

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 June 2006 (08.06.2006)

PCT

(10) International Publication Number
WO 2006/059781 A1

(51) International Patent Classification:
C07D 215/22 (2006.01)

(21) International Application Number:
PCT/JP2005/022412

(22) International Filing Date:
30 November 2005 (30.11.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2004-348425 1 December 2004 (01.12.2004) JP

(71) Applicant (for all designated States except US): **OTSUKA PHARMACEUTICAL CO., LTD.** [JP/JP]; 9, Kandatsukasa-cho 2-chome, Chiyoda-ku, Tokyo, 1018535 (JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **NISHITANI, Shinji** [JP/US]; c/o Otsuka Maryland Research Institute, Inc., 2440 Research Boulevard, Rockville, Maryland, 20850 (US). **FUKUDA, Norio** [JP/JP]; c/o OTSUKA PHARMACEUTICAL CO., LTD., 224-18, Hiraishi-Ebisuno, Kawauchi-cho, Tokushima-shi, Tokushima, 7710132 (JP).

(74) Agents: **KAWAMIYA, Osamu** et al.; AOYAMA & PARTNERS, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 5400001 (JP).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

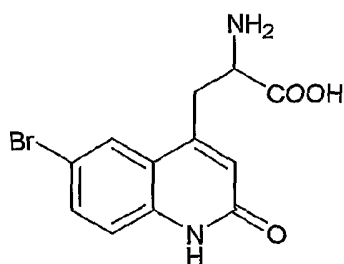
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

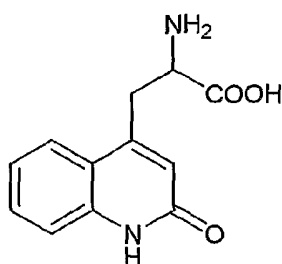
— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

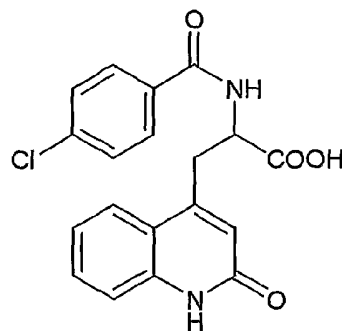
(54) Title: IMPROVED PROCESS FOR PREPARING REBAMIPIDE



(11)



(5)



(1)

(57) Abstract: The invention provides an improved process for preparing rebamipide that is useful as a medicament, which makes it possible to prepare rebamipide with high purity and high yield. The invention is an improved process for preparing rebamipide of the formula (1), comprising subjecting a carbostyryl amino acid compound of the formula (5) or a salt thereof containing a compound of the formula (11) as an impurity to a reduction treatment in the presence of hydrogen and a catalyst in a basic aqueous solution, thereby selectively reducing the impurity compound (11) to transform into the carbostyryl amino acid compound (5); and then acylating the compound (5) in a basic aqueous solution to give rebamipide (1).

DESCRIPTION

IMPROVED PROCESS FOR PREPARING REBAMIPIDE

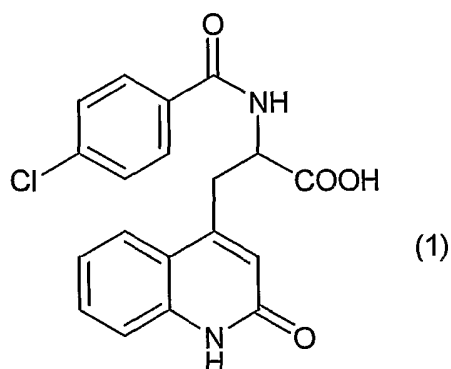
TECHNICAL FIELD

5 The invention relates to an improved process for preparing rebamipide that is useful as a medicament for treating gastric ulcer and the like, which makes it possible to prepare rebamipide with high purity and high yield.

10

BACKGROUND ART

 Rebamipide, which means a carbostyryl compound (chemical name: 2-(4-chlorobenzoylamino)-3-[2(1H)-quinolon-4-yl]propionic acid) of the following formula (1), is a
15 medicament that has a potent effect on the treatment of gastric ulcer, acute gastritis, or gastric mucosa lesion affected in acute exacerbation of chronic gastritis.



 As an example of the process for preparing rebamipide, a process shown in the following scheme 1 is known (JP-A-
20 60-19767). The process is illustrated as follows:

 That is,

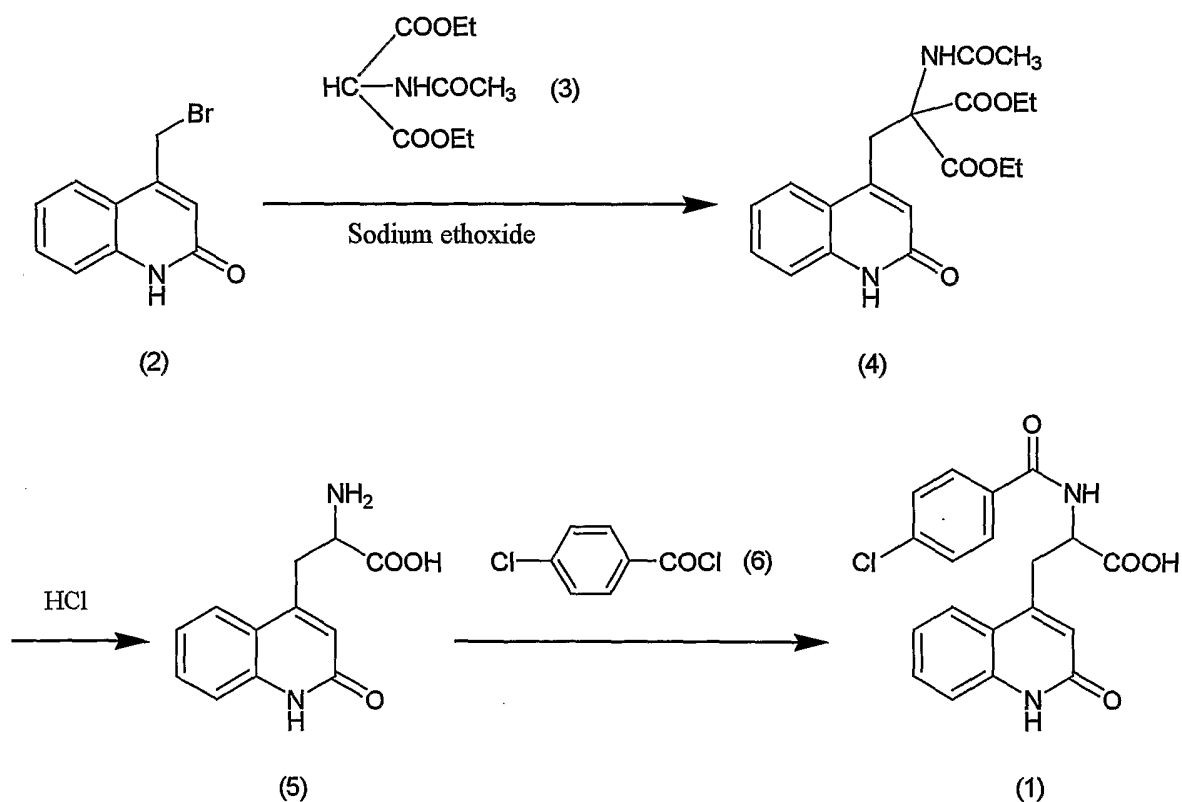
 bromomethyl carbostyryl (2) is reacted with

diethylacetamide malonate (3) in the presence of a base such as sodium ethoxide to give carbostyryl malonate compound (4);

the compound (4) is hydrolyzed and decarboxylated in the presence of a mineral acid such as hydrochloric acid to prepare carbostyryl amino acid compound (5); and then

the compound (5) is acylated with 4-chlorobenzoyl chloride (6) to prepare the desired rebamipide of the formula (1).

Scheme 1



The above starting material, bromomethyl carbostyryl (2), can be prepared, for example, as shown in the following scheme 2:

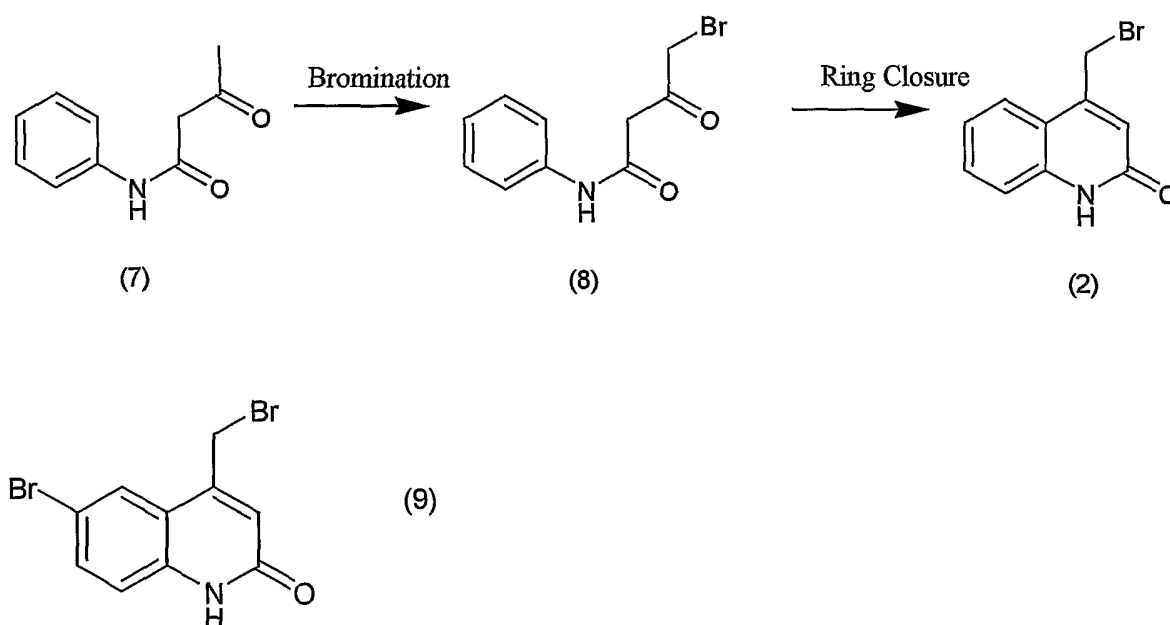
That is,

acetoacetanilide (7) is brominated with bromine, N-bromosuccinimide, or the like to give a compound of the

formula (8); and then

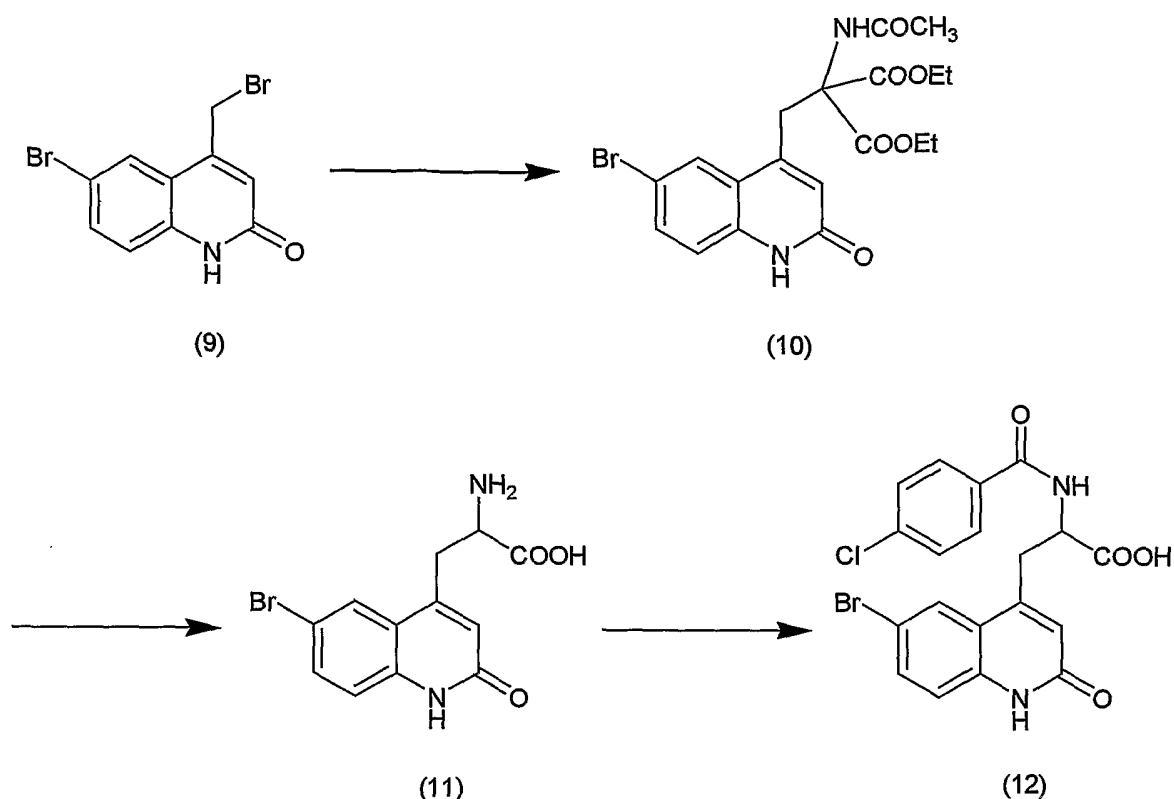
the compound (8) is ring-closed with a condensing agent such as concentrated sulfuric acid to prepare the compound (2). However, the product (2) contains 6-bromocarbo-
5 bromostyryl compound of the following formula (9) as an impurity, which is one of by-products produced from the above bromination.

Scheme 2



On transforming the bromomethyl carbostyryl (2) to rebamipide (1) according to the above scheme 1, the above
10 impurity contained in the bromomethyl carbostyryl (2), i.e. 6-bromocarbo-
bromostyryl compound (9), is reacted in the same behavior of the bromomethyl carbostyryl (2), as shown in the following scheme 3, to give the corresponding 6-bromo
15 compound of the formula (12) via the corresponding compounds of the formula (10) and formula (11), and thereby the impurity (12) is contained in the desired rebamipide (1).

Scheme 3



It is possible to partly decrease the amount of the produced impurity 6-bromocarbostyryl compound (9) by controlling the condition of the bromination shown in the above-mentioned scheme 2, for example, engaging an equimolar or less amount of used bromine to the amount of the acetoacetanilide (7) and making the reaction temperature 50°C or less, however, it might be limitative to decrease the preparation of the 6-bromocarbostyryl compound (9) without significantly decreasing the yield of the desired bromocarbostyryl (2) by only controlling the reaction condition.

Accordingly, it is necessary to remove such contaminated impurity 6-bromo compound (12) when the desired rebamipide (1) is used as a medicament, however, it

is difficult to prepare rebamipide with high purity and high yield since such removal is really difficult, and the impurity is not fully removed by recrystallizing or washing with solvent, and additionally it is accompanied with loss of the desired rebamipide by the operation. From such viewpoint, it started to study the removal of the 6-bromocarbostryril compound (9) contained in the bromomethyl carbostryril (2).

Thus, the method of removing the contaminated impurity 6-bromocarbostryril compound (9) from the bromomethyl carbostryril (2) includes, for example, recrystallizing from various solvents and dispersing/washing with various solvents; however, such methods do not provide any sufficient effect of the removal. Also, for example, using N,N-dimethyl formamide, N,N-dimethyl acetamide, 1-methyl-2-pyrrolidone and the like, a certain effect of the removal will be observed; however, in this case the bromomethyl carbostryril (2) will be lost a lot due to transference into the filtrate. Accordingly, such method is also not useful in fact.

Additionally, if the derivatives of the contaminated impurity 6-bromo compound is tried to be removed as the following steps: that is, removing the corresponding 6-bromo compound (10) from carbostryril malonate compound (4) in the above-mentioned scheme 1, or removing the corresponding 6-bromo compound (11) from the carbostryril amino acid compound (5) in the same scheme, the same problem will arise.

DISCLOSURE OF INVENTION

Problem to be solved by the invention

Thus, the present inventors have extensively studied which step in the procedure is effective to remove the contaminated impurity 6-bromo compound, and have found that
5 the desired rebamipide could be prepared with high purity and high yield

by subjecting the carbostyryl amino acid compound (5) containing the 6-bromocarbostyryl amino acid compound (11)
10 as an impurity to a reduction treatment just before converting compound (5) into the desired rebamipide by the acylation, thereby selectively reducing only the compound (11) to transform into the useful carbostyryl amino acid compound (5); and then acylating the produced compound (5).
15 Based upon the new findings, the present invention has been completed.

An object of the present invention is to provide an improved process for preparing rebamipide that is useful as a medicament, which makes it possible to prepare rebamipide
20 with ease, high purity and high yield.

Another object of the present invention is to provide a method of effectively removing the 6-bromo compound produced as a by-product in the process for preparing rebamipide.

25 More another object of the present invention is to provide a method of preparing the desired rebamipide with higher purity and higher yield in the step from the bromomethylcarbostyryl (2) to the desired rebamipide (1) through the removal of the impurity

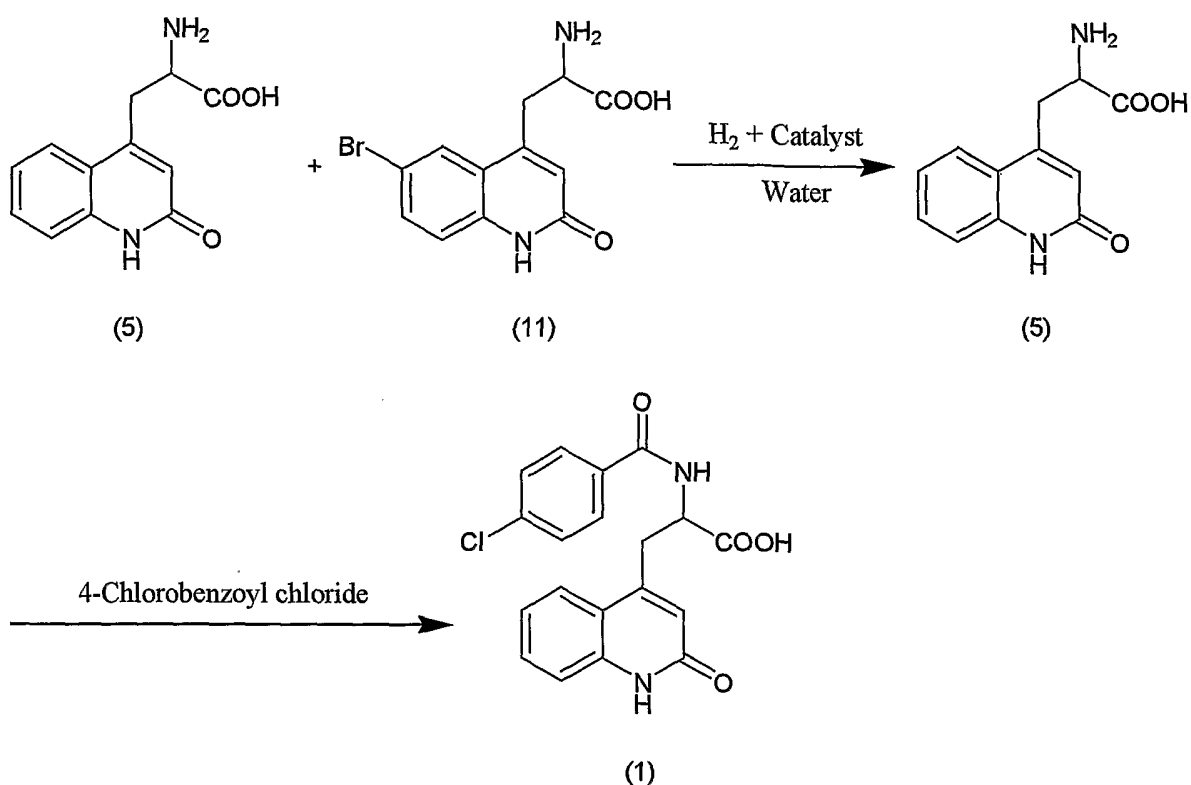
by selectively reducing the 6-bromocarbostyryl amino acid compound (11) contained as an impurity in the carbostyryl amino acid compound (5) just before the acylation, to transform into the useful carbostyryl amino acid compound (5); and then acylating the produced compound (5).

Means to solve the problem

According to the present invention, the desired rebamipide (1) can be prepared

by subjecting the carbostyryl amino acid compound (5) or the salt thereof containing the 6-bromocarbostyryl amino acid compound (11) as an impurity to a reduction treatment in the presence of hydrogen and a catalyst in a basic aqueous solution, thereby selectively reducing only the impurity compound (11) to transform into the carbostyryl amino acid compound (5); and then

acylating the carbostyryl amino acid compound (5) with 4-chlorobenzoyl chloride in a basic aqueous solution. The method of the invention is shown in the following scheme 4.

Scheme 4

The process of the invention is not a conventional method of removing impurities such as recrystallization using a solvent, dispersing/washing, and column chromatography; but a purification method through reduction wherein the desired compound itself is not reduced, but the impurity contained in the desired compound is reduced to be transformed into the desired compound; and thereby the purity of the product is enhanced. Using such unconventional purification method, the desired rebamipide can be prepared in higher yield.

BEST MODE FOR CARRYING OUT THE INVENTION

The example of a salt of the carbostyryl amino acid compound (5) containing the 6-bromocarbostyryl amino acid

compound (11) as an impurity, used herein, includes a mineral acid salt such as hydrochloride, sulfate, hydrobromide and the like; and an alkali metal salt such as sodium salt, lithium salt and the like.

5 In order to carry out the invention, water and a basic compound is added to the carbostyryl amino acid compound (5) or a salt thereof containing the impurity 6-bromocarbostyryl amino acid compound (11) to prepare a basic aqueous solution. The water added herein is
10 generally about 5-50 parts by weight to 1 part by weight of the carbostyryl amino acid compound (5) or a salt thereof containing the impurity.

 The examples of the basic compound which is added to basify the aqueous solution include, for example, a mineral
15 basic compound such as sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, and lithium carbonate, which is preferably added so that the pH of the aqueous solution may exhibit below 14. However, when the carbostyryl amino acid compound (5)
20 containing the impurity is transformed into a metal salt thereof with, for example, sodium salt, potassium salt, and lithium salt, then it is not necessary to add an additional basic compound due to the basicity of the aqueous solution.

 The examples of the catalyst in the invention which is
25 used to subject the impurity 6-bromocarbostyryl amino acid compound (11) to the selective reduction, include palladium catalysts and nickel catalysts, preferably Raney nickel catalyst. The amount of the used catalyst is generally about 0.01-0.50 parts, preferably about 0.02-0.20 parts by

weight to 1 part by weight of the carbostyryl amino acid compound (5) or a salt thereof containing the impurity.

The reduction of the invention is carried out generally at atmospheric pressure to 10 atm, preferably at atmospheric pressure to 4 atm, and generally at 0-40°C, preferably at 10-30°C. This reduction will be effectively advanced if using stirring.

After completing the reduction, the catalyst is removed off, a filtrated basic solution of the carbostyryl amino acid compound (5) is reacted with 4-chlorobenzoyl chloride to give the desired rebamipide (1). The above reaction can be easily carried out according to a conventional method, for example, via Schotten-Baumann reaction.

The amount of 4-chlorobenzoyl chloride used in the above acylation is an equimolar, preferably an equimolar to 2 moles, to 1 mole of the carbostyryl amino acid compound (5).

In the acylation, to a basic solution of the carbostyryl amino acid compound (5) prepared by removing the catalyst, an additional basic compound (for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate and the like) may be optionally added, and then 4-chlorobenzoyl chloride itself or a solution of 4-chlorobenzoyl chloride in an organic solvent such as acetone, acetonitrile, and ethyl acetate is added, and the resulting reaction can be carried out at about -10°C to 100°C, preferably about 0°C to 36°C, for about 5 minutes to

15 hours.

Example

Hereinafter, the present invention is further illustrated by example.

5 Example 1

To 10 g of 2-amino-3-[2(1H)-quinolon-4-yl]propionic acid monohydrochloride dihydrate (the compound of the formula (5), purity by HPLC analysis: 98.56%) containing 2-amino-3-[6-bromo-2(1H)-quinolon-4-yl]propionic acid (the compound of the formula (11), percentage by HPLC analysis: 1.09%) as an impurity, 200 mL of water and 10 mL of 25 % aqueous sodium hydroxide were added, and the mixture was dissolved. To the solution, 2 g of 50% water-contained Raney nickel catalyst was added and stirred under 2 atm of hydrogen for 2 hours at room temperature, and then the catalyst was filtrated off. After 2 hour-stirring, a HPLC analysis indicated that the amount of 2-amino-3-[6-bromo-2(1H)-quinolon-4-yl]propionic acid (the compound of the formula (11)) was 0.01% and the amount of 2-amino-3-[2(1H)-quinolon-4-yl]propionic acid (the compound of the formula (5)) was 99.73%. After adding 10 mL of 25% aqueous solution of sodium hydroxide to the catalyst-removed solution, a solution of 10 g of 4-chlorobenzoyl chloride in 50 mL of acetone was added thereto dropwise under ice temperature. After the addition, the reaction mixture was allowed to be acidified with hydrochloric acid and the resultant crystal was filtrated. The crystal was washed with water and acetone, and air-dried at about 80°C to give 11.7 g of rebamipide (1) (yield: 96.2%, purity by HPLC

analysis: 99.60%).

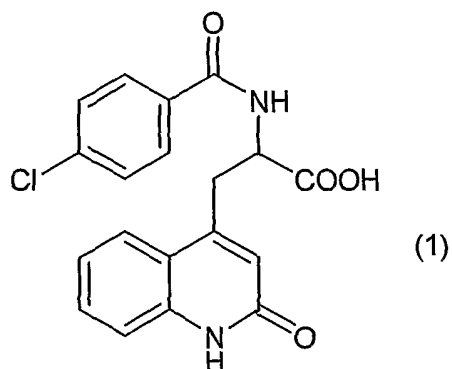
INDUSTRIAL APPLICABILITY

The invention provides a highly effective purification
5 method without loss of the desired compound, by converting
the contaminated impurity 6-bromo compound, which is hardly
removed by a conventional purification method, into the
desired compound by selective reduction thereof and thereby
the purity of the whole desired compound can be enhanced.
10 Accordingly, the method of the invention might be
advantageously used in the industrial process for preparing
rebamipide to be used as a medicament in which higher
purity is required.

According to the method of the invention, the desired
15 compound can easily be produced on industrial scale by easy
operation since water may be used as a solvent for the
reduction and the reaction may be carried out under a mild
condition for relatively short time. Furthermore, after
completion of the reduction in the former step, the basic
20 aqueous solution obtained by removing the catalyst can be
used in the next acylation step without further treatment,
and hence the invention will be so useful to produce the
desired rebamipide with high yield on large scale.

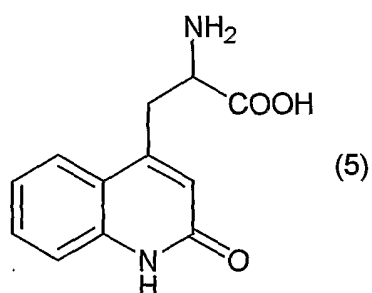
CLAIMS

1. An improved process for preparing rebamipide of the formula (1):



5 comprising:

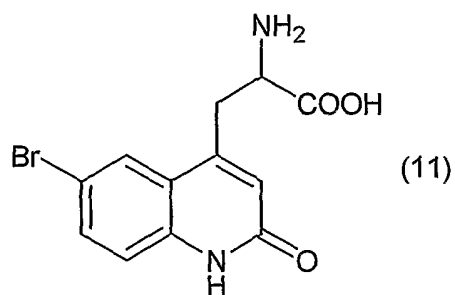
subjecting a carbostyryl amino acid compound of the formula (5):



or a salt thereof

containing a 6-bromocarbostyryl amino acid compound of the formula (11):

10



as an impurity to a reduction treatment in the presence of hydrogen and a catalyst in a basic aqueous solution,

thereby selectively reducing the impurity compound (11) to transform into the carbostyryl amino acid compound (5); and then

5 reacting the carbostyryl amino acid compound (5) with 4-chlorobenzoyl chloride in a basic aqueous solution to give rebamipide (1).

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2005/022412

A. CLASSIFICATION OF SUBJECT MATTER

C07D215/22

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)
C07D

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 practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 009, no. 134 (C-285), 8 June 1985 (1985-06-08) & JP 60 019767 A (OTSUKA SEIYAKU KK), 31 January 1985 (1985-01-31) cited in the application abstract	1
Y	R. G. CHUDGAR; K. N. TRIVEDI: "Studies in the synthesis of quinoline derivatives: Part I: Synthesis of bromoquinolines" J. INDIAN CHEM. SOC., vol. 46, no. 6, 1969, pages 537-540, XP009062194 table 2; compound 4 ----- -/--	1



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 February 2006

Date of mailing of the international search report

02/03/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlean 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Lauro, P

INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2005/022412

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 60019767 A	31-01-1985	JP 1635550 C	20-01-1992
		JP 2061923 B	21-12-1990