylamino pentane

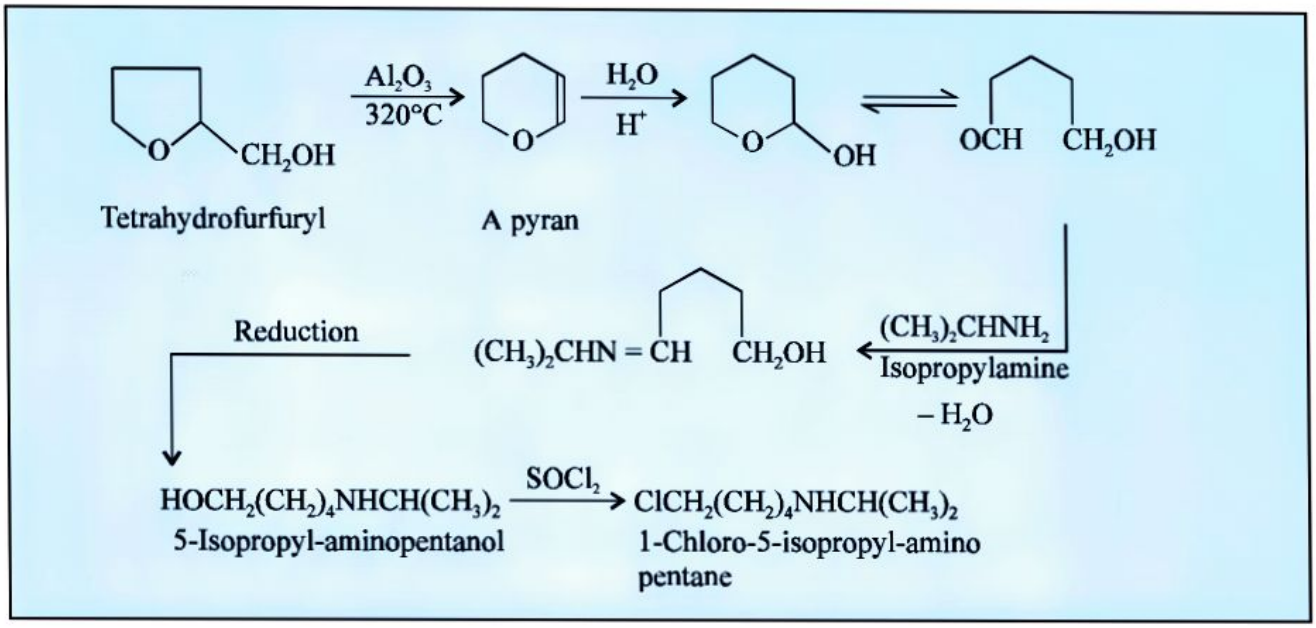
(*c*) Condensation of (*a*) and (*b*) and

(*d*) Phosphate salt.

(*a*) Preparation of 8-amino-6-methoxy quinoline

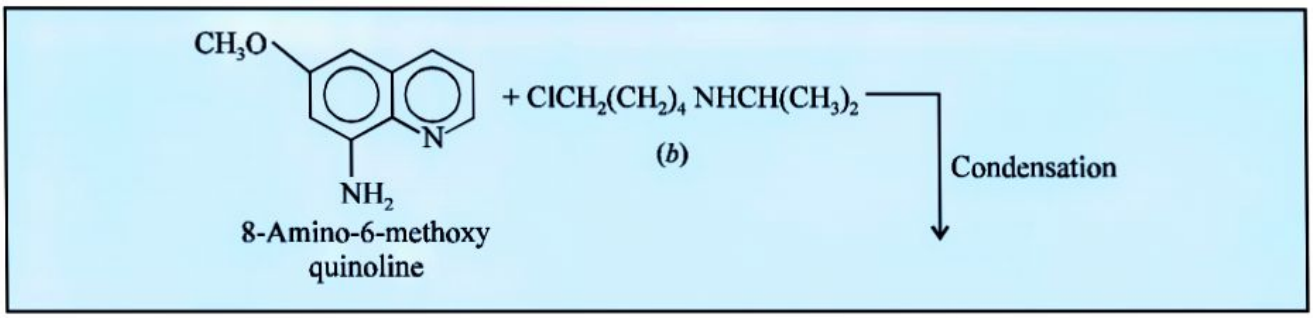
It is prepared as described under pamaquine.

(*b*) Preparation of 1-chloro-5-isopropylamino pentane



Tetrahydrofurfuryl alcohol on heating with aluminium oxide at 320° forms a partially saturated pyran which upon hydrolysis in an acidic medium yields a hydroxy analogue of pyran. This undergoes cleavage and the cleaved product on treatment with isopropyl amine forms an intermediate which on reduction gives rise to 5-isopropyl amino pentanol. Chlorination with thionyl chloride yields-1-chloro-5-isopropyl amino pentane.

(*c*) Condensation of (*a*) and (*b*), (*d*) Treatment with H_3PO_4



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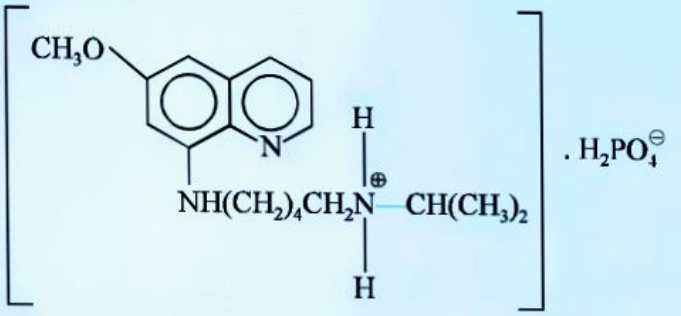


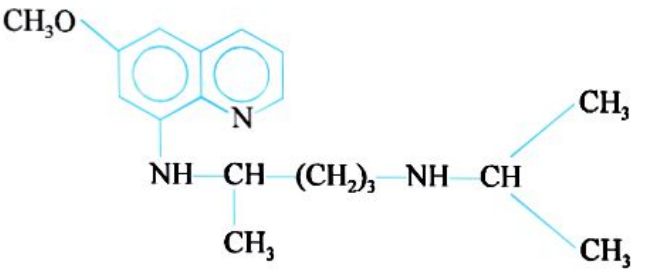
Pentaquine Phosphate

Condensation of the quinoline residue (*a*) and the side chain (*b*) yields the pentaquine base which on treatment with one mole of phosphoric acid forms the official compound.

Its actions and uses are similar to those of primaquine.

Dose : *100 mg per day.*

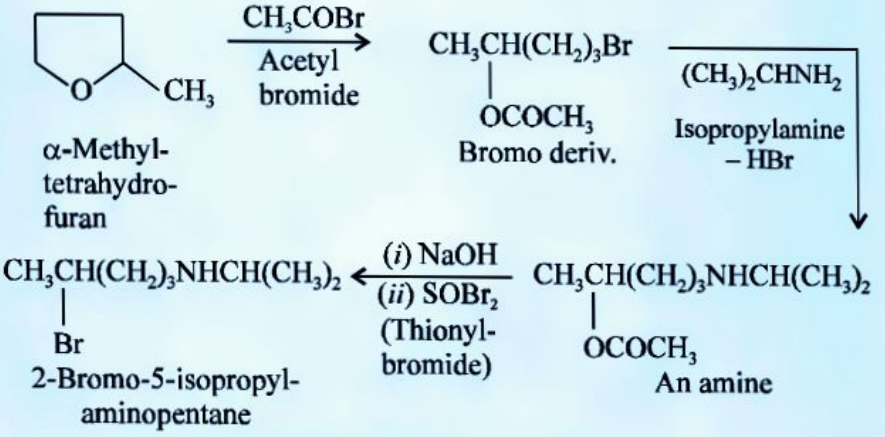
D. Isopentaquine



8-[[4-(Isopropylamino)-4-methylbutyl] amino]-6-methoxy-quinoline.

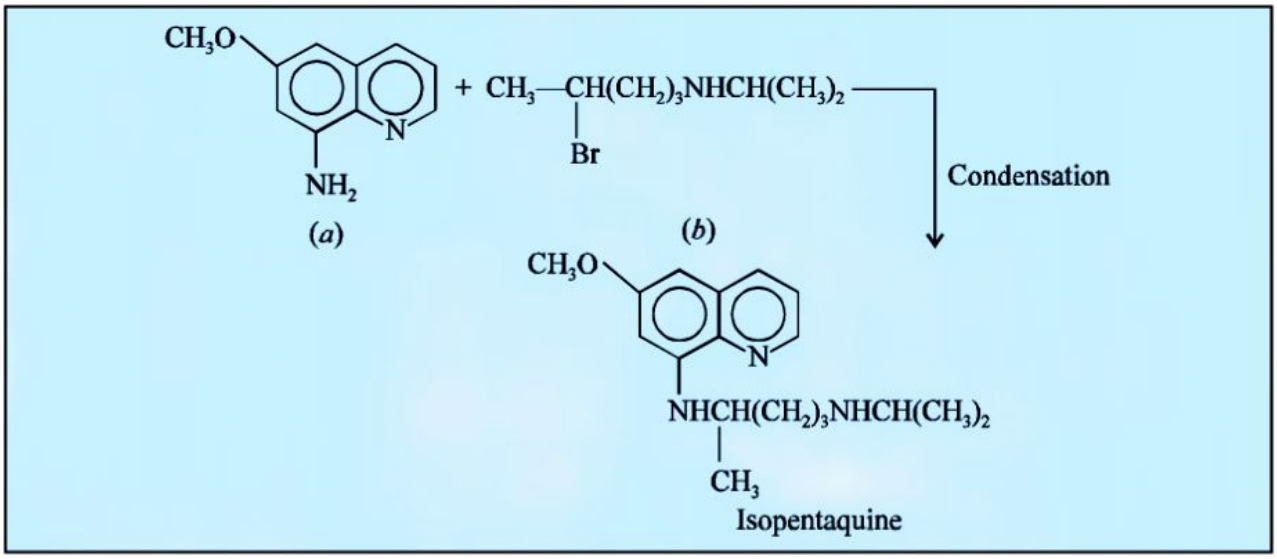
Synthesis

It consists of the preparation of the side chain 2-bromo-5-isopropylaminopentane as given below :



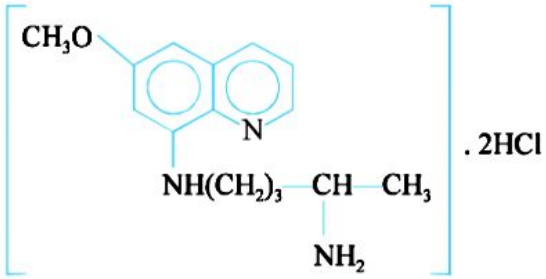
Interaction between α-methyl-tetrahydrofuran and acetyl bromide yields bromo derivative which on treatment with isopropyl amine forms a corresponding amine derivative. This on treatment with aqueous NaOH and thionyl bromide gives the side chain.

Treatment of the 8-amino-6-methoxy quinoline residue (*a*) with the side chain (*b*) yields the isopentaquine as shown below :



Isopentaquine is an isomer of **pentaquine,** and reported to be more active than the later as an antimalarial agent. It is also less toxic than pentaquine.

E. Quinocide Hydrochloride BAN, Quinocide INN, USAN,



8-(4-Aminopentylamino)-6-methoxyquinoline dihydrochloride.

It is a structural isomer of **primaquine,** has actions and uses resembling to those of **primaquine phosphate.**

Dose : *30 mg per day.*

2.2.1. Mechanism of Action

The mechanism of action of the various compounds discussed under Section 20.2.2. are dealt with separately in the pages that follows :

2.2.1.1. Pamaquine

The **'drug'** exerts its action against the exoerythrocytic stages of *P. ovale* and primary exoerythrocytic stages of *P. falciparum.* It has also been observed that it particularly inhibits the **gametocyte stage,** that essentially helps to eliminate the form required to infect the *'mosquito carrier'.* It also appears to disrupt and destabilize the parasite's mitochondria *via* several processes that include maturation into the subsequent resulting forms. The glaring advantage being the destruction of the exoerythrocytic forms before the parasite may actually infect the erythrocytes *i.e.,* the specific stage in the *'infectious process'* which ultimately renders malaria so weakening.

SAR of Pamaquine. It is indeed structurally related to the cinchona alkaloids essentially having a 6-methoxy group like quinine, but the various substituents on the '**quinoline nucleus**' are strategically positioned at C-8 rather than C-4 as found on the cinchona alkaloids. It has a *four-carbon alkyl linkage* or *bridge between the two N-atoms.* It has only one **chiral centre.** Though it has been critically observed that there exists certain differences in the metabolism of each stereoisomer and type of adverse response, there is hardly any difference in the antimalarial action based on the **pamaquin's stereochemistry.**

2.2.1.2. Primaquine

Its mechanism of action is very much similar to that of '**pamaquin**'. However, its spectrum of activity is regarded to be one of the narrowest of all the currently employed antimalarials ; and is recommended exclusively for exoerythrocytic *P. vivax* malaria.

SAR of Primaquine. Structural modifications of **pamaquine** produced the *unsubstituted primary aminoalkyl derivative i.e.,* **primaquine,** whose relatively more predominant therepeutic activity and significantly much lower toxicity (specifically the tendency for causing hemolysis) essentially replaced pamaquine virtually as the most well recognized **tissue schizonticide** of choice.

2.2.1.3. Pentaquine

The degree of toxicity in the **8-amino quinoline structural analogues** appears to be directly associated with the degree of substitution at the terminal amino function.* Using the said criterion **pamaquine**, having a *tertiary amino moiety,* happens to be **more toxic** than **primaquine,** having a *primary terminal nitrogen ;* whereas, **pentaquine** and **isopentaquine,** having *secondary terminal amino moieties,* are found to be **intermediate in toxicity.**

SAR of Pentaquine. It may be observed that with the exception of **pentaquine**, the other *three* **8-aminoquinolines** *viz.*, **pamaquin, primaquine** and **isopentaquine** have only one **chiral centre** (*i.e.,* asymmetric carbon). In fact, certain differences do take place in the actual metabolism of individual stereoisomer, but there exists practically little difference in the antimalarial profile based on the compound's stereochemistry.

2.2.1.4. Isopentaquine

The '**drug**' possesses an intermediate degree in toxicity because it has an essential secondary terminal amino moiety. Besides, the two N-atoms are duly separated by a chain of four C-atoms.

2.2.1.5. Quinocide (Chinocide)

The *'drug'* is an isomer of **primaquine,** has been studied extensively by Russian researchers.** It has been used widely in the Eastern Europe, but despite claims to the contrary its chemotherapeutic index is appreciably lower in comparison to **primaquine**.***

2.3. 9-Aminoacridines

The earlier hypothesis put forward by Ehrlich that methylene blue exerts antimalarial activity paved the way for the discovery of a number of acridine analogues. The 9-aminoacridine analogues, however, are found to be extremely toxic in nature and, therefore, they have been successfully replaced by the **4-aminoquinoline analogues** to a great extent. A few typical examples of this category are discussed below :

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*Edgeombe JH *et al. J Natl Malaria Soc,* **9**, 285 (1950).

Lysenko AJ *et al. Med Parasitol Parasit Dis* (USSR) **24, 132, 137, (1955).

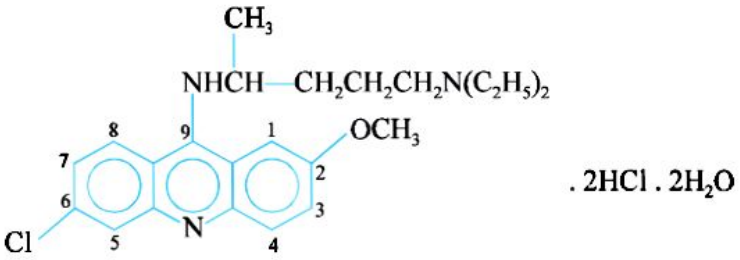
***Powell RD : *Clin Pharmacol Therap.* **7**, 48, (1966).

A. Mepacrine Hydrochloride BAN, Quinacrine Hydrochloride USAN, Mepacrine INN,

6-Chloro-9-[[4-(diethylamino)-1-methylbutyl] amino]-2-methoxy-acridine dihydrochloride dihydrate ; 1, 4-Pentane-diamine, N^4-(6-chloro-2-methoxy-9-acridinyl)-N^1, N^1-diethyl-, dihydrochloride, dihydrate ; Acrinamine ; Mepacrine Hydrochloride BP ; Eur. P ; Int. P ; Ind. P ;

Quinacrine Hydrochloride USP ;

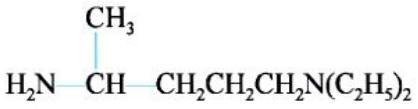
Atabrine Hydrochloride(R) (Winthrop).



Synthesis :

It essentially consists of the following steps :

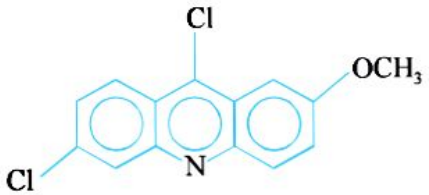
(*i*) **Preparation of the side chain :**



4-Diethylamine-1-methylbutylamine ;

4-Diethylamine-1-methylbutylamine ;

(*ii*) **Preparation of the acridine nucleus :**



2, 5-Dichloro-7-methoxy-acridine ;

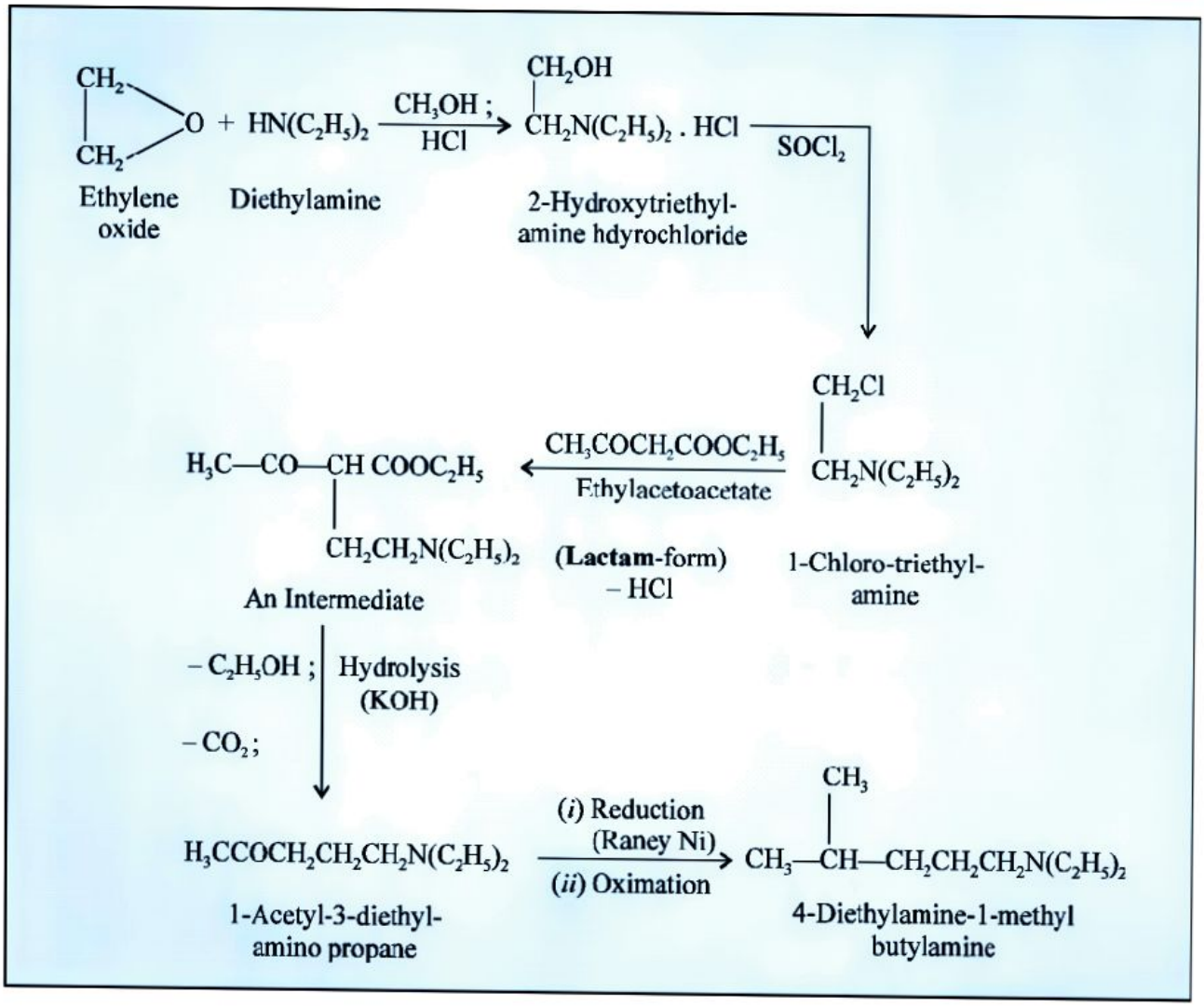
2, 5-Dichloro-7-methoxy-acridine ;

(*iii*) **Condensation of (*i*) and (*ii*)**

(*iv*) Preparation of the hydrochloride salt.

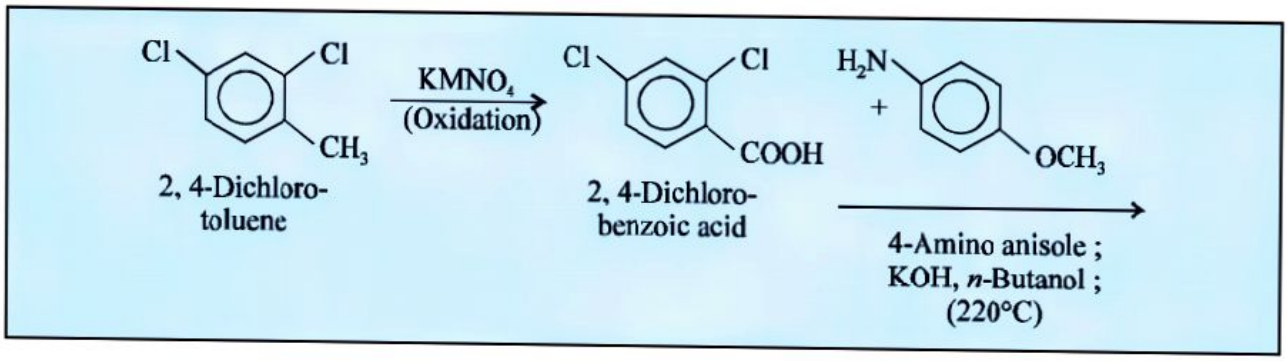
(*a*) **Preparation of the side chain**

2-Hydroxy triethylamine hydrochloride is obtained by the interaction of ethylene oxide and diethylamine in the presence of methanol and hydrochloric acid which on chlorination with thionylchloride yields 1-chloro-triethylamine.



The resulting compound on treatment with the *lactam*-form of ethylacetoacetate forms an intermediate which when subjected to reduction and oximation gives 4-diethylamine-1-mthyl butylamine.

(*b*) **Preparation of the acridine nucleus**



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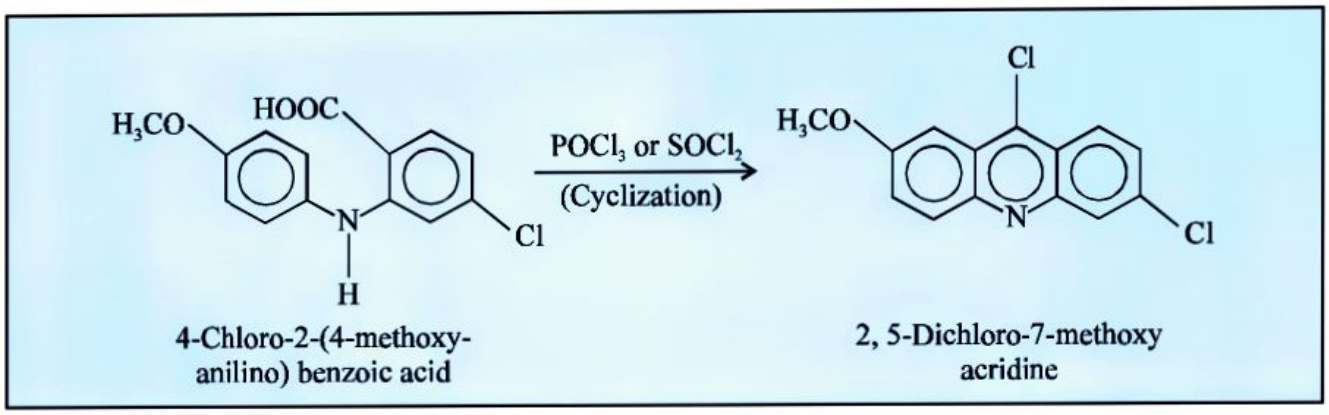
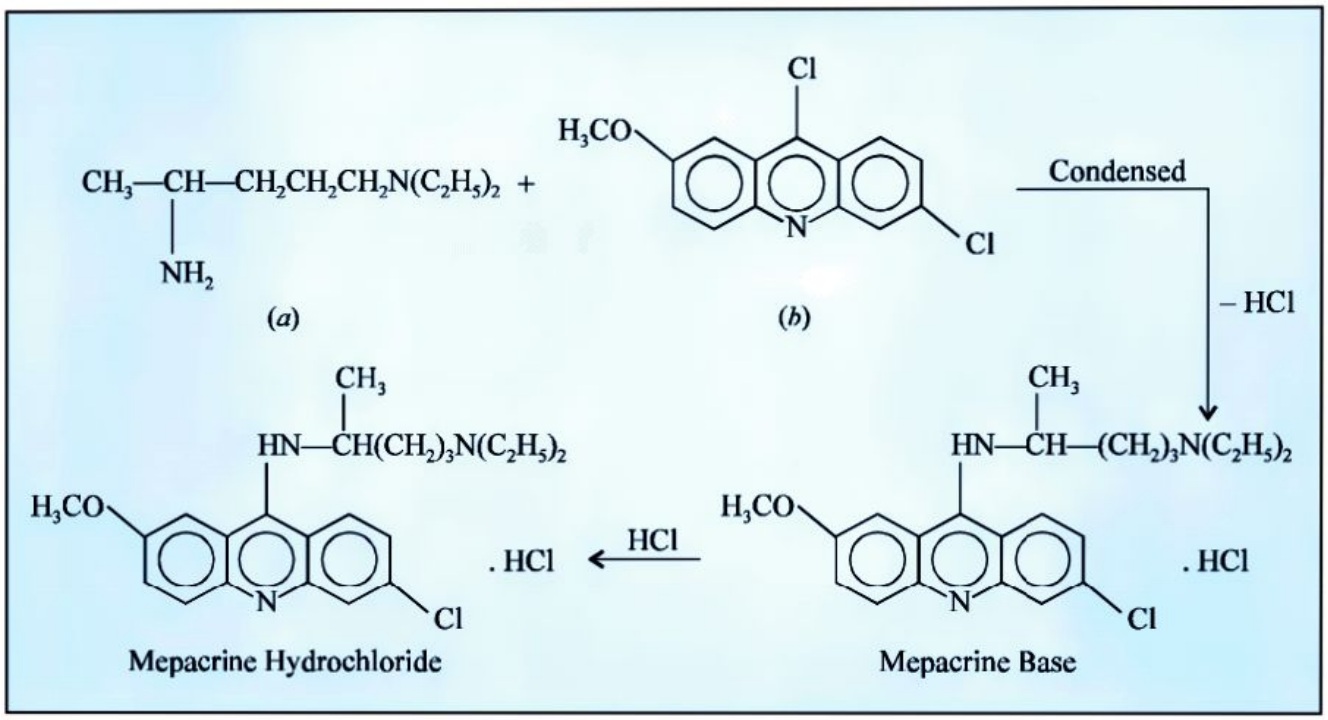


4-Chloro-2-(4-methoxy-anilino) benzoic acid

2, 5-Dichloro-7-methoxy acridine

(*c*) **Condensation of (*a*) and (*b*) above ; and (*d*) Treatment with Hydrochloric Acid**



Mepacrine Hydrochloride

Mepacrine Base

2, 5-Dichloro-7-methoxy acridine may be prepared by the oxidation of 2, 4-dichloro toluene and treating the resulting acid with 4-amino anisole at 220°C in the presence of KOH and *n*-butanol ; the additional compound when reacted with either $POCl_3$ or $SOCl_2$ undergoes cyclization. One mole each of the side chain and the acridine residue get condensed to yield the **mepacrine base** which on treatment with hydrochloric acid gives the official compound.

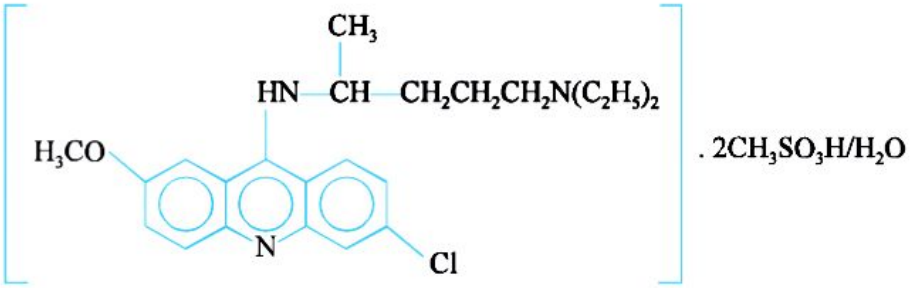
Mepacrine hydrochloride inhibits the erythrocytic state of development of the malarial parasite. It is considered neither as a causal prophylactic nor as a radical curative agent. It is found to be more toxic and less effective than chloroquine. *Besides, it has also been used in giardiasis, amebiasis, tapeworm and pinworm infestations.*

Dose : *As therapeutic, 200 mg with 300 mg of sodium bicarbonate each 6 hours up to 5 doses, followed by 100 mg 3 times per day for 6 days ; as suppressive, 100 mg once daily.*

B. Mepacrine Mesylate BAN,

Mepacrine Methanesulphonate ; Quinacrine methanesulphonate ; BPC ; (1963) ;

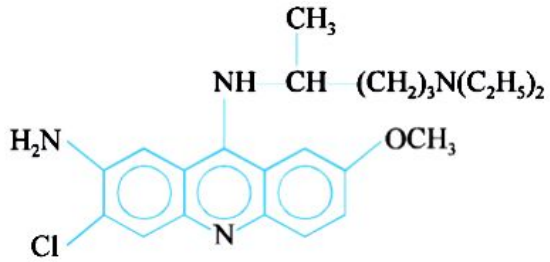
Quinacrine Soluble(R) (May and Baker).



It is much more soluble than mepacrine hydrochloride. It has been used more conveniently for parenteral administration in acute cases of *falciparum* malaria.

Dose : *360 mg intramuscularly in 2 to 4 ml 'Water for Injection'.*

C. Aminoacrichin



7-Amino-6-chloro-9-[[4-(diethylamine)-1-methylbutyl] amino] 2-methoxy-acridine ;

Its use as an **antimalarial drug** has been discontinued and replaced by more effective and less toxic agents.

2.3.1. Mechanism of Action

The mechanism of action of the antimalarial agents described under Section 20.2.3. shall now be treated individually as under :

2.3.1.1. Quinacrine Hydrochloride

The *'drug'* almost exhibits the same effects as those caused by the **4-aminoquinolines**. The GI irritancy is registered to be much higher than the **4-aminoquinolines** ; and, therefore, it is a common practice to administer sodium bicarbonate concomitantly.

It is absorbed quite rapidly from the GI-tract and also from IM and intracavitary sites of injection. The *'drug'* gets excreted very gradually in the urine and gets accumulated in tissues on chronic administration.

Interestingly, the **'drug'** is believed to act at several sites within the cell, including **intercalation of DNA strands, succinic dehydrogenase, mitochondrial electron transport system,** and **cholinesterase.** It may serve as *tumorigenic* and *mutagenic,* and hence, has been employed profusely as a **sclerosing agent**.*

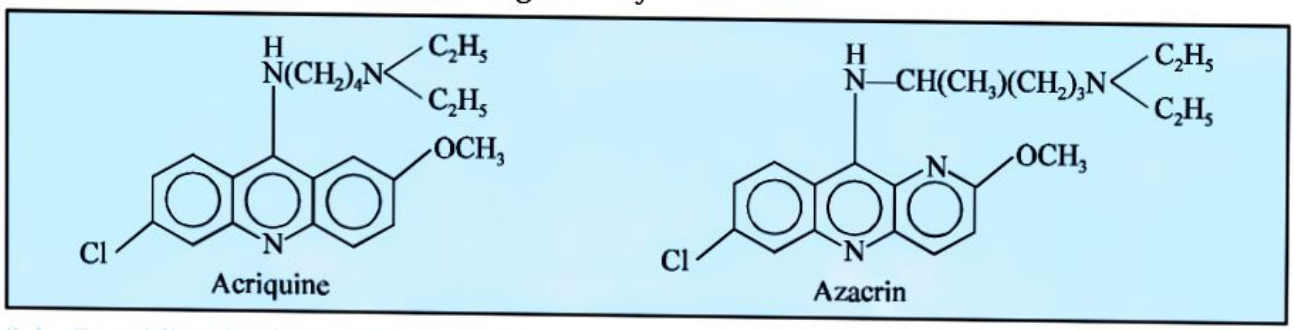
*An agent that causes or developes *sclerosis* (*i.e.,* hardening or induration of an organ or tissue, especially that due to excessive growth of fibrous tissue.

2.3.1.2. Mepacrine Mesylate

The '**drug**' is a methanesulphonate salt of **mepacrine** (or **quinacrine**) whose therapeutic potency is relatively higher than its corresponding HCl-salt.

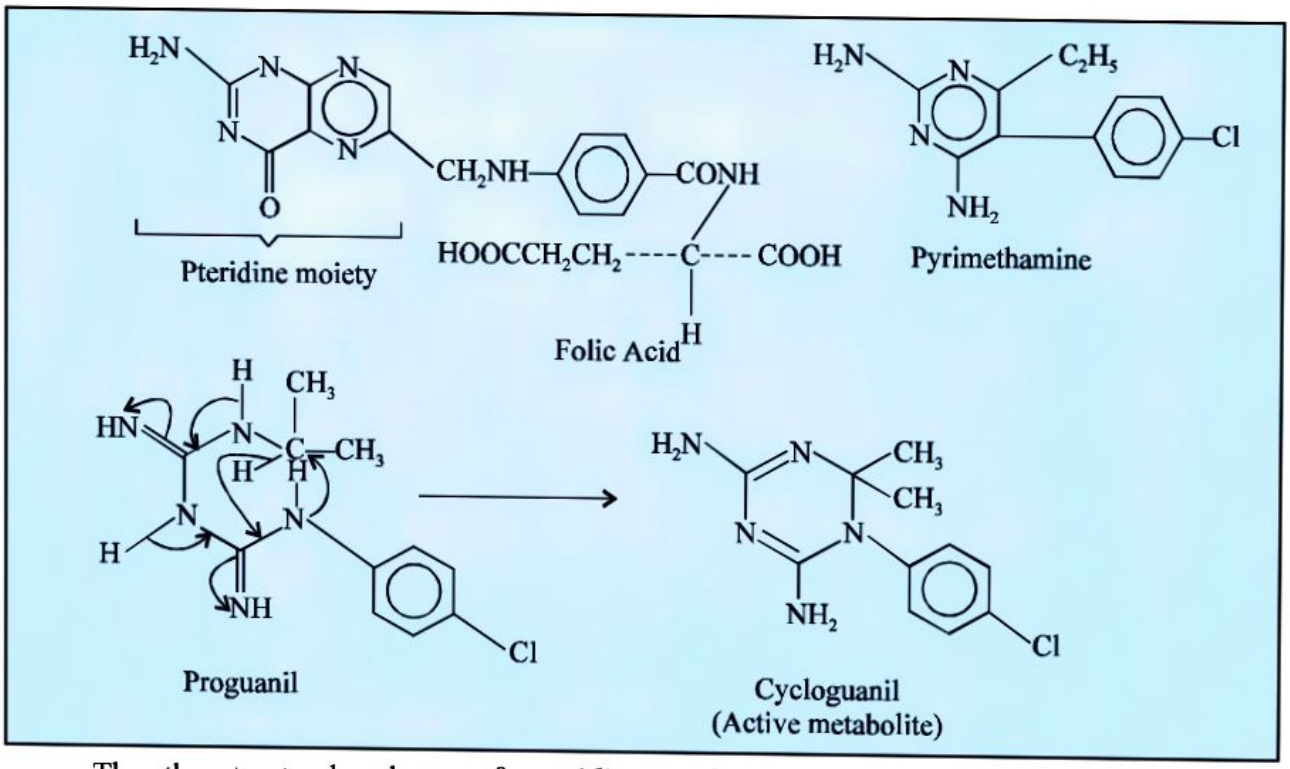
2.3.1.3. Aminoacrichin

The '**drug**' along with its two other acridine structural analogues, namely : **acriquine** and **azacrin** were introduced based on a combined structural features of **8-aminoquinoline** and **4-aminoquinoline**, but were not so successful due to their high toxicity.



2.4. Guanidine Analogues (Biguanides)

The **guanidine analogues**, in general, are not found to be active unless and until they get cyclized metabolically to a **dihydro-s-triazine analogue** having a close resemblance either to the **pteridine moiety** of folic acid or **pyrimethamine** as shown below :



The other structural analogues of **guanidine** are also metabolised in a similar fashion.

A few members of this class of compounds are described below, *viz.*, **Proguanil hydrochloride ; Cycloguanil embonate ; Chlorproguanil ; Bromoguanil.**

A. Proguanil Hydrochloride BAN, Proguanil INN, Chlorguanide Hydrochloride USAN,

1-(*p*-Chlorophenyl)-5-isopropylbiguanide hydrochloride ; Imidodicarbonimidic diamide, N-(4-chlorophenyl)-N′-(1-methyl-phenyl)-, monohydrochloride ; Proguanide Hydrochloride ; Proguanil Hydrochloride BP ; Int. P ; Ind. P ; Chlorguanide Hydrochloride USPXIV ;

Paludrine(R) (ICI Pharmaceuticals, U.K.).

Synthesis

It consists of the preparation of :

(*a*) *p*-Chlorophenyl guanidine

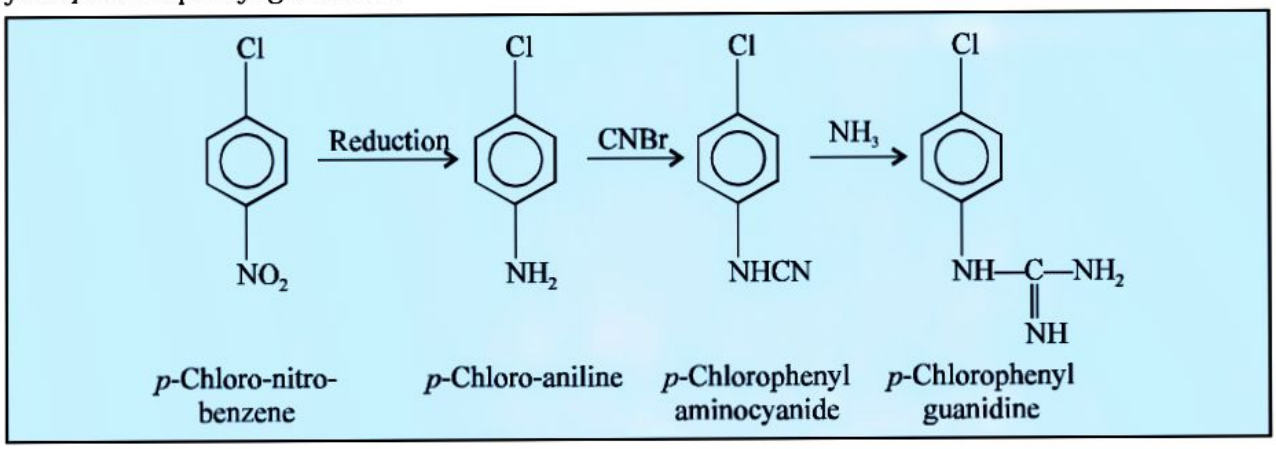
(*b*) Iso-propyl cyanamide

(*c*) Condensation (*a*) and (*b*)

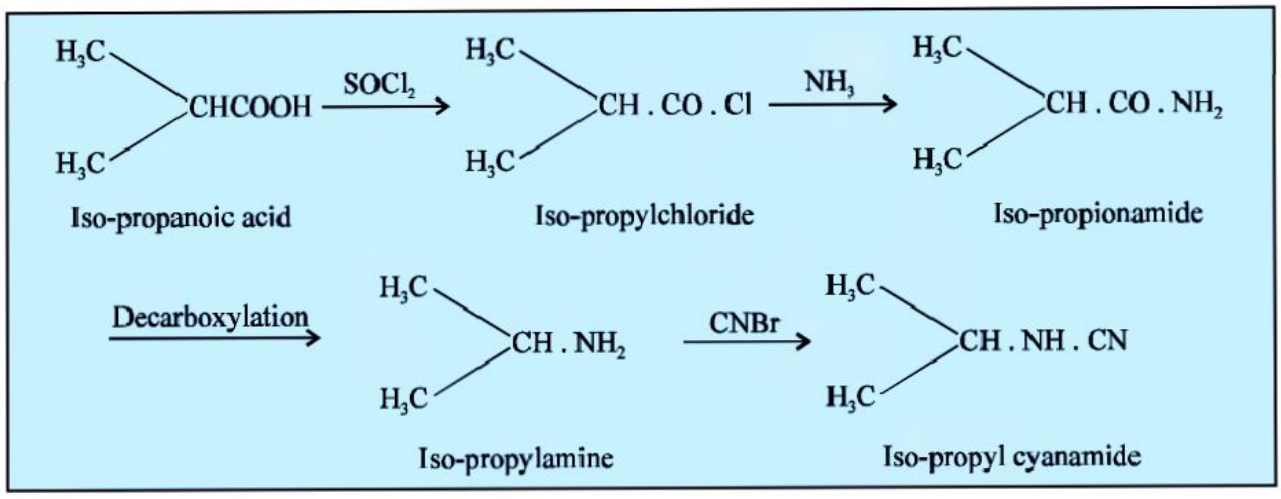
(*d*) Hydrochloride salt.

(*a*) **Preparation of p-Chlorophenyl guanidine**

p-Chloro-nitrobenzene is subjected to reduction, treatment with cyanobromide and amination to yield *p*-chlorophenyl guanidine.



(*b*) **Preparation of iso-propyl cyanamide**



Iso-propyl cyanamide may be prepared by the chlorination of iso-propionic acid followed by amination, decarboxylation and finally treating with cyanogen bromide.

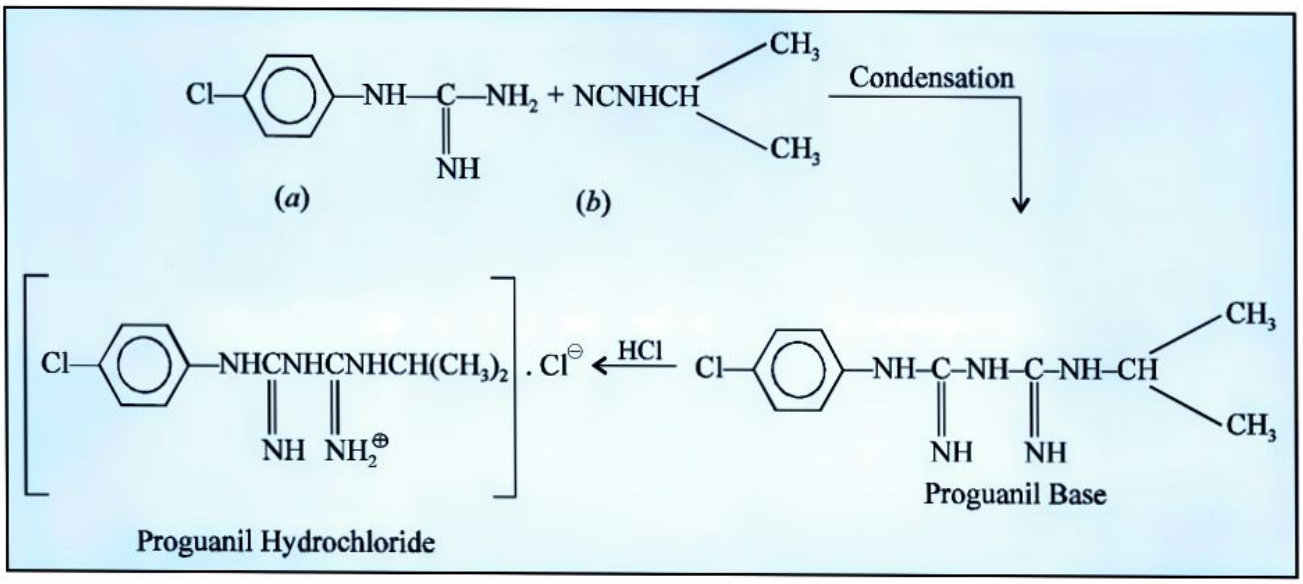
(*c*) Condensation of (*a*) and (*b*) ; (*d*) Formation of Hydrochloride Salt

Condensation of *p*-chlorophenyl guanidine with iso-propyl cyanamide gives the **proguanil base** which on treatment with one mole of hydrochloric acid yields **proguanil hydrochloride**.

It is an antimalarial drug whose metabolite is a potent dihydrofolate reductase inhibitors. It is active against the pre-erythrocytic (liver) forms of malaria. It is also active against the erythrocytic forms but their activity is slow.

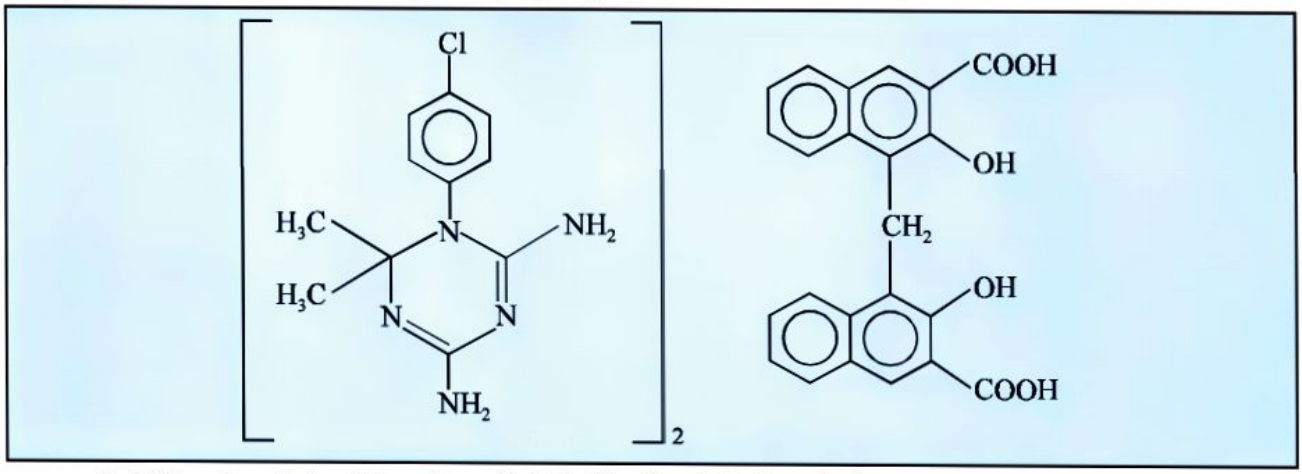
Hence, proguanil is used mainly for prophylactic treatment of malaria.

Dose : As prophylactic and suppressant, 100 to 200mg per day in non-imune subjects ; 300mg per week or 200mg 2 times per week in semi-imune subjects ; in acute vivax malaria, initial loading dose



300 to 600mg followed by 300mg per day for 5 to 10 days ; in falciparum malaria, 300mg 2 times daily for 5 days.

B. Cycloguanil Embonate INN, BAN, Cycloguanil Pamoate USAN,



4, 6-Diamino-1-(*p*-chlorophenyl)-1, 2-dihydro-2, 2-dimethyl-s-triazine compound (2:1) with 4, 4′ methylene-bis [3-hydroxy-2-naphthoic acid] ;

Camolar(R) (Parke-Davis).

Cycloguanil is the active metabolite of **proguanil** as shown earlier. Its actions and uses are similar to paludrine. It has been recognized as a dihydrofolate reductase inhibitor and employed for the suppression of malaria, but failed to achieve a wide acceptance. It exerts little therapeutic value in such cases where resistance to either **proguanil** or **pyrimethamine** is prevalent. *To attain prolonged immunization in areas infested with hyperendemic malaria, administration of cycloguanil and amodiaquine every 4 months is recommended.*

Dose : *Usual, adult, intramuscular, 350mg of cycloguanil base every 4 months.*

2.4.1. Mechanism of Action

The mechanism of action of two drug substances discussed under section 20.2.4. shall be dealt with separately as under :

2.4.1.1. Chlorguanide Hydrochloride (Proguanil HCl)

British scientists during World War II had adopted an altogether different line of action in breaking away from the normal quinoline and acridine types of structure, and eventually paved the way in the epoch making discovery of the biguanide, **chlorguanide.**

The **'drug'** gets metabolised into a product which has proved to be a potent **dihydrofolate reductase inhibitor.**

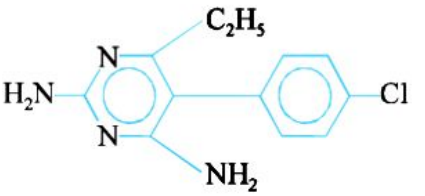
2.4.1.2. Cycloguanil Pamoate

The **'drug'** is proved to afford a high percentage of cures in *L. brasiliensis** and *L. mexicana*** pathogenic infections even with a single IM dosage.

2.5 Pyrimidine Analogues (Diaminopyrimidines)

The **pyrimidine analogues** have a close similarity to the pteridine moiety of dihydrofolic acid, and are directly responsible for its subsequent reduction to tetrahydrofolic acid by means of the enzyme dihydrofolate reductase. The site of action of **pyrimidine analogues** are exoerythrocytic and erythrocytic forms of *P. falciparum,* together with the exoerythrocytic forms of *P. vivax.* A few examples of this category of antimalarials are described below :

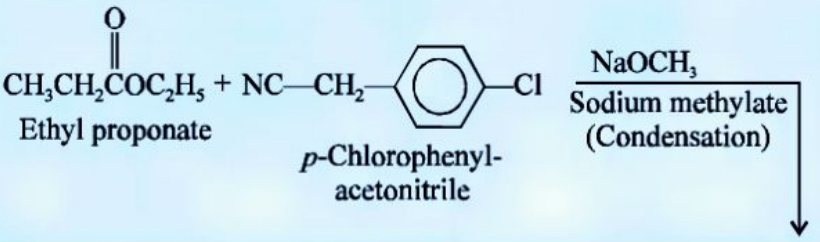
A. Pyrimethamine INN, BAN, USAN,



2, 4-Diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine ; 2, 4-Pyrimidinediamine, 5-(4-chlorophenyl)-6-ethyl-; BP ; USP ; Int. P. ;

Daraprim(R) (Burroughs Wellcome).

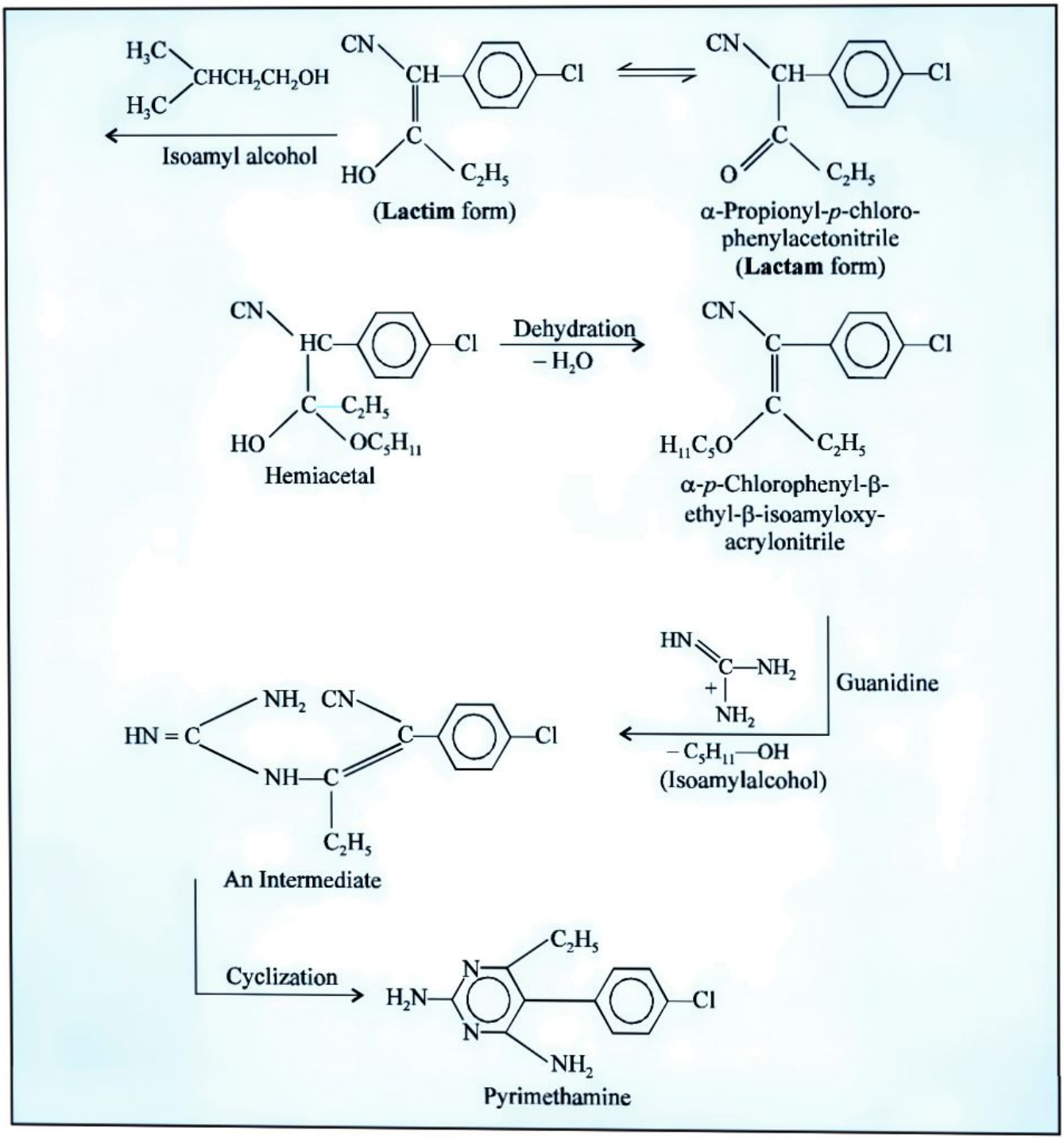
Synthesis



(*Contd...*)

*Pena-Chavarria *et al. J Am Med Assoc,* **194**, 1142 (1965).

Beltran F *et al. Prensa Med Mex,* **31, 365 (1966).



α-Propionyl-*p*-chlorophenylacetonitrile (*lactum*-form) is prepared by the condensation of ethyl propionate and *p*-chlorophenylacetonitrile which undergoes **tautomerism** to form the corresponding *lactim*-form. This on reaction with isoamyl alcohol forms the hemiacetal which upon dehydration yields α-(*p*-chlorophenyl)-β-ethyl-β-isoamyloxyacrylo-nitrile. The resulting product on treatment with guanidine affords cyclization *via* two different steps : *first*, elimination of a mole of isoamyl alcohol by condensation involving the imino hydrogen of guanidine, and *secondly*, an addition reaction between an amino group of guanidine and the nitrile group of the intermediate compound.

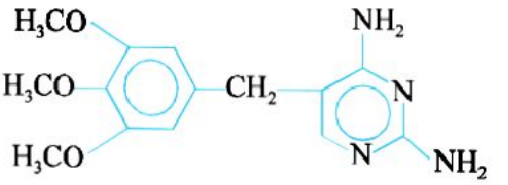
Like the **biguanides** it is a potent **inhibitor of dihydrofolate reductase** of the plasmodium (mammalian enzyme is about 200 times less sensitive). Thus it blocks the synthesis of tetrahydrofolic from dihydrofolic acid and this is essential for the synthesis of purines and pyrimidines and hence DNA.

It finds its extensive use as a suppressive prophylactic for the preventation of severe attacks due to P. falciparum and P. vivax. It is also used in the treatment of toxoplasmosis and as an immunosuppressive agent.

Pyrimethamine in conjunction with **sulfadoxine** (25mg : 500mg), under the brand name **Fansidar(R) (Roche),** has been used successfully as an **antimalarial drug** for those subjects who display sensitization towards **chloroquine** therapy in malaria.

Dose : *As suppressive, 25 mg once a week ; as therapeutic, 50 to 75 mg once a day for 2 days when used alone, otherwise 25 mg.*

B. Trimethoprim INN, BAN, USAN,

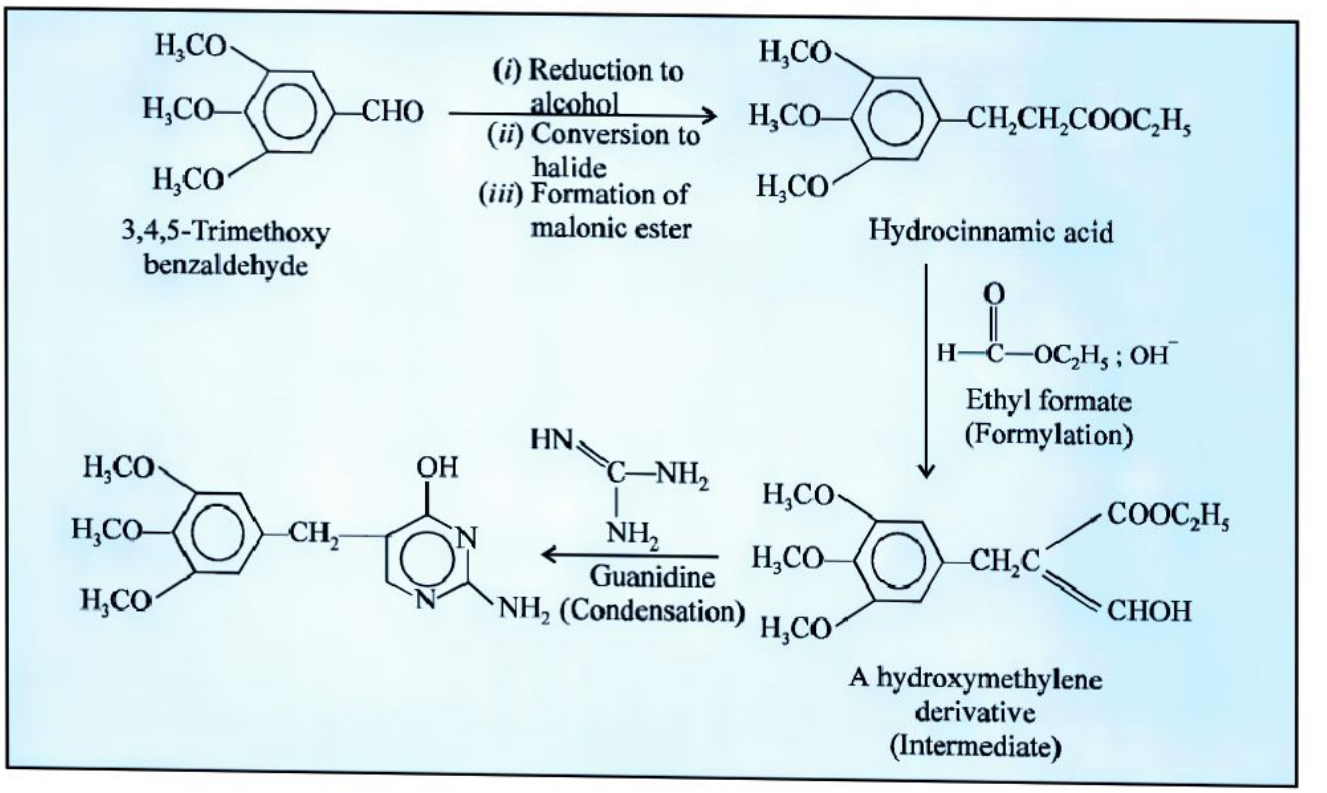


2, 4-Diamino-5-(3,4,5-Trimethoxybenzyl) pyrimidine ; 2,4-Pyrimidinediamine, 5-[(3,4,5-trimethoxyphenyl) methyl]-; Trimethoxyprim ; BP ; USP ;
Proloprim(R) (Burroughs Wellcome) ; Trimpex(R) (Roche).

Synthesis

It may be prepared by *two* different methods described below :

Method-1. From 3, 4, 5-trimethoxy benzaldehyde via hydrocinnamic acid



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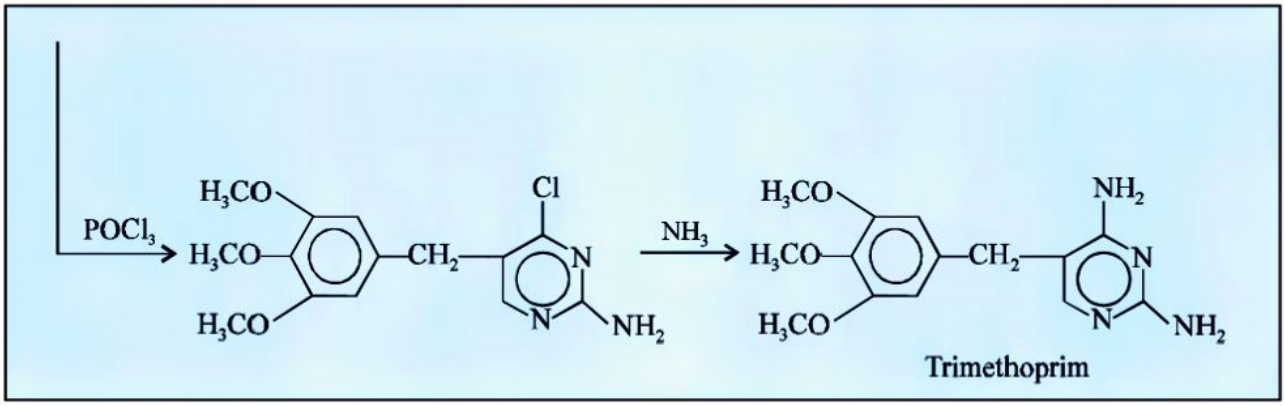
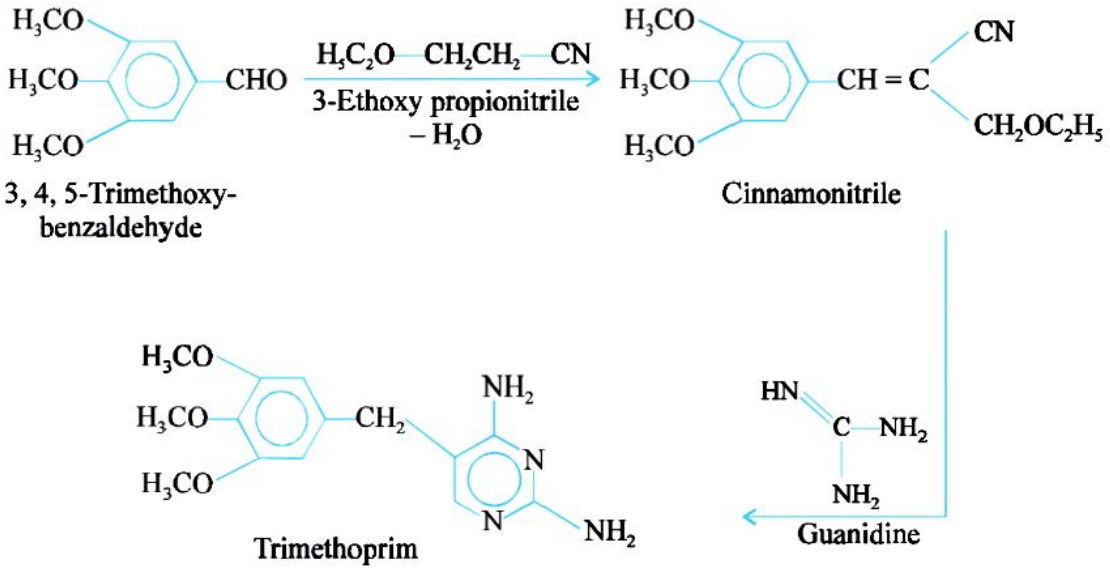


Hydrocinnamic acid is prepared by the bishomologation of 3, 4, 5-trimethoxy benzaldehyde, *i.e.*, subjecting the later to reduction forming an alcohol, coversion to halide and finally formation of the malonic ester. This is then subjected to formylation with ethyl formate and base to yield the corresponding hydroxymethylene derivative. Condensation of this intermediate with guanidine gives the pyrimidine residue, by a scheme very similar to the one discussed under pyrimethamine. The hydroxyl moiety present in the pyrimidine nucleus is converted to the chloro group by treatment with phosphorus oxychloride and finally amination leads to the formation of the official compound.

Method-II. From 3, 4, 5-trimethoxybenzaldehyde via cinnamonitrile



It is comparatively a shorter course of reaction whereby cinnamonitrile is prepared by the interaction of 3, 4, 5-trimethoxy-benzaldehyde with 3-ethoxy propionitrile with the elimination of a mole of water. The resulting product on treatment with guanidine affords the formation of **trimethoprim** directly.

Like **pyrimethamine, trimethoprim is a potent inhibitor of dihydrofolate reductase.** It has been employed in conjunction with **sulfametopyrazine** in the treatment of **chloroquine-resistant malaria** but unfortunately could not attain wide acceptance. *It has also been used in conjunction with* **sulphonamides** *in the treatment of bacterial infections viz.,* **trimethoprim with sulphamethoxazole.**

Dose : *1.5 g with 1 g of sulfametopyrazine per day for 3 days.*

2.5.1. Mechanism of Action

The mechanism of action of the compounds described under Section 20.2.5. are dealt with individually in the sections that follows :

2.5.1.1. Pyremethamine

The **'drug'** inhibits dehydrofolate reductase in plasmodia* ; and thereby the developing parasite cannot synthesize and use nucleic acid precursors needed for their normal growth. Furthermore, its prevailing action in checking the development of the erythrocytic phase of the parasite is slow and sluggish ; therefore, it is of rather little value in the suppression of acute attacks, except as an adjunct to quinine. Importantly, it is invariably employed as a *suppressive prophylactic* for the prevention of clinical attacks by *Plasmodium falciparum* in regions particularly where the **organism is resistant to chloroquine,** in which instance it is administered in conjunction with **sulfadoxine.**

Besides, it also helps in rendering the *'parasite'* incapable of sporulating in the mosquito whereby the **'life-cycle of the parasite'** is disrupted squarely.

It has been duly reported that success rate of the **'drug'** is almost 90% in certain regions, which may be increased to even 95% by the addition of **quinine.** However, in the control, management and treatment of *toxoplasmosis*** it is usually combined with **trisulfapyrimidines.**

2.5.1.2. Trimethoprim

The **'drug'** also shows its action by the inhibition of dihydrofolate reductase, though its potency is appreciably lower. However, it is found to be most important as an **'antibacterial agent'.** It is worthwhile to mention here that the **bacterial dihydrofolate reductases** are invariably more susceptible in comparison to the plasmodial ones. Hence, the **'drug'** is observed to be extremely effective against all bacteria which should exclusively synthesize their own **folinic acid (leucovorin)**. This specific characteristic profile renders the **'drug'** to acclaim a broad spectrum against a host of pathogenic (causative) microorganisms, such as :

Streptopyrogenes, viridans, and *pneumoniae* ; *Staphylococcus aureus* and *epidermidis ; H. influenzae ; Klebsiella-Enterobacter Serratia, E. coli,* different *Shigella* and *Salmonella, Bordetella pertussis ; Vibrio cholerae ; Pneumocystis carinii, Toxoplasma gondii ;* and *Plasmodia.*

It is, however, pertinent to mention here that the **mammalian dihydrofolate reductase** is approximately 1 : 10,000 to 1 : 50,000 as sensitive to it as the bacterial enzymes, so that there prevails almost **little interference with folate metabolism in humans.**

The volume of distribution is nearly 1.8 mL g^{-1}. The concentration in the cerebrosphinal fluid (CSF) attains a level ranging between 30-50% of the drug in plasma. It gets excreted mostly into the urine. The plasma half-life ranges between 9 to 12 hr. in normal adults having normal kidney-function ; however, it may be enhanced even upto 2 to 3 times in a situation whereby the **creatinine clearance** falls below 10 mL . min^{-1}.

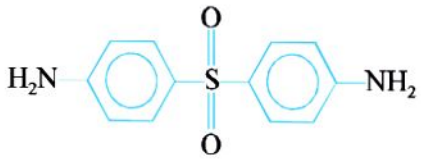
2.6. Sulfones

A large number of **diphenylsulfone analogues** have been developed for the treatment of leprosy. Incidentlly one such member chemically known as **4, 4'-diaminodiphenyl sulfone (dapsone)** exhibited prophylactic activity against resistant *P. falciparum.* Dapsone in conjunction with **pyrimethamine** has been effectively used in the treatment of malaria due to chloroquine resistant *P. falciparum.*

Med. Lett. **29,** 53, 1987.

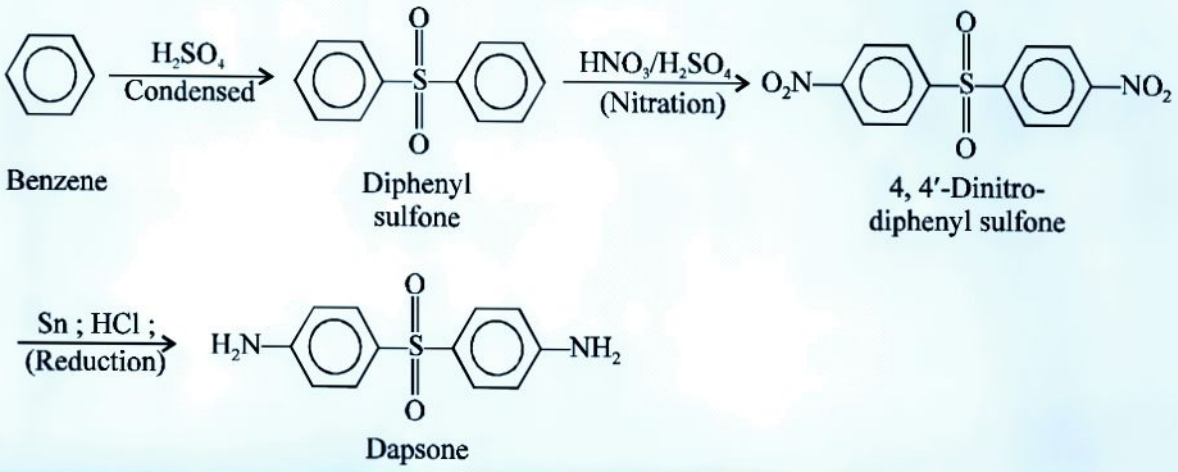
**A disease caused by infection with the protozoan *Toxoplasma gondii.*

A. Dapsone INN, BAN, USAN,



4, 4′-Sulfonyldianiline ; Benzeneamine, 4, 4′-sulfonylbis-; 4, 4′-Diaminodiphenyl sulfone ; Diaphenylsulfone ; Disulone ; BP ; USP ; Int. P ; Ind. P. ;
Avlosulfon(R) (Ayerst).

Synthesis



Diphenyl sulfone is prepared by the condensation of benzene with sulphuric acid. Nitration is afforded by treatment with a mixture of nitric acid and sulphuric acid to yield **4, 4′-dinitrodiphenyl sulfone** which on reduction with tin and hydrochloric acid gives the official compound.

Dapsone possesses limited therapeutic value in the treatment of malaria, except when combined with other agents for the treatment of chloroquine-resistant cases.

2.6.1. Mechanism of Action

The mechanism of action of **'dapsone'** shall be discussed as under :

2.6.1.1. Dapsone

Its mechanism of action is very much similar to that of **sulphanilamide.** It is employed profusely in the treatment of both *lepromatous* and *tuberculoid* types of leprosy. However, in combination with **rifampin,** it is regarded as the **'drug of choice'** in the chemotherapy of leprosy. Besides, the combination with **clofazimine** affords a similar therapeutic effect. The *'drug'* is the most preferred **'sulfone'** because of the two cardinal facts, such as : (*a*) cost-effective ; and (*b*) equally efficacious to other sulfones.

Interestingly, when combined with **trimethoprim,** it is found to exert almost identical activity as **trimethoprim-sulfamethoxazole** in the plausible treatment of *Pneumocystis carinii pneumonia.* Also used with **pyrimethamine** for treatment of malaria.

It is most absorbed by the oral administration. Absorption is more efficient at low than high dosage regimen. Finally, it gets eliminated in the liver by acetylation. Patients may respond to this *'drug'* as 'slow' and 'fast' acetylators. The plasma half-life ranges between 10 to 50 hours ; and at least 8 hours are needed to accomplish plateau concentrations.

2.7. Quinine Analogues

Quinine is an alkaloid obtained from the bark of *Cinchona officinalis* Linne (*C. ledgeriana* Moens) belonging to the family *Rubiaceae* or other species of *Cinchona.*

A. Quinine Sulphate BAN, Quinine Bisulfate USAN,

Quinine sulphate (2:1) salt dihydrate ; Quinine Sulphate BP ; Quinine sulfate USP ; Quinine Bisulate NFXI ;

Kinine$^{(R)}$ (ICN, Canada) ;

Preparation

The **quinine** is isolated from the bark of *Cinchona* sp., after recrystallization several times from mildly acidified (H_2SO_4) hot water. **Quinine sulphate** obtained after recrystallization retains up to seven moles of water, but undergoes efflorescence in dry environment to lose up to five moles of water.

However, the dihydrate salt is fairly stable and hence is the official compound.

Quinine only affects the erythrocytic form of the plasmodia. *It is employed extensively for the suppression and control of malaria caused due to P. vivax, P. malariae and P. ovale.* It has been found to be less effective in *P. falciparum.* It is rarely used now except for chloroquine-resistance cases when its administration is followed by combination of purimethamine and sulfadoxine [*i.e.,* Fansidar$^{(R)}$ (Roche)].

2.7.1. Mechanism of Action

The mechanism of action of **quinine sulphate** is discussed as under :

2.7.1.1. Quinine Sulfate

The **'drug'** only affects the erythrocytic form of the plasmodia ; and, therefore, is employed particularly as a suppressive in the management and treatment of severe attacks of *P. vivax. P. malariae* and *P. ovale* malaria. It may cure upto 50% of infections caused by *P. falciparum.* The *'drug'* may be employed in combination with **pyrimethamine** and a **sulphonamide,** but it seems to be antagonized by **chloroquine.**

Choice of combinations with other drugs : A few typical examples are as follows :

(*i*) **Quinine-pyrimethamine-sulfadiazine (or sulfadoxine).** In the treatment of choice for infections caused by chloroquine-resistant *Plasmodium falciparum ;*

(*ii*) **Quinine-tetracycline.** In infections produced by chloroquinine-resistant *P. falciparum.*

(*iii*) **Quinine-Clindamycin.** In the treatment of choice for *babesiosis.*

The **'drug'** has a tendency to suppress neuromuscular transmission, and hence used in **myotonia congentia** or **Thomsen's disease.**

Note. The 'drug' is mostly given orally after meals to minimize gastric irritation.

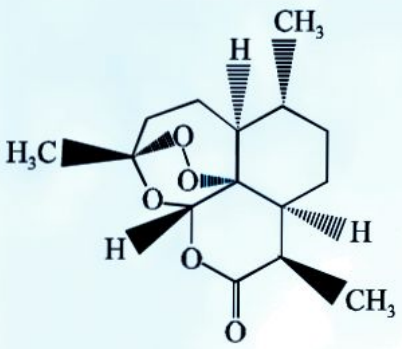
2.8. New Antimalarial Drugs

A few important **newer antimalarial drugs** are discussed as under :

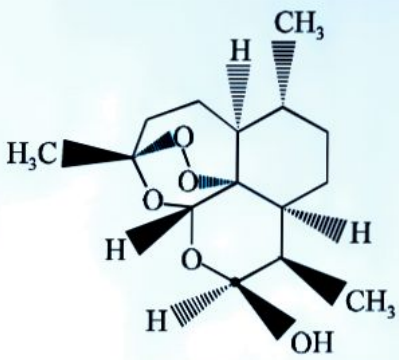
2.8.1. Artemisinin

The marked and pronounced antimalarial activity of **'Quinghausu'** as the constituent of a traditional Chinese medicinal herb *Artemisia annuna* L., **(sweet wormwood)** has been known in China for over 200 years. However, the active principle was first isolated in 1972 and found to be a sesquiterpene lactone with a peroxy moiety.

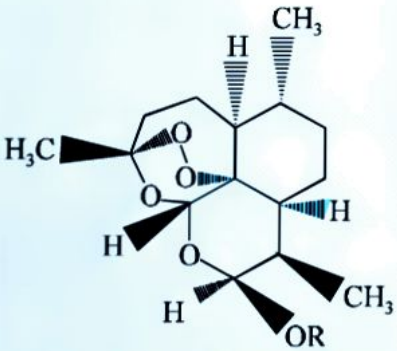
The following *four* chemical structures, namely : (*i*) **artemisinin ;** (*ii*) **dihydroartemisinin ;** (*iii*) **artemether (oil-soluble) ;** (*iv*) **artemotil (oil soluble)** ; and (*v*) **artesunate (water soluble)** are found to be active against the entire *Plasmodium* genera that cause malaria predominantly across the tropical regions of the globe, such as : Africa, Indian sub-continent, South East Asia and the like.



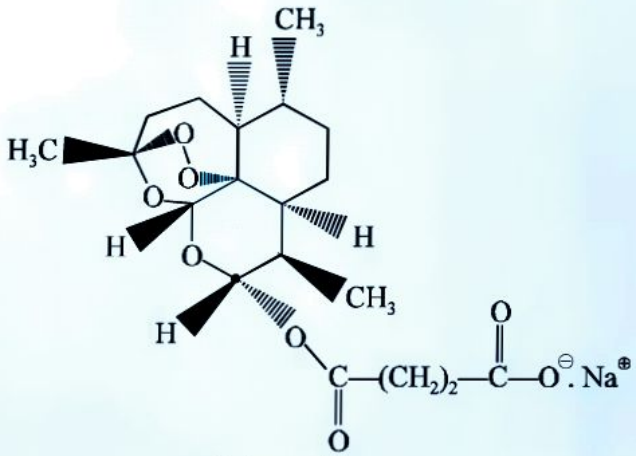
Artemisinin*



Dihydroartemisinin



Artemether [R = CH_3]
Artemotil [R = C_2H_5]



Artesunate

SAR of Artemisinin. The most important, critical and key structure of the **'drug'**, artemisinin, is the presence of a **'trioxane'** moiety which essentially consists of the **endoepoxide** and **doxepin oxygens** that is evidently displayed by a rather simplified versions of *3-aryltrioxanes* as shown in the following section, which are responsible for exerting the antimalarial activity against the parasite.

It is, however, pertinent to state here that the prevailing stereochemistry at C-12 is not so critical and vital.**

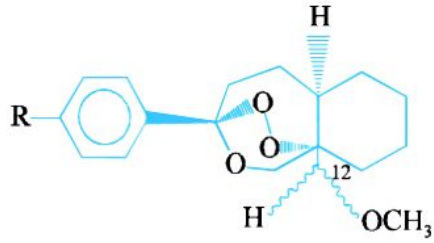
Mechanism of Action. In humans (*i.e.*, the host) erythrocyte, it has been observed that the *malaria parasite* actually consumes the haeomoglobin comprising mainly of Fe^{2+} iron, thereby changing it to the corresponding *toxic hematin* consisting of Fe^{3+} iron, subsequently get reduced to heme with its Fe^{2+} iron. Later on, the resulting **'heme iron'** eventually interacts with the prevailing *trioxane moiety,* thereby releasing the **'reactive oxygen' carbon radicals** and the extremely reactive $\mathbf{Fe^{IV} = O}$ species. It has been established that the latter is proved to be lethal to the parasite.***

***Chemical name of Artemisinin** :

(3α, 5αβ, 6β, 8αβ, 9α, 12β, 12aR')- (+)-Octahydro-3, 6, 9-trimethyl-3, 12-epoxy-12H-pyrano [4, 3-j]-1, 2-benzodioxepin-10 (3H)-one ; ($C_{15}H_{22}O_5$).

Posner GH *et al. J Med Chem* **44, 3054, 2001.

***Posner GH *et al. J Am Chem Soc,* **118,** 3537, 1996.



Aryltrioxanes [R = – F or —COOH]
(Simplified Versions)

Interestingly, the reduction of **artemisinin** to **dihydroartemisinin** gives rise to a **chiral centre,** as shown by a bold black spot in the structure of dihydro artemisinin that may ultimately lead to the formation of '**prodrugs**' which could be either oil soluble or water soluble.

A few characteristic vital features of the above cited '**prodrugs**' are enumerated as under :

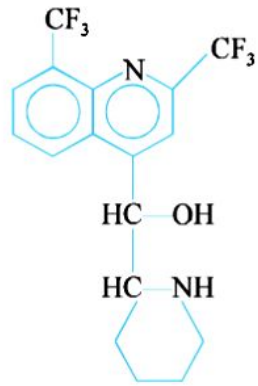
(*i*) The two prevailing stereoisomers are found to be **active,** just as with the simpler aryltrioxanes.

(*ii*) Only one isomer of the ensuing **artemisinin prodrug** exhibits predominance exclusively.

(*iii*) The α-isomer predominates in forming the subsequent hemisuccinate ester which is water-soluble.

(*iv*) The β-isomer predominates in producing the subsequent nonpolar methyl and ethyl ethers.

2.8.2. Mefloquine INN, USAN, Mefloquine Hydrochloride BAN,



DL-*erythro*-α-2-Piperidyl-2-, 8-*bis* (trifuoromethyl)-4-quinolinemethanol ; 4-Quinolinemethanol, α-2-piperidinyl-2, 8-*bis* (trifuoromethyl)-, (R^*, S^*)-(±)-;

This is the outcome of many years of research by the United States department of the Army. It belongs to the 4-quinoline methanol series, several of which were found to have potent schizonticidal activity but could not be used clinically, because they possessed photosensitizing activity in man. Mefloquine is devoid of this effect.

It is very effective against the erythrocytic forms of malaria. However, its use is restricted to cases of chloloquine-resistant falciparum malaria in order to prevent the emergence of parasites that are resistant to it.

Dose : *Oral single dose, 0.4 to 1.5 g.*