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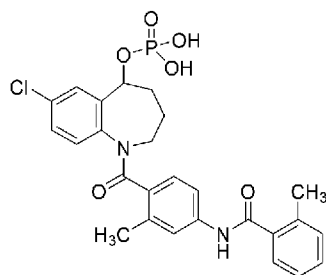
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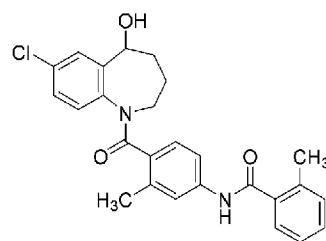
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(54) Title: METHOD FOR PRODUCING BENZOAZEPINE COMPOUND



(1)



(2)

(57) Abstract: A method for producing an alkali metal salt or alkaline earth metal salt of a phosphate compound represented by formula (1); the method comprising a step of subjecting a compound represented by formula (2): a phosphorus oxyhalide, and one or more members selected from alkali metal hydroxides and alkaline earth metal hydroxides to a telescoping continuous reaction.

## Description

### Title of Invention: METHOD FOR PRODUCING BENZOAZEPINE COMPOUND

#### Technical Field

[0001] The present invention relates to a method for producing a benzoazepine compound.

#### Background Art

[0002] Tolvaptan has vasopressin V2 receptor antagonistic activity, and is used as a diuretic etc.

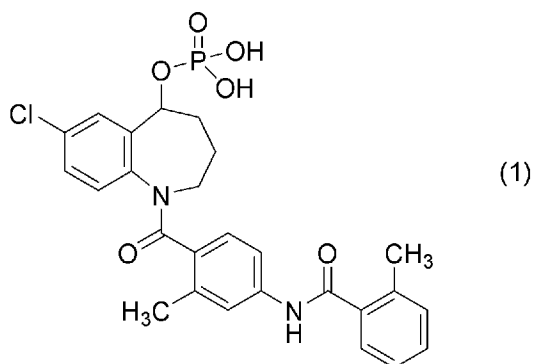
[0003] However, since tolvaptan is sparingly soluble in water, its dosage form and administration route are strictly limited. Patent Literature 1 suggests a prodrug of tolvaptan having excellent water solubility.

[0004] The use of such prodrugs may allow many dosage forms to receive the benefit of the pharmacological effects of tolvaptan.

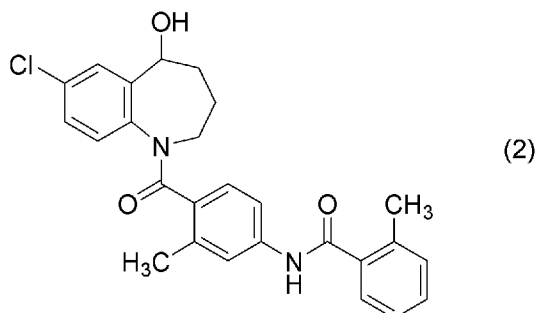
[0005] At the same time, if such prodrugs can be obtained with fewer reaction steps, significant advantages in terms of cost and production efficiency will be obtained.

[0006] Tolvaptan prodrugs have high water solubility, and are difficult to separate from a large amount of inorganic salts produced during a hydrolysis reaction with an alkali metal hydroxide and an alkaline earth metal hydroxide. Accordingly, the conventional tolvaptan prodrug production method requires two steps: a step of reacting a compound represented by formula (2) below, a phosphorus oxyhalide, and one or more members selected from alkali metal hydroxides and alkaline earth metal hydroxides, to isolate a compound represented by formula (1) below as an amorphous compound; and a step of making the phosphate compound represented by formula (1) below a salt of an alkali metal or alkaline earth metal.

[0007]



[0008]



[0009] In addition, the isolation of the amorphous compound requires neutralization and two-time extraction. Moreover, isolation is not suitable for mass synthesis due to poor properties of the amorphous compound, and is disadvantageous in terms of cost and production efficiency.

### Citation List

#### Patent Literature

[0010] PTL 1: Japanese Patent No. 4644287

### Summary of Invention

#### Technical Problem

[0011] In view of the above, an object of the present invention is to provide a method for producing a prodrug of tolcaptan having excellent water solubility, with a fewer number of steps than those of conventional methods.

#### Solution to Problem

[0012] The present inventors conducted extensive research to solve the above problem. As a result, they found that by a telescoping continuous reaction using a phosphorus oxyhalide and one member selected from alkali metal hydroxides and alkaline earth metal hydroxides, a prodrug of tolcaptan having excellent water solubility can be obtained with a fewer number of steps and operations, without isolating the phosphate compound represented by formula (1). The present inventors conducted further research based on this finding, and accomplished the present invention.

[0013] Specifically, the present invention provides the following benzoazepine compound production methods.

#### Item 1.

A method for producing an alkali metal salt or alkaline earth metal salt of a phosphate compound represented by formula (1),



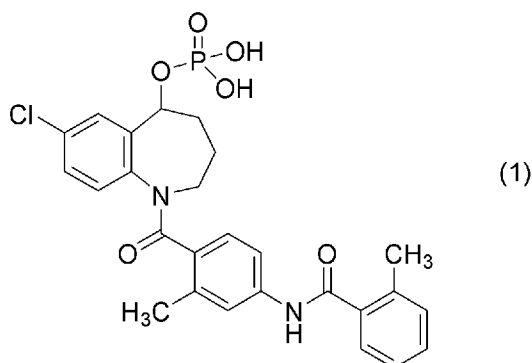
(2)

[0014] According to the production method of the present invention, a prodrug of tolvaptan having excellent water solubility can be obtained without isolating an intermediate from the tolvaptan. Thus, the production method of the present invention is simple,

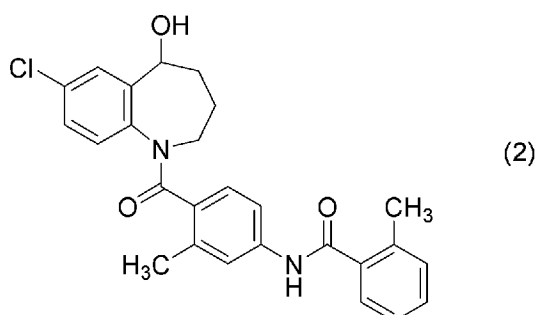
excellent in workability, and industrially advantageous.

[0015] The benzoazepine compound (an alkali metal salt or alkaline earth metal salt of a phosphate compound represented by formula (1)) can be obtained by subjecting a compound (common name: tolvaptan) represented by formula (2), a phosphorus oxyhalide, and one or more hydroxides selected from alkali metal hydroxides and alkaline earth metal hydroxides to a telescoping continuous reaction. In addition, the benzoazepine compound can be produced without isolating the phosphate compound represented by formula (1).

[0016]



[0017]



[0018] In the production method of the present invention, the compound represented by formula (2), phosphorus oxyhalide, and hydroxide are present in the reaction system. Specifically, it is preferable that the phosphorus oxyhalide and the basic compound are added to a reaction solvent containing the compound represented by formula (2) to perform dihalogen phosphorylation of a hydroxyl group, after which the hydroxide is added. The addition order is preferably such that the hydroxide is added after the addition of the phosphorus oxyhalide and the basic compound.

[0019] A wide variety of known phosphorus oxyhalides can be used, without particular limitation. Specifically, one or more members selected from the group consisting of phosphorus oxychloride, phosphorus oxyfluoride, phosphorus oxybromide, phosphorus oxyiodide, and the like can be used. These can be used alone, or in a combination of two or more. Of these, phosphorus oxychloride is preferably used because of low cost and ease of availability.

[0020] A wide variety of known alkali metal hydroxides can also be used, without particular limitation. Specifically, one or more members selected from the group consisting of

lithium hydroxide, sodium hydroxide, and potassium hydroxide can be used. These can be used alone, or in a combination of two or more. Of these, sodium hydroxide is preferably used because of low cost.

[0021] A wide variety of known alkaline earth metal hydroxides can be used, without particular limitation. Specifically, one or more members selected from the group consisting of beryllium hydroxide, magnesium hydroxide, and calcium hydroxide can be used. These can be used alone, or in a combination of two or more. Of these, calcium hydroxide is preferably used because of low cost.

[0022] The reaction is preferably performed in a suitable solvent. As the solvent, a wide variety of known organic solvents can be used, without particular limitation. Specific examples include halogenated hydrocarbon solvents, such as methylene chloride, chloroform, 1,2-dichloroethane, and carbon tetrachloride; esters, such as ethyl acetate; aromatic hydrocarbons, such as benzene, toluene, and xylene; acetonitrile; and the like. These can be used alone, or in a combination of two or more.

[0023] In addition, the reaction step in which phosphorus oxyhalide and one member selected from alkali metal hydroxides and alkaline earth metal hydroxides are subjected to a telescoping continuous reaction with the compound represented by formula (2) in the production method of the present invention is preferably performed in the presence of a basic compound.

[0024] Examples of the basic compound include carbonates, such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, and cesium carbonate; alkali metal hydroxides, such as sodium hydroxide and potassium hydroxide; alkaline earth metal hydroxides, such as calcium hydroxide; phosphates, such as potassium phosphate and sodium phosphate; organic bases, such as pyridine, imidazole, N-ethyldiisopropylamine, dimethylaminopyridine, triethylamine, trimethylamine, dimethylaniline, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,4-diazabicyclo[2.2.2]octane (DABCO); and mixtures thereof.

[0025] Regarding the amount of each compound to be used, to allow the reaction to promptly proceed, the amount of the phosphorus oxyhalide is preferably 1 mole to a large excess molar amount, more preferably 1 to 20 moles, even more preferably 1 to 10 moles, particularly preferably 1 to 5 moles, and most preferably 2 to 5 moles, per mol of the compound represented by formula (2).

[0026] In addition, to allow hydrolysis and salt formation to promptly proceed, the amount of one or more members selected from the group consisting of alkali metal hydroxides and alkaline earth metal hydroxides is preferably 5 to 40 moles, and more preferably 10 to 20 moles, per mol of the compound represented by formula (2).

[0027] The reaction temperature is preferably set to -100 to 50°C, more preferably -50°C to

room temperature, and even more preferably -30°C to room temperature, in order to inhibit the generation of impurities.

[0028] A reaction step in which phosphorus oxyhalide and one member selected from alkali metal hydroxides and alkaline earth metal hydroxides are subjected to a telescoping continuous reaction with the compound represented by formula (2) in the production method of the present invention is preferably performed in the presence of one or more members selected from the group consisting of triethylamine, trimethylamine, 1,8-diazabicyclo[5.4.0]undecene-7 (DBU), and 1,4-diazabicyclo[2.2.2]octane (DABCO).

[0029] By performing a salting-out operation and a desalting operation from the extracted aqueous layer after the reaction, a prodrug of tolvaptan having excellent water solubility can be obtained with fewer steps, without isolating the phosphate compound represented by formula (1).

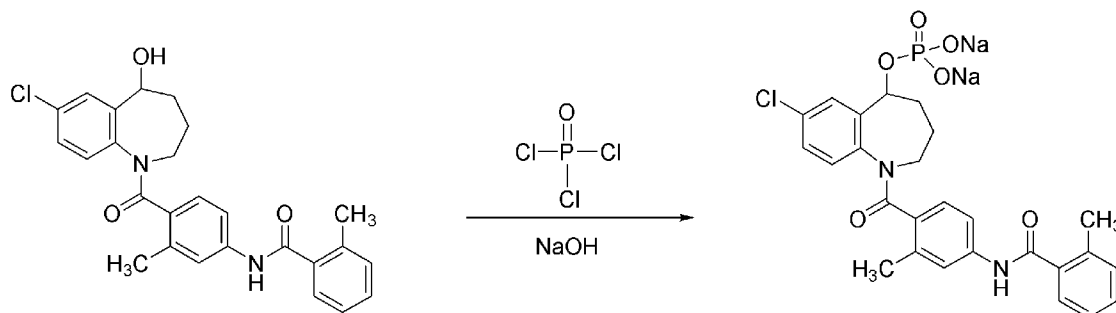
[0030] The alkali metal salt or alkaline earth metal salt of the phosphate compound represented by formula (1), which is synthesized by the above reaction, can be isolated and purified from the reaction product by known isolation means and purification means. Specifically, after the reaction, the reaction mixture is cooled, and a crude reaction product is isolated by an isolation operation, such as filtration, concentration, or extraction. Subsequently, an ordinary purification operation, such as column chromatography or recrystallization, is performed to isolate or purify the alkali metal salt or alkaline earth metal salt of the phosphate compound from the reaction mixture.

[0031] The embodiments of the present invention are explained above; however, the present invention is not limited to these examples, and can obviously be performed in various forms in the range that does not deviate from the gist of present invention.

### Examples

[0032] Embodiments of the present invention will be described in more detail below, based on Examples; however, the present invention is not limited thereto.

[0033]



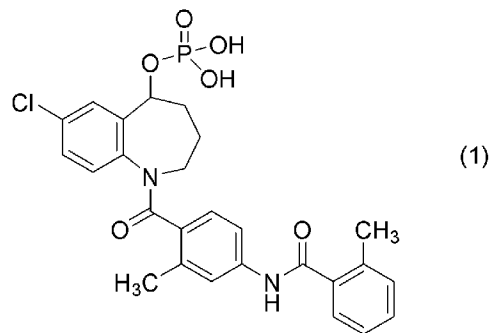
[0034] Example 1

80 L of 1,2-dimethoxyethane (DME) and 20 kg of triethylamine (201 moles, 9 equivalents) were added to 10 kg (22 moles) of tolvaptan, and the mixture was cooled to -18°C in a nitrogen stream. 10 kg (66 moles, 3 equivalents) of phosphorus oxy-

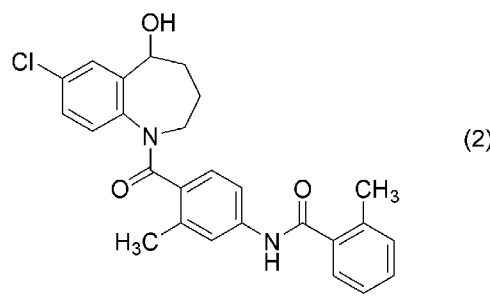
chloride ( $\text{POCl}_3$ ) was added dropwise to the obtained mixture at an internal temperature of  $-8^\circ\text{C}$  or lower, and then the mixture was stirred at  $-13^\circ\text{C}$  for 2 hours. 64 kg of a 25% sodium hydroxide aqueous solution (sodium hydroxide, 397 moles, 18 equivalents) was added to 200 L of water, and the mixture was cooled to  $-3^\circ\text{C}$ . The reaction mixture was added thereto while stirring. The obtained mixture was stirred at  $30^\circ\text{C}$  for 30 minutes, and 100 L of toluene was added thereto. The mixture was heated to  $50^\circ\text{C}$ , and then separated into an aqueous layer and a toluene layer. 100 L of toluene was added to the aqueous layer, followed by heating to  $50^\circ\text{C}$ , and separation into an aqueous layer and a toluene layer. The obtained aqueous layer was allowed to stand overnight, cooled to  $10^\circ\text{C}$ , and then stirred for 4 hours to prepare a suspension. The obtained suspension was collected by filtration to obtain 48 kg of hygroscopic salted-out crystals. 120 L of acetone was added to the 48 kg of hygroscopic salted-out crystals; and the mixture was heated to reflux, and stirred for 30 minutes under reflux. The mixture was cooled to  $40^\circ\text{C}$ , and filtration was performed to remove insoluble matter to obtain a filtrate. 10 L of water was added to the filtrate, and heating and stirring was performed until the temperature became  $50^\circ\text{C}$ . The resultant was cooled to  $40^\circ\text{C}$ , and insoluble matter was removed by filtration, to obtain a filtrate. After the filtrate was heated to  $49^\circ\text{C}$ , and the absence of insoluble matter was confirmed, the filtrate was cooled to  $10^\circ\text{C}$  to perform recrystallization. The obtained suspension was filtered to obtain a crystalline powder wet with acetone. The hygroscopic crystalline powder was dried at room temperature for 18 hours, and subsequently dried at  $50^\circ\text{C}$  for 9 hours and 30 minutes, to obtain 11 kg of sodium salt (yield: 86%).

## Claims

- [Claim 1] A method for producing an alkali metal salt or alkaline earth metal salt of a phosphate compound represented by formula (1):



the method comprising a step of subjecting a compound represented by formula (2):



a phosphorus oxyhalide, and one or more members selected from alkali metal hydroxides and alkaline earth metal hydroxides to a telescoping continuous reaction.

- [Claim 2] The production method according to claim 1, wherein the phosphorus oxyhalide is used in an amount of 1 to 20 moles per mol of the compound represented by formula (2).

- [Claim 3] The production method according to claim 1 or 2, wherein the reaction is performed under a temperature condition of -100 to 50°C.

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/JP2020/002171A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07F9/553  
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                               | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | WO 2007/074915 A1 (OTSUKA PHARMA CO LTD [JP]; KOMATSU MAKOTO [JP] ET AL.)<br>5 July 2007 (2007-07-05)<br>cited in the application<br>the whole document<br>----- | 1-3                   |



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/JP2020/002171

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