



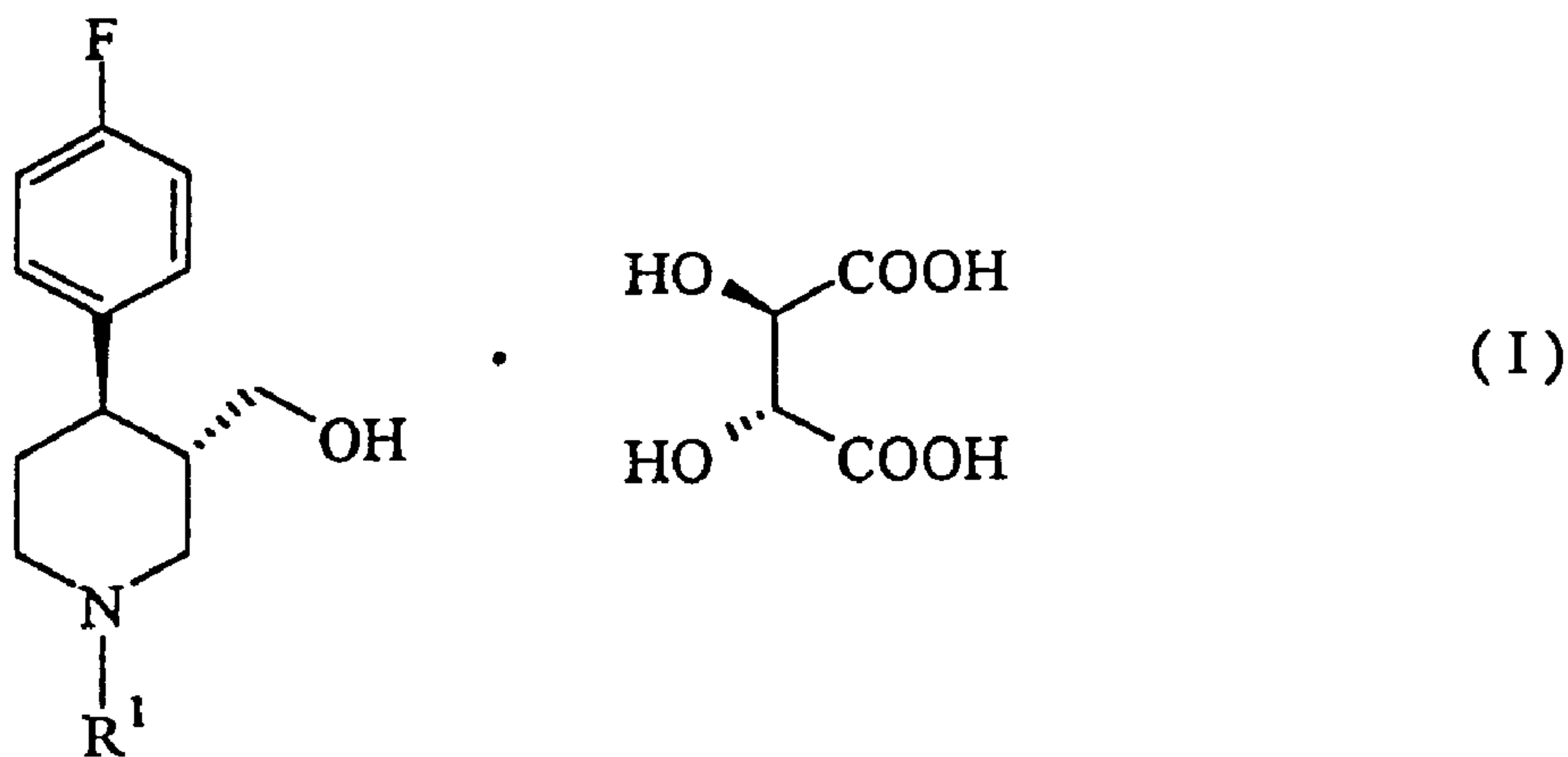
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(54) **COMPOSE DE L-TARTRE DE TRANS-(-)-4-(4-  
FLUOROPHENYLE)-3-HYDROXYMETHYLPIPERIDINE ET  
PROCESSUS DE PREPARATION DE CELUI-CI**

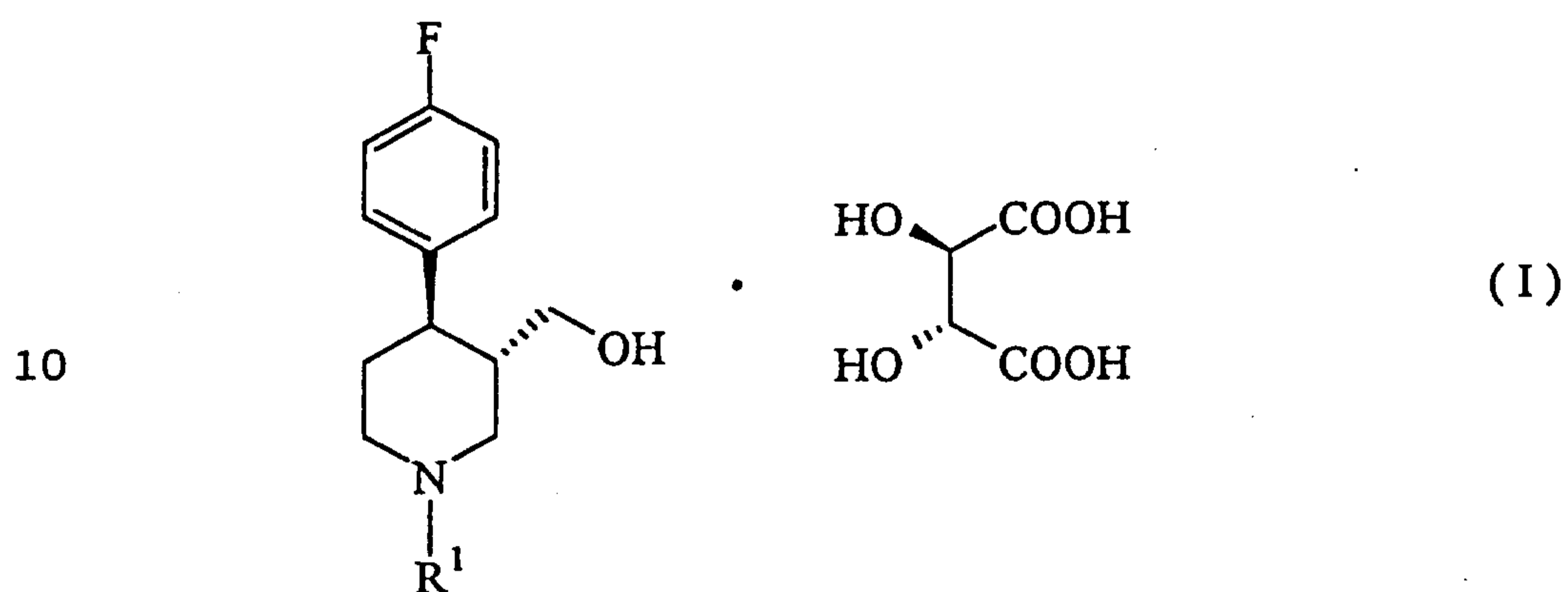
(54) **L-TARTRATE OF TRANS-(-)-4-(4-FLUOROPHENYL)-3-  
HYDROXYMETHYLPIPERIDINE COMPOUND AND  
PROCESS FOR PREPARING THE SAME**



(57) An L-tartrate of a trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound, represented by the formula (I): (see formula I) wherein R<sup>1</sup> is hydrogen atom, a substituted or unsubstituted, linear or branched alkyl group having 1 to 6 carbon atoms, or an aralkyl group having 7 to 12 carbon atoms. The L-tartrate of trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound can be suitably used as an intermediate for pharmaceuticals such as paroxetine which is useful, for example, as an antidepressant.

## ABSTRACT OF THE DISCLOSURE

An L-tartrate of a trans-(-)-4-(4-fluorophenyl)-  
3-hydroxymethylpiperidine compound, represented by the  
5 formula (I):



wherein  $R^1$  is hydrogen atom, a substituted or  
15 unsubstituted, linear or branched alkyl group having 1 to  
6 carbon atoms, or an aralkyl group having 7 to 12 carbon  
atoms. The L-tartrate of trans-(-)-4-(4-fluorophenyl)-  
3-hydroxymethylpiperidine compound can be suitably used as  
an intermediate for pharmaceuticals such as paroxetine  
20 which is useful, for example, as an antidepressant.

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L-TARTRATE OF TRANS-(-)-4-(4-FLUOROPHENYL)-  
3-HYDROXYMETHYLPIPERIDINE COMPOUND AND  
PROCESS FOR PREPARING THE SAME

5 BACKGROUND OF THE INVENTION

Field of the Invention

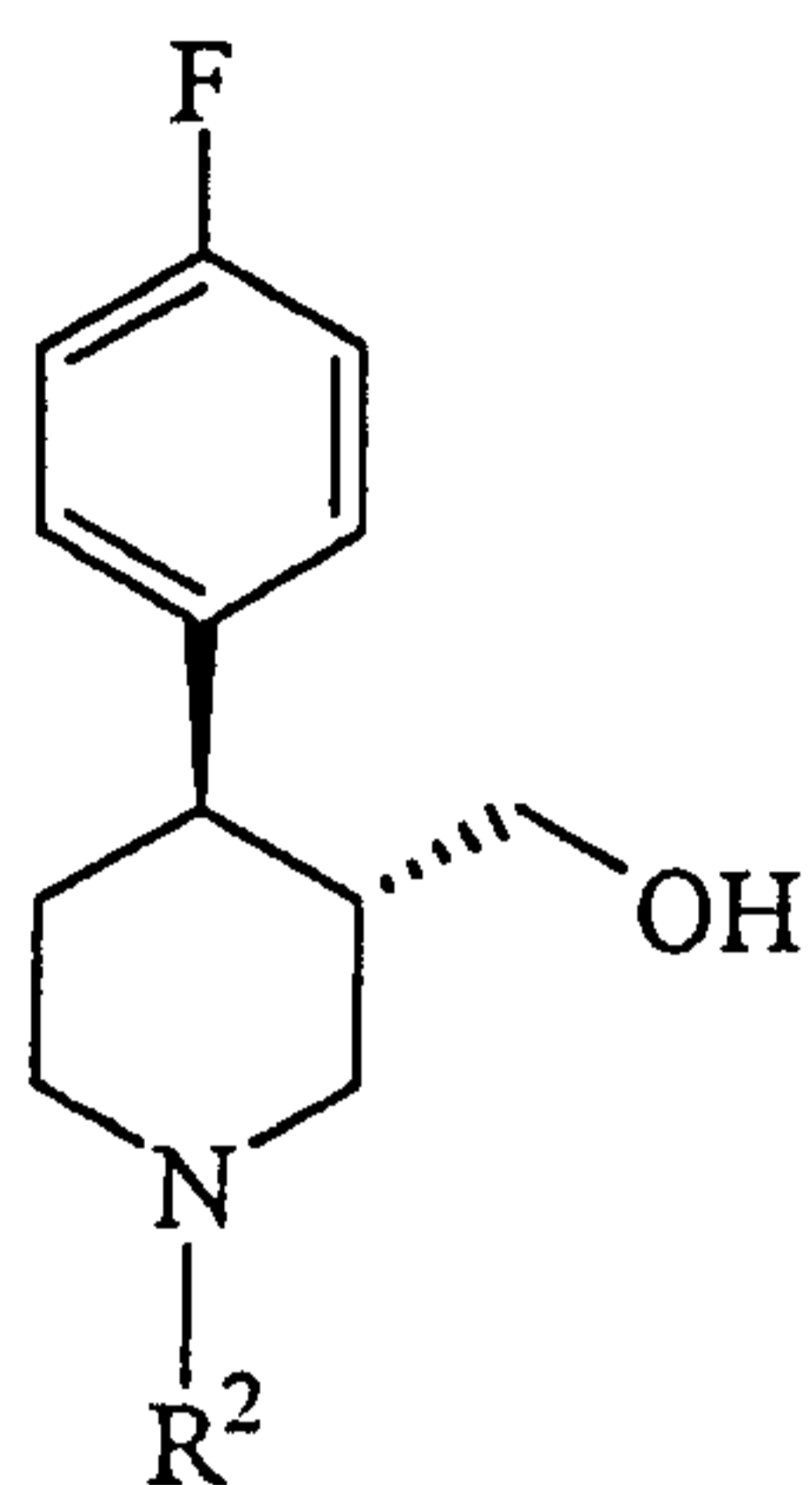
The present invention relates to an L-tartrate of a  
trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine  
compound, and a process for preparing the same. More  
10 specifically, the present invention relates to an  
L-tartrate of a trans-(-)-4-(4-fluorophenyl)-  
3-hydroxymethylpiperidine compound which is useful as an  
intermediate for pharmaceuticals such as paroxetine which  
is useful, for example, as an antidepressant, and a  
15 process for preparing the same.

Discussion of the Related Art

Conventionally, a salt of tartranilic acid derivative  
of a trans-(-)-4-(4-fluorophenyl)-  
20 3-hydroxymethylpiperidine compound, represented by the  
formula (III):

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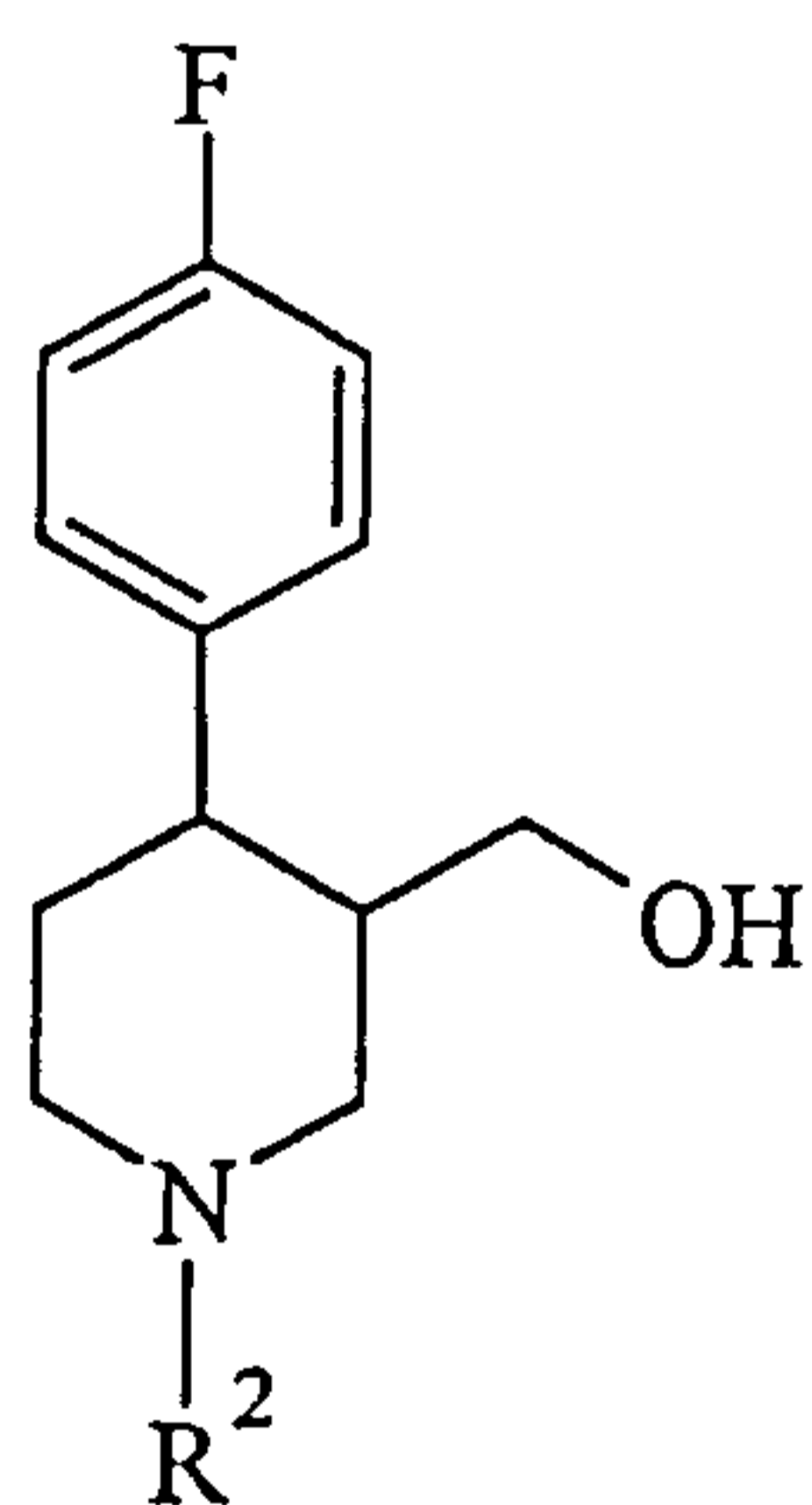
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(III)

10 wherein  $R^2$  is hydrogen atom, methyl group or benzyl group,  
has been prepared by optically resolving a  
trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine  
compound represented by the formula (IV):

15



(IV)

20

wherein  $R^2$  is the same as defined above,  
with a tartranilic acid derivative, such as  
(+)-2'-nitrotartranilic acid or (+)-2'-chlorotartranilic  
25 acid, as an optically resolving agent.

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However, since the tartranilic acid derivative used as an optically resolving agent is extremely expensive, there is a defect in this process that a complicated procedure of collecting the tartranilic acid derivative after its use and purifying it for reuse is necessitated.

In addition, since the salt of tartranilic acid of the resulting trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound prepared by using the optically resolving agent has a low bulk density of 230 g/l or so, there arises a defect of poor production efficiency.

In view of the above problems, an object of the present invention is to provide a compound capable of being suitably used as an intermediate for pharmaceuticals such as paroxetine which is useful, for example, as an antidepressant, and a process for preparing the compound using an inexpensive optically resolving agent with high production efficiency.

These and other objects of the present invention will be apparent from the following description.

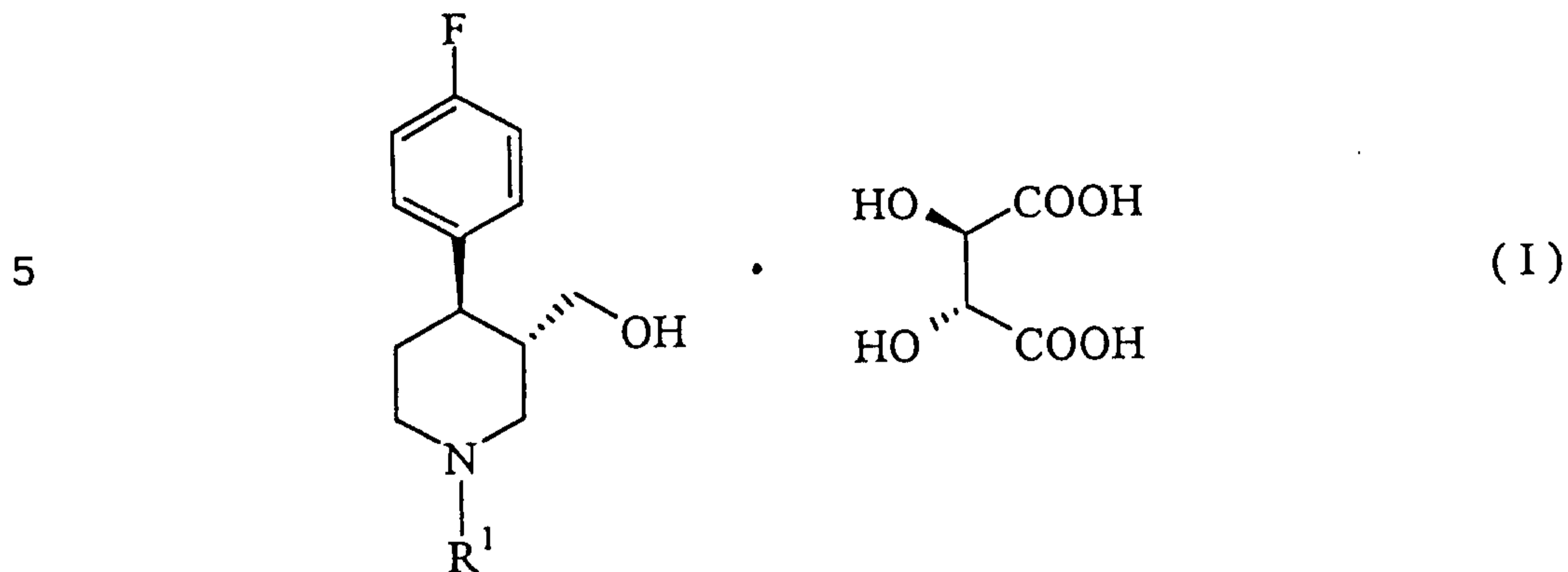
#### SUMMARY OF THE INVENTION

The present invention pertains to:

[1] an L-tartrate of a trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound, represented by the

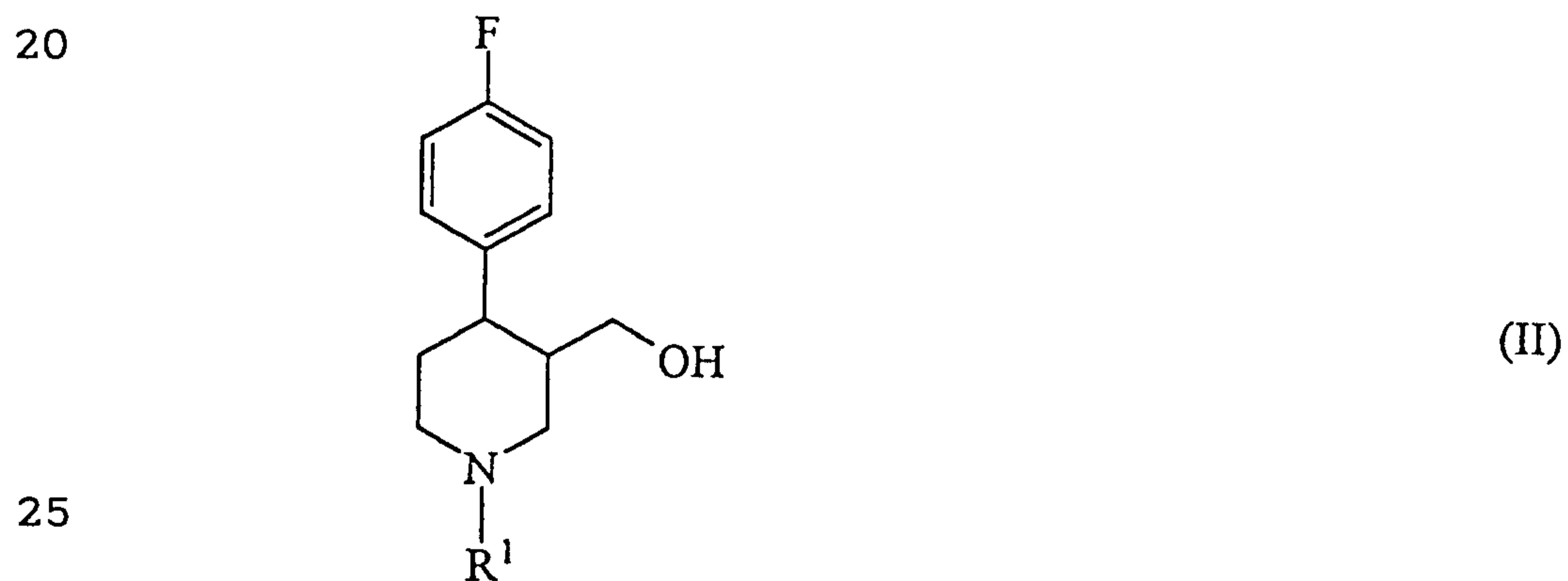
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formula (I):



10 wherein R<sup>1</sup> is hydrogen atom, a substituted or unsubstituted, linear or branched alkyl group having 1 to 6 carbon atoms, or an aralkyl group having 7 to 12 carbon atoms; and

[2] a process for preparing a  
 15 trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound, represented by the formula (I), comprising reacting a trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound represented by the  
 20 formula (II):



- 5 -

wherein R<sup>1</sup> is the same as defined above,  
with L-tartaric acid.

## BRIEF DESCRIPTION OF THE DRAWINGS

5           The present invention will become more fully  
understood from the detailed description given hereinbelow  
and the accompanying drawings which are given by way of  
illustration only, and thus, are not limitative of the  
present invention, and wherein:

10           Figure 1 is a chart showing an infrared absorption  
spectrum of the L-tartrate of  
trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine  
prepared in Reference Example;

15           Figure 2 is a chart showing an infrared absorption  
spectrum of the L-tartrate of  
trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine  
prepared in Example 1;

20           Figure 3 is a chart showing an infrared absorption  
spectrum of the L-tartrate of  
trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine  
prepared in Example 2; and

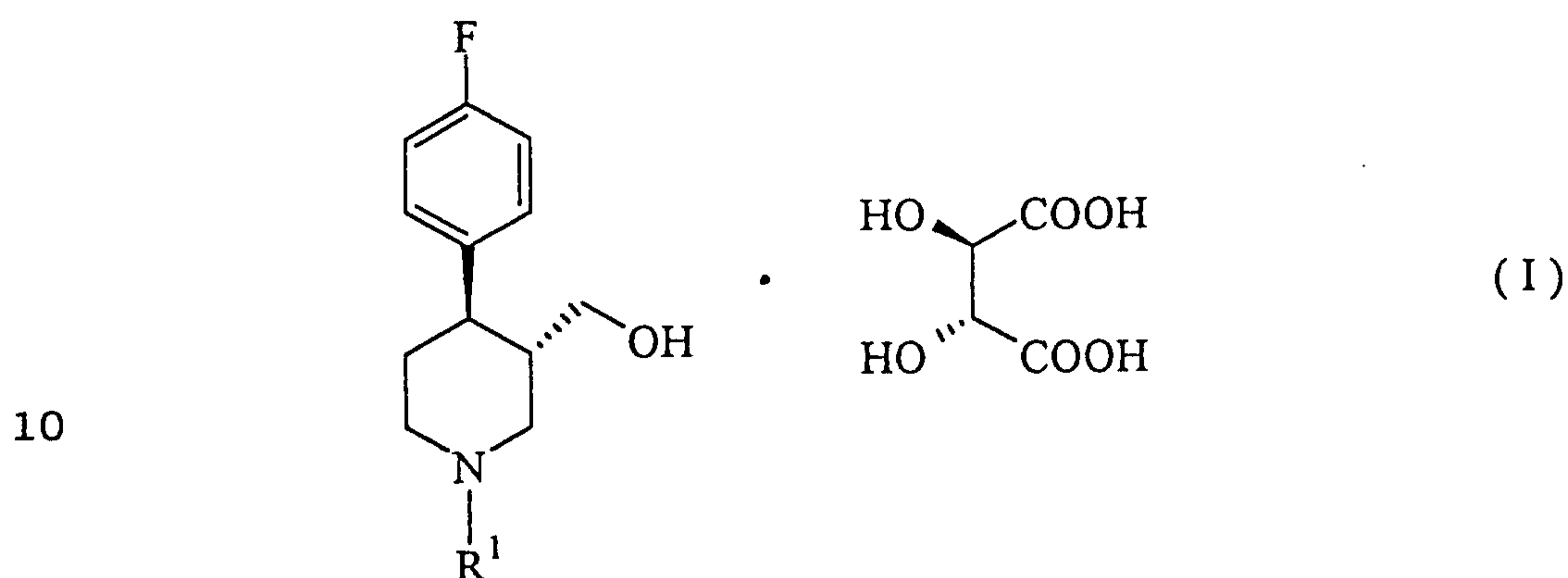
25           Figure 4 is a chart showing an infrared absorption  
spectrum of the L-tartrate of  
trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine  
prepared in Example 3.

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## DETAILED DESCRIPTION OF THE INVENTION

The L-tartrate of a trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound of the present invention represented by the formula (I):

5



10

wherein  $R^1$  is hydrogen atom, a substituted or unsubstituted, linear or branched alkyl group having 1 to 6 carbon atoms, or an aralkyl group having 7 to 12 carbon atoms,

15

is a novel compound.

20

In the formula (I),  $R^1$  is hydrogen atom, a substituted or unsubstituted, linear or branched alkyl group having 1 to 6 carbon atoms, or an aralkyl group having 7 to 12 carbon atoms.

25

The linear or branched alkyl group having 1 to 6 carbon atoms includes, for instance, linear alkyl groups having 1 to 6 carbon atoms, such as methyl group, ethyl group, n-propyl group, n-butyl group, n-pentyl group and

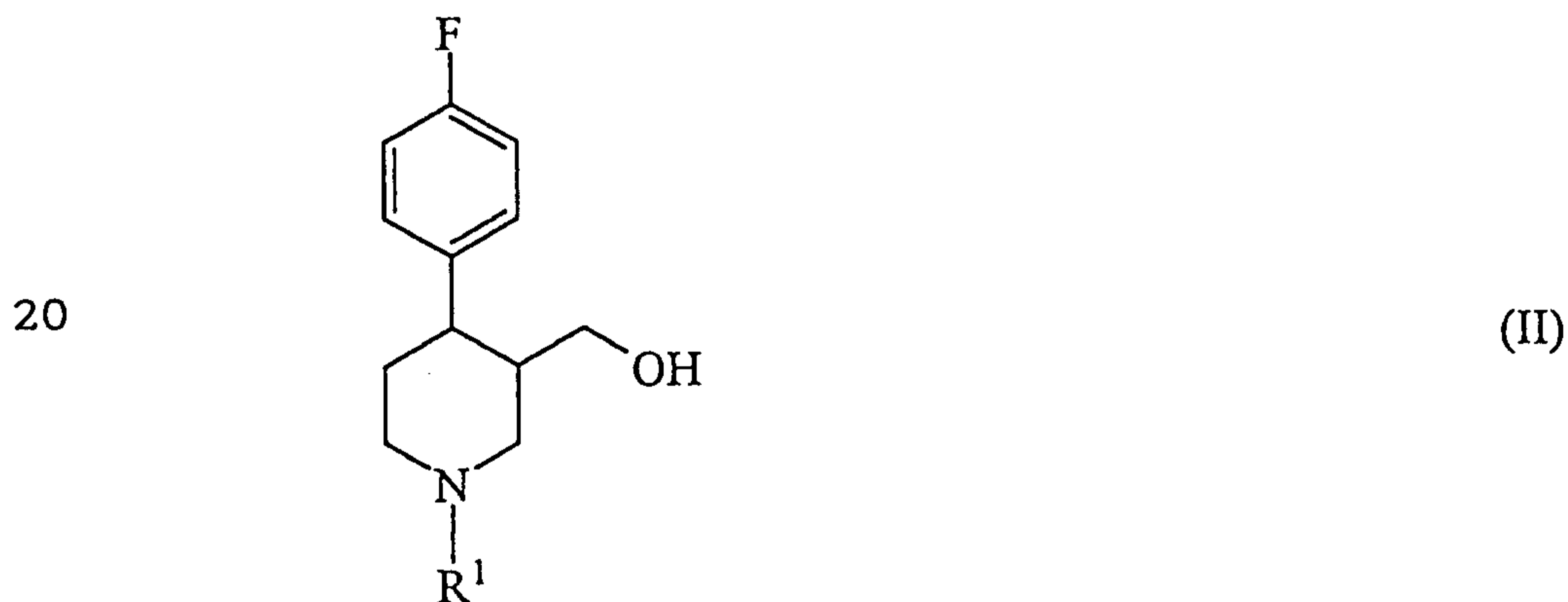
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n-hexyl group; branched alkyl groups having 3 to 6 carbon atoms, such as isopropyl group, sec-butyl group and tert-butyl group, and the like. Among R<sup>1</sup> mentioned above, hydrogen atom and methyl group are preferable.

5 The aralkyl group of 7 to 12 carbon atoms having a linear or branched alkyl group includes, for instance, benzyl group, and the like.

Incidentally, the alkyl group and the aralkyl group may have a substituent. The substituent includes, for instance, a halogen atom, methoxy group, an alkoxy carbonyl group having 2 to 8 carbon atoms.

The L-tartrate of a trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound, represented by the formula (I) can be prepared by reacting a trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound represented by the formula (II):



wherein R<sup>1</sup> is the same as defined above,  
25 with L-tartaric acid to form a salt.

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One of the major features in the present invention resides in the use of L-tartaric acid as an optically resolving agent. Since the L-tartaric acid is an inexpensive and readily available compound, there are  
5 advantageous merits not only that the process of the present invention has excellent productivity on an industrial scale, but also that an L-tartrate of a trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound, having an extremely high bulk density of 650 to  
10 700 g/l or so can be efficiently prepared. Moreover, when the L-tartaric acid is used, there can be exhibited an excellent effect that the amount of the solvent used during the formation of a salt can be dramatically reduced as compared to a case where conventional optically  
15 resolving agents such as a tartranilic acid derivative are used.

As described above, according to the process of the present invention, numerous remarkably excellent effects can be exhibited by using L-tartaric acid as an optically  
20 resolving agent, thereby enjoying remarkably excellent productivity on an industrial scale.

The trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound represented by the formula (II), is readily available from processes as  
25 disclosed, for instance, in Japanese Examined Patent

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Publication No. Hei 6-96551 and Japanese Patent Laid-Open No. Hei 9-278754.

When the trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound represented by the formula (II) is reacted with L-tartaric acid, a solvent can be used. The solvent includes, for instance, monohydric alcohols having 1 to 4 carbon atoms, such as methanol, ethanol, isopropanol; ketones, such as acetone and methyl ethyl ketone, and the like. Those solvents can be used alone or in an admixture thereof. Among them, a solvent comprising methanol as a main component is desirable from the viewpoint of obtaining trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound having high optical purity. In the present specification, the solvent comprising methanol as a main component refers to a solvent containing at least 50% by volume of methanol. Among the solvents comprising methanol as a main component, methanol or a mixed solvent of methanol and at least one compound of isopropyl alcohol and acetone is desirable from the viewpoint of obtaining trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound having higher optical purity. Also, the mixed solvent of methanol and at least one compound of isopropyl alcohol and acetone is also desirable from the viewpoint of obtaining trans-(-)-4-(4-fluorophenyl)-

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3-hydroxymethylpiperidine compound in high yields. It is desired that the ratio of methanol to at least one compound of isopropyl alcohol and acetone is such that the amount of at least one compound of isopropyl alcohol and acetone is at least 10 parts by volume, preferably at least 20 parts by volume, more preferably at least 30 parts by volume, based on 100 parts by volume of methanol, from the viewpoint of obtaining the L-tartrate of a trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound in high yields. In addition, the ratio of methanol to at least one compound of isopropyl alcohol and acetone cannot be absolutely determined, because the optical purity of the resulting trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound may differ depending upon several factors such as amount of the solvent, temperatures during the formation of a salt, and period of time required for the formation of a salt as well as the ratio of methanol to at least one compound of isopropyl alcohol and acetone. Generally, in accordance with the increase of the ratio of methanol to at least one compound of isopropyl alcohol and acetone, its optical purity tends to be lowered. Accordingly, it is desired that the amount of at least one compound of isopropyl alcohol and acetone is usually at most 500 parts by volume, preferably at most 200 parts by volume, more

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preferably at most 100 parts by volume, further preferably at most 60 parts by volume, particularly preferably at most 40 parts by volume, based on 100 parts by volume of methanol, from the viewpoint of improvement in optical  
5 purity.

It is desired that the amount of the solvent is at least 200 parts by weight, preferably at least 500 parts by weight, based on 100 parts by weight of the trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine  
10 compound, from the viewpoint of giving an L-tartrate of a trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound with high optical purity, and that the amount of the solvent is at most 2000 parts by weight, preferably at most 700 parts by weight, based on 100 parts by weight of  
15 the trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound, from the viewpoint of improvement in yields.

When the trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound is reacted with L-tartaric acid to form a salt in a solvent, any of the  
20 trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound and L-tartaric acid can be firstly dissolved in the solvent.

It is desired that the amount of L-tartaric acid is at least 0.8 mol, preferably at least 0.9 mol, per one mol  
25 of the trans-(±)-4-(4-fluorophenyl)-

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3-hydroxymethylpiperidine compound, from the viewpoint of giving a compound with high optical purity, and that the amount of L-tartaric acid is at most 2 mol, preferably at most 1.2 mol, per one mol of the

5 trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound, from the viewpoint of suppression of the residual L-tartaric acid and economic advantages.

It is desired that the temperature during the formation of a salt is at least 0°C, preferably at least 10°C, more  
10 preferably at least 20°C, from the viewpoint of acceleration of the formation of a salt, and that the temperature is at most a boiling point of the solvent used, preferably at most 40°C. Particularly, it is desired that the temperature during the formation of a salt is 20° to 35°C, from the  
15 viewpoint of giving a L-tartrate of a trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound having high optical purity in high yields.

The atmosphere the formation of a salt is not limited to specified ones, and it may be air, or an inert gas such  
20 as nitrogen gas.

The time period required for the formation of a salt cannot be absolutely determined, because it may differ depending upon the conditions for the formation of a salt. Usually, the time period for the reaction is 1 to 24 hours  
25 or so. However, since the time period for the reaction is

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longer, the optical purity of the resulting L-tartrate of a trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound tends to be lowered, it is desired that the time period is as short as possible, for instance, at most 5 hours, preferably at most 3 hours.

Thus, the L-tartrate of a trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound can be precipitated as crystals by reacting the trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound with L-tartaric acid to form a salt. The resulting L-tartrate of a trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound can be isolated and purified by, for instance, separating by such means as filtration, and as occasion demands, washing with the solvent and drying.

The resulting L-tartrate of a trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine compound can be suitably used as an intermediate for pharmaceuticals such as paroxetine which is useful, for example, as an antidepressant, as described above.

#### EXAMPLES

The present invention will be more specifically described by the following examples, without intending to restrict the scope or spirit of the present invention

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thereto.

Reference Example [Preparation of L-Tartrate of  
trans-(-)-4-(4-Fluorophenyl)-3-hydroxymethylpiperidine]

5           A trans-(-)-4-(4-fluorophenyl)-  
3-hydroxymethylpiperidine monohydrate which was previously  
optically resolved and desalted was prepared.

          Subsequently, 10.00 g (44.0 mmol) of the  
trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine  
10           monohydrate, 6.60 g (44.0 mmol) of L-tartaric acid, and  
50 ml of methanol were mixed together, and 50 ml of  
isopropanol was added to the resulting mixture under  
ice-cooling. The mixture was allowed to stand to  
precipitate crystals, and the resulting crystals were  
15           filtered. The crystals were washed with a 10 ml mixed  
solvent of 5 ml of methanol and 5 ml of isopropanol and  
dried, to give 5.60 g (15.6 mmol) of L-tartrate of  
trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine  
(yield: 35.5%).

20           The physical properties of the resulting L-tartrate  
of trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine  
were as follows:

          Optical purity [(-)-isomer]: 100.0%

          Optical rotation  $[\alpha]_D^{20}$ :  $-11.8^\circ$  (0.5%, water, 100 mm)

25           Melting point:  $161.0^\circ\text{C}$

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IR (Infrared absorption spectrum): The results are shown in Figure 1.

Elemental Analysis:

Calculated Value: C 53.5%; H 6.2%; N 3.9%

5 Found Value: C 53.3%; H 6.2%; N 3.7%

Example 1

There were mixed 10.00 g (47.8 mmol) of trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine,  
10 7.17 g (47.8 mmol) of L-tartaric acid, and 50 ml of methanol, and the resulting mixture was then stirred at about 10°C for four hours and allowed to stand to precipitate the crystals. The precipitated crystals were collected by filtration.

15 The resulting crystals were washed with 10 ml of methanol, and then dried, to give 5.60 g (15.6 mmol) of L-tartrate of trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine (yield: 32.6%).

It was confirmed that the resulting compound was  
20 L-tartrate of trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine from the fact that the infrared absorption spectrum was identified to that of the L-tartrate of trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine which has previously been  
25 prepared in Reference Example. The infrared absorption

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spectrum is shown in Figure 2.

The physical properties of the resulting L-tartrate of trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine were as follows:

5           Optical purity [(-)-isomer]: 98.5%

          Optical rotation  $[\alpha]_D^{20}$ : -12.1° (0.5%, water, 100 mm)

          Melting point: 160.9°C

          Bulk density: 680 g/l (measured by graduated cylinder method, the same applied hereinbelow)

10

#### Example 2

          There were dissolved 10.00 g (47.8 mmol) of trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine and 7.17 g (47.8 mmol) of L-tartaric acid in 50 ml of  
15           methanol, and 30 ml of acetone was added to the resulting solution. The mixture was then stirred at about 30°C for four hours and allowed to stand to precipitate the crystals. The precipitated crystals were collected by filtration.

20           The resulting crystals were washed with 10 ml of a mixed solvent of acetone and methanol (volume ratio of acetone/methanol: 3/5), and then dried, to give 5.37 g (14.9 mmol) of L-tartrate of trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine (yield: 31.3%).

25           It was confirmed that the resulting compound was

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L-tartrate of trans-(-)-4-(4-fluorophenyl)-  
3-hydroxymethylpiperidine from the fact that the infrared  
absorption spectrum was identified to that of the  
L-tartrate of trans-(-)-4-(4-fluorophenyl)-  
5 3-hydroxymethylpiperidine which has previously been  
prepared in Reference Example. The infrared absorption  
spectrum is shown in Figure 3.

In addition, the physical properties of the resulting  
L-tartrate of trans-(-)-4-(4-fluorophenyl)-  
10 3-hydroxymethylpiperidine were as follows:

Optical purity [(-)-isomer]: 99.5%

Optical rotation  $[\alpha]_D^{20}$ :  $-11.7^\circ$  (0.5%, water, 100 mm)

Melting point:  $162.3^\circ\text{C}$

Bulk density: 680 g/l

15

### Example 3

There were dissolved 10.00 g (47.8 mmol) of  
trans-(±)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine and  
7.17 g (47.8 mmol) of L-tartaric acid in 50 ml of  
20 methanol, and 20 ml of isopropanol was added to the  
resulting solution. The mixture was then stirred at about  
20°C for four hours and allowed to stand to precipitate  
the crystals. The precipitated crystals were collected by  
filtration.

25 The resulting crystals were washed with 10 ml of a

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mixed solvent of isopropanol and methanol (volume ratio of isopropanol/methanol: 2/5), and then dried, to give 6.53 g (18.2 mmol) of L-tartrate of trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine (yield: 38.0%).

5           It was confirmed that the resulting compound was L-tartrate of trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine from the fact that the infrared absorption spectrum was identified to that of the L-tartrate of trans-(-)-4-(4-fluorophenyl)-  
10 3-hydroxymethylpiperidine previously prepared in Reference Example. The infrared absorption spectrum is shown in Figure 4.

In addition, the physical properties of the resulting L-tartrate of trans-(-)-4-(4-fluorophenyl)-  
15 3-hydroxymethylpiperidine were as follows:

Optical purity [(-)-isomer]: 98.2%

Optical rotation  $[\alpha]_D^{20}$ :  $-10.6^\circ$  (0.5%, water, 100 mm)

Melting point:  $160.0^\circ\text{C}$

Bulk density: 680 g/l

20

#### Examples 4 and 5

The same procedures as in Example 3 were carried out except that the temperature during stirring was changed from  $20^\circ\text{C}$  to  $25^\circ\text{C}$  (Example 4) or  $31^\circ\text{C}$  (Example 5),  
25 respectively, to prepare L-tartrate of

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trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine.  
As a result, the resulting L-tartrate of  
trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine  
obtained in Example 4 had optical purity of 99.2%, and  
5 yield of 38.6%, and the L-tartrate obtained in Example 5  
had an optical purity of 99.9% and yield of 36.4%.

From the above results, it can be seen that according  
to the processes of Examples 1 to 5, the L-tartrate of  
10 trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine can  
be prepared with high production efficiency by using an  
inexpensive optically resolving agent.

The L-tartrate of trans-(-)-4-(4-fluorophenyl)-  
3-hydroxymethylpiperidine of the present invention can be  
15 suitably used as an intermediate for pharmaceuticals such  
as paroxetine which is useful, for example, as an  
antidepressant.

In addition, according to the process of the present  
invention, the L-tartrate of trans-(-)-4-(4-fluorophenyl)-  
20 3-hydroxymethylpiperidine can be prepared with a high  
production efficiency by using an inexpensive optically  
resolving agent.

The present invention being thus described, it will  
be obvious that the same may be varied in many ways. Such  
25 variations are not to be regarded as a departure from the

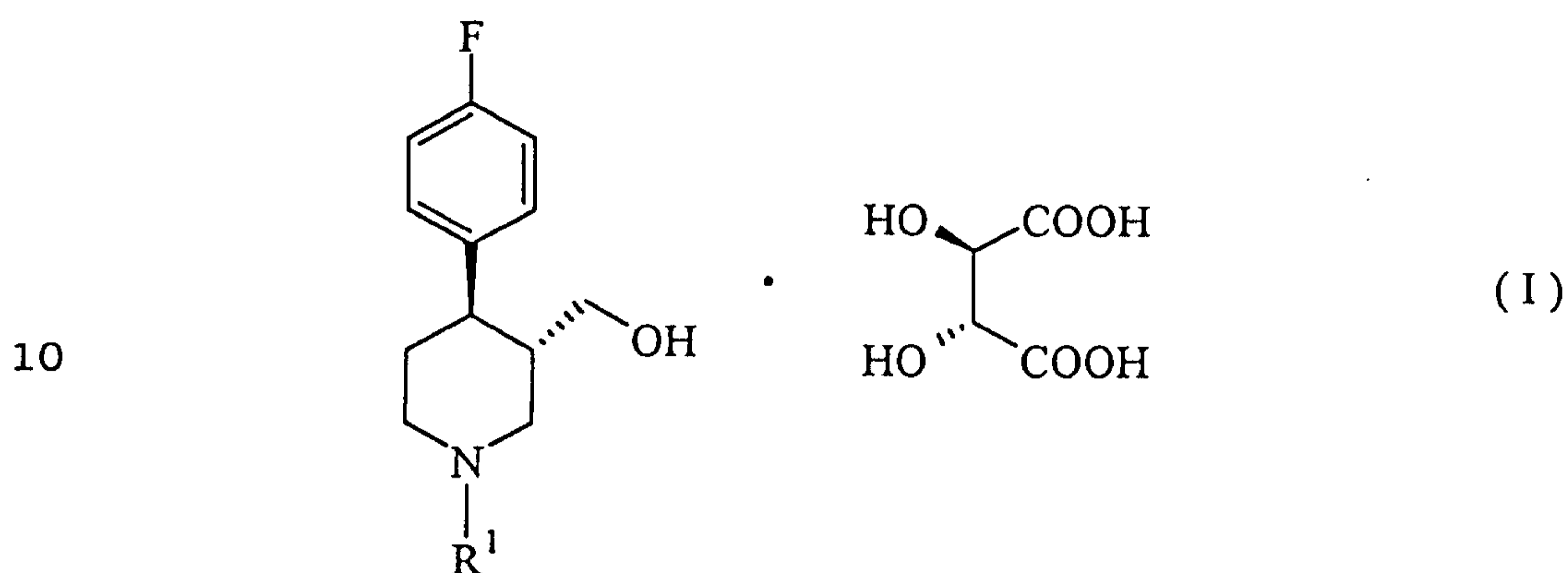
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spirit and scope of the invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

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WHAT IS CLAIMED IS:

1. An L-tartrate of a trans-(-)-4-(4-fluorophenyl)-  
3-hydroxymethylpiperidine compound, represented by the  
5 formula (I):



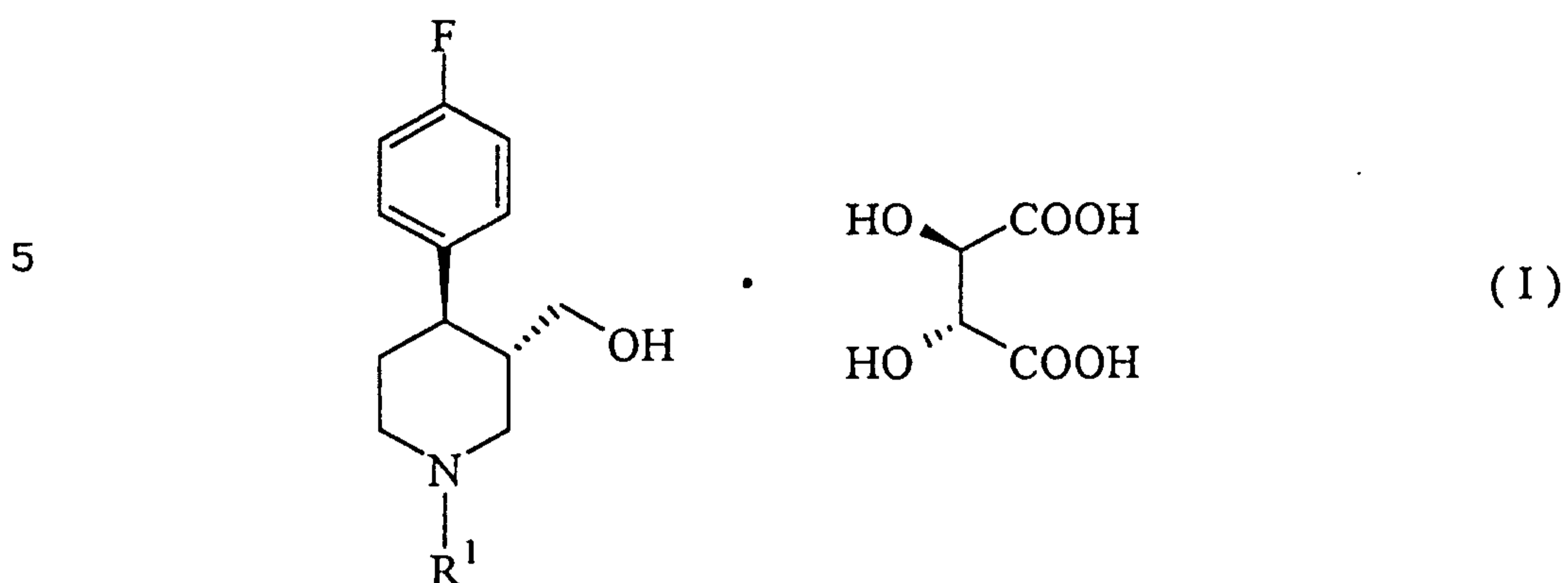
wherein  $R^1$  is hydrogen atom, a substituted or  
15 unsubstituted, linear or branched alkyl group having 1 to  
6 carbon atoms, or an aralkyl group having 7 to 12 carbon  
atoms.

2. The L-tartrate of a  
20 trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine  
compound according to claim 1, wherein  $R^1$  is hydrogen atom  
or methyl group.

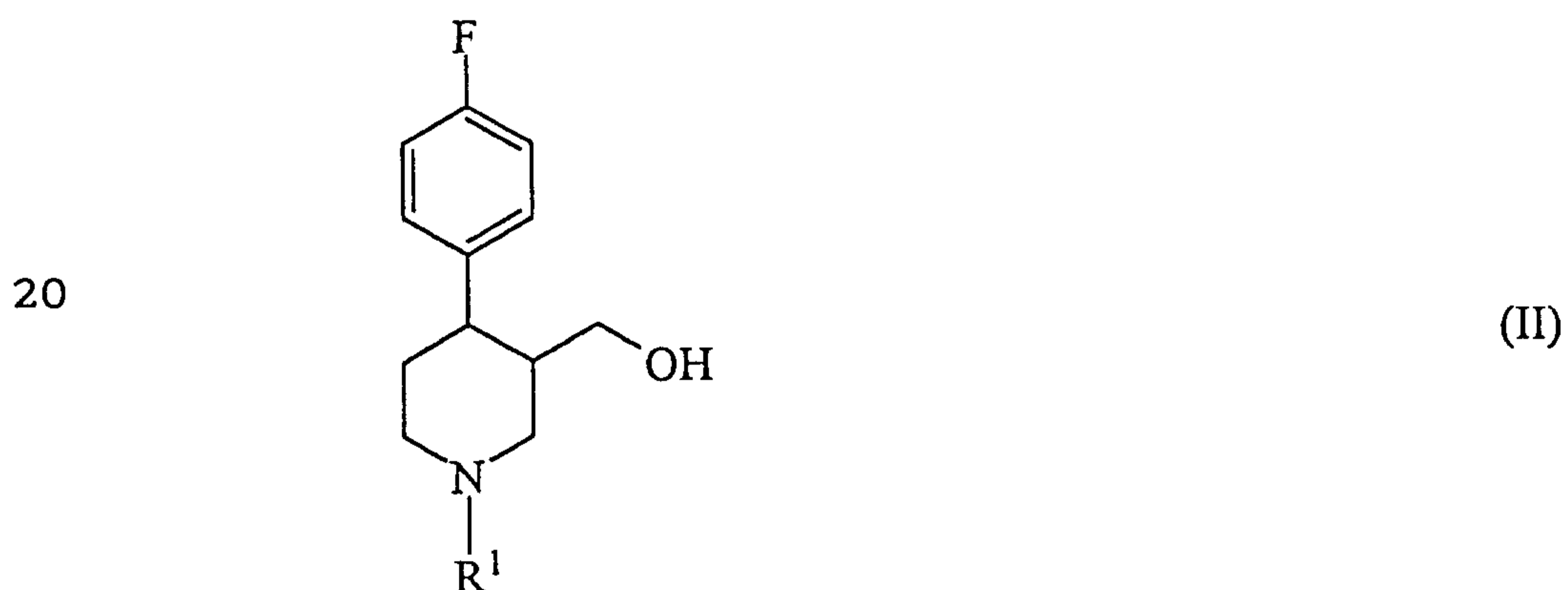
3. A process for preparing a  
25 trans-(-)-4-(4-fluorophenyl)-3-hydroxymethylpiperidine

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compound, represented by the formula (I):



10 wherein R<sup>1</sup> is hydrogen atom, a substituted or  
 unsubstituted, linear or branched alkyl group having 1 to  
 6 carbon atoms, or an aralkyl group having 7 to 12 carbon  
 atoms,  
 comprising reacting a trans-(±)-4-(4-fluorophenyl)-  
 15 3-hydroxymethylpiperidine compound represented by the  
 formula (II):



25 wherein R<sup>1</sup> is the same as defined above,

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with L-tartaric acid.

4. The process according to claim 3, wherein a solvent comprising methanol as a main component is used  
5 when the trans-(±)-4-(4-fluorophenyl)-  
3-hydroxymethylpiperidine compound represented by the formula (II) is reacted with L-tartaric acid.

5. The process according to claim 4, wherein said  
10 solvent is methanol, or a mixed solvent of methanol and at least one compound of isopropyl alcohol and acetone.

FIG. 1

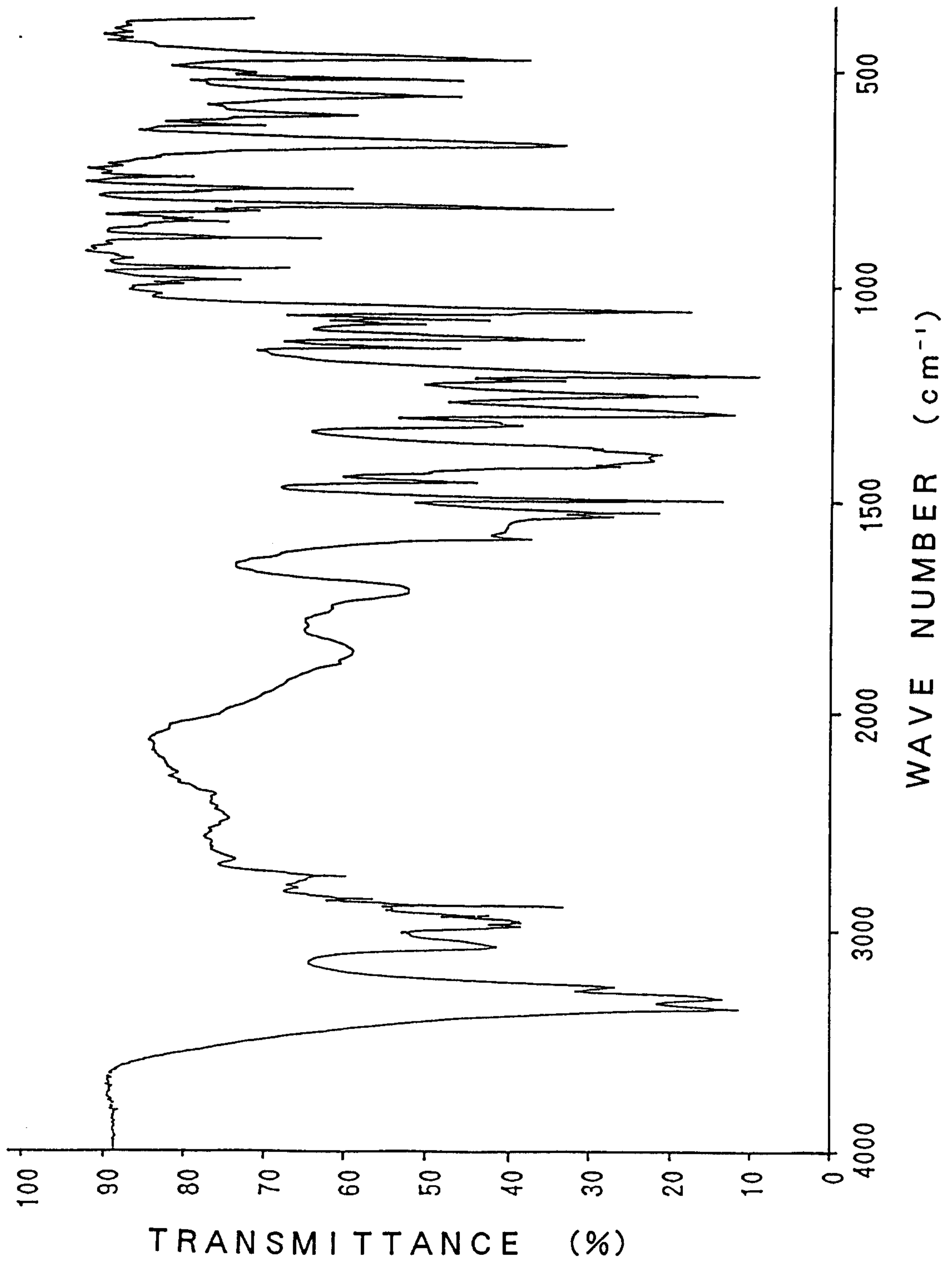


FIG. 2

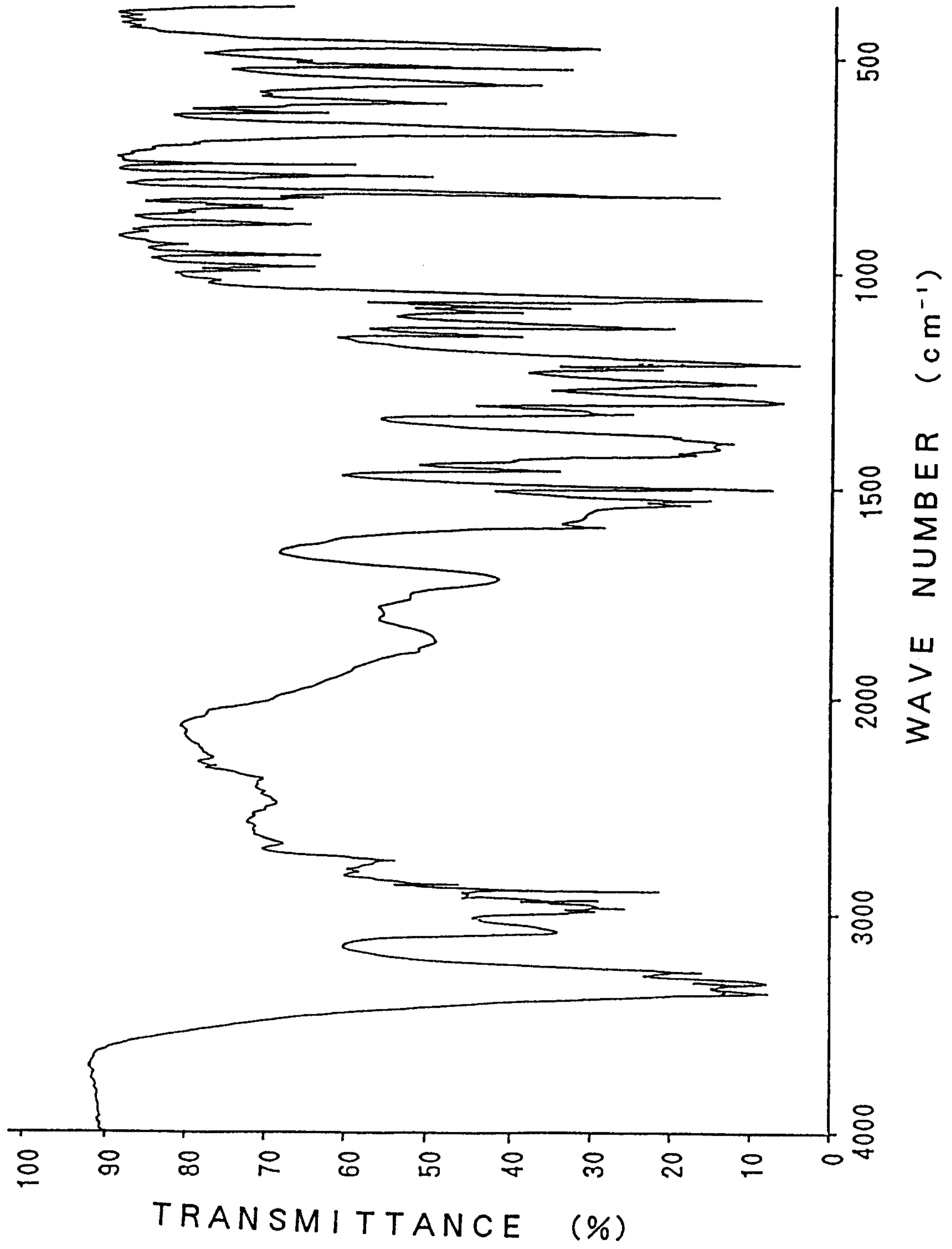


FIG. 3

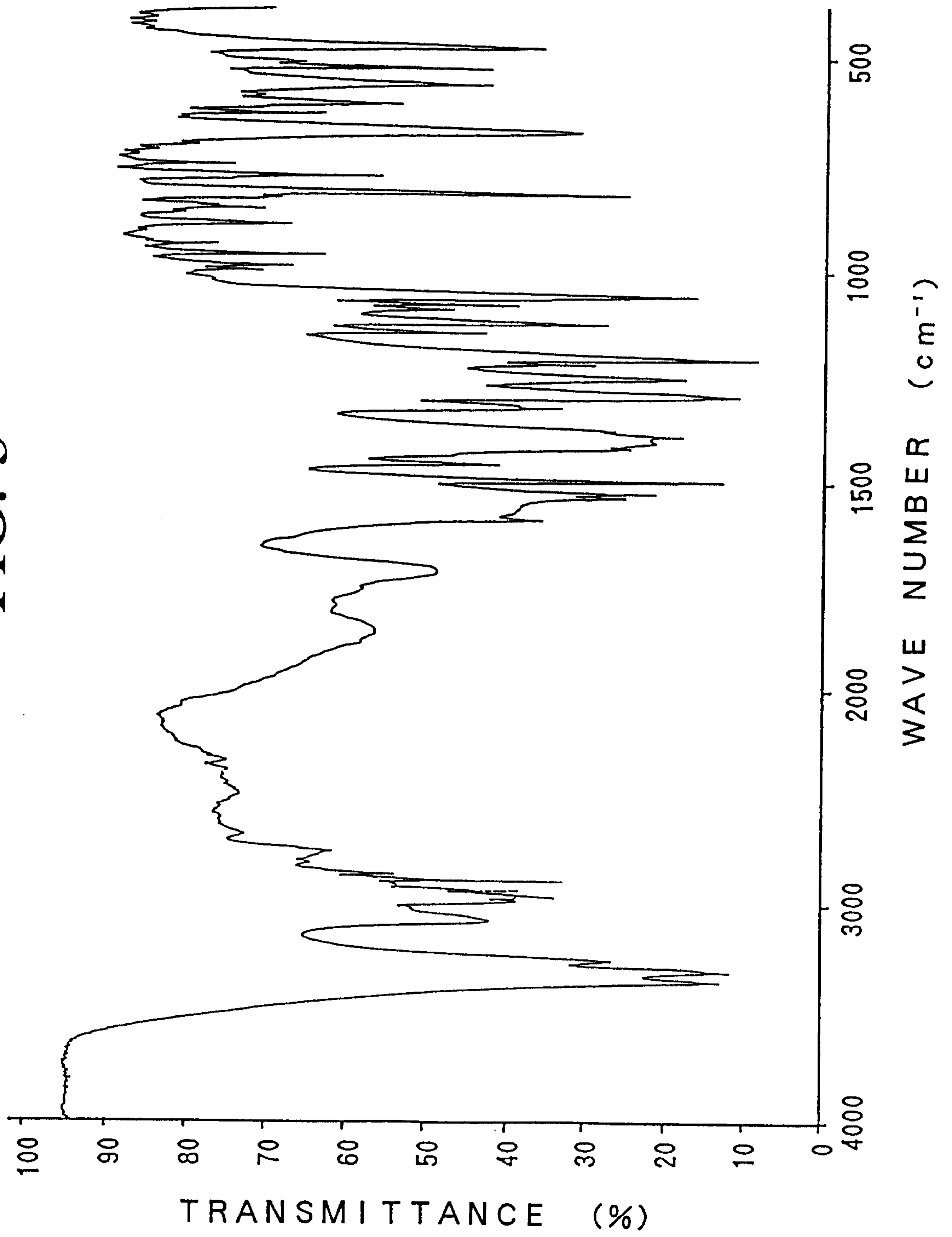


FIG. 4

