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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF 7-CHLORO-4-(5-N-EHTYL-N-2-HYDROXYETHYLAMINE)-2-PENTYL] AMINOQUINOLINE AND ITS INTERMEDIATES

(57) Abstract: Disclosed herein is an improved process for the preparation of 7-chloro-4-[5-(N-ethyl-N-2-hydroxyethylamino)-2-pentyl]aminoquinoline comprising of condensation reaction of 4,7 - dichloro quinoline with 5-(n-ethyl-N-2-hydroxyethyl amino)-2-pentylamine and its intermediates which comprises the reaction of protected 1-chloro-4-pentanone with substituted amine followed by deprotection of ketogroup and reductive amination yielding 5-(N-ethyl-N-2-hydroxyethyl amino)-2-pentylamine or 5 - (N,N-diethylamino) - 2 - pentylamine.



WO 2005/062723 A2

**AN IMPROVED PROCESS FOR THE PREPARATION OF 7-CHLORO-4-(5-(N-ETHYL-N-2-HYDROXYETHYLAMINE)-2-PENTYL] AMINOQUINOLINE AND ITS INTERMEDIATES**

**Related Applications**

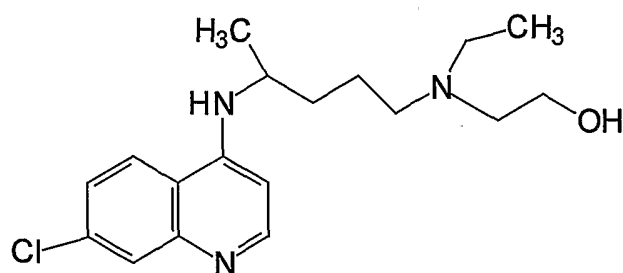
This application claims priority from Indian national applications 1213/MUM/2003 filed on 24<sup>th</sup> November 2003 and 1215/MUM/2003 filed on 24<sup>th</sup> November 2003.

**Field of Invention**

The present invention relates to an improved process for the preparation of hydroxychloroquine, which is useful as an anti-malarial, anti-rheumatic agent. The present invention further relates to a process for preparation of the intermediates of hydroxychloroquine such as 5-(N-ethyl-N-2-hydroxyethyl amino)-2-pentylamine (HNDA).

**Background and prior art**

Hydroxychloroquine is chemically known as 7-chloro-4-(5-N-ethyl-N-2-hydroxyethylamine)-2-pentyl] aminoquinoline and is represented by the structural Formula shown below.



Hydroxychloroquine is in a class of drugs called anti-malarials and is used to treat acute attacks of malaria. It is also used to treat discoid or systemic lupus erythematosus and rheumatoid arthritis in patients whose symptoms have not improved with other treatments. It is used in combination with cyclophosphamide and azathioprine in the treatment of rheumatoid arthritis.

Racemic hydroxychloroquine which is 7-chloro-4-(5-(N-ethyl-N-2-hydroxyethylamino)-2-pentyl]aminoquinoline, reported in the US patent 2546658 (1951), is sold as Sulfate salt by Sanofi -Winthrop Pharmaceuticals under the trade name Plaquenil RTM. It is also useful in treating lupus erythematosus and rheumatoid arthritis.

Pharmacokinetics of racemic hydroxychloroquine as studied by S.E Tett et.al. Br. J. Chin Pharmac, 26, 303-313, (1988), is similar to that of chloroquine. However, hydroxy chloroquine is preferred over chloroquine because it is significantly less retinotoxic at the current recommended dose (400mg/day according to FDA) than chloroquine.

5-(N-ethyl-N-2-hydroxyethyl amino)-2-pentylamine and 4,7-dichloro-2,3-quinoline are the key intermediates in the preparation of hydroxychloroquine. United states patent No 2546658 described a method for preparing hydroxychloroquine involves condensation of 4,7-dichlorquinoline and 5-(N-ethyl-N-2-hydroxyethyl amino)-2-pentylamine in presence of phenol at about 125 to 130°C. This reaction has many disadvantages: higher level of impurity generation in the reaction; deterioration of product at higher temperature; use of phenol in the reaction makes the isolation of product or removal of phenol from the reaction mass difficult and requires many additional purification stages to yield a pharmaceutical standard product. The over all yield of product remains very low.

Another report, RO63271, discloses method for synthesis of hydroxychloroquine which comprises the condensation of 7-chloro-2,3-dihydro-4-quinolone with 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine at 130-160° C. The driving force for the reaction is high temperature and leads to problems such as incomplete reaction, further removal of unreacted starting materials, and product deterioration at higher temperature.

US patent 2,546,658 describes a process for preparation of hydroxy novoldiamine a key intermediate which comprises condensation of 1-halo-4-pentanone with N-ethyl-N-2-hydroxyethylamine to yield a 1-(N-ethyl-N-2-hydroxyethylamine)-4-pentanone intermediate and further subjected to reductive amination to give 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine. Under the reaction conditions described, the 1-halo-4-pentanone undergoes self reaction, to a larger extent, to form an impurity called 1-cyclopropyl-acetone resulting in poor yield and makes the isolation of 1-(N-ethyl-N-2-hydroxyethylamine)-4-pentanone rather difficult. Also, due to the higher reactivity of 1-chloro-4-pentanone with the amines, the reaction leads to uncontrollable exotherm at large scale. The impurity also undergoes second reaction, again making the reaction mass more complex. The overall process is not plant friendly and required repeated purification by fractional distillation to get purified product at a very low yield, which increases the manufacturing cost.

US patent 2,365,825 discloses a method for preparation of N,N-diethylamino alcohols, particularly N,N-diethyl-1-amino-4-pentanol used as intermediate for chloroquine which comprises reacting 1,4-pentanediol with diethylamine in the presence of a metal hydrogenation catalyst more specifically Ni /H<sub>2</sub> at temperature range within 120-250° C. The N,N-diethyl-1-amino-4-pentanol obtained was further oxidized and subjected to reductive amination with ammonia to form the penultimate intermediate 5-(N,N-diethylamino)-2-pentylamine. This method of production is not applicable for the production of 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine as it contains primary alcohol functional group on the side chain ethyl group, which needs to be protected before oxidation.

Yet another process disclosed in United States patent No. 2915523 uses the reaction conditions where the mixture of 2-ethylaminoethanol and 5-chloro-2-pentanone was reacted in xylene in presence of sodium chloride. The resulting 1-(N-ethyl-N-2-hydroxyethylamine)-4-pentanone was reductively aminated to the target intermediate. Again the same problems as described in the '658 patent but to a lesser degree. Also encountered are problems in isolation of product from the high level of impurity and high boiling solvent by fractional distillation.

There are a few reports [RO 62684, GB1157637, US 4910343] on other routes of manufacture of N-ethyl-N-hydroxyethyl-1,4-pentanediamine. Although the chemistry involved is not too difficult but involves many steps, or encountered impurity generation or costly raw materials or complex synthetic procedures etc.

The above said intermediates of chloroquine and hydroxychloroquine viz., novoldiamine and hydroxy novoldiamine are prepared by various synthetic routes in prior art as described above. The drawback of the processes described in the prior art is that the isolation of the required compound is very difficult because of the higher concentrations of impurities in the product and therefore gives very poor yields of the pure compound.

In a nutshell, the process mentioned in prior art are not plant friendly and economically viable and require repeated purification such as high vacuum fractional distillation for getting the intermediate of desired quality for using in the final condensation reaction with 4,7-dichloroquinoline, which ultimately leads to increased cost of manufacture of the final compound.

Further drawback of the reported processes in the prior art are the use of stoichiometric amount of phenol in condensation reaction and inherent problems faced in removing the phenol from the reaction mass, after the completion of this reaction.

The present invention overcomes the problems faced by prior art by providing an improved synthetic route and modifying the reaction parameters to obtain the desired products in good quality and high yield.

### **Objective of the present invention**

It is an objective of the invention to eliminate the disadvantages of the prior art or to provide a useful alternative.

It is also an objective of the present invention in its preferred form to provide a simple, economical, environmental-friendly process for the manufacture of 7-chloro-4-[5-(N-ethyl-N-2-hydroxyethylamino)-2-pentyl]aminoquinoline in higher yield eliminating the use of phenol in the condensation reaction and carrying out the reaction at lower temperature to avoid the impurity formation due to degradation at higher temperature.

Another objective of the present invention is to provide a useful alternative to the production of 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine from 1-chloro-4-pentanone in very high yield and purity in comparison with the prior processes.

### **Summary of the invention**

The present invention discloses an improved process for the preparation of 7-chloro-4-[5-(N-ethyl-N-2-hydroxyethylamino)-2-pentyl]aminoquinoline and its acid addition salts which are useful as anti-malarial and anti-rheumatic agents.

In another aspect of the present invention, there is provided a direct condensation of 4,7-dichloroquinoline of the Formula (VII) with 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine of the Formula (V) catalyzed by potassium iodide in presence of organic or inorganic bases such as triethyl amine, di-isopropylamine, sodium hydroxide, potassium

hydroxide, potassium carbonate and potassium t-butoxide in the absence of any solvents to give hydroxychloroquine of Formula I.

In the process in its preferred form, a mixture of 4,7-dichloroquinoline, 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine, catalytic amount of potassium iodide, and a molar amount of sodium hydroxide is heated at a temperature of about 100 to 150°C till completion of reaction.

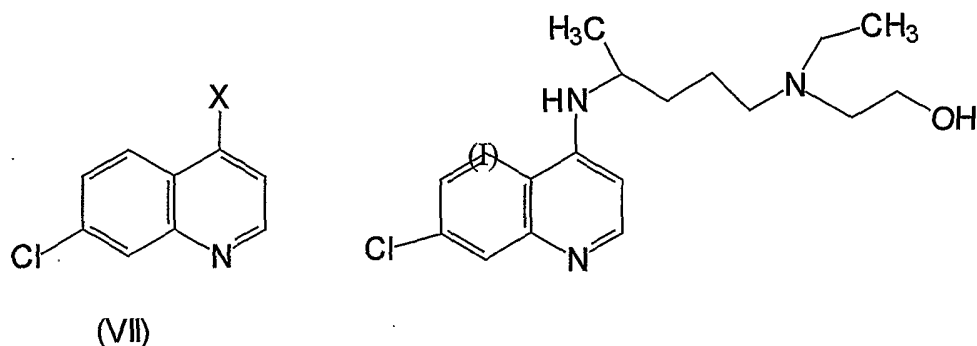
In one aspect of the present invention there is provided a process for preparation of 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine or 5-[N,N-diethylamino]2-pentylamine of Formula V in which the carbonyl group of 1-chloro-4-pentanone was protected with a ketone protecting group such as mono ethylene glycol or neopentyl glycol to provide a compound of Formula II followed by condensation with an amine of Formula VI (wherein R1 and R2 are independently ethyl or hydroxyethyl), removal of protective group and reductive amination to yield the desired intermediate of Formula (V) in high purity and higher yield with simple industrial isolation techniques.

Yet another aspect of the invention, the quinoline base of Formula I was converted into acid addition salts by dissolving in alcohols such as primary and secondary alcohols followed by treating with corresponding acids.

### **Detailed description**

As per the present invention the preparation of hydroxychloroquine, the intermediate 5-(N-ethyl-N-2-hydroxy ethylamino)-2-pentylamine of the Formula (V) is condensed with 4,7-dichloroquinoline of the Formula (VII) in presence of catalytic amount of potassium iodide and in presence of organic or inorganic bases to give corresponding substituted amino quinolines of the Formula I (hydroxyl chloroquine). The organic base used for the condensation reaction is selected form organic bases such as triethyl amine;

di-isopropylamine, and inorganic bases selected from sodium hydroxide, potassium hydroxide, potassium carbonate or potassium alkoxide such as potassium t-butoxide.



X = Halogens such as Cl, Br, or I.

The condensation reaction is preferably carried out by treating 4,7-dichloroquinoline (VII) with 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine of the Formula (V) in the molar ratio of 1.1 to 5.0 preferably 1.7 to 2.0 in presence of catalytic amount of potassium iodide and the base in a molar ratio ranging from about 0.1 to 1.0 mole preferably 0.2 mole at a temperature ranging from 100 to 150°C for a period of 45 to 50 hours to yield hydroxychloroquine of Formula I. The preferred temperature range for the condensation reaction is 105 to 115°C.

The condensation process of the present invention is advantageous as it eliminates the use of phenol, which facilitates the isolation of product in higher purity and yield. Also the completion of reaction can be achieved at a lower temperature where the deterioration of product or the intermediates is minimal, ideal for high throughput conditions. The present invention also provides a high purity intermediate 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine, which also makes the reaction neat with minimal impurity generation or side reaction.



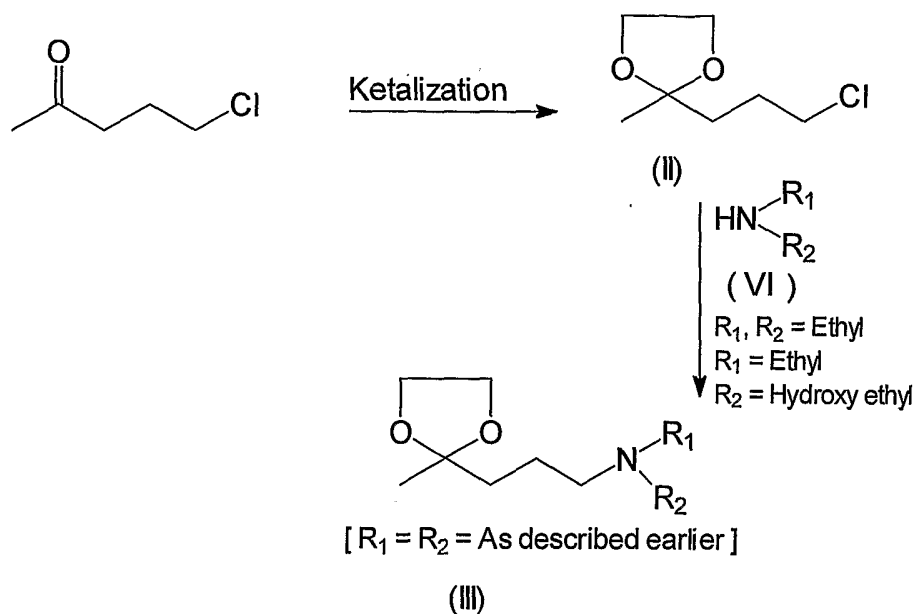
The quinoline base was isolated by the following steps: cooling the reaction mixture, suspending the reaction mass in methanol and filtering. The base may be isolated by concentrating the methanol or by acid base treatment or directly taken for the salt formation.

Accordingly, the quinoline base of Formula (I) was dissolved in alcohols like primary or secondary alcohols followed by treatment with corresponding acids such as phosphoric acid or sulphuric acid at reflux temperature for 3-4 hrs to obtain the corresponding acid addition salts of hydroxychloroquine.

In another embodiment of the present invention, there was provided a process for preparation of amino pentylamines in higher yield and purity wherein the carbonyl group of 1-chloro-4-pentanone is protected with protecting groups like monoethylene glycol, neopentyl glycol to provide a 2-(3'-chloropropyl)-2-methyl 1,3-dioxalane, 2-(3'-chloropropyl)-2,5,5-trimethyl-1, 3-dioxalane of Formula (II) in the first step of the reaction.

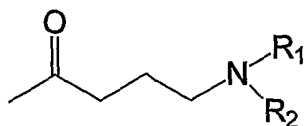
The ketalization reaction is carried out by known general methods. The suitable conditions for the reaction of 1-chloro-4-pentanone with monoethylene glycol or neopentyl glycol is in non-polar solvents like toluene, xylene, cyclohexane, hexane and heptane, using acid catalyst like Para-toluene sulphonic acid, methane sulphonic acid, perchloric acid etc. at a temperature ranging from 80 to 140°C. The monoethylene glycol or neopentyl glycol is preferably used in a molar ratio ranging from about 1:1 to 1: 2.0 and the preferable reaction temperature is ranging between about 80 to 90°C for a period of 15 to 30 hours to obtain the compound of Formula II.

The compound of Formula (II) so obtained was then condensed with amines of Formula VI (wherein R<sub>1</sub>, R<sub>2</sub> are independently ethyl or hydroxyl ethyl) namely N-ethyl-N-2-hydroxyethyl amine, or N,N-diethylamine of Formula VI to give the condensed product of Formula(III) with or without the isolation of Formula II.



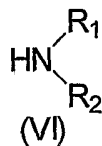
The said reaction was carried out between Formula (II) with substituted amines of Formula (VI) such as N-ethyl-N-2-hydroxy ethyl amine, N,N-diethylamine in the molar ratio of 2.0 to 5.0 preferably 2.2 in a non-polar solvents like toluene, xylene, cyclohexane at a temperature ranging from 90 to 140°C, preferably 120 to 130°C, for a period of 18 to 20 hours. When the reaction is carried out without isolating compound of Formula II, then an excess amount of amine is used to neutralize the acid catalyst used in the previous stage.

The compound of Formula (III) was then hydrolyzed in acidic condition to give desired ketone of the Formula (IV) in higher purity in almost quantitative yield.



[R<sub>1</sub> = R<sub>2</sub> = As described earlier]

(IV)



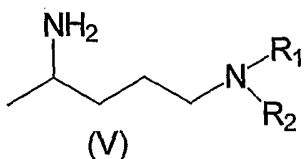
(VI)

R<sub>1</sub>, R<sub>2</sub> = Ethyl

R<sub>1</sub> = Ethyl

R<sub>2</sub> = Hydroxy ethyl

The product of the Formula (III) is hydrolyzed in acidic conditions using acids like hydrochloric acid, sulphuric acid, perchloric acid, phosphoric acid, para-toluene sulphonic acid, methane sulphonic acid, trifluoro acetic acid etc. in the molar ratio of 1.1 to 5.0 preferably 1.5 in aqueous condition at a temperature ranging from 10 to 50°C preferably 25 to 35°C for a period of 6 to 7 hours. The compound of Formula IV upon reductive amination yielded the desired compounds of Formula (V).



(V)

i) R<sub>1</sub>, R<sub>2</sub> = Ethyl → 5-[N,N-diethylamino]-2-pentylamine]

ii) R<sub>1</sub> = Ethyl, R<sub>2</sub> = Hydroxy ethyl → 5-[N-ethyl-N-2-hydroxyethylamino]-2-pentylamine

The reductive amination was carried out between condensed ketone of Formula (IV) in presence of ammoniacal alcoholic solvents like methanol, ethanol, isopropanol in presence of catalyst, Raney Nickel, under hydrogen pressure ranging from 10 to 30 kg/cm<sup>2</sup> preferably 20 to 22 kg/cm<sup>2</sup> at a temperature ranging from 40 to 130°C preferably 80 to 85°C for a period of 2 to 5 hours to yield the compounds of Formula (V).

The following examples illustrate the process of the invention in greater details and are not limited in any manner to the specific embodiments presented therein.

**Examples:****Example 1:**

Preparation of 7-chloro-4-[5-(N-ethyl-N-2-hydroxyethylamino)-2-pentyl] aminoquinoline.

A mixture of (100gm) of 4,7-dichloroquinoline of Formula VII, (146gm) of 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine of Formula V, (4.0gm) of potassium iodide & 8.0 gm of sodium hydroxide were heated with stirring for 40 to 50 hours at 110 to 115° C. Then the reaction mixture cooled, methanol (400ml) was added and the reaction mixture was charcolized. The clear filtrate was treated with phosphoric acid (130gm) to give (250gm) 7-chloro-4-[5-(N-ethyl-N-2-hydroxyethylamino)-2-pentyl] aminoquinoline diphosphate.

The above diphosphate was dissolved in water (500ml), basified with ammonium hydroxide (300ml) solution and the resulting liberated quinoline base was extracted with methylene dichloride (400ml × 2). After complete removal of methylene chloride, the quinoline base of Formula I was isolated. Melting point is 89 to 91°C. The yield of the product is 130gms.

**Example 2:**

Preparation of 7-chloro-4-[5-(N-ethyl-N-2-hydroxyethylamino)-2-pentyl] aminoquinoline diphosphate.

The above quinoline base of Formula I (100gm) was dissolved in methanol (400ml). The reaction mixture was cooled to 5 to 10°C and the phosphoric acid (30gm) was added. The reaction mixture refluxed for 3 to 4 hours to get the desired acid addition salt of the quinoline base. The yield of the product is 100gms.

**Example 3:**

Preparation of 7-chloro-4-[5-(N-ethyl-N-2-hydroxyethylamino)-2-pentyl] aminoquinoline sulphate.

The above quinoline base of Formula I (100gm) was dissolved in methanol (400ml). The reaction mixture was cooled to 5 to 10°C. Sulphuric acid (35gm) was added. The reaction mixture refluxed for 3 to 4 hours to get the desired acid addition salt of the quinoline base. The yield of the product is 100gms.

Example 4:

Preparation of 1-chloro-4-pentanone:

Acetyl butyrolactone (100gm) was added dropwise in a mixture of water (100gm), hydrochloric acid (120gm) and sodium chloride (20gm) at 100 to 105°C. After completing the reaction, the resulting product was collected by distillation. The yield of the product was 80gm.

Example 5:

Preparation of 2-(3'-chloropropyl)-2-methyl-1,3-dioxalane:

Ethylene glycol (40gms), cyclohexane (160ml) & para-toluene sulphonic acid (1gm) are added to 1-chloro-4-pentanone (80gm). The reaction mixture was heated to 80 to 90°C for 20 to 25 hours and removes the water azeotropically from the reaction mixture. The reaction mass was cooled. Water (40 ml) was added to the reaction mass and separated the aqueous layer. Organic layer was distilled under vacuum to isolate the oily product of Formula II. The yield of the product was 100gms.

Example 6:

Preparation of 2-(3'-N-ethyl-N-2-hydroxyethylaminopropyl)-2-methyl-1,3-dioxalane (HNK Ketal)

Toluene (200ml) and ethylamino ethanol of Formula VI (130gm) are added to product of Formula (II) (100gm). The reaction mass was heated to 125 to 130°C for 15 to 18 hours. The reaction was cooled. Water (10ml) added and the aqueous layer was separated. The organic layer was distilled out to isolate the product of Formula III. The yield of the product was 110gms.

**Example 7:**

Preparation of 1-(N-ethyl-N-2-hydroxyethyl amino)-4-pentanone.

Water (100ml) and conc. hydrochloric acid (10ml) was added to the HNK Ketal of Formula III (110gm). The reaction mass was stirred for 4 to 5 hours at 30° C - 40° C. Then the reaction mixture was neutralized with caustic lye solution. Aqueous layer was separated to isolate the product layer. The yield of the product of Formula IV was 100gm.

**Example 8:**

Preparation of 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine:

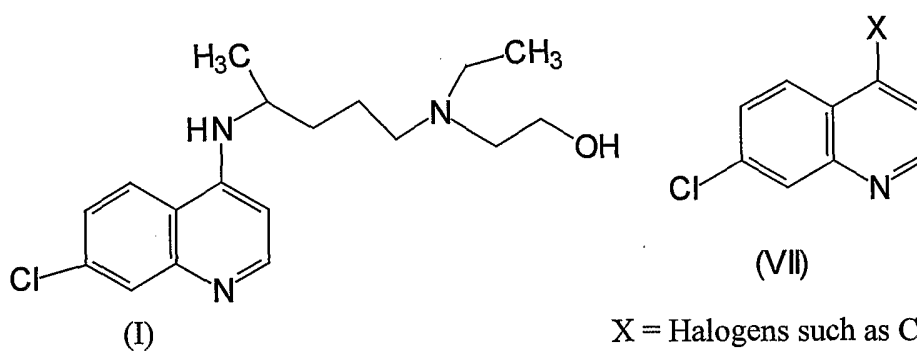
The 1-(N-ethyl-N-2-hydroxyethylamino)-4-pentanone of Formula IV (100gm) was diluted with ammoniacal methanol (400ml) and reduced catalytically with Raney Nickel (5gm) at 40°C to 80°C using 15 to 20 kg hydrogen pressure in 4 to 5 hours.

After completion of the reaction, catalyst was filtered and methanol was distilled out at atmospheric pressure, fractionally distilling Formula V to yield 80gm pure 5-(N-ethyl-N-2-hydroxyethyl amino)-2-pentylamine.

While we have described our preferred embodiments in the examples here, variations on this disclosure can be discerned by one of skill in the art. Thus we intend the legal coverage of our patent to be defined not by the specification and its examples, but by the appended claims.

**We claim,**

1. A process for manufacture of hydroxychloroquine (7-chloro-4-[5-(N-ethyl-N-2-hydroxyethylamino)-2-pentyl]aminoquinoline) of Formula I and its acid addition salt characterized by the step of heating a mixture of 4,7-dichloroquinoline, 5-(N-ethyl-N-2-hydroxy ethylamino) -2-pentylamine, and an inorganic or organic base in presence of potassium iodide to form a reaction mass containing hydroxychloroquine, and isolating the hydroxychloroquine from the said reaction mass..

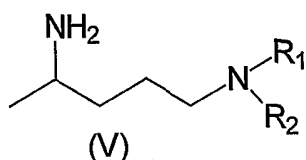
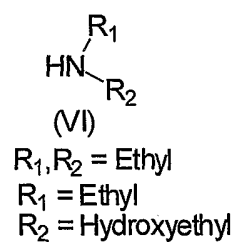
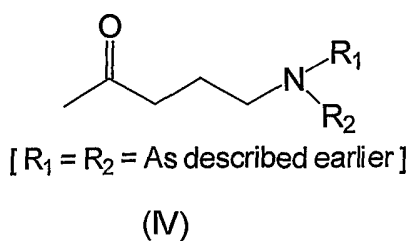
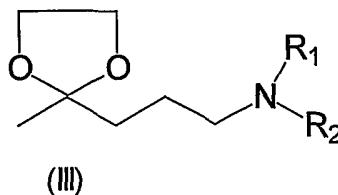
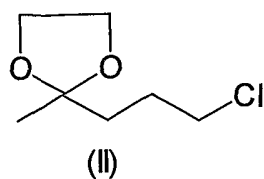


I.

2. The process according to claim 1, wherein the inorganic base is selected from sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate, metal alcoholates etc.
3. The process according to claim 1, wherein the organic base is selected from triethylamine, diisopropylethylamine or the like.
4. The process according to any one of the preceding claims, wherein the base is used in a molar amount of 0.1 to 1 mole relative to the starting 4,7-dichloroquinoline.

5. The process according to any one of the preceding claim, wherein the mixture of reactants are heated to a temperature ranging from 100 to about 150°C in order to effect the reaction.
6. The process according to any one of the preceding claims, wherein the mixture of reactants are heated to a temperature ranging between about 105 to 115°C.
7. The process according to any one of the preceding claim, wherein the potassium iodide is used in catalytical quantity in the order of about 4% by weight of 4,7-dichloroquinoline.
8. The process according to any one of the preceding claims, wherein the reaction is conducted in the absence of solvent.
9. A process according to claim 1, wherein the said 5-(N-ethyl-N-2-hydroxyethyl amino) -2-pentylamine is prepared by the following steps:  
condensation of a compound of Formula II with an amine of Formula VI (wherein R1, R2 are independently ethyl or hydroxyl ethyl) in a non-polar solvent to form a compound of Formula III;  
removing the protective group at the 2-position of Compound of Formula III to form a 5-(N-ethyl-N-2-hydroxyethylamino) -2-pentanone of Formula IV; and  
subjecting the compound of Formula IV to reductive amination in presence of Raney Nickel in an atmosphere of hydrogen and ammonia to form 5-(N-ethyl-N-2-hydroxyethylamino) -2-pentylamine





i) R<sub>1</sub>, R<sub>2</sub> = Ethyl → 5-[N,N-diethylamino]-2-pentylamine]

ii) R<sub>1</sub> = Ethyl, R<sub>2</sub> = Hydroxy ethyl → 5-[N-ethyl-N-2-hydroxyethylamino]-2-pentylamine

10. The process according to claim 9, wherein the protective groups on compound of Formula II is selected from monoethylene glycol and neopentyl glycol.
11. The process according to claim 9 or 10 wherein the non-polar solvents used in the said condensation step is selected from toluene, xylene, cyclohexane, hexane and heptane
12. The process according to claim 11, wherein the condensation of compound of Formula II and Formula VI are conducted at a temperature ranging from about 90 to 140°C.
13. The process as claimed in claim 12, wherein said substituted amines of Formula VI are N-ethyl-N-2-hydroxy ethylamine or N, N-diethylamine.

14. The process according to claim 9 or 13, wherein the deprotection of keto-group of compound of Formula III is effected under aqueous acidic condition.
15. The process according to claim 9 or 14, wherein the reductive amination of compound of Formula IV is performed in ammoniacal alcoholic solvents selected from methanol, ethanol, isopropanol or the like.
16. The process according to claim 15, wherein the reductive amination is carried out at a temperature ranging between about 40° to 130°C under a hydrogen pressure ranging from about 10 to 30 kg/cm<sup>2</sup>
17. The process according to claim 16, wherein the temperature is about 80 to 85°C under a hydrogen pressure of about 20 to 22 kg/cm<sup>2</sup>
18. The process according to any one of the preceding claim, wherein the said hydroxychloroquine is isolated by the following steps of:
  - suspending the reaction mass in an alcoholic solvent selected from methanol, ethanol, isopropyl alcohol or the like;
  - treating with an adsorbent and filtering to remove the insolubles;
  - precipitating the hydroxychloroquine as a salt by addition of an inorganic acid such as phosphoric acid or sulphuric acid or the like;
  - optionally purifying the said salt by repeated acid-base treatment.
19. The process according to any one of the preceding claims, wherein the hydroxy chloroquine is converted into its sulphate salt.
20. Hydroxychloroquine sulphate directly obtained by a process as claimed in any one of the preceding claim.

21. An improved process for the manufacture of 7-chloro-4-[5-(N-ethyl-N-2-Hydroxyethylamino)-2-pentyl] aminoquinoline (Hydroxychloroquine) and their acid addition salts, as substantially described herein with reference to the foregoing examples 1 to 8.