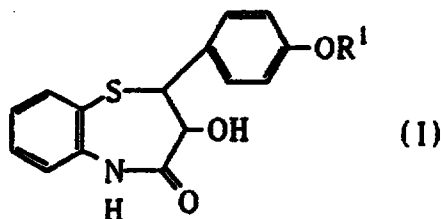


Description

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



wherein R¹ is a C₁ to C₄ alkyl group, or a salt thereof.

The above 2-(4-lower alkoxyphenyl)-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one is useful as an intermediate for the synthesis of medical compounds, for example, (+)-cis-2-(4-methoxyphenyl)-3-acetoxy-5-(β-dimethylaminoethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (generic name : Diltiazem) which is excellent coronary vasodilator.

Heretofore, there have been known that said intermediate can be prepared by the two steps of, for example, hydrolyzing ethyl 2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)propionate with alkali to give corresponding free acid and then subjecting it to intramolecular cyclization under heating (Japanese Patent Publication (examined) No. 8982/1971).

EP-A-0 343 474 describes a process for preparing a 1,5-benzothiazepine derivative by cyclizing a phenyl cyclohexyl ester by reflux in xylene in the presence of p-toluene sulfonic acid.

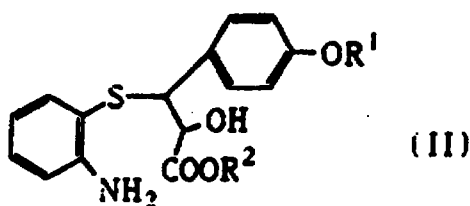
EP-A-0 098 422 describes an intermolecular reaction comprising condensing methyl 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide and 2-aminopyridine in the presence of alkyl- or arylsulfonic acids.

EP-A-0 378 455 cited under Article 54(3) EPC describes in Examples 1 to 3 the intramolecular cyclization of the methyl ester of (2S,3S)-2-hydroxy-3-(4-methoxyphenyl)-3-(2-aminophenylthio)propionic acid in the presence of methanesulfonic acid and chlorobenzene.

EP-A-0 392 543, also cited under Article 54(3) EPC, describes in its Example 10 the intramolecular cyclization of the methyl ester of (2S,3S)-2-hydroxy-3-(4-methoxyphenyl)-3-(2-aminophenylthio)propionic acid in the presence of p-toluenesulfonic acid monohydrate under reflux in xylene.

It is an object of the present invention to provide a novel process for preparing said intermediates from 2-hydroxy-3-(2-aminophenylthio)-3-(4-lower alkoxyphenyl)propionate in a high yield by one step.

According to the present invention, 1,5-benzothiazepine derivatives of the formula (I) can be prepared by subjecting a propionate derivative of the formula:



wherein R² is a C₁ to C₄ alkyl group and R¹ is the same as defined above, to intramolecular cyclization in the presence of a sulfonic acid compound of the formula:



wherein R³ is a lower alkyl group or a substituted or unsubstituted phenyl group, in a non-halogenated organic solvent, provided that the intramolecular cyclization of methyl (2S,3S)-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)-propionate in the presence of p-toluenesulfonic acid monohydrate in xylene at reflux is disclaimed.

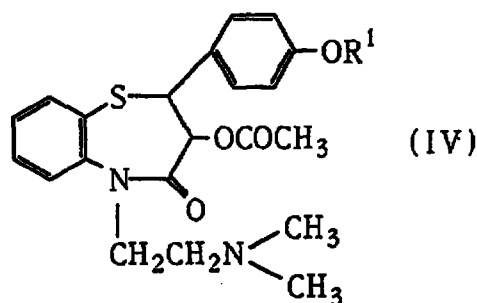
Examples of the sulfonic acid compound (III) to be used in the intramolecular cyclization include, for example, the compound wherein R³ of the formula (III) is an alkyl group having 1 to 4 carbon atoms such as methyl group, ethyl group, propyl group or butyl group or phenyl group which may be substituted by at least one of these alkyl groups. Among them, more preferred are methanesulfonic acid and p-toluenesulfonic acid. An amount of the sulfonic acid compound is not particularly limited but generally, it is preferably used at an amount

of about 0.1 to 10 w/w %, more preferably about 0.5 to 6 w/w %, based on the compound (II).

The solvents used in the invention are not particularly limited and any of non-halogenated organic solvent which will not hinder the reaction can be used. Examples of such solvents include a high boiling point solvent, for example, ethers such as n-propyl ether, n-butyl ether, isobutyl ether, n-pentyl ethers or dioxane; non-halogenated aromatic solvents such as xylene, toluene, ethylbenzene, isobutylbenzene, isopropylbenzene, n-propylbenzene or anisole; aliphatic hydrocarbons such as n-pentane, n-octane or n-nonane.

It is especially preferred to use toluene, ethylbenzene or xylene. It is preferable to carry out intramolecular cyclization at 90 to 160 °C in the above mentioned solvent, especially 110 to 145 °C. Since the above-mentioned reaction is carried out without racemization, the desired compound (I) in the optically active form can be obtained by using the optically active compound (II) as the starting material.

The desired compound (I) thus obtained can be converted to the corresponding 3-acetoxy-5-(β-dimethylaminoethyl)-2,3-dihydro-1,5-benzothiazepine derivatives of the formula:



wherein R¹ is the same as defined above, or a pharmaceutically acceptable salt thereof in a known method, for example, in a method described in Japanese Patent Publication (examined) Nos. 18038/1978 and 43785/1971 and U.S. Patent Nos. 3,562,257 and 4,438,035, the contents of which are hereby incorporated herein by reference.

According to the process of the present invention, 1,5-benzothiazepine derivatives (I) can be obtained in a high yield of more than 85% by one step. Therefore, as compared with the known methods, the process of the invention is extremely excellent for the industrial process.

Further, when the starting compound (II) is prepared by reacting 2-aminothiophenol with 2,3-epoxy-3-(4-lower alkoxyphenyl) propionate in a non-halogenated organic solvent used in the invention, the reaction mixture can be subjected to the intramolecular cyclization without isolating said starting compound (II) from the mixture. In this case, the process of the present invention is advantageous for the industrial scale in that the desired compound (I) can be obtained from epoxy compounds by a substantially single reaction operation in a short time and a high yield.

When the intramolecular cyclization is carried out in the absence of the sulfonic acid compound (III) of the invention, a long time and a high temperature of 160 to 180°C is required for the reaction and the yield of the desired compound is insufficient.

However, according to the process of the present invention, the reaction can be completed in a shorter time at a lower temperature as compared with the above case and the yield of the desired compound (I) is high.

Throughout the specification, the term "lower alkyl" and "lower alkoxy" are interpreted as the alkyl of 1 to 4 carbon atoms and alkoxy of 1 to 4 carbon atoms, respectively.

Example 1

A mixture of 40 g of methyl (2R,3S)-2,3-epoxy-3-(4-methoxyphenyl)propionate, 26.5 g of 2-aminothiophenol and 300 ml of xylene is heated at 110 to 120 °C for 1 hour, whereby the reaction mixture containing methyl (2S,3S)-3-[(2-aminophenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propionate is obtained. 380 mg of methanesulfonic acid are added to the mixture and the mixture is refluxed for 7 hours. During the reaction, methanol formed is removed by the azeotropic distillation with xylene. The mixture is cooled to under 10 °C and then stirred for 1 hour. Precipitated crystals are collected by filtration, washed with cooled methanol and then dried, whereby 49.1 g of (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one are obtained.

Yield : 84.8 %
m.p. : 204 - 205 °C

$[\alpha]_D^{20} + 115^\circ$ (c=0.5, dimethylformamide)

Example 2

A mixture of 40 g of methyl (2R,3S)-2,3-epoxy-3-(4-methoxyphenyl)propionate, 26.5 g of 2-aminothiophenol and 300 ml of toluene is heated at 110 to 115 °C for 1 hour, whereby the reaction mixture containing methyl (2S,3S)-3-[(2-aminophenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propionate is obtained. After cooled to 80 to 90 °C, 1.5 g of methanesulfonic acid are added to the mixture and the mixture is refluxed for 18 hours. During the reaction, methanol formed is removed by the azeotropic distillation with toluene. Then the mixture is treated in the same manner as described in Example 1, whereby 46.9 g of (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine-4(5H)-one are obtained.

Yield : 81.0 %

m.p. : 203 - 204 °C

$[\alpha]_D^{20} + 115^\circ$ (c=0.5, dimethylformamide)

Example 3

A mixture of 40 g of methyl (2R,3S)-2,3-epoxy-3-(4-methoxyphenyl)propionate, 26.5 g of 2-aminothiophenol and 250 ml of xylene is heated at 110 to 120 °C for 1 hour, whereby the reaction mixture containing methyl (2S,3S)-3-[(2-aminophenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propionate is obtained. 600 mg of p-toluenesulfonic acid hydrate are added to the mixture and the mixture is refluxed for 8 hours. During the reaction, methanol formed is removed by the azeotropic distillation with xylene. Then the mixture is treated in the same manner as described in Example 1, whereby 47.5 g of (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine-4(5H)-one are obtained.

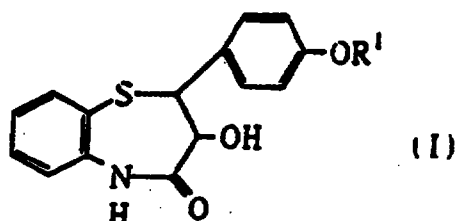
Yield : 82.1 %

m.p. : 203 - 204 °C

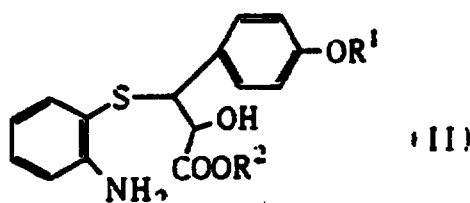
$[\alpha]_D^{20} + 115^\circ$ (c=0.5, dimethylformamide)

Claims

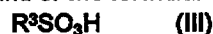
1. A process for preparing 1,5-benzothiazepine derivatives of the formula:



wherein R¹ is a C₁ to C₄ alkyl group, or a salt thereof which comprises subjecting a propionate derivative of the formula:



wherein R² is a C₁ to C₄ alkyl group and R¹ is the same as defined above, to intramolecular cyclization in the presence of a sulfonic acid compound of the formula:





$[\alpha]_D^{20} + 115^\circ$ (c=0.5, dimethylformamide)

Example 2

A mixture of 40 g of methyl (2R,3S)-2,3-epoxy-3-(4-methoxyphenyl)propionate, 26.5 g of 2-aminothiophenol and 300 ml of toluene is heated at 110 to 115 °C for 1 hour, whereby the reaction mixture containing methyl (2S,3S)-3-[(2-aminophenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propionate is obtained. After cooled to 80 to 90 °C, 1.5 g of methanesulfonic acid are added to the mixture and the mixture is refluxed for 18 hours. During the reaction, methanol formed is removed by the azeotropic distillation with toluene. Then the mixture is treated in the same manner as described in Example 1, whereby 46.9 g of (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine-4(5H)-one are obtained.

Yield : 81.0 %

m.p. : 203 - 204 °C

$[\alpha]_D^{20} + 115^\circ$ (c=0.5, dimethylformamide)

Example 3

A mixture of 40 g of methyl (2R,3S)-2,3-epoxy-3-(4-methoxyphenyl)propionate, 26.5 g of 2-aminothiophenol and 250 ml of xylene is heated at 110 to 120 °C for 1 hour, whereby the reaction mixture containing methyl (2S,3S)-3-[(2-aminophenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propionate is obtained. 600 mg of p-toluenesulfonic acid hydrate are added to the mixture and the mixture is refluxed for 8 hours. During the reaction, methanol formed is removed by the azeotropic distillation with xylene. Then the mixture is treated in the same manner as described in Example 1, whereby 47.5 g of (2S,3S)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine-4(5H)-one are obtained.

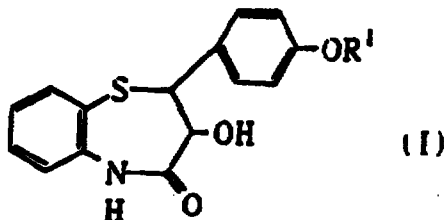
Yield : 82.1 %

m.p. : 203 - 204 °C

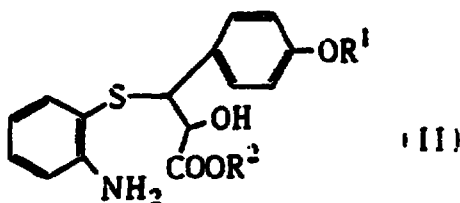
$[\alpha]_D^{20} + 115^\circ$ (c=0.5, dimethylformamide)

Claims

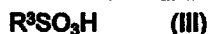
1. A process for preparing 1,5-benzothiazepine derivatives of the formula:



wherein R¹ is a C₁ to C₄ alkyl group, or a salt thereof which comprises subjecting a propionate derivative of the formula:



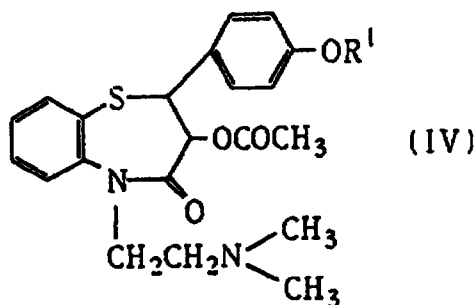
wherein R² is a C₁ to C₄ alkyl group and R¹ is the same as defined above, to intramolecular cyclization in the presence of a sulfonic acid compound of the formula:



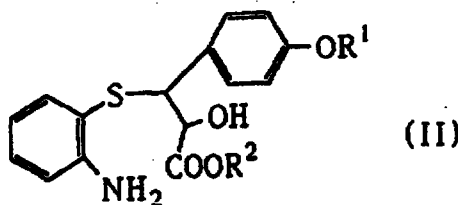


wherein R^3 is a C_1 to C_4 alkyl group or a substituted or unsubstituted phenyl group, in a non-halogenated organic solvent and, if desired, converting the product to a salt thereof provided that the intramolecular cyclization of methyl (2S,3S)-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)-propionate in the presence of p-toluenesulfonic acid monohydrate in xylene at reflux is disclaimed.

2. A process according to Claim 1, wherein R^3 of the formula (III) is a methyl group, ethyl group, propyl group, or a phenyl group which may be substituted by at least one group selected from the methyl group, ethyl group, propyl groups and butyl groups.
3. A process according to Claim 2, wherein the sulfonic acid compound (III) is methanesulfonic acid or p-toluenesulfonic acid.
4. A process according to Claim 2 or 3, wherein the non-halogenated organic solvent is an ether, a non-halogenated aromatic solvent or an aliphatic hydrocarbon.
5. A process according to Claim 4, wherein the non-halogenated organic solvent is isobutylbenzene, isopropylbenzene, n-propylbenzene or anisole.
6. A process according to Claim 4, wherein the non-halogenated organic solvent is xylene or toluene.
7. A process according to Claim 1, wherein the sulfonic acid (III) is used at an amount of 0.1 to 10 w/w % based on the compound (II).
8. A process according to Claim 7, wherein the sulfonic acid (III) is used at an amount of 0.5 to 6 w/w % based on the compound (II).
9. A process for preparing 3-acetoxy-5-(β -dimethylaminoethyl)-2,3-dihydro-1,5-benzothiazepine derivatives of the formula:



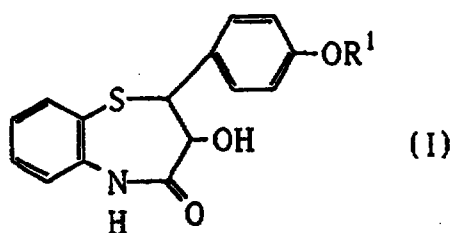
wherein R^1 is a C_1 to C_4 alkyl group,
or a pharmaceutically acceptable salt thereof which comprises the step of:
a) subjecting a propionate derivative of the formula:



wherein R^2 is a C_1 to C_4 alkyl group and R^1 is the same as defined above, to intramolecular cyclization in the presence of a sulfonic acid compound of the formula:



wherein R^3 is a C_1 to C_4 alkyl group or a substituted or unsubstituted phenyl group, in a non-halogenated organic solvent to give a 1,5-benzothiazepine derivative of the formula:



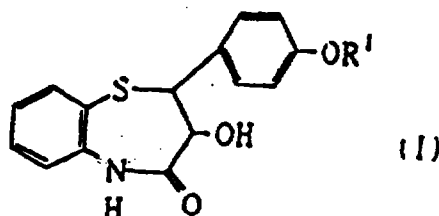
10 wherein R¹ is the same as defined above, and

b) 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, provided that the intramolecular cyclization of methyl (2S,3S)-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)-propionate in the presence of p-toluenesulfonic acid monohydrate in xylene at reflux is disclaimed.

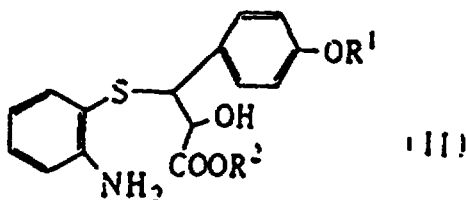
15

Patentansprüche

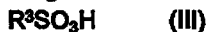
- 20 1. Verfahren zum Herstellen von 1,5-Benzothiazepinderivaten der Formel:



30 worin R¹ eine C₁ bis C₄ Alkylgruppe oder ein Salz davon ist, umfassend das Unterwerfen eines Propionatderivats der Formel:



45 worin R² eine C₁ bis C₄ Alkylgruppe ist und R¹ wie oben definiert ist, einer intramolekularen Cyclisierung in der Gegenwart einer Sulfonsäureverbindung der Formel:



worin R³ eine C₁ bis C₄ Alkylgruppe oder eine substituierte oder unsubstituierte Phenylgruppe ist, in einem nicht-halogenierten organischen Lösungsmittel und, wenn es erwünscht ist, Überführen des Produkts in ein Salz davon, vorausgesetzt, daß die intramolekulare Cyclisierung von Methyl-(2S,3S)-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)-propionat in der Gegenwart von p-Toluolsulfonsäuremonohydrat in Xylol unter Rückfluß ausgenommen ist.

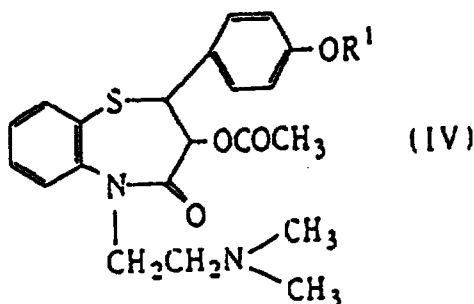
50

- 55 2. Verfahren nach Anspruch 1, worin R³ der Formel (III) eine Methylgruppe, Ethylgruppe, Propylgruppe oder eine Phenylgruppe ist, welche durch wenigstens eine Gruppe ausgewählt aus der Methylgruppe, Ethylgruppe, den Propylgruppen und Butylgruppen substituiert sein kann.
3. Verfahren nach Anspruch 2, worin die Sulfonsäureverbindung (III) Methansulfonsäure oder p-Toluolsulfonsäure ist.
4. Verfahren nach Anspruch 2 oder 3, worin das nicht-halogenierte organische Lösungsmittel ein Ether, ein



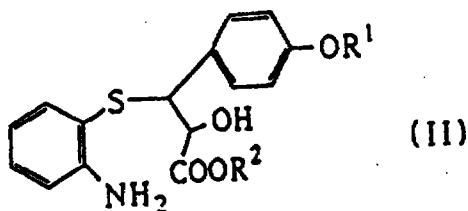
nicht-halogeniertes aromatisches Lösungsmittel oder ein aliphatischer Kohlenwasserstoff ist.

5. Verfahren nach Anspruch 4, worin das nicht-halogenierte organische Lösungsmittel Isobutylbenzol, Isopropylbenzol, n-Propylbenzol oder Anisol ist.
6. Verfahren nach Anspruch 4, worin das nicht-halogenierte organische Lösungsmittel Xylol oder Toluol ist.
7. Verfahren nach Anspruch 1, worin die Sulfonsäure (III) in einer Menge von 0,1 bis 10 Gew./Gew.-% basierend auf der Verbindung (II) verwendet wird.
8. Verfahren nach Anspruch 7, worin die Sulfonsäure (III) in einer Menge von 0,5 bis 6 Gew./Gew.-% basierend auf der Verbindung (II) verwendet wird.
9. Verfahren zum Herstellen von 3-Acetoxy-5-(β -dimethylamino-ethyl)-2,3-dihydro-1,5-benzothiazepinderivaten der Formel:



worin R¹ eine C₁ bis C₄ Alkylgruppe oder ein pharmazeutisch verträgliches Salz davon ist, umfassend den Schritt

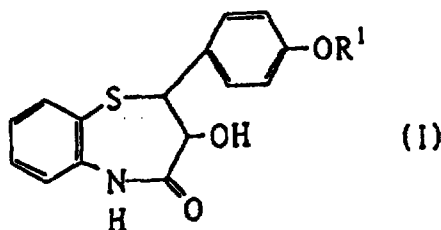
a) Unterwerfen eines Propionatderivats der Formel:



worin R² eine C₁ bis C₄ Alkylgruppe ist und R¹ wie oben definiert ist, einer intramolekularen Cyclisierung in der Gegenwart einer Sulfonsäureverbindung der Formel:



worin R³ eine C₁ bis C₄ Alkylgruppe oder eine substituierte oder unsubstituierte Phenylgruppe ist, in einem nicht-halogenierten organischen Lösungsmittel, um ein 1,5-Benzothiazepinderivat der Formel:



zu erhalten, worin R¹ wie oben definiert ist und

b) Überführen der Verbindung (I) in das entsprechende 3-Acetoxy-5-(β -dimethylaminoethyl)-1,5-benzothiazepinderivat oder ein pharmazeutisch verträgliches Salz davon mit einem bekannten Verfahren, vorausgesetzt, daß die intramolekulare Cyclisierung von Methyl-(2S,3S)-2-hydroxy-3-(2-



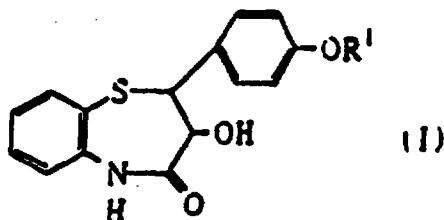
aminophénylthio)-3-(4-méthoxyphényl)-propionat in der Gegenwart von p-Toluolsulfonsäuremonohydrat in Xylol unter Rückfluß ausgenommen ist.

5

Revendications

1. Procédé de préparation de dérivés de 1,5-benzothiazépine de la formule :

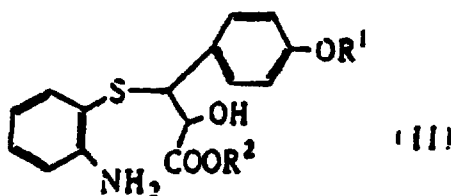
10



15

dans laquelle R¹ représente un groupe alkyle en C₁ à C₄, ou d'un sel de ces derniers, comprenant une exposition d'un dérivé propionate de la formule :

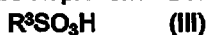
20



25

dans laquelle R² représente un groupe alkyle en C₁ à C₄ et R¹ a la même signification que celle donnée ci-dessus, à une cyclisation intramoléculaire en présence d'un composé d'acide sulfonique de la formule :

30



dans laquelle R³ représente un groupe alkyle en C₁ à C₄ ou un groupe phényle substitué ou non substitué, dans un solvant organique non halogéné, et, si on le souhaite, une conversion du produit en un sel de ce dernier, pourvu que la cyclisation intramoléculaire de (2S,3S)-2-hydroxy-3-(2-aminophénylthio)-3-(4-méthoxyphényl)-propionate de méthyle en présence de monohydrate d'acide p-toluènesulfonique dans du xylène au reflux soit exclue.

35

2. Procédé suivant la revendication 1, caractérisé en ce que R³ de la formule (III) est un groupe méthyle, éthyle ou propyle, ou un groupe phényle qui peut être substitué par au moins un groupe choisi parmi les groupes méthyle, éthyle, propyle et butyle.

40

3. Procédé suivant la revendication 2, caractérisé en ce que le composé d'acide sulfonique (III) est de l'acide méthanesulfonique ou de l'acide p-toluènesulfonique.

45

4. Procédé suivant l'une des revendications 2 et 3, caractérisé en ce que le solvant organique non halogéné est un éther, un solvant aromatique non halogéné ou un hydrocarbure aliphatique.

5. Procédé suivant la revendication 4, caractérisé en ce que le solvant organique non halogéné est de l'isobutylbenzène, de l'isopropylbenzène, du n-propylbenzène ou de l'anisole.

50

6. Procédé suivant la revendication 4, caractérisé en ce que le solvant organique non halogéné est du xylène ou du toluène.

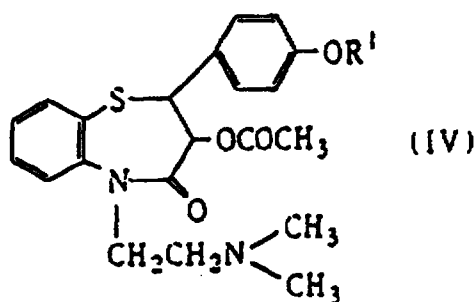
7. Procédé suivant la revendication 1, caractérisé en ce que l'acide sulfonique (III) est utilisé en une quantité de 0,1 à 10 % en poids/poids, par rapport au composé (II).

55

8. Procédé suivant la revendication 7, caractérisé en ce que l'acide sulfonique (III) est utilisé en une quantité de 0,5 à 6 % en poids/poids, par rapport au composé (II).

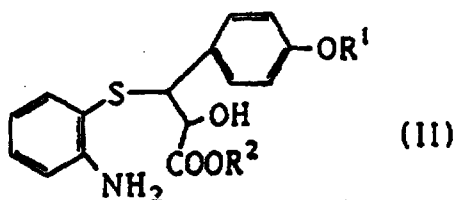


9. Procédé de préparation de dérivés de 3-acétoxy-5-(β -diméthylaminoéthyl)-2,3-dihydro-1,5-benzothiazépines de la formule :



dans laquelle R^1 représente un groupe alkyle en C_1 à C_4 , ou d'un sel pharmaceutiquement acceptable de ces derniers, comprenant les étapes :

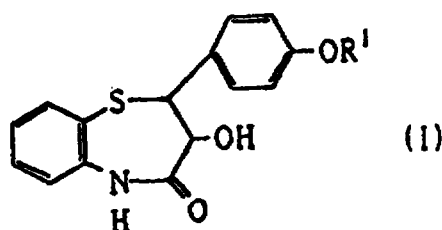
a) d'exposition d'un dérivé propionate de la formule :



dans laquelle R^2 représente un groupe alkyle en C_1 à C_4 et R^1 a la même signification que celle donnée ci-dessus, à une cyclisation intramoléculaire en présence d'un composé d'acide sulfonique de la formule :



dans laquelle R^3 représente un groupe alkyle en C_1 à C_4 ou un groupe phényle substitué ou non substitué, dans un solvant organique non halogéné, pour former un dérivé de 1,5-benzothiazépines de la formule :



dans laquelle R^1 a la même signification que celle donnée ci-dessus, et

b) de conversion du composé (I) en le dérivé de 3-acétoxy-5-(β -diméthylaminoéthyl)-1,5-benzothiazépines correspondant ou en un sel pharmaceutiquement acceptable de celui-ci suivant un procédé connu, pourvu que la cyclisation intramoléculaire de (2S,3S)-2-hydroxy-3-(2-aminophénylthio)-3-(4-méthoxyphényl)-propionate de méthyle en présence de monohydrate d'acide p-toluènesulfonique dans du xylène au reflux soit exclue.

50

55