(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 949 260 A1

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
13.10.1999 Bulletin 1999/41

(21) Application number: **97949235.2**

(22) Date of filing: **25.12.1997**

(51) Int. Cl.[6]: **C07D 401/12**
// (A61K31/445, C07M7:00)

(86) International application number:
PCT/JP97/04826

(87) International publication number:
WO 98/29409 (09.07.1998 Gazette 1998/27)

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **26.12.1996 JP 34785196**
26.12.1996 JP 34785396
26.12.1996 JP 34789596

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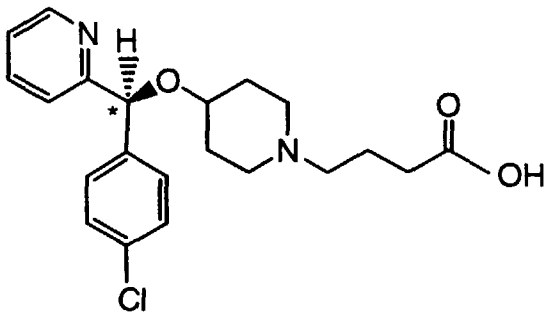
(54) ACID-ADDITION SALTS OF OPTICALLY ACTIVE PIPERIDINE COMPOUND AND PROCESS FOR PRODUCING THE SAME

(57) The present invention is to provide a benzenesulfonic acid salt and a benzoic acid salt of (S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino]butanoic acid represented by the formula (I):



(I)

wherein * represents an asymmetric carbon, which are excellent in antihistaminic activity and anti-allergic activity, and a process for producing the same.

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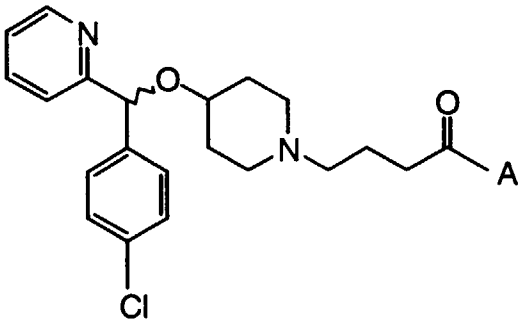
Description

Technical field

[0001] This invention relates to benzenesulfonic acid salt or benzoic acid salt of (S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino]butanoic acid which is excellent in antihistaminic activity and antiallergic activity, a process for preparing the same, and an optically resolving method of 4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidine which is important as a racemic intermediate thereof. The acid addition salt has little hygroscopicity and excellent in physicochemical stability so that it is particularly suitable compound as a medicine. Also, the present invention relates to a medical composition containing the compound as an effective ingredient.

Background art

[0002] A piperidine compound (II) represented by the formula (II):



(II)

where in A represents a lower alkyl group, hydroxyl group, a lower alkoxy group, amino group, a lower alkylamino group, phenyl group or a lower alkyl-substituted phenyl group,

or a salt thereof described in Japanese Provisional Patent Publication No. 25465/1990 has characteristics that a secondary effect such as stimulation or suppression on the central nerves, which often appears in the conventional antihistaminic compound, can be reduced as little as possible, and is expected to be a medicine for therapeutic treatment of allergic skin diseases such as a nettle rash, eczema, dermatitis and the like, allergic rhinitis, sneeze, mucus, cough due to respiratory inflammation such as cold and the like, and bronchial asthma.

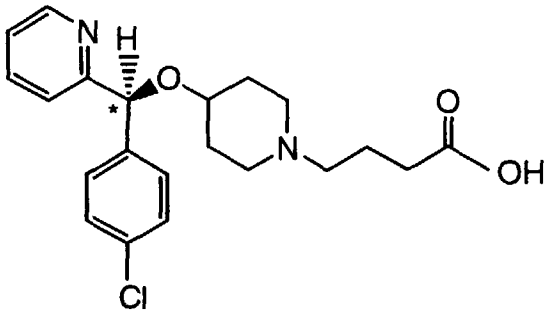
[0003] For producing the piperidine compound (II) effectively as a more preferred optical isomer for a medicine, it is desired to use the optically resolved product as a starting material by optically resolving an intermediate. However, this piperidine compound (II) has one asymmetric carbon atom but the method of isolating its optically active isomer from the racemic mixture has not been known as of today.

[0004] It has been generally known that optical isomers show different pharmacological activity or safety and there are also differences in the metabolic rates and the protein binding ratios therebetween (Pharmacia, 25 (4), pp. 311-336, 1989). Accordingly, for providing a medicine, a pharmaceutically preferable optical isomer with high optical purity is required. Also, in order to secure high quality of said optical isomer as a medicine, it is desirable that the isomer has superior properties in physicochemical stability.

[0005] The present inventors have studied intensively to solve the above problems. As the result, they have found that a benzenesulfonic acid salt or a benzoic acid salt of optically active (S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]-piperidino]butanoic acid represented by the following formula (I) has excellent stability which is preferred as a medicine whereby accomplished the present invention.

Disclosure of the invention

[0006] The first invention relates to a benzenesulfonic acid salt or a benzoic acid salt of an optically active piperidine compound (I) represented by the formula (I):



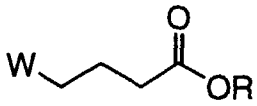
(I)

wherein * represents an asymmetric carbon, which has an absolute configuration of (S).

[0007] The second invention relates to a process for preparing a benzenesulfonic acid salt or a benzoic acid salt of an optically active piperidine compound by reacting the optically active piperidine compound represented by the above formula (I) with an absolute configuration of (S) with benzenesulfonic acid or benzoic acid to form a salt.

[0008] The third invention relates to a medical composition which comprises a benzenesulfonic acid salt of (S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino]butanoic acid or a benzoic acid salt of the same as an effective ingredient.

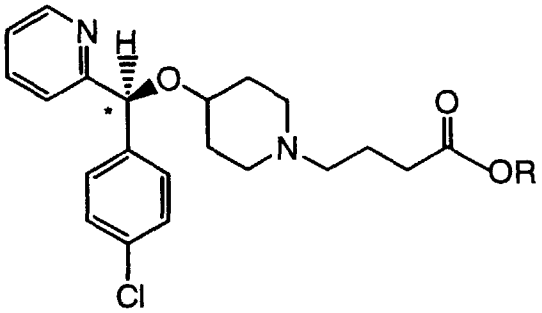
[0009] The invention further relates to a process for preparing a benzenesulfonic acid salt or a benzoic acid salt of the optically active piperidine compound (I) represented by the above formula (I) which comprises reacting (±)-4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidine with the optically active propionic acid compound (VII) represented by the following formula (VII) or the optically active N-acyl-amino acid; separating and collecting less soluble diastereomeric salt by utilizing the difference in solubilities of the formed two kinds of diastereomeric salts; decomposing the resulting salt; reacting an ester represented by the formula (V):



(V)

wherein R represents a lower alkyl group such as methyl group, ethyl group, etc., and W represents a leaving group such as a halogen atom or a reactive ester group such as methanesulfonyloxy group, p-toluenesulfonyloxy group, etc.,

with the resulting (S)-4-[(4-chlorophenyl)(2-pyridyl)-methoxy]piperidine to obtain (S)-4- [(4-chlorophenyl)(2-pyridyl)methoxy]piperidine butanoic acid ester represented by the formula (VI):



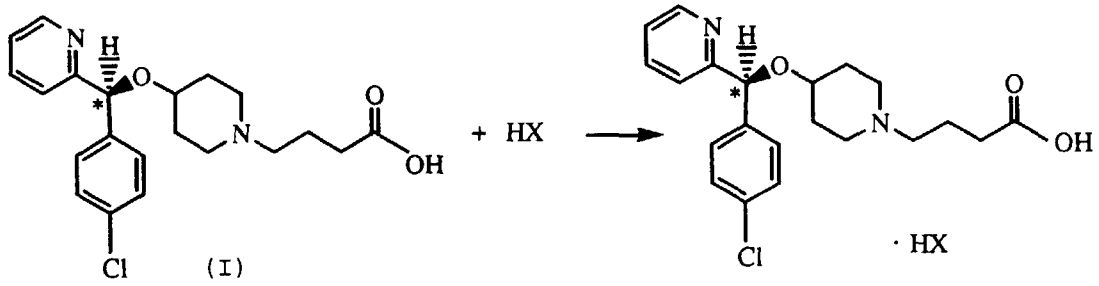
(VI)

wherein R and * have the same meaning as defined above, hydrolyzing the resulting compound; and reacting the hydrolyzed compound with benzenesulfonic acid or benzoic acid to form a salt.

Best mode for carrying out the invention

[0010] A benzenesulfonic acid salt or a benzoic acid salt of (S)-piperidine compound (I) can be produced by the method represented by the following reaction scheme (1):

Reaction scheme (1)



wherein HX represents benzenesulfonic acid or benzoic acid, and * has the same meaning as defined above, (hereinafter referred to as a salt-forming reaction).

[0011] In the salt-forming reaction, benzenesulfonic acid or benzoic acid can be used in an amount of 0.8 to 2.5-fold mole, preferably 0.9 to 1.2-fold mole based on 1 mole of the (S)-piperidine compound (I).

[0012] As a solvent to be used in the salt-forming reaction, it is not particularly limited so long as it does not participate in the reaction, and there may be mentioned, for example, nitriles such as acetonitrile and propionitrile; esters such as methyl acetate and ethyl acetate; alcohols such as methanol, ethanol, 1-propanol, 2-propanol, etc.; acetone, dimethylformamide, etc., and preferably ethanol, 2-propanol, acetonitrile and ethyl acetate. The solvent to be used in the present invention may be used alone or may be in admixture of the above-mentioned two or more kinds of optional solvents.

[0013] An amount of the solvent to be used in the salt-forming reaction is usually 0.5 to 30 liters, preferably 0.8 to 20 liters, more preferably 1 to 10 liters per mole of the (S)-piperidine compound (I).

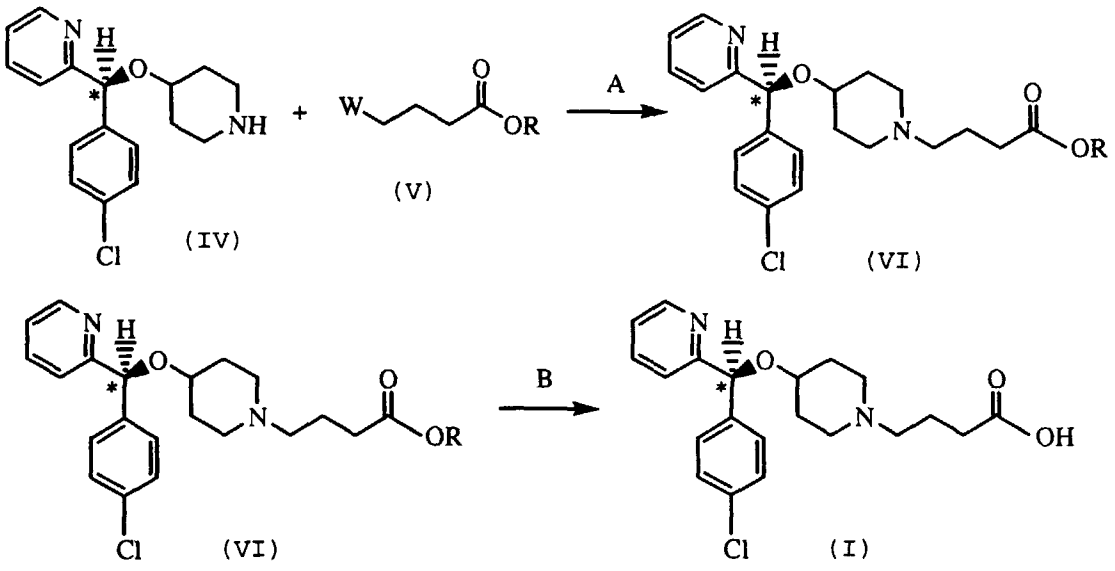
[0014] A temperature of the salt-forming reaction is, for example, 5 to 50 °C, preferably 10 to 35 °C, and a temperature at the time of salt precipitation is, for example, -30 °C to 30 °C, preferably -10 °C to 15 °C. Also, a method of addition is not particularly limited, but, for example, there may be mentioned a method in which benzenesulfonic acid or benzoic acid dissolved in a solvent is added to a mixed solution of the (S)-piperidine compound (I) and a solvent.

[0015] The formed salt of the (S)-piperidine compound (I) can be easily obtained in accordance with the conventional method in this field of technology by, for example, collecting after separation with filtration, centrifugation, etc., washing and then drying.

[0016] Next, a process for preparing an (S)-piperidine compound (I) of the present invention will be explained.

[0017] The (S)-piperidine compound (I) of the present invention can be prepared by the method shown in the following reaction scheme (2):

Reaction scheme (2)



wherein W represents a leaving group, including a halogen atom such as chlorine atom, bromine atom, iodine atom, etc.; or a reactive ester group such as methanesulfonyloxy group, p-toluenesulfonyloxy group, etc., and R repre-

sents a lower alkyl group such as methyl group, ethyl group, etc., and * has the same meaning as defined above.

[0018] The step A is an N-alkylation reaction of (S)-piperidine intermediate (IV), and the reaction can proceed by using 1 to 3-fold mole, preferably 1 to 1.5-fold mole of the ester (V) based on 1 mole of the (S)-piperidine intermediate (IV). The above reaction can be carried out in an inert solvent. As a suitable solvent, there may be mentioned, for example, water; lower alcohols such as methanol, ethanol, propanol, butanol, etc.; nitriles such as acetonitrile, propionitrile, etc.; aromatic hydrocarbons such as benzene, toluene, xylene, etc.; ethers such as 1,4-dioxane, tetrahydrofuran, etc.; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, etc.; amides such as N,N-dimethylformamide, etc.; and preferably water, acetonitrile, acetone, and N,N-dimethylformamide. These solvents may be used alone or may be used in admixture of two or more kinds with a suitable mixing ratio.

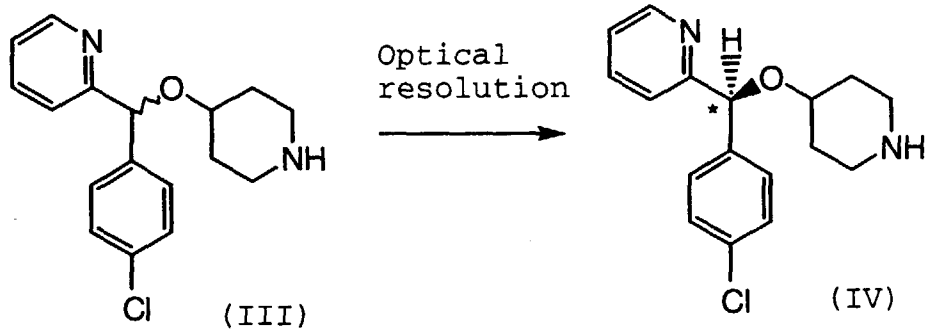
[0019] The reaction is preferably carried out in the presence of a base, and as the preferred base, there may be mentioned, for example, alkali metal hydroxides such as sodium hydroxide, etc.; alkaline earth metal hydroxides such as calcium hydroxide, etc.; alkali metal carbonates such as potassium carbonate, etc.; alkaline earth metal carbonates such as calcium carbonate, etc.; alkali metal acidic carbonates such as sodium hydrogen carbonate, etc.; alkali metal hydrides such as sodium hydride, etc.; alkaline earth metal hydrides such as calcium hydride, etc.; alkali metal alkoxides such as sodium methoxide, etc.; trialkylamines such as triethylamine, etc., and a pyridine compound, etc., and preferably sodium carbonate, potassium carbonate, sodium hydrogen carbonate or potassium hydrogen carbonate. These bases are each used in an amount of 1 to 3-fold moles, preferably 1 to 1.5-fold moles based on 1 mole of the (S)-piperidine intermediate (IV) when the base is monovalent. When the base is divalent, it is used in an amount of 0.5 to 1.5-fold mole, preferably 0.6 to 1-fold mole based on the same.

[0020] Also, as a reaction accelerator, a small amount of a metal iodide such as, for example, sodium iodide or potassium iodide may be added. The reaction can be carried out at a reflux temperature of the reaction mixture, for example, 5 to 150 °C, preferably 20 to 100 °C. The reaction time is 2 to 24 hours.

[0021] The step B is a hydrolysis reaction of an (S)-ester (VI). The reaction can be carried out in an aqueous alcohol such as aqueous methanol, aqueous ethanol, etc., and by using an inorganic base such as sodium hydroxide, potassium hydroxide, etc. in an amount of 1 to 5-fold mole, preferably 1 to 3-fold mole per mole of the (S)-ester (VI). A reaction temperature is, for example, 5 to 90 °C, preferably 15 to 70 °C. A reaction time is generally 1 to 10 hours. After completion of the reaction, the reaction mixture is subjected to neutralization treatment by using a mineral acid such as hydrochloric acid, sulfuric acid, etc. or an organic acid such as acetic acid, oxalic acid, etc. to produce an (S)-piperidine compound (I).

[0022] To obtain an optical isomer in general, methods such as an asymmetric synthesis, optical resolution by fractional crystallization or by an enzyme such as lipase, fractionation by an optical resolution column, and the like have been known. For preparing an optically active (S)-piperidine compound (I) efficiently in the present invention, as shown in the following reaction scheme (3):

Reaction scheme (3)



wherein * represents an asymmetric carbon, (±)-4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidine which is a starting compound and represented by the formula (III) is previously optically resolved and the resulting optically active (S)-4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidine represented by the formula (IV) is used as a synthetic intermediate.

[0023] The said optical resolution can be effectively carried out by the following procedure. That is, by reacting a racemic piperidine compound represented by the formula (III):

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