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(54) **Title:** NOVEL DIASTERIOMERIC SALTS OF ATENOLOL AND THEIR USE IN THE PRODUCTION OF OPTICALLY ACTIVE ATENOLOL

(57) **Abstract:** Novel diasteriomeric tartaric acid salts of atenolol namely, (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate, (2R)-1isopropylamino-3-[p-(2-methoxyethyl)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyltartrate and their use in the preparation of optically active atenolol by a simple industrial racemic resolution is disclosed herein.

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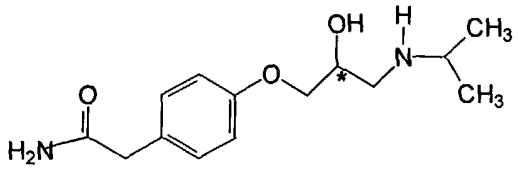
Field of the Invention

The present invention relates to novel optically active atenolol tartrate salts, their use in the process for preparing optically active atenolol and a process for manufacturing the same.

Background of the invention

It is known that atenolol is useful as beta-adrenergic blocker for the treatment of angina pectoris, arrhythmia and hypertension. It is also known that atenolol has an 1-aryloxy-3-aminopropan-2-ol nucleus wherein the hydroxy-bonded carbon is an asymmetric carbon and hence includes optical isomers, namely, R- and S-isomers (notation), and the S-isomer thereof is particularly useful as beta-adrenergic blocker in view of its superior pharmacological activities. It is reported that only S-isomer of atenolol has hypotensive activity and activity on brachycardia (cf. A.A. Pearson, T.E. Gaffney, T. Walle, P.J. Privitera; J. Pharmacol. Exp.Ther., 250 (3), 759, 1989). The chemical name of atenolol is 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy] benzene acetamide and is represented by the structure Formula I(where * denotes the chiral carbon atom).



Formula I

While racemic atenolol is presently marketed widely for the treatment of hypertension, angina, and has shown to promise in the treatment of post myocardial infraction, the S-isomer is found to avoid the occasional side effect of a lowered heart rate sometimes encountered with the racemate(racemic atenolol). It is therefore important to develop an industrial method for the preparation of S-atenolol.

Atenolol was prepared by reacting 4-hydroxyphenylacetamide with epihalohydrin (e.g. epichlorohydrin) to obtain a glycidyl ether intermediate which is then reacted with isopropyl amine (Ref. U.S. Patent Nos. 3,663,607, 3,836,671 and 3,934,032).

Optically active atenolol was prepared by using an optically active epichlorohydrin in the process in place of racemic epichorohydrin. However, according this process, if an optically active epichlorohydrin is used, racemization occurs during its reaction with the 4-hydroxyphenylacetamide under basic conditions and hence, the optical purity of the intermediate glycidyl ether intermediate becomes less than 70 % ee resulting in the final product having less than 70 % ee. Moreover, this process requires a large amount of the expensive optically active epichlorohydrin for the formation of glycidyl ether, and even though the excess amount of epichlorohydrin can be recovered, it can not be reused because of its lower optical purity. Accordingly, this process is not suitable for producing an optically active atenolol and intermediate thereof, either.

A simple and direct method for separating racemates is by optical resolution which is carried out by reacting a racemic compound with a suitable optically active organic acid/base to form diatsteriomeric salts which have different crystallization characteristics followed by fractional crystallization. It has been studied to produce optically active atenolol by optical resolution but any practical method has not been reported for the same to the best of our knowledge.

It is reported that S-atenolol having a high optical purity is obtained from the racemic mixture by derivatisation of racemic atenolol using (R,R)-O,O-di-p-toluoyltartaric acid anhydride to give a mixture of diasteriomeric tartaric acid monoesters (ref.- Wilson M.J. et al., J. Chromatogr. (NLD) 431 (1), 222-227, 1988 and United States patent US4652672). However, this method of derivatisation requires troublesome extraction, a number of stages to obtain free optically active

atenolol and also requires a large amount of solvent apart from being non-attractive from the view point of recovery and recyclability of (R,R)-O,O-di-p-toluoyl-tartaric acid anhydride, and hence, this method is not suitable for the practical production of optically active atenolol.

Another process on derivatization based optical resolution of atenolol was reported in US patent 4463176. This process comprised of; reaction of atenolol with a chiral isocyanate compound to obtain diasteriomeric urea derivatives; separation of the resulting diastariomers into its optical antipodes and regenerating optically active atenolol. This method also suffers from the point of view of industrial applicability as it involves number of stages, troublesome purification procedures. Since the recycling of chiral isocyanate compound is also not technically feasible, it leads to escalation of the cost of production thus the process is uneconomical.

The present inventors have intensively explored selective isolation of various diasterioisomeric salts of atenolol prepared by reaction with chiral acids in order to find a suitable process for simple isolation and purification of atenolol in optically pure form, and have found that the diasteriomeric tartaric acid salts can be prepared and used for separation of racemic atenolol into optical antipodes in higher enantiomeric purity.

Objective of the present invention

The objective of the present invention is to provide novel diasteriomeric tartaric acid salts of atenolol and process for their preparation, and thereby to provide a method for industrially viable preparation of optically active S- atenolol, which function as a cure for essential hypertension, angina pectoris, and tachycardiac arhythmia.

Summary of the invention

The present invention discloses a novel diasteriomeric tartaric acid salts of atenolol namely, (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate (Formula III) (2R)-1-isopropylamino-3-[p-(2-methoxyethyl)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyltartrate(Formula V) and their use in the preparation of optically active atenolol.

Accordingly, the present invention discloses the use of above diasteriomeric tartrate salts of atenolol in the separation of S- and R-isomers of atenolol by a simple industrial racemic resolution.

The present invention further provides the process for the preparation of the above novel tartaric acid diasterioisomers of atenolol.

In one embodiment of the invention, the racemic atenolol was reacted with (2S,3S)-O,O-di-p-toluoyltartaric acid in a suitable inert solvent to crystallize out one of the diasteriomeric tartrate salt namely, (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate, the latter on neutralization with base such as sodium hydroxide or potassium hydroxide generates S-atenolol.

In another embodiment of the present invention the racemic atenolol was reacted with -(2R,3R)-O,O-di-p-toluoyltartaric acid in a suitable inert solvent to crystallize out one of the diasteriomeric tartrate salt namely, (2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyltartrate, from the solvent which is used to prepare R-atenolol by treating it with a suitable base such as sodium hydroxide, potassium hydroxide etc..

In the process of the present invention, the suitable solvents used for the selective crystallization of above diasteriomeric salts include C_1 to C_4 alcohols or their mixture thereof or mixture of C_1 to C_4 alcohols with hydrocarbon solvents such as n-hexane, cyclohexane, toluene, and ether solvents like diisopropyl ether, tetrahydrofuran etc.

In yet another embodiment of the present invention, the racemic diasteriomeric tartrate of atenolol is prepared in a suitable solvent like methanol at a temperature ranging from room temperature to reflux temperature and is selectively crystallized from the aforementioned crystallization solvents to give optically active tartaric acid salts of the present invention.

Detailed description of the present invention

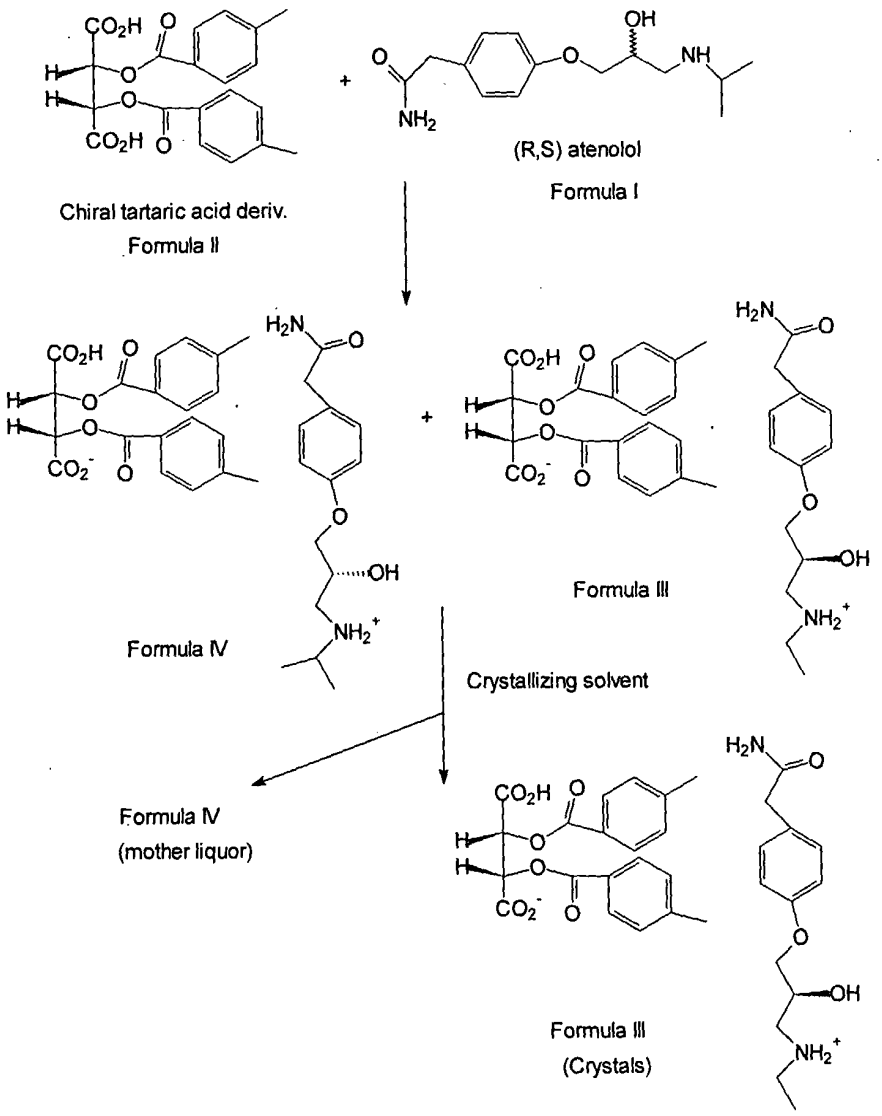
The present invention thus relates to the optical resolution of racemic atenolol into its enantiomers in substantially pure form. Racemic atenolol hereinafter means atenolol containing identical quantities of optical antipodes (dextro and levorotatory isomers). Optical resolution or separation, herein after, are synonymous and is a direct method of separation of pure enantiomers by reacting racemic compound with optically active acids/bases to form racemic diatsteriomeric salts which have different crystallization characteristics and can be separated by fractional crystallization using a suitable solvent followed by the liberation of the optically active enantiomer from its salt by neutralization.

Accordingly, the optically active acids for the resolution of racemic atenolol are selected from the group consisting of (O,O)-di-p-toluoyltartaric acid, and (O,O)-di-benzoyl tartaric acid. The optically active acid advantageously used in the present invention are (2R,3R)-(O,O)-di-p-toluoyltartaric acid and (2S,3S)-(O,O-di-p-toluoyltartaric acid or their monohydrate solvates.

The resultant diasterioisomers namely, (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate,(Formula – III) and (2R)-1-isopropylamino-3-[p-(2-methoxyethyl) phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyltartrate (Formula – V) are not known in the literature or prepared earlier and are parts of the present invention.

In the process of the present invention, one and the same solvent may be used in the salt formation and subsequent fractional crystallization /recrystallizations.

In the process of the present invention, according to a general preparative method, the optically active ditoluoyltartaric acid of Formula II is allowed to react with racemic atenolol of Formula I in an inert solvent according to the following scheme.



The salt formation may be carried out in solvents such as alcohols, ketones, a mixture of alcohol and hydrocarbon solvents selected from hexane, cyclohexane, toluene, or a mixture of alcohol with ether solvents like diisopropyl ether, THF etc. A mixture of two diasteriomers of Formula III and IV are formed in the reaction namely, (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate and (2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate respectively, when (S,S) ditoluoyl tartaric acid is reacted with racemic atenolol. The (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate isomer selectively crystallized from suitable crystallizing solvent and the (2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate isomer remain in mother liquor.. The salt formation may be effected at ambient temperatures or at elevated temperatures.

The solvents advantageously used for the salt formation and selective crystallization of one of the diasteriomeric salt is selected from alcohols such as ethanol, isopropyl alcohol or a mixture of above alcohols with methanol or a mixture of C_1 to C_4 alcohol with hydrocarbon solvents like hexane, cyclohexane, toluene or mixture of alcohols with ether solvents like diisopropylether, tetrahydrofuran. The most preferred solvent is ethanol or isopropyl alcohol.

The individual diasteriomeric salt may be purified by repeated crystallization from the same or different solvent as described above to enrich one of the diasteriomer in pure form, if necessary. After each crystallization, the optical rotatory power of the precipitate is measured using a polarimeter at 20°C in methanol at a concentration varying between 1.0 and 2g per 100ml. The optical purity of the diasteriomer is also analyzed using HPLC with a chiral stationary column e.g. Chiropak*. Further, the diasteriomers are recrystallized, if required, to get a constant optical purity.
(* trade name)

In the process of the invention, preferably one molar equivalent of the (O,O)ditoluoyltartaric acid is mixed with racemic atenolol during the salt formation stage. The salt formation is advantageously effected at a temperature ranging from 25° to 75° C and most preferably in the temperature range of 40° to 60° C.

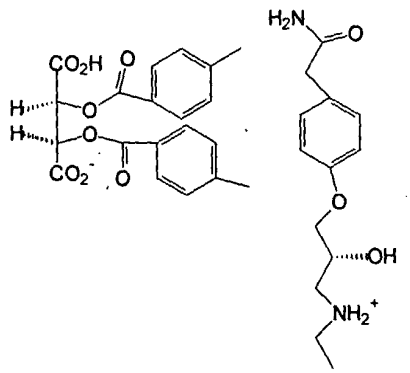
Consequently, (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate is prepared by reacting (2S,3S)-O,O-di-p-toluoyltartaric acid with racemic atenolol in ethanol at a temperature of 40 ° to 60 ° C for a period of 1 hour to effect complete salt formation. The two diasteriomeric salts, Formula III and Formula IV so formed in the reaction mixture are then cooled to a temperature of 25 ° to 40 ° C in order to effect fractional crystallization of one of the diasteriomer. The precipitated (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate (Formula III) is filtered off and dried in an oven to give white crystals having a melting point between 150.9 to 151.5°C. The specific rotation is measured as +79.9 ° to +81° (1.0 % methanol at 20° C)

The physico-chemical properties of this diasteriomer are as follows:
The FT Infrared absorption spectra of the (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate showed the absorption at wavelength 3400 cm^2, 1720 cm^2, 1610 cm^2, 1510 cm^2, 1380 cm^2, 1275 cm^2, 1185 cm^2, 1110 cm^2, 1055 cm^2, 1020 cm^2, 760cm^2, 710cm^2 .

The delta values of the proton nuclear magnetic resonance spectra (Instrument: Brucker - 400MHz, Solvent $DMSOd^6$) are δ1.1(d 6H -$(CH3)_2$) , δ2.3(s 6H -CH3), δ3.0-3.2(m 2H N-CH2), δ3.3 (m 1H N-CH), δ 3.39 (s 2H -COCH2-), δ4.2(m 1H -C-OH), δ5.7(s 1H -CH), δ6.7(m3H NH Ar.), δ 7.0(d 2H Ar), δ7.3 (dd 4H Ar), δ 7.5(s 1H -NH), δ7.8(dd 4H Ar), δ 8.5(broad s –COOH).

Moreover, the result of the elemental analysis was 61.1% C, 5.97% H and 4.2%N and 28.71 % O and the rational Formula of the resultant compound is determined to be $C_{34}H_{40}N_2O_{12}$ as calculated values of $C_{34}H_{40}N_2O_{12}$ agrees with 61.07% C, 5.92% H and 4.19% N and 28.74% O.

The (2R)-1-isopropylamino-3-[p-(2-methoxy ethyl)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyltartrate(Formula – V) of the present invention is prepared by reacting (-)-(2R,3R)-O,O-di-p-toluoyltartaric acid with racemic atenolol in ethanol at a temperature of 40 ° to 60°C for a period of 1 to 3 hours to effect complete salt formation. The two diasteriomeric salts namely, (2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyl tartrate and (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyltartrate, so formed in the reaction mixture is then cooled to a temperature of 35° to 40° C in order to effect fractional crystallization of one of the diasteriomer. The precipitated (2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyltartrate is filtered off and dried in an oven to give white crystals having a melting point between 144.1 to 149.0°C. The specific rotation is measured as –76.5 (1.0 % methanol at 20° C).



Formula V

The physico-chemical properties of this diasteriomer are as follows:
The FT Infrared absorption spectra of the (2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyltartrate showed the absorption at wavelength 3400 cm^2, 1720 cm^2, 1610 cm^2, 1510 cm^2, 1380 cm^2, 1275 cm^2, 1185 cm^2, 1110 cm^2, 1055 cm^2, 1020 cm^2, 760cm^2, 710cm^2 .

The delta values of the proton nuclear magnetic resonance spectra (Instrument: Brucker - 400MHz, Solvent $DMSOd^6$) are δ1.1(d 6H -$(CH3)_2$) , δ2.3(s 6H -CH3), δ3.0-3.2(m 2H N-CH2), δ3.3 (m 1H N-CH), δ 3.39 (s 2H -COCH2-), δ4.2(m 1H -C-OH), δ5.7(s 1H -CH), δ6.7(m3H NH Ar.), δ 7.0(d 2H Ar), δ7.3 (dd 4H Ar), δ 7.5(s 1H -NH), δ7.8(dd 4H Ar), δ 8.5(broad s –COOH).

Moreover, the result of the elemental analysis was 61.1% C, 5.97% H and 4.2%N and 28.71 % O and the rational Formula of the resultant compound is determined to be $C_{34}H_{40}N_2O_{12}$ as calculated values of $C_{34}H_{40}N_2O_{12}$ agrees with 61.07% C, 5.92% H and 4.19% N and 28.74% O.

These optically active atenolol tartrate salts of the invention are easily hydrolyzed with a base such as sodium hydroxide or potassium hydroxide in a solvent like water to yield optically active atenolol.
Therefore, the pure isomers of atenolol is prepared by the action of a base such as sodium hydroxide or sodium carbonates with the optically active diasteriomeric tatrate salts of the present invention in aqueous media at temperatures ranging between 10 to 30 °C

Consequently, R-Atenolol (dextro rotatory) is prepared from (2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-benzoyltartrate and, the S-Atenolol (levo rotatory) is prepared from (2S)-1-isopropylamino-3-[4-(2-

acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-benzoyltartrate by neutralization using sodium hydroxide in aqueous media to precipitate the required enantiomer.

The pure enantiomers of atenolol are isolated by normal work-up procedures like precipitation or extraction etc.

Alternately, the racemic diaterioisomeric salts of tartaric acid may be prepared separately into a solvent such as methanol by conducting the reaction of racemic atenolol with tartaric acid derivative used in the present invention in the said solvents and isolating as a mixture of two diasteriomers by solvent evaporation. For example, the mixture of two diasteriomers, e.g. (2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyltartrate and (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyl tartrate formed by the reaction of racemic atenolol with (-)-(2R,3R)-O,O-di-p-toluoyltartaric acid, are separated by fractional crystallization from the solvents described hereinbefore. The suitable conditions are such that the mixture of diasterioisomers are dissolved in suitable solvent at ambient temperature or elevated temperature and cooling/chilling to yield crystals of one of the diasteriomer in substantially pure form.

The invention is further illustrated with the following actual examples and is not intended to be limiting in any manner to the scope of the invention as substantially described.

Examples

Example **1**

(2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate

Atenolol (racemic) 100 gm. in 2 litres of ethanol and (+)-(2S,3S)-O,O-di-p-toluoyltartaric acid (120 gm.) was heated to 60 to 65 ° C for 3 hours. The mixture was then cooled to 30 ° C and maintained for 2 hours under stirring. The precipitated crystals are filtered off and dried to give 101 gm of (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyltartrate. Optical purity 98% (chiral HPLC, Chiropack* column) and specific rotation +80 ° (c =1.0% in methanol)

The delta values of the proton nuclear magnetic resonance spectra (Instrument: Brucker - 400MHz, Solvent DMSOd^6) are δ1.1(d 6H -$(CH3)_2$) , δ2.3(s 6H -CH3), δ3.0-3.2(m 2H N-CH2), δ3.3 (m 1H N-CH), δ 3.39 (s 2H -COCH2-), δ4.2(m 1H -C-OH), δ5.7(s 1H -CH), δ6.7(m3H NH Ar.), δ 7.0(d 2H Ar), δ7.3 (dd 4H Ar), δ 7.5(s 1H -NH), δ7.8(dd 4H Ar), δ 8.5(broad s –COOH).

Example **2**

(2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyltartrate

Atenolol (racemic) 100 gm. in 2 litres of ethanol and (-)-(2R,3R)-O,O-di-p-toluoyltartaric acid (120 gm.) was heated to 60 to 65°C for 3 hours. The mixture was then cooled to 30 ° C and maintained for 2 hours under stirring.The precipitated crystals are filtered off and dried to give 101 gm of (2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyltartrate. Optical purity 98% (chiral HPLC, Chiropack* column) and Specific rotation -76.5 ° (c= 1.0% in methanol)

The delta values of the proton nuclear magnetic resonance spectra (Instrument: Brucker - 400MHz, Solvent DMSOd^6) are δ1.1(d 6H -$(CH3)_2$) , δ2.3(s 6H -CH3), δ3.0-3.2(m 2H N-CH2), δ3.3 (m 1H N-CH), δ 3.39 (s 2H -COCH2-), δ4.2(m 1H -C-

OH), δ5.7(s 1H -CH), δ6.7(m3H NH Ar.), δ 7.0(d 2H Ar), δ7.3 (dd 4H Ar), δ 7.5(s 1H -NH), δ7.8(dd 4H Ar), δ 8.5(broad s –COOH).

Example **3**

S-atenolol

The (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyl tartrate obtained as in example 1 (101 gm) was mixed with 400 ml water in a reaction vessel and NaOH solution (100 gm in 100 water) was added dropwise. The reaction mixture was stirred for 2 hours at 10 to 15 °C. The precipitate was filtered and washed with cold water. The S-atenolol obtained is dried at 70 ° C to give 34 gm optically pure S-atenolol

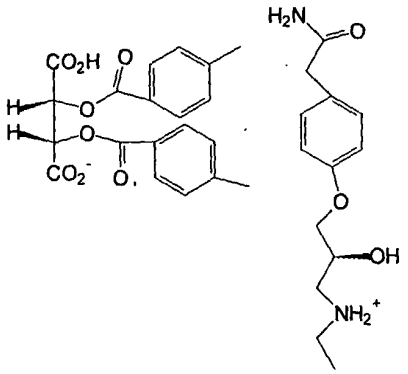
Example **4**

R-atenolol

The (2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyl tartrate obtained as in example 2 (101 gm) was mixed with 400 ml water in a reaction vessel and NaOH solution (100 gm in 100 water) was added dropwise. The reaction mixture was stirred for 2 hours at 10 to 15 °C. The precipitate was filtered and washed with cold water. The R-atenolol obtained is dried at 70 ° C to give 35 gm optically pure R-atenolol

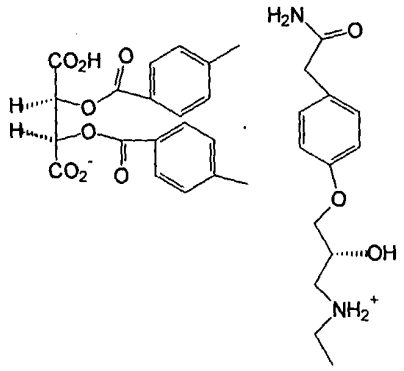
We claim,

1. (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyl tartrate of Formula III in substantially optically active form



Formula III

2. (2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyl tartrate of Formula V in substantially optically active form



Formula V

3. A process for the preparation of Compound of Formula III claimed in claim 1 comprising: treating atenolol containing both optical isomers with (+)-(2S,3S)-O,O-di-p-toluoyl tartaric acid in a solvent to produce a mixture of diasteriomeric salts; and fractionally crystallizing compound of Formula III from the said salts in a suitable solvent in substantially optically pure form.

4. A process for the preparation of Compound of Formula V claimed in claim 2 comprising: treating atenolol containing both optical isomers with (+)-(2R,3R)-O,O-di-p-toluoyl tartaric acid in a solvent to produce a mixture of diasterimeric salts; and fractionally crystallizing compound of Formula V from the said salts in a suitable solvent in substantially optically pure form.
5. A process according to claim 3 or 4, wherein the salt forming and crystallizing/recrystallizing solvents are same.
6. A process according to claim 3 or 4, wherein the solvents for fractional crystallization of Formula III or V is selected independently from C_1 to C_4 alcohol, mixture of C_1 to C_4 alcohols, mixture of C1 to C4 alcohols with hydrocarbon solvents such as hexane, cyclohexane, toluene, or a mixture of alcohol with ether solvents like diisopropyl ether, THF, and ethyl acetate.
7. A process according to claim 3 further comprising reacting compound of Formula III with a base to produce levorotatory atenolol (S-atenolol) substantially free of R-atenolol.
8. A process according to claim 4 further comprising reacting compound of Formula V with a base to produce dextrorotatory atenolol (R-atenolol) substantially free of S-atenolol.
9. A process according to claim 7 or 8, wherein the base is selected from inorganic bases like alkali metal carbonates or alkali metal hydroxides.
10. A process according to claim 9, wherein the reaction is performed in aqueous medium.
11. A process according to any one of the claim 7 to 10 wherein the reaction is performed in water.
12. (2S)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2S,3S)-O,O-di-p-toluoyl tartrate of Formula III and (2R)-1-isopropylamino-3-[4-(2-acetamido)phenoxy]-2-propanol-(2R,3R)-O,O-di-p-toluoyl tartrate of Formula V and the processes for preparation of said salts and its derivatives S-atenolol and

R-atenolol as substantially described herein with reference to the foregoing examples 1 to 4.