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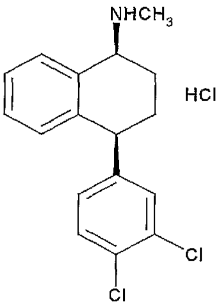
(54) **Title:** IMPROVED MANUFACTURING PROCEDURE FOR THE PREPARATION OF POLYMORPHIC FORM II OF CIS-(lS)-N-METHYL-4-(3,4-DICHLOROPHENYL)-l,2,3,4-TETRAHYDRO-l-NAPTHLENEAMINE HYDROCHLORIDE (SERTRALINE HYDROCHLORIDE)



(1)

(57) **Abstract:** The present invention relates to the improved, scalable and efficient manufacturing procedure for the preparation of the antidepressant Cis-(lS)-N-Methyl-4-(3,4-Dichlorophenyl)-l,2,3,4-tetrahydro-l-napthaleneamine hydro chloride, Sertraline Hydrochloride polymorphic form II. The present invention further relates to the improved and modified procedures for preparing, separating and isolating the key intermediates involved in the preparationof Sertraline Hydrochloride polymorphic form II. The present invention also further relates to the use of novel reagents or a combination thereof and new methodologies to prepare some o'f the key intermediates involved in the preparation of Polymorphic Form II of Sertraline Hydrochloride.

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TITLE - IMPROVED MANUFACTURING PROCEDURE FOR THE PREPARATION OF POLYMORPHIC FORM II OF CïS-(lS)-N-METHYL-4-(3,4-DICHLOROPHENYL)-I ,2,S^-TETRAHYDRO-I-NAPTHLENEAMINE HYDROCHLORIDE (SERTRALINE HYDROCHLORIDE)

BACKGROUND OF THE INVENTION

The present invention relates to the improved scalable and efficient manufacturing procedure for the preparation of polymorphic form II of Cis-(lS)-N-Methyl-4-(3,4-Dichlorophenyl)-l,2,3,4-tetrahydro-l-napthaleneamine hydrochloride, Sertraline Hydrochloride.

Sertraline Hydrochloride (Zoloft) is a useful antidepressant. It blocks the synaptosomal uptake of Serotonin (5-Hydroxytryptamine) abnormalities at central receptor sites. It possess negligible monoamine oxidase inhibition anticholinergic and psychomotor stimulation activities. Effects on the cardiovascular system are minimal hence it belongs to a major category of anti-depressant agent.

TECHNICAL FIELD

The first method of preparing Sertraline Hydrochloride (1) is described in the product patent US 4,536.518 and by W.M. Welch et.al, in Journal of Medicinal Chemistry 1984, 27, 1508. The process described in the preceding references uses methods as described by Daub in Organic Reactions, VoI VI. pages 1-73 and in European patent No. 30081 for some of the initial steps.

The process described in US patent 4,536,518 and by W.M. Welch et.al, in Journal of Medicinal Chemistry 1984, 27, 1508 involves (a) the reaction of 3,4-dichlorobenzoyl chloride with benzene in the presence of aluminium chloride to form 3,4-dichlorobenzophenone; (b) condensation of 3,4-Dichlorobenzophenone under the conditions of Stobbe reaction in the presence of potassium tertiarybutoxide with Diethylsuccinate; (c) Decarboxylation of the product obtained using aqueous Hydrobromic acid solution and to form 4,4'diarylbutenoic acid; (d) hydrogenation of said acid on Palladium charcoal to form the corresponding 4,4'diarylbutanoic acid; (e) cyclization of the 4.4'diarylbutanoic acid into 4-(3,4-dichlorophenyl)-tetralone by means of hydrofluoric acid or polyphosphoric acid, or, after transformation to acid reaction; (f) treating 4-(3,4-dichlorophenyl)-tetralone so formed with gaseous Methyl chloride, by the action of Aluminium chloride under the conditions of Friedal-Crafts amine in the presence of an acid catalyst e.g. TiCU to yield an imine intermediate which is then hydrogenated to the methyl amine intermediate over 10% Palladium carbon; (g) conversion of the obtained amine intermediate to crude Cis-(1 S)(I R)-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro-l-napthalenamine Hydrochloride followed by crystallization in Methanol - ether mixture to pure Cis-(1 S)(I R)-N-Methyl-4-(3,4-dichlorophenyl)-l ,2,3,4-tetrahydro-l -napthalenamine Hydrochloride; (h) conversion of the pure Cis-(lS)(lR)-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3;4-tetrahydro-1-napthalenamine Hydrochloride converted to Cis-(lS)-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro-l-naptlialenamine mandelate; (i) and final conversion of the mandelate salt to free amine and then to Sertraline Hydrochloride. This method provides essentially polymorphic form II as inferred from US 5248699

The method discussed in US Patent No. 4,536,518 has many synthetic drawbacks.

(a) Firstly it employs expensive 3,4-Dichlorobenzoylchloride for the preparation of 3,4-Dichlorobenzophenone an key starting material involved in the preparation of Sertraline Hydrochloride. Also the low yield is obtained for this intermediate.

(b) The next stage Stobbe condensation involving the condensation of 3,4-Dichlorobenzophenone with diethylsuccinate in the presence of Potassium tert-butoxide requires longer reaction time and isolation includes cumbersome work up procedure.

(c) The decarboxylation stage also includes a longer reaction time, an isolation procedure involving number of steps resulting in low yield of the intermediate.

(d) The intramolecular Friedal- Craft cyclisation reaction involving conversion of 4-(3,4-Dichlorophenyl)-4'-phenylbutanoicacid to 4-(3,4-Dichlorophenyl)-tetralone a key intermediate used in the preparation of Sertraline Hydrochloride also involves a longer reaction time and is also low yielding.

(e) Imine formation stage includes a condensation reaction of 4-(3,4-dichlorophenyl)-3,4-dihydro-l-(2H)-napthalenone with gaseous monomethylamine (gas), which is catalysed by titanium tetrachloride yielding N-[4-(3,4-dichlorophenyl)-3,4-dihydro- 1-(2H)-napthalenylidene]methanamine. Titanium tetrachloride however is extremely reactive with water and side products formed are hazardous.

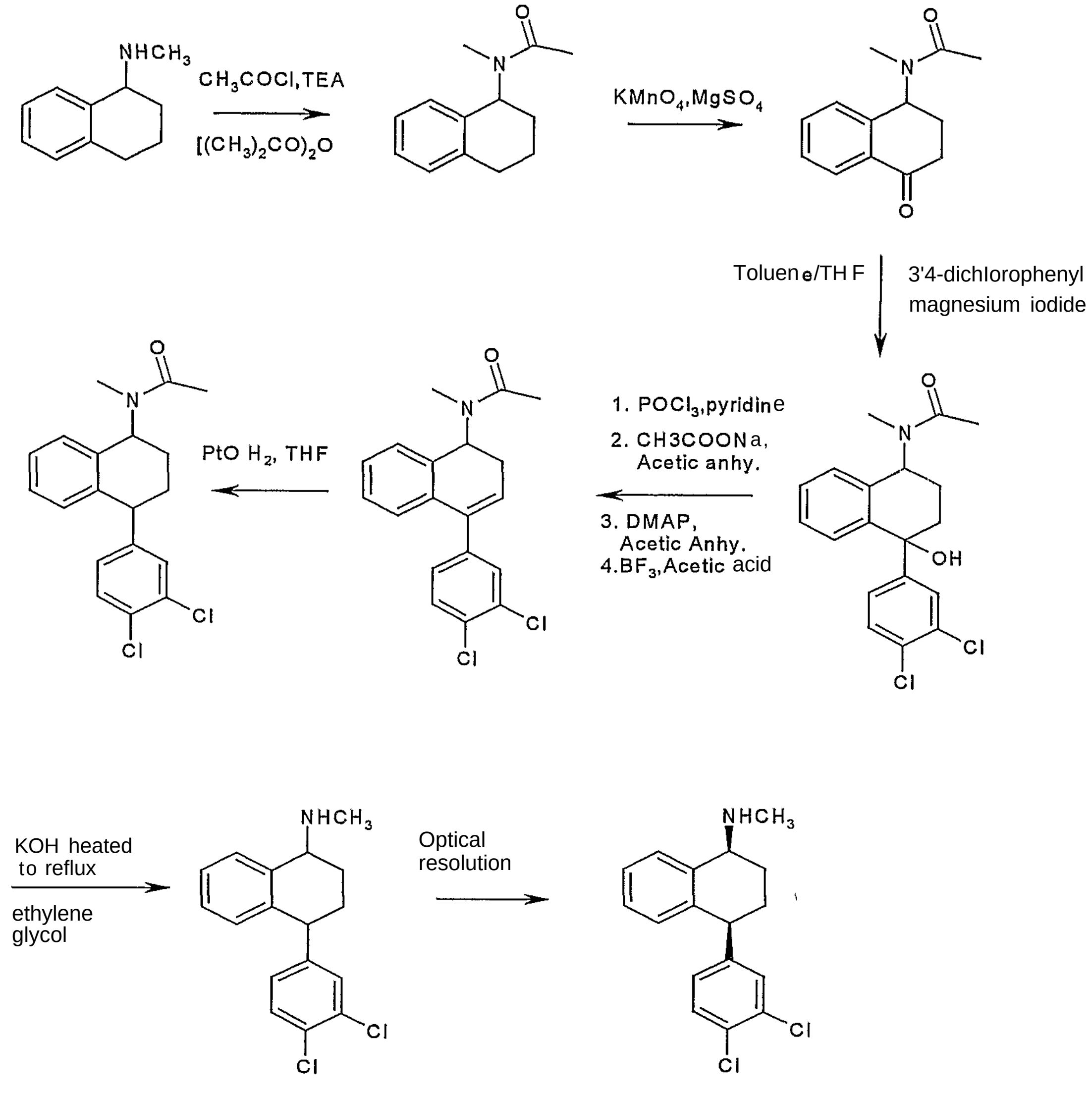
(1) CiS-(I S)(lR)-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetraliydro-l-napthalenamine Hydrochloride is prepared from the reduced (lS-Cis)-4-(3,4-dichloro- phenyl)-l,2,3,4-tetrahydro-N-methyl-l-napthalenamine by Hydrogen chloride gas treatment in Ether followed by crystallization.

(g) Cis-(1 S)-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro-l -napthalenamine mandelate salt is isolated in two crops.

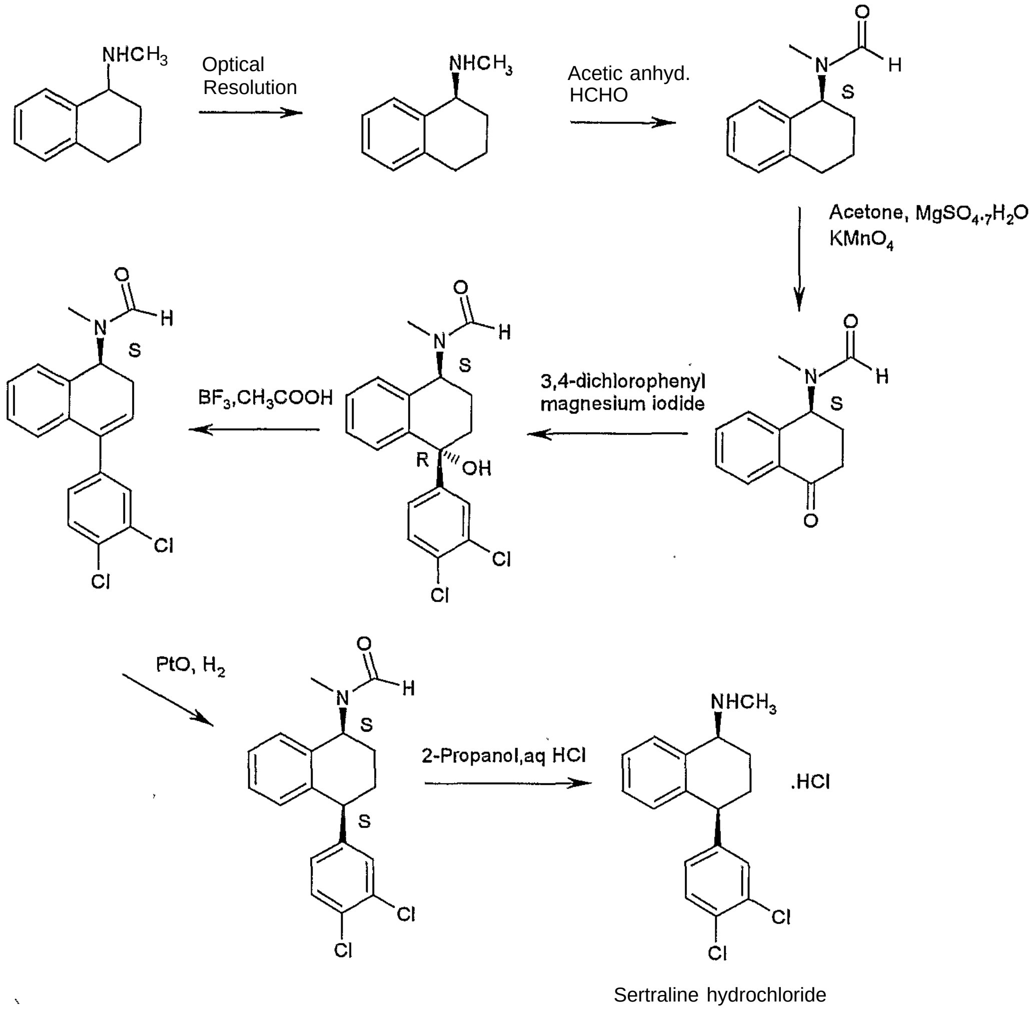
(h) The mandelate salt so prepared has to be converted to the Cis-sertraline base for its final conversion to Sertraline Hydrochloride thus increasing the operation.

(i) Conversion of Cis-Sertraline Base to Sertraline Hydrochloride requires longer time period as per the process.

EP 594666 describes two multistep processes starting from 1-N-Alkyl-naphthalene for the preparation of Sertraline and Sertraline hydrochloride as per scheme 01 and Scheme 02.


NHCH$_3$
CH$_3$COCl,TEA
[(CH$_3$)$_2$CO)$_2$O
N
O
KMnO$_4$,MgSO$_4$
Toluene/THF
3'4-dichlorophenyl magnesium iodide
OH
Cl
1. POCl$_3$,pyridine
2. CH3COONa, Acetic anhy.
3. DMAP, Acetic Anhy.
4.BF$_3$,Acetic acid
PtO H$_2$, THF
KOH heated to reflux
ethylene glycol
Optical resolution
Sertraline hydrochloride

Scheme Ol



Scheme 02

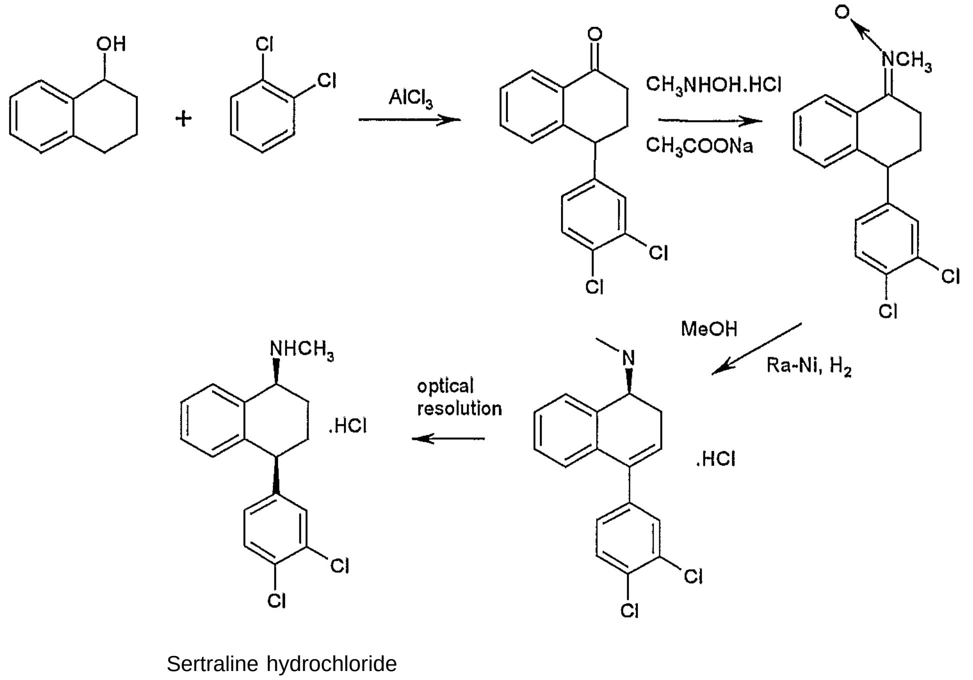
Both the methods as described in EP 594666 have the following drawbacks

a) the methods use hazardous chemicals such as Phosphorous oxytrichloride, pyiridine etc.

b) the procedures also uses costly catalyst Platinum oxide for reduction which makes it essential to be recovered.

c) the effluent load due to the use of various hazardous reagents is more.

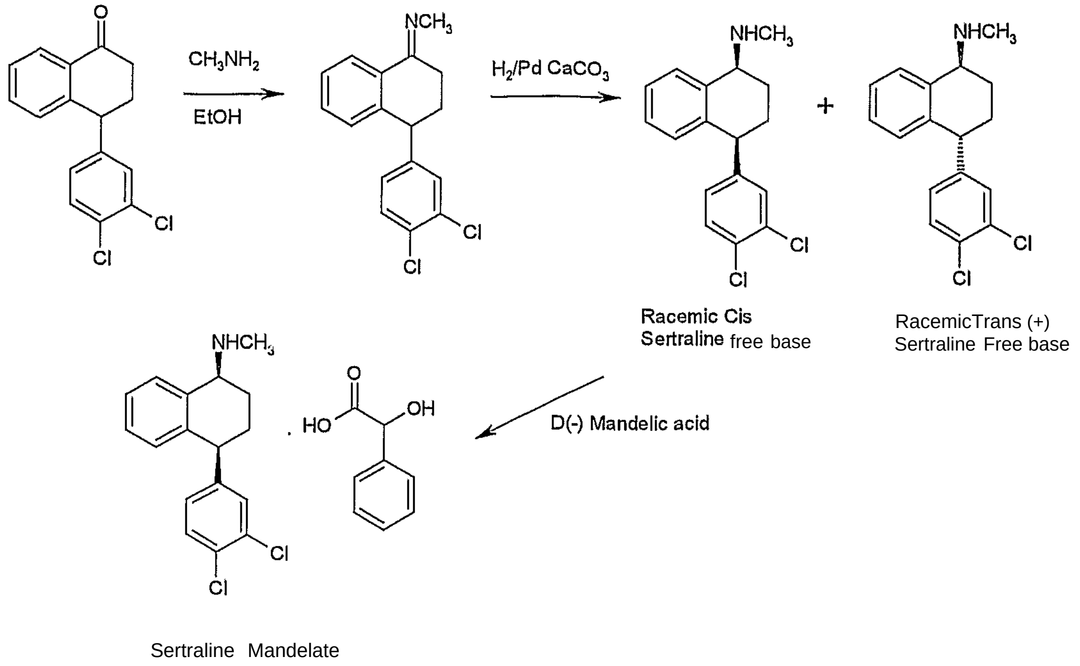
Another synthetic process for the preparation of Sertraline hydrochloride is mentioned in EP 946493 & EP 1200387 which involve the preparation of the key intermediate 4-(3,4-dichlorophenyl)-tetralone by known methods and then its further conversion to Sertraline Hydrochloride as per scheme 03



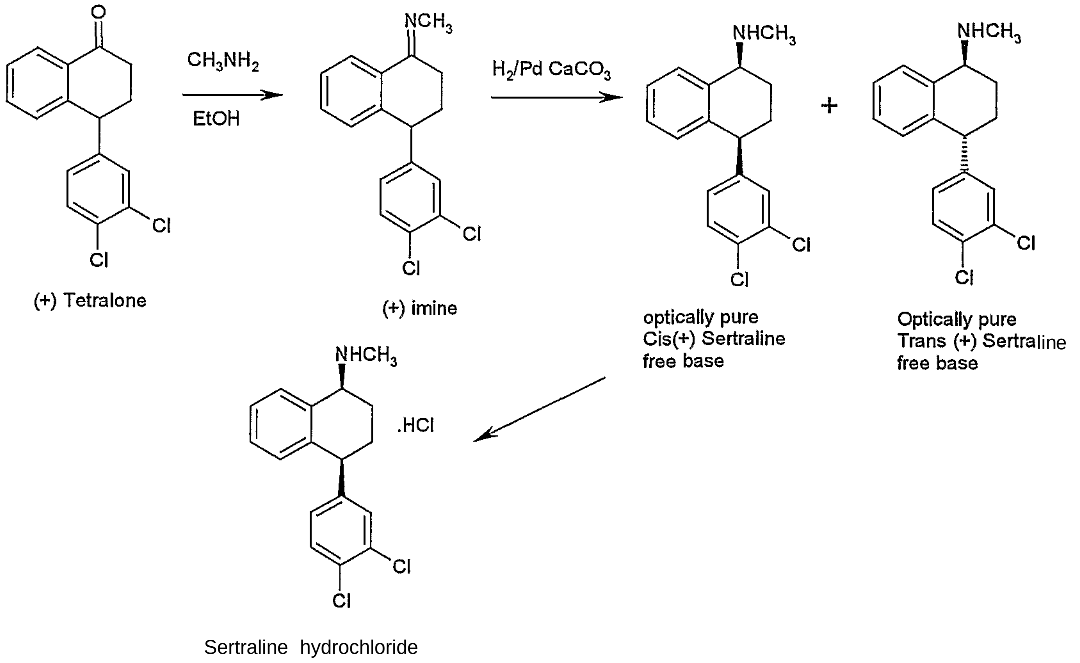
Scheme 03

The above procedure handles costly and hazardous Raney-Nickel for the reduction step.

In US 6232500 a process for the preparation of Sertraline Hydrochloride from the key intermediate 4-(3,4-dichlorophenyl)-tetralone is described, which involves the preparation of imine, reduction with Palladium on Calcium carbonate under hydrogen pressure and finally resolution of the obtained racemic Cis-Sertraline free base to yield Sertraline mandelate which can be converted to Sertraline Hydrochloride. It also discloses a method wherein Sertraline Hydrochloride is prepared from chiral tetralone. Processes as per the patent are represented by scheme 04 and scheme 05



Scheme 04



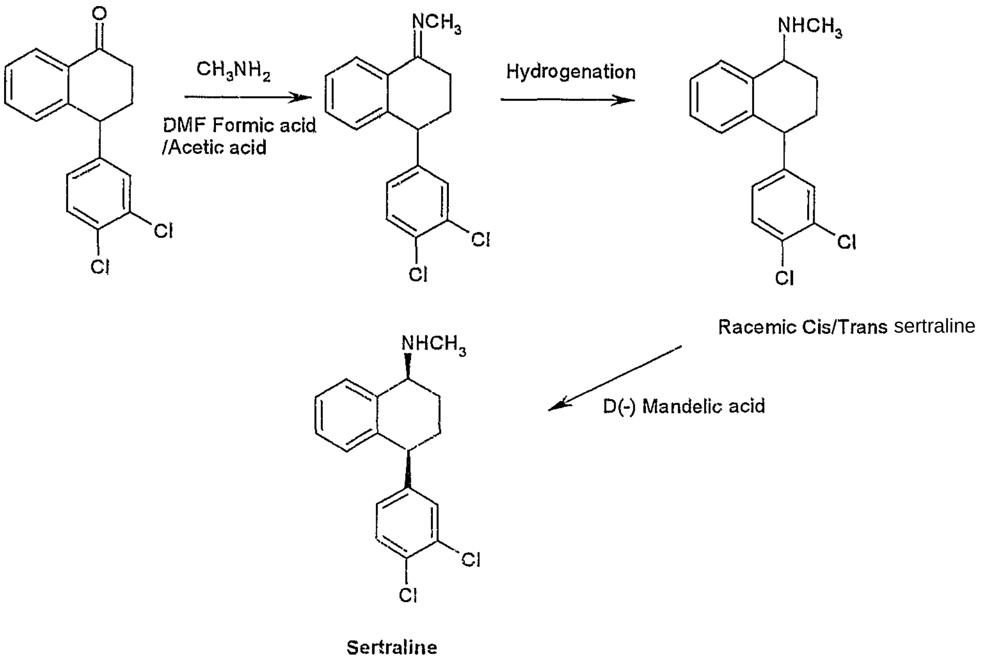
Scheme 05

Process described in US 6232500 have the following drawbacks

a) it uses excess of methyl amine gas which has to be removed after the imine formation

b) use of costly catalyst Palladium on Calcium carbonate again requiring an efficient procedure for the recovery of the catalyst after the reaction.

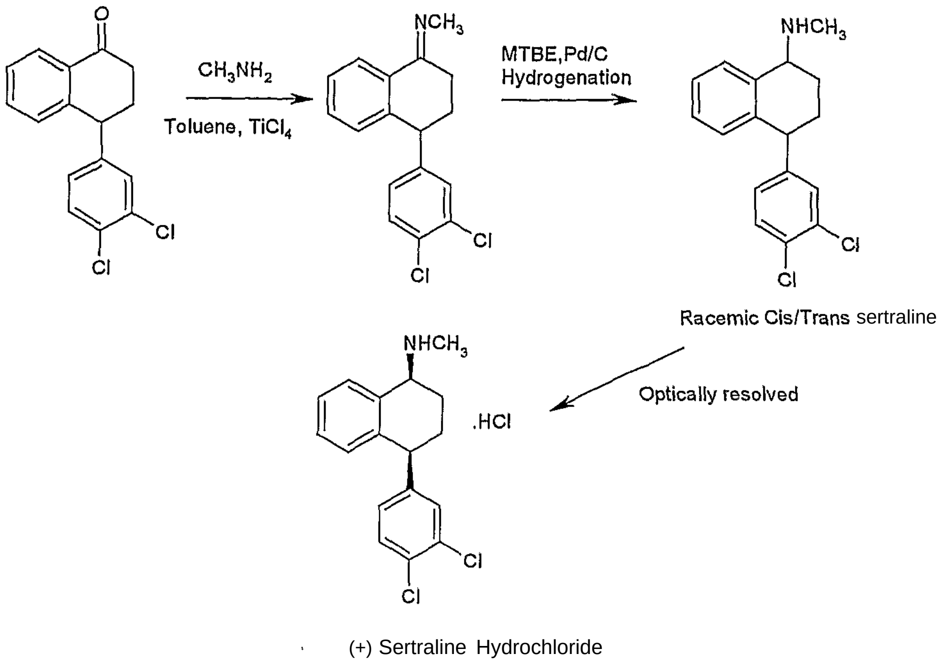
WO 2002096860 Al also describes a process starting from the key intermediate 4-(3,4-dichlorophenyl)-tetralone, which includes imine formation in DMF in the presence of formic acid or acetic acid at 50^{0}C, followed by hydrogenation and resolution and is depicted in scheme 06



Scheme 06

The above procedure as per WO 2002096860 Al again uses Methyl amine gas hence suffering from the drawbacks as regards to effluent in terms of excess Monomsthylarnine gas. etc.

Another prior art US6552227 discloses a process for the preparation of sertraline hydrochloride from the intermediate 4-(3,4-dichlorophenyl)-tetralone which involves the formation of imine in the presence of titanium tetrachloride, reduction of imine in the presence of a Palladium or platinum catalyst to the Cis/trans Sertraline Base which is further converted to Sertraline Hydrochloride.



Scheme 07

The procedure described in scheme 07 has the following drawbacks

a) it uses monomethylamine gas in the imine formation step

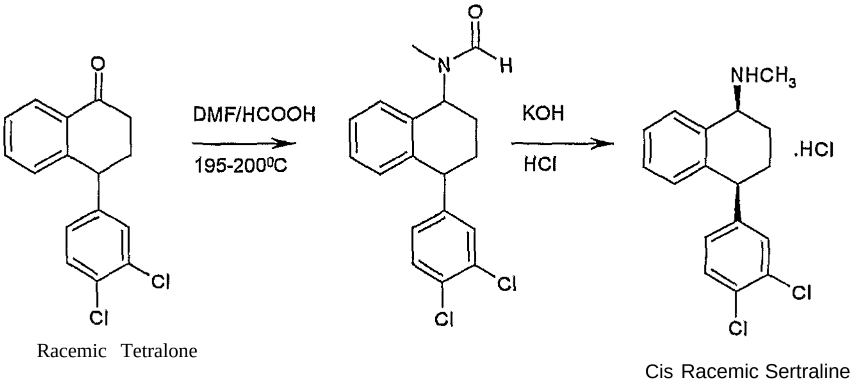
b) uses Titaniumtetrachloride which is quite hazardous and toxic and also leads to various side products in combination with monomethylarnine

c) it uses ethereal solvent for reduction of the amine with hydrogen gas which may be not feasible at a industrial scale due to potential danger.

Another preparation disclosed in WO 2004087732 A2 also starts from the key intermediate tetralone which includes the formation of imine in Polyethylene glycol, reduction of the imine followed by the optical resolution of the obtained Cis/Trans mixture.

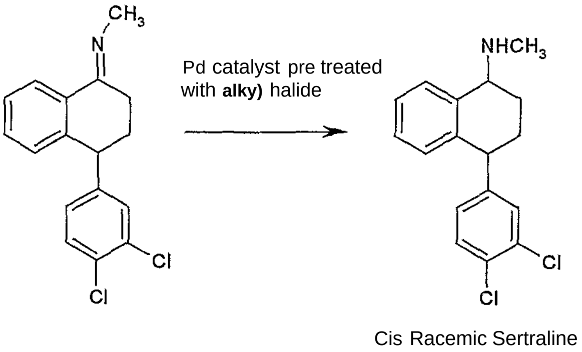
US 6723878 describes a process for the preparation of sertraline hydrochloride which starts from imine intermediate and involves reduction in the presence of a Palladium or Platinum catalyst and a dehalogenation inhibitor and finally optical resolution to give Sertraline.

US 6262308 provides a two step procedure for the preparation of racemic Sertraline hydrochloride starting with the key intermediate Tetralone and follows Scheme 09



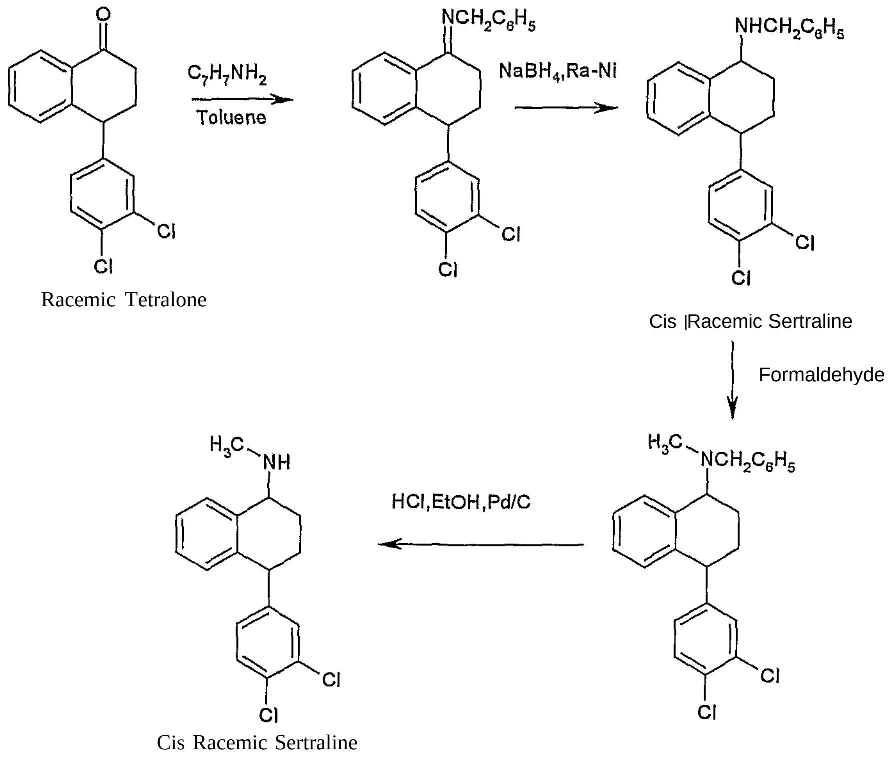
Scheme 09

WO 9957093 A1 describes the preparation of racemic Sertraline hydrochloride from imine intermediate as follows



Scheme 10

5 In another prior art WO 2001030742 A1 a procedure for the preparation of racemic sertraline starting from tetralone is described in scheme 11



Scheme 11

The involved methodology as seen in some of the prior art methods for the preparation of Racemic Sertraline involve drawbacks such as

a) reaction involving higher temperatures,

b) use of Palladium catalyst for imine reduction,

c) increased no of steps involving reduction / deprotection etc. from Tetralone

Polymorphism present in Sertraline Hydrochloride is disclosed in US 5248699 which designates the polymorphic form of Sertraline Hydrochloride obtained as per the product patent US4536518 as Fonn II and gives a rapid crystallization method from solvents such as isopropyl alcohol, ethyl acetate etc. This patent also discusses the preparation of Polymorph I, III, IV and V also.

WO 003255 Al describes the preparation of Sertraline hydrochloride polymorph II from Sertraline Base by dissolving it in acetone and lowering the pH of the solution by addition of Hydrogen chloride solution, such as hydrogen chloride in isopropanol. The patent further describes the recrystallisation of Sertraline hydrochloride using Dimethyl formamide or cyclohexanol.

US 0132828 discloses the preparation of Sertraline Form II wherein the solution of Sertraline free amine in ketonic solvent is seeded with crystals of Form II at room temperature to 55-60 °C and hydrogen chloride solution in water or acetone is added.

WO 01/45692 A1 describes the process for preparing Sertraline hydrochloride foπn II from Sertraline hydrochloride form XTV or XV or form XVI.

WO 031099761 A1 describes the preparation of form II by dissolving the Sertraline base in 2-propanol and precipitating with 1.25 molar excess of 3M 2-propanol hydrochloric acid and Diisopropyl ether. The product is recrystallised using Dimethylformamide.

WO 02/09859A1 disclosed the conversion of Sertraline mandelate into Sertraline base in ethylacetate. Ethylacetate is distilled off and replaced with Isopropanol. The solution of Sertraline base in Isopropanol is reacted with a solution of 12-14 % of Hydrochloric acid in Ethyl acetate at 40-65 °C using the seed crystals of Polymorphic Form II.

WO 03/093217A1 describes the preparation of Form II substantially free of Form I using Sertraline base or Sertraline Mandelate in suitable solvents like n-butanol, cyclohexane, ethylacetate, acetone, hexane, t-butylmethyl ether, Dimethylformamide and mixture there of by contacting the solution or the slurry with a flow of gaseous hydrogen chloride at 30 to 60°C

SUMMARY OF THE INVENTION

The aim of the present invention is consequently to overcome the drawbacks and thus to provide an improved, scalable and efficient manufacturing procedure for the preparation of polymorphic form II of the antidepressant Cis- (lS)-N-Methyl-4-(3,4-Dichlorophenyl)-! ,2,3,4-tetrahydro-l -napthaleneamine hydrochloride (Sertraline Hydrochloride).

Accordingly, the first object of the present invention is to provide an improved, scalable manufacturing procedure for preparing polymorphic form II Sertraline hydro chloride.

It is another object of the present invention to provide an improved, scalable and efficient procedure for preparing polymorphic form II of Sertraline Hydrochloride which are convenient to carry out.

It is another object of the present invention to provide an improved, scalable and efficient procedure for preparing polymorphic form II of Sertraline Hydrochloride in reasonably good yield.

It is another object of the present invention to provide an improved, scalable and efficient procedure for preparing the intermediates involved in the preparation of polymorphic form II of Sertraline Hydrochloride.

It is another object of the present invention to provide an improved, scalable and efficient procedure for preparing the intermediates involved in the preparation of polymorphic form II of Sertraline Hydrochloride which are convenient to carry out.

It is another object of the present invention to provide an improved, scalable and efficient procedure for preparing the intermediates involved in the preparation of polymorphic form II of Sertraline Hydrochloride in reasonably good yield.

It is another object of the present invention to provide novel processes for some of the key intermediates involved in the preparation of polymorphic form II of Sertraline Hydrochloride.

It is another object of the present invention to provide novel isolation procedures for some of the intermediates involved in the preparation of polymorphic form II of Sertraline hydrochloride.

It is another object of the present invention to provide an improved, scalable and efficient procedure for the preparation of polymorphic form II of Cis- (1S)-N-Methyl-

4-(3,4-Dichlorophenyl)-l,2,3,4-tetrahydro-l-napmaleneamine hydrochloride that is Sertraline Hydrochloride.

It is another object of the present invention to provide an improved, scalable and efficient procedure for the preparation of polymorphic form II bf Cis- (lS)-N-Methyl-4-(3,4-Dichlorophenyl)-l,2,3,4-tetrahydro-l-napthaleneamine hydrochloride that is Sertraline Hydrochloride which is convenient to carry out.

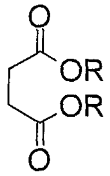
It is another object of the present invention to provide an improved, scalable and efficient procedure for the preparation of polymorphic form II of Cis- (lS)-N-Methyl-4-(3,4-Dichlorophenyl)-l,2,3,4-tetrahydro-l-napthaleneamine hydrochloride that is Sertraline Hydrochloride in reasonably good yield.

These and other objects, which will be apparent during the following detailed description, have been achieved by the inventor's.

Thus, in a first embodiment the present invention provides an improved, scalable and efficient procedure for the preparation of polymorphic form II of Cis- (lS)-N-Methyl-4-(3,4-Dichlorophenyl)-l,2,3,4-tetrahydro-l-napthaleneamine (Sertraline Hydrochloride), said process comprises of ;

(1) reacting benzoyl chloride with orthodichlorobenzene in the presence of a lewis acid without solvent wherein the desired regioisomer 3,4-dichlorobenzophenone is separated from the undesired 2,3-dichlorobenzophenone by treatment of the crude mixture with a solvent chosen from ethyl acetate, isopropyl acetate etc.

(2) reacting 3,4-dichlorobenzophenone so formed in the process of the invention is reacted with Dialkyl succinate of the general formula II



II

Wherein R is hydrogen or C_{1-6} alkyl group, which can be substituted, in an alcoholic solvent in the presence of a strong base preferably chosen from metal alkali hydride wherein the product is isolated in a simplified procedure.

(3) decarboxylation Stobbe product so formed in the presence of aqueous hydrobromic acid at a temperature ranging from 115-120 ^{0}C for 28.0-30.0 hours wherein the product is isolated either by direct precipitation of the product from the reaction mixture by the addition of water or by simple extraction work up in a yield ranging from 88-95%.

(4) reduction of the decarboxylated product with palladium carbon as a catalyst.

(5) cyclization of 4-(3,4-Dichlorophenyl)-3,4—dihydro-l-(2H)-napthalenone with Sulpuric acid with or without solvent or with a mixture of Triflouroacetic anhydride and Boron triflouride Etherate with or without solvent at temperature ranging from room temperature to reflux temperature of the used solvent wherein the cyclized product is isolated in more than 85% yield.

(6) conversion of the so formed 4-(3,4-Dichlorophenyl)-3,4-dihydro-l-(2H)-napthalenone to Cis/Trans-N-methyl-4-(3,4-dichlorophenyl)- 1,2,3,4-tetrahydro-1-napthalenamine by first converting the tetralone intermediate to the imine intermediate by reacting it with Methylammonium hydrochloride in the presence of a inorganic base such as Sodium hydroxide, Potassium hydroxide etc in an alcoholic solvent followed by its insitu reduction with sodiumborhydride.

(7) conversion of Cis/Trans-N-methyl-4-(3,4-dichlorophenyl)-l,2 ,3,4-tetrahydro-l-napthalenamine to Cis(lS)(lR)-N-methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetra-hydro-1-napthalenamine hydrochloride in which the Cis/Trans free base is treated with concentrated Hydrochloric acid in an alcoholic solvent and purified from hot alcoholic solvent to furnish the desired compound.

(8) conversion of Cis(lS)(lR)-N-methyl-4-(3 $_5$4-dichlorophenyl)-l,2,3 ;4-tetrahydro-1-napthalenamine hydrochloride to Cis(lS)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-l-napthalenamine hydrochloride (Sertraline Hydrochloride) of the desired polymorph Form II via a simple displacement of Mandelic acid

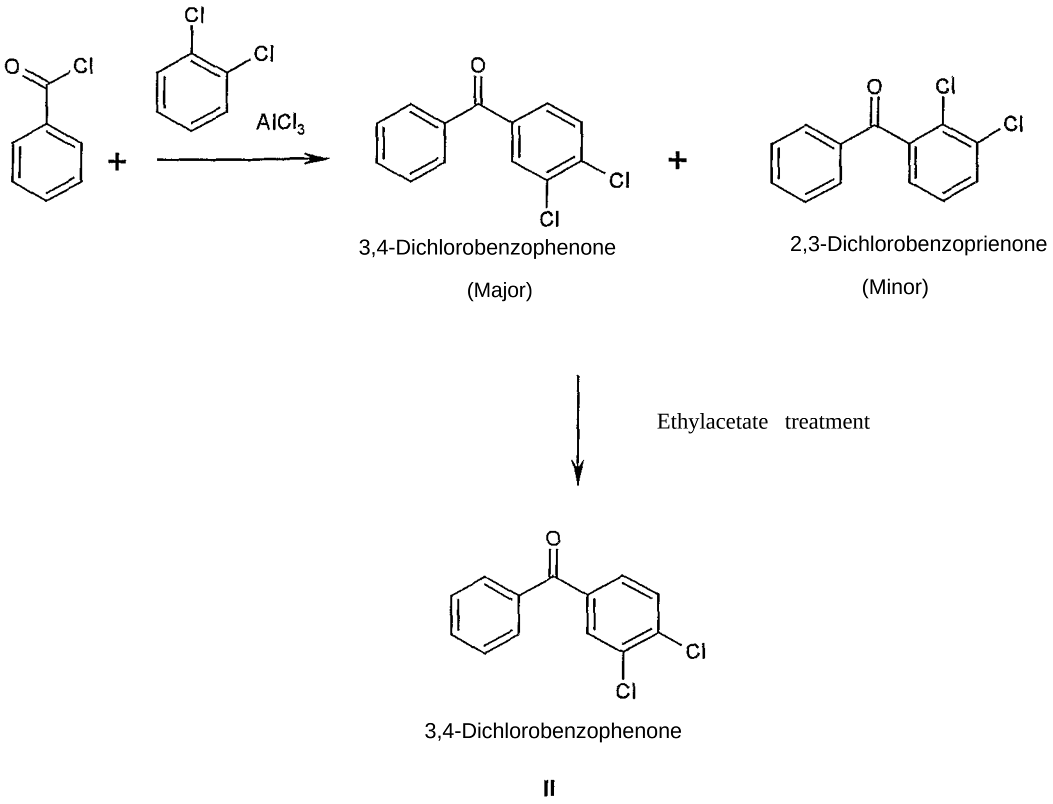
part of Cis(lS)-N-methyl-4-(3 $_5$4-dichlorophenyl)-l,2,3,4-tetrahydro-l-napthalenamine mandelate with Concentrated Hydrochloric acid followed by precipitation with or without seeding of the desired polymorph II in acetonitrile.

DESCRIPTION OF FIGURES

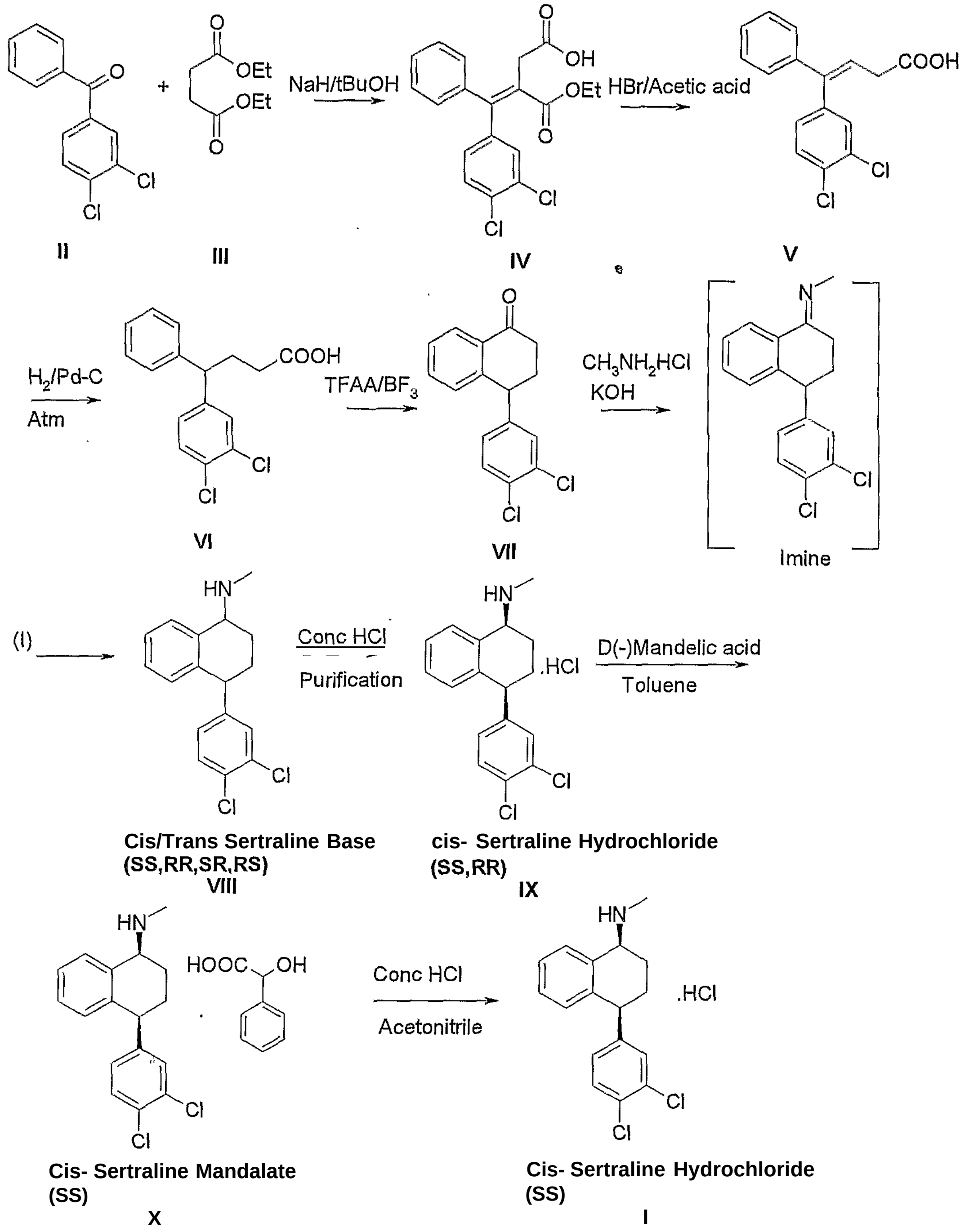
Figure 1 shows the XRPD of Sertraline Hydrochloride Form-II prepared using the process of the invention

DETAILED DESCRIPTION OF THE INVENTION

The process of this invention is illustrated in the scheme 12 and described below.



Scheme 12



Scheme 12 contd

In accordance with the process of this invention the first step involves a neat reaction of benzoyl chloride with orthodichlorobenzene in the presence of a lewis acid such as Aluminium trichloride, Boron triflouride etc without solvent wherein the desired regioisomer 3,4-dichlorobenzophenone is separated from the undesired 2,3-dichlorobenzophenone by treatment of the crude mixture with a solvent choosen from ethyl acetate, n-propyl acetate, tertiarybutyl actetate etc. The desired regioisomer is isolated in a reasonable yield.

The next step is a base catalyzed Stobbe condensation of the so prepared 3,4-dichlorobenzophenone with diethylsuccinate or dimethyl succinate in an alcoholic solvent. The base is a suitable metal alkali hydride e.g. Sodium Hydride, Potassium hydride etc. The reaction time for Stobbe condensation is preferably between 2 to 5 hours. The isolation procedure involves removal of solvent followed by extractive work up and provides Stobbe product in good yield.

The next step is a hydrolysis and decarboxylation in the presence of aqueous hydrobromic acid at a temperature ranging from 115-120 ^{0}C for 28.0-30.0 hours wherein the product is preferably isolated either by direct precipitation of the product from the reaction mixture by the addition of excess water or by simple extraction work up in a yield ranging from 88-95%.

The next step is reduction of the decarboxylated product by known means which is C3'clized to 4-(3,4-Dichlorophenyl)-3,4-diliydro-l-(2H)-napthalenone preferably with Sulpuric acid with or without solvent or with a mixture of Trilïouroacetic anhydride and Boron triflouride Etherate with or without solvent at temperature ranging from room temperature to reflux temperature of the used solvent wherein the cyclized product is isolated in more than 85% yield.

The next step of the process involves the conversion of the so formed 4-(3,4-Dichlorophenyl)-3,4-dihydro-1 -(2H)-napthalenone to Cis/Trans-N-methyl-4-(3,4-dichlorophenyl)-l,2.3,4-tet τahydro-l-napthalenamine by first converting the tetralone intermediate to the imine intermediate by reacting it with Methylammonium hydrochloride in the presence of a inorganic base such as Sodium hydroxide, Potassium hydroxide etc in an alcoholic solvent followed by its in situ reduction with sodiumhorhydride or Pd/C. Most preferably this reaction is performed with 1.5 equivalent to 2.5 equivalent of Methylammonium hydrochloride. The most preferable base used is Potassium hydroxide. Preferable reaction temperature lie between 25 to 50^{0}C.

The next step involves the conversion of Cis/Trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-l-napthalenamine to Cis(lS)(lR)-N-methyl-4-(3,4-dichloropheny I)-1,2,3,44etrahydro-l -napthalenamine hydrochloride in which the obtained Cis/Trans free base is treated with 35% Hydrochloric acid (aqueous) in an alcoholic solvent choosen from Methanol, ethanol, propanol etc and purified from hot alcohol chosen from methanol, ethanol and propanol solvent treatment to furnish the desired Cis intermediate.

The next step involves the conversion of Cis(lS)(lR)-N-methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro-l-napthalenamine hydrochloride to polymorphic form II Cis(l S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro- 1-napthalenamine hydrochloride (Sertraline Hydrochloride) via a simple displacement of Mandelic acid part of Cis(lS)-N-methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro-l-napthalenamine mandelate with Concentrated Hydrochloric acid. In this step Cis(l S)-N-methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro-l-napthalenamine mandelate is prepared in a solvent chosen from the likes of Toluene, Xylene etc most preferably in Toluene at a Temperature ranging from 60^{0}C temperature to reflux temperature preferably at reflux temperature of the used solvent. The next step involves the insitu displacement of mandelate intermediate with Concentrated Hydrochloric acid in aqueous medium or water miscible solvent such as any solvent chosen from acetonitrile, methanol, ethanol etc at a temperature ranging from 0^{0}C to reflux temperature of the chosen reaction medium followed by precipitation of polymorphic form II Sertraline hydrochloride with or without seeding of the desired polymorph form II.

Thus the present invention provides an improved manufacturing procedure for the production of polymorphic form II Cis(lS)-N-methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro-1-napthalenamine hydrochloride or Sertraline Hydrochloride which overcomes the drawbacks of the earlier methods.

The present invention thus provides a procedure to isolate the desired key raw material 3,4-dichlorobenzophenone in a cheaper and efficient way. It also provides reduced reaction time , better methods for the isolation and provides novel methodology for the preparation of some of the intermediates involved in the preparation of polymorphic form II of Sertraline hydrochloride. The process of the invention also eliminates the use of hazardous and expensive Monomelhylamine gas and reagents such as Titanium tetrachloride which helps in reducing the effluent burden occurring due to the side products such as titanium dioxide.

The XRPD spectrum of Sertraline Hydrochloride of the present invention matches with the authentic Form II material and the characterization data on Sertraline hydrochloride Form II is disclosed in US 5248699

The following examples illustrates, but do not limit in scope the novel improved process of this invention

EXAMPLE 1

Preparation of 3,4-Dichlorobenzophenone

To a stirred solution of benzoyl chloride (500 ml, 4.3 mol) in 1,2-dichlorobenzene (486 ml, 4.3 mol) anhydrous Aluminiumtrichloride (862.0 g, 6.46 mol) was added in lots between 25-30^{0}C. After the addition was complete the reaction mixture was heated to 115-120^{0}C maintained at this temperature for ~4.0 hours. Then the hot reaction mixture was quenched into ice water mixture (3200 ml) under stirring. The resulting mixture was then stirred at 25-30^{0}C for 12-13 hours. After which concentrated hydrochloric acid (2200 ml) was added. Resulting clear solution was then extracted with Dichloromethane (2500 ml) . The obtained Dichloromethane layer after separation was washed twice with water (4000.0 ml), dried over sodium sulphate and concentrated under vacuum to give a crude residue. The crude residue was treated with Ethylacetate (1000.0 ml) the resulting slurry was stirred for 15-20 minutes. The solid was then filtered and dried at 50^{0}C under vacuum for 2.0 hours.
Yield: 480.O g (53.7 %)

EXAMPLE 2

Conversion of 3,4-Dichlorobenzophenone to 3-Ethoxycarbonyl-4-(3 $_3$4-dichlorophenyl)-4-phenyl-but-3-enoic acid

3,4-Dichlorobenzophenone (50.0 g, 0.199 mol) followed by diethylsuccinate (42 ml, 0.25 mol) was charged into t-butyl alcohol (200.0 ml) with stirring at 25-30 ^{0}C under nitrogen atmosphere. To the obtained slurry Sodium hydride 60% dispersion in oil (10 g, 0.25 mol) was added slowly in lots. The contents were then heated to 85-90 ^{0}C and were maintained at this temperature for 4.0 hours. Reaction mixture was then concentrated under vacuum. To the obtained residue water (500.0 ml) was added and was washed with a 20% mixture of ethylacetate in Hexane (500.0 ml). The aqueous layer after separation was then acidified with concentrated hydrochloric acid (25 ml) and extracted once with Dichlorornethane (500.0 ml). The Dichloromethane layer was then washed twice with water , dried over sodium sulphate and evaporated under vacuum to a Light Brown oil (74 g, 98% yield).

EXAMPLE 3

Conversion of 3-Ethoxycarbonyl-4-(3,4-dichlorophenyl)-4-phenyl-but-3-enoic acid to 4-(3,4-dichlorophenyl)-4-phenyl-but-3-enoic acid

A suspension of 3-Ethoxycarbonyl-4-(3,4-dichlorophenyl)-4-phenyl-but-3-enoic acid (116g, 0.306 mole) in 1: 1 mixture of 48% Hydrobromic acid and acetic acid (460.0 ml) was stirred between 115-120 ^{0}C for 36 hours. The reaction mixture was then cooled to 25-30 ^{0}C whereupon water (1160.0 ml) was added slowly under stirring. The resulting yellow solid was separated by filtration and washed with hexane (100 ml) and dried under vacuum for a period of 4 hours between 25-30 ^{0}C. Yield: 86g (92% by theory)

EXAMPLE 4

Conversion of 4-(3,4-dichlorophenyl)-4-phenyl-but-3-enoic acid to 4-(3,4-dichlorophenyl)-4-phenyl-butanoic acid

4-(3,4-dichlorophenyl)-4-phenylbut-3-enoic acid (5Og, 0.163 mol.) was charged in ethylacetate (500 ml) and was stirred at 25-30 ^{0}C. To the resulting solution 5% dry Pd/C catalyst (10% w/w) was charged. Then Hydrogen gas was bubbled at

atmospheric pressure through the reaction mixture at 25-30 ^{0}C for 24 hours. The Pd/C catalyst was then filtered off through a bed of celite. The celite bed was washed with ethyl acetate (50 ml). The combined ethyl acetate layer was then evaporated under vacuum to a light yellow oil, which became solid on standing.
Yield: 50 g (99 % by theory)

EXAMPLE 5

Conversion of 4-(3,4-dichlorophenyl)-4-phenyl-butanoic acid to 4-(3,4-dichloro phenyl)-3,4-dihydro- 1-(2H)-napthalenone

A solution of 4-(3,4-dichlorophenyl)-4-phenyl-butanoic acid (25g, 0.081 mol.) in Dichloromethane (150 ml) was treated with trifluoro acetic anhydride (100 ml.0.718 mol.). To the resulting solution, BF_3-etherate (25 ml, 0.1987 mol.) was added dropwise under stirring. After addition was complete the reaction mixture was heated at 40-45 ^{0}C for 5 hours. Reaction mixture was then concentrated under vacuum to a residue (3Og). The obtained residue was swapped twice with dichloromethane (250ml) under vacuum at temperature 30-35 ^{0}C. The resulting residue was then recrystallized from methanol (50ml) and the obtained solid was dried under vacuum 60-65 ^{0}C for 2 hours.
Yield: 22g(93% by theory)

EXAMPLE 6

Conversion of 4-(3,4-dichlorophenyl)-4-phenyl-butanoic acid to 4-(3,4-dichlorophenyl)-3,4-dihydro- 1-(2H)-napthalenone

To a solution of 4-(3,4-ch'chlorophenyl)-4-phenyl-butanoic acid (5Og, 0.1618 mol.) in benzene (500 ml), cone. sulfuric acid (100 ml) was added with stirring at 23-28 ^{0}C . The reaction mixture was then heated and maintained at 78-80 ^{0}C for 8 hours. Then solvent was distilled off from the reaction mixture under reduced pressure to dryness. To the obtained residue process water.(200 ml) and 20% Sodium hydroxide (800ml) was added. This aqueous solution was then extracted twice with dichloromethane (500 ml). The combined dichloromethane extract was then evaporated under vacuum at 23-28 ^{0}C. The resulting crude product was then recrystallized from methanol (50 ml). The Solid was dried under vacuum 60-65 ^{0}C for 2 hours.

Yield: 3Og (65% by theory)

EXAMPLE 7

Preparation of Cis (lS)(lR)-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3 ,4-teraliydro-l-(2H)-napthalenamine Hydrochloride

a) Cis/Trans-N-Methyl-4-(3,4-dichlorophenyl)-l,2 ,3,4-terahydro-l-(2H)-napthalenamine.

To a solution of 4-(3,4-dicblorophenyl)-3,4-dihydro-l-(2H)naphthalenone (25Og, 0.859 mol.) in methanol (2500 ml), methylamine hydrochloride (116g, 1.718 mol.) followed by KOH pellets (142g$_5$ 2.15 mol.) was added at 25-30 ^{0}C. The resulting slurry was then stirred at 25-30 ^{0}C for 24 hours. The reaction mixture was then cooled between - 5 to 0^{0}C after which sodium borohydride (28g, 0.74 mol.) was charged in 3 lots in ~2 hours at the same temperature. The reaction mixture was then stirred for 10-12 hours at 20-25°C.Then the reaction mixture was concentrated under vacuum to an oily residue. To the residue water (1250 ml) was charged and was extracted with dichloromethane (1250 ml). Dichloromethane layer was then separated , dried over anhydrous sodium sulphate and was concentrated under vacuum. at 30-35 ^{0}C to yield a light yellow oil.

Yield: 25Og (95.0 % by theory)

b) Cis(l S)(l R)-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3,4-terahydro-l-(2H)-napthalenamine Hydrochloride

Cis/Trans-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3,4-terahydro-l-(2H)-napthalenamine (25Og, 0.817 mole) was dissolved in methanol (1350 ml) and cooled between 0 to 5^{0}CTo the clear reaction mixture cone. HCl (250ml) was charged drop wise in. ~ 1 hour while maintaining the temperature between 0- 10^{0}C. The resulting white slurry was stirred for 1.0 hour at 0- 10^{0}C . The precipitated solid was then filtered on buchner funnel and suck dried. This crude product was slurry washed with methanol (1350 ml) at 60-65 ^{0}C for 1 hour and the solid was filtered off and suck dried.

Yield: HOg (79.0 % Based on the available Cis(l S)(IR) N-Methyl-4-(3,4-dichlorophenyl)-! ,2,3,4-terahydro-l -(2H)-napthalenamine)

EXAMPLE 8

Preparation of Cis(lS)(4S)-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3,4-terahydro-l-(2H)-napthalenamine mandelate

Cis(lS)(lR)-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3,4-teraliydro-l-(2H)-napthalenamine Hydrochloride (75 g, 0.219 mol) followed by Toluene (270 ml) was charged to a solution of Sodium hydroxide (18 g, 0.45 mol) in water (310 ml) at 25-30^{0}C. The reaction mixture was heated between 83-88^{0}C for 60 minutes and then cooled to 30-35^{0}C. Then the Toluene layer was separated and washed thrice with water (300 ml). The final toluene layer was diluted with extra toluene (480 ml) and D(-)-Mandelic acid (18.3g, 0.120 mol) was charged to it at 25-30^{0}C. The resulting reaction mass was then stirred at 100-110^{0}C till the reaction mixture became clear. The clear solution was then cooled to 30-35^{0}C and the precipitated solid was then filtered, washed thrice with Toluene (75 ml) and dried at 75-80^{0}C for 5-6 Hours.

Yield : 40.0 g (80.0 % based on the desired isomer)

EXAMPLE 9

Conversion Cis(l S)(4S)-N-Methyl-4-(3,4-dichlorophenyl)-I ,2,3,4-terahydro-l -(2H)-napthalenamine mandelate to polymorphic form II of Cis (lS)(4S)-N-Mefhyl-4-(3,4-dichlorophenyl)-l ,2,3.4-terahydro-l -(2H)-napthalenamine Hydrochloride

Cis(lS)(4S)-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3,4-terahydro-l-(2H)-napthalenamine mandelate (10.0g, 0.0218 mol) in Acetonitrile (100.0 ml) was cooled to 10-15^{0}C and 1.0 g of Sertraline hydrochloride Form II seed was added. Then 15% Hydrochloric acid solution in acetonitrile (25.0 ml) was added gradually and the reaction mixture was then stirred at 0-5^{0}C for 1.0 hours .The resulting precipitate was then filtered, washed twice with Acetonitrile (10.0 ml) and then dried at 70-75^{0}C under vacuum to give the desired Sertraline hydrochloride Polymorphic form II.

Yield: 6.2 g (82.6%)

EXAMPLE 10

Conversion Cis(l S)(4S)-N-Methyl-4-(3,4-dichlorophenyl)-l ,2,3,4-terahydro-l -(2H)-napthalenamine mandelate to polymorphic form II of Cis (lS)(4S)-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3,4-terahydro-l-(2H)-napthalenamine Hydrochloride

Cis(lS)(4S)-N-Methyl-4-(3,4-dichlorophenyl)-l,2,3,4-teraliydro-l-(2H)-napthalenamine mandelate (10.0g, 0.0218 mol) in Acetonitrile (100.0 ml) was cooled to 10-15^{0}C and 1.0 g of Sertraline hydrochloride Form II seed was added. Then 35% aqueous Hydrochloric acid (5.0 ml) was added gradually and the reaction mixture was then stirred at 0-5^{0}C for 30.0 minute .The resulting precipitate was then filtered, washed twice with Acetonitrile (10.0 ml) and then dried at 70-75^{0}C under vacuum to give the desired Sertraline hydrochloride Polymorphic form II.
Yield: 6.57 g (86.6%)

WE CLAIM

1. An improved manufacturing procedure for the preparation of polymorphic Form II of Cis(l S)(4S)-N-Methyl-4-(3,4-dichlorophenyl)-l ,2,3,4-terahydro-l ~(2H)-napthalenamine Hydrochloride or Sertraline hydrochloride which comprises the following steps
   a) a neat reaction of molar equivalents of benzoyl chloride and orthodichloro benzene in the presence of a lewis acid such as Aluminium trichloride or Boron triflouride to form 3,4-dichlorobenzophenone in a reasonable yield.

   b) reacting 3,4-dichlorobenzophenone with dialkyl succinate most preferably with diethylsuccinate in an alcoholic solvent chosen from methanol, ethanol, propanol and tertiary butanol in the presence of a suitable metal alkali hydride chosen from Sodium Hydride and potassium hydride to give 3-Ethoxyoxycarbonyl-4-(3,4-dichlorophenyl)-4-phenyl-but-3-enoic acid in a reasonably good yield.

   c) hydrolysis and decarboxylation of 3-Ethoxyoxycarbonyl-4-(3,4-dichlorophenyl)-4-phenyl-but-3-enoic acid in the presence of aqueous hydrobromic acid at a temperature ranging from 115-120^{0}C for 28.0-30.0 hours wherein the product is preferably isolated either by direct precipitation of the product from the reaction mixture by the addition of excess water or by simple extraction work up in a yield ranging from 88-95%.

   d) reduction of the decarboxylated product by known means which is then cyclized to 4-(3,4-Dichlorophenyl)-3,4-dihydro-l-(2H)-napthalenone preferably with Sulphuric acid with or without solvent or with a mixture of Triflouroacetic anhydride and Boron triflouride Etherate with or without solvent at temperature ranging from room temperature to reflux temperature of the used solvent wherein the cyclized product is isolated in more than 85% yield.

   e) conversion of 4-(3,4-Dichlorophenyl)-3,4-dihydro-l-(2H)-napthalenone to Cis/Trans-N-methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro-l-napthaleneamine by first converting the tetralone intermediate to the imine intermediate by reacting it with Methylammonium hydrochloride in the presence of a inorganic base such as Sodium hydroxide, Potassium hydroxide etc in an alcoholic solvent followed by its in situ reduction with sodiumborhydride or Pd/C.

f) conversion of Cis/Trais-N-methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro-1-napthalenamine to Cis(l S)(I R)-N-methyl-4-(3,4-dichlorophenyl)- 1,2,3,4-tetrahydro-1-napthalenamine hydrochloride in which the obtained Cis/Trans free base is treated with 35% Hydrochloric acid (aqueous) in an alcoholic solvent chosen from Methanol, ethanol or propanol and obtained crude Cis(lS)(lR)-N-methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro-l-napthaienamine hydrochloride with hot methanol to remove the undesired trans isomer.

g) conversion of the so obtained Cis(lS)(lR)-N-methyl-4-(3,4-dichlorophenyl)-1.2,3,4-tetrahydro-l -napthalenamine hydrochloride to Cis(1S)-N-methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro-l -napthalenamine mandelate.

h) and finally conversion of the so obtained Cis(IS)(I R)-N-methyl-4-(3,4-dichloropheny^-l^^^-tetrahydro-l-napthalenamine mandelate to Cis (IS) -N-tnethyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro- J-napthalenamine hydrochloride of polymorpMc form II.

2. A process as claimed in claim 1, wherein step (a), 3,4-dichlorobenzophenone is prepared by a neat reaction of molar equivalents of benzo}4 chloride and orthodichlorobenzene in the presence of 2.0-2.5 molar equivalents of aluminium trichloride.

3. A process as claimed in claim 1, wherein step (a), the desired 3,4-dichlorobenzophenone is separated from the undesired 2,3-dichlorobenzophenone by treatment of the crude mixture with a solvent chosen from ethylacetate, n-propylacetate etc., most preferably ethylacetate.

4. A process as claimed in claim 1, wherein step (b), Sodium hydride is the preferred base used in the reaction.

5. A process as claimed in claim 1, wherein step (d), the Conversion of 4-(3,4-di cbIorophenyl)-4-phenyl-butanoic acid to 4-(3,4-dichlorophenyl)-3,4-dihydro-l-(2H)-napthalenone is done with a mixture of Triflouro acetic anhydride and Boron triflouride etherate in a suitable halogenated solvent such as Dichloromethane, Chloroform most preferably Dichloromethane.

6. A process as claimed in claim 1, wherein step (d) 1.0 to 11.0 equivalent of TrifJouroacetic anhydride is used, preferably 1.0 equivalent.

7. A process as claimed in claim 1, wherein step (d), 1.0-1.2 equivalent equivalent of Boron triflouride etherate is used.

8. A process as claimed in claim I, wherein step (d) is carried out at the reflux temperature of the solvent.

9. A process as claimed in claim I, wherein step (e) imine intermediate is prepared by reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-l-(2H)-napthalenone with methylammonium hydrochloride and Potassium hydroxide or Sodium hydroxide in a suitable alcoholic solvent.

10. A process as claimed in claim 9, wherein 2.0 to 2.5 molar equivalent methylammonium hydrochloride is used.

11. A process as claimed in claim 9, wherein 2.0 to 2.5 molar equivalent of potassium hydroxide or sodium hydroxide is used.

12. A process as claimed in claim 13 wherein methanol is the suitable solvent.

13. A process as claimed in claim I, wherein step *(f)*, the desired Qs(IS)(I R)-N-methyl-4-(3,4-dichlorophen3'l)-l ,2,3,4-tetrahydro-l-naptlialenamine bydrochl oride is obtained from the crude mixture by hot methanol treatment.

14. A process as claimed in claim I_3 wherein step (g), Cis(lS)(4S)~N-methyl-4-(3,4-dichlorophenyl)-l,2 ,3,4-tetrahydro-l-napthalenamine Mandelate is prepared in a suitable solvent chosen from Toluene and Xylene at a temperature ranging from 25^{0}C to reflux temperature of the solvent, wherein Toluene is the preferred solvent.

15. A process as claimed in claim 14, wherein the reaction is carried out between 65 to reflux temperature of the solvent used, preferably at reflux temperature of the solvent used.

16. A process as claimed in claim 1, wherein step (h), Cis(lS)-N-methyl-4-(3,4-dichlorophenyl)-l,2,3,4-tetrahydro-l-napthalenamine hydrochloride of Polymorphic form II is prepared via a simple displacement of Mandelic acid part of Cis(l S)-N-methyl-4-(3,4-dichlorophenyl)-l 2,3,4-tetrahydro-l-napthalenamine mandelate with Concentrated Hydrochloric acid using Acetonitrile as solvent.

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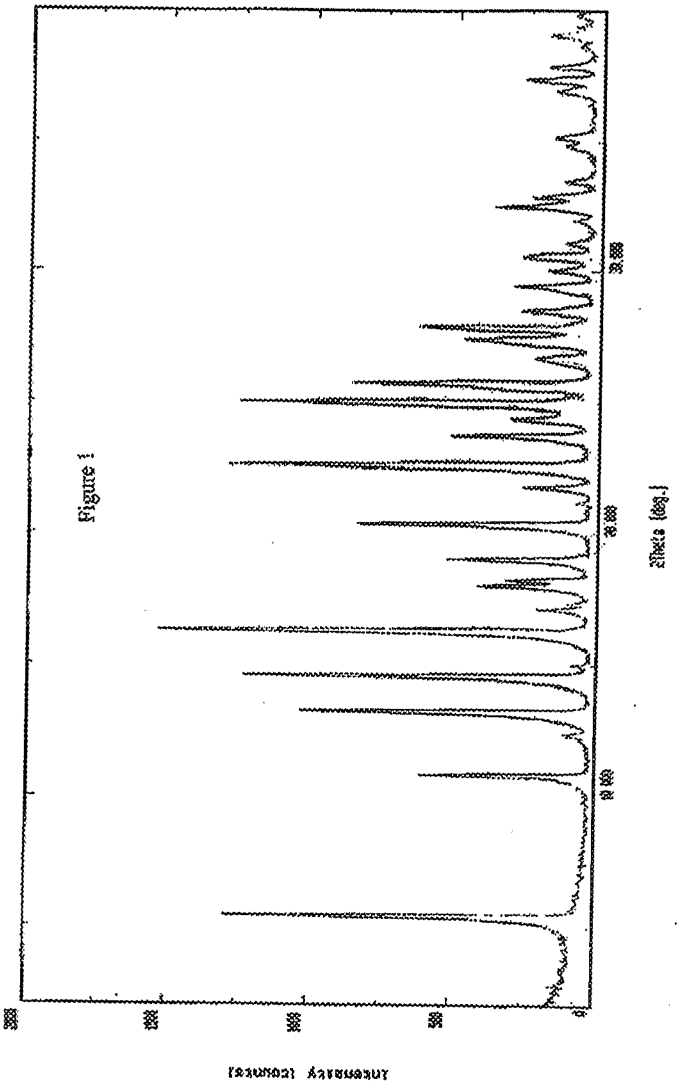

Figure 1