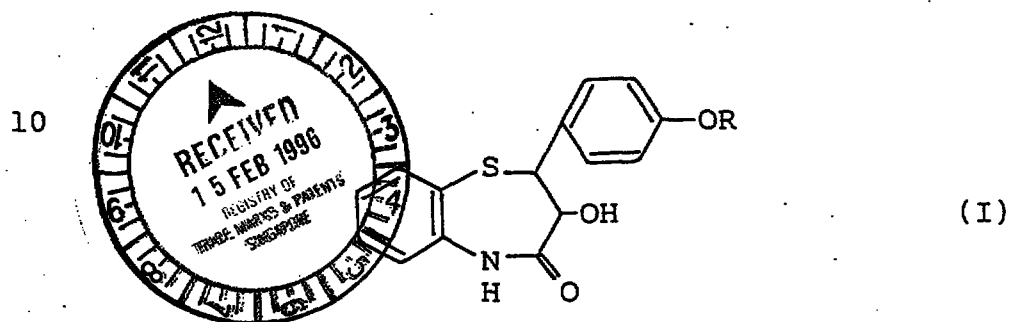


- 1 -

Process for preparing 1,5-benzothiazepine derivatives

BACKGROUND OF THE INVENTION

5 This invention relates to a novel process for preparing
1,5-benzothiazepine derivatives represented by the
formula:



15

wherein R represents a lower alkyl group.

The above 1,5-benzothiazepine derivatives (I) are useful
compounds as an intermediate for the synthesis of medical
20 compounds, for example, (+)-cis-2-(4-methoxyphenyl)-3-
acetoxy-5-(β -dimethylaminoethyl)-2,3-dihydro-1,5-benzo-
thiazepin-4(5H)-one (generic name: Diltiazem) having
excellent coronary vasodilating activity.

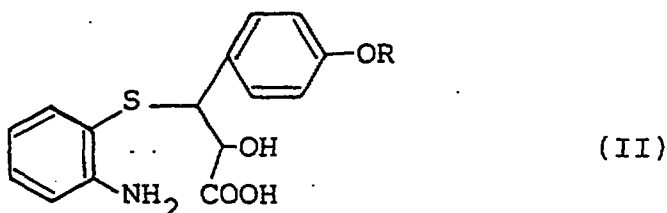
25 Heretofore, as a process for preparing 1,5-benzothiazepine
derivatives (I), for example, the method in which 2-hydroxy-
3-(2-aminophenylthio)-3-(4-methoxyphenyl)propionic acid is

subjected to intramolecular ring closing reaction in xylene under reflux (Japanese Patent Publication No. 18038/1978) has been known. However, this method is disadvantageous in that a long time (12 hours in Examples of the above publication) is required for completing the reaction.

SUMMARY OF THE INVENTION

The present inventors have studied various research and as a result, they have found that, when the intramolecular ring closing reaction of a specific propionic acid compound (II) is carried out in the presence of a specific sulfonic acid compound, the reaction time can be remarkably shortened and the compound (I) can be prepared in good yield.

That is, according to the process of the present invention, the desired product represented by the formula (I) can be prepared by subjecting a propionic acid derivative represented by the formula (II):



wherein R has the same meaning as defined above, to intramolecular ring closing reaction in the presence of a sulfonic acid compound represented by the formula:



wherein R^1 represents a lower alkyl group or a substituted or unsubstituted phenyl group.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

5 Examples of the sulfonic acid compound (III) to be used in the intramolecular ring closing reaction of the present invention include, for example, the compounds wherein R¹ in the formula (III) is an alkyl group having 1 to 4 carbon atoms such as methyl group, ethyl group, propyl group or butyl group or a phenyl group which may be substituted by at least one of these alkyl groups. Of these, 10 more preferred are methanesulfonic acid and p-toluenesulfonic acid. An amount of the said sulfonic acid is not particularly limited but generally, it is preferably used at an amount of 0.5 to 10 w/w %, more preferably about 1 to 6 w/w % based on the compound (II).

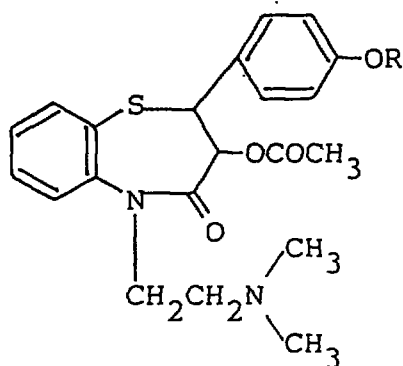
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The above reaction is preferably carried out in a high boiling point solvent such as xylene, toluene, etc. under reflux.

20 The desired compound (I) formed can be isolated as a pure product containing no sulfonic acid compound (III) by simple and easy operations as, for example, cooling the reaction mixture, collecting precipitated crystals by filtration, and washing them with a suitable solvent (e.g. 25 ethanol, aqueous ethanol, etc.).

The thus obtained compound (I) can be converted to the corresponding 3-acetoxy-5-(β-dimethylaminoethyl)-1,5-benzothiazepine derivatives represented by the formula:

30



(IV)

35

wherein R has the same meaning as defined above,
or a pharmaceutically acceptable salt thereof in a known
method, for example, in a method described in Japanese
Patent Publications (unexamined) No. 18038/1978 and No.
5 43785/1971 and U.S. Patents No. 3,562,257 and No. 4,438,-
035, the contents of which are hereby incorporated herein
by reference.

According to the process of the present invention as
10 mentioned above, a time required for the intramolecular
ring closing reaction can be markedly shortened and the
desired compound can be obtained in high yield and high
purity. Therefore, the process of the present invention
is extremely excellent as the industrial process.

15 Throughout the specification and claims, the term "lower
alkyl" should be interpreted as referring to an alkyl
having one to four carbon atoms.

20 Experimental example

For forming (+)-cis-2-(4-methoxyphenyl)-3-hydroxy-2,3-di-
hydro-1,5-benzothiazepin-4(5H)-one by refluxing by heating
12.75 g of (+)-threo-2-hydroxy-3-(2-aminophenylthio)-3-(4-
25 methoxyphenyl)propionic acid in 52 ml of xylene or toluene,
under continuous removal of formed water, the effects of
presence of a sulfonic acid compound in the reaction system
were examined. The results are shown in Tables 1 and 2.

30 In the tables, the amount of the sulfonic acid compound is
based on the starting compound, and p-toluenesulfonic acid
is used as a monohydrate.

Table 1 (in xylene)

	Sulfonic acid compound	Amount used (w/w %)	Reaction time	Yield of desired product (%)
Process of this invention	p-Toluene-sulfonic acid	5.4	30 min	94
		2.7	60 min	93.9
		1.1	1 hr & 15 min	95.5
		0.6	2 hrs & 15 min	95.4
	Methanesulfonic acid	5.4	45 min	93
Control*	—	—	12 hrs	82.2

*: Control is Example described in Japanese Patent Publication No. 18038/1978

Table 2 (in toluene)

	Sulfonic acid compound	Amount used (w/w %)	Reaction time	Yield of desired product (%)
Process of this invention	p-Toluenesulfonic acid	5.4	5 hrs	92
	Methanesulfonic acid	5.4	5 hrs	92
Control	—	—	7 hrs	< 50

As seen from the above Table 1 and Table 2, it can be understood that by the existance of p-toluenesulfonic acid or methanesulfonic acid in the reaction system, the desired product can be obtained within extremely short time in good yield.

Example 1

A mixture of 12.75 g of (+)-threo-2-hydroxy-3-(2-amino-phenylthio)-3-(4-methoxyphenyl)propionic acid, 140 mg of

p-toluenesulfonic acid monohydrate and 52 ml of xylene is refluxed by heating for about 1 hour and 15 minutes. During the reaction, water formed is continuously removed. After cooling, precipitated crystals are collected by
5 filtration and washed with cooled ethanol to give 11.5 g of (+)-cis-2-(4-methoxyphenyl)-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one.

Yield: 95.5 %
10 m.p.: 203 to 204 °C
[α]_D²⁰ + 116 ° (c = 0.5, dimethylformamide)

Example 2

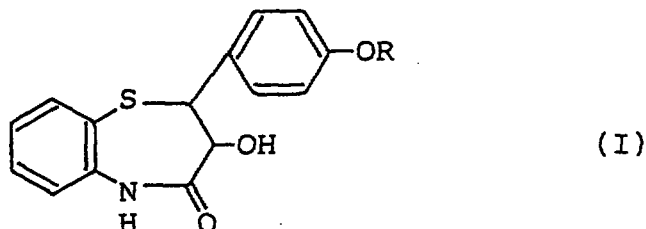
15 A mixture of 12.75 g of (+)-threo-2-hydroxy-3-(2-amino-phenylthio)-3-(4-methoxyphenyl)propionic acid, 690 mg of p-toluenesulfonic acid monohydrate and 52 ml of toluene is refluxed by heating for about 5 hours. During the reaction, water formed is continuously removed. After cooling,
20 ing, precipitated crystals are collected by filtration and washed with cooled ethanol to give 11 g of (+)-cis-2-(4-methoxyphenyl)-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one.

25 Yield: 92 %
m.p.: 203 to 204.5 °C
[α]_D²⁰ + 118 ° (c = 0.5, dimethylformamide)

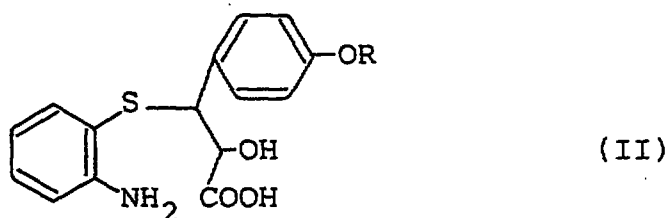


Claims:

1. A process for preparing 1,5-benzothiazepine derivatives represented by the formula:



wherein R is a lower alkyl group,
which comprises subjecting a propionic acid compound
represented by the formula:



wherein R has the same meaning as defined above,
to intramolecular ring closing reaction in the presence of
a sulfonic acid compound represented by the formula:



wherein R^1 represents a lower alkyl group or a substituted or unsubstituted phenyl group.

2. A process for preparing 1,5-benzothiazepine derivatives according to Claim 1, wherein R^1 in the the sulfonic acid compound (III) is methyl group, ethyl group, propyl group, butyl group or phenyl group which may be substituted by at least one selected from methyl group, ethyl group, propyl group and butyl group.

3. A process for preparing 1,5-benzothiazepine derivatives according to Claim 2, wherein the sulfonic acid



compound (III) is methanesulfonic acid or p-toluenesulfonic acid.

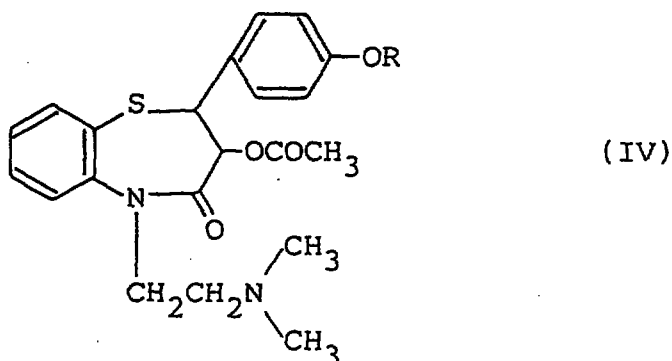
4. A process for preparing 1,5-benzothiazepine derivatives according to Claim 1, wherein the reaction is carried out in an appropriate solvent under reflux.

5. A process for preparing 1,5-benzothiazepine derivatives according to Claim 4, wherein the solvent is at least one selected from xylene, toluene and dichlorobenzene.

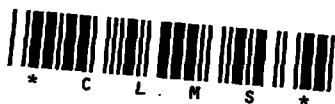
6. A process for preparing 1,5-benzothiazepine derivatives according to Claim 1, wherein the sulfonic acid (III) is used at an amount of 0.5 to 10 w/w % based on the compound (II).

7. A process for preparing 1,5-benzothiazepine derivatives according to Claim 6, wherein the sulfonic acid (III) is used at an amount of 1 to 6 w/w % based on the propionic acid compound (II).

8. A process for preparing 3-acetoxy-5-(β -dimethylaminoethyl)-1,5-benzothiazepine derivatives represented by the formula:



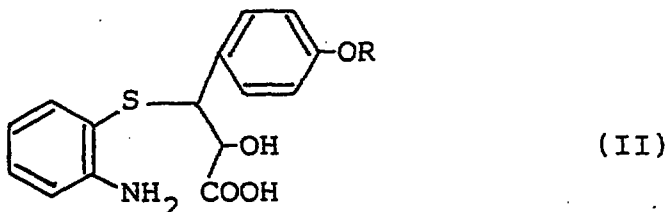
wherein R is a lower alkyl group,



or a pharmaceutically acceptable salt thereof which comprises the steps of:

subjecting a propionic acid compound represented by the formula:

5



10

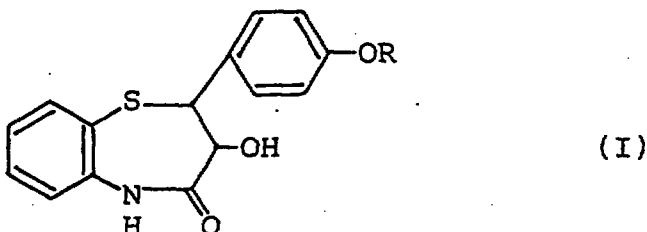
wherein R has the same meaning as defined above, to intramolecular ring closing reaction in the presence of a sulfonic acid compound represented by the formula:

15



wherein R^1 represents a lower alkyl group or a substituted or unsubstituted phenyl group, to give a compound represented by the formula:

20



25

wherein R has the same meaning as defined above, and converting the compound (I) to the corresponding 3-acetoxy-5-(β -dimethylaminoethyl)-1,5-benzothiazepine derivative or a pharmaceutically acceptable salt thereof in a known method.