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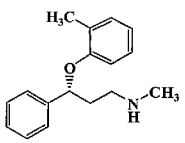

(I)

(57) Abstract: The present invention relates to a process for the preparation of highly pure atomoxetine of formula (I) and pharmaceutically acceptable salts thereof Formula (I) The present invention also aims at novel processes for the preparation and purification of intermediates involved in the process of the present invention.

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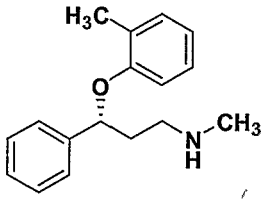
AN IMPROVED PROCESS FOR SYNTHESIZING HIGHLY PURE ATOMOXETINE

FIELD OF THE INVENTION

The present invention relates to an improved process for synthesizing highly pure atomoxetine of formula I and pharmaceutically acceptable salts thereof.

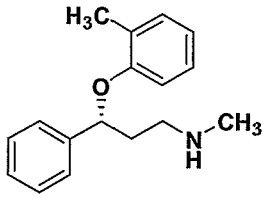


Formula I

The present invention also aims at novel processes for the preparation and purification of intermediates involved in the process of the present invention.

BACKGROUND OF THE INVENTION

Atomoxetine of formula I marketed under the name STRATTERA® in the form of its hydrochloride salt and chemically known as (i?)-7V-methyl-3-(o-tolyloxy)-3-phenylpropylamine is the first non-stimulant drug approved for the treatment of attention-deficit hyperactivity disorder (ADHD).

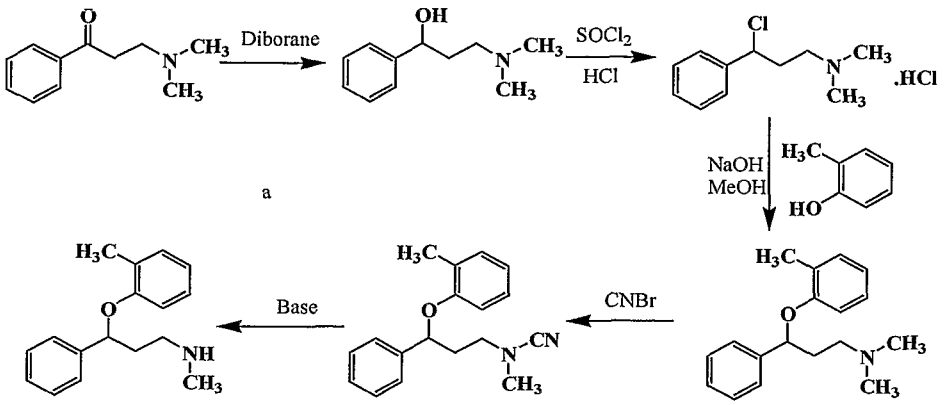


Formula I

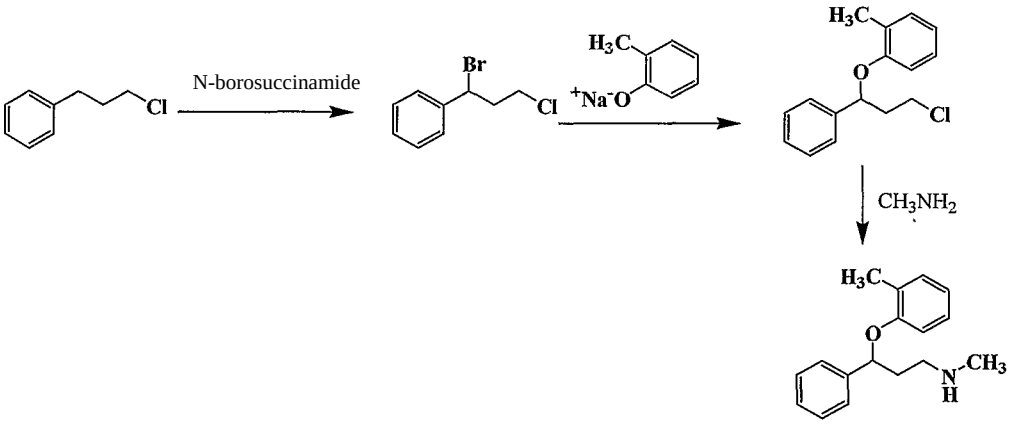
Atomoxetine, the (/?)-(-) enantiomer of tomoxetine, is an aryloxyphenylpropylamine and is a selective norepinephrine reuptake inhibitor. It is about twice as effective as the racemic mixture and about nine times more effective than the (+)-enantiomer and, moreover, exhibits less anticholinergic side effects, as disclosed in U.S. Patent No. 4,018,895, EP O 052 492, and EP 0 721 777.

U.S. Patent No. 4,314,081 discloses tomoxetine, the racemic analogue of atomoxetine. This patent discloses the process for synthesizing tomoxetine and related compounds in two different ways, which are incorporated herein for reference. According to one of the processes, tomoxetine is prepared by reducing β-dimethylaminopropiophenone produced by the Mannich reaction to the corresponding hydroxyl derivative using diborane. Further the hydroxyl

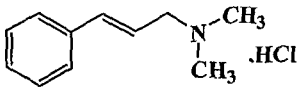
derivative is chlorinated using dry hydrogen chloride and thionyl chloride in the presence of chloroform followed by condensation with ortho-cresol in the presence of methanol and equimolar sodium hydroxide. This reaction is carried out in methanol at reflux temperature for duration of five days. This is followed by demethylation with cyanogen bromide and hydrolysis to give tomoxetine. The scheme can be outlined as follows:



Other process involves the preparation of the tomoxetine by the bromination of 3-phenyl chloropropylamine by N-bromosuccinimide followed by condensation with sodium salt of ortho-cresol to give an intermediate which is then subjected to amination using methylamine to form tomoxetine. The scheme can be outlined as follows:

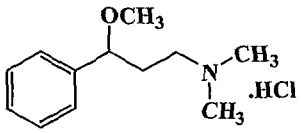


The processes disclosed above suffers from several drawbacks like use of costly reagent such as diborane, toxic and corrosive reagent like cyanogen bromide and N-bromosuccinimide which make the processes not viable for use on commercial scale. It has been observed that chlorination of hydroxyl derivative to the corresponding chloro derivative by using the above specified harsh acidic conditions causes the acid catalysed elimination of water from the hydroxyl derivative and yields the olefmic impurity of formula A as a by-product in more than 30%, thus reducing the overall yield and purity of the final product.



Formula A

Further recrystallization of the chloro intermediate with acetone as reported therein does not remove the impurity below acceptable limits. Also the condensation of chloro derivative with ortho-cresol is performed in the presence of methanol and equimolar sodium hydroxide which takes five days for reaction completion and is thus a time consuming process. In our hands we have found that the reaction does not goes to completion even in five days or more and presence of methanol and strong base such as sodium hydroxide results in the formation of methoxy derivative of formula B in more than 30% yield, thus further reducing the overall yield and affecting the purity of the final product.



Formula B

E.P. Patent No. 0 052 492 discloses (-)-enantiomer of tomoxetine i.e. atomoxetine and process for the preparation thereof wherein tomoxetine is prepared by demethylating *N,N*-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine by reaction with phenyl chloroformate in the presence of toluene to form carbamate intermediate and hydrolyzing the intermediate with sodium hydroxide in the presence of propylene glycol to form tomoxetine. Tomoxetine is then resolved using (S)-(+)-mandelic acid and resulting atomoxetine is treated with hydrogen chloride gas to afford atomoxetine hydrochloride. Atomoxetine hydrochloride is then recrystallized from ethyl acetate, dichloromethane and diethyl ether. The patent teaches the use of propylene glycol which is a costly reagent, hence not recommended on industrial scale.

U.S. Patent No. 4,868,344 discloses the use of Mitsunobu reaction for the synthesis of atomoxetine by condensing (*S*)-1-chloro-3-phenyl-3-propanol with ortho-cresol in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) followed by reaction with methylamine and ethanol. The patent teaches the use of triphenylphosphine and DEAD which needs special handling and results in the formation of a large number of by-products like phosphine oxide and hydrazine derivatives, which are difficult to remove. Also phosphine containing waste is a big problem and is thus not recommended on a large scale. In addition to this, DEAD is an expensive and highly carcinogenic reagent.

Above drawbacks call the need for an improved process of preparing atomoxetine and pharmaceutically acceptable salts thereof, which will be suitable for large-scale preparation, in terms of simplicity, cost effectiveness and purity of the product. Additionally, in order to achieve

high efficiency of reaction for industrial scale synthesis of atomoxetine and pharmaceutically acceptable salts thereof, it is necessary to minimize the process related impurities, and obtain the product in high purity to comply with the requirements of Pharmacopoeias.

OBJECT OF THE INVENTION

The principal object of the present invention is to provide improved, low cost and simple process for preparing atomoxetine and pharmaceutically acceptable salts thereof, unique with respect to its simplicity, scalability and low processing time.

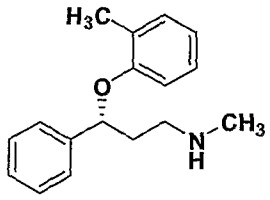
One another object of the present invention is to provide a process for the preparation of highly pure atomoxetine, wherein the formation of impurity of formula A is minimized by using suitable acid scavenger during chlorination of hydroxyl derivative.

One another object of the present invention is to provide a process for the preparation of highly pure atomoxetine, wherein the formation of impurity of formula B is avoided by making use of inert solvent during condensation reaction.

Yet one another object of the present invention is to provide a novel process for the preparation and purification of intermediates involved in the process of the present invention.

SUMMARY OF THE INVENTION

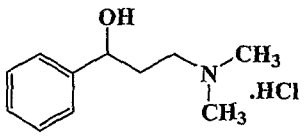
Accordingly, the present invention provides an improved and industrially advantageous process for the preparation of atomoxetine of formula **I** and pharmaceutically acceptable salts thereof,



Formula I

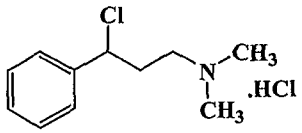
which comprises:

a. reacting *N,*iV-dimethyl 3-phenyl-3-hydroxypropylamine hydrochloride of formula II



Formula II

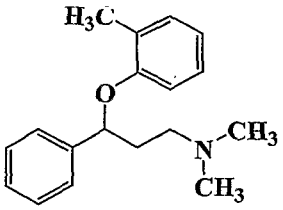
with thionyl chloride in the presence of a suitable acid scavenger to form *N,*iV-dimethyl 3-phenyl-3-chloropropylamine hydrochloride of formula III;



Formula III

b. optionally purifying iST.JV-dimethyl 3-phenyl-3-chloropropylamine hydrochloride with a suitable organic solvent;

c. condensing AζV-dimethyl 3-phenyl-3-chloropro ρylamine hydrochloride with ortho-cresol in the presence of a base in suitable inert solvent to form *N,N-άimeihyl* 3-(o-tolyloxy)-3-phenylpropylamine of formula IV;



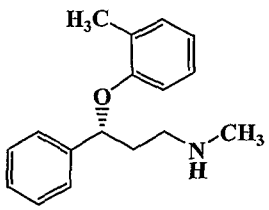
Formula IV

d. converting JV.iV-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine to atomoxetine of formula **I** and pharmaceutically acceptable salts thereof.

The present invention further provides novel processes for the purification of intermediates involved in the process of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an improved process for the preparation of highly pure atomoxetine of formula **I** and pharmaceutically acceptable salts thereof starting from ***N,N***-dimethyl 3-phenyl-3-hydroxypropylamine or acid addition salt thereof.



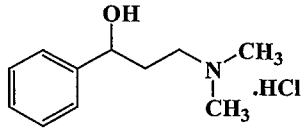
Formula I

N,N-Dimethyl 3-phenyl-3-hydroxypropylamine or acid addition salt thereof used as starting material can be prepared by the methods well known in the art or as described in U.S. Patent Nos. 4,314,081, 5,019,592 etc. Preferably, standard Mannich reaction conditions are .employed to synthesize β-dimethylaminopropiophenone hydrochloride from acetophenone, paraformaldehyde and dimethylamine hydrochloride, which is then reduced with a hydride reducing agent, such as sodium borohydride, employing standard reduction conditions to form

A^iV-dimethyl 3-phenyl-3-hydroxypropylamine. *N,N*-dimethyl 3-phenyl-3-hydroxypropylamine so formed is then converted to its acid addition salt by the methods well known in art.

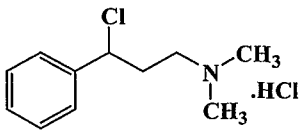
Specifically, ∧*I,N*-dimethyl 3-phenyl-3-hydroxypropylamine can be converted to its hydrochloride salt by contacting it with a solution of hydrogen chloride in a suitable solvent like ethers. Ether can be selected from diisopropyl ether, methyl tertiarybutyl ether and the like. Preferably the ether is diisopropyl ether. The reaction is preferably conducted at a temperature of about less than 5 °C with stirring for a period of about 1-5 hours followed by filtration and isolation of *N,N*-dimethyl 3-phenyl-3-hydroxypropylamine hydrochloride.

One embodiment of the present invention provides an improved and efficient process for preparing atomoxetine of formula I which comprises reacting ∧*I,N*-dimethyl 3-phenyl-3-hydroxypropylamine hydrochloride of formula II,



Formula II

with thionyl chloride in the presence of a suitable acid scavenger to form ∧*I*,iV-dimethyl 3-phenyl-3-chloropropylamine hydrochloride of formula III.



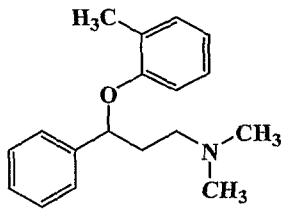
Formula III

Typically, *N,N*-dimethyl 3-phenyl-3-hydroxypropylamine hydrochloride is added to thionyl chloride in the presence of a suitable solvent at a temperature of -10 to -30 °C. Solvent can be selected from, but not limited to toluene, xylene, ethyl benzene, chloroform, dichloromethane, C_1-C_6 ethers, the like and mixtures thereof. The reaction is preferably conducted in the presence of a suitable acid scavenger preferably an orthoester of an organic acid. A suitable acid scavenger is a material that consumes the extra acid present in the reaction mixture to minimize the acid catalysed elimination of water from the compound of formula II and reduces the formation of olefinic impurity of formula A. Orthoester of an organic acid can be selected from the group consisting of triethyl, trimethyl, tripropyl, triisopropyl, tributyl, triisobutyl, and triamyl orthoesters of formic, acetic, oxalic, succinic and adipic acid; preferably triethyl orthoformate, triethyl orthoacetate, and the like and more preferably triethyl orthoformate is used. *N,N*-Dimethyl-3-phenyl-3-chloro ρropylamine hydrochloride of formula III thus formed can be isolated from the reaction mixture by any standard method known in the art such as by filtration,

centrifugation or decantation. Typically, this product is isolated by filtration when any of the solvents within the scope of the process are used. Thus, the present invention is advantageous over prior art processes as it provides *N*,iV-dimethyl 3-ρhenyl-3-chloropropylamine hydrochloride of formula III in better purity having olefmic impurity of formula A less than 1% area by HPLC.

iV,iV-Dimethyl-S-phenyl-S-chloropropylamine hydrochloride of formula III so formed can further be purified by dissolving in a suitable organic solvent, if required with heating, followed by inducing precipitation preferably by cooling the solution to ambient temperature to form highly pure *N*,iV-dimethyl 3-phenyl-3-chloropro ρylamine hydrochloride of formula III having purity greater than 99.5%. The solvent can be selected from nitriles such as acetonitrile, propionitrile, butyronitrile, isobutyronitrile and the like. Preferably acetonitrile is employed.

According to another embodiment of the present invention, ΛζiV-dimethyl 3-phenyl-3-chloropropylamine hydrochloride is condensed with ortho-cresol in the presence of a base in suitable inert solvent to form iV.iV-dimethyl3-(o-tolyloxy)-3-phenylpropylamine of formula IV.



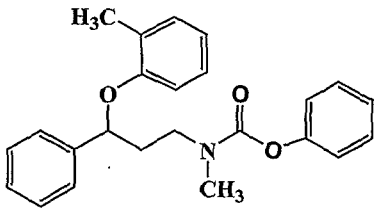
Formula IV

Typically, o-cresol is preferably first treated with a suitable base to convert into a salt, particularly into a metal salt, for example an alkali metal salt such as lithium, sodium or potassium salt. Preferably, the base can be selected from a reagent which forms metal salts such as metal hydride, hydroxide, carbonate, bicarbonate or alcoholate. More preferably, the base can be selected from an alkali metal hydride or amide such as lithium hydride, potassium hydride sodium amide or potassium amide; a metal alcoholate preferably having C_1-C_4 atoms, for example lithium, sodium or potassium methylate, ethylate, tert-butylate, methylate, ethylate; or a metal hydroxide, carbonate or bicarbonate preferably sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium bicarbonate, sodium carbonate and the like. Preferably, sodium hydroxide is employed. The reaction is advantageously effected in the presence of an inert solvent or mixture of solvents. Inert solvent can be selected from hydrocarbons such as hexane, benzene, ethyl benzene, toluene or xylene; ethers such as diethyl ether, diisopropyl ether, methyl tertiarybutyl ether, tetrahydrofuran, dioxane or diethylene glycol dimethyl ether; amides such as dimethylformamide and dimethylsulfoxide, or mixtures thereof. Preferably toluene or a mixture of toluene with other solvents such as dimethylsulfoxide or water is employed.

The condensation reaction is conducted at a temperature of about *50-95 °C,* preferably 70-95 °C and it takes about 2-15 hours for completion of reaction. Thereafter, the reaction mass is cooled followed by the addition of water. The layers are separated and aqueous layer is extracted with suitable organic solvent stated above. All organic extracts are combined, washed with aqueous sodium hydroxide, brine and then with water and dried over sodium sulfate. The solvent is distilled off under vacuum to obtain *N,*JV-dimethyl 3-(o-tolyloxy)-3-phenyl ρropylamine of formula IV.

JV,*N*-Dimethyl 3-(o-tolyloxy)-3-phenylpro ρylamine of formula IV is then converted to atomoxetine of formula I or pharmaceutically acceptable salts thereof by the processes well known in art or as incorporated herein for reference. Preferably, compound of formula IV is demethylated *to* form tomoxetine.

Demethylation of compound of formula IV proceeds through carbamate intermediate, 7V-methyl-[3-(o-tolyloxy)-3-phenylpropyl]-carbamic acid phenyl ester of formula V.



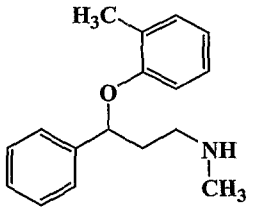
Formula V

Specifically, JV,iV-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine of formula IV is treated with a chloroformate, such as phenyl chloroformate, ethyl chloroformate, trichloroethyl chloroformate and the like in a suitable solvent and optionally in the presence of a base. The base can be selected from triethylamine, pyridine, Λ',iV-diisopropylethylamine, and the like. The solvent can be selected from toluene, xylene, ethyl benzene, dichloromethane, tetrahydrofuran, dimethyl sulfoxide and the like. Particularly the reaction is carried out in anhydrous conditions to achieve better yield and purity. If moisture is detected in the reaction mass, then reaction mass is first azeotropically refluxed till anhydrous conditions before adding chloroformate to the reaction mass. Typically the reaction is carried out at temperatures of from about room temperature to the reflux temperature of the solvent and takes about 1 hour to 24 hours. The carbamate intermediate so formed can be isolated and optionally purified by techniques well known in the art, such as slurry wash or crystallization from a suitable solvent.

According to one another embodiment of the present invention, the carbamate intermediate of formula V is dissolved in a solvent selected from ethereal solvent like isopropyl ether, methyl tertiarybutyl ether, diethyl ether, the like or mixture thereof; if required with heating, followed by

cooling the solution to form a precipitate; and isolating highly pure carbamate intermediate therefrom.

The carbamate intermediate of formula V is then hydrolyzed to give tomoxetine of formula VI.



Formula VI

Typically, the carbamate intermediate is treated with base like alkali metal hydroxide preferably sodium hydroxide or potassium hydroxide in the presence of suitable solvent, such as toluene, xylene, ethyl benzene, water, dimethyl sulfoxide, C_2-C_6 alcohols, the like and suitable mixtures thereof. Typically hydrolysis is carried out at temperatures of from about room temperature to about 100 ^{0}C preferably 80 ^{0}C for a period of about 1 hour to 24 hours. The product can be isolated and purified by techniques well known in the art, such as filtration, evaporation, extraction, crystallization and the like.

Tomoxetine so formed is preferably purified by forming a salt of tomoxetine with an acid followed by converting the salt to free base. Acid can be selected from inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid, and the like, or an organic acid such as glutaric acid, lactic acid, citric acid, malic acid, fumaric acid, oxalic acid, and the like. Preferably tomoxetine is converted to tomoxetine oxalate by reaction with oxalic acid in the presence of suitable solvent like ethyl acetate, water, acetonitrile, tetrahydrofuran and the like. Tomoxetine oxalate is then converted to corresponding free base by treatment with an appropriate base with stirring. Base can preferably be selected from alkali metal carbonates, bicarbonates and hydroxides. Preferably, base is selected from sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide and the like. Tomoxetine so obtained is isolated by extraction with suitable solvent like toluene, isopropyl ether, methyl tertiarybutyl ether and the like, washed with water followed by the removal of the solvent by distillation.

Tomoxetine so obtained by the processes of the present invention can be resolved to optically aetive (i?)-(J-)sfetiaatiomer of tomoxetine, i.e atomoxetine by the methods well known *in* art or as incorporated herein for reference. Typically, the process involves treating tomoxetine with an optically active acid so as to form a mixture of the diastereomeric salts of tomoxetine with optically active acid. The optically active acid can be selected from mandelic acid,

camphorsulfonic acid, camphoric acid, *N*-protected amino acids, maleic acid, tartaric acid, o,o'-dibenzoyltartaric acid, glucuronic acid or ascorbic acid. The preferred one being *(S)-(+)*-mandelic acid. The reaction is performed in the presence of suitable solvent selected from toluene, methyl tertiarybutyl ether, acetonitrile, xylene, ethyl benzene, ethyl acetate, dichloromethane, ethanol, butanol, hexane, the like and a suitable mixture thereof. Preferably the solvent employed is toluene, methyl tertiarybutyl ether, acetonitrile or mixtures thereof.

In another embodiment, the precipitation of mandelate salt can preferably be initiated by seeding with pure (R)-tomoxetine (S)-mandelate salt. Typically, present invention provides an improved process for preparing (R)-tomoxetine (S)-mandelate salt characterized in that a suspension of tomoxetine and (5)-(+)-mandelic acid in a suitable solvent is heated till dissolution, followed by cooling. The reaction mass is then seeded with pure (R)-tomoxetine (S)-mandelate salt and stirred at a suitable temperature in order to effect transformation of tomoxetine into (R)-tomoxetine (S)-mandelate salt in high enantiomeric purity. It has been observed that if the reaction proceeds without seeding, the mandelate salt is contaminated with up to 20% of the corresponding undesired S-enantiomer, thus reducing the yield and purity of the final product.

According to one another embodiment of the invention (R)-tomoxetine (S)-mandelate salt can further be purified by recrystallization with a suitable solvent like acetonitrile, toluene, methyl tertiarybutyl ether or mixtures thereof. If required, the recrystallization step can be repeated several times to obtain the desired purity.

The mandelate. salt so obtained is then converted to atomoxetine free base by treating with a base in the presence of an organic solvent. Base can be selected from metal hydroxides, carbonates and bicarbonates. Preferably aqueous sodium carbonate or potassium carbonate can be employed. Solvent can be selected form methyl tertiarybutyl ether, toluene, isopropyl ether and the like. The reaction is usually performed at a temperature of below 15 °C. The resulting atomoxetine is isolated by extracting it from the aqueous solution with methyl tertiarybutyl ether.

It is usually preferred to isolate atomoxetine in salt form. Such pharmaceutically acceptable salts can be prepared by conventional means, such as by dissolving the base in a suitable solvent and adding a stoichiometric amount of an appropriate acid. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, sulfuric acid, phosphoric acid, oxalic acid, acetic acid, citric acid, formic acid and the like.

Preferably, atomoxetine is converted to the corresponding hydrochloride salt by reacting it with a solution of hydrogen chloride in a suitable solvent like ester, more preferably ethyl acetate at an

appropriate temperature preferably ambient temperature. Atomoxetine hydrochloride is then isolated by conventional procedures well known in art, preferably by filtration. If required the product can further be purified by crystallization with a suitable solvent like acetonitrile.

Although, the following examples illustrate the practice of the present invention in some of its embodiments, the examples should not be construed as limiting the scope of the invention. Other embodiments will be apparent to one skilled in the art from consideration of the specification and examples. It is intended that the specification, including the examples, is considered exemplary only, with the scope and spirit of the invention being indicated by the claims which follow.

EXAMPLES

Example 1: Preparation of β-dimethylaminopropiophenone hydrochloride

A solution of acetophenone (300 g), *N,N*-dimethylamine hydrochloride (256.2 g), paraformaldehyde (110.7g), concentrated hydrochloric acid (12ml) and isopropanol (600ml) was stirred at 80-85 ^{0}C for 5 hours. The solvent was distilled off and reaction mass was cooled to 25-30 °C. To the reaction mass, acetone was added (900ml), cooled to 0-5 °C and further stirred for 1 hour. The solid, thus obtained was filtered, washed with chilled acetone (600ml) and dried to obtain 510.7g (95.7%) of title compound having purity 95.19% by HPLC.

Example 2: Preparation of JV,7V-dimethyl3-phenyl-3-hydroxypropylamine

To a solution of sodium hydroxide (103g) in water (1.5 It), sodium borohydride (43.9g) was added at 25-30 °C with stirring. The reaction mixture was cooled to 0 °C followed by addition of β-dimethylaminopropiophenone hydrochloride (500g). Temperature of reaction mixture was raised to 40-45 °C and maintained for 4 hours. The reaction mixture was then cooled to 0 °C followed by the addition of concentrated hydrochloric acid (471 ml, 30%) with stirring for 30 minutes at 0-5 °C. The reaction mixture was washed with n-hexane, cooled to 0 °C, basified with 40% aqueous sodium hydroxide (pH 10-12) and extracted with isopropylether at 25-35 °C. AU organic extracts were combined, washed with water and solvent was distilled off under vacuum at 50-55 °C to obtain 356g (85%) of title compound having purity 90% by HPLC.

Example 3: Preparation of JV,iV-dimethyl3-phenyl-3-hydroxypropylamine hydrochloride

To a stirred solution of AζJV-dimethyl 3-phenyl-3-hydroxypro ρylamine (25g) and isopropylether (25 ml) at 0 °C, isopropylether-hydrochloride was added and stirred for 1 hour. The solid, thus obtained was filtered and washed with isopropylether (50 ml) to obtain 29.5g of title compound having purity 99% by HPLC.

Example 4: Preparation of 7V,iV-dimethyI3-phenyl-3-chloropropylamine hydrochloride

iV.iV-Dimethyl 3-phenyl-3-hydroxypropylamine hydrochloride (14Og) was added to a solution of toluene (700ml), thionyl chloride (72ml) and triethyl orthoformate (140ml) at -20 to -30 ^{0}C and followed by stirring for 5 hours. The reaction mixture was filtered, washed with chilled toluene and dried to obtain 144g (94.7%) of title compound having purity 97% by HPLC.

Example 5: Purification of iV,*N*-dimethyl 3-phenyl-3-chloropropylamine hydrochloride

N,N-dimethyl 3-phenyl-3-chloropropylamine hydrochloride (7Og, HPLC purity: 97%) in acetonitrile (600 ml) was stirred at 80 °C till complete dissolution. The mixture was cooled to ambient temperature till complete precipitation and filtered to obtain 58.5g of pure title compound having purity 99.68% by HPLC.

Example 6: Preparation of JV,iV-dimethyl3-(o-tolyloxy)-3-phenylpropylamine

Method-A

i\f,7V-Dimethyl 3-phenyl-3-chloropropylamine hydrochloride (1Og) and water (2ml) were added to a stirred suspension of sodium hydroxide (5g), toluene (50ml) and ortho-cresol (6.92g) and further stirred for 7 hours at 85-90 °C. The reaction mixture was cooled and water was added to the mixture. The layers were separated and aqueous layer was extracted with toluene. All organic extracts were combined, washed with 10% sodium hydroxide, brine, then with water and dried over sodium sulfate. The solvent was distilled off to obtain 10.2g (88.9%) of the title compound having purity 90.0% by HPLC.

Method-B

N,iV-Dimethyl 3-phenyl-3-chloropropylamine hydrochloride (1Og) was added to a suspension of sodium hydroxide (5g), dimethyl sulfoxide (50ml) and ortho-cresol (6.9g) and further stirred for 12 hours at 85-90 ^{0}C. Reaction mixture was cooled and water was added to the reaction mass. The layers were separated and aqueous layer was extracted with toluene. All organic extracts were combined, washed with 10% sodium hydroxide, brine, then with water and dried over sodium sulfate. The solvent was distilled off to obtain 9.8g (85.4%) of crude title compound having purity 89.0% by HPLC.

Method-C

N, iV-Dimethyl 3-phenyl-3-chloropropylamine hydrochloride (10 g) was added to a stirred suspension of sodium hydroxide (3.6 g), toluene (36 ml), dimethyl sulfoxide (4.0 ml) and o-

cresol (5.54g) followed by stirring at 85-90 °C for 7 hours. Reaction mixture was cooled and water was added to the mixture. The layers were separated and aqueous layer was extracted with toluene. All organic extracts were combined, washed with 10% sodium hydroxide, brine, then with water and dried over sodium sulfate. The solvent was distilled off to obtain H g (95.97%) crude title compound having purity 93.88% by HPLC.

Example 7: Preparation of iV-methyl-[3-(o-tolyloxy)-3-phenylpropyl]-carbamic **acid** phenyl **ester**

A mixture of *N,N*-dimethyl-(3-phenyl-3-o-tolyloxy-propyl)-amine (5g) and toluene (25ml) was azeotroped followed by the addition of phenylchloroformate (4.36ml) and refluxed for 1 hour with stirring at 25-30 ^{0}C for 16 hours. The reaction mixture was washed with aqueous sodium hydroxide. The layers were separated and aqueous layer was extracted with toluene. All organic extracts were combined and washed IN hydrochloric acid, brine and then with water. The organic extract was dried over sodium sulfate and solvent was distilled off to obtain 5.5g of crude title compound having purity 93% by HPLC. This was stirred in isopropyl ether (25 ml),at 0-5 °C for 1 hour, filtered and washed with isopropyl ether to obtain 4.6g of pure title compound having purity 99% by HPLC.

Example 8: Purification of iV-methyl-[3-(o-tolyloxy)-3-phenylpropyl]-carbamic **acid** phenyl **ester**

N-Methyl-[3-(o-tolyloxy)-3-phenylpropyl]-carbamic acid phenyl ester (5 g, 93% by HPLC) was dissolved in isopropyl ether (20 ml) by heating at 55-60 °C. The reaction mixture was cooled to ambient temperature with stirring for 1 hour. The product was filtered under vacuum to obtain 4.8 g of title compound having purity 99.7% by HPLC.

Example 9: Preparation of tomoxetine

To an azeotroped solution of *N*-Methyl-[3-(o-tolyloxy)-3-phenylpropyl]-carbamic acid phenyl ester (69.7g) and toluene (349 ml) was added potassium hydroxide (41.6 g) at 25-30 °C. The reaction mixture was refluxed for 5 hours and cooled to 25-30 °C. Water (250 ml) was added to the reaction mass and stirred. The layers were separated and aqueous layer was extracted with toluene. AU organic extracts were combined, washed with 10% sodium hydroxide, brine and then with water. The organic extract was dried over sodium sulfate and solvent was distilled off to obtain 43g (91%) of crude title compound having purity 80% by HPLC.

Example 10: Purification of tomoxetine

Step (1) Preparation of tomoxetine oxalate

Tomoxetine (43g) was added to a stirred solution of oxalic acid (21.25g) and ethyl acetate (215ml) and stirred for 1 hour. Precipitated solid was filtered and dried to obtain 35.7 g of title compound.

Step (2) Preparation of tomoxetine

Above prepared oxalate salt was added to aqueous potassium carbonate (21g in 175ml water) and stirred for 1 hour. The mixture was extracted with toluene, washed with water and dried over sodium sulfate. The solvent was distilled off to obtain 23Ag of pure title compound having purity 99.26% by HPLC.

Example 11: Preparation of (R)-tomoxetine (S)-mandelate

Method A:

Step (1): Preparation of crude (R)-tomoxetine (S)-mandelate

To a stirred solution of tomoxetine (20g) in toluene (100ml) and methyl tertiarybutyl ether (100ml), S(+) mandelic acid (5.8g) was added and stirred for 3.5 hours. The solid obtained was filtered, washed with a mixture of toluene and methyl tertiarybutyl ether (20ml, 1:1) and dried to obtain 13g of the title compound (S isomer = 9.8% by HPLC).

Step (2): Purification of crude (R)-tomoxetine (S)-mandelate

To (R)-tomoxetine (S)-mandelate (5g), acetonitrile (50ml) was added and stirred at 75-80 °C till dissolution. The mixture was cooled to ambient temperature till complete precipitation and filtered to obtain 4.2g of pure mandelate salt (S isomer = 1.8% by HPLC). This mandelate salt (4.2g) was further re-crystallized twice from acetonitrile to obtain 3.8 g of mandelate salt (S isomer = 0.03% by HPLC).

Method B:

Step (1): Preparation of crude (R)-tomoxetine (S)-mandelate

A stirred solution of tomoxetine (1.5 g), S(+) mandelic acid (0.48 g) in acetonitrile (8 ml), was heated to 35 °C and crystallization was initiated by seeding with pure (R)-tomoxetine (S)-mandelate at 28 °C. The mixture was stirred for 3 hours and the solid obtained was filtered,

washed with acetonitrile (2ml) and dried to obtain 0.55g of title compound (S isomer = 4.07% by HPLC).

Step (2): Purification of crude (R)-tomoxetine (S)-mandelate

A stirred suspension of above (R)-tomoxetine (S)-mandelate in acetonitrile (2 ml) was heated (75-80 °C) till dissolution. The solution was allowed to cool spontaneously to 75 °C and crystallization was initiated by seeding with pure (R)-tomoxetine (S)-mandelate at this temperature. The suspension was stirred for 3 hours and the solid filtered, washed with acetonitrile (2 ml) and dried to afford 0.3 g of the mandelate salt (S isomer = 0.61% by HPLC). This above mandelate salt was re-crystallized from acetonitrile to obtain 0.2g of pure title compound (S isomer = 0.12% by HPLC).

Method C:

Step (1): Preparation of crude (R)-tomoxetine (S)-mandelate

A stirred suspension of tomoxetine (2g) and S(+)-mandelic acid (0.62g) in toluene (16ml) was heated to 70 ^{0}C till dissolution. The solution was allowed to cool spontaneously to 45 ^{0}C and crystallization was initiated by seeding with pure (R)-tomoxetine (S)-mandelate salt. The reaction mixture was stirred for 3 hours and the solid was filtered, washed with toluene (2 ml) and dried to obtain 1.25g of the title compound (S isomer = 4.69% by HPLC).

Step (2): Purification of crude (R)-tomoxetine (S)-mandelate

A stirred suspension of above (R)-tomoxetine (S)-mandelate in toluene (12.5 ml) was heated (90 °C) to dissolution. The solution was allowed to cool spontaneously to 75 °C and crystallization was initiated by seeding with pure (R)-tomoxetine (S)-mandelate. The suspension was stirred for 3 hours and the solid filtered, washed with toluene (2 ml) and dried to obtain 1.15g of the title compound (S isomer = 0.56% by HPLC). The above mandelate salt was again recrystallized from toluene to obtain l.lg of pure title compound (S isomer = 0.13% by HPLC).

Example 12: Preparation of atomoxetine

To a solution of (R)-tomoxetine (S)-mandelate (9g) in methyl tertiarybutyl ether (45 ml) at 10 ^{0}C, aqueous sodium carbonate solution (3.5g in 20ml water) was added till a pH of 8-10 and followed by stirring for 30 minutes. The layers were separated and aqueous layer was extracted with methyl tertiarybutyl ether. All organic extracts were combined, washed with water and

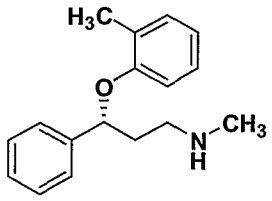
dried over sodium sulfate. The solvent was distilled off to obtain 5.5g of pure title compound having chemical purity 99.8 % and S isomer = 0.04%.by HPLC.

Example 13: Preparation of atomoxetine hydrochloride

To a solution of atomoxetine (5.Og) in ethyl acetate (5ml), ethyl acetate- hydrochloride (8.7ml, 8%) was added and further stirred at 25-30 ^{0}C for 30 minutes. The reaction mass was filtered and washed with ethyl acetate and dried to obtain 5.7g of title compound having a purity of 98% by HPLC. Resulting atomoxetine hydrochloride was crystallized from acetonitrile to obtain 5.2g of title compound having chemical purity 99.90% and S isomer = nil by HPLC.

WE CLAIM

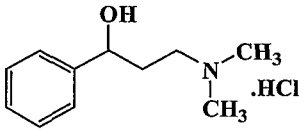
1. A process for the preparation of atomoxetine of formula I, and pharmaceutically acceptable salts thereof,



Formula I

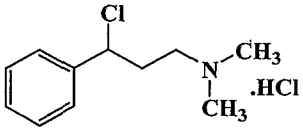
which comprises:

a), reacting *N,N*-dimethyl 3-phenyl-3-hydroxypropylamine hydrochloride of formula II,



Formula II

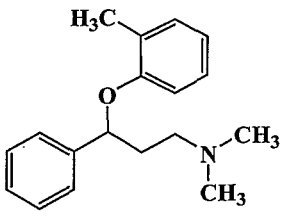
with thionyl chloride in the presence of a suitable acid scavenger to form *N,*iV-dimethyl 3-phenyl-3-chloropropylamine hydrochloride of formula III;



Formula III

b). optionally purifying *N*,vV-dimethyl 3-phenyl-3-chloropropylamine hydrochloride with a suitable solvent;

c). condensing ʌ*I,N*-dimethyl 3-phenyl-3-chloropropylamine hydrochloride with ortho-cresol in the presence of a base in suitable inert solvent to form *N*,iV-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine of formula IV; and



Formula IV

d). converting *N,N*-diṅiethyl 3-(o-tolyloxy)-3-phenylpropylamine to atomoxetine of formula I and pharmaceutically acceptable salts thereof.

2. The process according to claim 1 wherein in step a) a suitable acid scavenger is an orthoester of an organic acid.

3. The process according to claim 2, wherein orthoester of organic acid is selected from the group consisting of triethyl, trimethyl, tripropyl, triisopropyl, tributyl, triisobutyl, and triamyl orthoesters of formic, acetic, oxalic, succinic and adipic acid; preferably triethyl orthoformate.

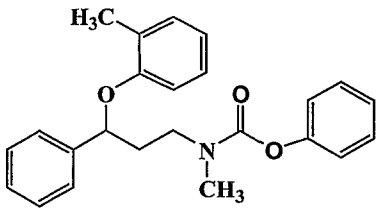
4. The process according to claim 1, wherein in step b) suitable solvent is nitrile solvent.

5. The process according to claim *4*, wherein in nitrile solvent is selected from acetonitrile, propionitrile, butyronitrile, isobutyronitrile and the like or mixture thereof.

6. The process according to claim 1, wherein in step c) inert solvent is selected from toluene or a mixture of toluene with other solvents like dimethylsulfoxide or water.

7. The process according to claim 1, wherein *N,N*-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine of formula IV is converted to atomoxetine of formula I comprising the steps of

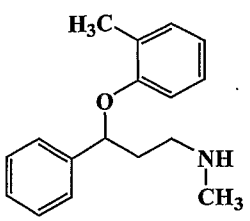
a), reacting *N,N*-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine of formula IV with a chloroformate, such as phenyl chloroformate in a suitable solvent to form iV-methyl-[3-(o-tolyloxy)-3-phenylpropyl]-carbamic acid phenyl ester of formula V;



Formula V

b). optionally purifying *N*-methyl-[3-(o-tolyloxy)-3-phenylpropyl]-carbamic acid phenyl ester of formula V with a suitable solvent;

c). converting *N*-methyl-[3-(o-tolyloxy)-3-phenylpropyl]-carbamic acid phenyl ester of formula V to tomoxetine of formula VI;



Formula VI

d). purifying tomoxetine by forming a salt with an acid;

e). treating the salt formed with a base;

i). resolving tomoxetine by treating with an optically pure (S)-mandelic acid in the presence of a suitable solvent to form (R)-tomoxetine (S)-mandelate salt optionally by seeding with (R)-tomoxetine (S)-mandelate salt;

g). purifying (R)-tomoxetine (S)-mandelate salt with a suitable organic solvent;

h). reacting (R)-tomoxetine (S)-mandelate salt with a suitable base preferably metal carbonate to form atomoxetine of formula I; and

i). converting atomoxetine to the corresponding hydrochloride salt by reacting it with hydrochloric acid or hydrogen chloride in suitable solvent.

8. The process according to claim 7, wherein in step a) suitable solvent is selected from toluene, xylene, dichloromethane, tetrahydrofuran, ethylbenzene, the like and mixtures thereof.

9. The process according to claim 7, wherein in step b) suitable solvent is selected from ethers like diisopropyl ether, methyl tertiarybutyl ether, diethyl ether and the like.

10. The process according to claim 7, wherein step c), iV-methyl-[3-(o-tolyloxy)-3-phenylpropyl]-carbamic acid phenyl ester of formula V is hydrolysed in the presence of a base in a suitable solvent to form tomoxetine.

11. The process according to claim 10, wherein base is selected from alkali metal hydroxide such as sodium hydroxide or potassium hydroxide and the like.

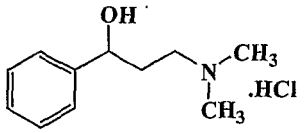
12. The process according to claim 10, wherein suitable solvent is selected from toluene, xylene, ethyl benzene, water, dimethyl sulfoxide, C_{2-6} alcohol and the like or mixture thereof.

13. The process according to claim 7, wherein in step d), acid is an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, nitric acid, and the like, or an organic acid like oxalic acid.

14. The process according to claim 7, wherein in step e) base is like alkali metal carbonate.

15. The process according to claim 7, wherein in steps f) and g) solvent is selected from toluene, methyl tertiarybutyl ether, acetonitrile and the like or mixtures thereof.

16. A process for the preparation of Λ/,TV-dimethyl 3-phenyl-3-hydroxypropyl amine hydrochloride of formula II,

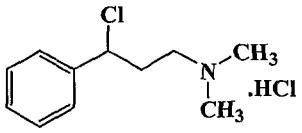


Formula II

which comprises reacting *N,N*-dimethyl 3-phenyl-3-hydroxypropylamine with a solution of hydrogen chloride in a suitable ethereal solvent at a temperature sufficient to convert to *N,N*-dimethyl 3-phenyl-3-hydroxypropyl amine hydrochloride of formula II.

17. The process according to claim 16, ethereal solvent is selected from diisopropyl ether, methyl tertiary butyl ether and the like.

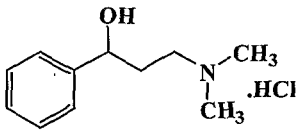
18. A process for the preparation of *N,*iV-dimethyl 3-phenyl-3-chloropropylamine hydrochloride of formula III;



Formula III

which comprises:

reacting A/,JV-dimethyl 3-phenyl-3-hydro χypropylamine hydrochloride of formula II,



Formula II

with thionyl chloride in suitable solvent in the presence of a suitable acid scavenger.

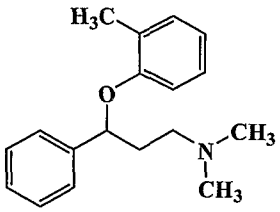
19. The process according to claim 18, wherein acid scavenger is an orthoester of an organic acid.

20. The process according to claim 19, wherein orthoester of an organic acid is selected from the group consisting of triethyl, trimethyl, tripropyl, triisopropyl, tributyl, triisobutyl, and triamyl orthoesters of formic, acetic, oxalic, succinic and adipic acid.

21. The process according to claim 19, wherein orthoester of an organic acid is preferably triethyl orthoformate.

22. The process according to claim 18, wherein solvent is selected from toluene, xylene, ethylbenzene, chloroform, dichloromethane, C_1-C_6 ethers, the like and mixtures thereof.

23. A process for the preparation of *N,N*-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine of formula IV;



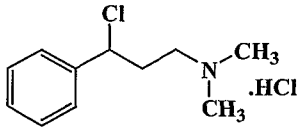
Formula IV

which comprises condensing *N,*iV-dimethyl 3-phenyl-3-chloropropylamine hydrochloride of formula III with ortho-cresol in the presence of inert solvent and a base at a temperature of 50-95 °C and isolating i\/,*N*-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine there from.

24. The process according to claim 23, wherein inert solvent is selected from toluene or toluene with other solvents like dimethylsulfoxide or water.

25. The process according to claim 23, wherein base is selected from metal hydrides, hydroxides, carbonates and bicarbonates.

26. A process for the purification of *N,*7V-dimethyl 3-phenyl-3-chloropropylamine hydrochloride of formula III



Formula III

which comprises the steps of:

a), dissolving Λ*I,*TV-dimethyl 3-phenyl-3-chloropropylamine hydrochloride of formula III in a solvent selected from nitriles;

b). cooling the solution to form a precipitate; and

c). isolating pure *N,*iV-dimethyl 3-phenyl-3-chloropropylamine hydrochloride.

27. The process according to claim 26, wherein step a) nitrile solvent is selected from acetonitrile, propionitrile, butyronitrile, isobutyronitrile and the like.

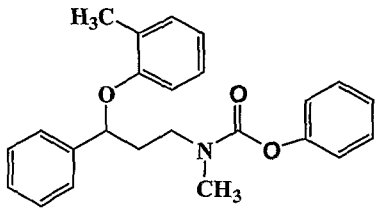
28. A process for the purification of (R)-tomoxetine (S)-mandelate salt which comprises the steps of:

a), dissolving (R)-tomoxetine (S)-mandelate salt in a solvent selected from acetonitrile, toluene, methyl tertiarybutyl ether or mixture thereof;

b). cooling and seeding the solution with pure (R)-tomoxetine (S)-mandelate salt to form a precipitate; and

c). isolating pure (R)-tomoxetine (S)-mandelate salt.

29. A process for the purification of 7V-methyl-[3-(o-tolyloxy)-3-phenylpropyl]-carbamic acid phenyl ester of formula V,



Formula V

which comprises the steps of:

a), dissolving JV-methyl-[3-(o-tolyloxy)-3-phenylpropyl]-carbamic acid phenyl ester in a solvent selected from ethereal solvent such as diisopropyl ether, methyl tertiarybutyl ether, diethyl ether and the like;

b). cooling the solution to form a precipitate; and

c). isolating pure iV-methyl-[3-(o-tolyloxy)-3-phenylpropyl]-carbamic acid phenyl ester.