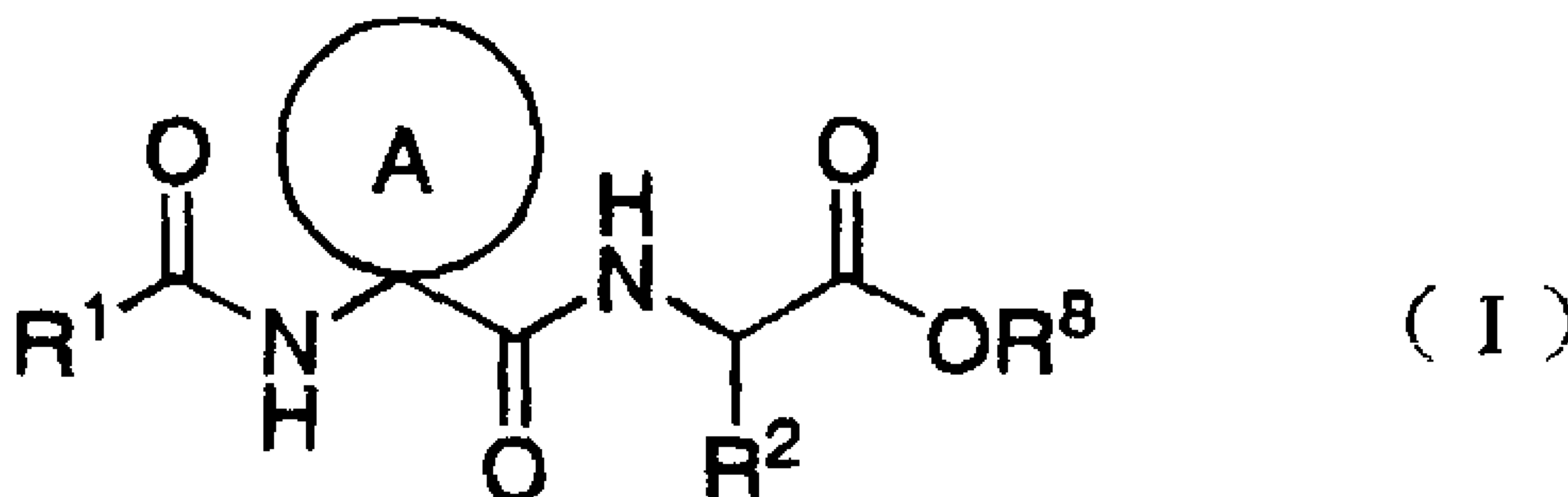




(86) **Date de dépôt PCT/PCT Filing Date:** 2007/01/10
(87) **Date publication PCT/PCT Publication Date:** 2007/07/19
(45) **Date de délivrance/Issue Date:** 2014/03/18
(85) **Entrée phase nationale/National Entry:** 2008/07/10
(86) **N° demande PCT/PCT Application No.:** JP 2007/050154
(87) **N° publication PCT/PCT Publication No.:** 2007/080884
(30) **Priorités/Priorities:** 2006/01/11 (JP2006-003508);
2006/12/20 (JP2006-343582)

(51) **Cl.Int./Int.Cl.** **C07K 5/065** (2006.01)
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(54) **Titre : DERIVE D'ESTER D'ACIDE CYCLOALKYLCARBONYLAMINO ET SON PROCEDE DE PRODUCTION**
(54) **Title: CYCLOALKYLCARBONYLAMINO ACID ESTER DERIVATIVE AND PROCESS FOR PRODUCING THE SAME**



(57) **Abrégé/Abstract:**

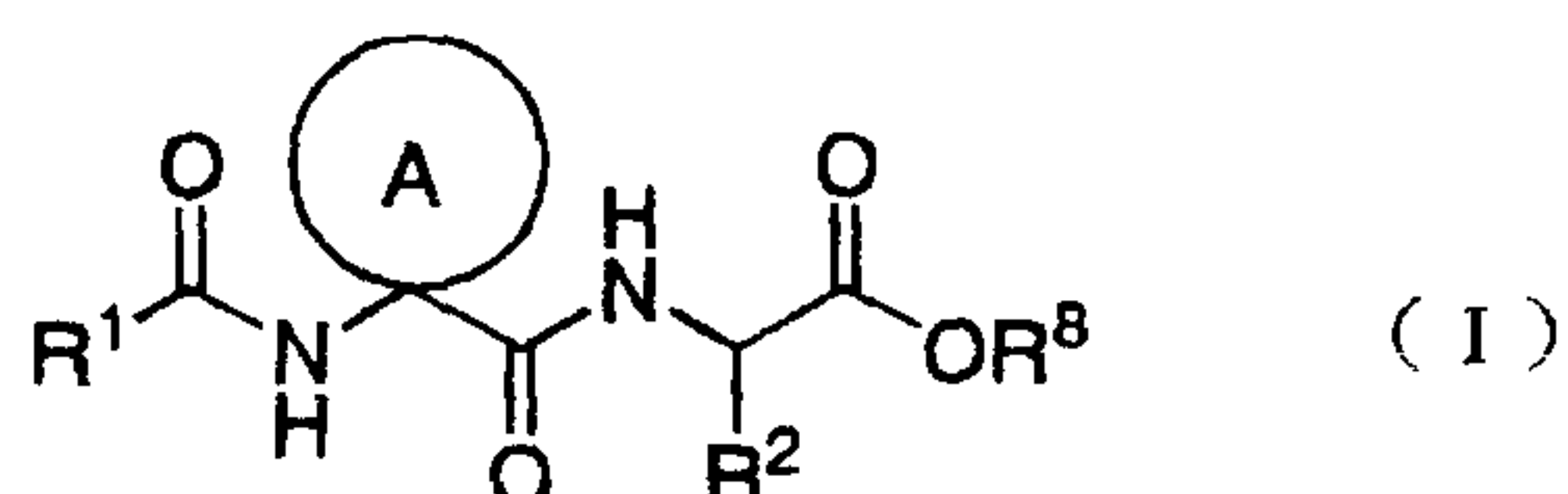
Cycloalkylcarbonylamino acid ester derivatives, which are raw material intermediates for a novel cycloalkane carboxamide derivative having an action that selectively inhibits cathepsin K, and a production process thereof, are provided. A cycloalkylcarbonylamino acid ester derivative represented by formula (I), or a pharmaceutically acceptable salt thereof: (see formula I) (wherein, R¹ and R² represent alkyl groups, alkenyl groups, alkynyl groups, aromatic hydrocarbon groups, heterocyclic groups, etc., R⁸ represents an alkyl group having 1 to 6 carbon atoms, and ring A represents a cyclic alkylidene group having 5, 6 or 7 carbon atoms).



ABSTRACT

Cycloalkylcarbonylamino acid ester derivatives, which are raw material intermediates for a novel cycloalkane carboxamide derivative having an action that selectively inhibits cathepsin K, and a production process thereof, are provided.

A cycloalkylcarbonylamino acid ester derivative represented by formula (I), or a pharmaceutically acceptable salt thereof:



(wherein, R^1 and R^2 represent alkyl groups, alkenyl groups, alkynyl groups, aromatic hydrocarbon groups, heterocyclic groups, etc., R^8 represents an alkyl group having 1 to 6 carbon atoms, and ring A represents a cyclic alkylidene group having 5, 6 or 7 carbon atoms).

DESCRIPTION

CYCLOALKYLCARBONYLAMINO ACID ESTER DERIVATIVE AND PROCESS
FOR PRODUCING THE SAME

5

TECHNICAL FIELD

[0001]

The present invention relates to a novel
cycloalkylcarbonylamino acid ester, a salt thereof, and to
10 a process for producing the same. More particularly, the
present invention relates to a novel
cycloalkylcarbonylamino acid ester derivative, useful as a
raw material intermediate for producing a cycloalkane
carboxamide derivative having an action that selectively
15 inhibits cathepsin K, an important cysteine protease
involved especially in bone resorption, and a
pharmaceutically acceptable salt thereof, and a process for
producing the same.

20

BACKGROUND ART

[0002]

Accompanying the rapid progression to an elderly
society in recent years, the number of patients with
geriatric diseases, and particularly those with bone
25 diseases, is continuing to increase. In particular,
osteoporosis, which is prevalent among women and especially
postmenopausal women, is becoming a serious problem. Since
accelerated bone resorption brought about by hormonal
imbalance and aging phenomena in postmenopausal women is
30 intimately related to the onset and progression of bone
disease, bone resorption inhibitors have been used during
the course of ordinary drug therapy for osteoporosis.
However, drugs currently in use that demonstrate bone

resorption inhibitory action, such as calcitonin preparations, estrogen preparations, vitamin K preparations and bisphosphonate preparations, have problems in terms of their therapeutic effects, rapid-acting, adverse side effects and patient compliance, thus desiring the development of a bone resorption inhibitor capable of being used as a more effective drug for the treatment or prevention of osteoporosis.

[0003]

10 In the living body, bone calcium concentrations and blood calcium concentrations are in a state of equilibrium, and calcium is constantly migrating between the bone and blood. This migration of calcium between the bone and blood is governed by dynamic shifts between bone formation and bone resorption. In the process of bone resorption, bone resorption is known to be accelerated as a result of activated osteoclasts eluting bone inorganic substances such as calcium simultaneous to cysteine proteases secreted from osteoclasts decomposing bone organic substances such as collagen. Cysteine proteases such as cathepsin B, cathepsin H, cathepsin L and cathepsin S are present in osteoclast lysosomes, and osteoclast-localized human cathepsin K was isolated in 1995, which was demonstrated to be expressed in osteoclasts in larger amounts than other cathepsins (Biochem. Biophys. Res. Commun., 206, 89 (1995); J. Biol. Chem., 271, 12511 (1996)). Moreover, the cathepsin K gene was demonstrated to mutate in patients with dwarfism presenting with bone resorption abnormalities (Science, 273, 1236 (1996)).

30 [0004]

 In this manner, attention has been focused on cathepsin K as the main cysteine protease involved in bone resorption, and considerable expectations are being placed

on cathepsin K inhibitors as inhibitors of bone resorption. Previously reported examples of compounds having cathepsin K inhibitory action include aldehyde derivatives, epoxy succinic acid derivatives (J. Biol. Chem., 271, p.2126
5 (1996); Biol. Pharm. Bull., 19, p.1026 (1996)) and vinylsulfonic acid derivatives (Nature Structural Biology, 4, p.105 (1997); J. Med. Chem., 38, p.3193 (1995)), and these derivatives have low selectivity and are known to strongly inhibit other cysteine proteases in addition to
10 cathepsin K (J. Enzyme Inhibition, 3, p.13 (1989); Biochem. Biophys. Res. Commun., 153, p.1201 (1988); J. Biochem., 87, p.39 (1980); J. Biochem., 88, p.1805 (1980)).

[0005]

Moreover, accompanying the growing interest in
15 cathepsin K as described above, research has also been actively conducted in the area of X-ray crystal analyses of cathepsin K and inhibitors (Nature Structural Biology, 4, p.105 (1997); Nature Structural Biology, 4, p.109 (1997)), and compounds are known that have a selective inhibitory
20 action on cathepsin K (Proc. Natl. Acad. Sci. USA, 94, p.14249 (1997); WO9801133; J. Am. Chem. Soc., 120, 9, p.9114 (1998); J. Med. Chem., 41, p.3563 (1988); Japanese Unexamined Patent Publication No. 2000-204071; Bioorg. Med. Chem. Lett., 14, p.4333 (2004); Bioorg. Med. Chem. Lett., 14, p.4897
25 (2004)). In addition, WO9716177 identifies the catalyst active site of cathepsin K and discloses a method for inhibiting cathepsin K using a compound that interacts with this active site.

Moreover, although not containing descriptions of
30 inhibition of cathepsin K, Japanese Unexamined Patent Publication Nos. H2-256654 and H2-268145 disclose various types of protease inhibitors as aldehyde derivatives.

[Non-Patent Document 1] Proc. Natl. Acad. Sci. USA,

94, p.14249 (1997)

[Non-Patent Document 2] J. Am. Chem. Soc., 120,
p.9114 (1998)

[Non-Patent Document 3] J. Med. Chem., 41, 3563
5 (1998)

[Non-Patent Document 4] Bioorg. Med. Chem. Lett., 14,
4333 (2004)

[Non-Patent Document 5] Bioorg. Med. Chem. Lett., 14,
4897 (2004)

10 [Patent Document 1] WO9801133

[Patent Document 2] WO9716177

[Patent Document 3] Japanese Unexamined Patent
Publication No. 2000-204071

[Patent Document 4] Japanese Unexamined Patent
15 Publication No. H2-256654

[Patent Document 5] Japanese Unexamined Patent
Publication No. H2-268145

DISCLOSURE OF THE INVENTION

20

[Problems to be Solved by the Invention]

[0006]

As has been described above, compounds that inhibit
cathepsin K have attracted attention as bone resorption
25 inhibitors, and although numerous derivatives have been
reported, none has yet been able to be used practically as
a therapeutic drug for metabolic bone diseases. As a
result of conducting extensive studies on novel compounds
having potent and selective cathepsin K inhibitory action,
30 the inventors of the present invention found that novel
cycloalkylcarbonyl-amino aldehyde derivatives represented
by a specific structural formula indicated by formula (XII)
to be described later selectively inhibit cathepsin K as

compared with conventional aldehyde derivatives known to be protease inhibitors. An object of the present invention is to provide a novel cycloalkylcarbonylamino acid ester derivative, which is a useful raw material compound for producing said cycloalkylcarbonylamino aldehyde derivatives, and a process for producing the same.

[Means for Solving the Problems]

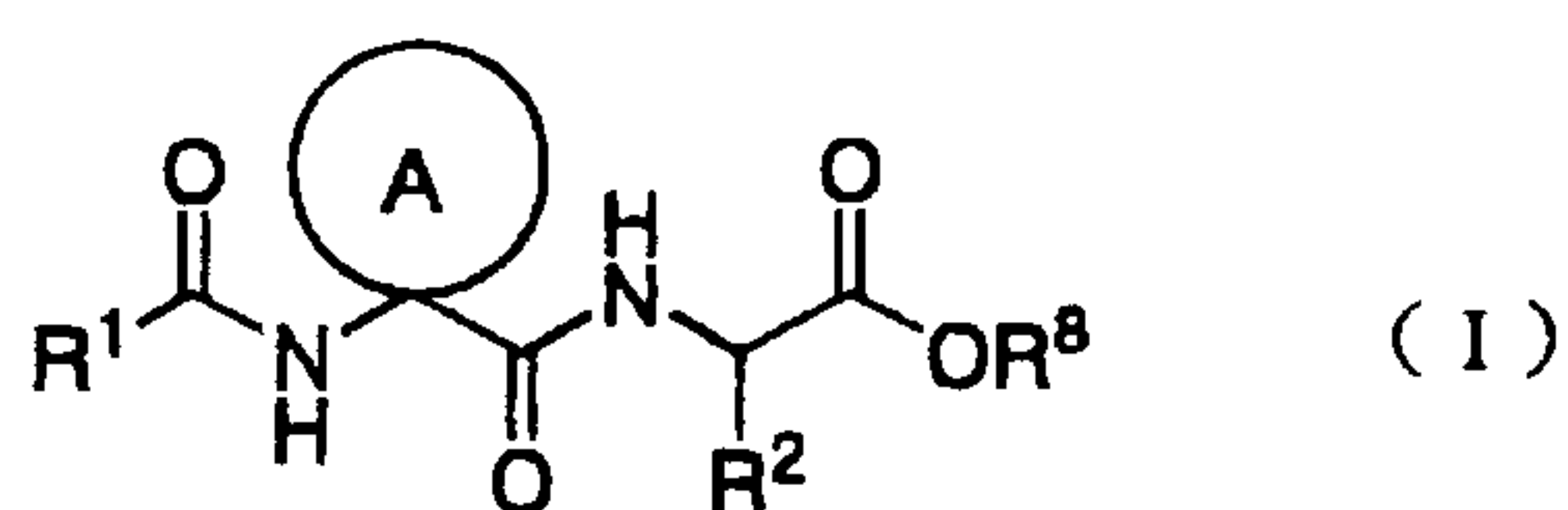
[0007]

The present invention relates to a novel cycloalkylcarbonyl-amino acid ester derivative represented by formula (I) having a non-naturally-occurring amino acid structure, which is a raw material compound for producing cycloalkylcarbonylamino aldehyde derivatives represented by formula (XII) to be described later having selective inhibitory action against cathepsin K, and to a process for producing the same, and the gist thereof lies in the cycloalkylcarbonylamino acid ester derivatives described in 1 to 10 below, pharmaceutically acceptable salts thereof, and a process for producing the same.

[0008]

1. A cycloalkylcarbonylamino acid ester derivative represented by formula (I) or a pharmaceutically acceptable salt thereof:

[0009]



25

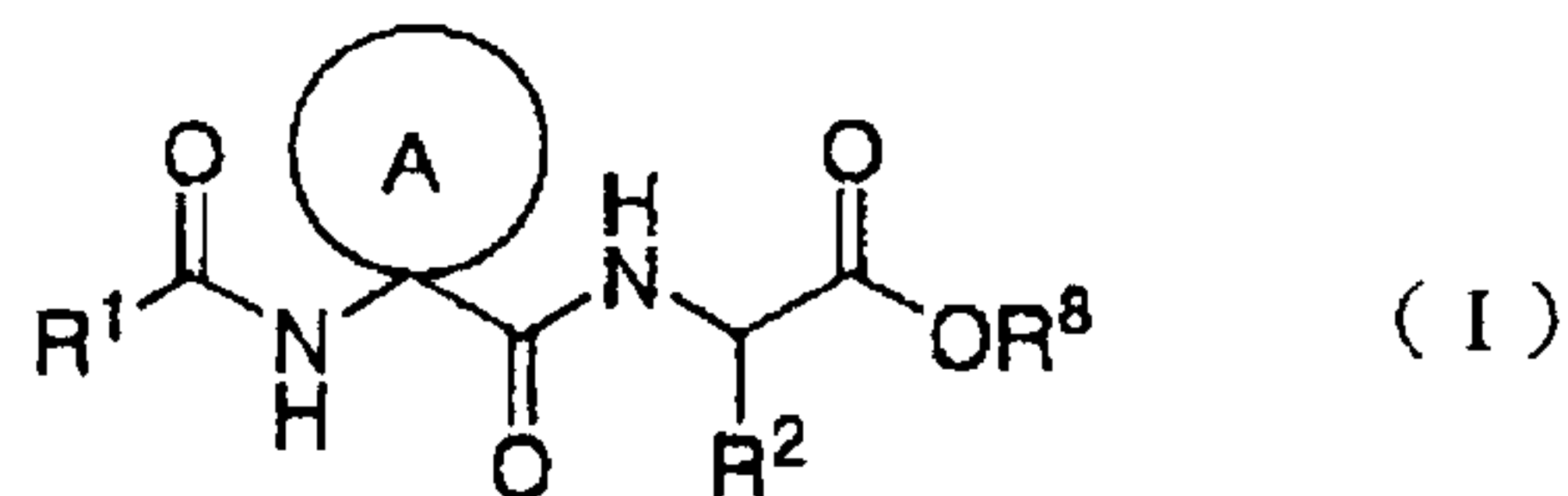
[0010]

[wherein, R¹ represents a substituted or unsubstituted alkyl group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group, substituted or

30

unsubstituted heterocyclic group, group represented by R^4O-
 , group represented by R^5S- or group represented by $R^6(R^7)N-$
 (wherein R^4 , R^5 , R^6 and R^7 respectively and independently
 represent a substituted or unsubstituted alkyl group,
 5 substituted or unsubstituted alkenyl group, substituted or
 unsubstituted alkynyl group, substituted or unsubstituted
 aromatic hydrocarbon group, or substituted or unsubstituted
 heterocyclic group, furthermore R^6 and R^7 may together form
 a ring); R^2 represents a primary or secondary substituted
 10 or unsubstituted alkyl group, substituted or unsubstituted
 alkenyl group, substituted or unsubstituted alkynyl group,
 substituted or unsubstituted aromatic hydrocarbon group or
 substituted or unsubstituted heterocyclic group; ring A
 represents a cyclic alkylidene group having 5, 6 or 7
 15 carbon atoms; and, R^8 represents a substituted or
 unsubstituted alkyl group having 1 to 6 carbon atoms;
 provided that, in the case R^2 is a carbamoylmethyl group or
 hydroxymethyl group, R^8 is not a t-butyl group, in the case
 R^2 is a benzyl group, 2,2-dimethylpropyl group, 2-propyl
 20 group or 1-hydroxyethyl group, R^8 is not a benzyl group,
 and in the case R^2 is a 1,1-dimethylethyl group, benzyl
 group, 2-(methylthio)ethyl group, 2-methylpropyl group, p-
 hydroxyphenylmethyl group or methyl group, R^8 is not a
 methyl group].

25 A cycloalkylcarbonylamino acid ester derivative
 represented by formula (I) or a pharmaceutically acceptable
 salt thereof:



wherein, R^1 represents a substituted or unsubstituted alkyl
 30 group, substituted or unsubstituted alkenyl group,

substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group, substituted or unsubstituted heterocyclic group, group represented by R^4O- , group represented by R^5S- or group represented by $R^6(R^7)N-$, wherein R^4 , R^5 , R^6 and R^7 respectively and independently represent a substituted or unsubstituted alkyl group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group, or substituted or unsubstituted heterocyclic group, furthermore R^6 and R^7 may together form a ring; R^2 represents a primary or secondary substituted or unsubstituted alkyl group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heterocyclic group; ring A represents a cyclic alkylidene group having 6 or 7 carbon atoms; and, R^8 represents a substituted or unsubstituted alkyl group having 1 to 6 carbon atoms; provided that, in the case R^2 is a carbamoylmethyl group or hydroxymethyl group, R^8 is not a t-butyl group, in the case R^2 is a benzyl group, 2,2-dimethylpropyl group, 2-propyl group or 1-hydroxyethyl group, R^8 is not a benzyl group, and in the case R^2 is a 1,1-dimethylethyl group, benzyl group, 2-(methylthio)ethyl group, 2-methylpropyl group, p-hydroxyphenylmethyl group or methyl group, R^8 is not a methyl group provided that the compounds, Z-Ac7c-L-Ala-OMe, Z-L-Ala-Ac7c-L-Ala-OMe, Z-(Ac7c)₂-L-Ala-OMe, Z-Ac7c-L-Val-OMe and Boc-L-Leu-Ac7c-L-Val-OMe, wherein Z represents benzyloxycarbonyl, Ac7c represents 1-aminocycloheptane-1-carbonyl and Boc represents t-butoxycarbonyl, are not encompassed herein.

[0011]

2. The cycloalkylcarbonylamino acid ester derivative or

pharmaceutically acceptable salt thereof described in 1
above, wherein the alkyl group in the groups represented by
 R^1 , R^2 , R^4 , R^5 , R^6 and R^7 in the formula (I) is a linear,
branched or cyclic alkyl group having 1 to 12 carbon atoms,
5 the alkenyl group is a linear, branched or cyclic alkenyl
group having 2 to 12 carbon atoms, the alkynyl group is a
linear, branched or cyclic alkynyl group having 2 to 12

carbon atoms, the aromatic hydrocarbon group is a monocyclic or polycyclic aromatic hydrocarbon group having 6 to 18 carbon atoms, and the heterocyclic group is a heterocyclic group of a 3- to 7-membered ring containing at least one nitrogen atom, oxygen atom or sulfur atom as a ring-composing atom.

[0012]

3. The cycloalkylcarbonylamino acid ester derivative or pharmaceutically acceptable salt thereof described in 1 or 2 above, wherein substituents of alkyl groups in the groups represented by R^1 , R^2 , R^4 , R^5 , R^6 , R^7 and R^8 in the formula (I) are respectively and independently groups selected from a hydroxyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, amido group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group, alkoxycarbonylamino group and $R_x(R_y)N$ group (wherein, R_x and R_y respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group); and,

substituents of alkenyl groups, alkynyl groups, aromatic hydrocarbon groups or heterocyclic groups in the groups represented by R^1 , R^2 , R^4 , R^5 , R^6 and R^7 are respectively and independently groups selected from a hydroxyl group, alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl

5

4. A cycloalkylcarbonylamino acid ester derivative represented by formula (I') or a pharmaceutically acceptable salt thereof:

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1 - \text{C} - \text{NH} - \text{C}(\text{A}) - \text{C}(=\text{O}) - \text{NH} - \text{CH}(\text{R}^{2'}) - \text{C}(=\text{O}) - \text{OR}^8 \end{array} \quad (\text{I}')$$

[0015]

20

25

Ra(Rb)CH- (wherein, Ra and Rb respectively and
 independently represent a hydrogen atom, substituted or
 unsubstituted alkyl group, substituted or unsubstituted
 aromatic hydrocarbon group, or substituted or unsubstituted
 5 heterocyclic group), substituted or unsubstituted alkenyl
 group, substituted or unsubstituted alkynyl group,
 substituted or unsubstituted aromatic hydrocarbon group or
 substituted or unsubstituted heterocyclic group; ring A
 represents a cyclic alkylidene group having 5, 6 or 7
 10 carbon atoms; and, R⁸ represents a substituted or
 unsubstituted alkyl group having 1 to 6 carbon atoms;
 [0016]

a substituent of an alkenyl group, alkynyl group or
 aromatic hydrocarbon group of R¹, and a substituent of an
 15 alkenyl group, alkynyl group, aromatic hydrocarbon group or
 heterocyclic group of R^{2'}, R⁴, R⁵, R⁶ and R⁷ are respectively
 and independently a group selected from a hydroxyl group,
 alkyl group, alkenyl group, alkynyl group, halogen atom,
 aromatic hydrocarbon group, heterocyclic group, alkoxy
 20 group, guanidino group, alkylthio group, alkoxycarbonyl
 group, aryloxy group, arylthio group, acyl group, sulfonyl
 group, heterocyclyloxy group, heterocyclylthio group, amido
 group, ureido group, carboxyl group, carbamoyl group, oxo
 group, sulfamoyl group, sulfo group, cyano group, nitro
 25 group, acyloxy group, azido group, sulfonamido group,
 mercapto group, alkoxycarbonylamino group and Rx(Ry)N group
 (wherein, Rx and Ry respectively and independently
 represent a hydrogen atom, alkyl group, alkenyl group,
 alkynyl group, aromatic hydrocarbon group or heterocyclic
 30 group);

a substituent of an alkyl group of R⁴, R⁵, R⁶, R⁷, R⁸,
 Ra and Rb is respectively and independently a group
 selected from a hydroxyl group, alkenyl group, alkynyl

group, halogen atom, aromatic hydrocarbon group,
heterocyclic group, alkoxy group, guanidino group,
alkylthio group, alkoxycarbonyl group, aryloxy group,
arylthio group, acyl group, sulfonyl group, heterocyclyloxy
5 group, heterocyclylthio group, amido group, ureido group,
carboxyl group, carbamoyl group, oxo group, sulfamoyl
group, sulfo group, cyano group, nitro group, acyloxy
group, azido group, sulfonamido group, mercapto group,
alkoxycarbonylamino group and Rx(Ry)N group (wherein, Rx
10 and Ry respectively and independently represent a hydrogen
atom, alkyl group, alkenyl group, alkynyl group, aromatic
hydrocarbon group or heterocyclic group);

[0017]

a substituent of an alkyl group of R¹ is respectively
15 and independently a group selected from a hydroxyl group,
alkenyl group, alkynyl group, halogen atom, aromatic
hydrocarbon group, heterocyclic group, alkoxy group,
guanidino group, alkylthio group, alkoxycarbonyl group,
aryloxy group, arylthio group, acyl group, sulfonyl group,
20 heterocyclyloxy group, heterocyclylthio group, ureido
group, carboxyl group, carbamoyl group, oxo group,
sulfamoyl group, sulfo group, cyano group, nitro group,
acyloxy group, azido group, sulfonamido group, mercapto
group and Rx(Ry)N group (wherein, Rx and Ry respectively
25 and independently represent a hydrogen atom, alkyl group,
alkenyl group, alkynyl group, aromatic hydrocarbon group or
heterocyclic group, provided that Rx and Ry are not
simultaneously hydrogen atoms);

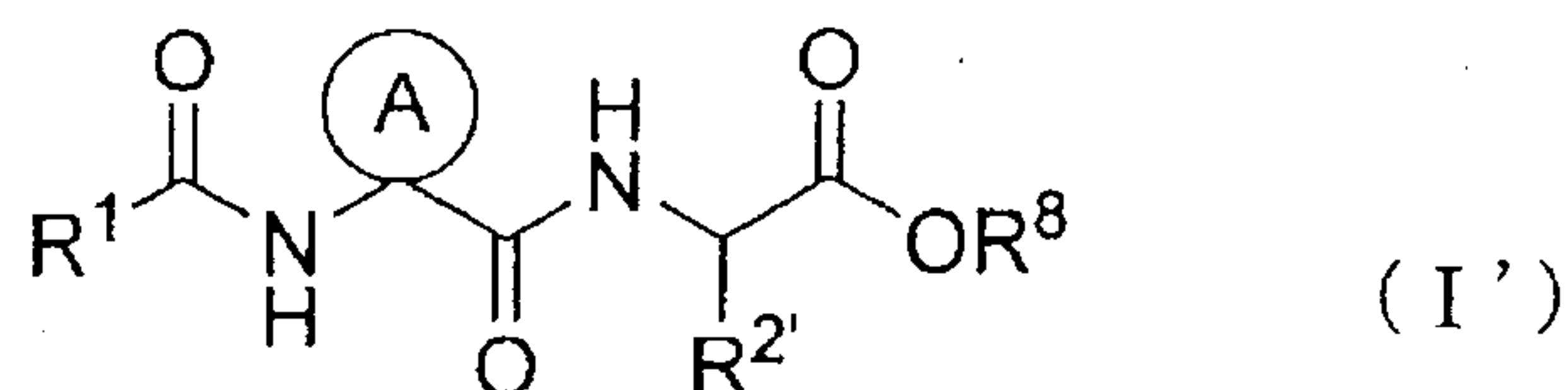
a substituent of a heterocyclic group of R¹ is a
30 group selected from a hydroxyl group, alkyl group, alkenyl
group, alkynyl group, halogen atom, aromatic hydrocarbon
group, heterocyclic group, alkoxy group, guanidino group,
alkylthio group, aryloxy group, arylthio group, sulfonyl

group, heterocyclyloxy group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group and Rx(Ry)N group (wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group); and,

[0018]

10 a substituent of an aromatic hydrocarbon group or heterocyclic group of Ra and Rb is respectively and independently a group selected from a hydroxyl group, alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, guanidino group, 15 alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido 20 group, sulfonamido group, mercapto group, alkoxycarbonylamino group and Rx(Ry)N group (wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group), provided that R⁴ 25 and R⁸ are not respectively t-butyl groups, and R^{2'}, R⁴ and R⁸ are not simultaneously benzyl groups].

A cycloalkylcarbonylamino acid ester derivative represented by formula (I') or a pharmaceutically acceptable salt thereof:



wherein, R^1 represents a substituted or unsubstituted alkyl group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group, substituted or unsubstituted heterocyclic group, group represented by R^4O- , group represented by R^5S- or group represented by $R^6(R^7)N$, wherein R^4 , R^5 , R^6 and R^7 respectively and independently represent a substituted or unsubstituted alkyl group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group, or substituted or unsubstituted heterocyclic group, furthermore R^6 and R^7 may together form a ring; $R^{2'}$ represents an alkyl group represented by $Ra(Rb)CH-$, wherein, Ra and Rb respectively and independently represent a hydrogen atom, substituted or unsubstituted alkyl group, substituted or unsubstituted aromatic hydrocarbon group, or substituted or unsubstituted heterocyclic group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group, or substituted or unsubstituted heterocyclic group; ring A represents a cyclic alkylidene group having 6 or 7 carbon atoms; and, R^8 represents a substituted or unsubstituted alkyl group having 1 to 6 carbon atoms;

a substituent of an alkenyl group, alkynyl group or aromatic hydrocarbon group of R^1 , and a substituent of an alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group of $R^{2'}$, R^4 , R^5 , R^6 and R^7 are respectively and independently a group selected from a hydroxyl group,

alkyl group, alkenyl group, alkynyl group, halogen atom,
aromatic hydrocarbon group, heterocyclic group, alkoxy
group, guanidino group, alkylthio group, alkoxycarbonyl
group, aryloxy group, arylthio group, acyl group, sulfonyl
5 group, heterocyclyloxy group, heterocyclylthio group, amido
group, ureido group, carboxyl group, carbamoyl group, oxo
group, sulfamoyl group, sulfo group, cyano group, nitro
group, acyloxy group, azido group, sulfonamido group,
mercapto group, alkoxycarbonylamino group and Rx(Ry)N
10 group, wherein, Rx and Ry respectively and independently
represent a hydrogen atom, alkyl group, alkenyl group,
alkynyl group, aromatic hydrocarbon group or heterocyclic
group;

a substituent of an alkyl group of R⁴, R⁵, R⁶, R⁷, R⁸,
15 Ra and Rb is respectively and independently a group
selected from a hydroxyl group, alkenyl group, alkynyl
group, halogen atom, aromatic hydrocarbon group,
heterocyclic group, alkoxy group, guanidino group,
alkylthio group, alkoxycarbonyl group, aryloxy group,
20 arylthio group, acyl group, sulfonyl group, heterocyclyloxy
group, heterocyclylthio group, amido group, ureido group,
carboxyl group, carbamoyl group, oxo group, sulfamoyl
group, sulfo group, cyano group, nitro group, acyloxy
group, azido group, sulfonamido group, mercapto group,
25 alkoxycarbonylamino group and Rx(Ry)N group, wherein, Rx
and Ry respectively and independently represent a hydrogen
atom, alkyl group, alkenyl group, alkynyl group, aromatic
hydrocarbon group or heterocyclic group;

a substituent of an alkyl group of R¹ is respectively
30 and independently a group selected from a hydroxyl group,
alkenyl group, alkynyl group, halogen atom, aromatic
hydrocarbon group, heterocyclic group, alkoxy group,
guanidino group, alkylthio group, alkoxycarbonyl group,

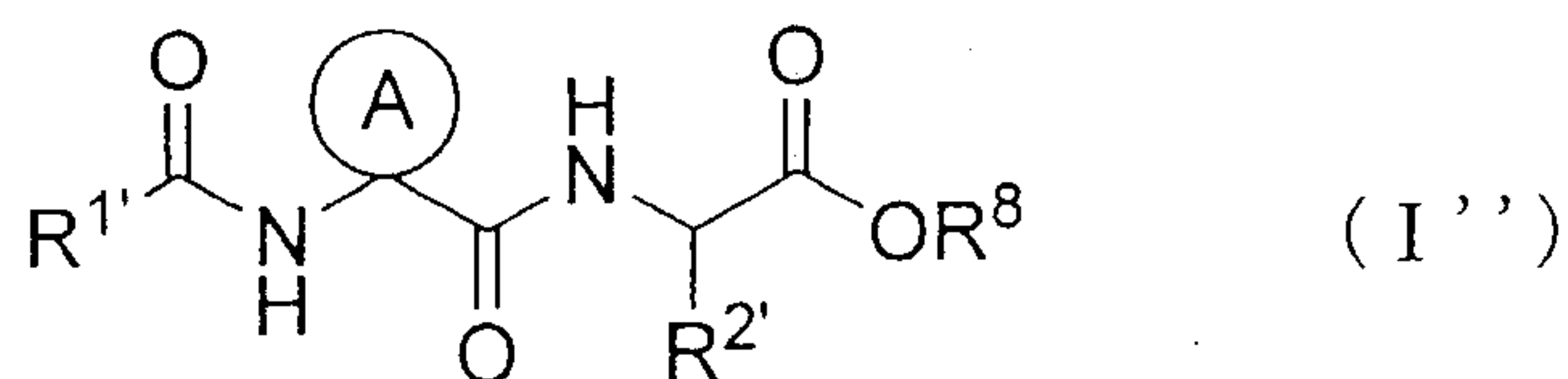
aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group and Rx(Ry)N group, wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group, provided that Rx and Ry are not simultaneously hydrogen atoms;

a substituent of a heterocyclic group of R¹ is a group selected from a hydroxyl group, alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, aryloxy group, arylthio group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group and Rx(Ry)N group, wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group; and,

a substituent of an aromatic hydrocarbon group or heterocyclic group of Ra and Rb is respectively and independently a group selected from a hydroxyl group, alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido

group, sulfonamido group, mercapto group,
 alkoxy carbonylamino group and $R_x(R_y)N$ group, wherein, R_x and
 R_y respectively and independently represent a hydrogen
 atom, alkyl group, alkenyl group, alkynyl group, aromatic
 5 hydrocarbon group or heterocyclic group, provided that R^4
 and R^8 are not respectively t-butyl groups, and $R^{2'}$, R^4 and
 R^8 are not simultaneously benzyl groups provided that the
 compounds, Z-Ac7c-L-Ala-OMe, Z-L-Ala-Ac7c-L-Ala-OMe, Z-
 (Ac7c)₂-L-Ala-OMe, Z-Ac7c-L-Val-OMe and Boc-L-Leu-Ac7c-L-
 10 Val-OMe, wherein Z represents benzyloxycarbonyl, Ac7c
 represents 1-aminocycloheptane-1-carbonyl and Boc
 represents t-butoxycarbonyl, are not encompassed herein.
 [0019]

5. A cycloalkylcarbonylamino acid ester derivative
 15 represented by formula (I'') or a pharmaceutically
 acceptable salt thereof:
 [0020]



[0021]
 20 [wherein, $R^{1'}$ represents a substituted or unsubstituted
 alkyl group, substituted or unsubstituted alkenyl group,
 substituted or unsubstituted alkynyl group, substituted or
 unsubstituted aromatic hydrocarbon group, substituted or
 unsubstituted heterocyclic group, group represented by R^5S-
 25 or group represented by $R^6(R^7)N-$ (wherein R^5 , R^6 and R^7
 respectively and independently represent a substituted or
 unsubstituted alkyl group, substituted or unsubstituted
 alkenyl group, substituted or unsubstituted alkynyl group,
 substituted or unsubstituted aromatic hydrocarbon group, or

substituted or unsubstituted heterocyclic group,
 furthermore R^6 and R^7 may together form a ring); $R^{2'}$
 represents an alkyl group represented by $R_a(R_b)CH-$
 (wherein, R_a and R_b respectively and independently
 5 represent a hydrogen atom, substituted or unsubstituted
 alkyl group, substituted or unsubstituted aromatic
 hydrocarbon group, or substituted or unsubstituted
 heterocyclic group), substituted or unsubstituted alkenyl
 group, substituted or unsubstituted alkynyl group,
 10 substituted or unsubstituted aromatic hydrocarbon group, or
 substituted or unsubstituted heterocyclic group; ring A
 represents a cyclic alkylidene group having 5, 6 or 7
 carbon atoms; and, R^8 represents a substituted or
 unsubstituted alkyl group having 1 to 6 carbon atoms;
 15 [0022]

a substituent of an alkenyl group, alkynyl group or
 aromatic hydrocarbon group of $R^{1'}$, and a substituent of an
 alkenyl group, alkynyl group, aromatic hydrocarbon group or
 heterocyclic group of $R^{2'}$, R^5 , R^6 and R^7 are respectively
 20 and independently a group selected from a hydroxyl group,
 alkyl group, alkenyl group, alkynyl group, halogen atom,
 aromatic hydrocarbon group, heterocyclic group, alkoxy
 group, guanidino group, alkylthio group, alkoxycarbonyl
 group, aryloxy group, arylthio group, acyl group, sulfonyl
 25 group, heterocyclyloxy group, heterocyclylthio group, amido
 group, ureido group, carboxyl group, carbamoyl group, oxo
 group, sulfamoyl group, sulfo group, cyano group, nitro
 group, acyloxy group, azido group, sulfonamido group,
 mercapto group, alkoxycarbonylamino group and $R_x(R_y)N$ group
 30 (wherein, R_x and R_y respectively and independently
 represent a hydrogen atom, alkyl group, alkenyl group,
 alkynyl group, aromatic hydrocarbon group or heterocyclic
 group);

a substituent of an alkyl group of R^5 , R^6 , R^7 , R^8 , R^a and R^b is respectively and independently a group selected from a hydroxyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxy carbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, amido group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group, alkoxy carbonylamino group and $R^x(R^y)N$ group (wherein, R^x and R^y respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group);

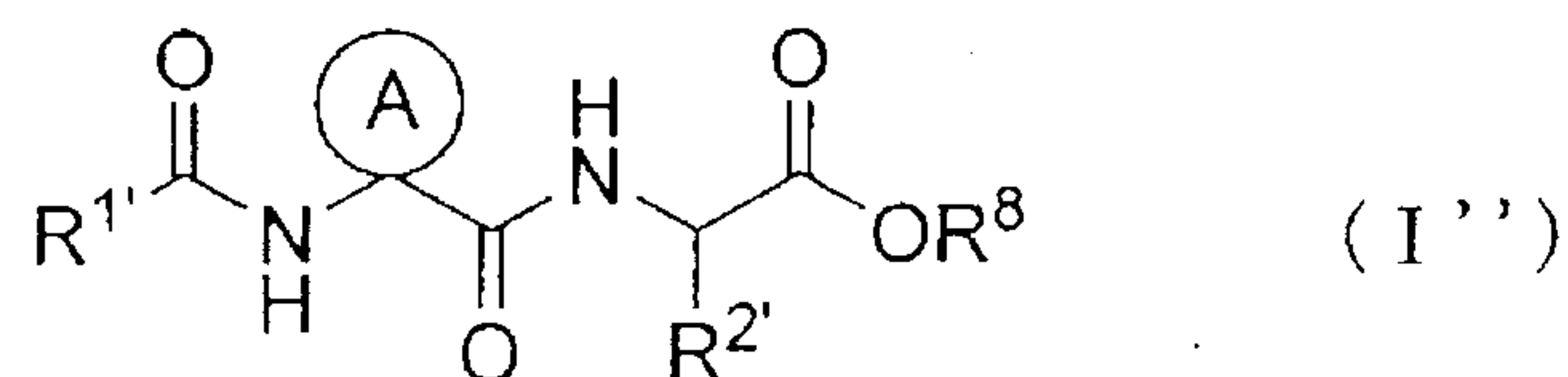
[0023]

a substituent of an alkyl group of $R^{1'}$ is a group selected from a hydroxyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxy carbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group and $R^x(R^y)N$ group (wherein, R^x and R^y respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group, provided that R^x and R^y are not simultaneously hydrogen atoms); and,

a substituent of a heterocyclic group of $R^{1'}$ is a group selected from a hydroxyl group, alkyl group, alkenyl

group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, aryloxy group, arylthio group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group and Rx(Ry)N group (wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group)].

A cycloalkylcarbonylamino acid ester derivative represented by formula (I'') or a pharmaceutically acceptable salt thereof:



wherein, R^{1'} represents a substituted or unsubstituted alkyl group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group, substituted or unsubstituted heterocyclic group, group represented by R⁵S- or group represented by R⁶(R⁷)N-, wherein R⁵, R⁶ and R⁷ respectively and independently represent a substituted or unsubstituted alkyl group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heterocyclic group, or R⁶ and R⁷ may together form a ring); R^{2'} represents an alkyl group represented by Ra(Rb)CH-, wherein, Ra and Rb respectively and independently represent a hydrogen atom, substituted or unsubstituted alkyl group, substituted or unsubstituted

aromatic hydrocarbon group, or substituted or unsubstituted heterocyclic group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heterocyclic group; ring A represents a cyclic alkylidene group having 6 or 7 carbon atoms; and, R^8 represents a substituted or unsubstituted alkyl group having 1 to 6 carbon atoms;

a substituent of an alkenyl group, alkynyl group or aromatic hydrocarbon group of $R^{1'}$, and a substituent of an alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group of $R^{2'}$, R^5 , R^6 and R^7 are respectively and independently a group selected from a hydroxyl group, alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, amido group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group, alkoxycarbonylamino group and $R_x(R_y)N$ group, wherein, R_x and R_y respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group;

a substituent of an alkyl group of R^5 , R^6 , R^7 , R^8 , R_a and R_b is respectively and independently a group selected from a hydroxyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group,

heterocyclylthio group, amido group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group,

5 alkoxycarbonylamino group and Rx(Ry)N group, wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group;

a substituent of an alkyl group of R^{1'} is a group
 10 selected from a hydroxyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy
 15 group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group and Rx(Ry)N group, wherein, Rx and Ry respectively and independently
 20 represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group, provided that Rx and Ry are not simultaneously hydrogen atoms; and,

a substituent of a heterocyclic group of R^{1'} is a
 25 group selected from a hydroxyl group, alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, aryloxy group, arylthio group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group,
 30 ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group and Rx(Ry)N group wherein, Rx and Ry respectively and

independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group provided that the compounds, Z-Ac7c-L-Ala-OMe, Z-L-Ala-Ac7c-L-Ala-OMe, Z-(Ac7c)₂-L-Ala-OMe, Z-Ac7c-L-Val-OMe and Boc-L-Leu-Ac7c-L-Val-OMe, wherein Z represents benzyloxycarbonyl, Ac7c represents 1-aminocycloheptane-1-carbonyl and Boc represents t-butoxycarbonyl, are not encompassed herein.

[0024]

10 6. The cycloalkylcarbonylamino acid ester derivative or pharmaceutically acceptable salt thereof described in 4 or 5 above, wherein in the formula (I') or (I'') above, the alkyl group in the groups represented by R¹ or R^{1'}, R⁴, R⁵, R⁶, R⁷, Ra, Rb, Rx and Ry is a linear, branched or cyclic

15

alkyl group having 1 to 12 carbon atoms, the aromatic hydrocarbon group in the groups represented by R^1 or $R^{1'}$, $R^{2'}$, R^4 , R^5 , R^6 , R^7 , R_a , R_b , R_x and R_y is a monocyclic or polycyclic aromatic hydrocarbon group having 6 to 18 carbon atoms, the heterocyclic group is a heterocyclic group of a 3- to 7-membered ring containing at least one nitrogen atom, oxygen atom or sulfur atom as a ring-composing atom, the alkenyl group in the groups represented by R^1 or $R^{1'}$, $R^{2'}$, R^4 , R^5 , R^6 , R^7 , R_x and R_y is a linear, branched or cyclic alkenyl group having 2 to 12 carbon atoms, and the alkynyl group is a linear, branched or cyclic alkynyl group having 2 to 12 carbon atoms.

[0025]

7. The cycloalkylcarbonylamino acid ester derivative or pharmaceutically acceptable salt thereof described in any one of 1 to 6 above, wherein in the formula (I), (I') or (I'') above, R^2 or $R^{2'}$ is a substituted or unsubstituted alkyl group, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heterocyclic group.

[0026]

8. The cycloalkylcarbonylamino acid ester derivative or pharmaceutically acceptable salt thereof described in any one of 1 to 6 above, wherein in the formula (I), (I') or (I''), the substituted or unsubstituted alkyl group represented by R^2 or $R^{2'}$, alkyl group represented by $R_a(R_b)CH-$ (wherein R_a and R_b respectively and independently represent a hydrogen atom, substituted or unsubstituted alkyl group, substituted or unsubstituted aromatic hydrocarbon group, or substituted or unsubstituted heterocyclic group), substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group, or

substituted or unsubstituted heterocyclic group is a group derived from an α -amino acid, and said α -amino acid is an α -amino acid selected from alanine, arginine, asparagine, aspartic acid, isoasparagine, γ -carboxyglutamic acid, cysteine, cystine, glutamine, glutamic acid, histidine, homoarginine, homocysteine, homocystine, homoserine, homophenylalanine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, phenylalanine, phenylglycine, serine, threonine, tryptophan, tyrosine, valine, 3,4-dihydroxyphenylalanine, allylglycine, neopentylglycine, allothreonine, homolysine, naphthylalanine, α -aminoadipic acid, thienylglycine, pyridylalanine and cyclohexylalanine.

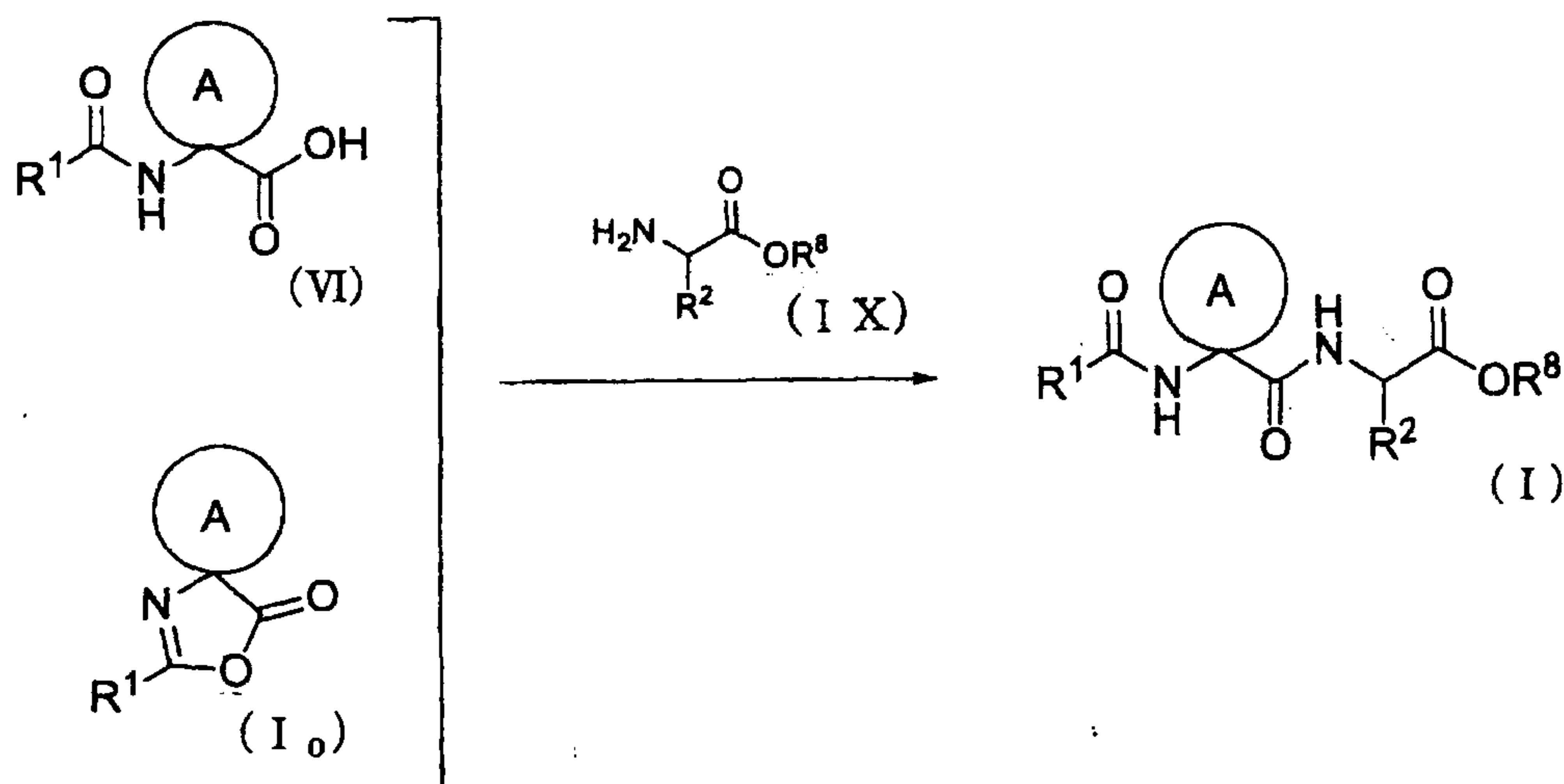
[0027]

9. The cycloalkylcarbonylamino acid ester derivative or pharmaceutically acceptable salt thereof described in any one of 1 to 8 above, wherein in the formula (I), (I') or (I'') above, R^1 or $R^{1'}$ represents a 3- to 7-membered substituted or unsubstituted heterocyclic group containing at least one nitrogen atom, oxygen atom or sulfur atom as a ring-composing atom, or a substituted aromatic hydrocarbon group, R^2 or $R^{2'}$ represents an alkyl group having 1 to 4 carbon atoms, R^8 represents an alkyl group having 1 to 6 carbon atoms, and ring A represents a cyclohexylidene group.

[0028]

10. A process for producing a cycloalkylcarbonylamino acid ester derivative represented by formula (I) comprising: reacting a carboxylic acid derivative represented by the following formula (VI) or an oxazolone derivative represented by the following formula (I₀) with an amino acid ester derivative represented by the following

formula (IX):



[0029]

(wherein, R¹, R², R⁸ and ring A are the same as previously
5 defined in 1 above).

[Effects of the Invention]

[0030]

A novel cycloalkylcarbonylamino aldehyde derivative
derived from the novel cycloalkylcarbonylamino acid ester
10 derivative of the present invention has highly active and
highly selective cathepsin K inhibitory activity. Thus,
compounds of the present invention are useful as
intermediates of drugs for the prevention and treatment of
diseases such as osteoporosis, hypercalcemia, Paget's
15 disease, bone resorption diseases, osteogenesis imperfecta,
osteoarthritis, rheumatoid arthritis, arthritis,
Klinefelter's syndrome, hereditary hyperphosphatasemia,
Charcot's neuroarthopathy, mastocytosis, Gaucher's disease,
cancer metastasis and multiple myeloma, and the
20 contribution thereof to the health care of these diseases
is considerable.

BEST MODE FOR CARRYING OUT THE INVENTION

[0031]

The cycloalkylcarbonylamino acid ester derivatives of the present invention are compounds represented by the aforementioned formula (I), (I') or (I'') and pharmaceutically acceptable salts thereof, and specific
5 examples of alkyl groups, alkenyl groups, alkynyl groups, aromatic hydrocarbon groups and heterocyclic groups included by the groups represented by substituents R^1 or $R^{1'}$, R^2 , R^4 , R^5 , R^6 , R^7 , R_a and R_b in these derivatives are listed below.

10 [0032]

The alkyl group may be a linear, branched or cyclic alkyl group having 1 to 12 carbon atoms, examples of which include a methyl group, ethyl group, n-propyl group, 2-propyl group, cyclopropyl group, n-butyl group, 2-methylpropyl group, 2-butyl group, 1,1-dimethylethyl group,
15 cyclobutyl group, n-pentyl group, 3-methylbutyl group, cyclopentyl group, 2,2-dimethylpropyl group, 1-methylcyclobutyl group, cyclobutylmethyl group, n-hexyl group, 4-methylpentyl group, cyclohexyl group, 1-methylcyclopentyl group, cyclopentylmethyl group, (1-methylcyclobutyl)methyl group, n-heptyl group, 5-methylhexyl group, 4,4-dimethylpentyl group, cycloheptyl group, cyclohexylmethyl group, (1-methylcyclopentyl)methyl group, n-octyl group, 6-methylheptyl group, 5,5-
20 dimethylhexyl group, (1-methylcyclohexyl)methyl group, n-nonyl group, 7-methyloctyl group, 6,6-dimethylheptyl group, n-decyl group, 8-methylnonyl group, n-dodecacyl group, 10-methylundecacyl group and 9,9-dimethyldecacyl group.

[0033]

30 Substituent R^8 of a compound represented by the aforementioned formula (I), (I') or (I'') is an alkyl group having 1 to 6 carbon atoms or alkyl group substituted with the following substituents among the previously listed

examples thereof.

The alkenyl group may be a linear, branched or cyclic alkenyl group having 2 to 12 carbon atoms, examples of which include a vinyl group, 1-propenyl group, 2-propenyl group, 1-methylethenyl group, 1-methyl-1-propenyl group, 1-methyl-2-propenyl group, 2-methyl-2-propenyl group, 1-propenyl group, 2-propenyl group, 1-butenyl group, 2-butenyl group, 2-pentenyl group, 1-pentenyl group, 1-hexenyl group and 2-hexenyl group.

10 [0034]

The alkynyl group may be a linear, branched or cyclic alkynyl group having 2 to 12 carbon atoms and may be substituted, examples of which include an ethynyl group, 1-propynyl group, 2-propynyl group and 2-butynyl group.

15 [0035]

The aromatic hydrocarbon group may be a monocyclic or polycyclic group having 6 to 18 carbon atoms, examples of which include a phenyl group, naphthyl group and anthranyl group.

20 The heterocyclic group may be a 3- to 7-membered ring group containing at least one heteroatom such as a nitrogen atom, oxygen atom or sulfur atom as a ring-composing atom, and these may condense with heterocyclic groups, aliphatic rings or aromatic rings and may form a spiro ring, examples of which include a furanyl group, thienyl group, pyrrolyl group, pyrazolyl group, thiazolyl group, oxazolyl group, isoxazolyl group, pyridinyl group, pirazinyl group, pyrimidinyl group, pyridazinyl group, pyranyl group, indolyl group, benzofuranyl group, benzimidazolyl group, 25 benzoxazolyl group, quinolyl group, isoquinolyl group, pyrrolidinyl group, piperizinyl group, piperazinyl group, morpholinyl group, indolinyl group and benzodioxolyl group. Preferable examples include a furanyl group and morpholinyl

30

group.

[0036]

In addition, examples of substituents which can be possessed by the above alkyl groups include groups selected from a hydroxyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, amido group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group, alkoxycarbonylamino group and an Rx(Ry)N group (wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group).

[0037]

Moreover, examples of substituents which can be possessed by the above alkenyl groups, alkynyl groups, aromatic hydrocarbon groups and heterocyclic groups include groups selected from a hydroxyl group, alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, amido group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group, alkoxycarbonylamino group and an Rx(Ry)N group (wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic

hydrocarbon group or heterocyclic group).

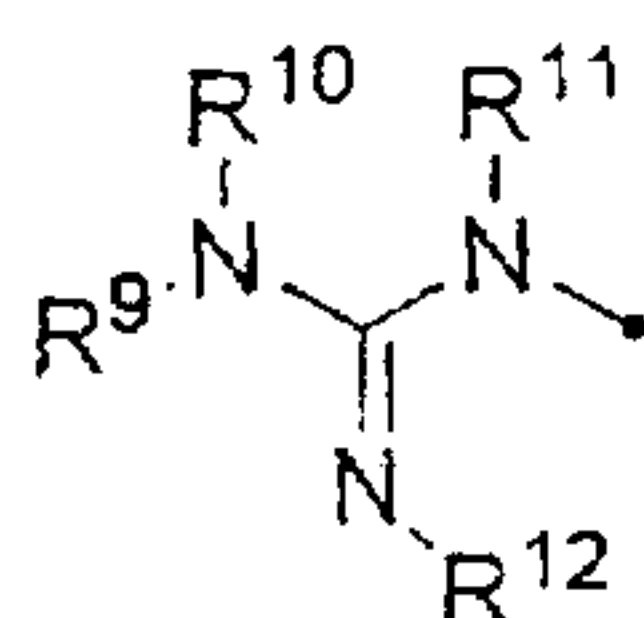
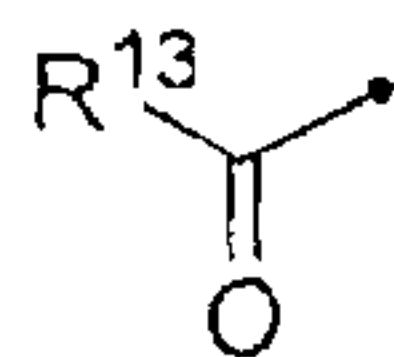
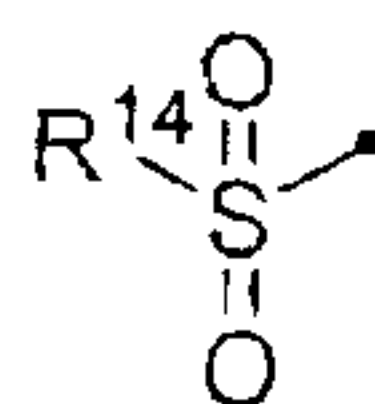
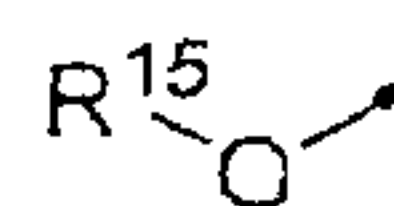
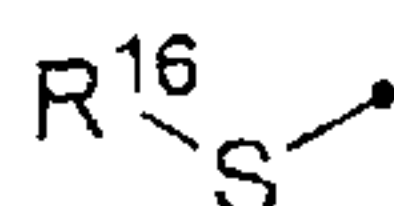
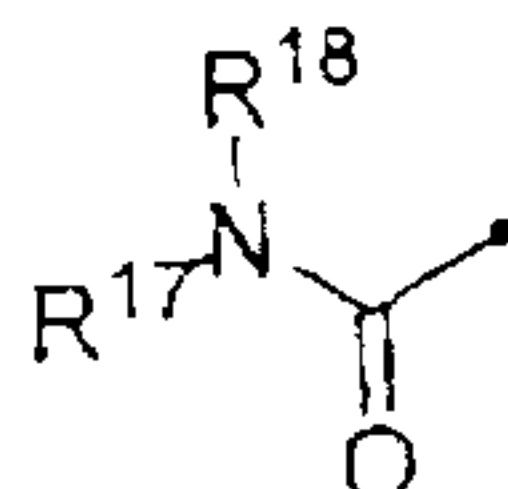
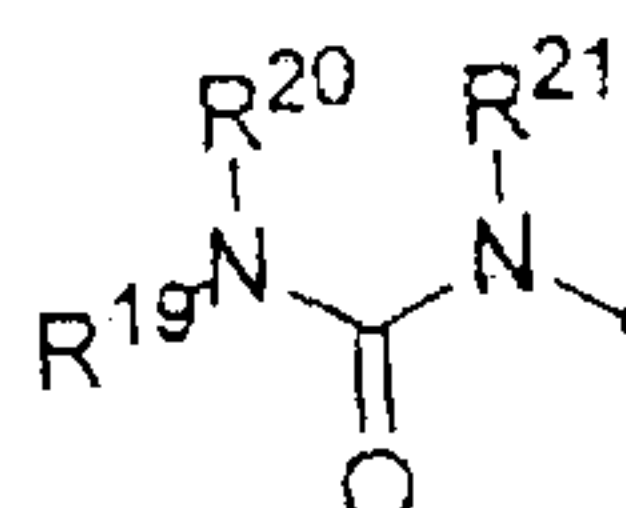
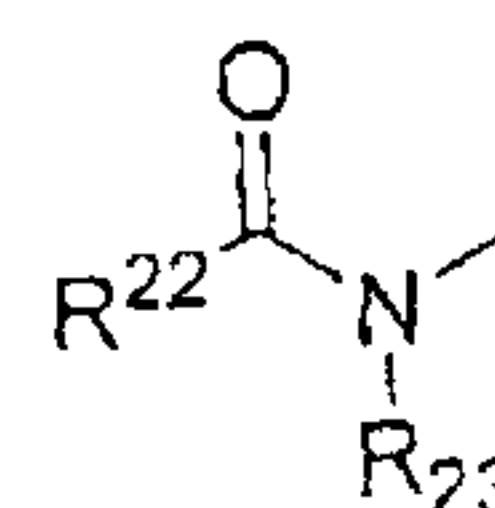
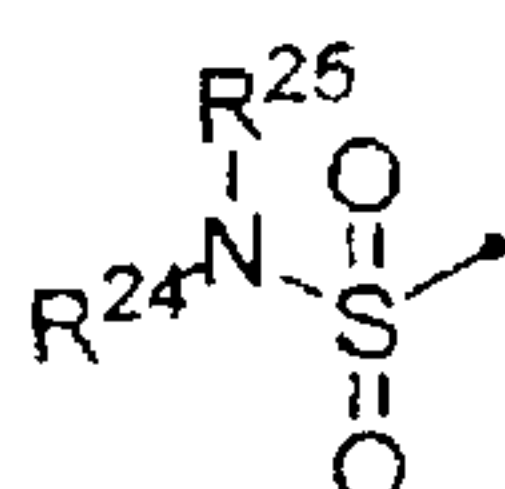
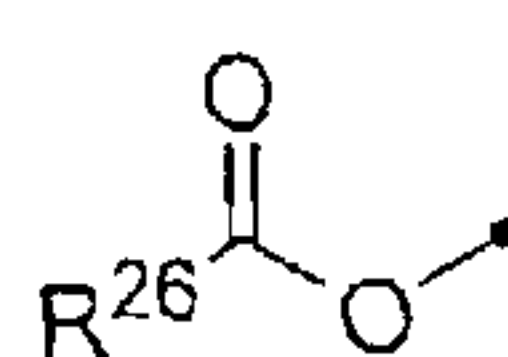
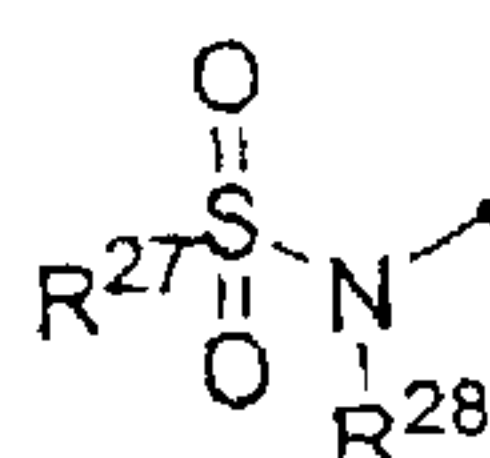
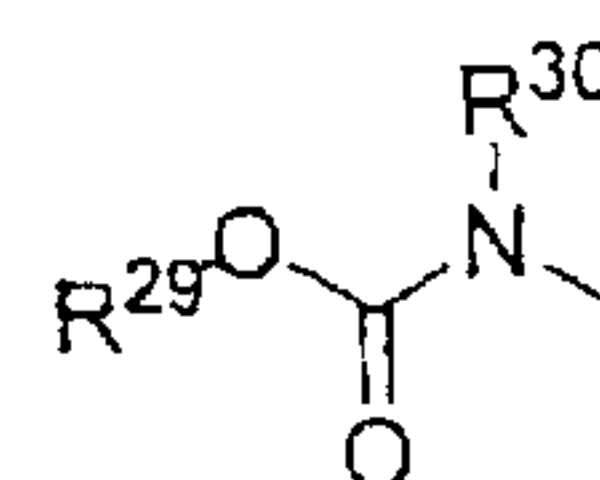
[0038]

Here, in the case R^2 is a carbamoylmethyl group or hydroxymethyl group, R^8 is not a t-butyl group, in the case
5 R^2 is a benzyl group, 2,2-dimethylpropyl group, 2-propyl group or 1-hydroxyethyl group, R^8 is not a benzyl group, and in the case R^2 is a 1,1-dimethylethyl group, benzyl group, 2-(methylthio)ethyl group, 2-methylpropyl group, p-hydroxyphenylmethyl group or methyl group, R^8 is not a
10 methyl group.

Furthermore, the alkyl groups, alkenyl groups, alkynyl groups, aromatic hydrocarbon groups and heterocyclic groups listed as examples of R_x , R_y and substituents include the same types of groups as the groups
15 represented by R^1 or $R^{1'}$, R^2 or $R^{2'}$, R^4 , R^5 , R^6 and R^7 . In addition, the alkyl groups of alkoxy groups, alkylthio groups, alkoxycarbonyl groups and alkoxycarbonylamino groups as substituent groups are also the same as the previously described alkyl groups having 1 to 12 carbon
20 atoms, and the aryl groups of aryloxy groups and arylthio groups are also the same as the previously described aromatic hydrocarbon groups having 6 to 18 carbon atoms.

In addition, examples of guanidino groups, acyl groups, sulfonyl groups, heterocyclyloxy groups,
25 heterocyclylthio groups, amido groups, ureido groups, carbamoyl groups, sulfamoyl groups, acyloxy groups, sulfonamido groups and alkoxycarbonylamino groups as substituent groups are indicated below.

[0039]

Guanidino group**Acyl group****Sulfonyl group****Heterocycloxy group****Heterocyclylthio group****Carbamoyl group****Ureido group****Amido group****Sulfamoyl group****Acyloxy group****Sulfonamido group****Alkoxy carbonyl-
amino group**

[0040]

(In the examples of groups indicated above, R⁹ to R¹², R¹⁷ to R²¹, R²³ to R²⁵, R²⁸ and R³⁰ represent hydrogen, substituted or unsubstituted alkyl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted aromatic hydrocarbon groups, or substituted or unsubstituted heterocyclic groups. R¹³, R¹⁴, R²², R²⁶, R²⁷ and R²⁹ represent substituted or unsubstituted alkyl groups, substituted or unsubstituted alkenyl groups, substituted or unsubstituted alkynyl groups, substituted or unsubstituted aromatic hydrocarbon groups, or substituted or unsubstituted heterocyclic groups. R¹⁵ and R¹⁶ represent substituted or unsubstituted heterocyclic groups.

In addition, examples of substituents of these substituted alkyl groups, substituted alkenyl groups, substituted alkynyl groups, substituted aromatic hydrocarbon groups and substituted heterocyclic groups

include the same groups as the substituents of these groups listed for R¹ in 3 above.)

[0041]

In a cycloalkylcarbonylamino acid ester derivative represented by formula (I), (I') or (I'') of the present invention, ring A is a cyclopentylidene group, cyclohexylidene group or cycloheptylidene group, and preferably a cyclohexylidene group.

In formula (I), (I') or (I''), the compound in which R¹ is a 3- to 7-membered heterocyclic group or substituted aromatic hydrocarbon group containing at least one nitrogen atom, oxygen atom or sulfur atom as a ring-composing atom, R² or R^{2'} is an alkyl group having 1 to 4 carbon atoms, R⁸ is an alkyl group having 1 to 6 carbon atoms, and ring A is a cyclohexylidene group is preferred.

[0042]

In the case a cycloalkylcarbonylamino acid ester derivative represented by formula (I) of the present invention has a basic site in a molecule thereof, a salt can be formed with an inorganic acid or organic acid, and examples of inorganic acids include hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and hydrobromic acid. In addition, examples of organic acids include acetic acid, propionic acid, benzoic acid, oxalic acid, malonic acid, succinic acid, phthalic acid, glycolic acid, lactic acid, glyceric acid, malic acid, tartaric acid, gallic acid, citric acid, maleic acid, fumaric acid, methanesulfonic acid, benzenesulfonic acid and toluenesulfonic acid.

[0043]

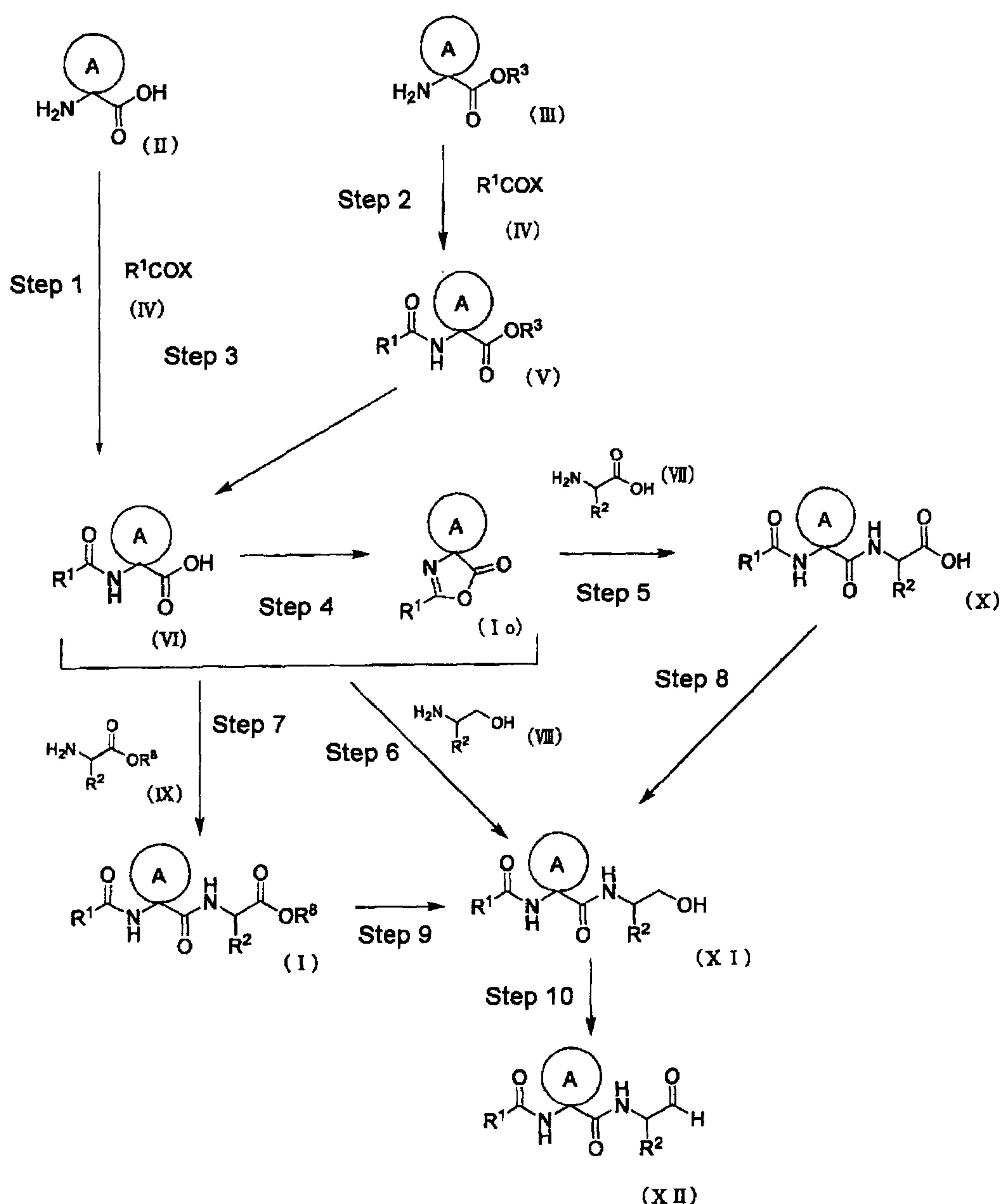
Moreover, in the case the cycloalkylcarbonylamino acid ester derivative has an acidic site in a molecule thereof, a salt can be formed with an alkaline metal such

as lithium, sodium or potassium, an alkaline earth metal
such as magnesium or calcium, aluminum salt or zinc salt.
In addition, a salt can also be formed with an organic
base, and examples of such an organic base include primary
5 amines such as methylamine, ethylamine or aniline,
secondary amines such as diethylamine, pyrrolidine,
piperidine, morpholine, piperazine or dicyclohexylamine,
tertiary amines such as trimethylamine, triethylamine, N,N-
diisopropylethylamine or pyridine, and ammonia.

10 [0044]

The following indicates examples of the production of
a cycloalkylcarbonylamino acid ester derivative represented
by formula (I) of the present invention and a
cycloalkylcarbonylamino aldehyde derivative represented by
15 formula (XII).

[0045]



[0046]

(In the above formulas, R^1 , R^2 , R^8 and ring A are the same as previously defined in the above formula (I), R^3 represents a substituted or unsubstituted alkyl group having 1 to 6 carbon atoms, and X represents a hydroxyl group or a leaving group.)

[0047]

Step 1:

10

This step is a step for producing a cycloalkylcarboxylic acid derivative represented by formula

(VI) above by condensing an amino acid represented by formula (II) above with a carboxylic acid derivative represented by formula (IV) above. Examples of carboxylic acid derivatives used include acid halides, active esters and acid anhydrides. In addition, this step can be carried out by adding a base as necessary. Examples of bases that can be used include pyridine, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine, N-methylmorpholine, sodium carbonate, potassium carbonate, sodium bicarbonate, sodium hydroxide and potassium hydroxide.

This step is preferably carried out in a solvent, examples of solvents that can be used include water and organic solvents such as methylene chloride, chloroform, dichloroethane, ethyl acetate, acetone, benzene, toluene, xylene, dimethylformamide, acetonitrile, tetrahydrofuran, dioxane, diethyl ether, isopropyl ether or dimethoxyethane, and a mixed solvent of an organic solvent and water can be used as necessary. The reaction is normally carried out at a reaction temperature within the range of -30 to 200°C and is preferably allowed to proceed within the range of -15 to 100°C.

[0048]

Step 2:

This step is a step for producing a cycloalkyl ester derivative represented by formula (V) above by a condensation reaction between an amino acid ester represented by formula (III) above and a carboxylic acid or carboxylic acid derivative represented by formula (IV) above. Examples of carboxylic acid derivatives used include acid halides, active esters and acid anhydrides. In this step, the reaction can be carried out by adding a condensation agent or base as necessary. Examples of

condensation agents that can be used include dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, diisopropylcarbodiimide and carbonyldiimidazole. Here, an activator such as 1-hydroxybenzotriazole can also be added as necessary. Examples of bases that can be used include pyridine, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino) pyridine, N-methylmorpholine, sodium carbonate, potassium carbonate and sodium bicarbonate.

10 [0049]

This step is preferably carried out in a solvent, examples of solvents that can be used include water and organic solvents such as methylene chloride, chloroform, dichloroethane, ethyl acetate, acetone, benzene, toluene, xylene, dimethylformamide, acetonitrile, tetrahydrofuran, dioxane, diethyl ether, isopropyl ether or dimethoxyethane, and a mixed solvent of an organic solvent and water can be used as necessary. The reaction is normally carried out at a reaction temperature within the range of -30 to 200°C and is preferably allowed to proceed within the range of -15 to 100°C.

[0050]

Step 3:

This step is a step for producing a compound of formula (VI) above by a hydrolysis reaction, or a hydrogenation reaction by catalytic reduction using a metal catalyst, of the cycloalkyl ester derivative represented by formula (V) above. Hydrolysis can be carried out in the presence of an acid and base. Examples of acids that can be used include hydrochloric acid, sulfuric acid, nitric acid and acetic acid. Examples of bases that can be used include sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate and potassium carbonate. This

step is preferably carried out in water or in a mixed solvent of an organic solvent and water, and examples of organic solvents that can be used include methanol, ethanol, isopropyl alcohol, tetrahydrofuran and
5 dimethoxyethane. The reaction is normally carried out at a reaction temperature within the range of -20 to 200°C and is preferably allowed to proceed within the range of 0 to 180°C. In addition, examples of metal catalysts that can be used in the catalytic hydrogenation reaction include
10 platinum, palladium, nickel, rhodium, ruthenium and copper. This step is preferably carried out in a solvent, and examples of solvents that can be used include methanol, ethanol, isopropyl alcohol, isopropyl ether, tetrahydrofuran, benzene, toluene, xylene,
15 dimethylformamide, dioxane and water. The reaction is normally carried out at a reaction temperature of -50 to 200°C and is preferably allowed to proceed within the range of 10 to 100°C.

[0051]

20 Examples of the carboxylic acid or carboxylic acid derivative represented by formula (IV) above include the compounds listed below.

Carboxylic acids: acetic acid, isobutyric acid, acrylic acid, propionic acid, cyclohexane carboxylic acid,
25 benzoic acid, cinnamic acid, 2-furan carboxylic acid, nicotinic acid, tetrahydrofuran-2-carboxylic acid, 1-acetyl-piperidine-2-carboxylic acid, 2-pyrrole carboxylic acid, 5-indole carboxylic acid;

Acid halides: acetyl chloride, benzoyl chloride,
30 pivaloyl chloride, 2-furan carbonyl chloride, 4-morpholine carbonyl chloride, 2-thiophene carbonyl chloride;

Active esters: 1-acetylimidazole, benzoic acid p-

nitrophenyl esters, benzoic acid N-hydroxysuccinimide esters, benzoic acid 1-hydroxybenzotriazole esters; and

Acid anhydrides: acid anhydrides of benzoic acid and methyl carbonate, acid anhydrides of benzoic acid and isobutyl carbonate, acid anhydrides of benzoic acid and pivalic acid, acid anhydrides of benzoic acid and methanesulfonic acid.

[0052]

Examples of the cycloalkylcarboxylic acid derivatives represented by formula (VI) above include the compounds listed below:

1-[(phenylacetyl)amino]cyclohexanecarboxylic acid, 1-[(1-oxo-3-phenylpropyl)amino]cyclohexanecarboxylic acid, 1-(benzoylamino)cyclohexanecarboxylic acid, 1-[(4-biphenylcarbonyl)amino]cyclohexanecarboxylic acid, 1-[(2-naphthylcarbonyl)amino]cyclohexanecarboxylic acid, 1-[(1-naphthylcarbonyl)amino]cyclohexanecarboxylic acid, 1-[[[(RS)-2,3-tetrahydrobenzofuran-2-yl]carbonyl]amino]cyclohexanecarboxylic acid, 1-[(2-furanylcarbonyl)amino]cyclohexanecarboxylic acid, 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid, 1-[[[(E)-3-(2-furanyl)-1-oxo-2-propenyl]amino]cyclohexanecarboxylic acid, 1-[(2-benzofuranylcarbonyl)amino]cyclohexanecarboxylic acid, 1-[(cyclohexylcarbonyl)amino]cyclohexanecarboxylic acid,

[0053]

1-[(6-benzothiazolylcarbonyl)amino]cyclohexanecarboxylic acid, 1-[[[(6-hydroxy-3-pyridinyl)carbonyl]amino]cyclohexanecarboxylic acid, 1-[(2-thienylcarbonyl)amino]cyclohexanecarboxylic acid, 1-[(2-pyridinylcarbonyl)amino]cyclohexanecarboxylic acid, 1-[(3-thienylcarbonyl)amino]cyclohexanecarboxylic acid, 1-[[[(3-ethoxy-2-thienyl)carbonyl]amino]cyclohexanecarboxylic acid,

1-[[(S) -1-oxo-2-phenylpropyl] amino] cyclohexanecarboxylic
 acid, 1-[(2-pyrazinylcarbonyl) amino] cyclohexanecarboxylic
 acid, 1-[[(5-methyl-2-
 thienyl) carbonyl] amino] cyclohexanecarboxylic acid, 1-[[(4-
 5 methoxyphenyl) carbonyl] amino] cyclohexanecarboxylic acid, 1-
 [[(3-methyl-2-thienyl) carbonyl] amino] cyclohexanecarboxylic
 acid, 1-[[(3-methyl-2-
 furanyl) carbonyl] amino] cyclohexanecarboxylic acid, 1-[(3-
 pyridinylcarbonyl) amino] cyclohexanecarboxylic acid, 1-[[(1-
 10 methyl-1H-pyrrol-2-yl) carbonyl] amino] cyclohexanecarboxylic
 acid, 1-[(R) -1-oxo-2-
 phenylpropyl] amino] cyclohexanecarboxylic acid, 1-[(1H-
 indol-5-ylcarbonyl) amino] cyclohexanecarboxylic acid,
 [0054]
 15 1-[(1-cyclopentenylcarbonyl) amino] cyclohexanecarboxylic
 acid, 1-[(4-pyridinylcarbonyl) amino] cyclohexanecarboxylic
 acid, 1-[[(1H-pyrrol-2-
 yl) carbonyl] amino] cyclohexanecarboxylic acid, 1-[[(6-
 hydroxy-2-pyridinyl) carbonyl] amino] cyclohexanecarboxylic
 20 acid, 1-[[(2-hydroxy-3-
 pyridinyl) carbonyl] amino] cyclohexanecarboxylic acid, 1-
 [[(6-hydroxy-3-
 pyridinyl) carbonyl] amino] cyclohexanecarboxylic acid, 1-
 [[[1-(2-propoxycarbonyl) piperidin-4-
 25 yl] carbonyl] amino] cyclohexanecarboxylic acid, 1-[[[1-
 (ethoxycarbonyl) piperidin-4-
 yl] carbonyl] amino] cyclohexanecarboxylic acid, 1-[[[1-(2-
 furanylcarbonyl) piperidin-4-
 yl] carbonyl] amino] cyclohexanecarboxylic acid, 1-[[[(2-
 30 furanylcarbonyl) amino] acetyl] amino] cyclohexanecarboxylic
 acid, 1-[[(benzoylamino) acetyl] amino] cyclohexanecarboxylic
 acid, 1-[[(2-oxo-2H-pyran-5-
 yl) carbonyl] amino] cyclohexanecarboxylic acid, 1-[(4-

fluorobenzoyl) amino] cyclohexanecarboxylic acid, 1-[[[4-(4-propylpiperazin-1-yl) phenyl] carbonyl] amino] cyclohexanecarboxylic acid, 1-[[[4-(4-propylpiperazin-1-yl) phenyl] carbonyl] amino] cyclohexanecarboxylic acid hydrochloride,
[0055]
[[(2,3-dihydro-2-oxo-5-benzoxazole) carbonyl] amino] cyclohexanecarboxylic acid,
10 [[(2,3-dihydro-1,4-benzodioxin-6-yl) carbonyl] amino] cyclohexanecarboxylic acid, [[(2,4-dioxo-3-thiazolidinyl) acetyl] amino] cyclohexanecarboxylic acid, [(1-oxo-3-phenyl-2-propenyl) amino] cyclohexanecarboxylic acid, [[1-oxo-3-(2-chlorophenyl)-2-propenyl] amino] cyclohexanecarboxylic acid, [[1-oxo-3-(4-chlorophenyl)-2-propenyl] amino] cyclohexanecarboxylic acid, [[1-oxo-3-(dichlorophenyl)-2-propenyl] amino] cyclohexanecarboxylic acid, [[1-oxo-3-(2-bromophenyl)-2-propenyl] amino] cyclohexanecarboxylic acid,
20 [[1-oxo-3-(4-bromophenyl)-2-propenyl] amino] cyclohexanecarboxylic acid, [[1-oxo-3-(dibromophenyl)-2-propenyl] amino] cyclohexanecarboxylic acid, [[(1-oxo-3-(2-fluorophenyl)-2-propenyl) amino] cyclohexanecarboxylic acid,
25 [0056]
[[1-oxo-3-(2-iodophenyl)-2-propenyl] amino] cyclohexanecarboxylic acid, [[oxo-3-(4-fluorophenyl)-2-propenyl] amino] cyclohexanecarboxylic acid, [[oxo-3-(difluorophenyl)-2-propenyl] amino] cyclohexanecarboxylic acid, [[1-oxo-3-(4-iodophenyl)-2-propenyl] amino] cyclohexanecarboxylic acid, [[1-oxo-3-(diiodophenyl)-2-propenyl] amino] cyclohexanecarboxylic acid, [[oxo-3-

(trifluorophenyl)-2-propenyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(2-methylphenyl)-2-propenyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(3-methylphenyl)-2-propenyl]amino]cyclohexanecarboxylic acid,
5 [[1-oxo-3-(4-methylphenyl)-2-propenyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(dimethylphenyl)-2-propenyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(2-methoxyphenyl)-2-propenyl]amino]cyclohexanecarboxylic acid,
10 [0057] [[1-oxo-3-(4-methoxyphenyl)-2-propenyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(dimethoxyphenyl)-2-propenyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(nitrophenyl)-2-propenyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(dinitrophenyl)-2-propenyl]amino]cyclohexanecarboxylic acid, [[oxo-3-(acetaminophenyl)-2-propenyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(2-pyridinyl)-2-propenyl]amino]cyclohexanecarboxylic acid,
20 [[1-oxo-3-cyclohexyl-2-propenyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-cyclopentyl-2-propenyl]amino]cyclohexanecarboxylic acid, [(1-oxo-3-phenyl-2-propynyl)amino]cyclohexanecarboxylic acid, [[1-oxo-3-(fluorophenyl)-2-propynyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(chlorophenyl)-2-propynyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(bromophenyl)-2-propynyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(iodophenyl)-2-propynyl]amino]cyclohexanecarboxylic acid,
25 [0058] [[1-oxo-3-(difluorophenyl)-2-propynyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(dibromophenyl)-2-propynyl]amino]cyclohexanecarboxylic

acid, [[1-oxo-3-(diiodophenyl)-2-propynyl]amino]cyclohexanecarboxylic acid, [[1-oxo-3-(trifluorophenyl)-2-propynyl]amino]cyclohexanecarboxylic acid, [(1-oxo-3-cyclohexyl-2-propynyl)amino]cyclohexanecarboxylic acid, [(1-oxo-3-cyclopentyl-2-propynyl)amino]cyclohexanecarboxylic acid, [[3-(2-furanyl)-1-oxo-2-propynyl]amino]cyclohexanecarboxylic acid, 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid acetate, 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid hydrobromide, 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid benzenesulfonate, 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid toluenesulfonate, 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid phthalate, 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid fumarate, and 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid citrate.

[0059]

25 Step 4:

This step is a step for producing an oxazolone derivative represented by formula (I₀) above by ring-closing the cycloalkylcarboxylic acid derivative represented by formula (VI) above by a dehydration reaction. The dehydration reaction of this step is preferably carried out in the presence of a condensation agent, halogenating agent, acid, acid anhydride or acid chloride or the like, and examples of condensation agents

that can be used include dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diisopropylcarbodiimide and carbonyldiimidazole. Examples of halogenating agents that can be used include chlorine, bromine, iodine, phosphorous pentachloride, thionyl chloride, oxalyl chloride and thionyl bromide. Examples of acids that can be used include acetic acid, sulfuric acid, hydrochloric acid, methanesulfonic acid and toluenesulfonic acid. Examples of acid anhydrides that can be used include acetic anhydride, methanesulfonic anhydride, toluenesulfonic anhydride and trifluoromethanesulfonic anhydride. Examples of acid chlorides that can be used include acetyl chloride, pivaloyl chloride, methanesulfonyl chloride, toluenesulfonyl chloride, methyl chloroformate, ethyl chloroformate, propyl chloroformate and isobutyl chloroformate.

[0060]

In addition, the reaction of this step can also be carried out by adding a base as necessary, and examples of bases that can be used include pyridine, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine, N-methylmorpholine, sodium carbonate, potassium carbonate and sodium bicarbonate.

This step is preferably carried out in a solvent, and examples of solvents that can be used include methylene chloride, chloroform, dichloroethane, ethyl acetate, acetone, benzene, toluene, xylene, dimethylformamide, acetonitrile, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether and dimethoxyethane.

The reaction is normally carried out at a reaction temperature within the range of -30 to 200°C and is preferably allowed to proceed within the range of 0 to 100°C.

[0061]

Step 5:

This step is a step for producing a cycloalkylcarbonyl amino acid derivative represented by formula (X) above by reacting the oxazolone derivative represented by formula (I₀) above with the amino acid derivative represented by formula (VII) above.

This step can be carried out in the presence of a base and in the presence or absence of a solvent, and examples of solvents that can be used include methylene chloride, chloroform, dichloroethane, ethyl acetate, acetone, benzene, toluene, xylene, dimethylformamide, acetonitrile, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, dimethoxyethane, dimethylsulfoxide, methanol, ethanol and 2-propanol. In addition, examples of bases that can be used include pyridine, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino) pyridine, N-methylmorpholine, sodium carbonate, potassium carbonate, sodium bicarbonate, sodium hydroxide and potassium hydroxide. The reaction is normally carried out at a reaction temperature within the range of -30 to 200°C and can be preferably allowed to proceed within the range of 20 to 200°C.

[0062]

Step 6:

This step is a step for producing a cycloalkylcarbonylamino alcohol derivative represented by formula (XI) above. In this step, a cycloalkylcarbonylamino alcohol derivative represented by formula (XI) above can be produced by two types of methods consisting of a method that uses a cycloalkylcarboxylic acid derivative represented by formula (VI) above for the starting raw material (Step 6-A), and a method using an

oxazolone derivative represented by formula (I₀) above for the starting raw material (Step 6-B).

[0063]

Step 6-A:

5 This step is a step for producing a cycloalkylcarbonylamino alcohol derivative represented by formula (XI) above by condensing a cycloalkylcarboxylic acid derivative represented by formula (VI) above with an amino alcohol derivative represented by formula (VIII) above.

10 Examples of condensation agents that can be used in this step include dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diisopropylcarbodiimide and carbonyldiimidazole. Here, an activator such as 1-hydroxybenzotriazole or N-hydroxysuccinimide can be added as necessary.

15 In addition, this step can also be carried out by condensing in the presence of a base according to a mixed acid anhydride method with an acid chloride. Examples of acid chlorides that can be used include pivaloyl chloride, isobutyl chloroformate, methyl chloroformate, ethyl chloroformate, methanesulfonyl chloride and toluenesulfonyl chloride. Examples of bases that can be used include pyridine, triethylamine, N,N-diisopropylethylamine, 4-

20 (dimethylamino)pyridine and N-methylmorpholine.

[0064]

25 This step is preferably carried out in a solvent, and examples of solvents that can be used include methylene chloride, chloroform, dichloroethane, ethyl acetate, acetone, benzene, toluene, xylene, dimethylformamide, acetonitrile, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether and dimethoxyethane.

 The reaction is normally carried out at a reaction

temperature within the range of -30 to 200°C and can be preferably allowed to proceed within the range of 0 to 100°C.

[0065]

5 Step 6-B:

 This step is a step for producing a cycloalkylcarbonylamino alcohol derivative represented by formula (XI) above by reacting an oxazolone derivative represented by formula (I₀) above with an amino alcohol
10 derivative represented by formula (VIII) above.

 This step can be carried out in the presence or absence of solvent, and examples of solvents that can be used include methylene chloride, chloroform, dichloroethane, ethyl acetate, acetone, benzene, toluene,
15 xylene, dimethylformamide, acetonitrile, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, dimethoxyethane, dimethylsulfoxide, methanol, ethanol and 2-propanol. In addition, in this step, a base can be added as necessary. Examples of bases that can be used include pyridine,
20 triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine and N-methylmorpholine. The reaction is normally carried out at a reaction temperature within the range of -30 to 200°C and can be preferably allowed to proceed within the range of 20 to 200°C.

25 [0066]

 Step 7:

 This step is a step for producing a cycloalkylcarbonylamino acid ester derivative represented by formula (I) above of the present invention. In this
30 step, a cycloalkylcarbonylamino acid ester derivative represented by formula (I) above can be produced by two types of methods consisting of a method that uses a

cycloalkylcarboxylic acid derivative represented by formula (VI) above for the starting raw material (Step 7-A), and a method that uses an oxazolone derivative represented by formula (I₀) above for the starting raw material (Step 7-B).

[0067]

Step 7-A:

This step is a step for producing a cycloalkylcarbonylamino acid ester derivative represented by formula (I) above by condensing a cycloalkylcarboxylic acid derivative represented by formula (VI) above with an amino acid ester derivative represented by formula (IX) above.

Examples of condensation agents that can be used in this step include dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diisopropylcarbodiimide and carbonyldiimidazole. Here, an activator such as 1-hydroxybenzotriazole or N-hydroxysuccinimide can be added as necessary.

In addition, this step can also be carried out by condensing in the presence of a base according to a mixed acid anhydride method with an acid chloride. Examples of acid chlorides that can be used include pivaloyl chloride, isobutyl chloroformate, methyl chloroformate, ethyl chloroformate, methanesulfonyl chloride and toluenesulfonyl chloride. Examples of bases that can be used include pyridine, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine and N-methylmorpholine.

This step is preferably carried out in a solvent, and examples of solvents that can be used include methylene chloride, chloroform, dichloroethane, ethyl acetate, acetone, benzene, toluene, xylene, dimethylformamide, acetonitrile, tetrahydrofuran, dioxane, diethyl ether,

diisopropyl ether and dimethoxyethane.

The reaction is normally carried out at a reaction temperature within the range of -30 to 200°C and can be preferably allowed to proceed within the range of 0 to

5 100°C.

[0068]

Step 7-B:

This step is a step for producing a cycloalkylcarbonylamino acid ester derivative represented by formula (I) above by reacting an oxazolone derivative represented by formula (I₀) above with an amino acid ester derivative represented by formula (IX) above.

This step can be carried out in the presence or absence of solvent, and examples of solvents that can be used include methylene chloride, chloroform, dichloroethane, ethyl acetate, acetone, benzene, toluene, xylene, dimethylformamide, acetonitrile, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, dimethoxyethane, dimethylsulfoxide, methanol, ethanol and 2-propanol. In addition, in this step, a base can be added as necessary. Examples of bases that can be used include pyridine, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine and N-methylmorpholine. The reaction is normally carried out at a reaction temperature within the range of -30 to 200°C and can be preferably allowed to proceed within the range of 20 to 200°C.

[0069]

Examples of the oxazolone derivatives represented by formula (I₀) above include the compounds listed below:

30 2-phenylmethyl-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-phenylethyl-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(4-biphenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(2-

naphthyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[(RS)-2,3-tetrahydrobenzofuran-2-yl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(6-benzothiazolyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(2-thienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-
 5 (1,3-benzoxol-5-yl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(2-benzofuranyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(2-pyridinyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(3-ethoxy-2-thienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(2-pyrazinyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(5-methylisoxazol-4-yl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one,
 10 2-cyclopentyl-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(5-methyl-2-thienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one,
 [0070]
 2-(4-methoxyphenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-
 15 (3-methyl-2-furanyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(1-methyl-1H-pyrrol-2-yl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(1H-indol-5-yl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(1-cyclopentenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(6-hydroxy-2-pyridinyl)-3-oxa-1-azaspiro[4.5]dec-1-
 20 en-4-one, 2-[2-(furanyl)ethyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[1-[(2-propoxy)carbonyl]piperidin-4-yl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[1-(ethoxycarbonyl)piperidin-4-yl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[1-(2-furanylcabonyl)piperidin-4-yl]-3-oxa-1-
 25 azaspiro[4.5]dec-1-en-4-one, 2-[(2-furanylcabonyl)amino]methyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[(benzoylamino)methyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(4-fluorophenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[[4-[(1-propyl)piperazin-1-yl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(2-furyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-cyclohexyl-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(2-propyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(1-acetyl-piperidin-4-yl)-3-

oxa-1-azaspiro[4.5]dec-1-en-4-one,

[0071]

2-[4-[2-(4-methyl-1-piperazinyl)-4-thiazolyl]phenyl]-3-oxa-

1-azaspiro[4.5]dec-1-en-4-one, 2-[4-[2-[4-(4-morpholinyl)-

5 1-piperidinyll-4-thiazolyl]phenyl]-3-oxa-1-

azaspiro[4.5]dec-1-en-4-one, 2-[4-(2-[1,4-bipiperidine]-1'-yl-4-thiazolyl)phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one,

2-[4-[2-[4-(1,1-dimethylethyl)-1-piperazinyl]-4-

thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-

10 ([1,1'-biphenyl]-3-yl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one,

2-[2-(4-pyridinyl)-4-thiazolyl]-3-oxa-1-azaspiro[4.5]dec-1-

en-4-one, 2-(4-aminophenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-

4-one, 2-[4-(4-morpholinyl)phenyl]-3-oxa-1-

azaspiro[4.5]dec-1-en-4-one, 2-(5-bromo-2-thienyl)-3-oxa-1-

15 azaspiro[4.5]dec-1-en-4-one, 2-[4-[(4-methyl-1-

piperazinyl)carbonyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-

4-one, 2-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-3-

oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4-

(dimethylamino)phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one,

20 2-(4-ethynylphenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-

[4'-(dimethylamino)[1,1'-biphenyl]-4-yl]-3-oxa-1-

azaspiro[4.5]dec-1-en-4-one, 2-[4-(4-methyl-1-

piperazinyl)phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-

[4'-(1-piperazinyl)[1,1'-biphenyl]-4-yl]-3-oxa-1-

25 azaspiro[4.5]dec-1-en-4-one,

[0072]

2-[4'-[[1-(2-hydroxyethyl)-4-piperidinyloxy][1,1'-

biphenyl]-4-yl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4'-

[(1-methyl-4-piperidinyloxy)[1,1'-biphenyl]-4-yl]-3-oxa-1-

30 azaspiro[4.5]dec-1-en-4-one, 2-[4'-[methyl(1-methyl-3-

pyrrolidinyl)amino][1,1'-biphenyl]-4-yl]-3-oxa-1-

azaspiro[4.5]dec-1-en-4-one, 2-[4'-[4-(1,1-dimethylethyl)-

1-piperidinyll[1,1'-biphenyl]-4-yl]-3-oxa-1-

azaspiro[4.5]dec-1-en-4-one, 2-[4'-(1-
 piperazinylsulfonyl)[1,1'-biphenyl]-4-yl]-3-oxa-1-
 azaspiro[4.5]dec-1-en-4-one, 2-[4'-(4-fluoro-4-
 piperidinyl)[1,1'-biphenyl]-4-yl]-3-oxa-1-azaspiro[4.5]dec-
 5 1-en-4-one, 2-[4'-[[4-(2,2,2-trifluoroethyl)-1-
 piperazinyl]sulfonyl][1,1'-biphenyl]-4-yl]-3-oxa-1-
 azaspiro[4.5]dec-1-en-4-one, 2-[4'-[(1-methyl-3-
 piperidinyl)oxy][1,1'-biphenyl]-4-yl]-3-oxa-1-
 azaspiro[4.5]dec-1-en-4-one, 2-[4'-[[1-(2-methoxyethyl)-4-
 10 piperidinyl]oxy][1,1'-biphenyl]-4-yl]]-3-oxa-1-
 azaspiro[4.5]dec-1-en-4-one
 [0073]
 2-[4'-[[2S)-1-methyl-2-pyrrolidinyl]methoxy][1,1'-
 biphenyl]-4-yl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4'-
 15 [4-[(1,1-dimethylethyl)amino]-1-piperidinyl][1,1'-
 biphenyl]-4-yl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4'-
 (5-isoxazolyl)[1,1'-biphenyl]-4-yl]-3-oxa-1-
 azaspiro[4.5]dec-1-en-4-one, 2-[4-[2-(4-morpholinylmethyl)-
 4-thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-
 20 [4-[2-[3-(dimethylamino)-1-pyrrolidinyl]-4-
 thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-
 [4-[2-(4-methyl-1-piperazinylmethyl)-4-thiazolyl]phenyl]-3-
 oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4-[2-(1,4-dimethyl-4-
 piperidinyl)-4-thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-
 25 1-en-4-one, 2-[4-[2-(1-methyl-4-piperidinyl)-4-
 thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-
 [4-[2-[(3R)-3-amino-1-pyrrolidinyl]-4-thiazolyl]phenyl]-3-
 oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4-[2-(4-
 piperidinyloxy)-4-thiazolyl]phenyl]-3-oxa-1-
 30 azaspiro[4.5]dec-1-en-4-one,
 [0074]
 2-[4-[2-(4-morpholinyl)-4-thiazolyl]phenyl]-3-oxa-1-
 azaspiro[4.5]dec-1-en-4-one, 2-[4-[2-[4-[(1-

methylethyl) amino] -1-piperidinyl] -4-thiazolyl] phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4-[2-[methyl(4-methyl-1-piperazinyl) amino] -4-thiazolyl] phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4-[2-[4-[methyl(1-methylethyl) amino] -1-piperidinyl] -4-thiazolyl] phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4-[2-[4-(tetrahydro-2H-pyran-4-yl) -1-piperazinyl] -4-thiazolyl] phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4-[2-[4-(2-methoxyethyl) -1-piperazinyl] -4-thiazolyl] phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[3-(4-morpholinyl) -1-propynyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-cycloheptyl-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4-(4-morpholinylmethyl) phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-cyclopropyl-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[2-(diethylamino) ethyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4-[(dimethylamino) methyl] phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(2-benzothienyl) -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(1-methyl-4-piperazinyl) -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[2-(1-piperazinyl) ethyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[3-(trifluoromethyl) phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[4-(trifluoromethoxy) phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one

[0075]

2-[4-(trifluoromethyl) phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[2-(trifluoromethyl) phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[3-(trifluoromethoxy) phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(4-pyridinyl) -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(3-fluorophenyl) -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(2-fluorophenyl) -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-[2-(trifluoromethoxy) phenyl] -3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-(3-methylphenyl) -3-oxa-1-azaspiro[4.5]dec-1-en-4-

one, 2-[4-[(methoxymethylamino)methyl]phenyl]-3-oxa-1-
 azaspiro[4.5]dec-1-en-4-one, 2-(3-methoxyphenyl)-3-oxa-1-
 azaspiro[4.5]dec-1-en-4-one, 2-(4-chlorophenyl)-3-oxa-1-
 azaspiro[4.5]dec-1-en-4-one

5 [0076]

2-(4-cyanophenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-
 [3-(4-morpholinylmethyl)phenyl]-3-oxa-1-azaspiro[4.5]dec-1-
 en-4-one, 2-(phenoxymethyl)-3-oxa-1-azaspiro[4.5]dec-1-en-
 4-one, 2-(2-chlorophenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-
 10 one, 2-(2-thienylmethyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-
 one, 2-(2-methylphenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-
 one, 2-(4-hydroxyphenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-
 one, 2-[3-[(dimethylamino)methyl]phenyl]-3-oxa-1-
 azaspiro[4.5]dec-1-en-4-one, 2-(4-methyl-1,2,3-thiadiazol-
 15 5-yl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, and 2-(2,5-
 dimethyl-3-furanyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one.

[0077]

In addition, examples of amino acid ester derivatives
 represented by formula (IX) above include the compounds
 20 listed below:

alanine methyl ester, N^ω-p-toluenesulfonyl-arginine ethyl
 ester, asparagine t-butyl ester, aspartic acid α-benzyl
 ester, aspartic acid dimethyl ester, isoasparagine ethyl
 ester, γ-carboxyglutamic acid dibenzyl ester, cysteine
 25 ethyl ester, S-benzylcysteine methyl ester, cystine
 dimethyl ester, glutamine ethyl ester, glutamic acid di-t-
 butyl ester, histidine methyl ester, homoarginine ethyl
 ester, homocysteine methyl ester, homocystine diethyl
 ester, homoserine benzyl ester, homophenylalanine methyl
 30 ester, isoleucine t-butyl ester, leucine cyclohexyl ester,
 N^ε-carbobenzoxyl-lysine methyl ester, methionine ethyl ester,
 norleucine isopropyl ester, t-leucine butyl ester,

norvaline methyl ester, N^δ-carbobenzoxy-ornithine benzyl ester, phenylalanine t-butyl ester, phenylglycine 3-pentyl ester, serine ethyl ester, threonine benzyl ester, tryptophan methyl ester, tyrosine ethyl ester, valine cyclopentyl ester, 3,4-dihydroxyphenylalanine ethyl ester, allyl glycine methyl ester, neopentyl glycine t-butyl ester, allothreonine benzyl ester, homolysin methyl ester, naphthylalanine ethyl ester, α -aminoadipic acid t-butyl ester, thienylglycine methyl ester, pyridylalanine benzyl ester, cyclohexylalanine t-butyl ester.

[0078]

Step 8:

This step is a step for producing a cycloalkylcarbonylamino alcohol derivative represented by formula (XI) above by carrying out a reduction reaction after activating a cycloalkylcarbonylamino acid represented by formula (X) above by a mixed acid anhydride method.

Examples of acid chlorides used in the reaction for forming a mixed acid anhydride in this step include pivaloyl chloride, isobutyl chloroformate, methyl chloroformate, ethyl chloroformate, methanesulfonyl chloride and toluenesulfonyl chloride. Examples of bases that can be used include pyridine, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino) pyridine and N-methylmorpholine.

This reaction is preferably carried out in a solvent, and examples of solvents that can be used include methylene chloride, chloroform, dichloroethane, benzene, toluene, xylene, dimethylformamide, acetonitrile, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether and dimethoxyethane.

The reaction is normally carried out at a reaction temperature within the range of -50 to 200°C and can be

preferably allowed to proceed within the range of -20 to 50°C.

In addition, examples of reducing agents that can be used in this step include sodium borohydride, lithium aluminum hydride, diisobutyl aluminum hydride, and sodium dihydro-bis(2-methoxyethoxy)aluminate (Red-Al).

[0079]

This step is preferably carried out in a solvent, and examples of solvents that can be used include methylene chloride, chloroform, dichloroethane, benzene, toluene, xylene, dimethylformamide, acetonitrile, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, dimethoxyethane, ethanol, 2-propanol and water.

The reaction is normally carried out at a reaction temperature within the range of -30 to 200°C and can be preferably allowed to proceed within the range of -20 to 80°C.

[0080]

Step 9:

This step is a step for producing a cycloalkylcarbonylamino alcohol derivative represented by formula (XI) above by reducing a cycloalkylcarbonylamino acid ester derivative represented by formula (I) above.

Examples of reducing agents that can be used in this step include sodium borohydride, lithium aluminum hydride, diisobutyl aluminum hydride, and Red-Al.

This reaction is preferably carried out in a solvent, and examples of solvents that can be used include methylene chloride, chloroform, dichloroethane, benzene, toluene, xylene, dimethylformamide, acetonitrile, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether and dimethoxyethane.

The reaction is normally carried out at a reaction temperature within the range of -100 to 200°C and can be preferably allowed to proceed within the range of -80 to 100°C.

5 [0081]

Step 10:

This step is a step for producing a cycloalkylcarbonylamino aldehyde derivative represented by formula (XII) above by oxidizing a cycloalkylcarbonylamino alcohol derivative represented by formula (XI) above.

Activated DMSO (dimethylsulfoxide) oxidation can be used for the oxidation reaction used in this step. Examples of electrophilic activating reagents used here include dicyclohexylcarbodiimide, phosphorous pentoxide, pyridine-sulfur trioxide complex, acetic anhydride, silver (II) acetate and oxalyl chloride. A hydrogen donor such as phosphoric acid, trifluoroacetic acid, dichloroacetic acid, pyridine-phosphoric acid or pyridine-trifluoroacetic acid can also be added in this step as necessary. In addition, an amine such as triethylamine, N,N-diisopropylethylamine or N-methylmorpholine can also be added as necessary.

This step can be carried out in dimethylsulfoxide, and a solvent such as methylene chloride, chloroform, dichloroethane, toluene, acetone or tetrahydrofuran can also be added as necessary.

The reaction is normally carried out at a reaction temperature within the range of -80 to 200°C and can be preferably allowed to proceed within the range of -40 to 40°C.

30 [0082]

In addition, in this step, an oxidation reaction can also be carried out by preparing an active species having a

structure resembling an activated DMSO reaction from a sulfide and halogenating agent. Examples of sulfides that can be used in this step include dimethyl sulfide and methyl phenyl sulfide. Examples of halogenating agents
5 that can be used include N-chlorosuccinimide and chlorine.

In this step, an amine such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) can also be added as necessary.

10 This step is preferably carried out in a solvent, and examples of solvents that can be used include methylene chloride, chloroform, dichloroethane, toluene and tetrahydrofuran.

The reaction is normally carried out at a reaction
15 temperature within the range of -80 to 200°C and can be preferably allowed to proceed within the range of -40 to 40°C.

[0083]

In addition, oxidation can also be carried out in
20 this step using a hypervalent iodine compound reagent. Examples of hypervalent iodine compounds that can be used in this step include Dess-Martin reagent (1,1,1-tris(acetoxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one) and IBX (1-hydroxy-1,2-benziodoxol-3-(1H)-1-oxide).

25 A base such as pyridine or sodium bicarbonate can be added in this step as necessary.

This step is preferably carried out in a solvent, and examples of solvents that can be used include methylene chloride, chloroform, dichloroethane, benzene, toluene,
30 xylene, dimethylformamide, acetonitrile, tetrahydrofuran, dioxane and dimethoxyethane.

The reaction is normally carried out at a reaction

temperature within the range of -20 to 200°C and can be preferably allowed to proceed within the range of 0 to 40°C.

[0084]

5 In addition, this step can also be carried out using oxidation with aluminum alkoxide and a hydrogen acceptor (Oppenauer's oxidation). Examples of aluminum alkoxides that can be used include aluminum isopropoxide and aluminum t-butoxide.

10 Examples of hydrogen acceptors that can be used include benzoquinone, benzophenone, acetone, cyclohexanone and benzaldehyde.

 This step is preferably carried out in a solvent, and examples of solvents that can be used include benzene,
15 toluene and xylene.

 The reaction is normally carried out at a reaction temperature within the range of -20 to 200°C and can be preferably allowed to proceed within the range of 0 to 150°C.

20 [0085]

 In addition, this step can also be carried out using an oxidation reaction with tetrapropylammonium perruthenate (TPAP). N-methylmorpholine-N-oxide or molecular oxygen can be used for the oxidizing agent.

25 This step is preferably carried out in a solvent, and examples of solvents that can be used include methylene chloride, acetonitrile and toluene.

 A molecular sieve can be added in this step as necessary.

30 The reaction is normally carried out at a reaction temperature within the range of -20 to 200°C and can be preferably allowed to proceed within the range of 0 to

40°C.

[0086]

In addition, an oxidation reaction with 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO) or derivative thereof can also be used in this step.

The oxidizing agent that can preferably be used includes hypochlorous acid salt, bromous acid salt and N-chlorosuccinimide.

This step is preferably carried out in a solvent, and examples of solvents that can be used include dimethylsulfoxide, N,N-dimethylformamide, methylene chloride, acetonitrile, toluene and ethyl acetate.

In addition, sodium bromide or water can also be added in this step as necessary.

The reaction is normally carried out at a reaction temperature within the range of -20 to 200°C and can be preferably allowed to proceed within the range of 0 to 40°C.

[0087]

Specific examples of cycloalkylcarbonylamino acid ester derivatives represented by formula (I) of the present invention include the compounds listed below.

N-[[1-[(phenylmethoxy)carbonyl]amino]cyclohexyl]carbonyl]-L-valine methyl ester, N-[[1-

[(phenylmethoxy)carbonyl]amino]cyclohexyl]carbonyl]-L-norleucine ethyl ester, N-[[1-[(2-

furanylcabonyl)amino]cyclohexyl]carbonyl]-L-valine benzyl ester, N-[[1-[(4-

morpholinylcarbonyl)amino]cyclohexyl]carbonyl]-L-norleucine t-butyl ester, N-[[1-

[(phenylmethoxy)carbonyl]amino]cyclohexyl]carbonyl]-L-methionine ethyl ester, N-[[1-[(2-

furanylcabonyl) amino] cyclohexyl] carbonyl] -L-phenylalanine
 benzyl ester, N-[[1-[(4-
 morpholinylcarbonyl) amino] cyclohexyl] carbonyl] -L-tryptophan
 methyl ester, N-[[1-
 5 [[(phenylmethoxy) carbonyl] amino] cyclohexyl] carbonyl] -L-
 tyrosine propyl ester, N-[[1-[(2-
 furanylcabonyl) amino] cyclohexyl] carbonyl] -L-phenylglycine
 2-propyl ester, N-[[1-[(4-
 morpholinylcarbonyl) amino] cyclohexyl] carbonyl] -L-histidine
 10 butyl ester, N-[[1-
 [[(phenylmethoxy) carbonyl] amino] cyclohexyl] carbonyl] -L-
 pyridyl glycine t-butyl ester, N-[[1-
 (acetamide) cyclohexyl] carbonyl] -L-valine methyl ester, N-
 [[1-
 15 [[(phenylmethylthio) carbonyl] amino] cyclohexyl] carbonyl] -L-
 valine benzyl ester, N-[[1-[(1-oxo-3-phenyl-2-
 propenyl) amino] cyclohexyl] carbonyl] -L-valine ethyl ester,
 N-[[1-[(1-oxo-3-phenyl-2-
 propynyl) amino] cyclohexyl] carbonyl] -L-valine benzyl ester,
 20 N-[[1-[(1-oxo-3-phenyl-2-
 propynyl) amino] cyclohexyl] carbonyl] -L-ally glycine t-butyl
 ester,
 [0088]
 N-[[1-[(2-benzothienylcarbonyl) amino] cyclohexyl] carbonyl] -
 25 L-phenylglycine methyl ester, N-[[1-[(2-
 benzothienylcarbonyl) amino] cyclohexyl] carbonyl] -L-
 methionine methyl ester, N-[[1-[[[4-
 [(dimethylamino)methyl] phenyl] carbonyl] amino] cyclohexyl] car
 bonyl] -L-phenylglycine methyl ester, N-[[1-[[[4-
 30 [(dimethylamino)methyl] phenyl] carbonyl] amino] cyclohexyl] car
 bonyl] -L-methionine methyl ester, N-[[1-[[[4-[2-(4-methyl-
 1-piperazinyl) -4-
 thiazolyl] phenyl] carbonyl] amino] cyclohexyl] carbonyl] -L-

methionine methyl ester, N-[[1-[[[4-[2-(4-methyl-1-piperazinyl)]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycine methyl ester, N-[[1-[[[4-[2-[4-(4-morpholinyl)]-1-piperidinyl]]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-methionine methyl ester, and N-[[1-[[[4-[2-[4-(4-morpholinyl)]-1-piperidinyl]]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycine methyl ester.

[0089]

As will be clear from the forthcoming test examples, although a cycloalkylcarbonylamino aldehyde derivative derived from a cycloalkylcarbonylamino acid ester derivative represented by formula (I) of the present invention has highly active and highly selective inhibitory activity against cathepsin K, as a result of having this selective inhibitory activity against cathepsin K, it is expected to be used as a useful drug for prevention or treatment of such diseases as osteoporosis, hypercalcemia, osteoarthritis and rheumatoid arthritis.

[0090]

Although the following provides a more detailed explanation of the present invention through reference examples and examples, the present invention is not limited to these examples provided they do not exceed the gist thereof.

Furthermore, "%" refers to "% by weight" unless specifically indicated otherwise.

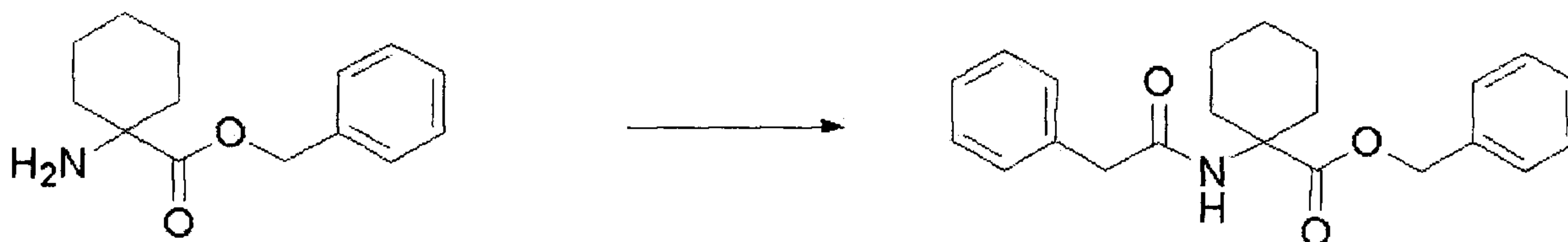
In addition, synthesis examples of cycloalkylcarboxylic acids represented by formula (VI) above and esters thereof, synthesis examples of oxazolone derivatives represented by formula (I₀), as well as

synthesis examples of cycloalkylcarbonylamino acid derivatives, cycloalkylcarbonylamino alcohol derivatives and cycloalkylcarbonylamino aldehyde derivatives represented by formulas (X), (XI) and (XII), respectively, which are intermediates for producing the cycloalkylcarbonylamino acid ester derivatives of the present invention, are indicated as reference examples.

[0091]

Reference Example 1

1-[(Phenylacetyl)amino]cyclohexanecarboxylic acid phenylmethyl ester



[0092]

1.21 g (12 mmol) of triethylamine was added to a solution of 2.33 g (10 mmol) of 1-aminocyclohexanecarboxylic acid phenylmethyl ester in 100 ml of tetrahydrofuran, 1.55 g (10 mmol) of phenylacetyl chloride was added dropwise thereto under ice-cooling, and the mixture was stirred overnight. The reaction solution was concentrated under reduced pressure, ethyl acetate was added thereto, and the mixture was successively washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by silica gel chromatography to obtain 3.21 g (91%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.10-1.23 (3H, m), 1.50-1.58 (3H, m), 1.74-1.80 (2H, m), 1.95-1.98 (2H, m), 3.57 (2H, s), 5.12

(2H, s), 5.48 (1H, br-s), 7.24-7.38 (10H, m)

[0093]

Reference Example 2

1-[(Phenylacetyl)amino]cyclohexanecarboxylic acid



[0094]

2.69 g (9.1 mmol) of 1-

[(phenylacetyl)amino]cyclohexanecarboxylic acid

phenylmethyl ester obtained in Reference Example 1 was

10 dissolved in 100 ml of methanol, 300 mg of 10% palladium-carbon was added thereto, and the mixture was stirred under a hydrogen atmosphere at room temperature overnight. After the reaction solution was filtered, the filtrate was concentrated under reduced pressure to obtain 1.96 g (98%)
15 of the title compound.

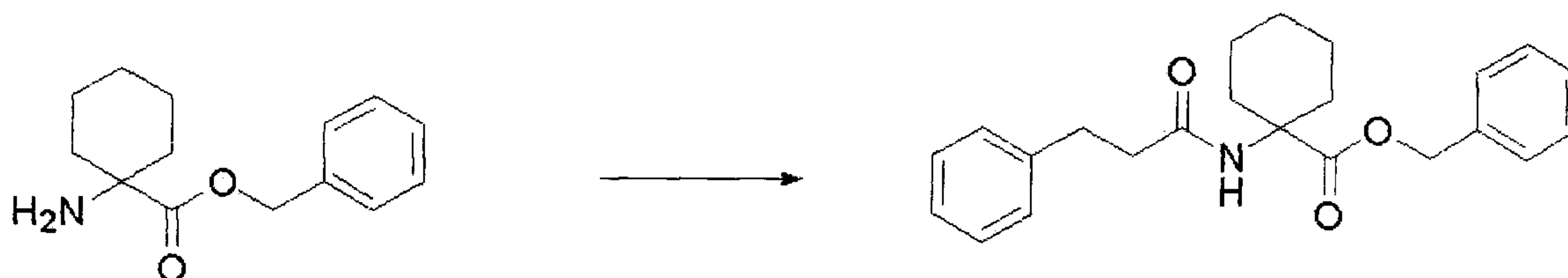
¹H-NMR (CDCl₃, δ): 1.01-1.10 (2H, m), 1.18-1.26 (1H, m), 1.49-1.59 (3H, m), 1.75-1.82 (2H, m), 1.97-2.00 (2H, m), 3.66 (2H, s), 5.67 (1H, br-s), 7.29-7.34 (3H, m), 7.37-7.40 (2H, m)

20 [0095]

Reference Example 3

1-[(1-Oxo-3-phenylpropyl)amino]cyclohexanecarboxylic acid

phenylmethyl ester



25 [0096]

1.68 g (10 mmol) of 3-phenylpropionyl chloride was used instead of phenylacetyl chloride in the process

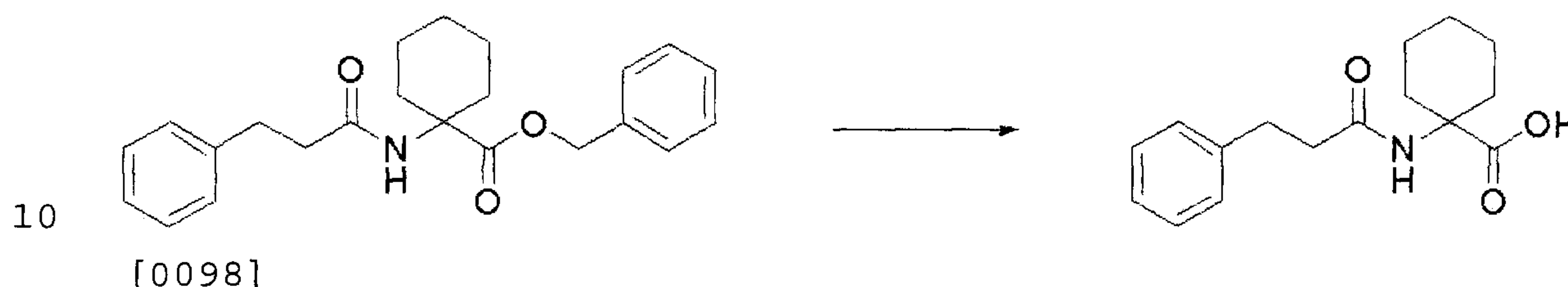
according to Reference Example 1 to obtain 3.47 g (95%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.19-1.26 (3H, m), 1.50-1.61 (3H, m), 1.78-1.84 (2H, m), 1.96-2.05 (2H, m), 2.50 (2H, t, J=7Hz),
 5 2.93 (2H, t, J=7Hz), 5.13 (2H, s), 5.45 (1H, br-s), 7.18-7.21 (4H, m), 7.26-7.37 (6H, m)

[0097]

Reference Example 4

1-[(1-Oxo-3-phenylpropyl)amino]cyclohexanecarboxylic acid



3.47 g (9.5 mmol) of 1-[(1-oxo-3-phenylpropyl)amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-

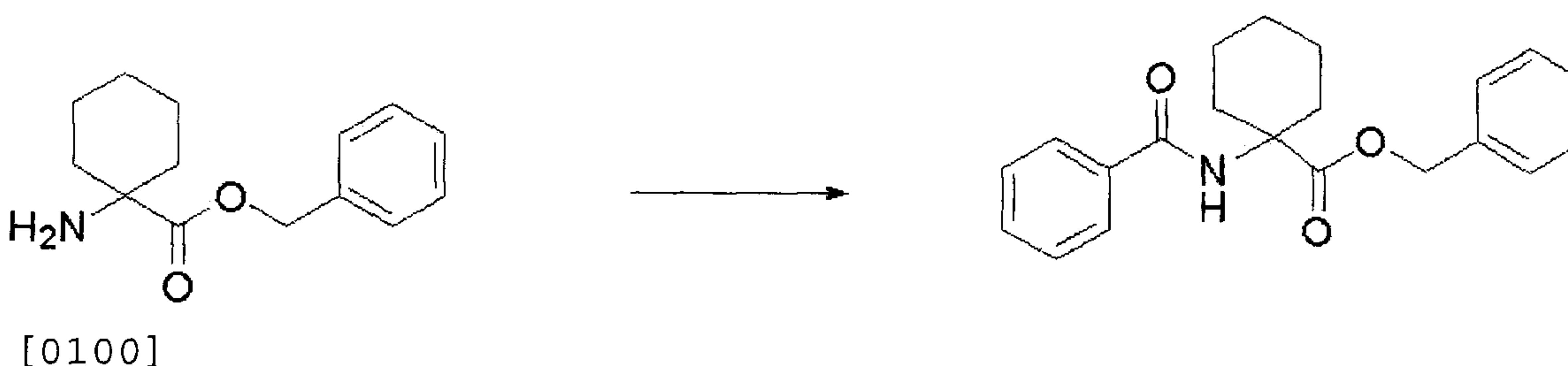
15 [(phenylacetyl)amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 2 to obtain 2.35 g (90%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.16-1.25 (3H, m), 1.48-1.51 (1H, m), 1.52-1.62 (2H, m), 1.84-1.97 (4H, m), 2.62 (2H, t, J=7Hz),
 20 3.00 (2H, t, J=7Hz), 5.43 (1H, br-s), 7.21-7.26 (3H, m), 7.29-7.33 (2H, m)

[0099]

Reference Example 5

25 1-(Benzoylamino)cyclohexanecarboxylic acid phenylmethyl ester



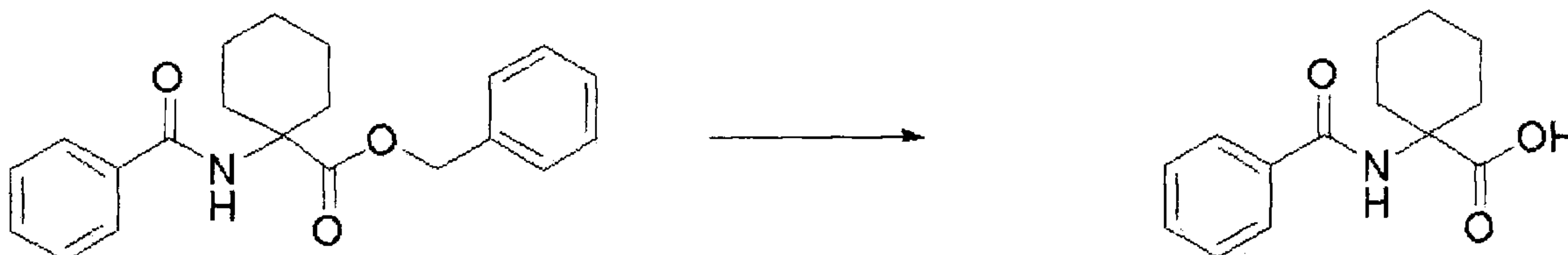
1.41 g (10 mmol) of benzoyl chloride was used instead of phenylacetyl chloride in the process according to Reference Example 1 to obtain 3.39 g (quantitative) of the title compound.

5 ¹H-NMR (CDCl₃, δ): 1.33-1.40 (1H, m), 1.45-1.54 (2H, m), 1.62-1.76 (3H, m), 1.93-1.99 (2H, m), 2.19-2.22 (2H, m), 5.17 (2H, s), 6.25 (1H, br-s), 7.25-7.32 (4H, m), 7.41-7.45 (3H, m), 7.49-7.52 (1H, m), 7.75-7.77 (2H, m)

[0101]

10 Reference Example 6

1-(Benzoylamino)cyclohexanecarboxylic acid



[0102]

3.39 g (10 mmol) of 1-

15 (benzoylamino)cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-

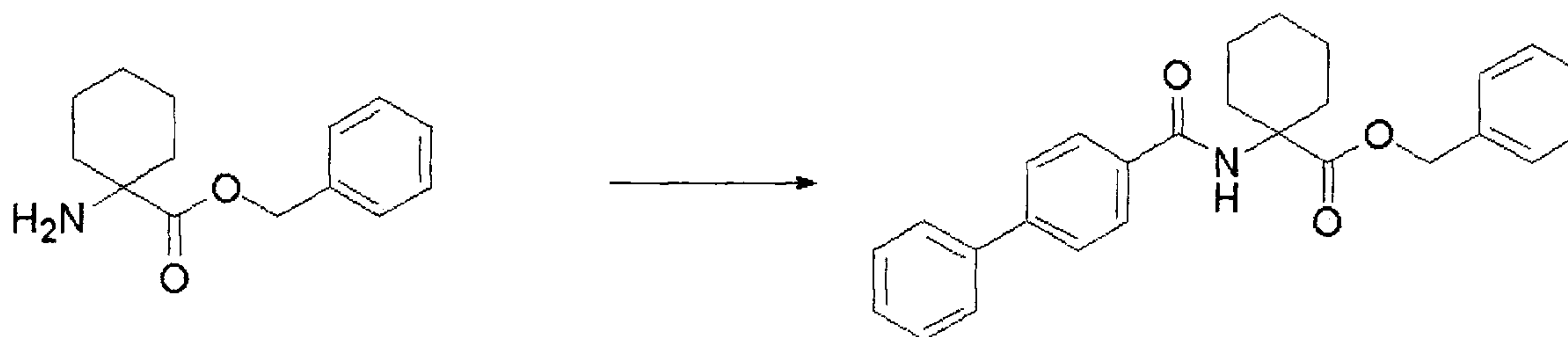
[(phenylacetyl)amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 2 to obtain 2.44 g (99%) of the title compound.

20 ¹H-NMR (CDCl₃, δ): 1.38-1.55 (3H, m), 1.67-1.71 (1H, m), 1.75-1.79 (2H, m), 1.98-2.04 (2H, m), 2.24-2.27 (2H, m), 6.26 (1H, br-s), 7.46 (1H, td, J=7Hz, 1Hz), 7.48 (1H, td, J=7Hz, 1Hz), 7.57 (1H, td, 7Hz, 1Hz), 7.79-7.82 (2H, m)

[0103]

25 Reference Example 7

1-[(4-Biphenylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester



[0104]

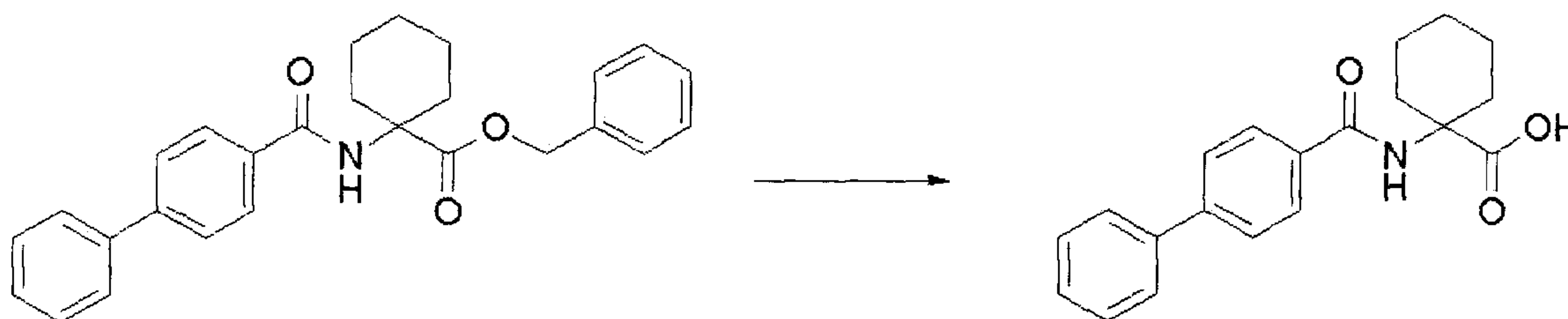
2.11 g (11 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added to
 5 a solution of 2.33 g (10 mmol) of 1-aminocyclohexanecarboxylic acid phenylmethyl ester, 1.68 g (11 mmol) of 1-hydroxybenzotriazole and 3.23 g (10 mmol) of 4-biphenylcarboxylic acid in 120 ml of methylene chloride under ice-cooling. After the mixture was stirred at room
 10 temperature overnight, the reaction solution was concentrated under reduced pressure, ethyl acetate was added thereto, and the mixture was successively washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and
 15 saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by silica gel chromatography to obtain 3.51 g (85%) of the title compound.

20 ¹H-NMR (CDCl₃, δ): 1.38-1.41 (1H, m), 1.51-1.61 (2H, m), 1.66-1.80 (3H, m), 1.95-2.05 (2H, m), 2.23-2.31 (2H, m), 5.20 (2H, s), 6.38 (1H, br-s), 7.24-7.34 (7H, m), 7.55-7.60 (2H, m), 7.81 (1H, dd, J=8Hz, 1Hz), 7.87-7.91 (3H, m), 8.26 (1H, d, J=1Hz)

25 [0105]

Reference Example 8

1-[(4-Biphenylcarbonyl)amino]cyclohexanecarboxylic acid



[0106]

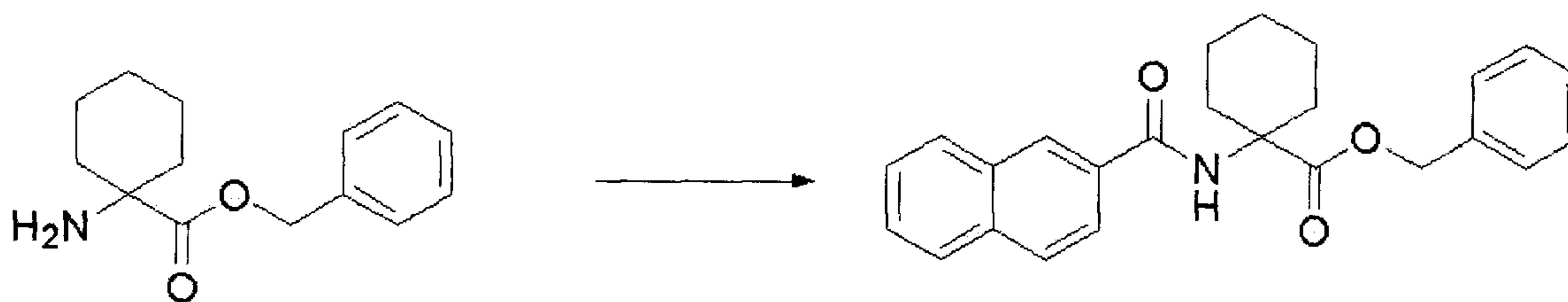
3.51 g (8.5 mmol) of 1-[(4-biphenylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 2 to obtain 2.75 g (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.37-1.48 (1H, m), 1.48-1.60 (2H, m), 1.66-1.73 (1H, m), 1.73-1.82 (2H, m), 2.00-2.10 (2H, m), 2.27-2.35 (2H, m), 6.32 (1H, br-s), 7.39-7.43 (1H, m), 7.46-7.49 (2H, m), 7.61-7.66 (2H, m), 7.68-7.70 (2H, m), 7.87-7.89 (2H, m)

[0107]

Reference Example 9

1-[(2-Naphthylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester



[0108]

1.28 g (7.4 mmol) of 2-naphthoic acid was used instead of 4-biphenylcarboxylic acid in the process according to Reference Example 7 to obtain 2.12 g (74%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.32-1.41 (1H, m), 1.48-1.61 (2H, m), 1.64-1.78 (3H, m), 1.95-2.01 (2H, m), 2.21-2.24 (2H, m),

5.19 (2H, s), 6.27 (1H, br-s), 7.27-7.36 (3H, m), 7.40 (1H, td, J=7Hz, 1Hz), 7.46-7.49 (2H, m), 7.61-7.63 (2H, m), 7.65-7.67 (2H, m), 7.83-7.85 (2H, m)

[0109]

5 Reference Example 10

1-[(2-Naphthylcarbonyl)amino]cyclohexanecarboxylic acid



[0110]

2.12 g (5.5 mmol) of 1-[(2-

10 naphthylcarbonyl)amino]cyclohexanecarboxylic acid

phenylmethyl ester was used instead of 1-

[(phenylacetyl)amino]cyclohexanecarboxylic acid

phenylmethyl ester in the process according to Reference

Example 2 to obtain 1.63 g (quantitative) of the title

15 compound.

¹H-NMR (CDCl₃, δ): 1.41-1.45 (1H, m), 1.52-1.60 (2H, m),

1.70-1.74 (1H, m), 1.77-1.82 (2H, m), 2.03-2.09 (2H, m),

2.29-2.32 (2H, m), 6.41 (1H, br-s), 7.56-7.63 (2H, m), 7.83

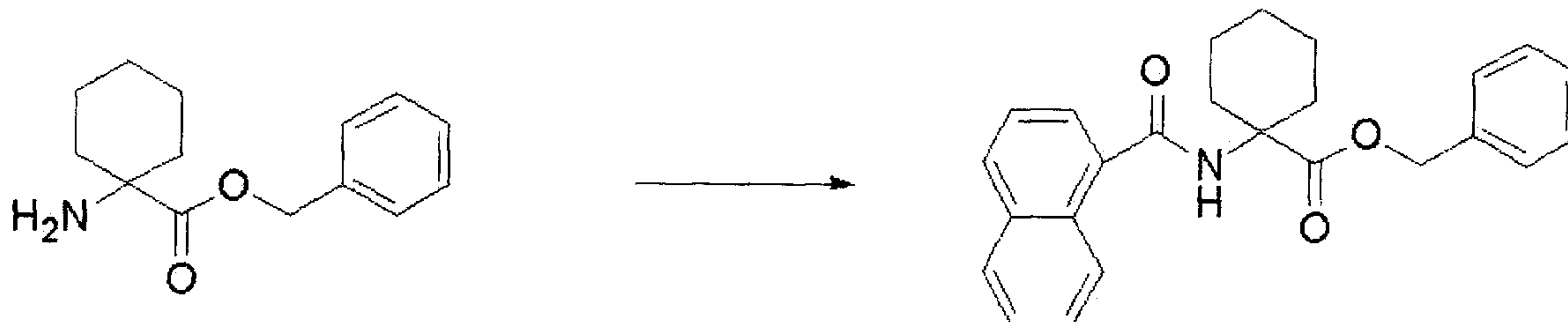
(1H, dd, J=8Hz, 2Hz), 7.89-7.96 (3H, m), 8.33 (1H, s)

20 [0111]

Reference Example 11

1-[(1-Naphthylcarbonyl)amino]cyclohexanecarboxylic acid

phenylmethyl ester



25 [0112]

1.72 g (10 mmol) of 1-naphthoic acid was used instead of 4-biphenylcarboxylic acid in the process

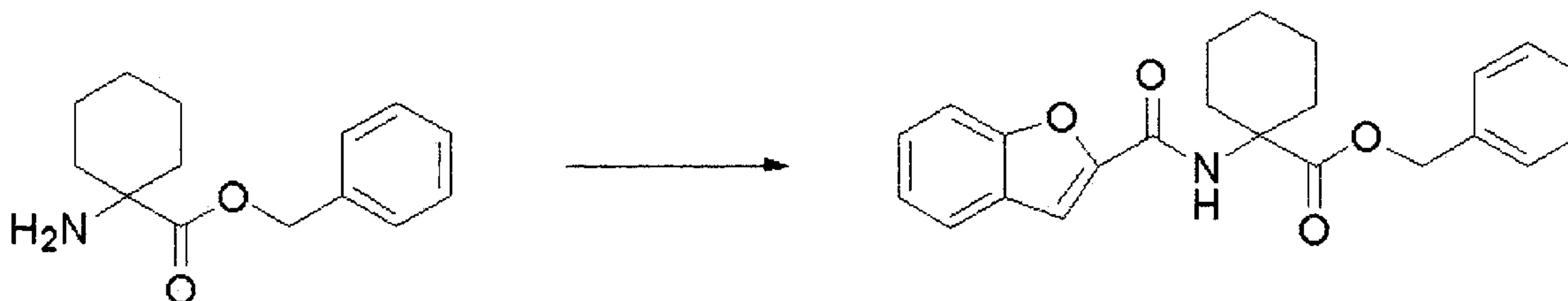
according to Reference Example 7 to obtain 3.87 g
(quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.31-1.42 (1H, m), 1.45-1.60 (2H, m),
1.65-1.71 (1H, m), 1.71-1.80 (2H, m), 1.98-2.05 (2H, m),
5 2.24-2.32 (2H, m), 5.26 (2H, s), 6.10 (1H, br-s), 7.32-7.37
(3H, m), 7.40-7.45 (4H, m), 7.48-7.52 (1H, m), 7.57 (1H,
dd, J=7Hz, 1Hz), 7.85 (1H, dd, J=7Hz, 1Hz), 7.91 (1H, dd,
J=7Hz, 1Hz), 8.25 (1H, dd, J=7Hz, 1Hz)

[0113]

10 Reference Example 12

1-[(2-Benzofuranylcarbonyl)amino]cyclohexanecarboxylic acid
phenylmethyl ester



[0114]

15 12.22 g (75.4 mmol) of benzofuran-2-carboxylic acid
was used instead of 4-biphenylcarboxylic acid in the
process according to Reference Example 7 to obtain 21.3 g
(75%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.26-1.42 (1H, m), 1.50-1.61 (2H, m),
20 1.64-1.77 (3H, m), 1.95-2.04 (2H, m), 2.21-2.28 (2H, m),
5.19 (2H, s), 6.77 (1H, br-s), 7.25-7.34 (6H, m), 7.44 (1H,
td, J=8Hz, 2Hz), 7.52 (1H, dd, J=8Hz, 2Hz), 7.57 (1H, dd,
J=8Hz, 2Hz), 7.68 (1H, dd, J=8Hz, 2Hz)

[0115]

25 Reference Example 13

1-[[[(RS)-2,3-Tetrahydrobenzofuran-2-
yl]carbonyl]amino]cyclohexanecarboxylic acid



[0116]

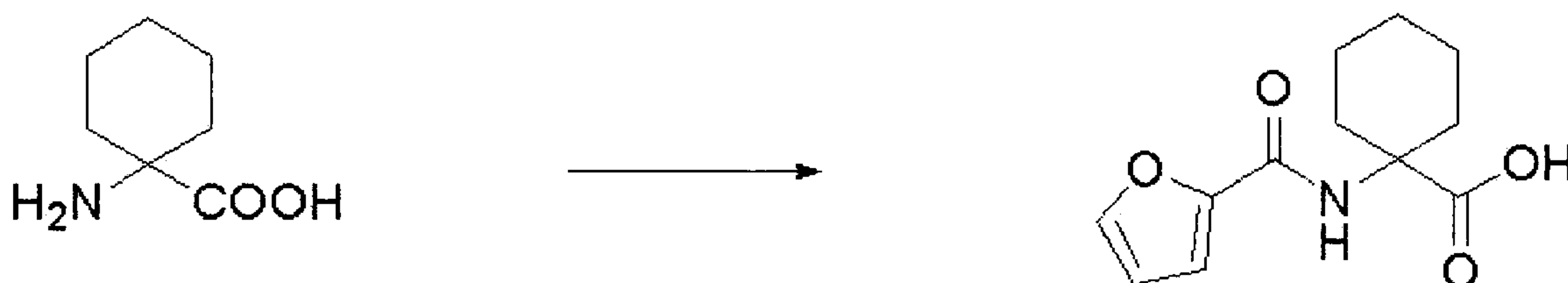
1.5 g of 10% palladium-carbon was added to a solution of 15 g (40 mmol) of 1-[(2-benzofuranylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester in 300 ml of 2-propanol, and the mixture was stirred under a hydrogen atmosphere at 60°C for 20 hours. After the reaction solution was filtered, the filtrate was concentrated under reduced pressure to obtain 11.57 g (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.07-1.19 (1H, m), 1.21-1.36 (2H, m), 1.50-1.63 (2H, m), 1.65-1.71 (1H, m), 1.80-1.88 (1H, m), 1.89-1.95 (1H, m), 2.04-2.15 (2H, m), 3.42 (1H, dd, J=17Hz, 7Hz), 3.60 (1H, dd, J=17Hz, 7Hz), 5.18 (1H, dd, J=7Hz, 7Hz), 6.84 (1H, br-s), 6.91 (1H, d, J=8Hz), 6.96 (1H, dd, J=8Hz, 1Hz), 7.18 (1H, td, J=8Hz, 1Hz), 7.22 (1H, dd, J=8Hz, 1Hz)

[0117]

Reference Example 14

1-[(2-Furanylcarbonyl)amino]cyclohexanecarboxylic acid



[0118]

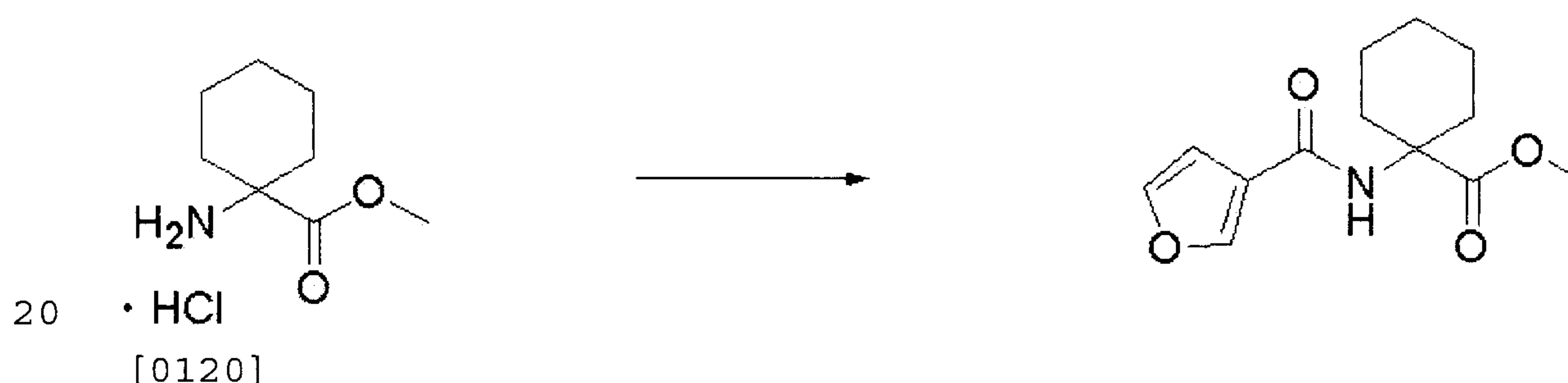
71.6 g (0.5 mol) of 1-aminocyclohexanecarboxylic acid was added to a solution of 20 g (0.5 mol) of sodium hydroxide in 250 ml of water, and the mixture was stirred at 80°C for 2 hours. The mixture solution was cooled by ice-water, 71.8 g (0.2 mol) of 2-furancarboxyl chloride and

a solution of 24 g (0.6 mol) of sodium hydroxide in 100 ml of water were simultaneously added thereto over approximately 1 hour. The reaction solution was slowly returned to room temperature and stirred overnight. After 5 80 ml of ethyl acetate was added to the reaction solution and the mixture was stirred for 1 hour, the insolubles were removed by filtration. The aqueous layer was separately collected, 49 ml of concentrated hydrochloric acid was added thereto under ice-cooling. The precipitated crystal 10 was collected by filtration and dried under reduced pressure to obtain 112.6 g (95%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.35-1.41 (1H, m), 1.48-1.53 (2H, m), 1.64-1.67 (1H, m), 1.71-1.76 (2H, m), 1.96-2.02 (2H, m), 2.20-2.24 (2H, m), 6.48 (1H, br-s), 6.55 (1H, dd, J=4Hz, 2Hz), 7.19 (1H, dd, J=4Hz, 1Hz), 7.50 (1H, dd, J=2Hz, 1Hz) [0119]

Reference Example 15

1-[(3-Furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester



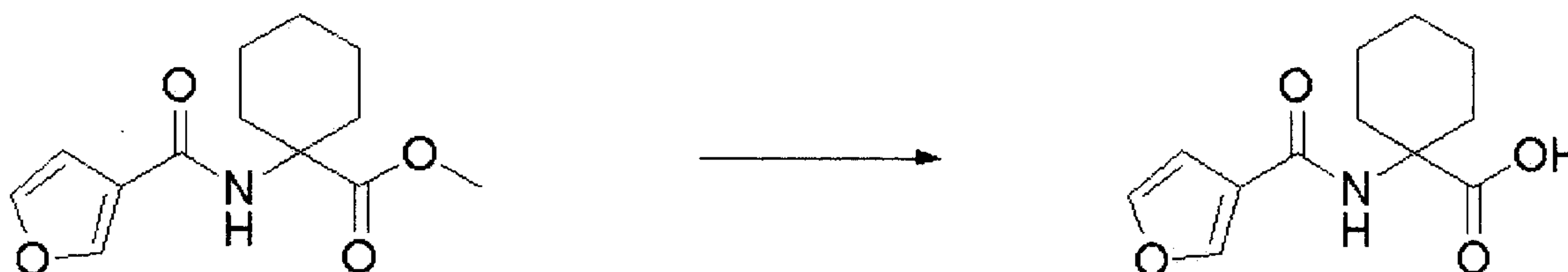
105 g (550 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added to a solution of 98.8 g (500 mmol) of 1-aminocyclohexanecarboxylic acid methyl ester hydrochloride, 84.2 g (550 mmol) of 1-hydroxybenzotriazole, 56.0 g (500 mmol) of 3-furancarboxylic acid and 152 g (1.5 mol) of triethylamine in 1000 ml of methylene chloride under ice-cooling. After the mixture was stirred at room temperature

overnight, the reaction solution was concentrated under reduced pressure. Ethyl acetate was added to the residue, and the mixture was successively washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the obtained crystal was washed with diisopropyl ether to obtain 114 g (91%) of the title compound.

1H-NMR (CDCl₃, δ): 1.34-1.40 (1H, m), 1.43-1.44 (2H, m), 1.62-1.73 (3H, m), 1.90-1.96 (2H, m), 2.10-2.14 (2H, m), 3.73 (3H, s), 5.87 (1H, br-s), 6.23 (1H, dd, J=2Hz, 1Hz), 7.44 (1H, dd, J=2Hz, 1Hz), 7.94 (1H, dd, J=2Hz, 1Hz)
[0121]

Reference Example 16

1-[(3-Furanylcarbonyl)amino]cyclohexanecarboxylic acid



[0122]

450 ml of 2N aqueous sodium hydroxide solution was added to a solution of 75.4 g (300 mmol) of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in 450 ml of tetrahydrofuran, and the mixture was heated under reflux for 3 hours. After ether was added to the reaction solution to wash it, the aqueous layer was neutralized by concentrated hydrochloric acid, and the mixture was extracted with ethyl acetate. After the obtained organic layer was washed with saturated brine, it was dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 68.8 g (97%) of the title compound.

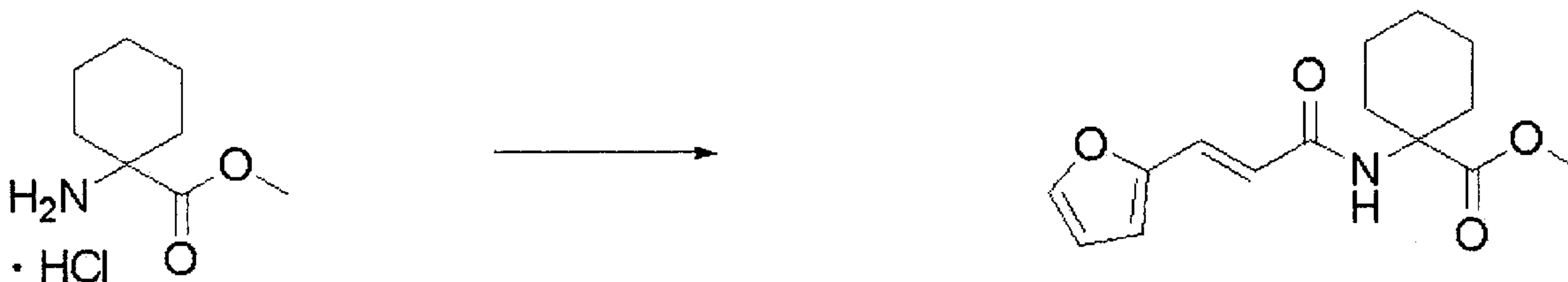
$^1\text{H-NMR}$ (CDCl_3 , δ): 1.37-1.50 (3H, m), 1.58-1.64 (1H, m),
1.68-1.80 (2H, m), 1.98-2.05 (2H, m), 2.14-2.23 (2H, m),
5.87 (1H, s), 6.63 (1H, d, $J=2\text{Hz}$), 7.49 (1H, d, $J=2\text{Hz}$),
8.00 (1H, s)

5 [0123]

Reference Example 17

1-[[(E) -3-(2-Furanyl)-1-oxo-2-

propenyl]amino]cyclohexanecarboxylic acid methyl ester



10 [0124]

80 g (362 mmol) of 2-furanacrylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 89 g (89%) of the title compound.

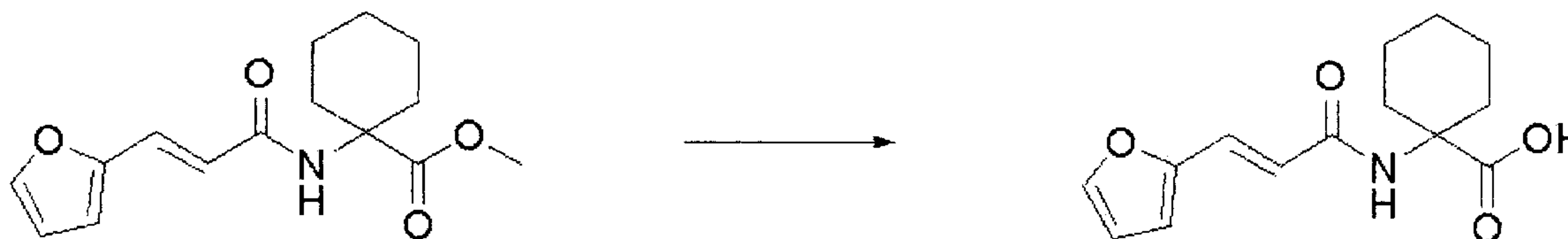
15 $^1\text{H-NMR}$ (CDCl_3 , δ): 1.29-1.39 (1H, m), 1.40-1.51 (2H, m),
1.58-1.71 (3H, m), 1.88-1.95 (2H, m), 2.05-2.14 (2H, m),
3.73 (3H, s), 5.67 (1H, br-s), 6.35 (1H, d, $J=16\text{Hz}$), 6.45
(1H, dd, $J=3\text{Hz}$, 2Hz), 6.54 (1H, d, $J=3\text{Hz}$), 7.37 (1H, d,
 $J=16\text{Hz}$), 7.40 (1H, d, $J=2\text{Hz}$)

20 [0125]

Reference Example 18

1-[[(E) -3-(2-Furanyl)-1-oxo-2-

propenyl]amino]cyclohexanecarboxylic acid



25 [0126]

44.9 g (162 mmol) of 1-[[(E) -3-(2-furanyl)-1-oxo-2-propenyl]amino]cyclohexanecarboxylic acid methyl ester was

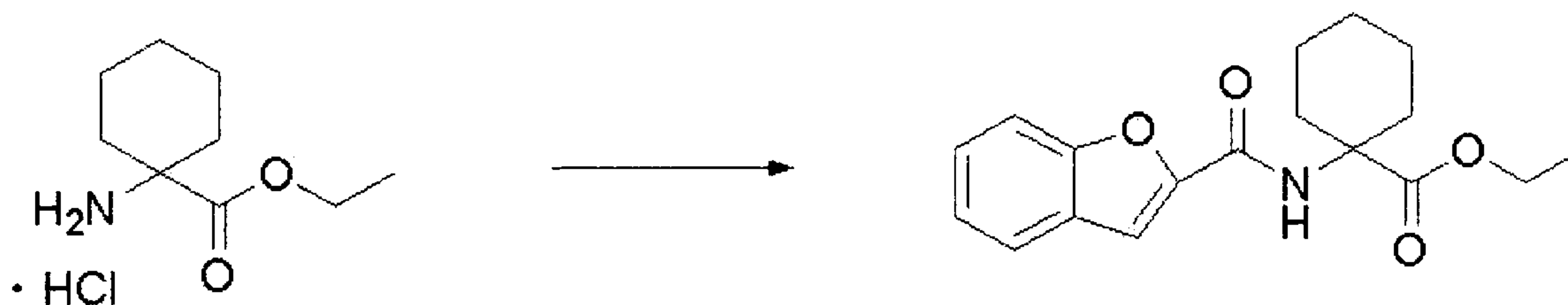
used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 37.5 g (quantitative) of the title compound.

5 ¹H-NMR (CDCl₃, δ): 1.32-1.85 (6H, m), 1.96-2.05 (2H, m), 2.15-2.18 (2H, m), 5.66 (1H, br-s), 6.36 (1H, d, J=15Hz), 6.49 (1H, dd, J=3Hz, 2Hz), 6.64 (1H, d, J=3Hz), 7.48 (1H, d, J=15Hz), 7.49 (1H, d, J=2Hz)

[0127]

10 Reference Example 19

1-[(2-Benzofuranylcarbonyl)amino]cyclohexanecarboxylic acid ethyl ester



[0128]

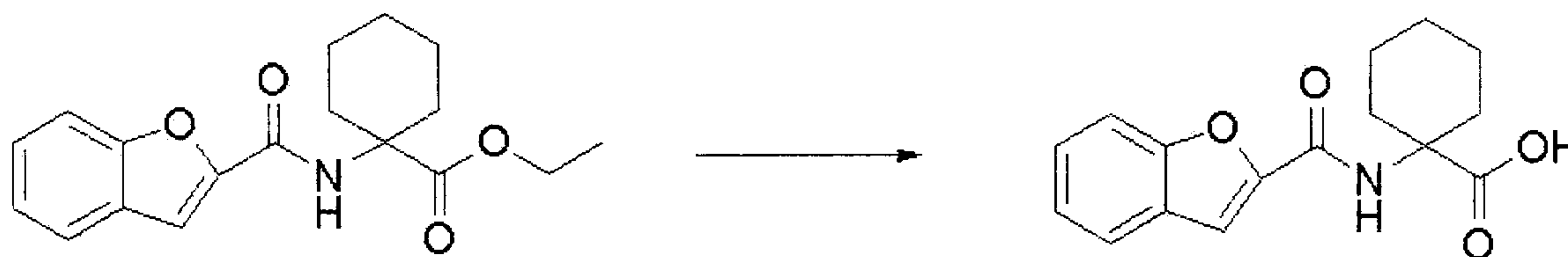
15 3.11 g (15 mmol) of 1-aminocyclohexanecarboxylic acid ethyl ester hydrochloride was used instead of 1-aminocyclohexanecarboxylic acid methyl ester hydrochloride, and 2.43 g (15 mmol) of benzofuran-2-carboxylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 3.80 g (80%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 1.33-1.42 (1H, m), 1.50-1.62 (2H, m), 1.65-1.78 (3H, m), 1.94-2.02 (2H, m), 2.19-2.27 (2H, m), 4.21 (2H, q, J=7Hz), 6.75 (1H, br-s), 7.30 (1H, td, J=8Hz, 1Hz), 7.43 (1H, td, J=8Hz, 1Hz), 7.45 (1H, d, J=1Hz), 7.53 (1H, dd, J=8Hz, 1Hz), 7.67 (1H, dd, J=8Hz, 1Hz)

[0129]

Reference Example 20

1-[(2-Benzofuranylcarbonyl)amino]cyclohexanecarboxylic acid



[0130]

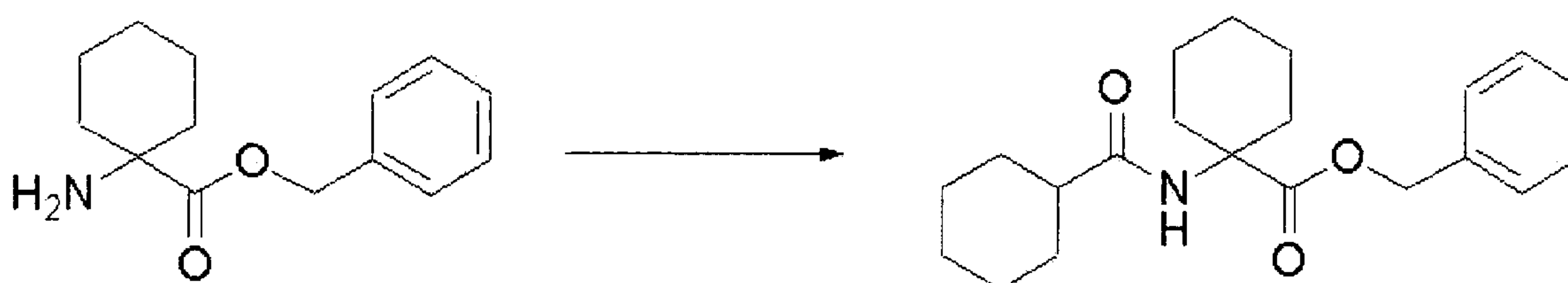
3.80 g (12 mmol) of 1-[(2-benzofuranylcarbonyl)amino]cyclohexanecarboxylic acid ethyl ester was used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 3.42 g (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.35-1.44 (1H, m), 1.50-1.62 (2H, m), 1.65-1.73 (1H, m), 1.74-1.82 (2H, m), 2.00-2.08 (2H, m), 2.25-2.33 (2H, m), 6.77 (1H, br-s), 7.32 (1H, td, J=8Hz, 1Hz), 7.46 (1H, td, J=8Hz, 1Hz), 7.53 (1H, d, J=1Hz), 7.55 (1H, dd, J=8Hz, 1Hz), 7.70 (1H, dd, J=8Hz, 1Hz)

[0131]

Reference Example 21

1-[(Cyclohexylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester



[0132]

3.85 g (30 mmol) of cyclohexanecarboxylic acid was used instead of 4-biphenylcarboxylic acid in the process according to Reference Example 7 to obtain 4.77 g (46%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.17-1.45 (8H, m), 1.59-1.77 (4H, m), 1.73-1.88 (6H, m), 2.03-2.11 (3H, m), 5.12 (2H, s), 5.55 (1H, br-s), 7.23-7.36 (5H, m)

[0133]

Reference Example 22

1-[(Cyclohexylcarbonyl)amino]cyclohexanecarboxylic acid



5 [0134]

5.62 g (16.3 mmol) of 1-

[(cyclohexylcarbonyl)amino]cyclohexanecarboxylic acid

phenylmethyl ester was used instead of 1-

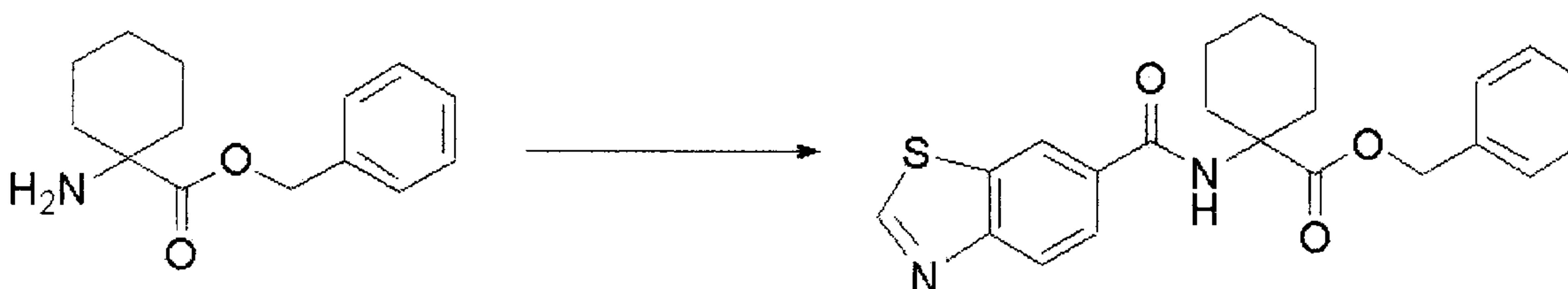
[(phenylacetyl)amino]cyclohexanecarboxylic acid

10 phenylmethyl ester in the process according to Reference
Example 2 to obtain 4.15 g (quantitative) of the title
compound.

1H-NMR (CDCl₃, δ): 1.18-1.50 (8H, m), 1.60-1.76 (4H, m),
1.78-1.95 (6H, m), 2.06-2.14 (2H, m), 2.16-2.23 (1H, m),
15 5.58 (1H, br-s)

[0135]

Reference Example 23

1-[(6-Benzothiazolylcarbonyl)amino]cyclohexanecarboxylic
acid phenylmethyl ester

20

[0136]

1.15 g (6.4 mmol) of benzothiazole-6-carboxylic acid
was used instead of 4-biphenylcarboxylic acid in the
process according to Reference Example 7 to obtain 1.58 g
25 (62%) of the title compound.

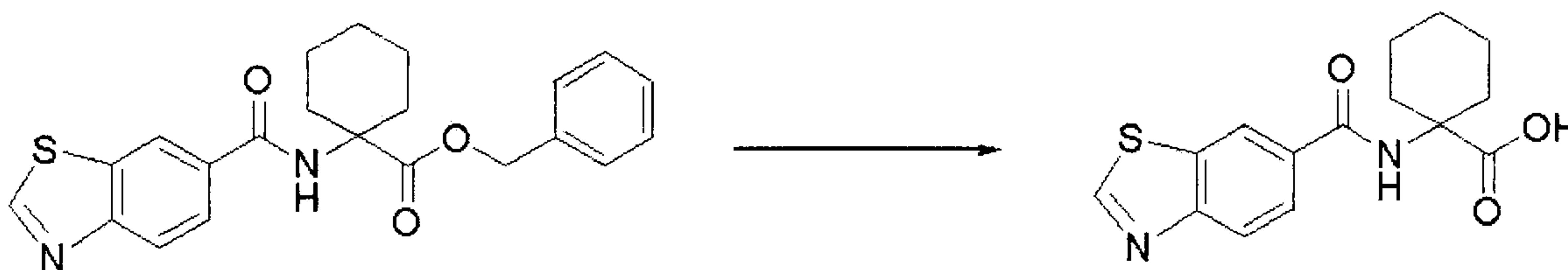
1H-NMR (CDCl₃, δ): 1.35-1.43 (1H, m), 1.49-1.60 (2H, m),
1.61-1.78 (3H, m), 1.96-2.06 (2H, m), 2.20-2.27 (2H, m),

5.19 (2H, s), 6.30 (1H, br-s), 7.28-7.75 (5H, m), 7.86 (1H, dd, J=7Hz, 2Hz), 8.17 (1H, dd, J=7Hz, 1Hz), 8.41 (1H, dd, J=2Hz, 1Hz), 9.12 (1H, s)

[0137]

5 Reference Example 24

1-[(6-Benzothiazolylcarbonyl)amino]cyclohexanecarboxylic acid



[0138]

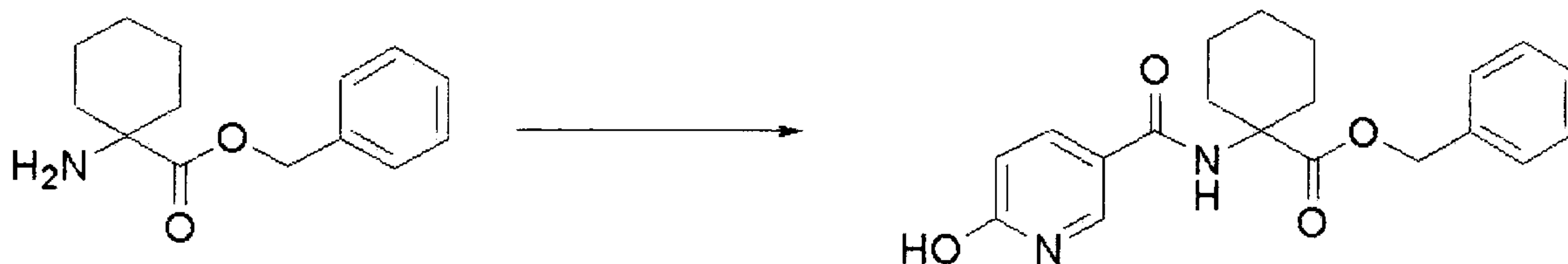
10 1.18 g (30 mmol) of 1-[(6-benzothiazolylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to
15 obtain 0.77 g (84%) of the title compound.

¹H-NMR (CD₃OD, δ): 1.38-1.46 (1H, m), 1.60-1.76 (5H, m), 1.91-2.01 (2H, m), 2.21-2.28 (2H, m), 7.98 (1H, dd, J=7Hz, 2Hz), 8.12 (1H, dd, J=7Hz, 1Hz), 8.54 (1H, dd, J=2Hz, 1Hz), 9.37 (1H, s)

20 [0139]

Reference Example 25

1-[[6-Hydroxy-3-pyridinyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester



25 [0140]

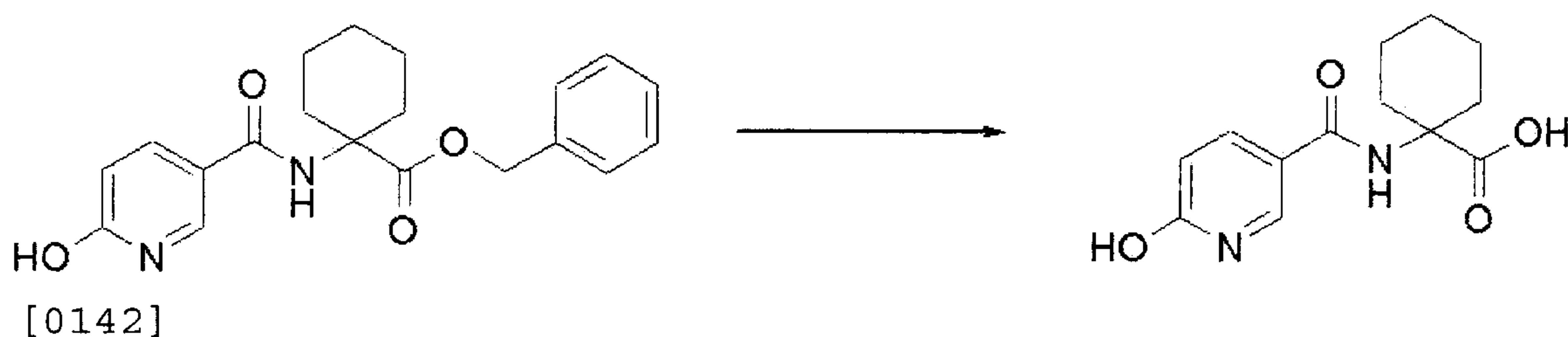
139 mg (1.0 mmol) of 6-hydroxy-3-pyridinecarboxylic

acid was used instead of 4-biphenylcarboxylic acid in the process according to Reference Example 7 to obtain 222 mg (62%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.30-1.40 (1H, m), 1.42-1.54 (2H, m),
 5 1.62-1.73 (3H, m), 1.91-1.98 (2H, m), 2.13-2.20 (2H, m),
 5.17 (2H, s), 6.22 (1H, s), 6.54 (1H, d, J=10Hz), 7.26-7.35
 (5H, m), 7.76 (1H, dd, J=10Hz, 3Hz), 7.93 (1H, d, J=3Hz)
 [0141]

Reference Example 26

10 1-[[(6-Hydroxy-3-pyridinyl)carbonyl]amino]cyclohexanecarboxylic acid

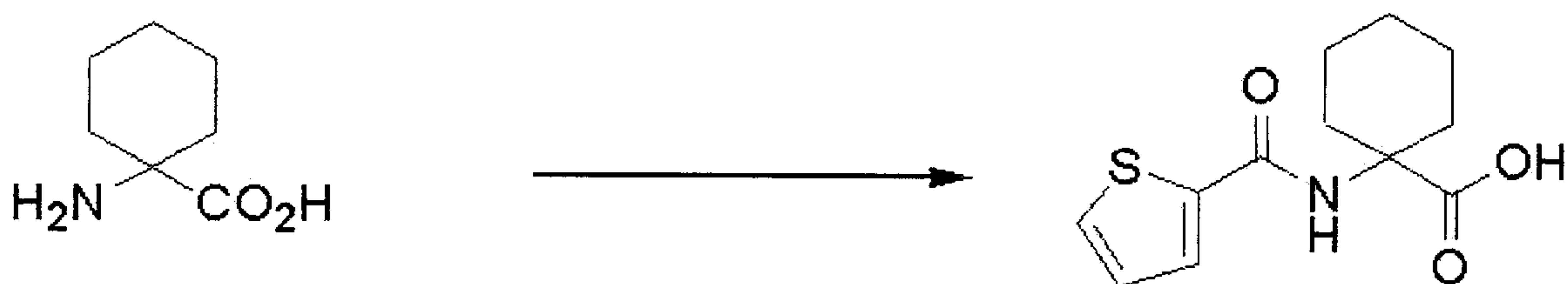


760 mg (2.2 mmol) of 1-[[(6-hydroxy-3-pyridinyl)carbonyl]amino]cyclohexanecarboxylic acid
 15 phenylmethyl ester was used instead of 1-
 [(phenylacetyl)amino]cyclohexanecarboxylic acid
 phenylmethyl ester in the process according to Reference
 Example 2 to obtain 565 mg (quantitative) of the title
 20 compound.

¹H-NMR (CD₃OD, δ): 1.21-1.30 (1H, m), 1.43-1.54 (5H, m),
 1.67-1.74 (2H, m), 2.03-2.09 (2H, m), 6.33 (1H, d, J=9Hz),
 7.84 (1H, dd, J=9Hz, 3Hz), 8.05 (1H, d, J=3Hz)
 [0143]

25 Reference Example 27

1-[(2-Thienylcarbonyl)amino]cyclohexanecarboxylic acid



[0144]

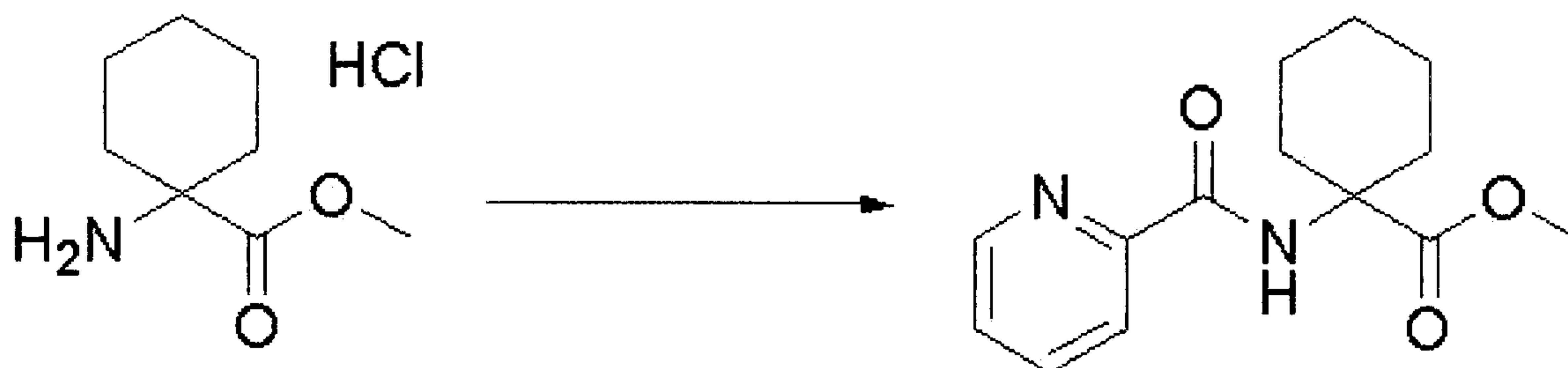
100 g (680 mmol) of 2-thiophenecarbonyl chloride was used instead of 2-furancarboxyl chloride in the process according to Reference Example 14 to obtain 57.6 g (51%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.35-1.54 (3H, m), 1.65-1.80 (3H, m), 1.98-2.05 (2H, m), 2.21-2.27 (2H, m), 6.06 (1H, br-s), 7.13 (1H, dd, J=5Hz, 3Hz), 7.57 (1H, dd, J=5Hz, 1Hz), 7.59 (1H, dd, J=3Hz, 1Hz)

[0145]

Reference Example 28

1-[(2-Pyridinylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester



[0146]

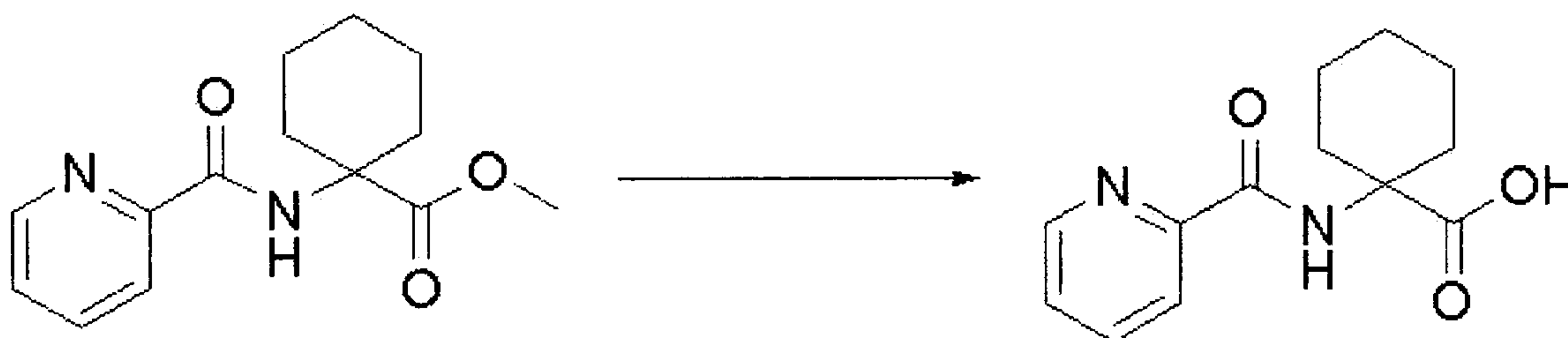
370 mg (3 mmol) of 2-pyridinecarboxylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 600 mg (76%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.31-1.42 (1H, m), 1.51-1.73 (5H, m), 1.95 (2H, td, J=13Hz, 4Hz), 1.99-2.08 (2H, m), 3.73 (3H, s), 7.44 (1H, ddd, J=8Hz, 5Hz, 2Hz), 7.84 (1H, dd, J=8Hz, 2Hz), 8.16 (1H, d, J=8Hz), 8.33 (1H, s), 8.57 (1H, dd, J=5Hz, 2Hz)

[0147]

Reference Example 29

1-[(2-Pyridinylcarbonyl)amino]cyclohexanecarboxylic acid



[0148]

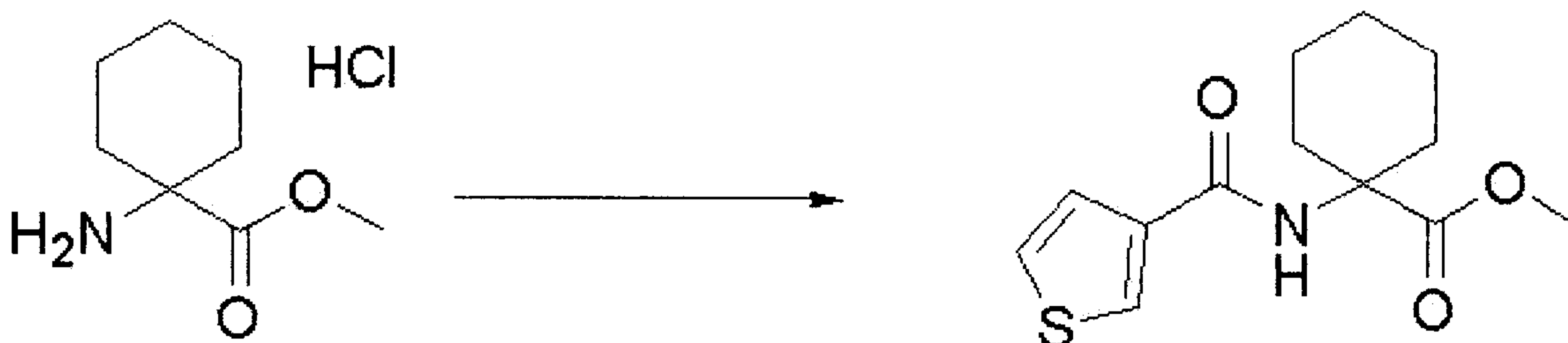
539 mg (2 mmol) of 1-[(2-pyridinylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 479 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.32-1.41 (1H, m), 1.48-1.57 (2H, m), 1.62-1.78 (3H, m), 1.98 (2H, m), 2.25-2.35 (2H, m), 7.50 (1H, ddd, J=8Hz, 5Hz, 2Hz), 7.89 (1H, dd, J=8Hz, 2Hz), 8.19 (1H, d, J=8Hz), 8.59 (1H, s), 8.60 (1H, dd, J=5Hz, 2Hz)

[0149]

Reference Example 30

1-[(3-Thienylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester



[0150]

384 mg (3 mmol) of 3-thiophenecarboxylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 759 mg (95%) of the title compound.

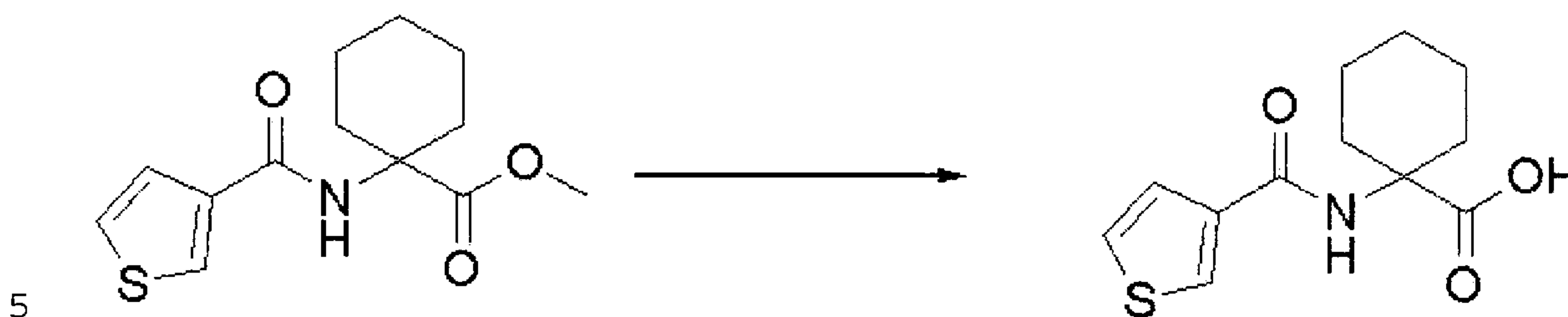
¹H-NMR (CDCl₃, δ): 1.32-1.41 (1H, m), 1.42-1.55 (2H, m), 1.61-1.75 (3H, m), 1.90-1.99 (2H, m), 2.11-2.18 (2H, m), 3.74 (3H, s), 6.26 (1H, br-s), 7.35 (1H, dd, J=5Hz, 2Hz),

7.39 (1H, dd, J=5Hz, 2Hz), 7.88 (1H, dd, J=3Hz, 2Hz)

[0151]

Reference Example 31

1-[(3-Thienylcarbonyl)amino]cyclohexanecarboxylic acid



[0152]

759 mg (2.8 mmol) of 1-[(3-thienylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 692 mg (96%) of the title compound.

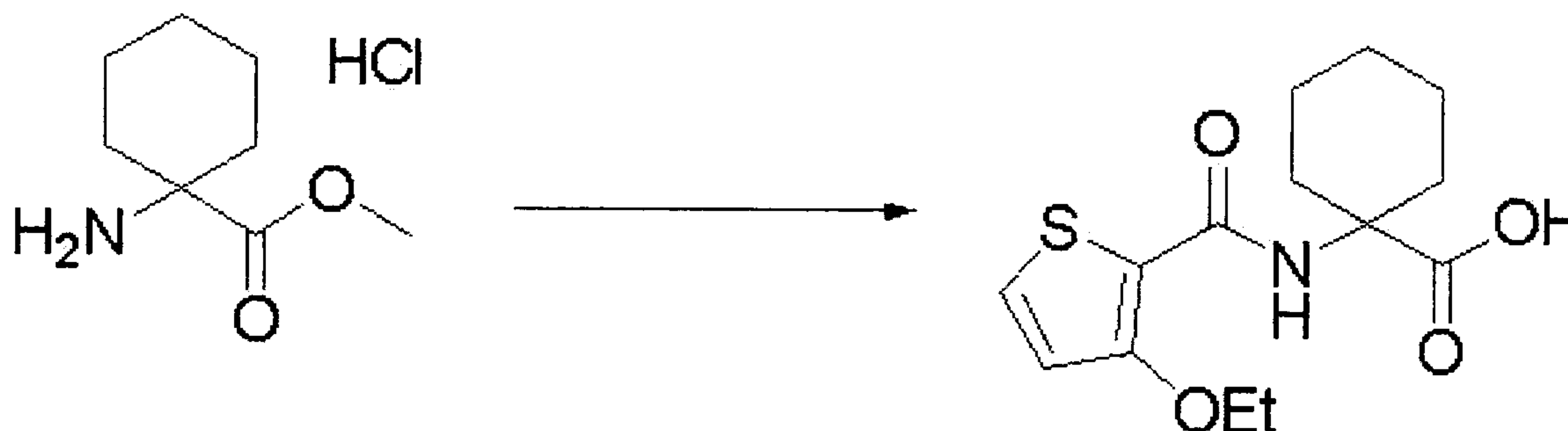
1H-NMR (DMSO-d₆, δ): 1.24-1.32 (1H, m), 1.45-1.55 (5H, m), 1.72-1.78 (2H, m), 2.05-2.12 (2H, m), 7.50 (1H, dd, J=5Hz, 2Hz), 7.57 (1H, dd, J=5Hz, 2Hz), 7.96 (1H, br-s), 8.21 (1H, dd, J=3Hz, 2Hz)

[0153]

Reference Example 32

1-[[3-Ethoxy-2-

20 thienyl)carbonyl]amino]cyclohexanecarboxylic acid



[0154]

633 mg (3.3 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added to

a solution of 581 mg (3 mmol) of 1-aminocyclohexanecarboxylic acid methyl ester hydrochloride, 482 mg (3.1 mmol) of 1-hydroxybenzotriazole, 517 mg (3 mmol) of 3-ethoxy-2-thiophenecarboxylic acid and 1.16 g (9 mmol) of diisopropylethylamine in 10 ml of methylene chloride under ice-cooling. After the mixture was stirred at room temperature overnight, the reaction solution was concentrated under reduced pressure, ethyl acetate was added thereto, and the mixture was washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and then saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, diisopropyl ether was added to the residue, and the mixture was stirred overnight, followed by collecting of the crystal by filtration. Then, the obtained crystal was dissolved in 3 ml of tetrahydrofuran solution, 2.8 ml of 2N aqueous NaOH solution was added thereto, and the mixture was heated under reflux for 3 hours. Ether was added to the reaction solution to separate the aqueous layer. After the separated aqueous layer was neutralized by concentrated hydrochloric acid, it was extracted with ethyl acetate. After the obtained organic layer was washed with saturated brine, it was dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 656 mg (73%) of the title compound.

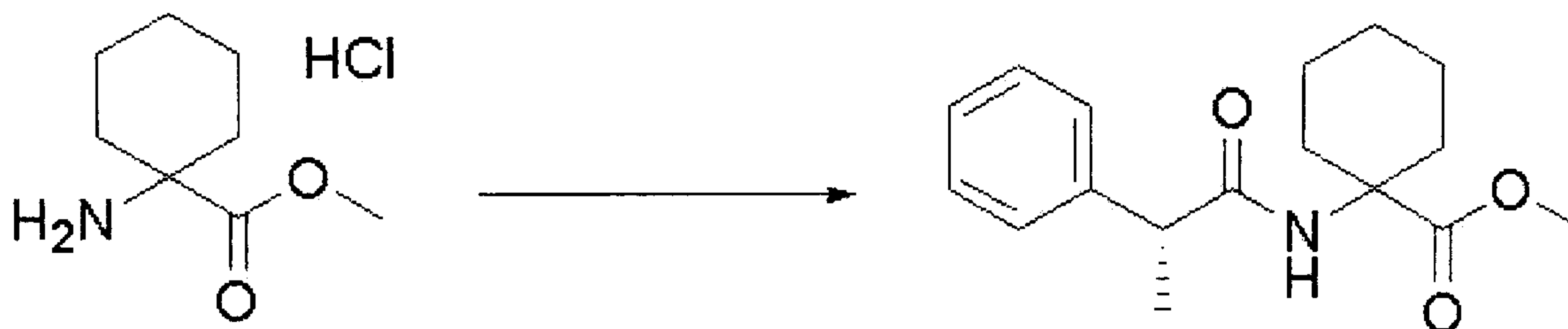
¹H-NMR (CDCl₃, δ): 1.29-1.40 (1H, m), 1.43-1.54 (2H, m), 1.50 (3H, t, J=7Hz), 1.62-1.76 (3H, m), 1.90-2.00 (2H, m), 2.22-2.30 (2H, m), 4.30 (2H, q, J=7Hz), 6.87 (1H, d, J=6Hz), 7.49 (1H, d, J=6Hz), 7.60 (1H, s)

[0155]

Reference Example 33

1-[[*(S)*-1-Oxo-2-phenylpropyl]amino]cyclohexanecarboxylic

acid methyl ester



[0156]

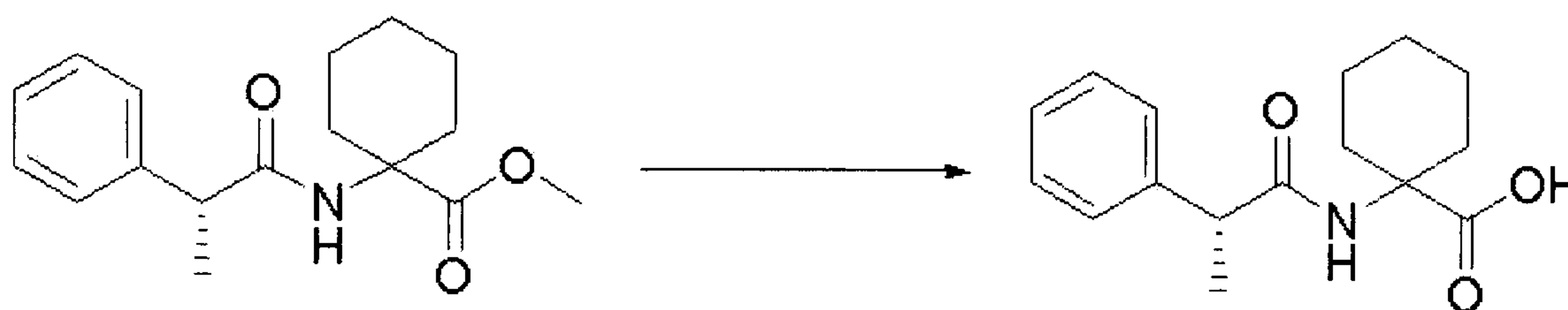
451 mg (3 mmol) of (S)-(+)-2-phenylpropionic acid was
 5 used instead of 3-furancarboxylic acid in the process
 according to Reference Example 15 to obtain 601 mg (69%) of
 the title compound.

¹H-NMR (CDCl₃, δ): 1.06-1.22 (2H, m), 1.48-1.61 (7H, m),
 1.71-1.77 (2H, m), 1.90-1.96 (2H, m), 3.60 (1H, q, 7Hz),
 10 3.67 (3H, s), 5.40 (1H, br-s), 7.27-7.39 (5H, m)

[0157]

Reference Example 34

1-[[[(S)-1-oxo-2-phenylpropyl]amino]cyclohexanecarboxylic
 acid



15

[0158]

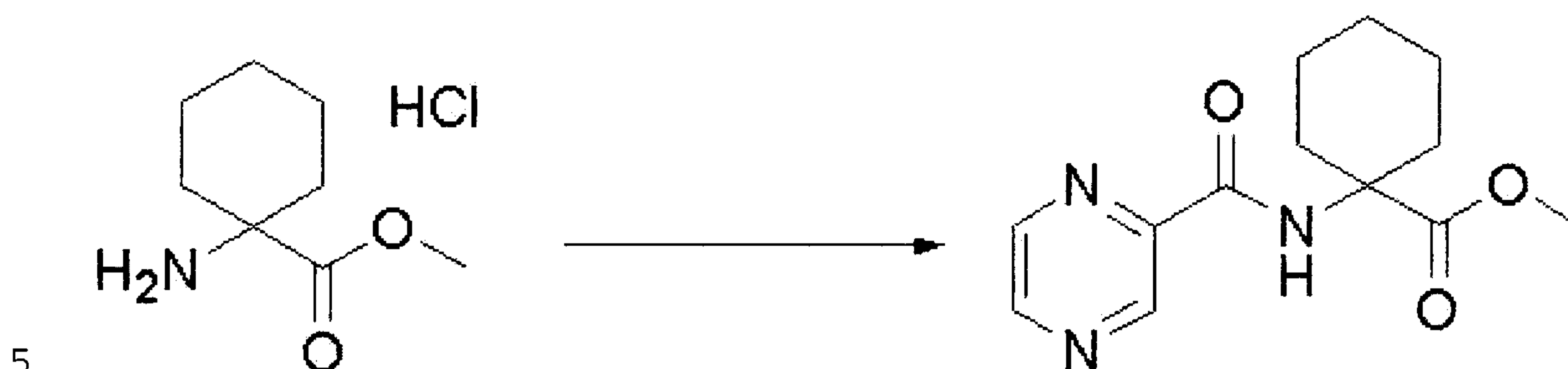
608 mg (2.1 mmol) of 1-[[[(S)-1-oxo-2-
 phenylpropyl]amino]cyclohexanecarboxylic acid methyl ester
 was used instead of 1-[(3-
 20 furanylcabonyl)amino]cyclohexanecarboxylic acid methyl
 ester in the process according to Reference Example 16 to
 obtain 366 mg (63%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.08-1.21 (2H, m), 1.28-1.47 (7H, m),
 1.53-1.62 (2H, m), 1.93 (2H, br-s), 3.79 (1H, q, J=7Hz),
 25 7.18-7.21 (1H, m), 7.27-7.33 (4H, m), 7.90 (1H, s), 12.00
 (1H, s)

[0159]

Reference Example 35

1-[(2-Pyrazinylcarbonyl)amino]cyclohexanecarboxylic acid
methyl ester



[0160]

372 mg (3 mmol) of 2-pyrazinecarboxylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 476 mg (60%) of the title compound.

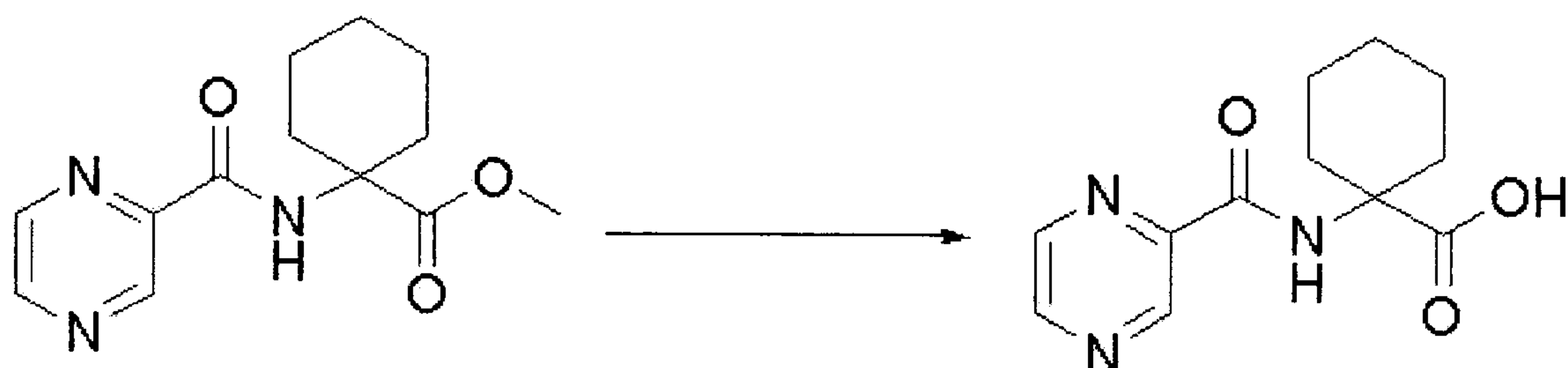
10

¹H-NMR (CDCl₃, δ): 1.35-1.40 (1H, m), 1.47-1.59 (2H, m), 1.65-1.75 (3H, m), 1.94-2.00 (2H, m), 2.18-2.29 (2H, m), 3.75 (3H, s), 8.03 (1H, s), 8.55 (1H, dd, J=3Hz, 1Hz), 8.77 (1H, d, J=3Hz), 9.38 (1H, d, J=1Hz)

15 [0161]

Reference Example 36

1-[(2-Pyrazinylcarbonyl)amino]cyclohexanecarboxylic acid



[0162]

20 476 mg (1.8 mmol) of 1-[(2-pyrazinylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcabonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to

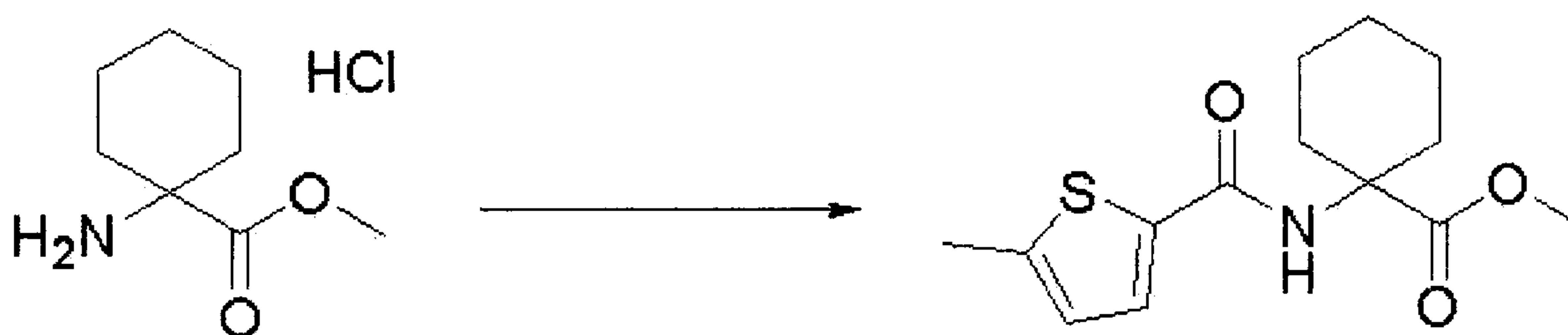
obtain 356 mg (79%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.28-1.59 (6H, m), 1.79 (2H, td, J=12Hz, 4Hz), 2.10-2.19 (2H, m), 8.35 (1H, s), 8.75 (1H, d, J=2Hz), 8.89 (1H, d, J=2Hz), 9.14 (1H, d, J=2Hz), 12.42 (1H, s)

[0163]

Reference Example 37

1-[[(5-Methyl-2-thienyl) carbonyl] amino] cyclohexanecarboxylic acid methyl ester



[0164]

427 mg (3 mmol) of 5-methyl-2-thiophenecarboxylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 812 mg (96%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.36-1.72 (6H, m), 1.92 (2H, td, J=13Hz, 4Hz), 2.11-2.19 (2H, m), 2.51 (3H, s), 3.73 (3H, s), 5.95 (1H, s), 6.74 (1H, d, J=4Hz), 7.34 (1H, d, J=4Hz)

[0165]

Reference Example 38

1-[[(5-Methyl-2-thienyl) carbonyl] amino] cyclohexanecarboxylic acid



[0166]

812 mg (2.9 mmol) of 1-[[(5-methyl-2-

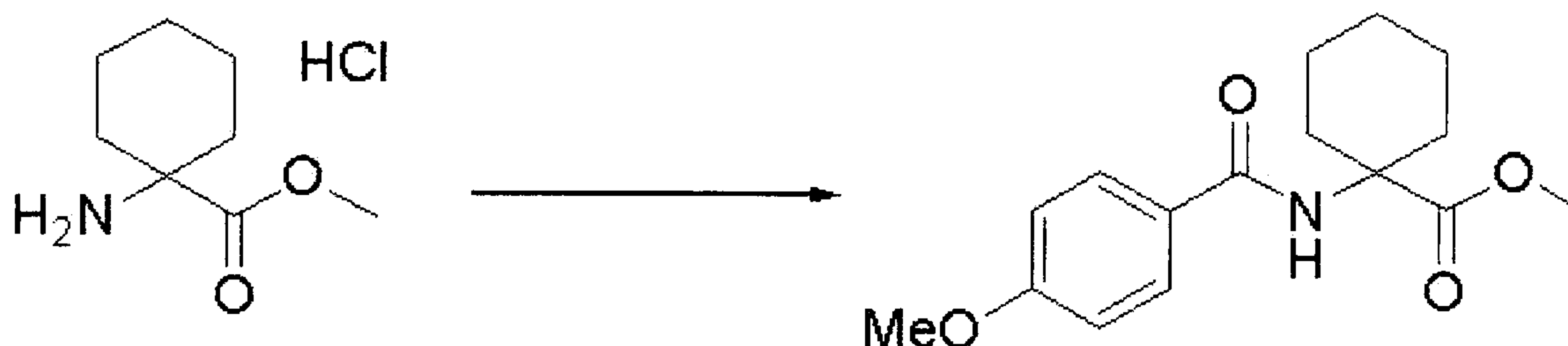
thienyl)carbonyl]amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 771 mg (99%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.21-1.38 (1H, m), 1.52 (5H, br-s), 1.68-1.80 (2H, m), 2.01-2.12 (2H, m), 2.46 (3H, s), 6.84 (1H, d, J=4Hz), 7.70 (1H, s), 8.02 (1H, s)

[0167]

10 Reference Example 39

1-[[(4-Methoxyphenyl) carbonyl] amino]cyclohexanecarboxylic acid methyl ester



[0168]

15 581 mg (3 mmol) of 1-aminocyclohexanecarboxylic acid methyl ester hydrochloride was used instead of 1-aminocyclohexanecarboxylic acid phenylmethyl ester, and 512 mg (3 mmol) of 4-methoxybenzoyl chloride was used instead of phenylacetyl chloride in the process according to Reference Example 1 to obtain 619 mg (71%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.32-1.41 (1H, m), 1.49-1.74 (5H, m), 1.94 (2H, td, J=13Hz, 4Hz), 2.12-2.22 (2H, m), 3.73 (3H, s), 3.85 (3H, s), 6.16 (1H, br-s), 6.92 (2H, dd, J=7Hz, 2Hz), 7.76 (2H, dd, J=7Hz, 2Hz)

[0169]

Reference Example 40

1-[[(4-Methoxyphenyl) carbonyl] amino]cyclohexanecarboxylic acid



[0170]

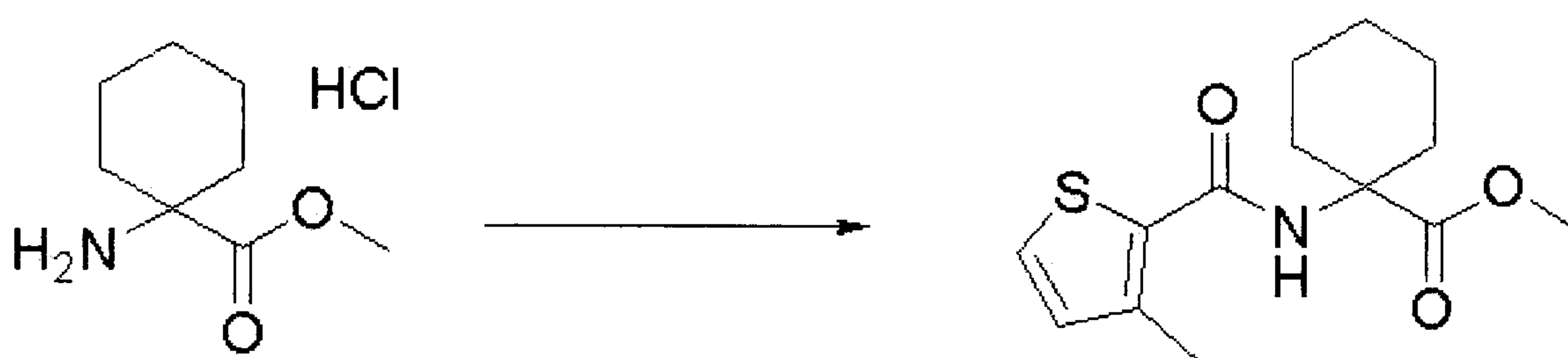
619 mg (2.1 mmol) of 1-[[[(4-methoxyphenyl)carbonyl]amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[[[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 552 mg (94%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.22-1.38 (1H, m), 1.51-1.60 (5H, br-s), 1.65-1.79 (2H, m), 2.04-2.19 (2H, m), 3.81 (3H, s), 6.98 (2H, d, J=9Hz), 7.83 (2H, d, J=9Hz), 8.04 (1H, s), 12.3 (1H, br-s)

[0171]

Reference Example 41

1-[[[(3-Methyl-2-thienyl)carbonyl]amino]cyclohexanecarboxylic acid methyl ester



[0172]

581 mg (3 mmol) of 1-aminocyclohexanecarboxylic acid methyl ester hydrochloride was used instead of 1-aminocyclohexanecarboxylic acid phenylmethyl ester, and 482 mg (3 mmol) of 3-methyl-2-thiophenecarbonyl chloride was used instead of phenylacetyl chloride in the process according to Reference Example 1 to obtain 394 mg (47%) of

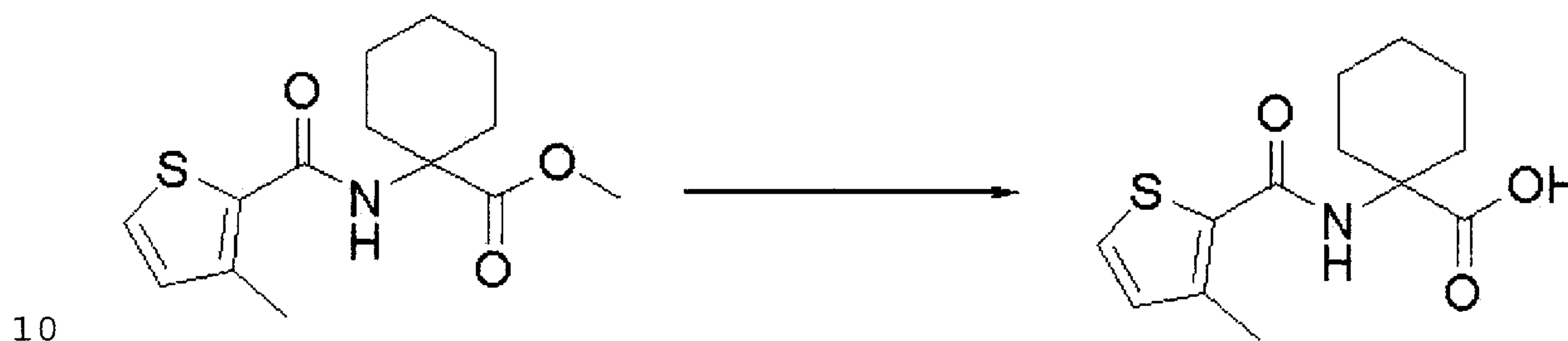
the title compound.

¹H-NMR (CDCl₃, δ): 1.32-1.42 (1H, m), 1.49-1.53 (2H, m),
1.70-1.72 (3H, m), 1.92 (2H, td, J=12Hz, 4Hz), 2.11-2.22
(2H, m), 2.36 (3H, s), 3.74 (3H, s), 6.33 (1H, d, J=2Hz),
5 6.44 (1H, br-s), 7.30 (1H, d, J=2Hz)

[0173]

Reference Example 42

1-[[(3-Methyl-2-
thienyl) carbonyl] amino] cyclohexanecarboxylic acid



[0174]

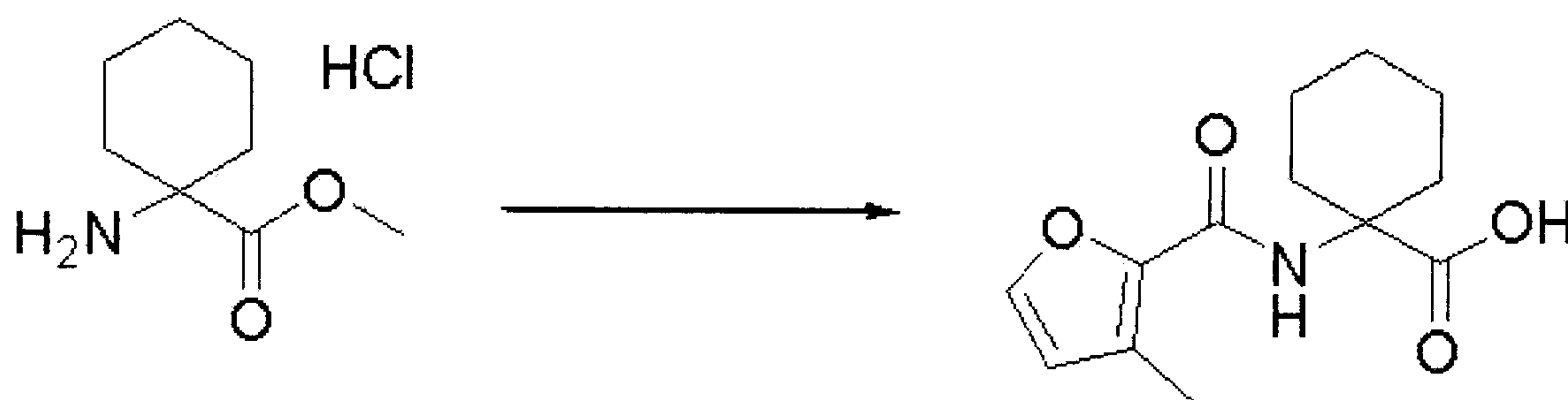
394 mg (1.4 mmol) of 1-[[(3-methyl-2-
thienyl) carbonyl] amino] cyclohexanecarboxylic acid methyl
ester was used instead of 1-[(3-
15 furanyl carbonyl) amino] cyclohexanecarboxylic acid methyl
ester in the process according to Reference Example 16 to
obtain 330 mg (88%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.36-1.53 (3H, m), 1.68-1.78 (3H, m),
1.96-2.05 (2H, m), 1.99-2.08 (2H, m), 2.55 (3H, s), 5.91
20 (1H, s), 6.94 (1H, d, J=5Hz), 7.35 (1H, d J=5Hz)

[0175]

Reference Example 43

1-[[(3-Methyl-2-
furanyl) carbonyl] amino] cyclohexanecarboxylic acid



[0176]

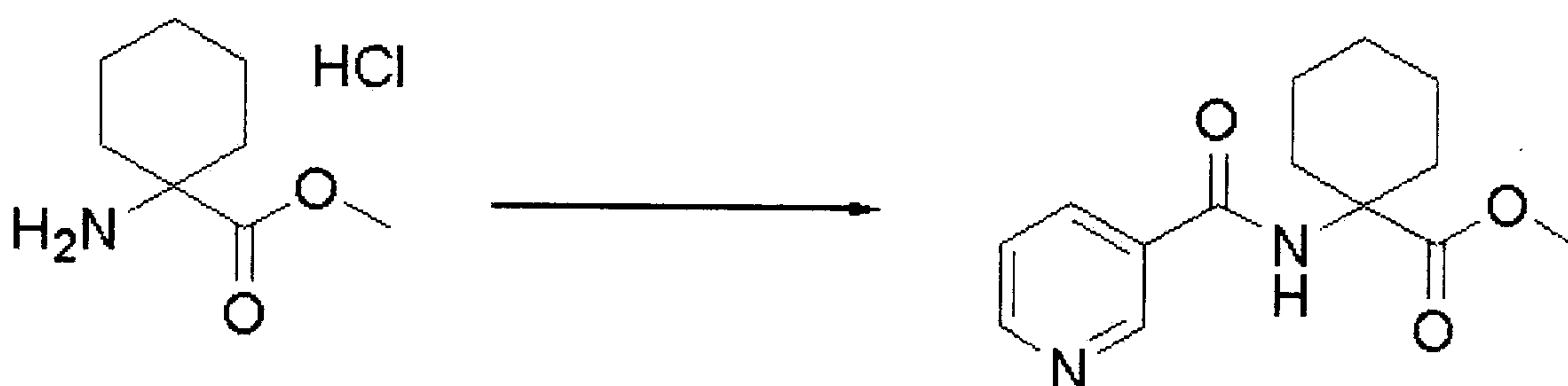
756 mg (6 mmol) of 3-methyl-2-furancarboxylic acid was used instead of 3-ethoxy-2-thiophenecarboxylic acid in the process according to Reference Example 32 to obtain 902 mg (59%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.20-1.38 (1H, m), 1.40-1.59 (5H, m), 1.70-1.80 (2H, m), 2.02-2.18 (2H, m), 2.25 (3H, s), 6.50 (1H, d, J=1Hz), 7.67 (1H, s), 7.68 (1H, d, J=1Hz)

10 [0177]

Reference Example 44

1-[(3-Pyridinylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester



15 [0178]

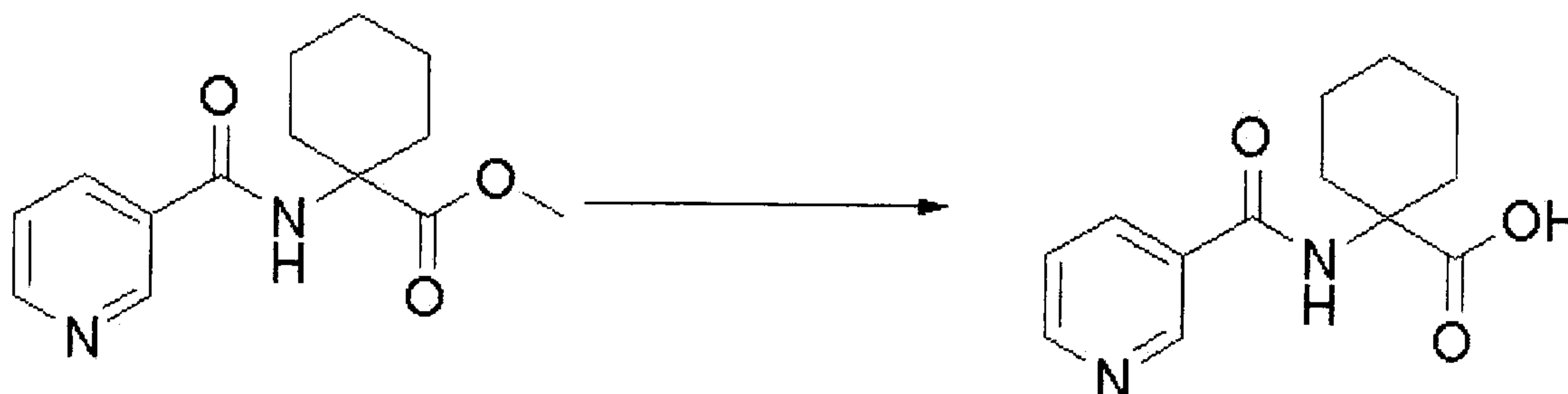
370 mg (3 mmol) of 3-pyridinecarboxylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 539 mg (68%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.32-1.42 (1H, m), 1.45-1.55 (2H, m), 1.62-1.78 (3H, m), 1.92-2.01 (2H, m), 2.12-2.21 (2H, m), 3.75 (3H, s), 6.27 (1H, s), 7.40 (1H, dd, J=8Hz, 5Hz), 8.12 (1H, d, J=8Hz), 8.74 (1H, d, J=5Hz), 9.00 (1H, s)

[0179]

Reference Example 45

1-[(3-Pyridinylcarbonyl)amino]cyclohexanecarboxylic acid



[0180]

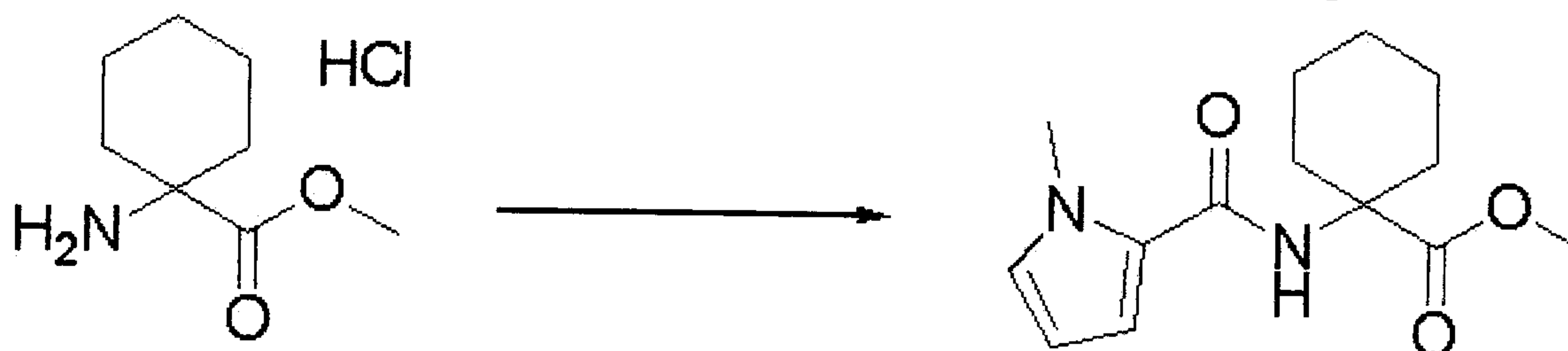
5 539 mg (2 mmol) of 1-[(3-pyridinylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to
 10 obtain 508 mg (quantitative) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.22-1.35 (1H, m), 1.49-1.62 (5H, m), 1.69-1.82 (2H, m), 2.09-2.17 (2H, m), 7.50 (1H, dd, J=8Hz, 5Hz), 8.16 (1H, d, J=8Hz), 8.44 (1H, s), 8.71 (1H, d, J=5Hz), 8.97 (1H, s), 12.24 (1H, br-s)

15 [0181]

Reference Example 46

1-[[[(1-Methyl-1H-pyrrol-2-yl)carbonyl]amino]cyclohexanecarboxylic acid methyl ester



20 [0182]

375 mg (3 mmol) of 1-methyl-2-pyrrolicarboxylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 320 mg (40%) of the title compound.

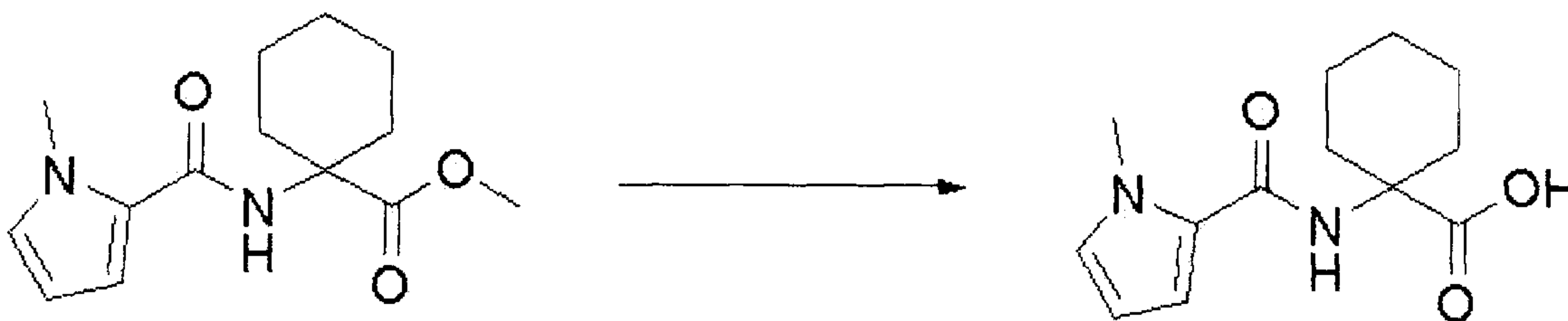
25 ¹H-NMR (CDCl₃, δ): 1.28-1.40 (1H, m), 1.44-1.55 (2H, m),

1.61-1.74 (3H, m), 1.86-1.95 (2H, m), 2.05-2.16 (2H, m),
 3.73 (3H, s), 3.89 (3H, s), 5.97 (1H, s), 6.09 (1H, dd,
 J=4Hz, 3Hz), 6.59 (1H, dd, J=4Hz, 2Hz), 6.71 (1H, dd,
 J=3Hz, 2Hz)

5 [0183]

Reference Example 47

1-[[[(1-Methyl-1H-pyrrol-2-yl)carbonyl]amino]cyclohexanecarboxylic acid



10 [0184]

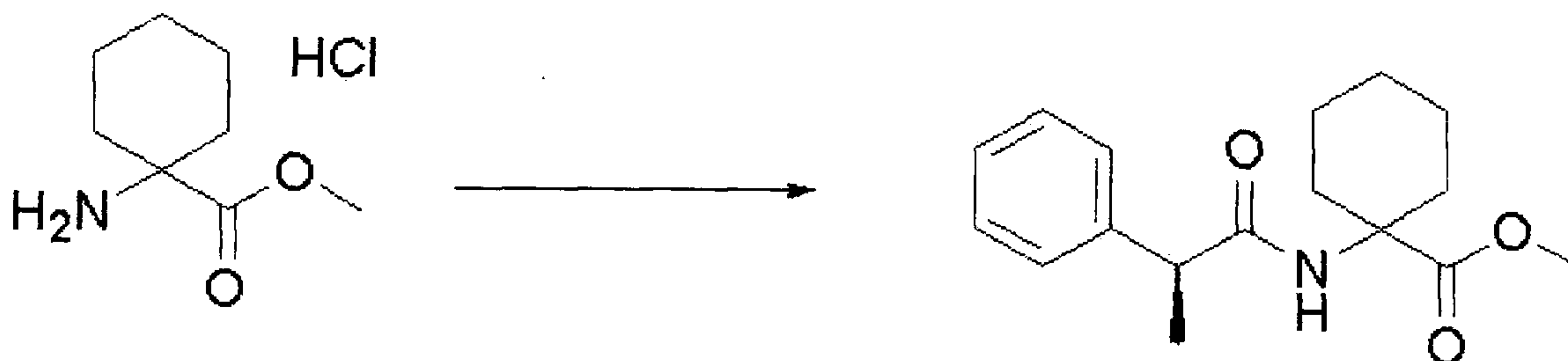
320 mg (1.2 mmol) of 1-[[[(1-methyl-1H-pyrrol-2-yl)carbonyl]amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcabonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 187 mg (62%) of the title compound.

1H-NMR (CDCl₃, δ): 1.31-1.53 (3H, m), 1.62-1.79 (3H, m),
 1.91-2.02 (2H, m), 2.18-2.24 (2H, m), 3.93 (3H, s), 5.92
 (1H, s), 6.14 (1H, dd, J=4Hz, 3Hz), 6.68 (1H, dd, J=4Hz,
 20 2Hz), 6.81 (1H, dd, J=3Hz, 2Hz)

[0185]

Reference Example 48

1-[[[(R)-1-Oxo-2-phenylpropyl]amino]cyclohexanecarboxylic acid methyl ester



25

[0186]

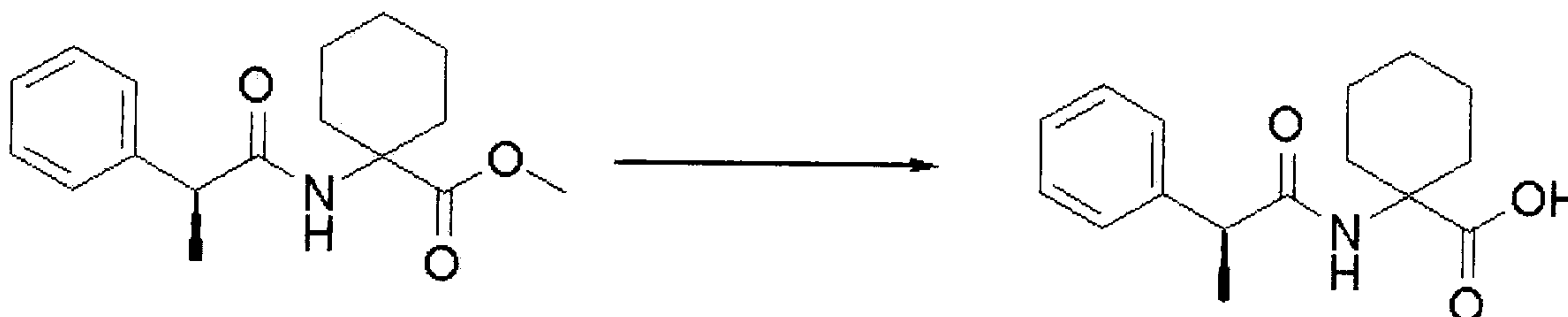
451 mg (3 mmol) of (R)-(-)-2-phenylpropionic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 435 mg (50%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.03-1.22 (3H, m), 1.48-1.62 (6H, m), 1.88-2.00 (2H, m), 3.60 (3H, q, J=7Hz), 3.68 (3H, s), 5.40 (1H, br-s), 7.27-7.39 (5H, m)

[0187]

10 Reference Example 49

1-[(R)-1-Oxo-2-phenylpropyl)amino]cyclohexanecarboxylic acid



[0188]

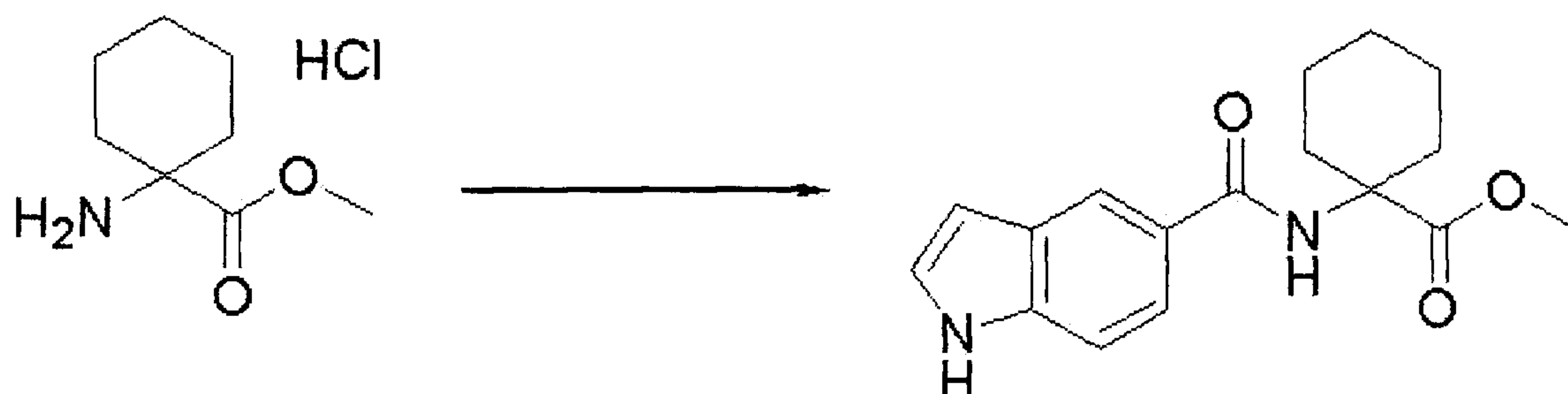
15 435 mg (1.5 mmol) of 1-[(R)-1-oxo-2-phenylpropyl)amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcabonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 349 mg (84%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.15-1.23 (2H, m), 1.29 (3H, d, J=7Hz), 1.35-1.53 (4H, m), 1.53-1.63 (2H, m), 1.91 (2H, br-s), 3.78 (1H, q, J=7Hz), 7.18-7.20 (1H, m), 7.21-7.32 (4H, m), 7.90 (1H, s), 12.00 (1H, s)

25 [0189]

Reference Example 50

1-[(1H-Indol-5-ylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester



[0190]

483 mg (3 mmol) of indole-5-carboxylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 766 mg (85%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.16-1.33 (1H, m), 1.54-1.63 (5H, m), 1.75-1.80 (2H, m), 2.04-2.18 (2H, m), 3.33 (3H, s), 6.52-6.56 (1H, m), 7.40 (1H, s), 7.41-7.44 (1H, m), 7.60 (1H, dd, J=9Hz, 2Hz), 8.14 (1H, d, J=2Hz), 8.18 (1H, s), 11.32 (1H, s)

[0191]

Reference Example 51

1-[(1H-Indol-5-ylcarbonyl)amino]cyclohexanecarboxylic acid



[0192]

766 mg (2.6 mmol) of 1-[(1H-indol-5-ylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcabonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 561 mg (77%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.22-1.38 (1H, m), 1.55-1.62 (5H, m), 1.63-1.79 (2H, m), 2.10-2.22 (2H, m), 6.54 (1H, d, J=3Hz), 7.40-7.43 (2H, m), 7.60 (1H, dd, J=3Hz, 1Hz), 8.03 (1H, s),

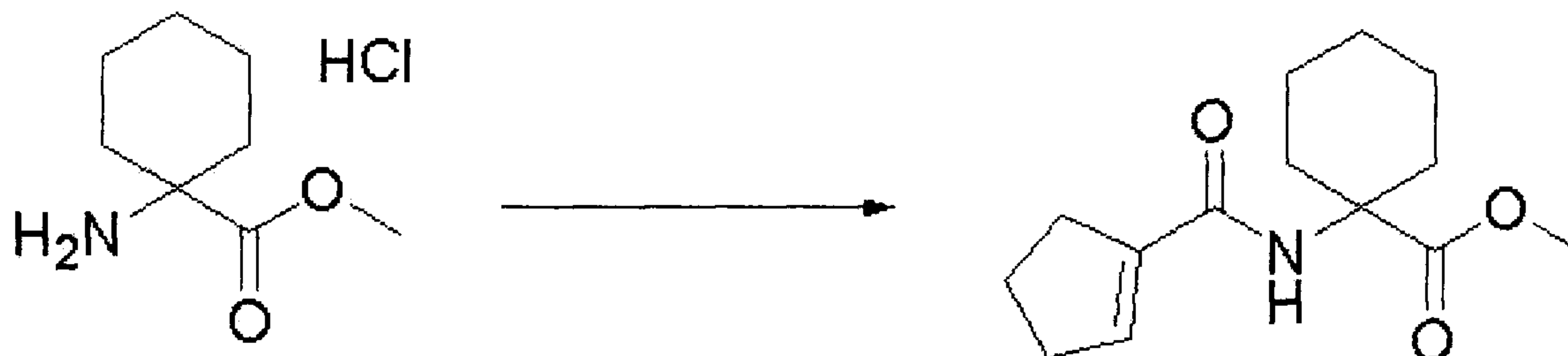
8.14 (1H, s), 11.31 (1H, s), 12.04 (1H, s)

[0193]

Reference Example 52

1-[(1-Cyclopentenylcarbonyl)amino]cyclohexanecarboxylic

5 acid methyl ester



[0194]

336 mg (3 mmol) of 1-cyclopentenecarboxylic acid was used instead of 3-furancarboxylic acid in the process

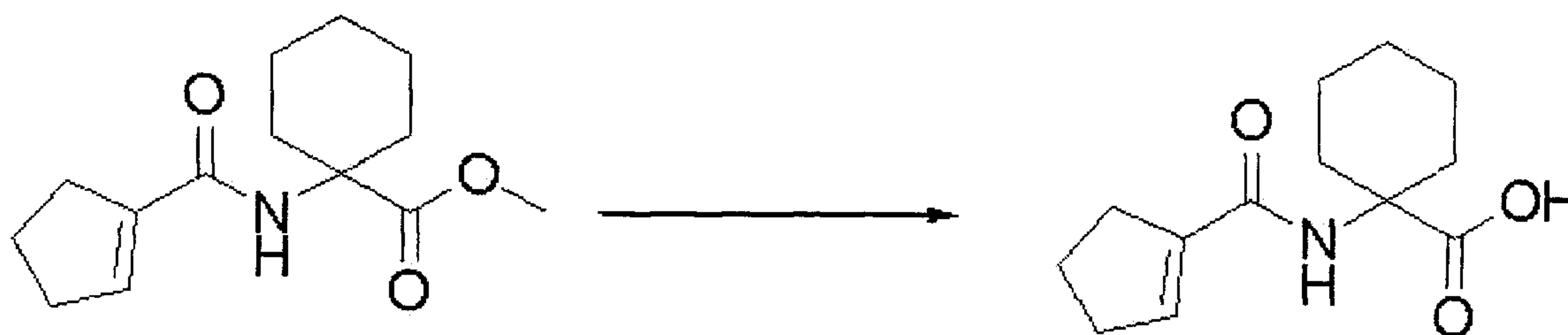
10 according to Reference Example 15 to obtain 717 mg (95%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.34-1.44 (2H, m), 1.60-1.70 (4H, m), 1.87 (2H, td, J=9Hz, 4Hz), 1.99-2.09 (4H, m), 2.49 (2H, m), 2.58 (2H, m), 3.72 (3H, s), 5.75 (1H, br-s), 6.55 (1H, t, J=2Hz)

[0195]

Reference Example 53

1-[(1-Cyclopentenylcarbonyl)amino]cyclohexanecarboxylic acid



[0196]

717 mg (2.9 mmol) of 1-[(1-cyclopentenylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl

ester in the process according to Reference Example 16 to obtain 588 mg (87%) of the title compound.

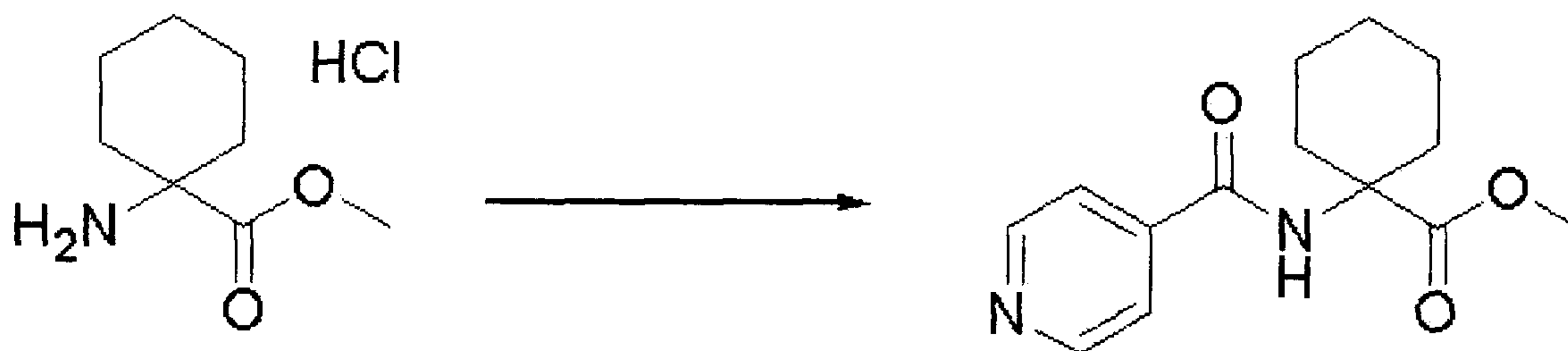
¹H-NMR (DMSO-d₆, δ): 1.24 (1H, d, J=8Hz), 1.40-1.50 (5H, m), 1.67 (2H, td, J=10Hz, 9Hz), 1.81-1.89 (2H, m), 1.91-2.09 (2H, m), 2.40-2.50 (4H, m), 6.53 (1H, t, J=3Hz), 7.46 (1H, s), 12.03 (1H, s)

[0197]

Reference Example 54

1-[(4-Pyridinylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester

[0198]



[0199]

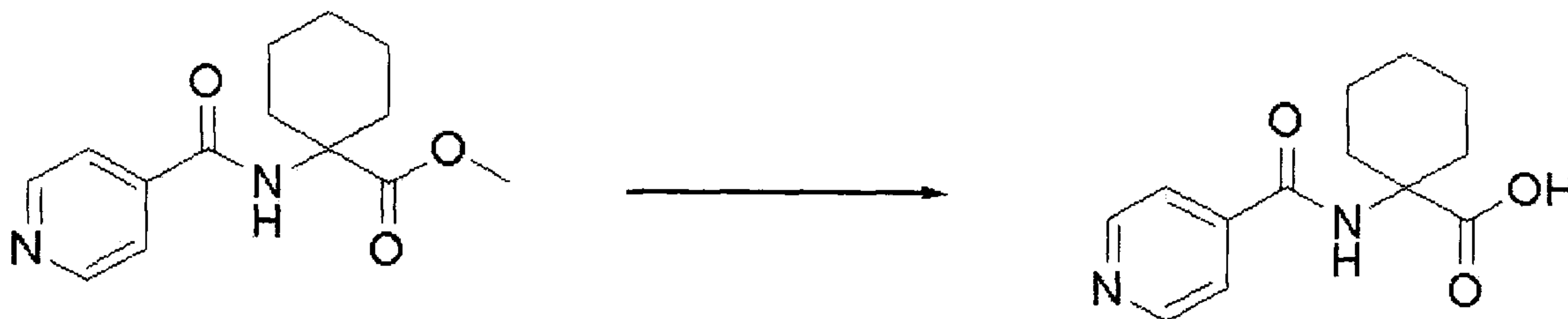
370 mg (3 mmol) of 4-pyridinecarboxylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 609 mg (77%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.32-1.53 (3H, m), 1.62-1.77 (3H, m), 1.92-2.03 (2H, m), 2.13-2.21 (2H, m), 3.75 (3H, s), 6.29 (1H, br-s), 7.62 (2H, dd, J=5Hz, 2Hz), 8.76 (2H, dd, J=5Hz, 2Hz)

[0200]

Reference Example 55

1-[(4-Pyridinylcarbonyl)amino]cyclohexanecarboxylic acid



25

[0201]

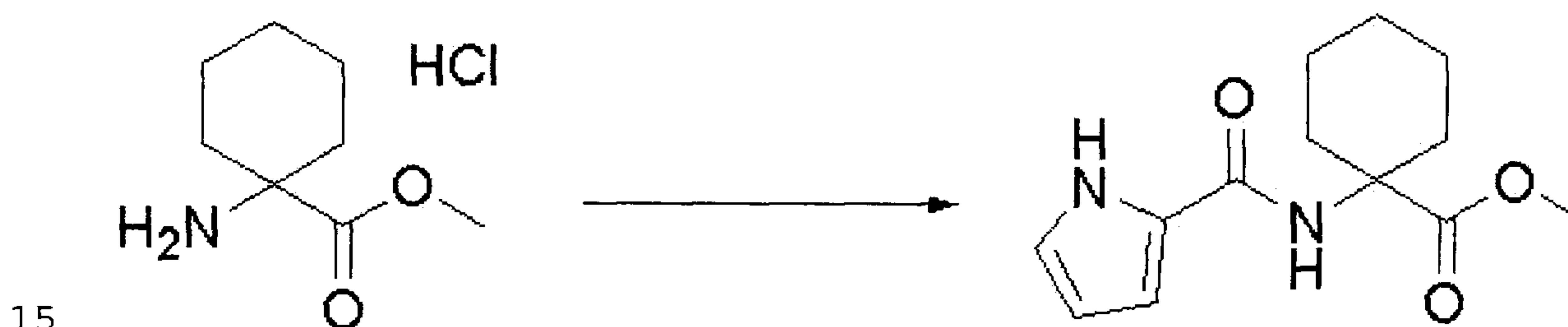
609 mg (2.3 mmol) of 1-[(4-pyridinylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 522 mg (97%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.22-1.33 (1H, m), 1.46-1.59 (5H, m), 1.70-1.80 (2H, m), 2.09-2.15 (2H, m), 7.73 (2H, dd, J=5Hz, 2Hz), 8.51 (1H, s), 8.72 (2H, dd, J=5Hz, 2Hz)

[0202]

Reference Example 56

1-[(1H-Pyrrol-2-ylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester



[0203]

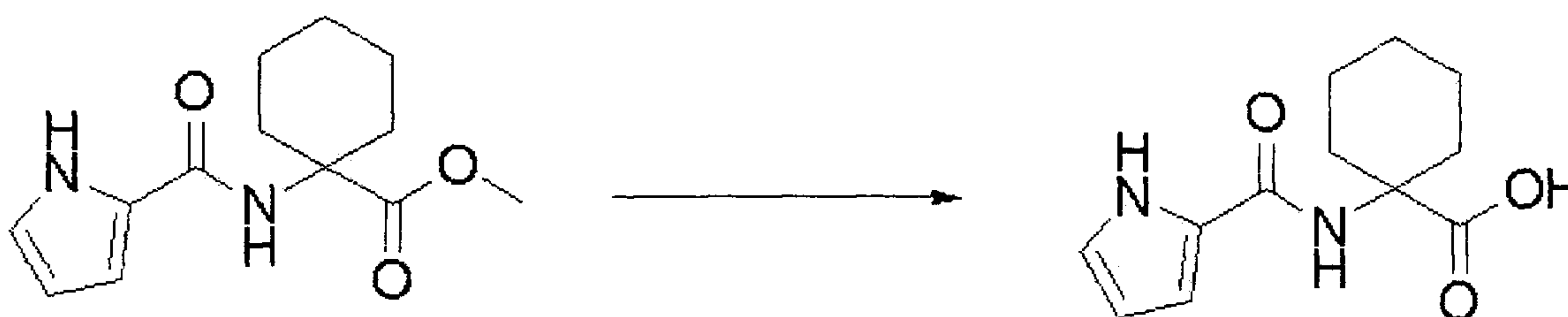
278 mg (2.5 mmol) of 2-pyrrolicarboxylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 534 mg (85%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.32-1.45 (2H, m), 1.45-1.53 (2H, m), 1.62-1.72 (2H, m), 1.93 (2H td, J=13Hz, 4Hz), 2.08-2.19 (2H, m), 3.70 (3H, s), 6.05 (1H, br-s), 6.23-6.25 (1H, m), 6.61 (1H, d, J=2Hz), 6.94 (1H, d, J=2Hz)

25 [0204]

Reference Example 57

1-[(1H-Pyrrol-2-ylcarbonyl)amino]cyclohexanecarboxylic acid



[0205]

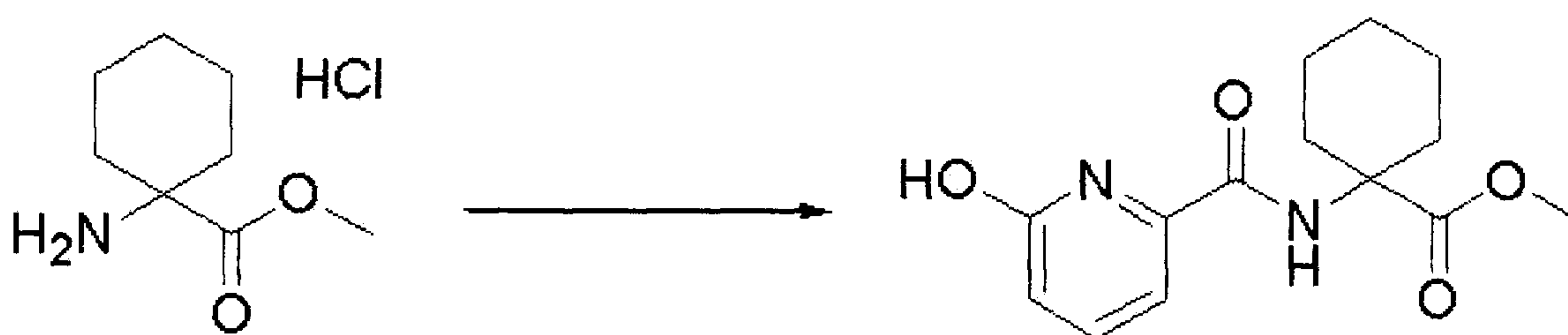
500 mg (2 mmol) of 1-[[[(1H-pyrrol-2-yl)carbonyl]amino]cyclohexanecarboxylic acid methyl ester
 5 was used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 338 mg (71%) of the title compound.

1H-NMR (DMSO-d₆, δ): 1.20-1.31 (1H, m), 1.52 (5H, br-s),
 10 1.70-1.80 (2H, m), 2.04-2.18 (2H, m), 6.08 (1H, dd, J=4Hz, 2Hz), 6.85-6.89 (2H, m), 7.59 (1H, s), 11.39 (1H, s), 12.09 (1H, br-s)

[0206]

Reference Example 58

15 1-[[[(6-Hydroxy-2-pyridinyl)carbonyl]amino]cyclohexanecarboxylic acid methyl ester



[0207]

20 1.39 g (10 mmol) of 6-hydroxy-2-pyridinecarboxylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 1.32 g (47%) of the title compound.

1H-NMR (CDCl₃, δ): 1.30-1.42 (1H, m), 1.65 (5H, m), 1.96
 25 (2H, td, J=12Hz, 4Hz), 2.10-2.21 (2H, m), 3.73 (3H, s),

6.71 (1H, d, J=9Hz), 7.20 (1H, d, J=7Hz), 7.62 (1H, dd, J=9Hz, 7Hz), 8.00 (1H, s)

[0208]

Reference Example 59

5 1-[[(6-Hydroxy-2-pyridinyl)carbonyl]amino]cyclohexanecarboxylic acid



[0209]

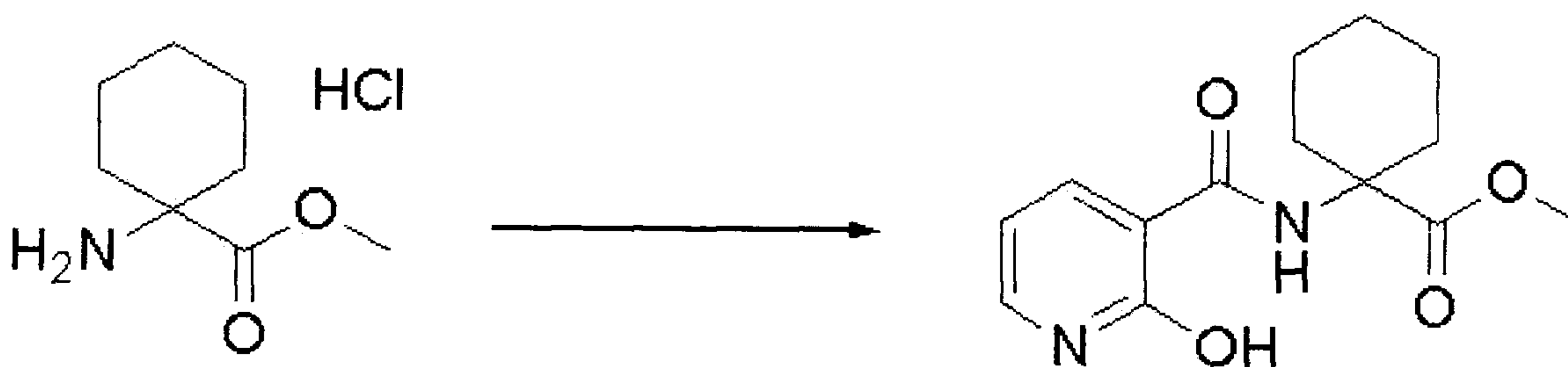
1.32 mg (4.7 mmol) of 1-[[(6-hydroxy-2-pyridinyl)carbonyl]amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 1.16 g (88%) of the title compound.

15 ¹H-NMR (DMSO-d₆, δ): 1.39-1.50 (1H, m), 1.39-1.50 (2H, m), 1.51-1.63 (3H, m), 1.70-1.82 (2H, m), 2.01-2.12 (2H, d, m), 6.78 (1H, d, J=8Hz), 7.32 (1H, br-s), 7.74 (1H, t, J=8Hz), 8.18 (1H, s)

[0210]

20 Reference Example 60

1-[[(2-Hydroxy-3-pyridinyl)carbonyl]amino]cyclohexanecarboxylic acid methyl ester



25 [0211]

1.39 g (10 mmol) of 2-hydroxynicotinic acid was used

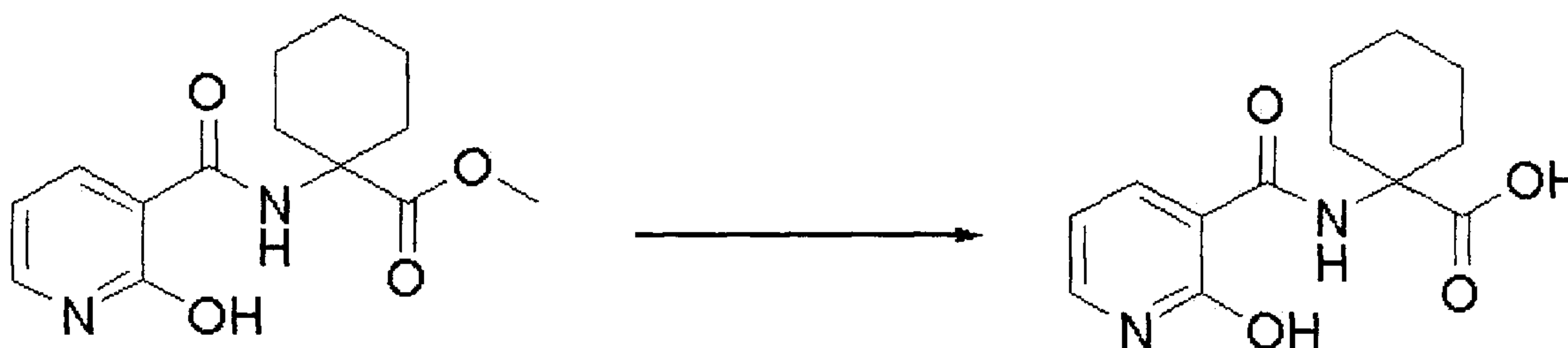
instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 697 mg (25%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.24-1.38 (1H, m), 1.50-1.62 (2H, m),
 5 1.64-1.74 (3H, m), 1.82-1.93 (2H, m), 2.15-2.24 (2H, m),
 3.74 (3H, s), 6.53 (1H, t, J=7Hz), 7.49 (1H, d, J=7Hz),
 8.57 (1H, d, J=7Hz), 10.04 (1H, s)

[0212]

Reference Example 61

10 1-[[(2-Hydroxy-3-pyridinyl)carbonyl]amino]cyclohexanecarboxylic acid



[0213]

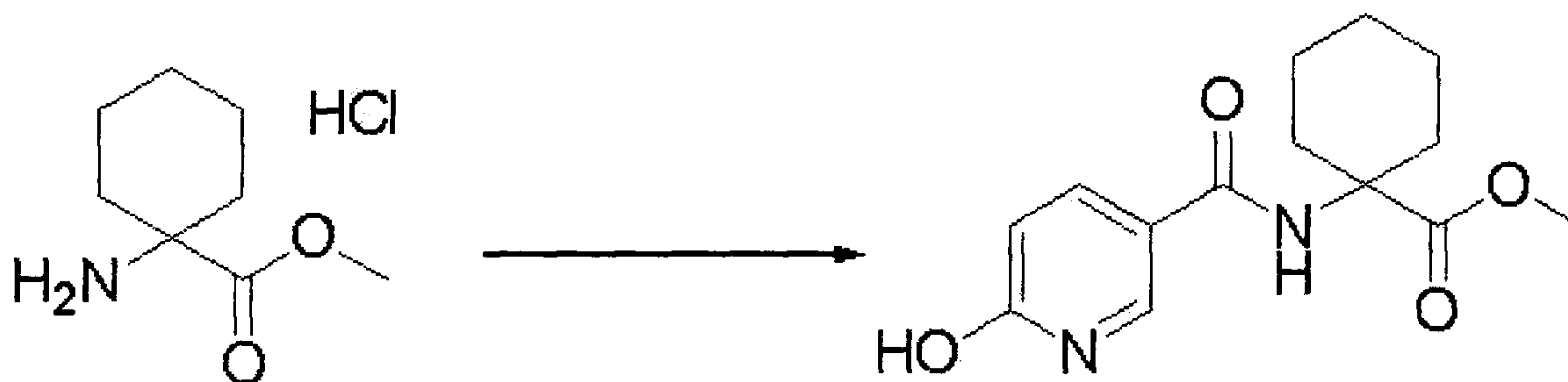
698 mg (2.5 mmol) of 1-[[(2-hydroxy-3-pyridinyl)carbonyl]amino]cyclohexanecarboxylic acid methyl
 15 ester was used instead of 1-[[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl
 ester in the process according to Reference Example 16 to
 obtain 580 mg (83%) of the title compound.

20 ¹H-NMR (DMSO-d₆, δ): 1.21-1.31 (1H, m), 1.38-1.41 (2H, m),
 1.59 (3H, d, J=10Hz), 1.67-1.72 (2H, m), 1.98-2.04 (2H, m),
 6.49 (1H, t, J=7Hz), 7.73 (1H, br-s), 8.28 (1H, d, J=7Hz),
 10.21 (1H, s), 12.19 (1H, s), 12.53 (1H, br-s)

[0214]

25 Reference Example 62

1-[[(6-Hydroxy-3-pyridinyl)carbonyl]amino]cyclohexanecarboxylic acid methyl
 ester



[0215]

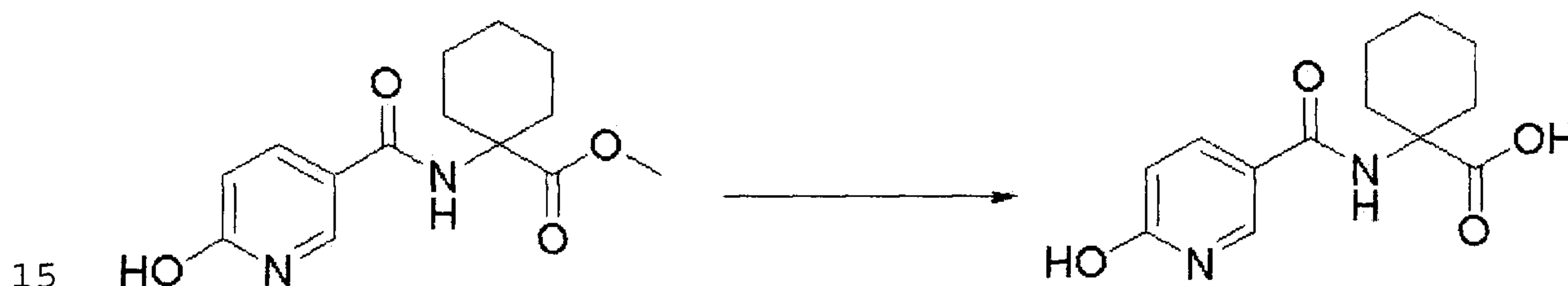
1.39 g (10 mmol) of 6-hydroxynicotinic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 869 mg (31%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.30-1.41 (1H, m), 1.43-1.58 (2H, m), 1.61-1.75 (3H, m), 1.89-1.99 (2H, m), 2.11-2.19 (2H, m), 3.74 (3H, s), 6.43 (1H, s), 6.53 (1H, d, J=10Hz), 7.82 (1H, dd, J=10Hz, 2Hz), 8.05 (1H, d, J=2Hz)

[0216]

Reference Example 63

1-[[6-Hydroxy-3-pyridinyl]carbonyl]amino]cyclohexanecarboxylic acid



[0217]

869 mg (3.1 mmol) of 1-[[6-hydroxy-3-pyridinyl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcabonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 818 mg (94%) of the title compound.

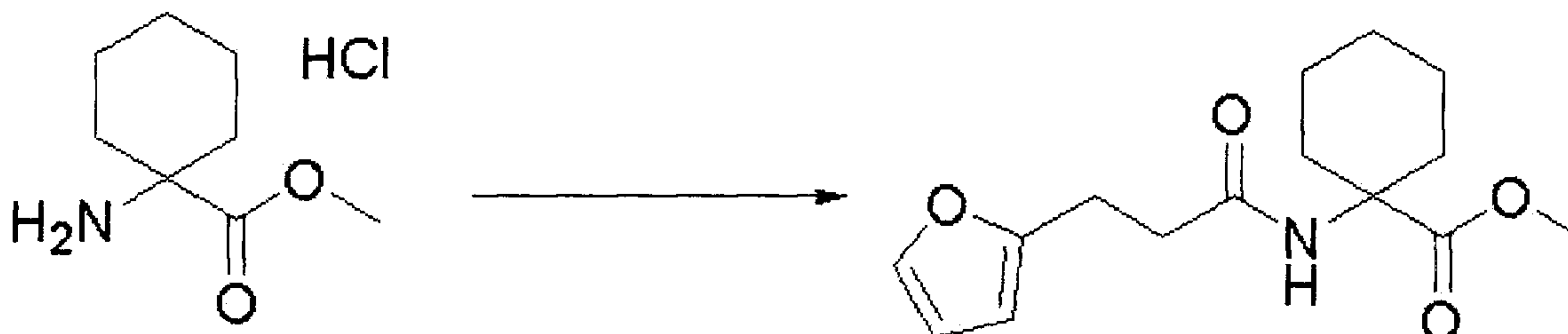
¹H-NMR (DMSO-d₆, δ): 1.19-1.31 (1H, m), 1.42-1.57 (5H, m), 1.67-1.78 (2H, m), 2.01-2.11 (2H, m), 6.34 (1H, d, J=10Hz), 7.84 (1H, dd, J=10Hz, 2Hz), 7.95 (1H, s), 8.05 (1H, d,

J=2Hz), 11.90-12.18 (2H, m)

[0218]

Reference Example 64

1-[[1-Oxo-3-(2-furanyl)propyl]amino]cyclohexanecarboxylic
5 acid methyl ester



[0219]

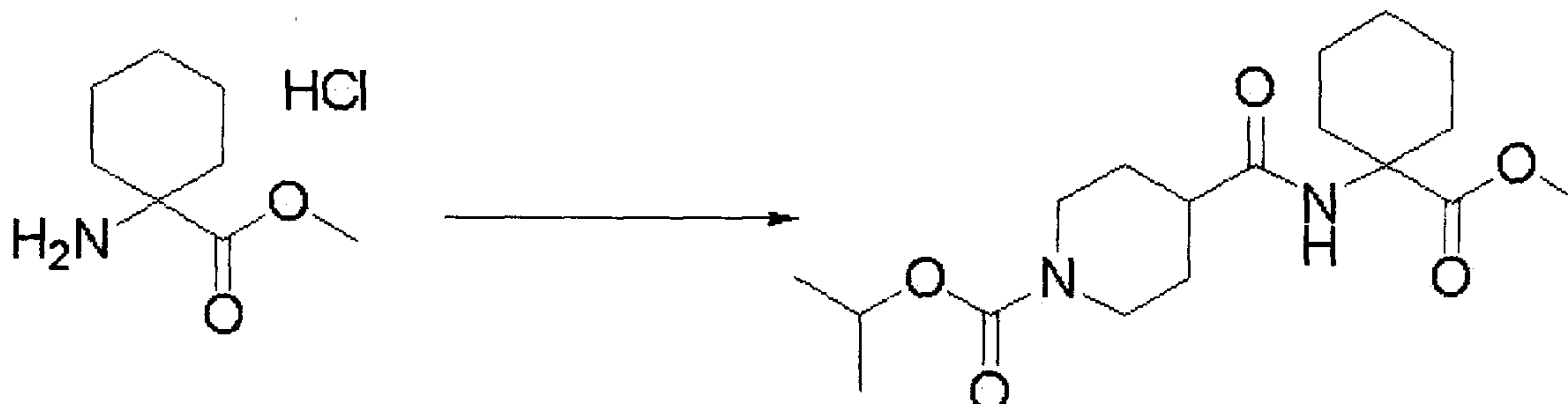
420 mg (3 mmol) of 3-(2-furyl)propionic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 478 mg (57%) of the title
10 compound.

¹H-NMR (CDCl₃, δ): 1.25-1.38 (3H, m), 1.57-1.65 (3H, m), 1.78-1.85 (2H, m), 1.96-2.01 (2H, m), 2.56 (2H, t, J=7Hz), 2.98 (2H, t, J=7Hz), 3.69 (3H, s), 5.56 (1H, br-s), 6.06
15 (1H, dd, J=3Hz, 2Hz), 6.29 (1H, dd, J=3Hz, 2Hz), 7.31 (1H, dd, J=3Hz, 2Hz)

[0220]

Reference Example 65

1-[[[1-(2-Propoxycarbonyl)piperidin-4-yl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester
20



[0221]

646 mg (3 mmol) of 1-(2-propoxycarbonyl)nipecotinic acid was used instead of 3-furancarboxylic acid in the

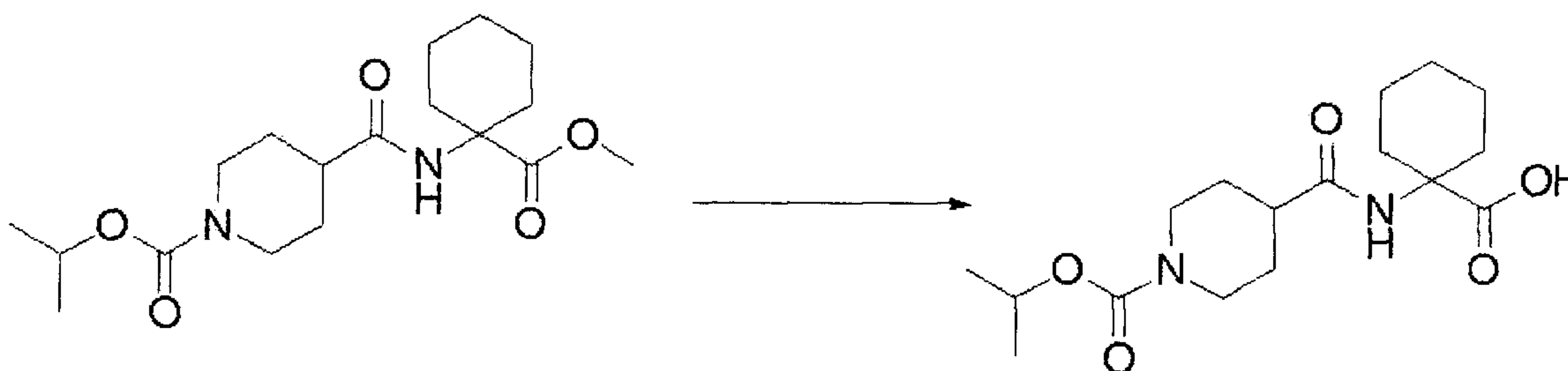
process according to Reference Example 15 to obtain 979 mg (92%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.24 (6H, d, J=6Hz), 1.25-1.44 (3H, m), 1.56-1.70 (5H, m), 1.79-1.90 (4H, m), 1.98-2.07 (2H, m),
 5 2.26-2.34 (1H, m), 2.75-2.88 (2H, m), 3.69 (3H, s), 4.17 (2H, br-s), 4.86-4.96 (1H, m), 5.58 (1H, s)

[0222]

Reference Example 66

1-[[[1-(2-Propoxycarbonyl)piperidin-4-yl]carbonyl]amino]cyclohexanecarboxylic acid
 10



[0223]

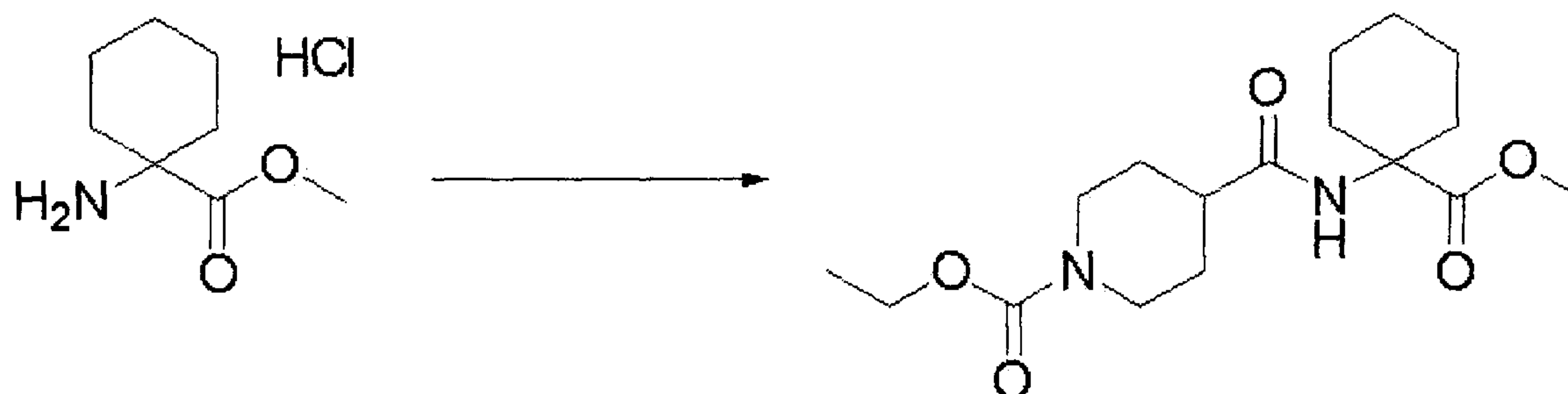
979 mg (2.76 mmol) of 1-[[[1-(2-propoxycarbonyl)piperidin-4-yl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester
 15 was used instead of 1-[(3-furanylcabonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 940 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.23-1.28 (7H, m), 1.34-1.39 (3H, m), 1.62-1.71 (6H, m), 1.85-1.91 (4H, m), 2.05-2.09 (2H, m),
 20 2.33-2.36 (1H, m), 2.74-2.84 (2H, m), 4.21 (1H, br-s), 4.91 (1H, q, J=7Hz), 5.67 (1H, s)

[0224]

25 Reference Example 67

1-[[[1-(Ethoxycarbonyl)piperidin-4-yl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester



[0225]

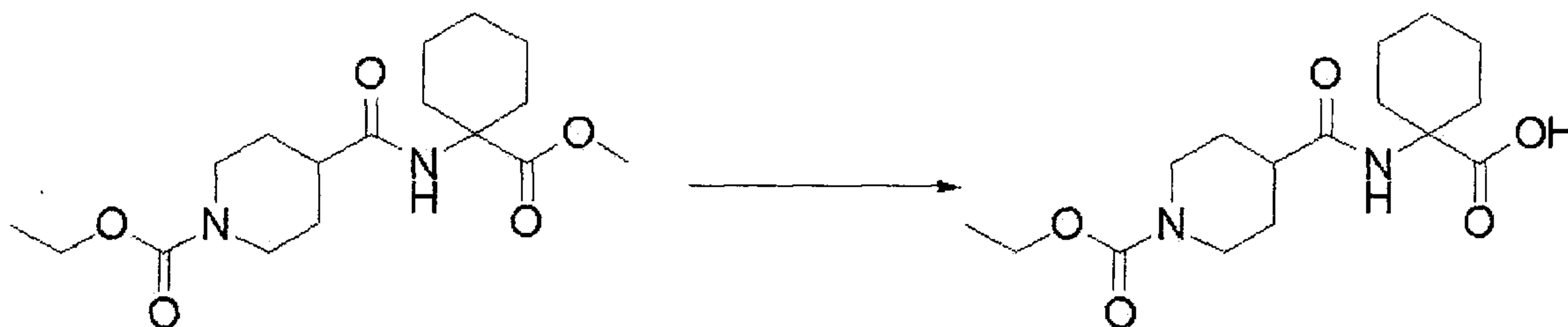
604 mg (3 mmol) of 1-ethoxycarbonylnipecotinic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 976 mg (95%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 1.25-1.42 (3H, m), 1.55-1.70 (3H, m), 1.81-1.86 (4H, m), 2.01-2.05 (3H, m), 2.26-2.32 (1H, m), 2.80-2.89 (2H, m), 3.69 (3H, s), 4.08-4.23 (3H, m), 4.13 (2H, q, J=7Hz), 5.54 (1H, br-s)

[0226]

Reference Example 68

1-[[[1-(Ethoxycarbonyl)piperidin-4-yl]carbonyl]amino]cyclohexanecarboxylic acid



[0227]

976 mg (2.87 mmol) of 1-[[[1-(ethoxycarbonyl)piperidin-4-yl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcabonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 935 mg (quantitative) of the title compound.

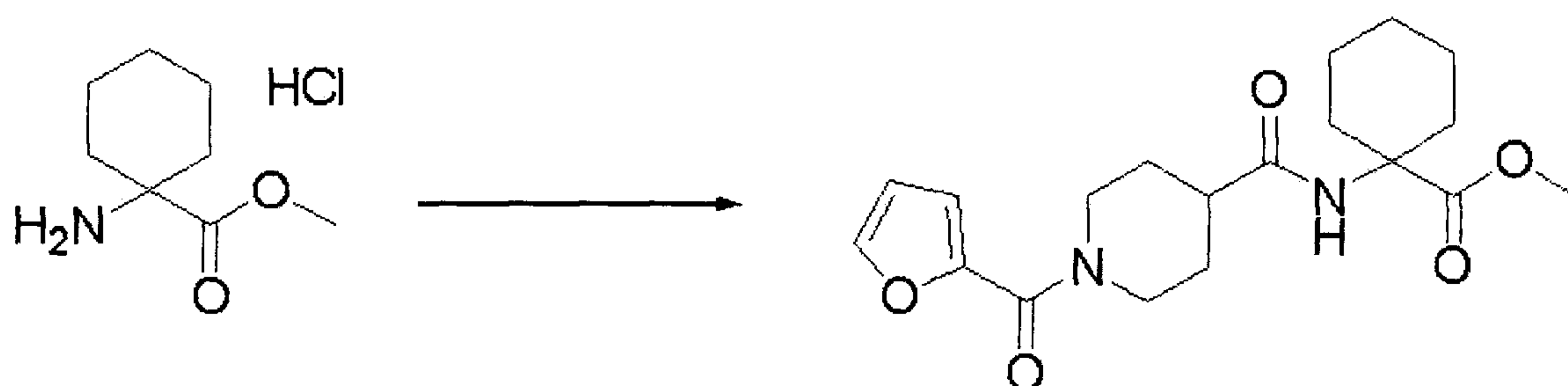
¹H-NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.30-1.42 (3H, m),

1.62-1.72 (5H, m), 1.85-1.91 (4H, m), 2.06-2.09 (2H, m),
2.34-2.39 (1H, m), 2.79-2.90 (2H, m), 4.10-4.25 (3H, m),
4.13 (2H, q, J=7Hz), 5.69 (1H, s)

[0228]

5 Reference Example 69

1-[[[1-(2-Furanylcarbonyl)piperidin-4-yl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester



[0229]

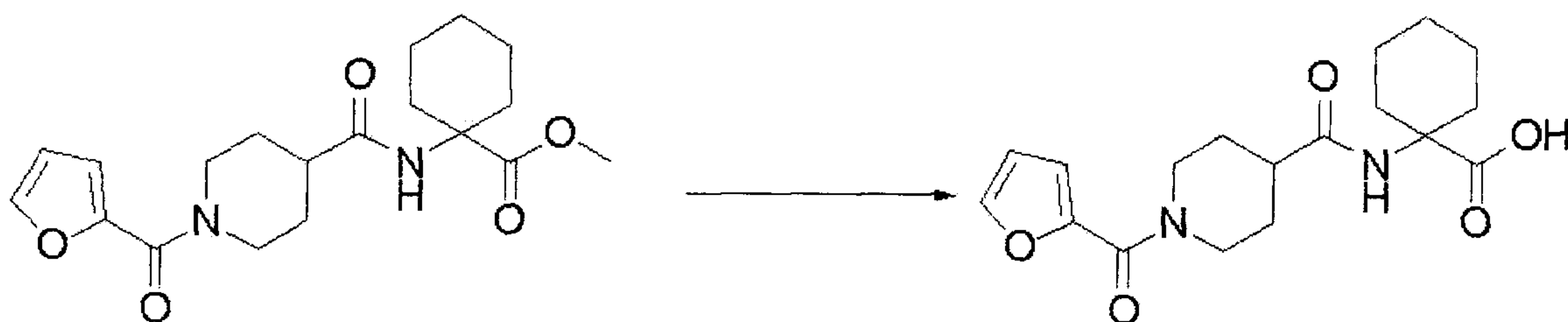
10 670 mg (3 mmol) of 1-(2-furanylcarbonyl)piperidine-4-carboxylic acid was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 910 mg (80%) of the title compound.

1H-NMR (CDCl₃, δ): 1.30-1.43 (3H, m), 1.53-1.69 (3H, m),
15 1.74-1.90 (4H, m), 1.91-2.05 (4H, m), 2.43-2.48 (1H, m),
2.89-3.21 (2H, m), 3.79 (3H, s), 4.40-4.56 (2H, m), 5.58
(1H, br-s), 6.47 (1H, dd, J=3Hz, 1Hz), 6.95 (1H, dd, J=3Hz,
1Hz), 7.48 (1H, dd, J=3Hz, 1Hz)

[0230]

20 Reference Example 70

1-[[[1-(2-Furanylcarbonyl)piperidin-4-yl]carbonyl]amino]cyclohexanecarboxylic acid



[0231]

25 910 mg (2.4 mmol) of 1-[[[1-(2-

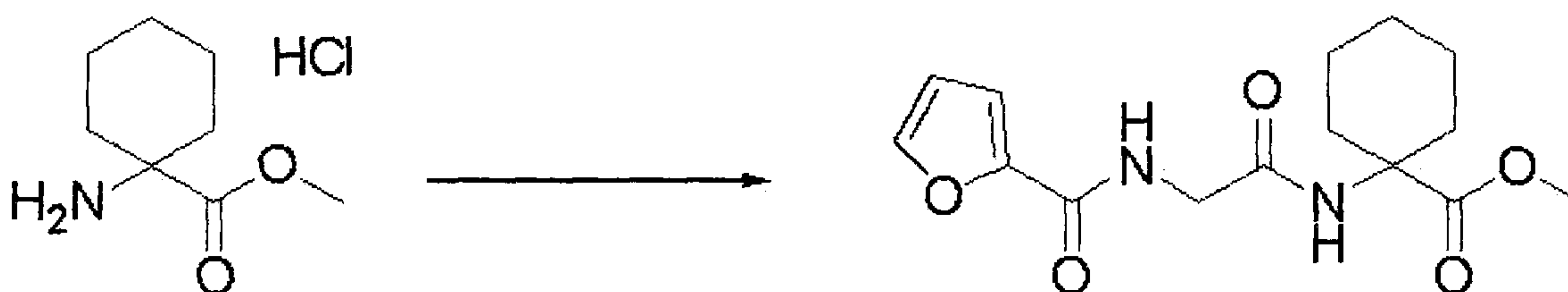
furanylcarbonyl)piperidin-4-yl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 196 mg (23%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.17-1.25 (1H, m), 1.40-1.58 (7H, m), 1.58-1.62 (2H, m), 1.73-1.76 (2H, m), 1.93-1.96 (2H, m), 2.51-2.61 (1H, m), 2.80-3.11 (2H, m), 4.22-4.33 (2H, m), 6.61 (1H, dd, J=3Hz, 1Hz), 6.95 (1H, dd, J=3Hz, 1Hz), 7.78 (1H, s), 7.82 (1H, dd, J=3Hz, 1Hz)

[0232]

Reference Example 71

1-[[[(2-furanylcarbonyl)amino]acetyl]amino]cyclohexanecarboxylic acid methyl ester



[0233]

507 mg (3 mmol) of N-(2-furanylcarbonyl)glycine was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 781 mg (88%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.22-1.38 (1H, m), 1.39-1.50 (2H, m), 1.58-1.69 (3H, m), 1.85 (2H, td, J=9Hz, 4Hz), 2.02-2.10 (2H, m), 3.70 (3H, s), 4.15 (2H, d, J=6Hz), 6.51 (1H, dd, J=2Hz, 1Hz), 6.67 (1H, s), 7.13 (2H, m), 7.47 (1H, dd, J=2Hz, 1Hz)

[0234]

Reference Example 72

1-[[[(2-

Furanylcarbonyl) amino] acetyl] amino] cyclohexanecarboxylic acid



[0235]

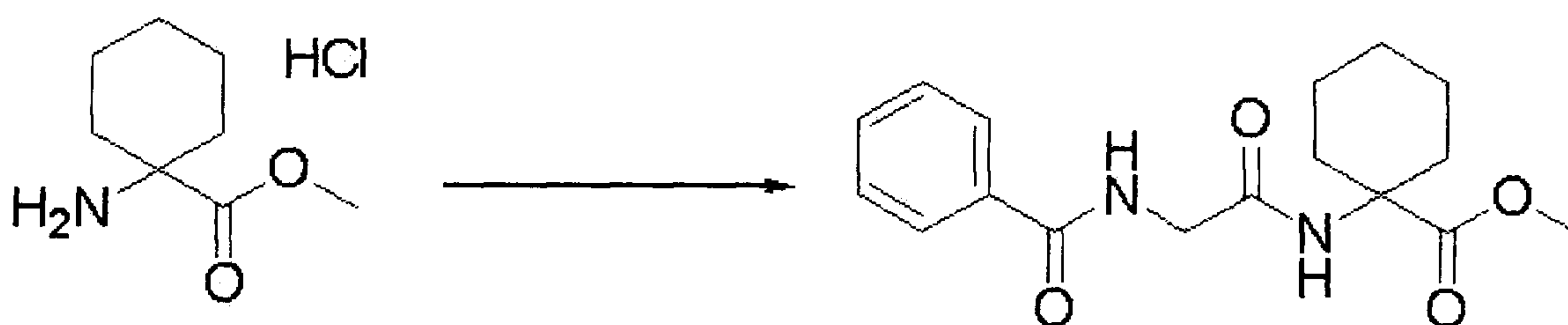
5 781 mg (2.7 mmol) of 1-[[[(2-furanylcarbonyl)amino]acetyl]amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to
10 obtain 320 mg (41%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.12-1.25 (1H, m), 1.39-1.58 (5H, m), 1.64 (2H, td, J=13Hz, 4Hz), 1.90-2.02 (2H, m), 3.88 (2H, d, J=6Hz), 6.62 (1H, dd, J=3Hz, 1Hz), 7.13 (1H, dd, J=3Hz, 1Hz), 7.84 (1H, d, J=1Hz), 7.87 (1H, s), 8.38 (1H, d, J=6Hz)

[0236]

Reference Example 73

1-[[[(Benzoylamino)acetyl]amino]cyclohexanecarboxylic acid methyl ester



[0237]

538 mg (3 mmol) of N-benzoylglycine was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 812 mg (81%) of the title
25 compound.

¹H-NMR (CDCl₃, δ): 1.23-1.38 (1H, m), 1.48 (2H, td, J=9Hz, 4Hz), 1.58-1.71 (3H, m), 1.84 (2H, dt, J=9Hz, 4Hz), 2.02-

2.10 (2H, m), 3.70 (3H, s), 4.21 (2H, d, J=7Hz), 7.08 (1H, br-s), 7.26-7.46 (3H, m), 7.54 (1H, td, J=8Hz, 1Hz), 7.84 (2H, dd, J=8Hz, 1Hz)

[0238]

5 Reference Example 74

1-[[(Benzoylamino)acetyl]amino]cyclohexanecarboxylic acid



[0239]

812 mg (2.4 mmol) of 1-

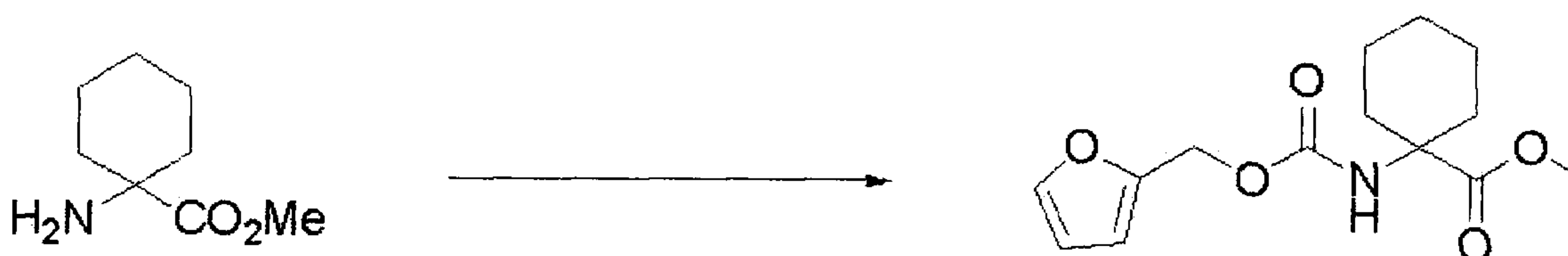
10 [[(benzoylamino)acetyl]amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 16 to obtain 724 mg (93%) of the title compound.

15 ¹H-NMR (DMSO-d₆, δ): 1.09-1.67 (8H, m), 1.96 (2H, d, J=11Hz), 3.93 (2H, d, J=6Hz), 7.47 (2H, td, J=6Hz, 1Hz), 7.52-7.55 (1H, m), 7.86-7.89 (3H, m), 8.64 (1H, t, J=6Hz)

[0240]

Reference Example 75

20 1-[[(2-Furanylmethoxy)carbonyl]amino]cyclohexanecarboxylic acid methyl ester



[0241]

3.67 g (30 mmol) of dimethylaminopyridine was added to a solution of 65.48 g (0.3 mol) of di-*t*-butyl dicarbonate in 300 ml of anhydrous toluene, and the mixture was stirred at room temperature for 15 minutes. A solution

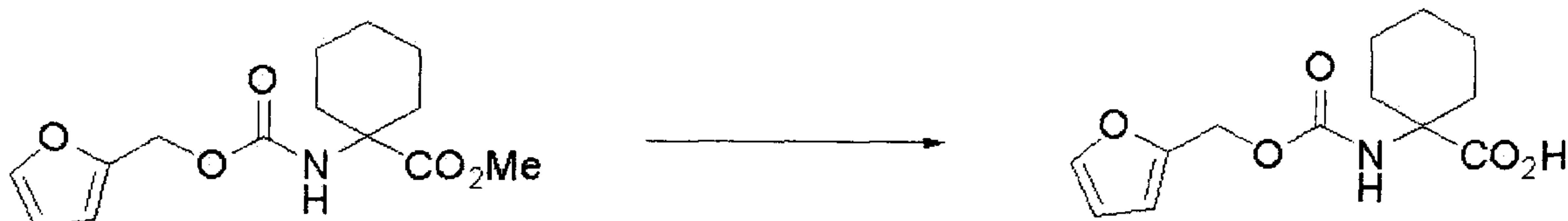
of 47.17 g (0.3 mol) of 1-aminocyclohexanecarboxylic acid methyl ester in 100 ml of anhydrous toluene was added to the reaction solution, and the mixture was stirred at room temperature for 1 hour. Further, after 60.71 g (0.6 mol) of triethylamine and 44.1 g (0.45 mol) of furfuryl alcohol were added, the mixture was heated under reflux for 3 hours. The reaction solution was returned to room temperature and was concentrated under reduced pressure. The obtained residue was crushed by a mortar and stirred in a mixture solution of 5 ml of hydrochloric acid and 3 L of water for 18 hours. The obtained crystal was collected by filtration to obtain 74.37 g (88%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.23-1.36 (1H, m), 1.38-1.51 (2H, m), 1.55-1.65 (3H, m), 1.80-1.88 (2H, m), 1.93-2.04 (2H, m), 3.71 (3H, br-s), 4.93 (1H, br-s), 5.04 (2H, s), 6.36 (1H, dd, J=3Hz, 2Hz), 6.41 (1H, d, J=3Hz), 7.43 (1H, d, J=2Hz)

[0242]

Reference Example 76

1-[[(2-Furanylmethoxy) carbonyl] amino] cyclohexanecarboxylic acid



[0243]

28.13 g (0.1 mol) of 1-[[(2-furanylmethoxy) carbonyl] amino] cyclohexanecarboxylic acid methyl ester was added to a mixture solution of 150 ml of 2N aqueous sodium hydroxide solution and 200 ml of tetrahydrofuran, and the mixture was heated under reflux for 18 hours. After the solvent was distilled off, water was added to the residue, and the mixture was washed with diethyl ether. After potassium hydrogensulfate was added

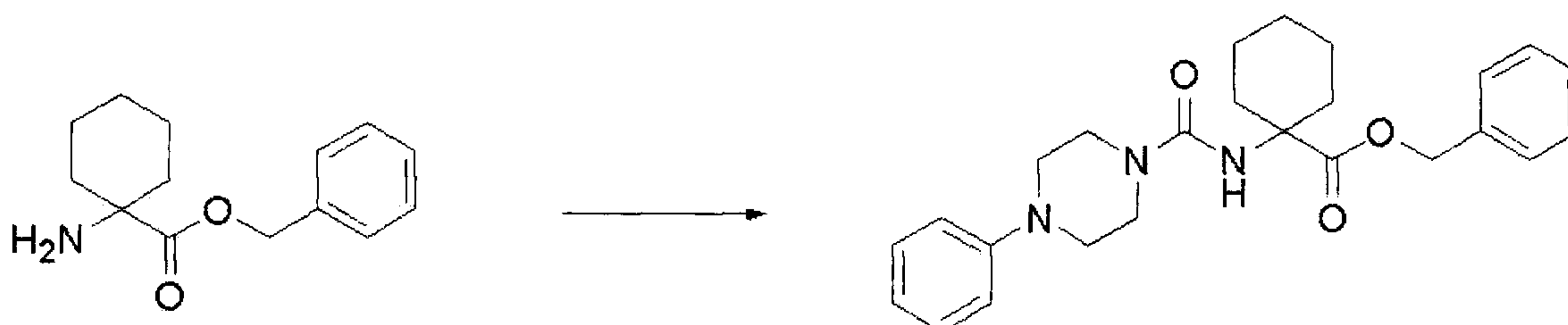
to the aqueous layer to acidify it, it was extracted with ethyl acetate twice. After the organic layer was washed with saturated brine and it was dried with anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. Diisopropyl ether was added to the residue, and the mixture was stirred for 18 hours. The obtained crystal was collected by filtration to obtain 19.89 g (74%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.24-1.37 (1H, m), 1.38-1.52 (2H, m), 1.59-1.71 (3H, m), 1.82-1.93 (2H, m), 1.99-2.12 (2H, m), 4.99 (1H, br-s), 5.07 (2H, s), 6.37 (1H, dd, J=3Hz, 2Hz), 6.42 (1H, d, J=3Hz), 7.43 (1H, d, J=2Hz)

[0244]

Reference Example 77

1-[[(4-Phenyl-1-piperazinyl) carbonyl] amino] cyclohexanecarboxylic acid phenylmethyl ester



[0245]

A solution of 366 mg (3 mmol) of N,N-dimethylaminopyridine and 6.99g (30 mmol) of 1-aminocyclohexanecarboxylic acid phenylmethyl ester in methylene chloride was added to a solution of 6.55 g (30 mmol) of di-t-butyl dicarbonate in 150 ml of methylene chloride, and the mixture was stirred at room temperature for 30 minutes. Thereafter, a solution of 6.07 g (60 mmol) of triethylamine and 5.11 g (33 mmol) of 1-phenylpiperazine in methylene chloride was added thereto and the mixture was stirred at room temperature overnight. The reaction

solution was concentrated, ethyl acetate was added thereto, and the mixture was successively washed with water, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the obtained crystal was washed with diethyl ether to obtain 8.88 g (70%) of the title compound.

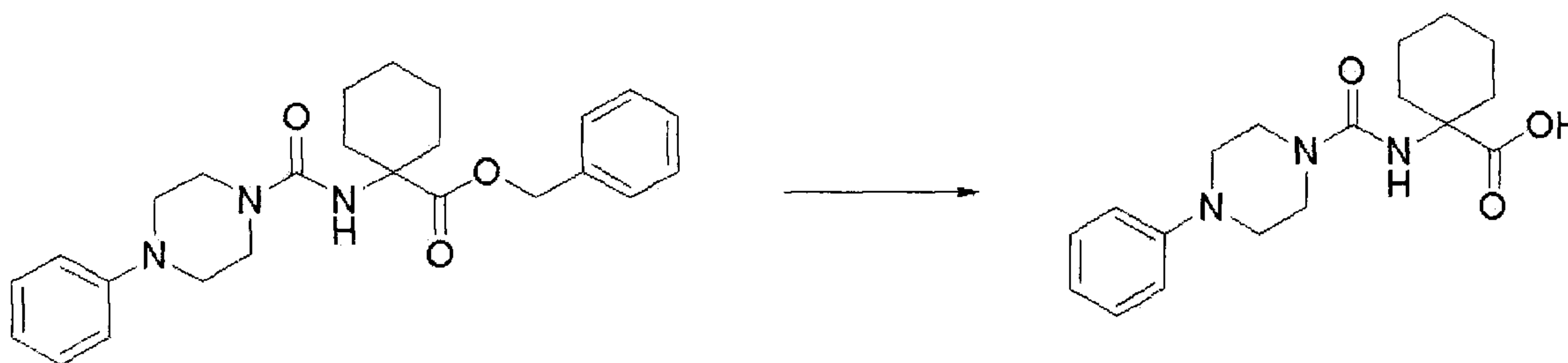
¹H-NMR (CDCl₃, δ): 1.25-1.37 (1H, m), 1.42-1.51 (2H, m), 1.50-1.69 (3H, m), 1.82-1.91 (2H, m), 2.03-2.10 (2H, m), 3.17 (4H, t, J=5Hz), 3.54 (4H, t, J=5Hz), 4.60 (1H, br-s), 5.15 (2H, s), 6.89-6.94 (3H, m), 7.26-7.35 (7H, m)

[0246]

Reference Example 78

1-[[[4-Phenyl-1-

piperazinyl)carbonyl]amino]cyclohexanecarboxylic acid



[0247]

8.88 g (21 mmol) of 1-[[[4-phenyl-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester obtained in Reference Example 77 was dissolved in 200 ml of methanol, 900 mg of 10% palladium-carbon was added thereto, and the mixture was stirred under a hydrogen atmosphere at room temperature overnight. After the reaction solution was filtered, the filtrate was concentrated under reduced pressure to obtain 6.96 g (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.22-1.30 (1H, m), 1.36-1.42 (2H, m), 1.50-2.05 (5H, m), 2.06-2.14 (2H, m), 3.24 (4H, t, J=5Hz), 4.61 (4H, t, J=5Hz), 4.51 (1H, br-s), 6.92-6.95 (2H, m),

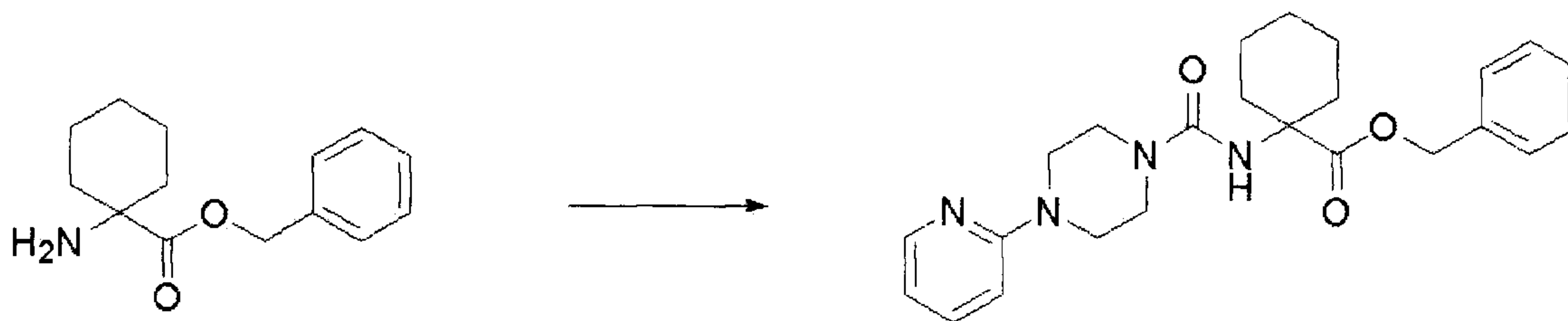
7.28-7.32 (3H, m)

[0248]

Reference Example 79

1-[[[4-(2-Pyridinyl)-1-

5 piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid
phenylmethyl ester



[0249]

3.43 g (21 mmol) of 1-(2-pyridinyl)piperazine was
10 used instead of 1-phenylpiperazine in the process according
to Reference Example 77 to obtain 7.33 g (87%) of the title
compound.

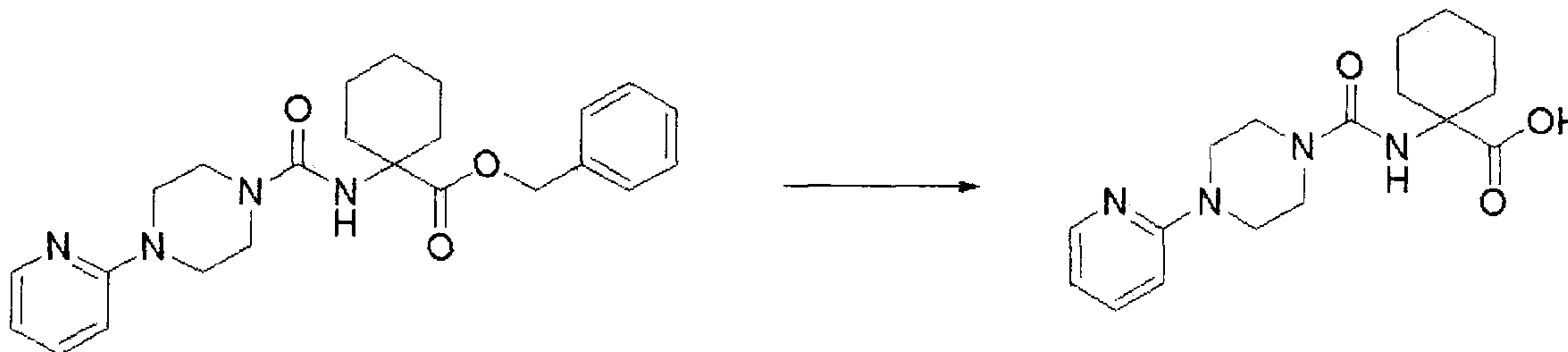
¹H-NMR (CDCl₃, δ): 1.26-1.35 (1H, m), 1.42-1.53 (2H, m),
1.60-1.68 (3H, m), 1.83-1.92 (2H, m), 2.02-2.10 (2H, m),
15 3.52 (4H, t, J=5Hz), 3.57 (4H, t, J=5Hz), 4.58 (1H, br-s),
5.15 (2H, s), 6.63 (1H, d, J=8Hz), 6.67 (1H, td, J=8Hz,
1Hz), 7.25-7.34 (5H, m), 7.51 (1H, td, J=8Hz, 1Hz), 8.20
(1H, dd, J=8Hz, 1Hz)

[0250]

20 Reference Example 80

1-[[[4-(2-Pyridinyl)-1-

piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid



[0251]

25 7.33 g (17.4 mmol) of 1-[[[4-(2-pyridinyl)-1-

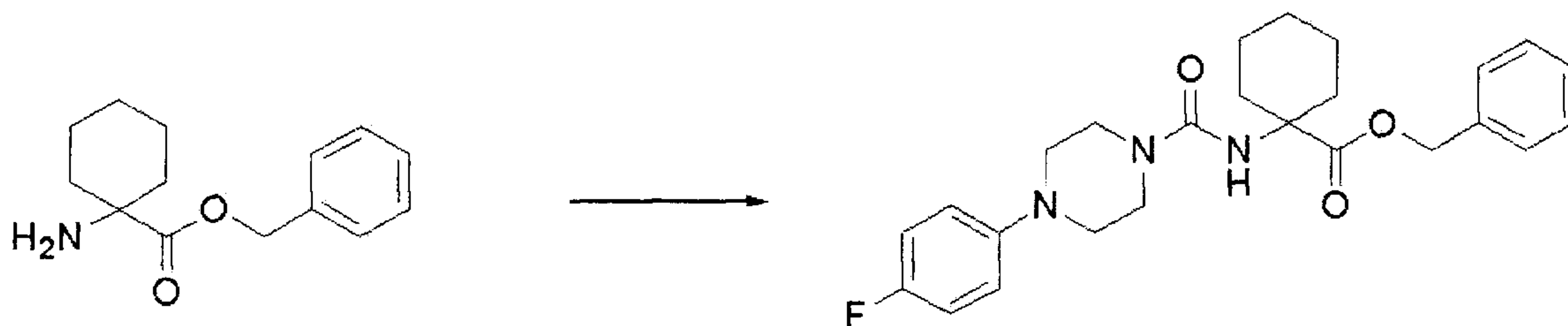
piperaziny]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-[[[4-phenyl-1-piperaziny]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 78 to obtain 5.75 g (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.30-1.43 (2H, m), 1.60-1.72 (4H, m), 1.89-1.99 (2H, m), 2.06-2.13 (2H, m), 3.61 (4H, t, J=5Hz), 3.66 (4H, t, J=5Hz), 4.61 (1H, br-s), 6.65 (1H, dd, J=8Hz, 1Hz), 6.69 (1H, td, J=8Hz, 1Hz), 7.52 (1H, td, J=8Hz, 1Hz), 8.20 (1H, dd, J=8Hz, 1Hz)

[0252]

Reference Example 81

1-[[[4-(4-Fluorophenyl)-1-piperaziny]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester



[0253]

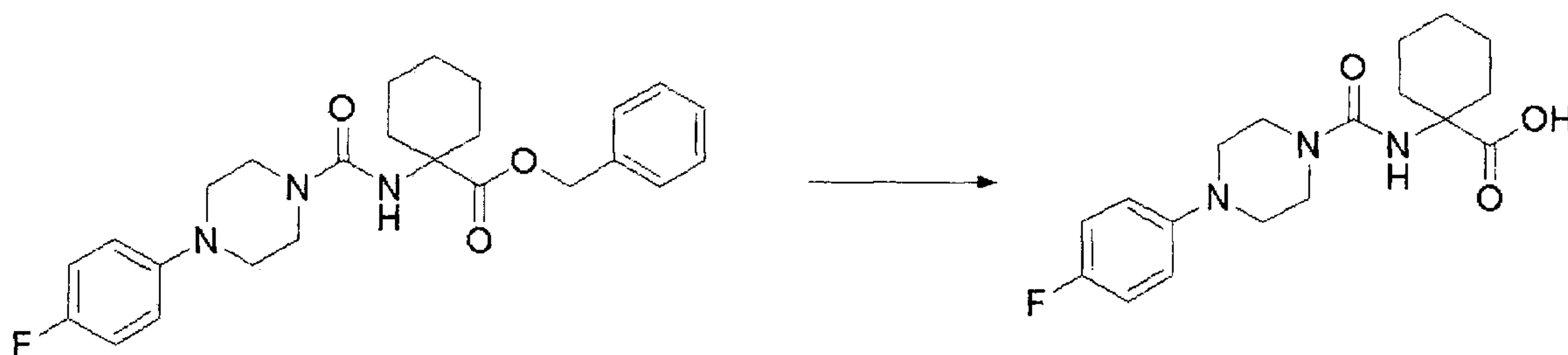
3.78 g (21 mmol) of 1-(4-fluorophenyl)piperazine was used instead of 1-phenylpiperazine in the process according to Reference Example 77 to obtain 4.48 g (51%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.22-1.35 (1H, m), 1.40-1.51 (2H, m), 1.55-1.70 (3H, m), 1.85-1.93 (2H, m), 2.02-2.09 (2H, m), 3.07 (4H, t, J=5Hz), 3.53 (4H, t, J=5Hz), 4.60 (1H, br-s), 5.15 (2H, s), 6.87 (2H, ddd, J=9Hz, 6Hz, 2Hz), 6.98 (2H, ddd, J=9Hz, 6Hz, 2Hz), 7.25-7.35 (5H, m)

[0254]

Reference Example 82

1-[[[4-(4-Fluorophenyl)-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid



[0255]

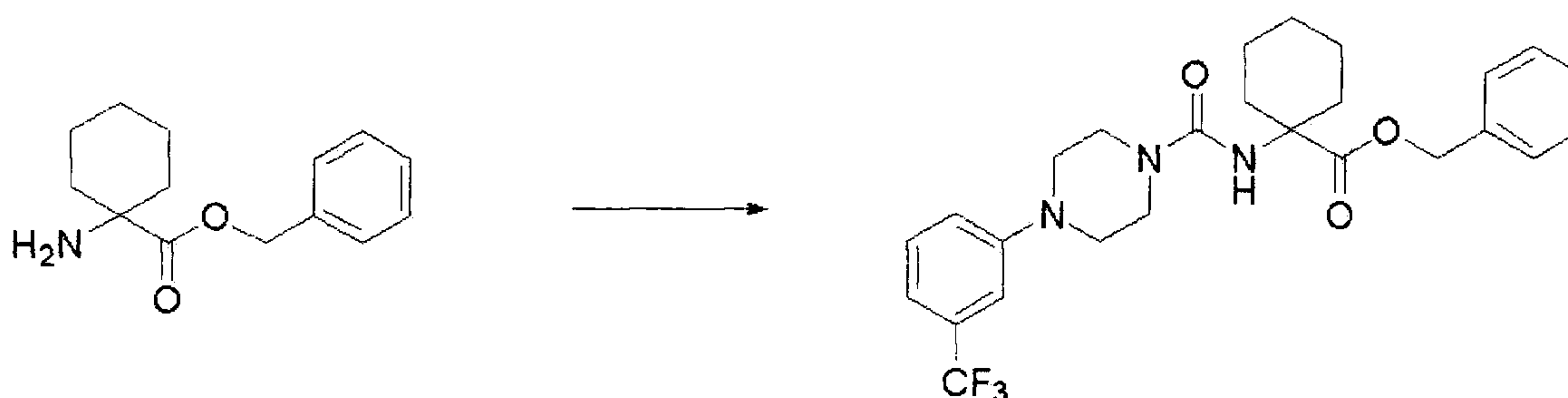
5 4.48 g (10 mmol) of 1-[[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-[[[4-phenyl-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference
10 Example 78 to obtain 3.56 g (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.31-1.43 (3H, m), 1.60-1.75 (3H, m), 1.89-2.01 (2H, m), 2.05-2.13 (2H, m), 3.14 (4H, t, J=5Hz), 3.61 (4H, t, J=5Hz), 4.55 (1H, br-s), 6.89 (2H, ddd, J=8Hz, 5Hz, 2Hz), 6.99 (2H, ddd, J=8Hz, 5Hz, 2Hz)

[0256]

Reference Example 83

1-[[[4-[3-(Trifluoromethyl)phenyl]-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid
20 phenylmethyl ester



[0257]

4.83 g (21 mmol) of 1-[3-(trifluoromethyl)phenyl]piperazine was used instead of 1-

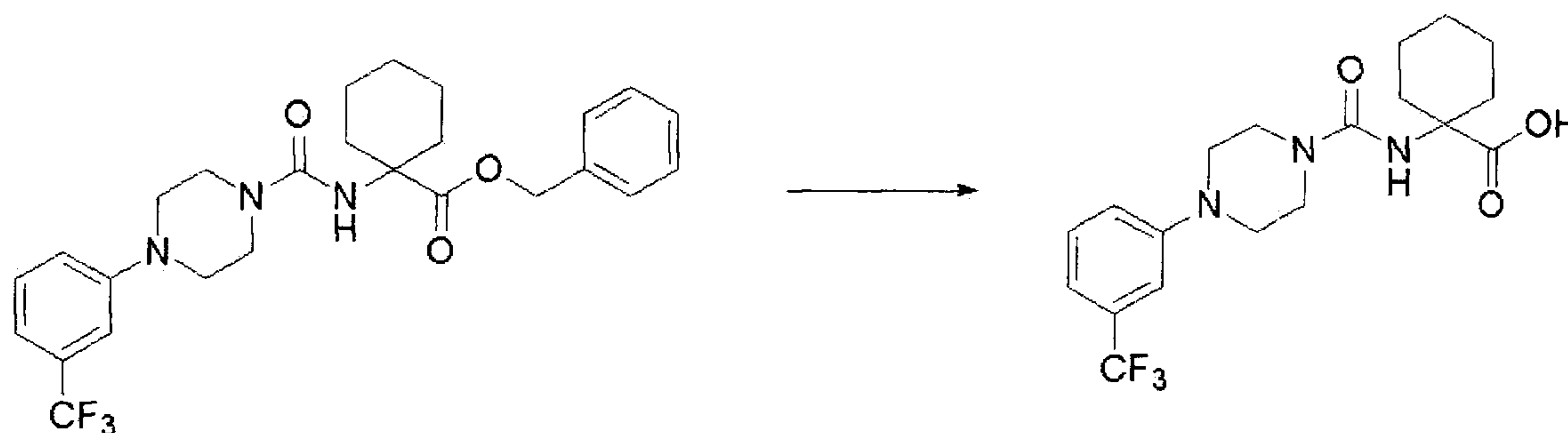
phenylpiperazine in the process according to Reference Example 77 to obtain 7.54 g (77%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.23-1.37 (1H, m), 1.42-1.53 (2H, m), 1.59-1.70 (3H, m), 1.85-1.94 (2H, m), 2.02-2.10 (2H, m), 3.21 (4H, t, J=5Hz), 3.55 (4H, t, J=5Hz), 4.60 (1H, br-s), 5.15 (2H, s), 7.05 (1H, dd, J=8Hz, 2Hz), 7.09 (1H, s), 7.12 (1H, dd, J=8Hz, 2Hz), 7.25-7.40 (6H, m)

[0258]

Reference Example 84

1-[[[4-[3-(Trifluoromethyl)phenyl]-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid



[0259]

7.54 g (15.4 mmol) of 1-[[[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-[[[4-phenyl-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 78 to obtain 5.92 g (96%) of the title compound.

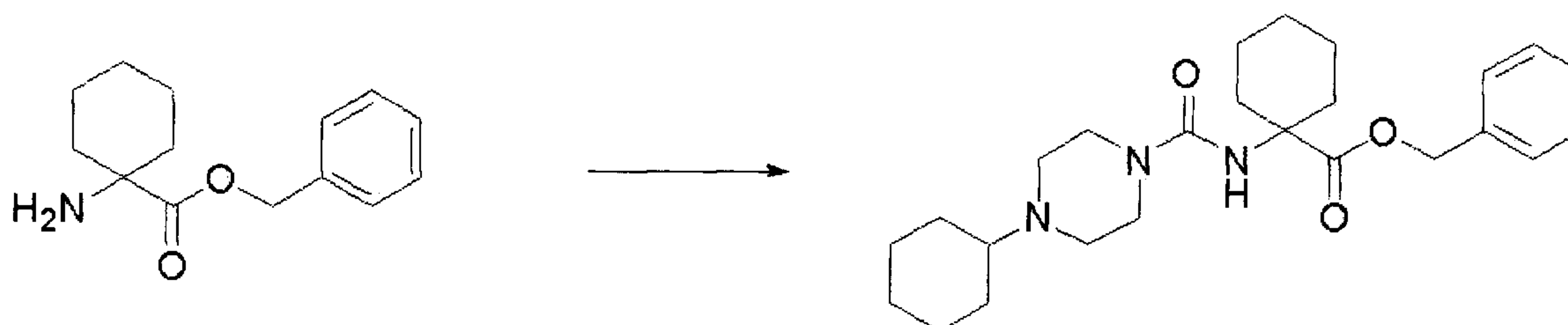
¹H-NMR (CDCl₃, δ): 1.36-1.44 (2H, m), 1.60-1.75 (4H, m), 1.91-2.00 (2H, m), 2.05-2.14 (2H, m), 3.30 (4H, t, J=5Hz), 3.63 (4H, t, J=5Hz), 4.63 (1H, br-s), 7.07 (1H, d, J=8Hz), 7.11 (1H, s), 7.15 (1H, d, J=8Hz), 7.38 (1H, t, J=8Hz)

[0260]

Reference Example 85

1-[[[4-Cyclohexyl-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid

phenylmethyl ester



[0261]

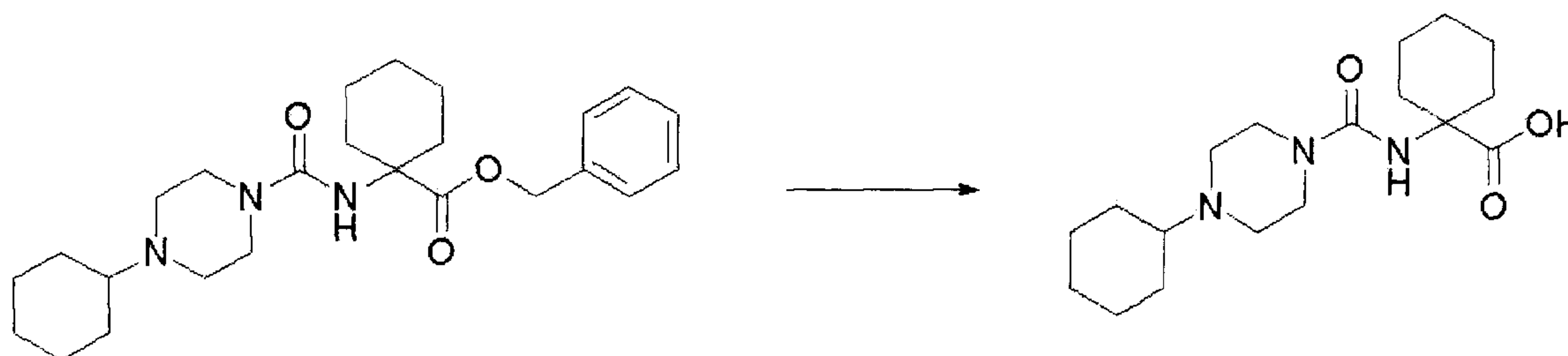
2.66 g (15.8 mmol) of 1-(cyclohexyl)piperazine was
5 used instead of 1-phenylpiperazine in the process according
to Reference Example 77 to obtain 3.21 g (50%) of the title
compound.

¹H-NMR (CDCl₃, δ): 1.22-1.45 (3H, m), 1.39-1.50 (3H, m),
1.51-1.67 (6H, m), 1.89-1.90 (6H, m), 2.01-2.07 (2H, m),
10 2.22-2.30 (1H, m), 2.54 (4H, t, J=5Hz), 3.38 (4H, t,
J=5Hz), 4.53 (1H, br-s), 5.14 (2H, s), 7.25-7.34 (5H, m)

[0262]

Reference Example 86

1-[[[4-Cyclohexyl-1-
15 piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid



[0263]

3.21 g (7.5 mmol) of 1-[[[4-(cyclohexyl)-1-
piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid
20 phenylmethyl ester was used instead of 1-[[[4-phenyl-1-
piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid
phenylmethyl ester in the process according to Reference
Example 78 to obtain 2.53 g (quantitative) of the title
compound.

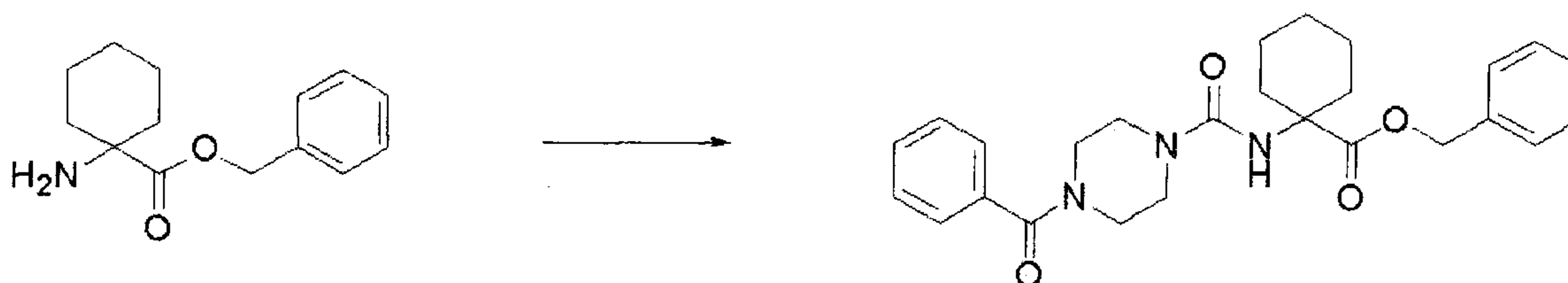
25 ¹H-NMR (CDCl₃, δ): 1.05-1.19 (1H, m), 1.10-1.19 (2H, m),

1.20-1.32 (2H, m), 1.58-1.97 (13H, m), 2.03-2.12 (2H, m),
2.35-2.44 (1H, m), 2.67 (4H, t, J=5Hz), 3.48 (4H, t,
J=5Hz), 4.59 (1H, br-s)

[0264]

5 Reference Example 87

1-[[[4-Benzoyl-1-
piperazinyl)carbonyl]amino]cyclohexanecarboxylic acid
phenylmethyl ester



10 [0265]

A solution of 114 mg (0.9 mmol) of N,N-
dimethylaminopyridine and 2.17g (9.3 mmol) of 1-
aminocyclohexanecarboxylic acid phenylmethyl ester in
methylene chloride was added to a solution of 2.03 g (9.3
15 mmol) of di-t-butyl dicarbonate in 60 ml of methylene
chloride, and the mixture was stirred at room temperature
for 30 minutes. Thereafter, a solution of 1.88 g (18.6
mmol) of triethylamine and 1.86 g (9.8 mmol) of 1-
(benzoyl)piperazine in methylene chloride was added
20 thereto, and the mixture was stirred at room temperature
overnight. After the reaction solution was concentrated,
the residue was dissolved in ethyl acetate, and the mixture
was successively washed with water, a 10% aqueous potassium
hydrogensulfate solution, a saturated aqueous sodium
25 hydrogencarbonate solution and saturated brine, followed by
drying with anhydrous sodium sulfate. After the solvent
was distilled off under reduced pressure, the obtained
crystal was washed with diethyl ether to obtain 3.60 g
(86%) of the title compound.

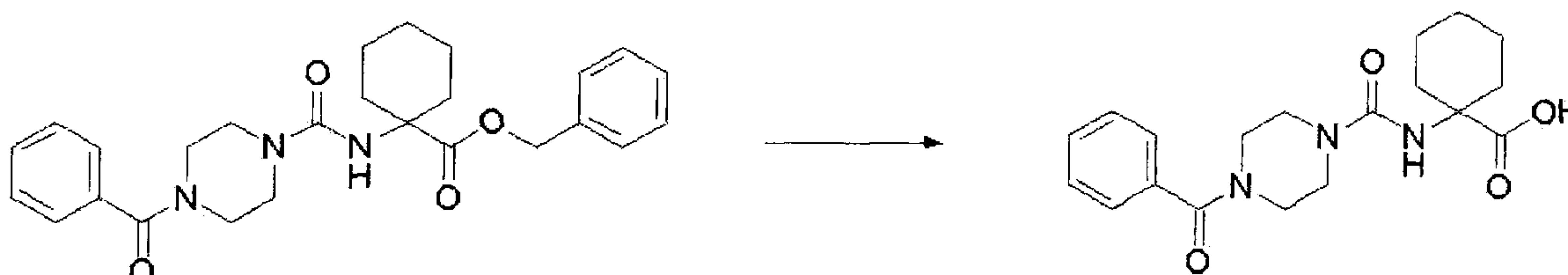
30 ¹H-NMR (CDCl₃, δ): 1.26-1.38 (1H, m), 1.39-1.50 (2H, m),

1.53-1.68 (3H, m), 1.85-1.93 (2H, m), 2.02-2.08 (2H, m),
3.28-3.57 (6H, m), 3.66-3.85 (2H, m), 4.57 (1H, br-s), 5.15
(2H, s), 7.31-7.39 (4H, m), 7.40-7.48 (6H, m)

[0266]

5 Reference Example 88

1-[[[4-Benzoyl-1-
piperazinyl)carbonyl]amino]cyclohexanecarboxylic acid



[0267]

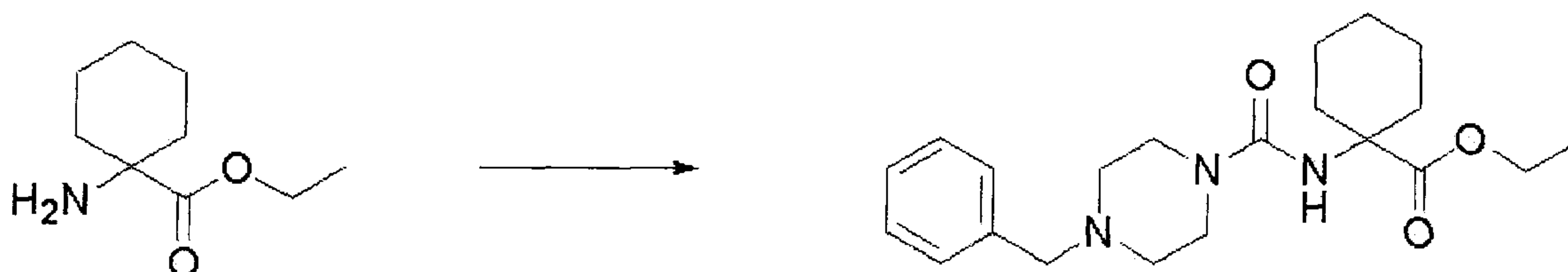
10 3.60 g (8 mmol) of 1-[[[4-benzoyl-1-
piperazinyl)carbonyl]amino]cyclohexanecarboxylic acid
phenylmethyl ester was used instead of 1-[[[4-phenyl-1-
piperazinyl)carbonyl]amino]cyclohexanecarboxylic acid
phenylmethyl ester in the process according to Reference
15 Example 78 to obtain 2.88 g (quantitative) of the title
compound.

¹H-NMR (CDCl₃, δ): 1.34-1.42 (2H, m), 1.59-1.74 (2H, m),
1.85-2.10 (6H, m), 3.42-3.58 (6H, m), 3.70-3.87 (2H, m),
4.60 (1H, br-s), 7.39-7.47 (5H, m)

20 [0268]

Reference Example 89

1-[[[4-(Phenylmethyl)-1-
piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid ethyl
ester



25 [0269]

5.82 g (33 mmol) of 4-(phenylmethyl)piperazine was

used instead of 1-phenylpiperazine, and 5.14 g (30 mmol) of 1-aminocyclohexanecarboxylic acid ethyl ester was used instead of 1-aminocyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 77 to obtain 7.62 g (68%) of the title compound.

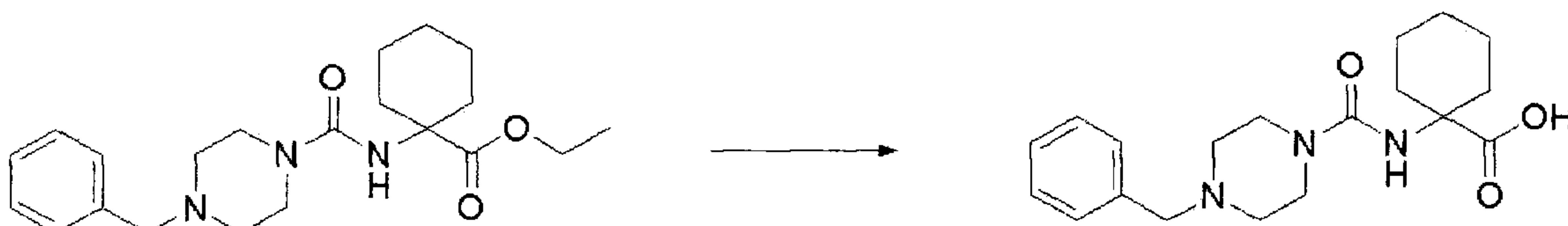
¹H-NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.24-1.39 (1H, m), 1.40-1.49 (2H, m), 1.55-1.64 (3H, m), 1.80-1.89 (2H, m), 1.97-2.04 (2H, m), 2.44 (4H, t, J=5Hz), 3.39 (4H, t, J=5Hz), 3.52 (2H, s), 4.17 (2H, q, J=7Hz), 4.50 (1H, br-s), 7.23-7.30 (1H, m), 7.30-7.37 (4H, m)

[0270]

Reference Example 90

1-[[[4-(Phenylmethyl)-1-

piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid



[0271]

600 ml of 1N aqueous sodium hydroxide solution was added to a solution of 7.62 g (20 mmol) of 1-[[[4-(phenylmethyl)-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid ethyl ester in 300 ml of ethanol, and the mixture was heated under reflux for 2 hours. After ether was added to the reaction solution to wash it, the aqueous layer was neutralized by concentrated hydrochloric acid, and the mixture was extracted with ethyl acetate. After the obtained organic layer was washed with saturated brine, it was dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 2.90 g (42%) of the title compound.

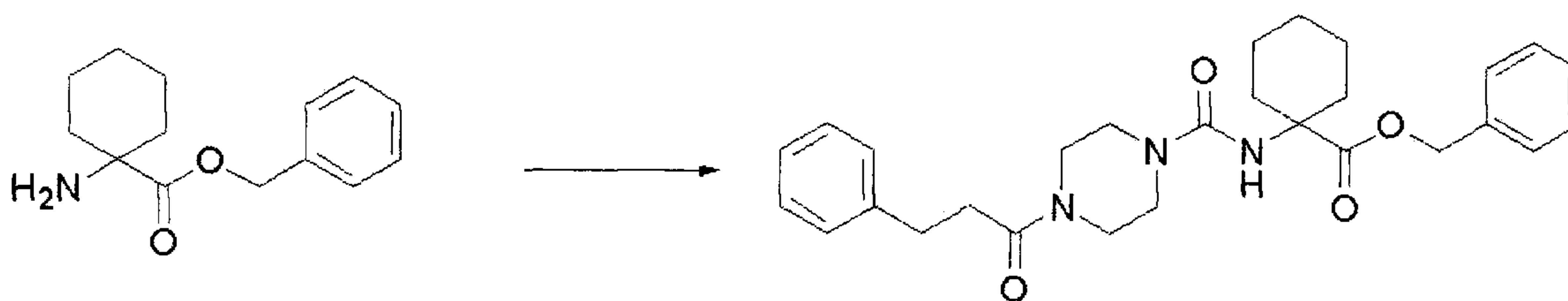
¹H-NMR (CDCl₃, δ): 1.28-1.38 (2H, m), 1.60-1.71 (4H, m),

1.88-1.98 (2H, m), 2.01-2.10 (2H, m), 2.49 (4H, t, J=5Hz),
3.45 (4H, t, J=5Hz), 3.55 (2H, s), 4.43 (1H, br-s), 7.24-
7.34 (5H, m)

[0272]

5 Reference Example 91

1-[[4-(1-Oxo-3-phenylpropyl)-1-
piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid
phenylmethyl ester



10 [0273]

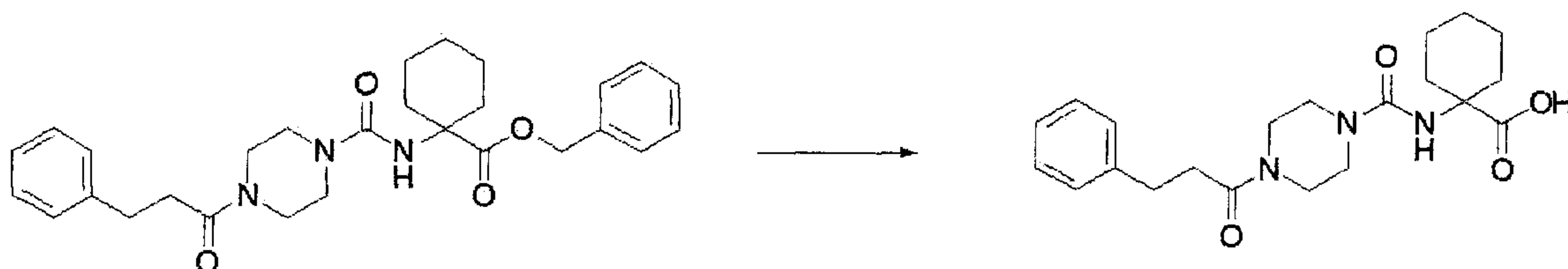
2.40 g (11 mmol) of 1-(1-oxo-3-
phenylpropyl)piperazine was used instead of 1-
(benzoyl)piperazine in the process according to Reference
Example 87 to obtain 3.53 g (74%) of the title compound.

15 ¹H-NMR (CDCl₃, δ): 1.22-1.39 (1H, m), 1.40-1.49 (2H, m),
1.58-1.67 (3H, m), 1.84-1.93 (2H, m), 2.00-2.07 (2H, m),
2.62 (2H, t, J=6Hz), 2.98 (2H, t, J=6Hz), 3.25-3.33 (6H,
m), 3.59-3.65 (2H, m), 4.52 (1H, br-s), 5.14 (2H, br-s),
7.18-7.23 (4H, m), 7.28-7.34 (6H, m)

20 [0274]

Reference Example 92

1-[[[4-(1-Oxo-3-phenylpropyl)-1-
piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid



25 [0275]

3.53 g (7.4 mmol) of 1-[[[4-(1-oxo-3-phenylpropyl)-1-
piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid

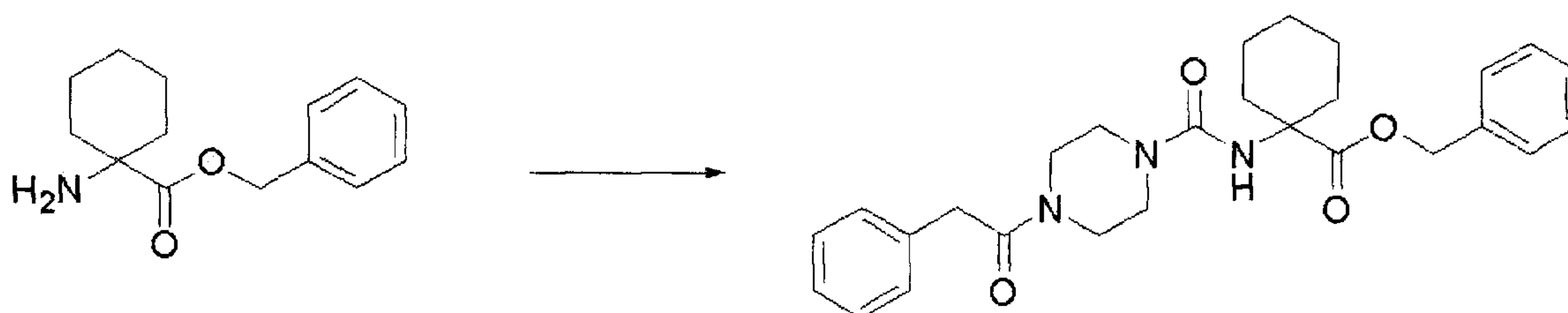
phenylmethyl ester was used instead of 1-[[[4-phenyl-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 78 to obtain 2.87 g (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.28-1.53 (3H, m), 1.57-1.70 (3H, m), 1.84-1.97 (2H, m), 2.00-2.08 (2H, m), 2.63 (2H, t, J=6Hz), 2.98 (2H, m, J=6Hz), 3.33-3.41 (6H, m), 3.67-3.71 (2H, m), 4.78 (1H, br-s), 7.18-7.25 (3H, m), 7.27-7.34 (2H, m)

[0276]

Reference Example 93

1-[[[4-(Phenylacetyl)-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester



[0277]

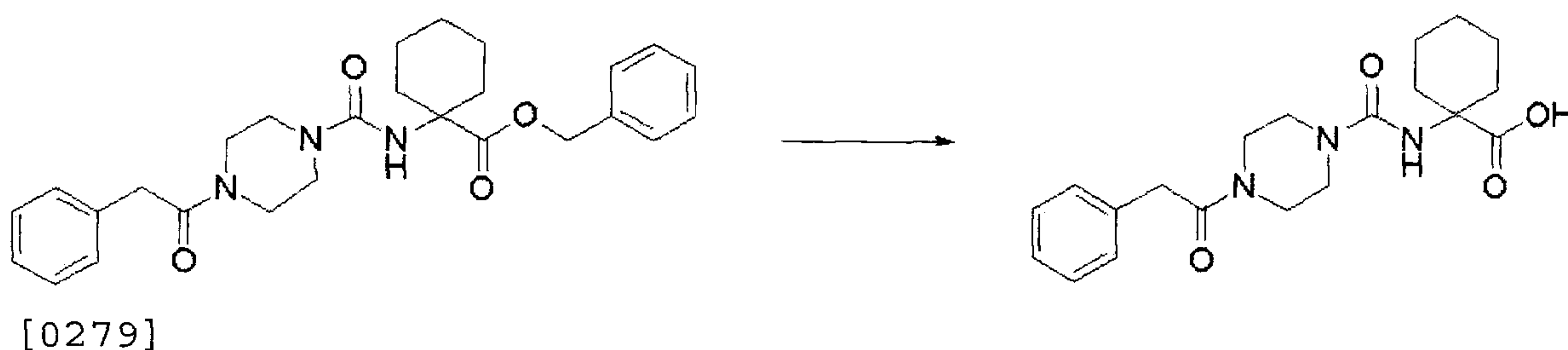
1.23 g (6 mmol) of 1-(phenylacetyl)piperazine was used instead of 1-(1-oxo-3-phenylpropyl)piperazine in the process according to Reference Example 87 to obtain 2.39 g (87%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.22-1.36 (1H, m), 1.37-2.06 (2H, m), 1.55-1.66 (3H, m), 1.83-1.92 (2H, m), 1.98-2.03 (2H, m), 3.20 (2H, t, J=5Hz), 3.31 (2H, t, J=5Hz), 3.41 (2H, t, J=5Hz), 3.63 (2H, t, J=5Hz), 3.74 (2H, s), 4.49 (1H, br-s), 5.12 (2H, s), 7.24-7.32 (10H, m)

[0278]

Reference Example 94

1-[[[4-(Phenylacetyl)-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid



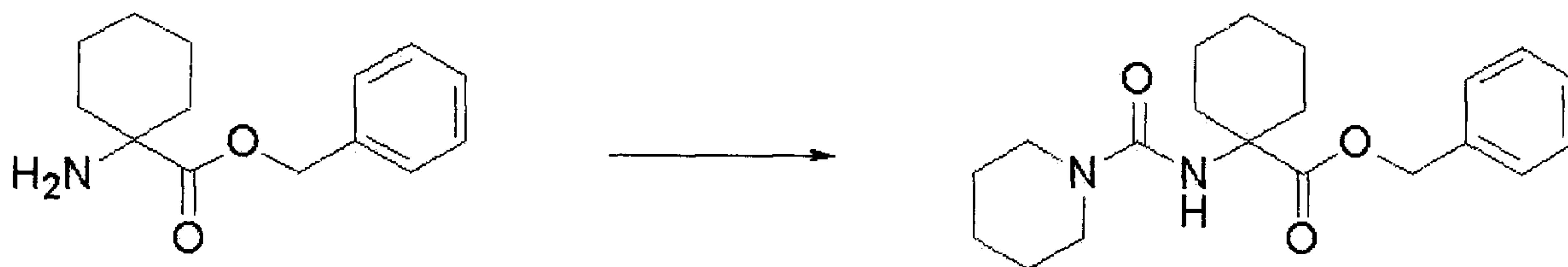
2.39 g (5.2 mmol) of 1-[[[4-(phenylacetyl)-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-[[[4-phenyl-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 78 to obtain 1.94 g (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.29-1.39 (3H, m), 1.58-1.70 (3H, m), 1.86-1.96 (2H, m), 1.99-2.07 (2H, m), 3.26 (2H, t, J=5Hz), 3.38 (2H, t, J=5Hz), 3.50 (2H, t, J=5Hz), 3.72 (2H, t, J=5Hz), 3.76 (2H, s), 4.50 (1H, br-s), 7.23-7.30 (3H, m), 7.30-7.35 (2H, m)

[0280]

Reference Example 95

1-[(1-Piperidinylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester



[0281]

1.34 g (15.8 mmol) of piperidine was used instead of 1-(1-oxo-3-phenylpropyl)piperazine in the process according to Reference Example 87 to obtain 4.59 g (89%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.22-1.34 (1H, m), 1.40-1.65 (11H, m), 1.82-1.90 (2H, m), 2.02-2.08 (2H, m), 3.32 (4H, t, J=5Hz), 4.53 (1H, br-s), 5.14 (2H, s), 7.29-7.35 (5H, m)

[0282]

Reference Example 96

1-[(1-Piperidinylcarbonyl)amino]cyclohexanecarboxylic acid



5 [0283]

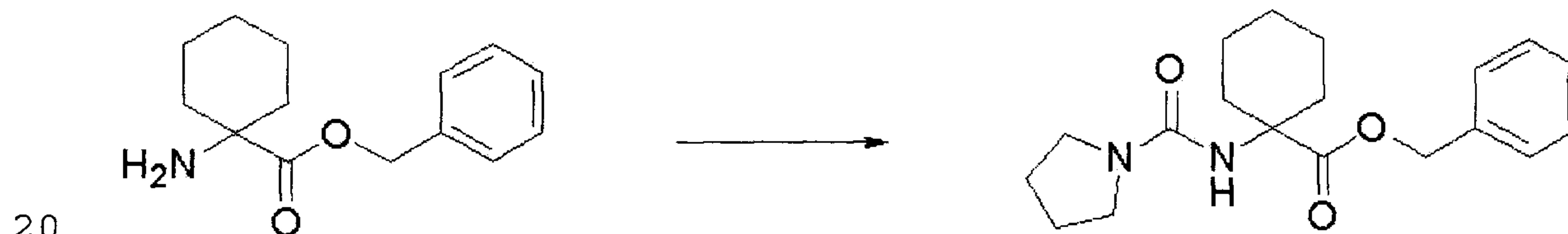
4.59 g (12 mmol) of 1-[(1-piperidinylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-[(4-phenyl-1-piperazinyl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 78 to obtain 3.05 g (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.30-1.41 (4H, m), 1.56-1.70 (8H, m), 1.85-1.96 (2H, m), 2.05-2.13 (2H, m), 3.89 (4H, t, J=5Hz), 4.51 (1H, br-s)

[0284]

Reference Example 97

1-[(1-Pyrrolidinylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester



20

[0285]

1.12 g (15.8 mmol) of pyrrolidine was used instead of 1-(1-oxo-3-phenylpropyl)piperazine in the process according to Reference Example 87 to obtain 3.23 g (65%) of the title compound.

25

¹H-NMR (CDCl₃, δ): 1.23-1.33 (1H, m), 1.42-1.51 (2H, m), 1.51-1.68 (3H, m), 1.82-1.95 (2H, m), 1.89 (4H, t, J=7Hz),

2.02-2.10 (2H, m), 3.35 (4H, t, J=7Hz), 4.33 (1H, br-s),
5.16 (2H, s), 7.26-7.36 (5H, m)

[0286]

Reference Example 98

5 1-[(1-Pyrrolidinylcarbonyl)amino]cyclohexanecarboxylic acid



[0287]

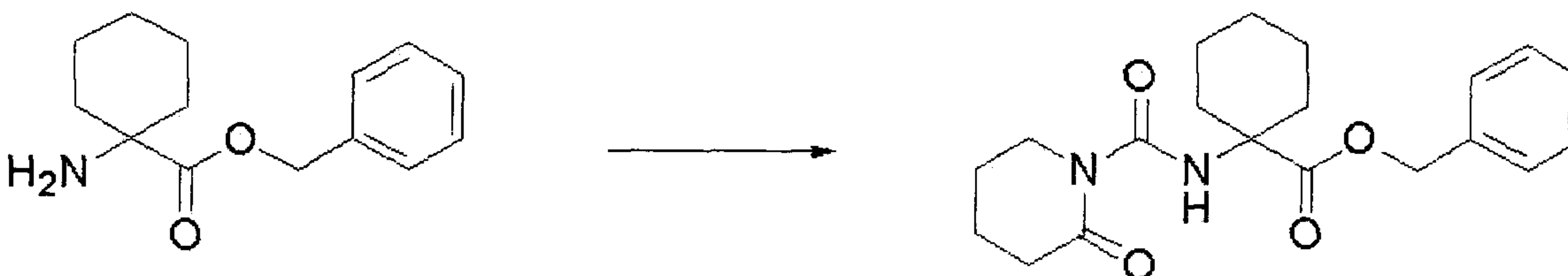
3.23 g (9.8 mmol) of 1-[(1-pyrrolidinylcarbonyl)amino]cyclohexanecarboxylic acid
phenylmethyl ester was used instead of 1-[(4-phenyl-1-piperazinyl)carbonyl]amino]cyclohexanecarboxylic acid
phenylmethyl ester in the process according to Reference
Example 78 to obtain 2.35 g (quantitative) of the title
compound.

15 ¹H-NMR (CDCl₃, δ): 1.29-1.42 (3H, m), 1.58-1.72 (3H, m),
1.88-2.00 (6H, m), 2.05-2.14 (2H, m), 3.40 (4H, t, J=6Hz),
4.34 (1H, br-s)

[0288]

Reference Example 99

20 1-[[(2-Oxo-1-piperidinyl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester



[0289]

25 A solution of 183 mg (1.5 mmol) of N,N-dimethylaminopyridine and 3.50g (15 mmol) of 1-aminocyclohexanecarboxylic acid phenylmethyl ester in

toluene was added to a solution of 3.27 g (15 mmol) of di-
t-butyl dicarbonate in 60 ml of toluene, and the mixture
was stirred at room temperature for 30 minutes.

Thereafter, 3.04 g (30 mmol) of triethylamine, 1.83 g (15
5 mmol) of N,N-dimethylaminopyridine and 1.56 g (15.8 mmol)
of 2-piperidone were added thereto, and the mixture was
heated under reflux overnight. Ethyl acetate was added to
the reaction solution, and the mixture was successively
washed with water, a 10% aqueous potassium hydrogensulfate
10 solution, a saturated aqueous sodium hydrogencarbonate
solution and saturated brine, followed by drying with
anhydrous sodium sulfate. The solvent was distilled off
under reduced pressure and the obtained residue was
purified by silica gel chromatography to obtain 4.10 g
15 (76%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.21-1.30 (1H, m), 1.42-1.53 (2H, m),
1.61-1.69 (3H, m), 1.78-1.90 (6H, m), 2.06-2.15 (2H, m),
2.54 (2H, t, J=6Hz), 3.73 (2H, t, J=6Hz), 5.16 (2H, s),
7.27-7.35 (5H, m), 9.85 (1H, br-s)

20 [0290]

Reference Example 100

1-[[(2-Oxo-1-

piperidiny1)carbonyl]amino]cyclohexanecarboxylic acid



25 [0291]

4.10 g (11.4 mmol) of 1-[[1-(2-oxo-1-
piperidiny1)carbonyl]amino]cyclohexanecarboxylic acid
phenylmethyl ester was used instead of 1-[[(4-phenyl-1-
piperaziny1)carbonyl]amino]cyclohexanecarboxylic acid
30 phenylmethyl ester in the process according to Reference

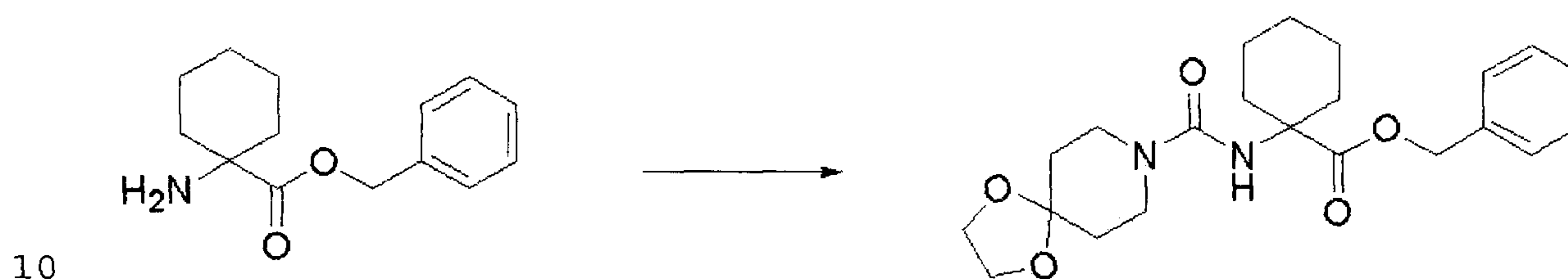
Example 78 to obtain 2.95 g (96%) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.24-1.35 (1H, m), 1.45-1.64 (2H, m), 1.50-1.71 (3H, m), 1.82-1.92 (6H, m), 2.12-2.16 (2H, m), 2.58 (2H, t, $J=6\text{Hz}$), 3.80 (2H, t, $J=6\text{Hz}$), 9.96 (1H, br-s)

5 [0292]

Reference Example 101

1-[(1,4-Dioxo-8-azaspiro[4.5]dec-8-ylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester



[0293]

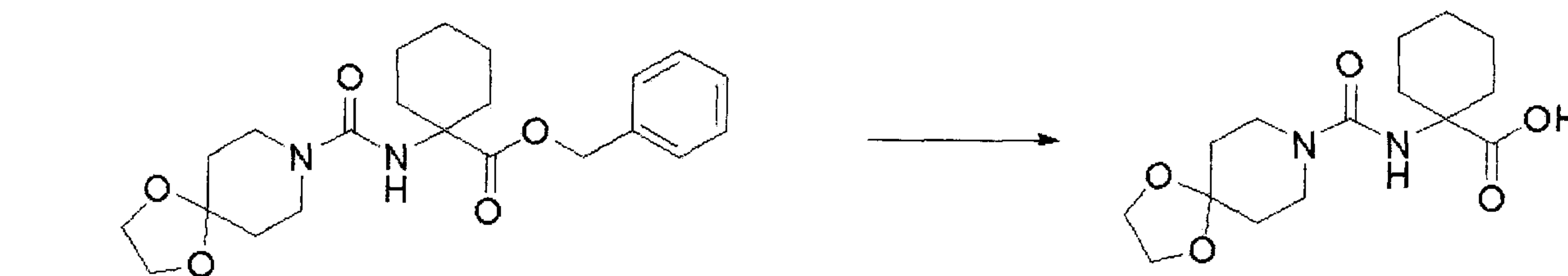
3.00 g (21 mmol) of 1,4-dioxo-8-azaspiro[4.5]decane was used instead of 1-(benzoyl)piperazine in the process according to Reference Example 87 to obtain 5.70 g (71%) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.23-1.34 (1H, m), 1.40-1.48 (2H, m), 1.59-1.67 (3H, m), 1.69 (4H, t, $J=6\text{Hz}$), 1.84-1.93 (2H, m), 2.00-2.08 (2H, m), 3.47 (4H, t, $J=6\text{Hz}$), 3.98 (4H, s), 4.59 (1H, br-s), 5.14 (2H, s), 7.27-7.36 (5H, m)

20 [0294]

Reference Example 102

1-[(1,4-Dioxo-8-azaspiro[4.5]dec-8-ylcarbonyl)amino]cyclohexanecarboxylic acid



[0295]

5.70 g (14.2 mmol) of 1-[(1,4-dioxo-8-

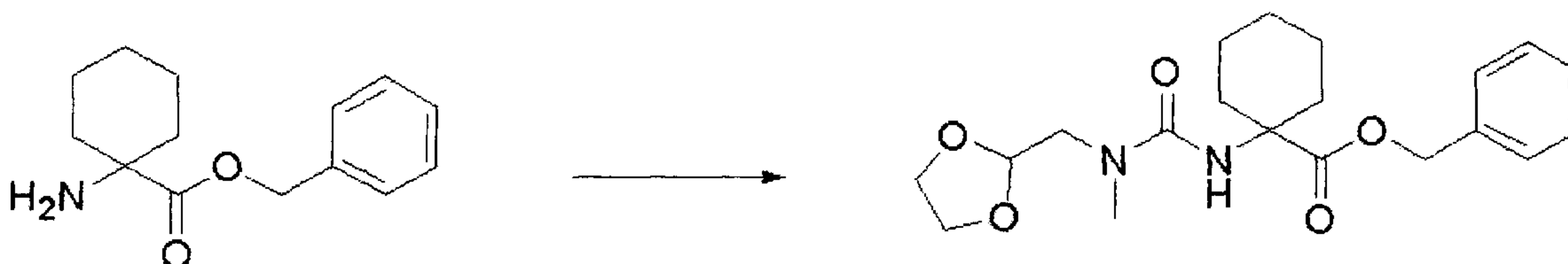
azaspiro[4.5]dec-8-ylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-[[[(4-phenyl-1-piperazinyl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 78 to obtain 4.38 g (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.30-1.42 (3H, m), 1.60-1.77 (3H, m), 1.75 (4H, t, J=6Hz), 1.88-2.01 (2H, m), 2.05-2.14 (2H, m), 3.54 (4H, t, J=6Hz), 3.99 (4H, s), 4.55 (1H, br-s)

[0296]

Reference Example 103

1-[[[(1,3-Dioxolan-2-ylmethyl)methylamino]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester



[0297]

2.46 g (21 mmol) of 2-[(methylamino)methyl]-1,3-dioxolane was used instead of 1-(benzoyl)piperazine in the process according to Reference Example 87 to obtain 6.05 g (80%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.22-1.34 (1H, m), 1.39-1.50 (2H, m), 1.59-1.68 (2H, m), 1.68-1.74 (3H, m), 1.82-1.91 (2H, m), 2.00-2.08 (2H, m), 3.44-3.50 (4H, m), 3.98 (4H, s), 4.59 (1H, br-s), 5.14 (2H, s), 7.27-7.36 (5H, m)

[0298]

Reference Example 104

1-[[[(1,3-Dioxolan-2-ylmethyl)methylamino]carbonyl]amino]cyclohexanecarboxylic acid



[0299]

6.05 g (16 mmol) of 1-[[[(1,3-dioxolan-2-ylmethyl)methylamino]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-[[[(4-phenyl-1-piperazinyl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 78 to obtain 4.45 g (97%) of the title compound.

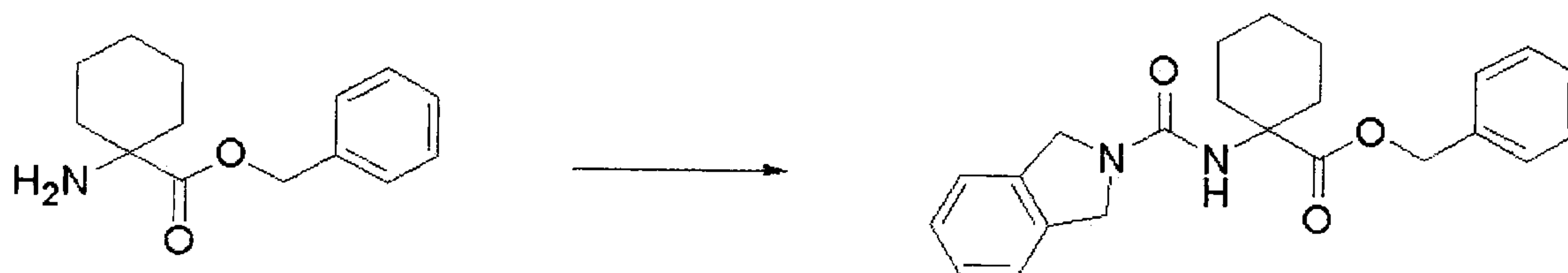
¹H-NMR (CDCl₃, δ): 1.30-1.41 (3H, m), 1.60-1.75 (5H, m), 1.88-1.97 (2H, m), 2.04-2.13 (2H, m), 3.48-3.59 (4H, m), 3.99 (4H, s), 4.53 (1H, br-s)

[0300]

Reference Example 105

1-[[[(1,3-Dihydro-2H-isoindol-2-

yl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester



[0301]

2.50 g (21 mmol) of isoindoline was used instead of 1-(benzoyl)piperazine in the process according to Reference Example 87 to obtain 5.95 g (79%) of the title compound.

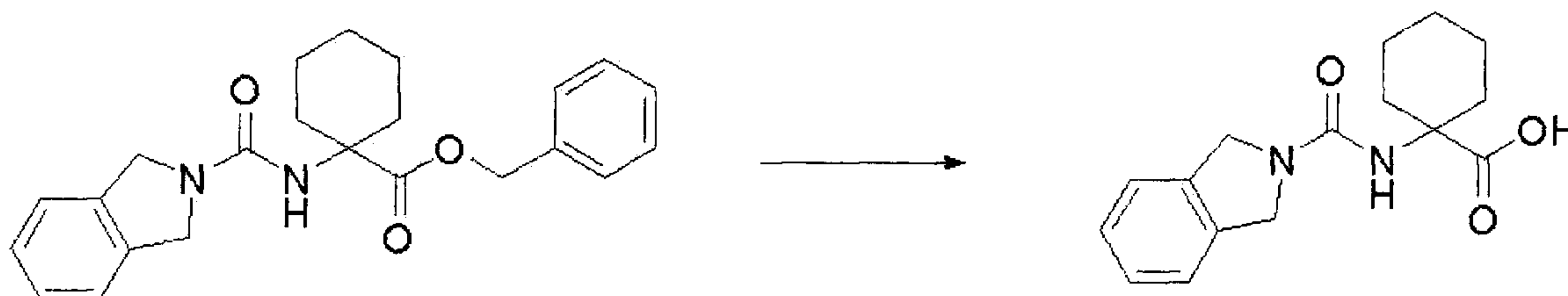
¹H-NMR (CDCl₃, δ): 1.23-1.38 (1H, m), 1.45-1.70 (5H, m), 1.89-1.97 (2H, m), 2.07-2.16 (2H, m), 4.48 (1H, br-s), 4.73 (4H, s), 5.17 (2H, s), 7.25-7.31 (7H, m), 7.31-7.36 (2H, m)

[0302]

Reference Example 106

1-[[[(1,3-Dihydro-2H-isoindol-2-

yl)carbonyl]amino]cyclohexanecarboxylic acid



[0303]

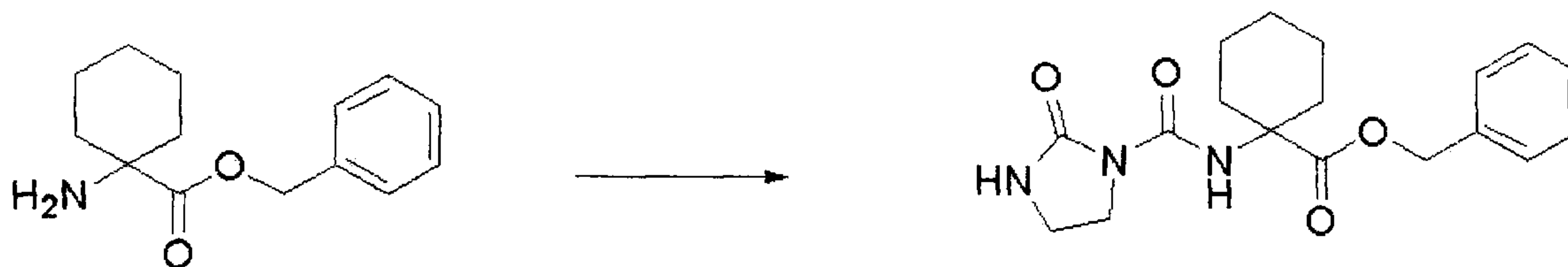
5.95 g (15.8 mmol) of 1-[[[(1,3-dihydro-2H-isoindol-2-yl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-[[[(4-phenyl-1-piperazinyl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 78 to obtain 3.09 g (68%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.23-1.30 (1H, m), 1.35-1.48 (2H, m), 1.59-1.76 (3H, m), 1.96-2.05 (2H, m), 2.10-2.17 (2H, m), 4.40 (1H, br-s), 4.78 (4H, br-s), 7.24-7.35 (4H, m)

[0304]

Reference Example 107

1-[[[(2-Oxo-1-imidazolidinyl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester



[0305]

1.38 g (9.3 mmol) of 2-oxo-1-imidazolidinecarbonyl chloride was added to a solution of 2.17 g (9.3 mmol) of 1-aminocyclohexanecarboxylic acid phenylmethyl ester and 1.04 g (10 mmol) of triethylamine in 100 ml of chloroform, and the mixture was stirred at 60°C for 4 days. The reaction solution was successively washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, and

it was dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the obtained crystal was washed with diethyl ether to obtain 2.64 g (82%) of the title compound.

5 ¹H-NMR (CDCl₃, δ): 1.22-1.31 (1H, m), 1.44-1.54 (2H, m), 1.60-1.68 (3H, m), 1.81-1.88 (2H, m), 2.08-2.16 (2H, m), 3.48 (2H, t, J=7Hz), 3.93 (2H, t, J=7Hz), 4.75 (1H, br-s), 5.17 (2H, s), 7.26-7.36 (5H, m), 8.45 (1H, br-s)
[0306]

10 Reference Example 108

1-[[[(2-Oxo-1-imidazolidinyl)carbonyl]amino]cyclohexanecarboxylic acid



[0307]

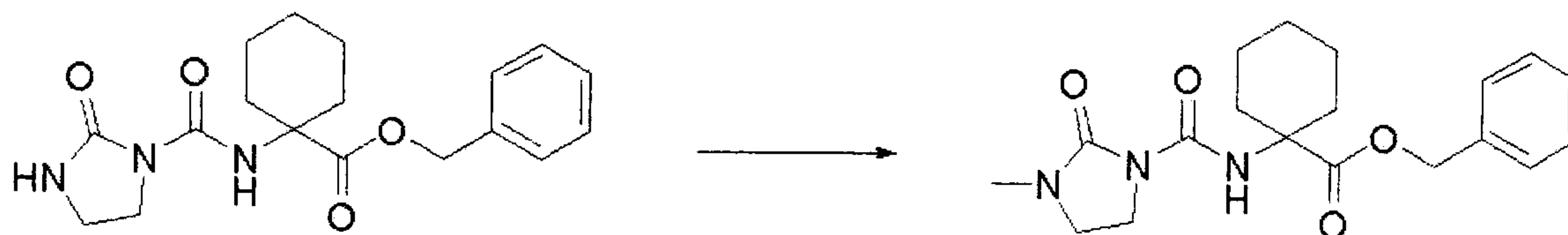
15 2.64 g (7.6 mmol) of 1-[[[(2-oxo-1-imidazolidinyl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-[[[(4-phenyl-1-piperazinyl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference
20 Example 78 to obtain 1.95 g (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.23-1.38 (1H, m), 1.41-1.70 (5H, m), 1.83-1.92 (2H, m), 2.11-2.20 (2H, m), 3.54 (2H, t, J=8Hz), 4.01 (2H, t, J=8Hz), 4.92 (1H, br-s), 8.53 (1H, br-s)

25 [0308]

Reference Example 109

1-[[[(3-Methyl-2-oxo-1-imidazolidinyl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester



[0309]

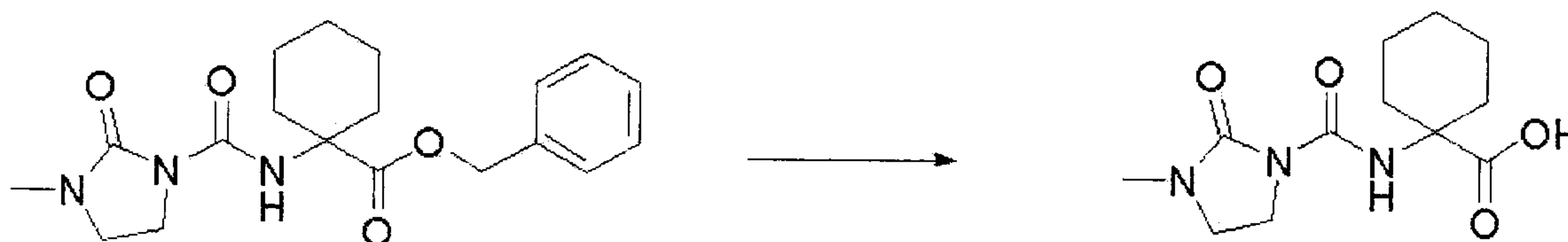
1.83 g (12.9 mmol) of methyl iodide was added to a solution of 1.50 g (4.3 mmol) of 1-[[[(2-oxo-1-imidazolidinyl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester and 1.78 g (12.9 mmol) of potassium carbonate in 100 ml of acetonitrile, and the mixture was heated under reflux overnight. The reaction solution was concentrated, ethyl acetate was added thereto, and the mixture was successively washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by silica gel chromatography to obtain 710 mg (50%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.21-1.30 (1H, m), 1.42-1.56 (2H, m), 1.61-1.69 (3H, m), 1.79-1.88 (2H, m), 2.08-2.17 (2H, m), 2.86 (3H, s), 3.40 (2H, t, J=8Hz), 3.81 (2H, t, J=8Hz), 5.17 (2H, s), 7.30-7.36 (5H, m), 8.55 (1H, br-s)

[0310]

Reference Example 110

1-[[[(3-Methyl-2-oxo-1-imidazolidinyl)carbonyl]amino]cyclohexanecarboxylic acid



[0311]

710 mg (2 mmol) of 1-[[[(3-methyl-2-oxo-1-imidazolidinyl)carbonyl]amino]cyclohexanecarboxylic acid

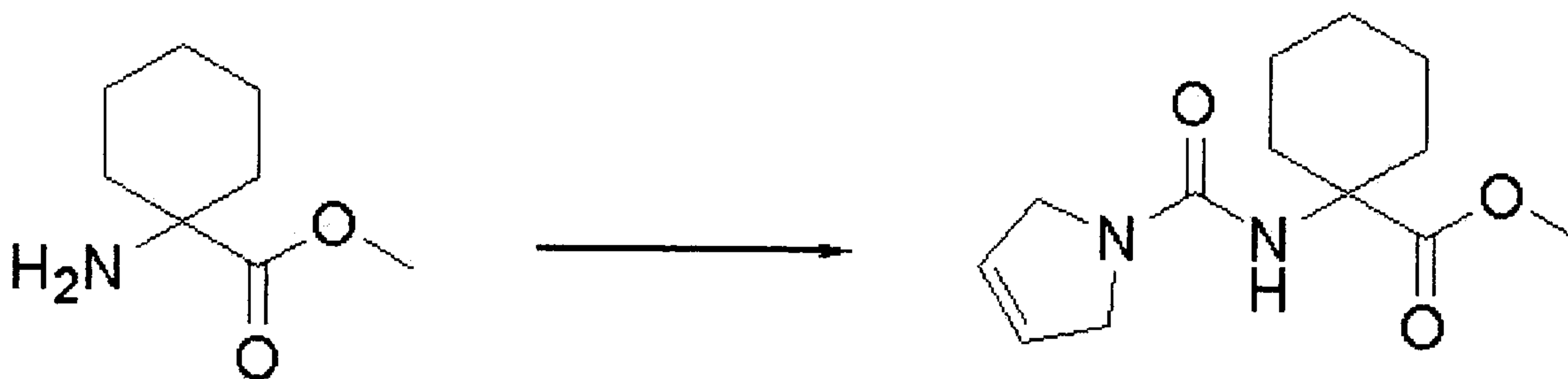
phenylmethyl ester was used instead of 1-[[[4-phenyl-1-piperazinyl)carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 78 to obtain 539 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.23-1.33 (1H, m), 1.42-1.53 (2H, m), 1.61-1.70 (3H, m), 1.82-1.89 (2H, m), 2.11-2.20 (2H, m), 2.89 (3H, s), 3.46 (2H, dd, J=10Hz, 8Hz), 3.91 (2H, dd, J=10Hz, 8Hz), 8.66 (1H, br-s)

[0312]

Reference Example 111

1-[[[2,5-Dihydro-1H-pyrrol-1-yl)carbonyl]amino]cyclohexanecarboxylic acid methyl ester



[0313]

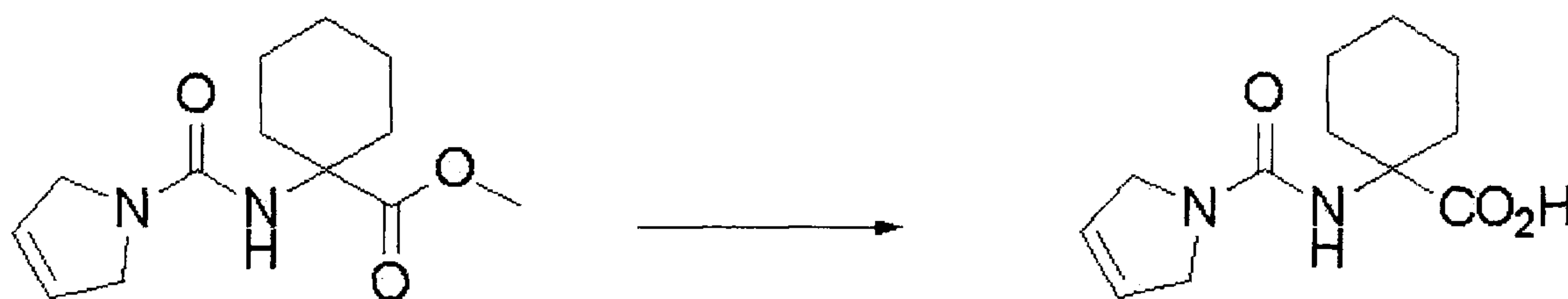
472 mg (3 mmol) of 1-aminocyclohexanecarboxylic acid methyl ester was used instead of 1-aminocyclohexanecarboxylic acid phenylmethyl ester, and 311 mg (4.5 mmol) of 2,5-dihydropyrrole was used instead of 1-phenylpiperazine in the process according to Reference Example 77 to obtain 698 mg (92%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.23-1.38 (1H, m), 1.42-1.53 (2H, m), 1.53-1.69 (3H, m), 1.82-1.92 (2H, m), 2.01-2.10 (2H, m), 3.73 (3H, s), 4.18 (4H, s), 4.31 (1H, s), 5.82 (2H, s)

[0314]

Reference Example 112

1-[[[2,5-Dihydro-1H-pyrrol-1-yl)carbonyl]amino]cyclohexanecarboxylic acid



[0315]

698 mg (2.8 mmol) of 1-[(2,5-dihydro-1H-pyrrol-1-yl)carbonyl]amino]cyclohexanecarboxylic acid methyl ester
 5 was used instead of 1-[[[4-(phenylmethyl)-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid ethyl ester in the process according to Reference Example 90 to obtain 453 mg (69%) of the title compound.

1H-NMR (CDCl₃, δ): 1.34-1.73 (6H, m), 1.92-2.22 (2H, m),
 10 2.24-2.36 (2H, m), 4.23 (4H, br-s), 4.23 (1H, br-s), 5.87 (2H, br-s)

[0316]

Reference Example 113

1-[(1H-Pyrrol-1-ylcarbonyl)amino]cyclohexanecarboxylic acid
 15 methyl ester



[0317]

1 g (6.36 mmol) of 1-aminocyclohexanecarboxylic acid methyl ester was used instead of 1-aminocyclohexanecarboxylic acid phenylmethyl ester, and 512
 20 mmol (7.6 mmol) of pyrrole was used instead of 1-phenylpiperazine in the process according to Reference Example 77 to obtain 1.52 g (95%) of the title compound.

1H-NMR (CDCl₃, δ): 1.36-1.57 (3H, m), 1.65-1.74 (3H, m),
 25 1.91-2.02 (2H, m), 2.08-2.19 (2H, m), 3.74 (3H, s), 5.58

(1H, s), 6.28 (2H, dd, J=2Hz, 1Hz), 7.19 (2H, dd, J=2Hz, 1Hz)

[0318]

Reference Example 114

5 1-[(1H-Pyrrol-1-ylcarbonyl)amino]cyclohexanecarboxylic acid



[0319]

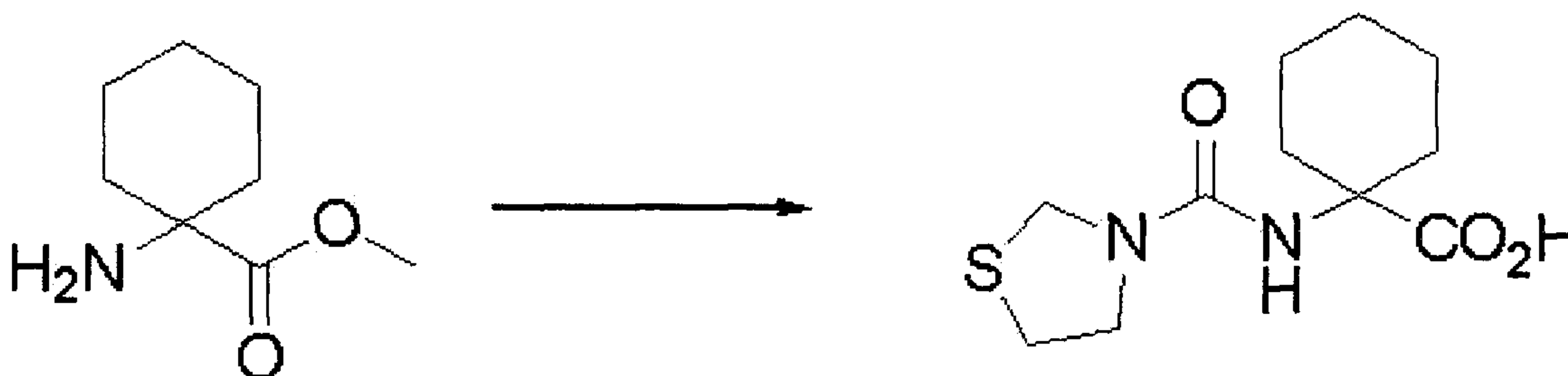
1.52 g (6 mmol) of 1-[[[4-(phenylmethyl)-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester
 10 was used instead of 1-[[[4-(phenylmethyl)-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid ethyl ester in the process according to Reference Example 90 to obtain 839 mg (58%) of the title compound.

1H-NMR (DMSO-d₆, δ): 1.15-1.61 (4H, m), 1.69-1.81 (2H, m),
 15 1.83-1.98 (2H, m), 2.08-2.19 (2H, m), 6.12 (2H, s), 6.21 (1H, d, J=2Hz), 7.42 (2H, d, J=2Hz), 7.88 (1H, dr-s)

[0320]

Reference Example 115

20 1-[(3-Thiazolidinylcarbonyl)amino]cyclohexanecarboxylic acid



[0321]

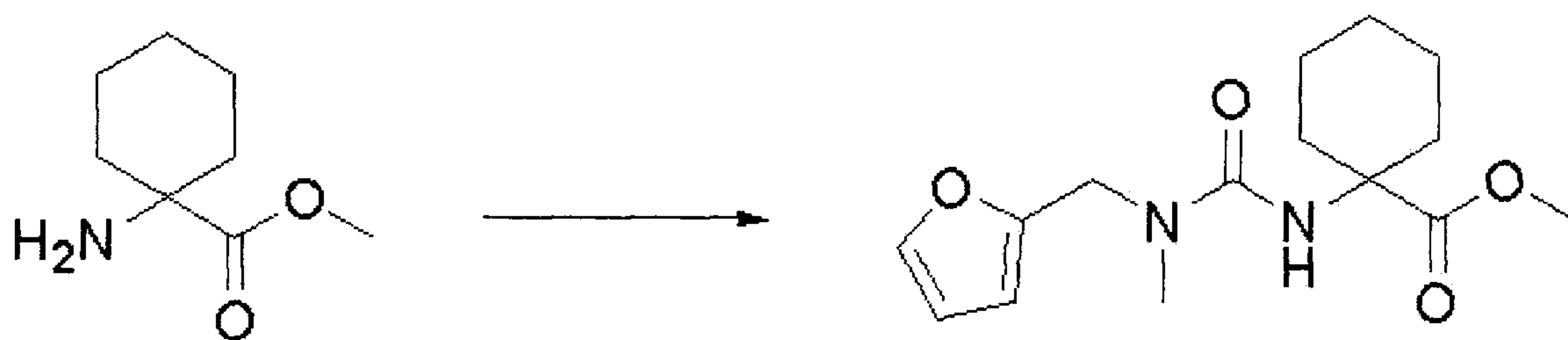
A solution of 78 mg (0.6 mmol) of N,N-dimethylaminopyridine and 1 g (6.36 mmol) of 1-aminocyclohexanecarboxylic acid methyl ester in methylene
 25

chloride was added to a solution of 1.39 mg (6.36 mmol) of di-t-butyl dicarbonate in 10 ml of methylene chloride, and the mixture was stirred at room temperature for 30 minutes. Thereafter, a solution of 1.29 g (12.7 mmol) of triethylamine and 680 mg (7.6 mmol) of thiazolidine in methylene chloride was added thereto, and the mixture was stirred at room temperature overnight. After the reaction solution was concentrated, the residue was dissolved in ethyl acetate, and the mixture was washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and then saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, tetrahydrofuran and 1N aqueous sodium hydroxide solution were added to the residue, and the mixture was heated under reflux for 3 hours. After ether was added to the reaction solution to wash it, the aqueous layer was neutralized by concentrated hydrochloric acid, and it was extracted with ethyl acetate. After the obtained organic layer was washed with saturated brine, it was dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 1.1 g (66%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.08-1.25 (1H, m), 1.36-1.69 (6H, m), 1.82-2.01 (3H, m), 2.93 (2H, t, J=7Hz), 3.59 (2H, t, J=7Hz), 4.43 (2H, s), 6.44 (1H, s), 11.99 (1H, br-s)
[0322]

Reference Example 116

1-[[[(2-Furanylmethyl)methylamino]carbonyl]amino]cyclohexanecarboxylic acid methyl ester



[0323]

2.83 g (18 mmol) of 1-aminocyclohexanecarboxylic acid methyl ester was used instead of 1-

5 aminocyclohexanecarboxylic acid phenylmethyl ester, and 2.18 g (18 mmol) of (2-furanylmethyl)methylamine was used instead of 1-phenylpiperazine in the process according to Reference Example 77 to obtain 4.27 g (78%) of the title compound.

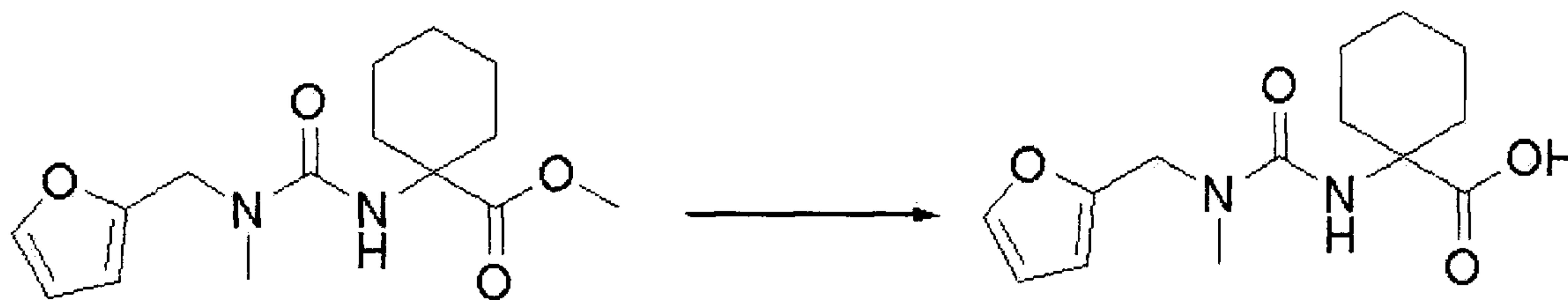
10 ¹H-NMR (CDCl₃, δ): 1.25-1.47 (3H, m), 1.57-1.68 (3H, m), 1.80-1.85 (2H, m), 1.97-2.20 (2H, m), 2.94 (3H, s), 3.71 (3H, s), 4.42 (2H, s), 4.74 (1H, s), 6.24 (1H, dd, J=3Hz, 1Hz), 6.34 (1H, dd, J=3Hz, J=3Hz, 2Hz), 7.37 (1H, dd, J=2Hz, 1Hz)

[0324]

Reference Example 117

1-[[[(2-

Furanylmethyl)methylamino]carbonyl]amino]cyclohexanecarboxylic acid



[0325]

4.27 g (14 mmol) of 1-[[[(2-furanylmethyl)methylamino]carbonyl]amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[[[4-(phenylmethyl)-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid ethyl

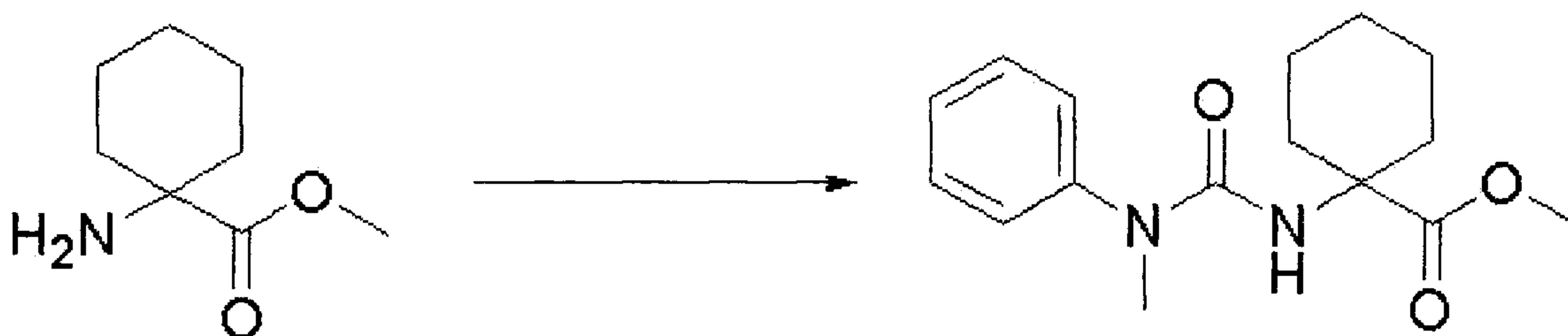
ester in the process according to Reference Example 90 to obtain 3.47 g (84%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.12-1.23 (1H, m), 1.38-1.52 (5H, m), 1.58-1.64 (2H, m), 1.80-2.22 (2H, m), 2.81 (3H, s), 4.42 (2H, s), 6.03 (1H, s), 6.24 (1H, dd, J=3Hz, 1Hz), 6.40 (1H, dd, J=3Hz, 2Hz), 7.57 (1H, dd, J=2Hz, 1Hz)

[0326]

Reference Example 118

1-[[(Methylphenylamino) carbonyl] amino] cyclohexanecarboxylic acid methyl ester



[0327]

472 mg (3 mmol) of 1-aminocyclohexanecarboxylic acid methyl ester was used instead of 1-

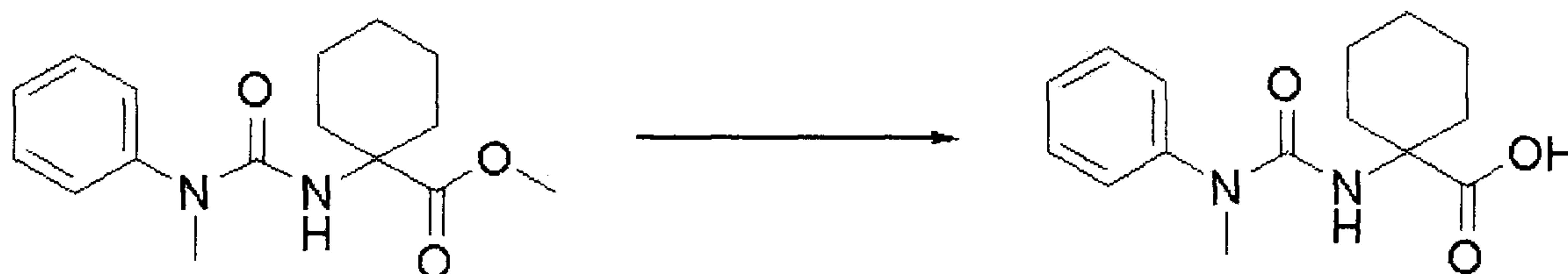
aminocyclohexanecarboxylic acid phenylmethyl ester, and 643 mg (6 mmol) of N-methylaniline was used instead of 1-phenylpiperazine in the process according to Reference Example 77 to obtain 834 mg (96%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.12-1.28 (2H, m), 1.48-1.62 (4H, m), 1.64-1.70 (2H, m), 1.90-1.98 (2H, m), 3.25 (3H, s), 3.74 (3H, s), 4.49 (1H, s), 7.26-7.36 (3H, m), 7.43-7.46 (2H, m)

[0328]

Reference Example 119

1-[[(Methylphenylamino) carbonyl] amino] cyclohexanecarboxylic acid



[0329]

834 mg (2.87 mmol) of 1-
[[(methylphenylamino) carbonyl] amino] cyclohexanecarboxylic
acid methyl ester was used instead of 1-[[[4-
5 (phenylmethyl)-1-
piperazinyl] carbonyl] amino] cyclohexanecarboxylic acid ethyl
ester in the process according to Reference Example 90 to
obtain 464 mg (59%) of the title compound.

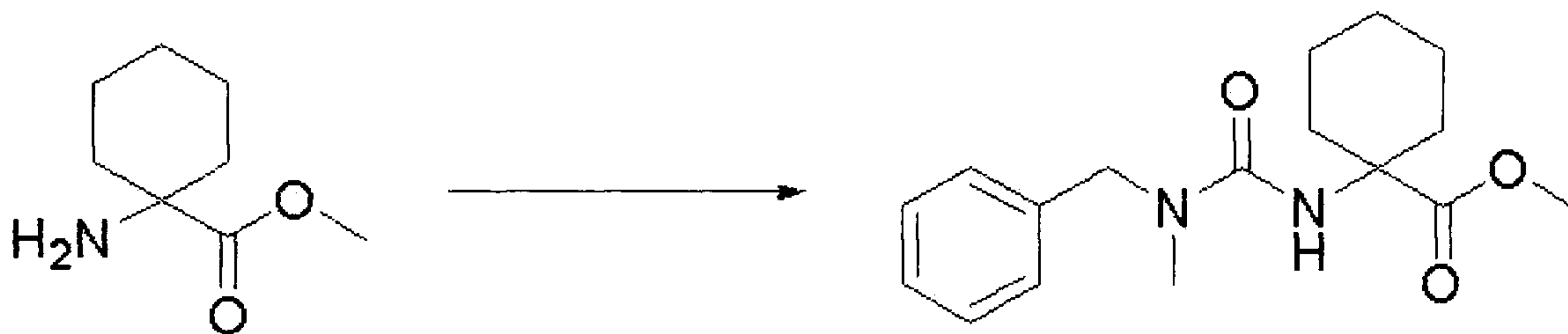
1H-NMR (CDCl₃, δ): 0.96-1.05 (2H, m), 1.19-1.30 (1H, m),
10 1.50-1.60 (3H, m), 1.70-1.81 (2H, m), 1.96-2.02 (2H, m),
3.31 (3H, s), 4.30 (1H, s), 7.26-7.33 (2H, m), 7.44 (1H, t,
J=9Hz), 7.51 (2H, t, J=9Hz)

[0330]

Reference Example 120

15 1-

[[[Methyl (phenylmethyl) amino] carbonyl] amino] cyclohexanecarb
oxylic acid methyl ester



[0331]

20 2.83 g (18 mmol) of 1-aminocyclohexanecarboxylic acid
methyl ester was used instead of 1-
aminocyclohexanecarboxylic acid phenylmethyl ester, and
2.18 g (18 mmol) of N-methylbenzylamine was used instead of
1-phenylpiperazine in the process according to Reference
25 Example 77 to obtain 4.27 g (78%) of the title compound.

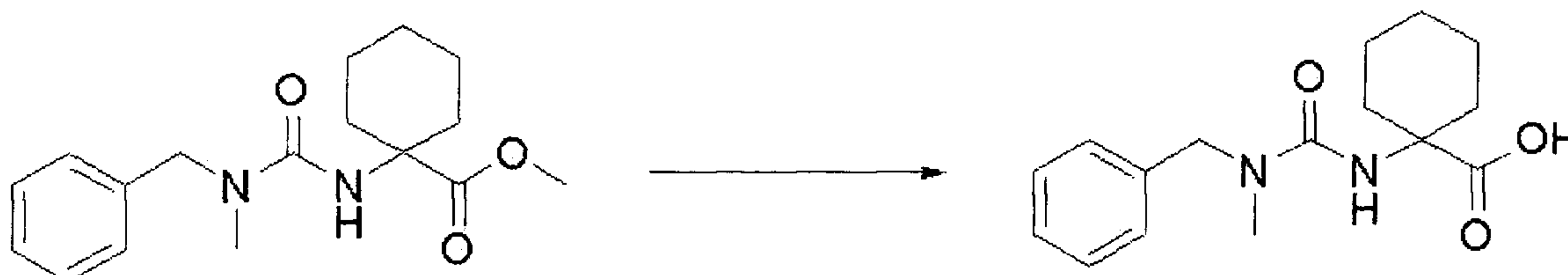
1H-NMR (CDCl₃, δ): 1.20-1.38 (3H, m), 1.50-1.63 (3H, m),
1.78-1.85 (2H, m), 1.97-2.03 (2H, m), 2.94 (3H, s), 3.73
(3H, s), 4.49 (2H, s), 4.51 (1H, s), 7.25-7.30 (3H, m),
7.35 (2H, dt, J=8Hz, 1Hz)

[0332]

Reference Example 121

1-

[[[Methyl(phenylmethyl)amino]carbonyl]amino]cyclohexanecarb
 5 oxylic acid



[0333]

4.27 g (14 mmol) of 1-

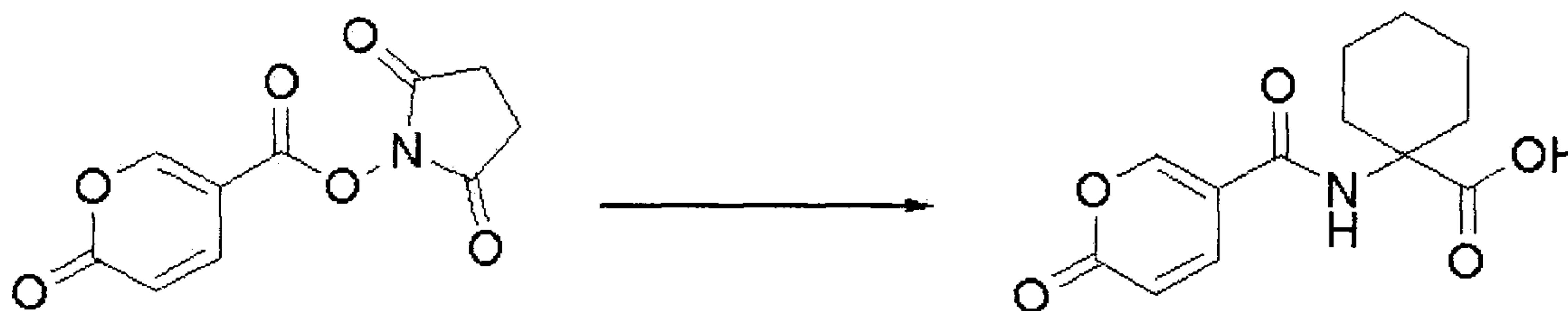
[[[methyl(phenylmethyl)amino]carbonyl]amino]cyclohexanecarb
 10 oxylic acid methyl ester was used instead of 1-[[[4-(phenylmethyl)-1-piperazinyl]carbonyl]amino]cyclohexanecarboxylic acid ethyl ester in the process according to Reference Example 90 to obtain 3.54 g (86%) of the title compound.

15 ¹H-NMR (DMSO-d₆, δ): 1.16-2.04 (1H, m), 1.39-1.47 (5H, m), 1.58-1.65 (2H, m), 1.97-2.22 (2H, m), 2.79 (3H, s), 4.44 (2H, s), 6.00 (1H, s), 7.21-7.34 (5H, m)

[0334]

Reference Example 122

20 1-[[[(2-Oxo-2H-pyran-5-yl)carbonyl]amino]cyclohexanecarboxylic acid



[0335]

2.37 g (10 mmol) of 5-coumalincarboxylic acid N-hydroxysuccineimide ester and a solution of 1.43 g (10 mmol) of 1-aminocyclohexanecarboxylic acid and 3.04 g (30

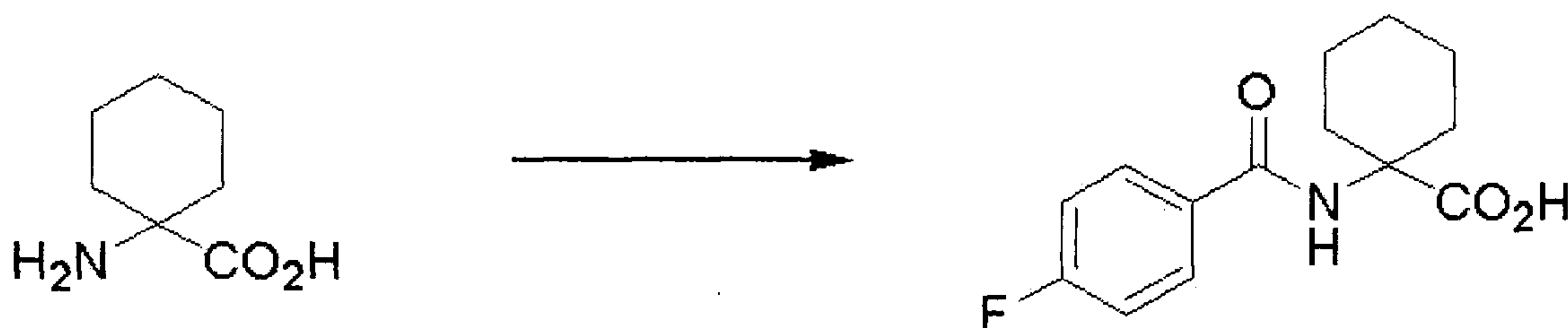
mmol) of triethylamine in 20 ml of dimethylformamide were stirred overnight. Ethyl acetate was added to the reaction solution, and the mixture was washed with a 10% aqueous potassium hydrogensulfate solution and then saturated
5 brine. After it was dried with anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain 1.42 g (60%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.30-1.44 (3H, m), 1.44-1.63 (3H, m), 1.95-2.09 (4H, m), 5.26 (1H, d, J=9Hz), 7.62 (1H, d, J=9Hz), 8.28 (1H, d, J=15Hz), 9.68 (1H, d, J=15Hz)

[0336]

Reference Example 123

1-[(4-Fluorobenzoyl)amino]cyclohexanecarboxylic acid



[0337]

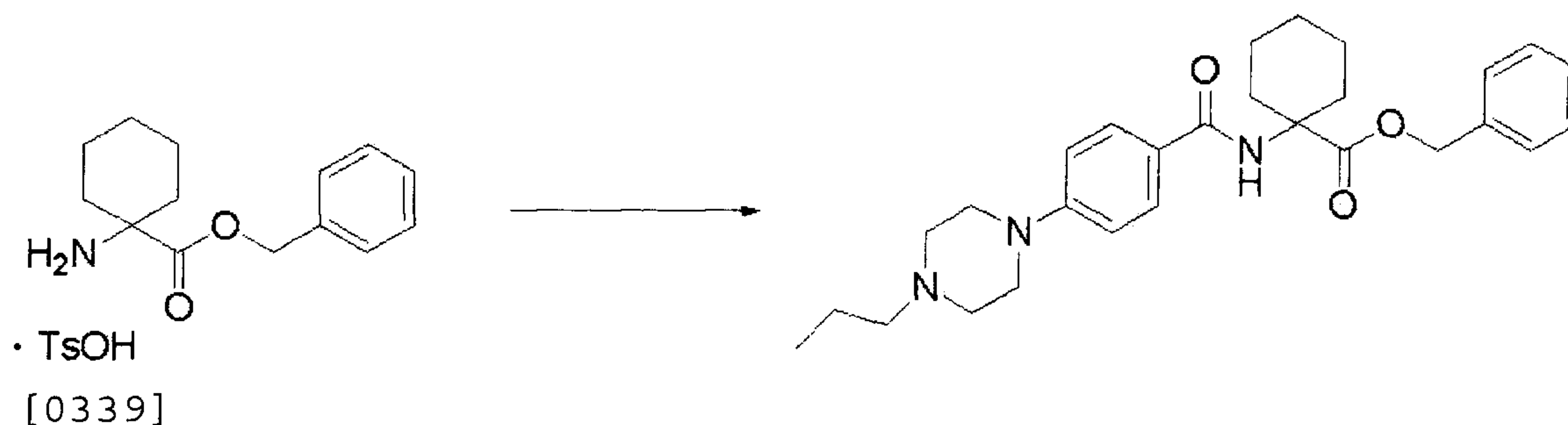
Under ice-cooling, a solution of 25.0 g (15.8 mmol) of 4-fluorobenzoyl chloride in 30 ml of ether was added dropwise to a mixture solution of 22.6 g (15.8 mmol) of 1-aminocyclohexanecarboxylic acid and 25.0 g (23.7 mmol) of sodium carbonate in 100 ml of ether and 300 ml of water,
20 and the mixture was stirred at room temperature overnight. After the ether layer was separated, under ice-cooling, the aqueous layer was neutralized by concentrated hydrochloric acid, and the precipitated crystal was collected by
25 filtration to obtain 27.7 g (66%) of the title compound.

[0338]

Reference Example 124

1-[[[4-(4-Propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid

phenylmethyl ester



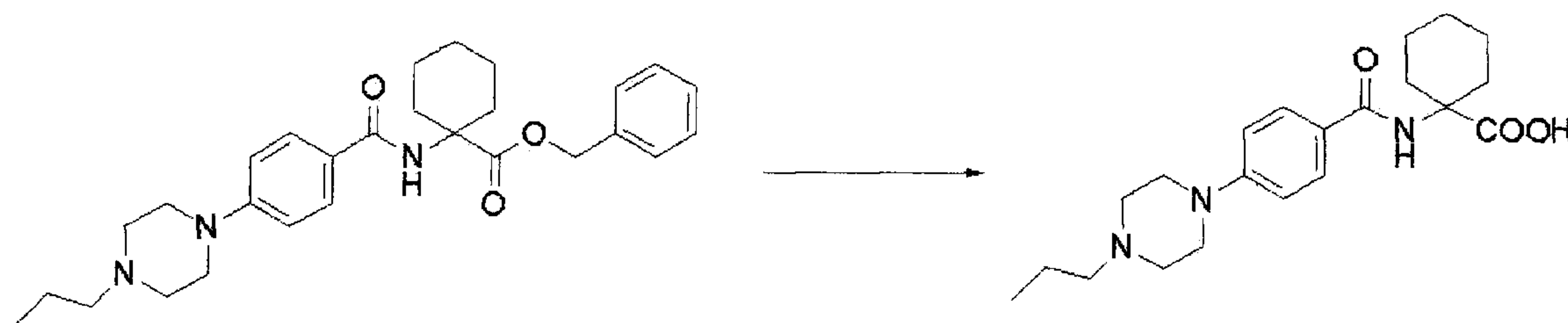
2.36 g (8.44 mmol) of 4-(4-propylpiperazin-1-yl)benzoic acid hydrochloride was used instead of phenylacetyl chloride in the process according to Reference Example 1 to obtain 1.79 g (46%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.94 (3H, t, J=7Hz), 1.28-1.40 (1H, m), 1.45-1.61 (4H, m), 1.61-1.72 (3H, m), 1.90-1.98 (2H, m), 2.15-2.23 (2H, m), 2.36 (1H, t, J=6Hz), 2.37 (1H, t, J=6Hz), 2.59 (4H, t, J=5Hz), 3.31 (4H, t, J=5Hz), 5.16 (2H, s), 6.13 (1H, br-s), 6.89 (2H, d, J=8Hz), 7.25-7.33 (5H, m), 7.68 (2H, d, J=8Hz)

[0340]

Reference Example 125

1-[[[4-(4-Propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid



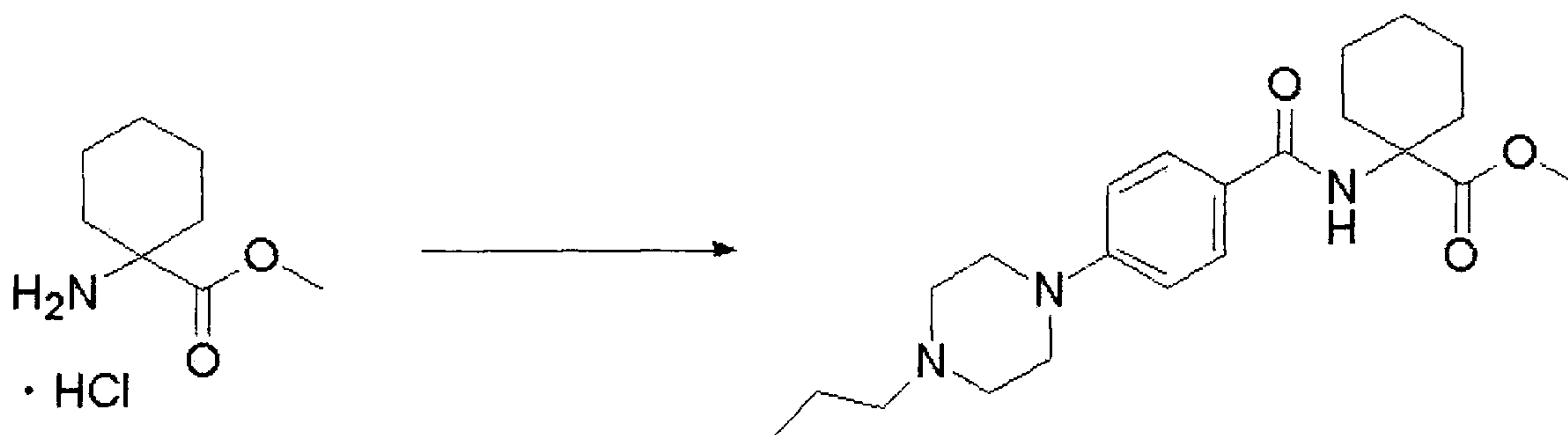
1.79 g (3.86 mmol) of 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 2 to obtain 1.43 g (quantitative) of the title

compound.

¹H-NMR (CDCl₃, δ): 0.95 (3H, t, J=8Hz), 1.39-1.61 (3H, m),
1.65-1.78 (4H, m), 1.94-2.03 (3H, m), 2.21-2.41 (2H, m),
2.45-2.54 (2H, m), 2.65-2.70 (4H, m), 3.27-3.35 (4H, m),
5 6.06 (1H, br-s), 6.85 (2H, d, J=8Hz), 7.65 (2H, d, J=8Hz)
[0342]

Reference Example 126

1-[[[4-(4-Propylpiperazin-1-
yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid methyl
10 ester



[0343]

1.00 g (3.57 mmol) of 4-(4-propylpiperazin-1-
yl)benzoic acid hydrochloride was used instead of 3-
15 furancarboxylic acid in the process according to Reference
Example 15 to obtain 602 g (44%) of the title compound.

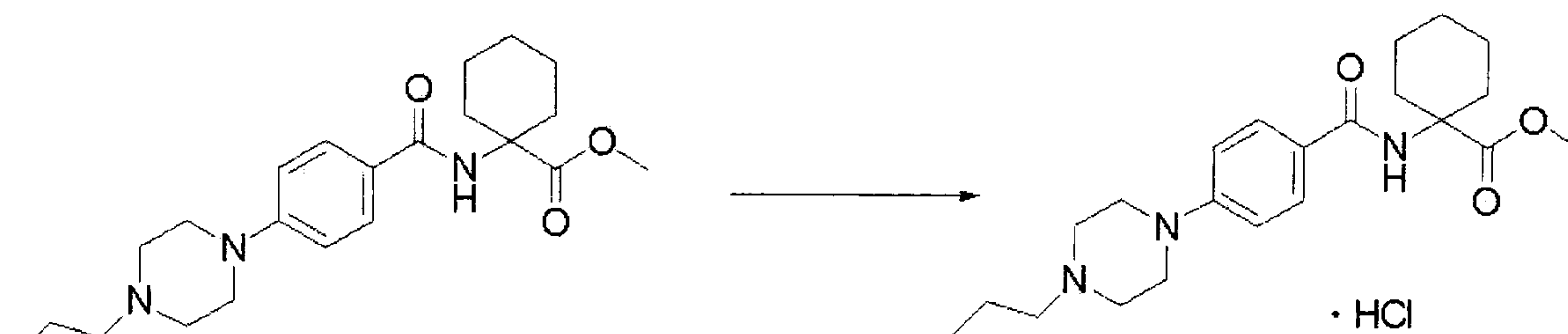
¹H-NMR (CDCl₃, δ): 0.94 (3H, t, J=8Hz), 1.31-1.40 (1H, m),
1.44-1.58 (4H, m), 1.62-1.74 (3H, m), 1.88-1.96 (2H, m),
2.11-2.19 (2H, m), 2.36 (1H, t, J=6Hz), 2.37 (1H, t,
20 J=6Hz), 2.59 (4H, t, J=5Hz), 3.30 (4H, t, J=5Hz), 3.72 (3H,
s), 6.12 (1H, br-s), 6.89 (2H, dd, J=2Hz, 7Hz), 7.69 (2H,
dd, J=2Hz, 7Hz)

[0344]

Reference Example 127

25 1-[[[4-(4-Propylpiperazin-1-
yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid methyl
ester hydrochloride

FP2863PCT



[0345]

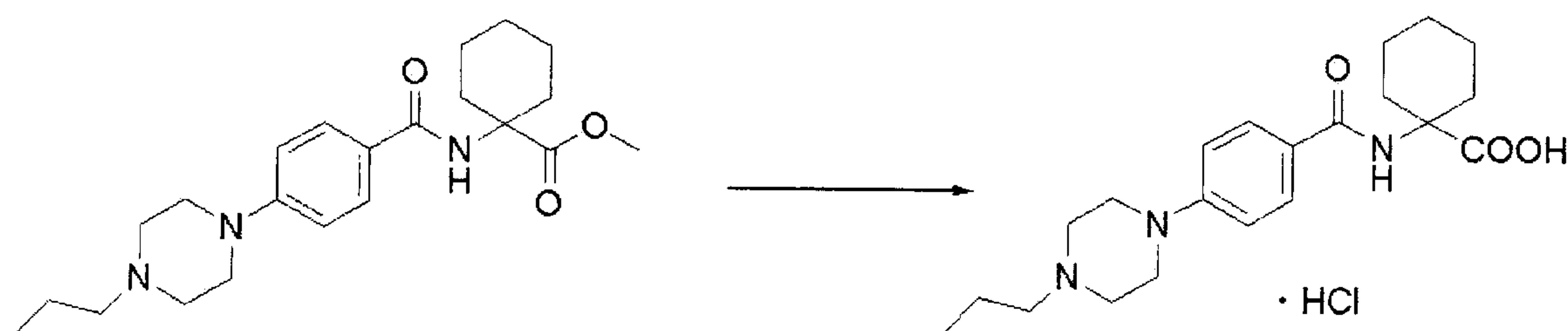
1 ml of 4N hydrochloric acid/ethyl acetate solution was added to a solution of 120 mg (0.31 mmol) of 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester in 10 ml of ethyl acetate, and the mixture was stirred at room temperature for 30 minutes. The precipitated crystal was collected by filtration to obtain 87 mg (66%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 0.91 (3H, t, J=8Hz), 1.21-1.35 (1H, m), 1.47-1.62 (5H, m), 1.70-1.81 (4H, m), 2.02-2.10 (2H, m), 3.01-3.14 (4H, m), 3.15-3.28 (2H, m), 3.50-3.58 (2H, m), 3.82-4.02 (5H, m), 7.04 (2H, dd, J=2Hz, 7Hz), 7.79 (2H, dd, J=2Hz, 7Hz), 8.11 (1H, s)

[0346]

Reference Example 128

1-[[[4-(4-Propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid hydrochloride



[0347]

3 ml of 4N hydrochloric acid was added to 600 mg (1.55 mmol) of 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid methyl

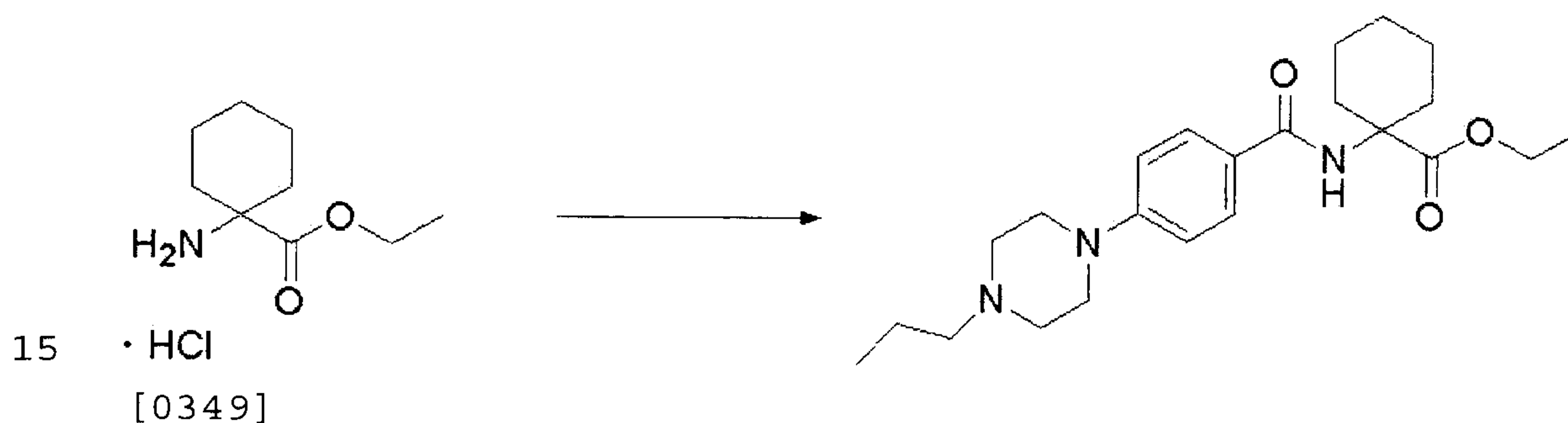
ester, and the mixture was heated under reflux for 6 hours. The mixture was cooled to room temperature, and the precipitated crystal was collected by filtration to obtain 258 mg (41%) of the title compound.

5 ¹H-NMR (CDCl₃, δ): 1.05 (3H, t, J=7Hz), 1.31-1.43 (1H, m), 1.45-1.56 (2H, m), 1.64-1.78 (3H, m), 1.90-2.02 (4H, m), 2.16-2.25 (2H, m), 2.95-3.28 (5H, m), 3.60-3.75 (4H, m), 3.78-3.89 (2H, m), 6.65 (1H, br-s), 6.92 (2H, d, J=8Hz), 7.97 (2H, d, J=8Hz)

10 [0348]

Reference Example 129

1-[[[4-(4-Propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid ethyl ester



741 mg (3.57 mmol) of 1-aminocyclohexanecarboxylic acid ethyl ester hydrochloride was used instead of 1-aminocyclohexanecarboxylic acid methyl ester hydrochloride, and 1.00 g (3.57 mmol) of 4-(4-propylpiperazin-1-yl)benzoic acid hydrochloride was used instead of 3-furancarboxylic acid in the process according to Reference Example 15 to obtain 928 mg (65%) of the title compound.

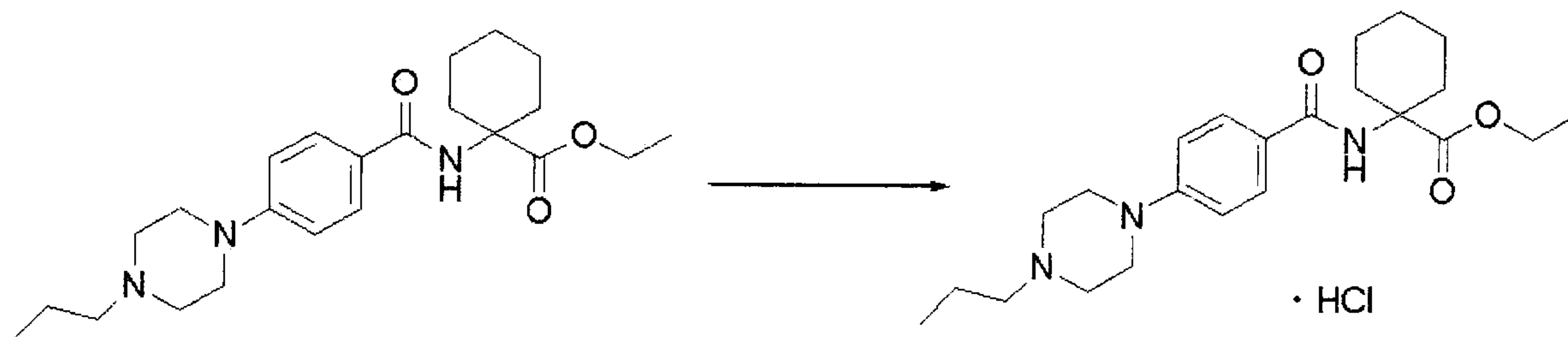
1H-NMR (CDCl₃, δ): 0.94 (3H, t, J=8Hz), 1.24 (3H, t, J=7Hz), 1.30-1.41 (1H, m), 1.43-1.71 (7H, m), 1.88-1.97 (2H, m), 2.10-2.20 (2H, m), 2.36 (1H, t, J=6Hz), 2.37 (1H, t, J=6Hz), 3.31 (4H, t, J=5Hz), 4.18 (4H, t, J=5Hz), 4.20 (2H, q, J=7Hz), 6.10 (1H, br-s), 6.89 (2H, dd, J=2Hz, 8Hz), 7.69

(2H, dd, J=2Hz, 8Hz)

[0350]

Reference Example 130

1-[[[4-(4-Propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid ethyl ester hydrochloride



[0351]

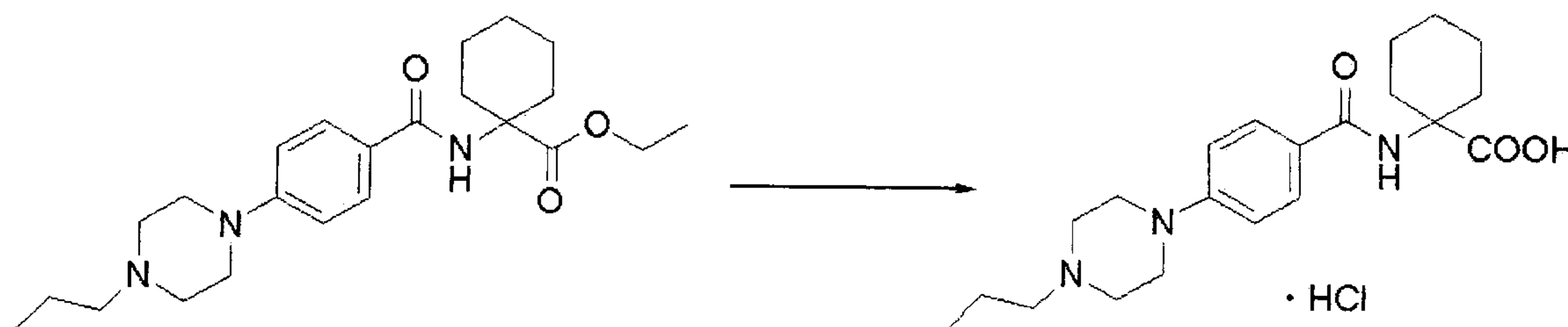
120 mg (0.3 mmol) of 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid ethyl ester was used instead of 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 127 to obtain 114 mg (87%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 0.93 (3H, t, J=8Hz), 1.11 (3H, t, J=7Hz), 1.23-1.32 (1H, m), 1.45-1.55 (5H, m), 1.68-1.80 (4H, m), 2.02-2.10 (2H, m), 3.03-3.18 (6H, m), 3.51-3.62 (2H, m), 3.95-4.04 (2H, m), 4.02 (2H, q, J=7Hz), 7.04 (2H, d, J=8Hz), 7.78 (2H, d, J=8Hz), 8.10 (1H, s)

[0352]

Reference Example 131

1-[[[4-(4-Propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid hydrochloride



[0353]

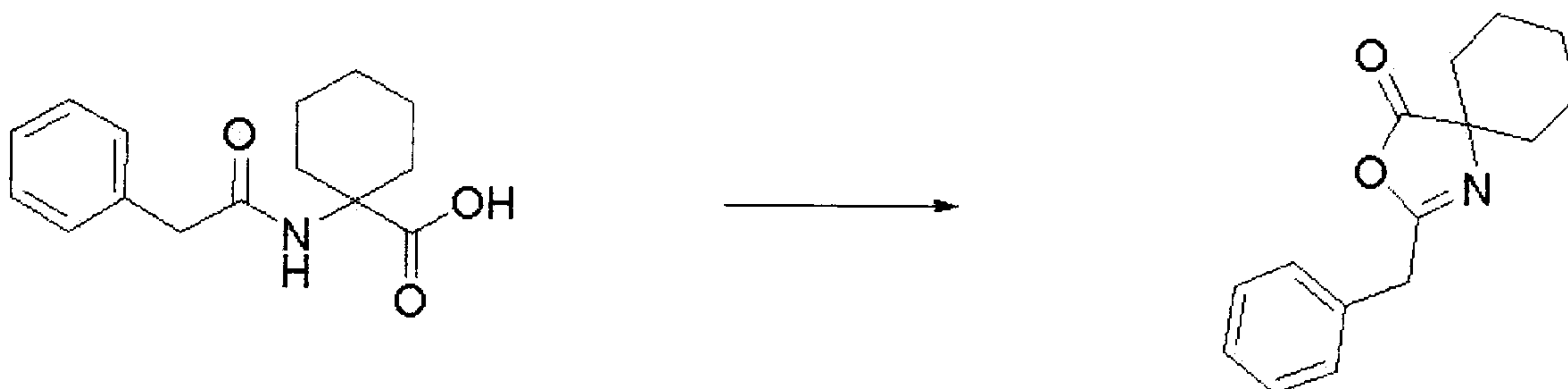
800 mg (1.99 mmol) of 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid ethyl ester was used instead of 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester in the process according to Reference Example 128 to obtain 197 mg (24%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.05 (3H, t, J=7Hz), 1.31-1.43 (1H, m), 1.45-1.56 (2H, m), 1.64-1.78 (3H, m), 1.90-2.02 (4H, m), 2.16-2.25 (2H, m), 2.95-3.28 (5H, m), 3.60-3.75 (4H, m), 3.78-3.89 (2H, m), 6.65 (1H, br-s), 6.92 (2H, d, J=8Hz), 7.97 (2H, d, J=8Hz)

[0354]

Reference Example 132

2-(Phenylmethyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0355]

633 mg (3.3 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added to a solution of 784 mg (3 mmol) of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid obtained in Reference Example 2 in 20 ml of methylene chloride. After the mixture was stirred at room temperature for 4 hours, the reaction solution was concentrated under reduced pressure, ethyl acetate was added thereto, and the mixture was successively washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by

drying with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 625 mg (86%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.48-1.51 (1H, m), 1.56-1.70 (3H, m),
5 1.70-1.79 (6H, m), 3.79 (2H, s), 7.28-7.36 (5H, m)

[0356]

Reference Example 133

2-(2-Phenylethyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



10 [0357]

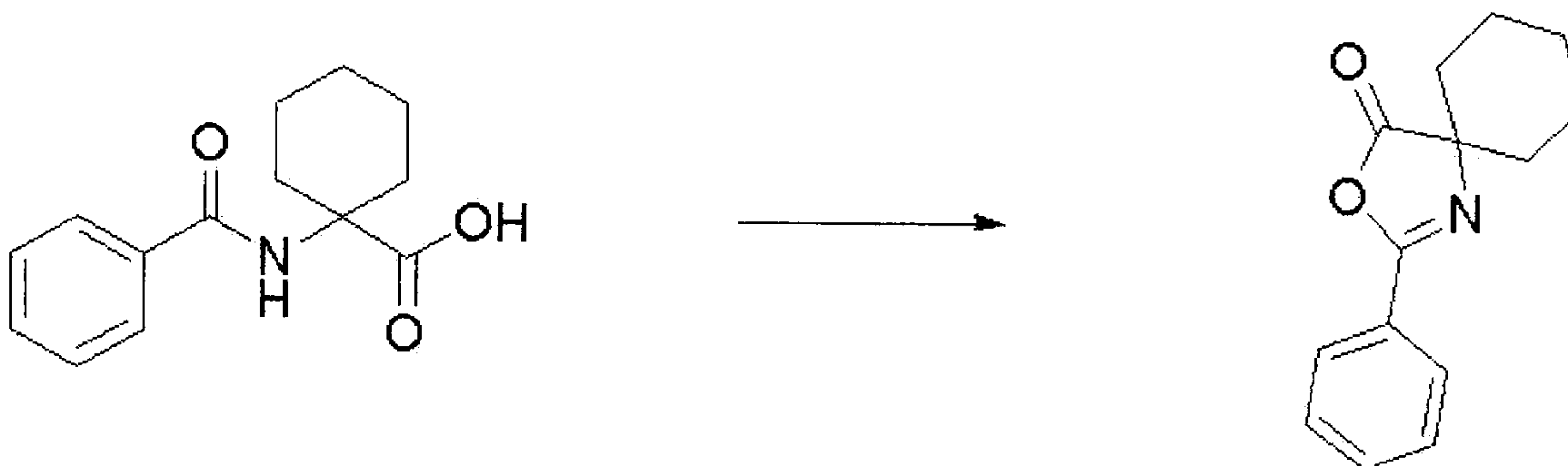
826 mg (3 mmol) of 1-[(1-oxo-3-phenylpropyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to
15 obtain 764 mg (99%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.47-1.55 (4H, m), 1.57-1.78 (6H, m),
2.79 (2H, t, J=7Hz), 3.02 (2H, t, J=7Hz), 7.20-7.23 (3H,
m), 7.28-7.31 (2H, m)

[0358]

20 Reference Example 134

2-Phenyl-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0359]

742 mg (3 mmol) of 1-

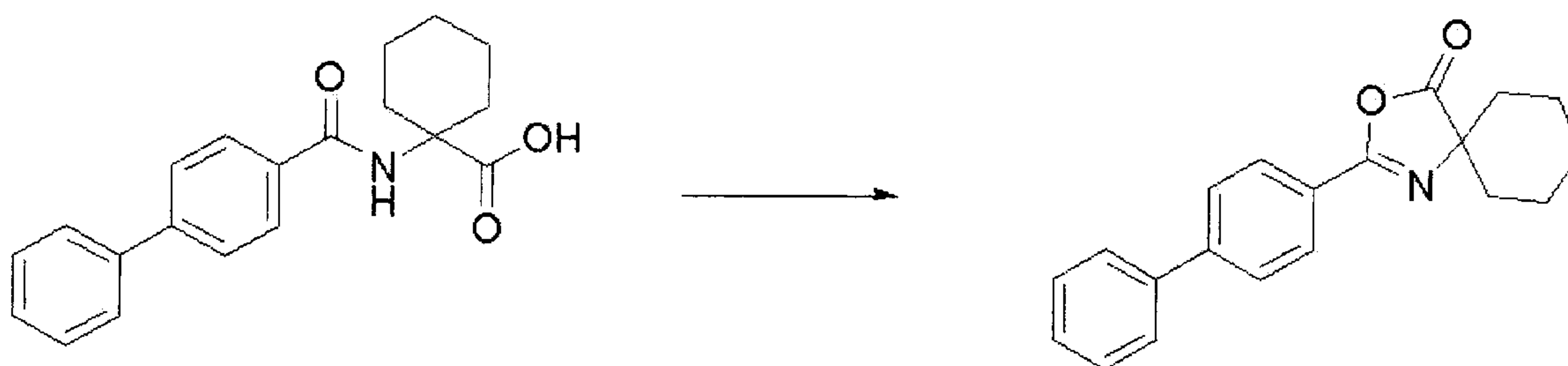
[(benzoyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 633 mg (92%) of the title compound.

5 ¹H-NMR (CDCl₃, δ): 1.52-1.58 (1H, m), 1.63-1.78 (3H, m), 1.79-1.89 (6H, m), 7.47 (1H, td, J=7Hz, 1Hz), 7.49 (1H, td, J=7Hz, 1Hz), 7.56 (1H, td, J=7Hz, 1Hz), 8.02 (2H, m)

[0360]

Reference Example 135

10 2-(4-Biphenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0361]

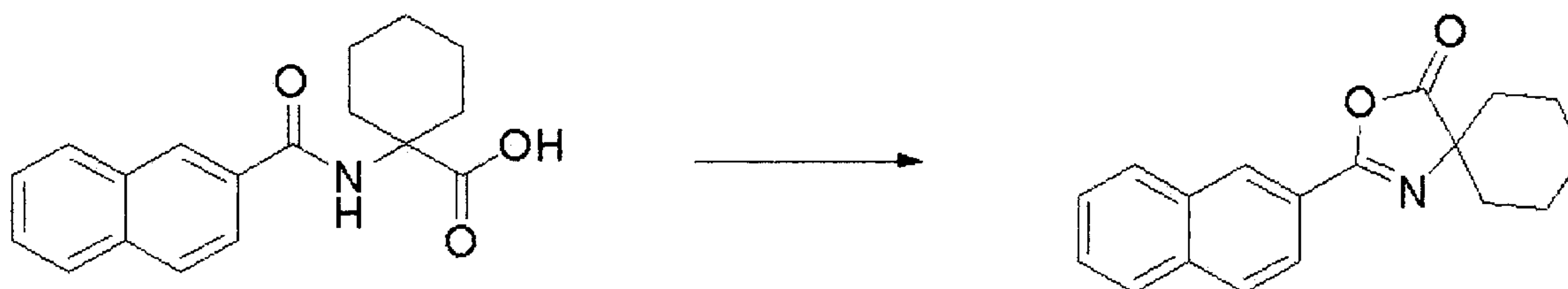
970 mg (3 mmol) of 1-[(4-biphenylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 914 mg (quantitative) of the title compound.

15 ¹H-NMR (CDCl₃, δ): 1.52 (2H, m), 1.63-1.71 (1H, m), 1.72-1.80 (2H, m), 1.81-1.90 (5H, m), 7.39-7.42 (1H, m), 7.47-7.50 (2H, m), 7.63 (1H, dd, J=7Hz, 1Hz), 7.65 (1H, dd, J=7Hz, 1Hz), 7.71 (1H, d, J=7Hz, 1Hz), 7.72 (1H, dd, J=7Hz, 1Hz), 8.07 (1H, dd, J=7Hz, 1Hz), 8.08 (1H, dd, J=7Hz, 1Hz)

[0362]

Reference Example 136

25 2-(2-Naphthyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0363]

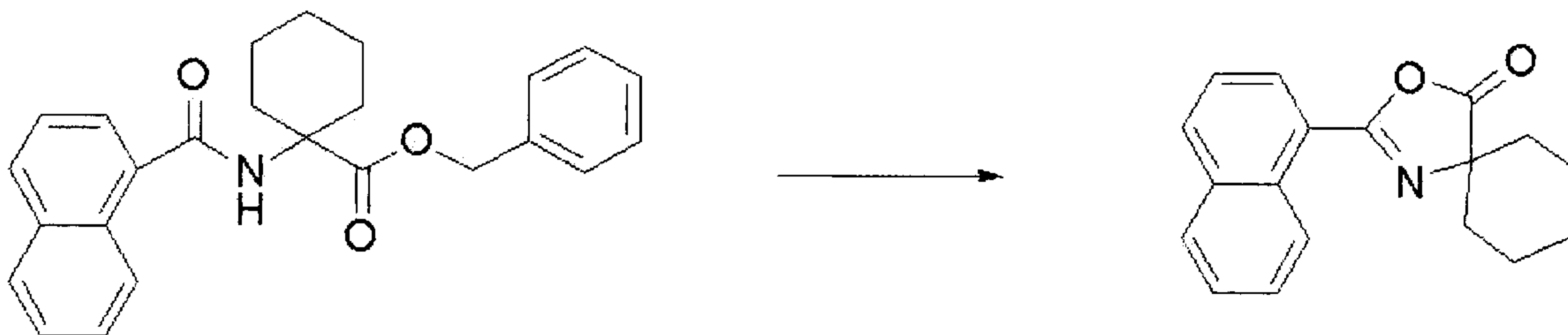
595 mg (2 mmol) of 1-[(2-naphthylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 562 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.54-1.68 (1H, m), 1.69-1.76 (1H, m), 1.78-1.94 (8H, m), 7.26-7.62 (2H, m), 7.89 (1H, d, J=8Hz), 7.92 (1H, dd, J=8Hz, 1Hz), 7.95 (1H, dd, J=8Hz, 1Hz), 8.09 (1H, dd, J=8Hz, 1Hz), 8.49 (1H, d, J=1Hz)

[0364]

Reference Example 137

2-(1-Naphthyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0365]

1.35 g (3.5 mmol) of 1-[(1-naphthylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester obtained in Reference Example 11 was dissolved in 50 ml of methanol, 150 mg of 10% palladium-carbon was added thereto, and the mixture was stirred under a hydrogen atmosphere at room temperature overnight. After reaction solution was filtered, the filtrate was concentrated under reduced pressure. The obtained residue was dissolved in 30 ml of methylene chloride, and 633 mg (3.3 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

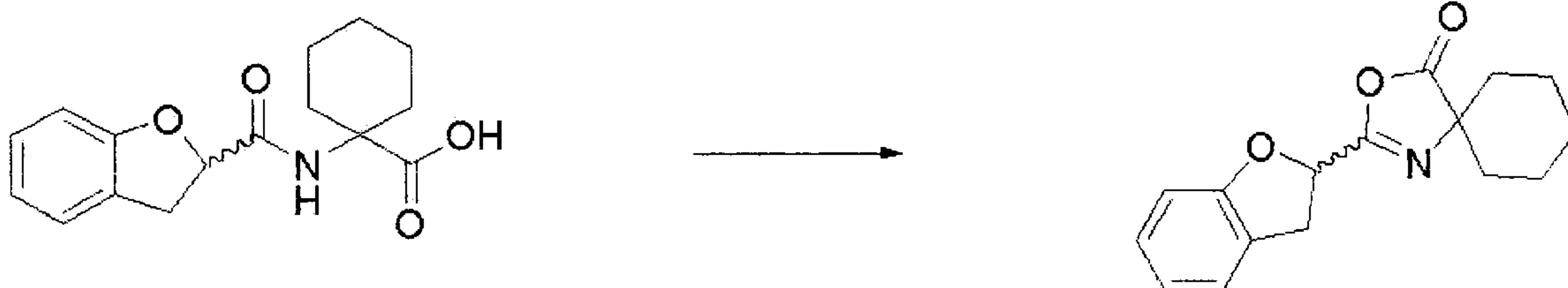
hydrochloride was added thereto. After the mixture was stirred at room temperature for 4 hours, under reduced pressure, the reaction solution was concentrated, ethyl acetate was added thereto, and the mixture was successively washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by drying with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 738 mg (88%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.50-1.68 (3H, m), 1.70-2.00 (7H, m), 7.53-7.60 (2H, m), 7.67 (1H, td, 7Hz, 1Hz), 7.92 (1H, dd, J=7Hz, 1Hz), 8.03 (1H, d, J=7Hz), 8.17 (1H, dd, J=7Hz, 1Hz), 9.33 (1H, dd, J=7Hz, 1Hz)

[0366]

Reference Example 138

2-[(RS)-2,3-Tetrahydrobenzofuran-2-yl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0367]

868 mg (3 mmol) of 1-[[[(RS)-2,3-tetrahydrobenzofuran-2-yl]carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 686 mg (87%) of the title compound.

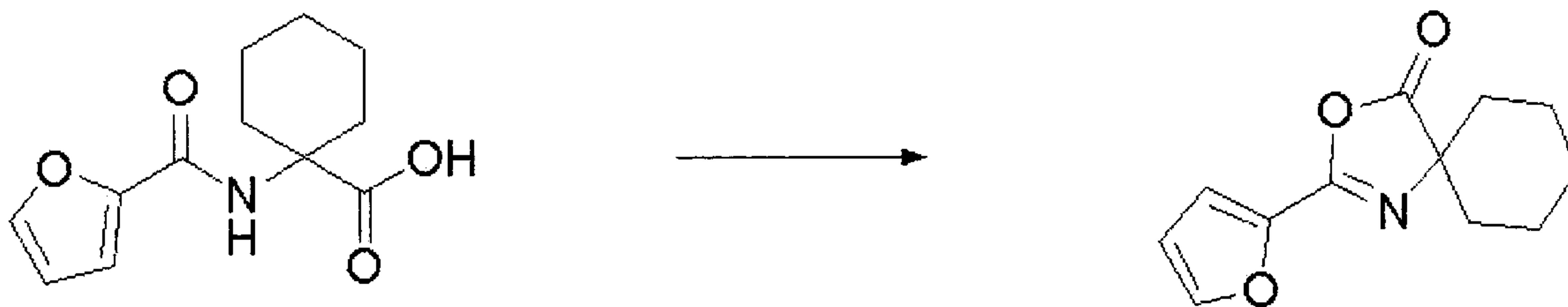
¹H-NMR (CDCl₃, δ): 1.43-1.82 (10H, m), 3.56 (2H, d, J=9Hz), 5.46(1/2H, d, J=10Hz), 5.48(1/2H, d, J=10Hz), 6.89 (1H, td, 8Hz, 1Hz), 6.93 (1H, dd, H=8Hz, 1Hz), 7.16 (1H, td, J=8Hz,

1Hz), 7.21 (1H, dd, J=8Hz, 1Hz)

[0368]

Reference Example 139

2-(2-Furanyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



5

[0369]

53.2 g (224 mmol) of 1-[(2-furanylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 49.8 g (quantitative) of the title compound.

10

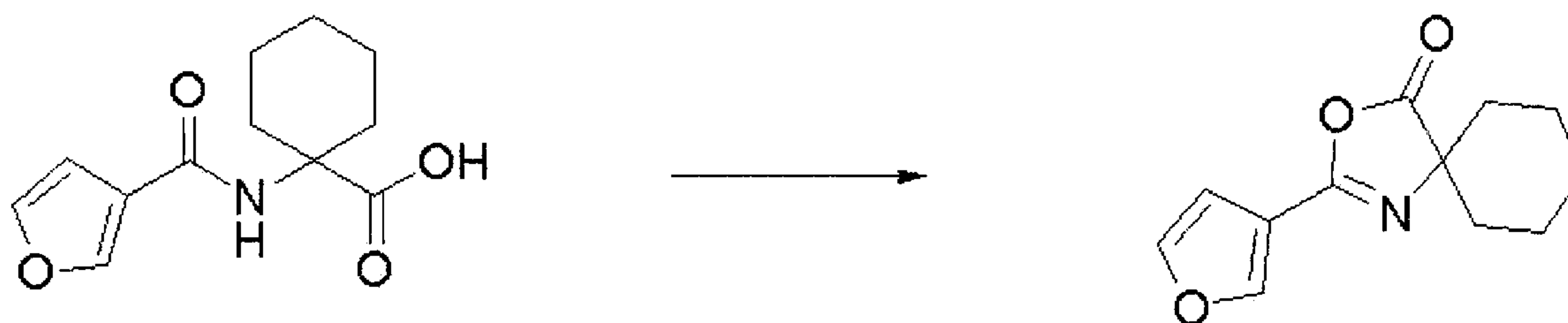
¹H-NMR (CDCl₃, δ): 1.53-1.57 (1H, m), 1.66-1.86 (9H, m), 6.58 (1H, dd, J=4Hz, 2Hz), 7.09 (1H, dd, J=4Hz, 1Hz), 7.65 (1H, dd, J=2Hz, 1Hz)

15

[0370]

Reference Example 140

2-(3-Furanyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0371]

20

4.48 g (18.9 mmol) of 1-[(3-furanylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 4.02 g (97%) of the title compound.

25

¹H-NMR (CDCl₃, δ): 1.54-1.57 (1H, m), 1.63-1.86 (9H, m), 6.86 (1H, dd, J=2Hz, 1Hz), 7.51 (1H, t, J=2Hz), 7.99 (1H,

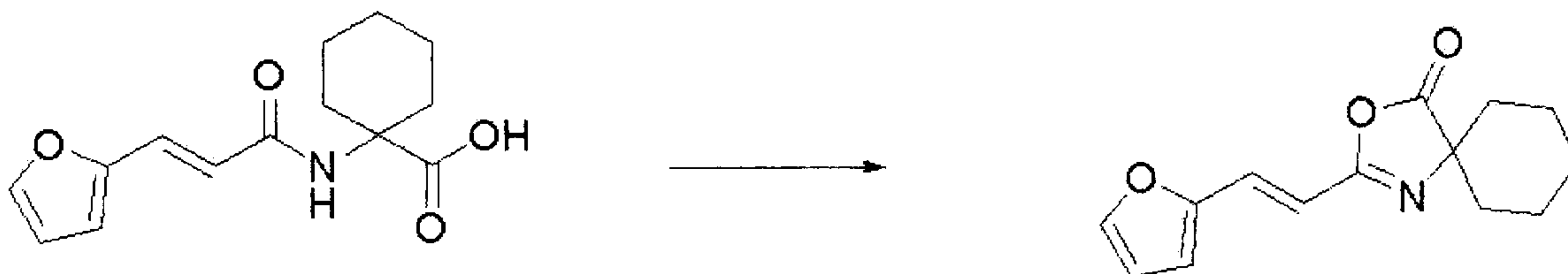
dd, J=2Hz, 1Hz)

[0372]

Reference Example 141

2-[2-(2-Furanyl)ethenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-

5 one



[0373]

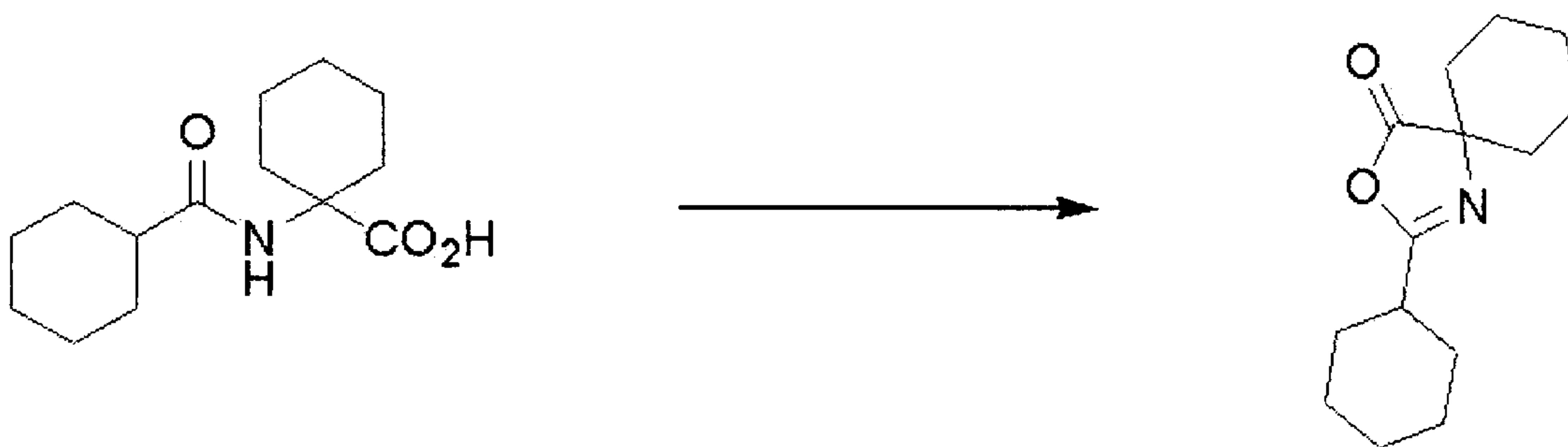
10.0 g (38 mmol) of 1-[[[(E)-3-(2-furanyl)-1-oxo-2-propenyl]amino]cyclohexanecarboxylic acid was used instead
 10 of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 8.92 g (96%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.26-1.54 (2H, m), 1.66-1.84 (8H, m), 6.48 (1H, dd, J=2Hz, 1Hz), 6.53 (1H, d, J=16Hz), 6.60 (1H, d, J=2Hz), 7.22 (1H, d, J=16Hz), 7.51 (1H, dd, J=2Hz, 1Hz)

[0374]

Reference Example 142

2-Cyclohexyl-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



20 [0375]

4.15 g (16.3 mmol) of 1-[(cyclohexylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the
 25 process according to Reference Example 132 to obtain 3.75 g

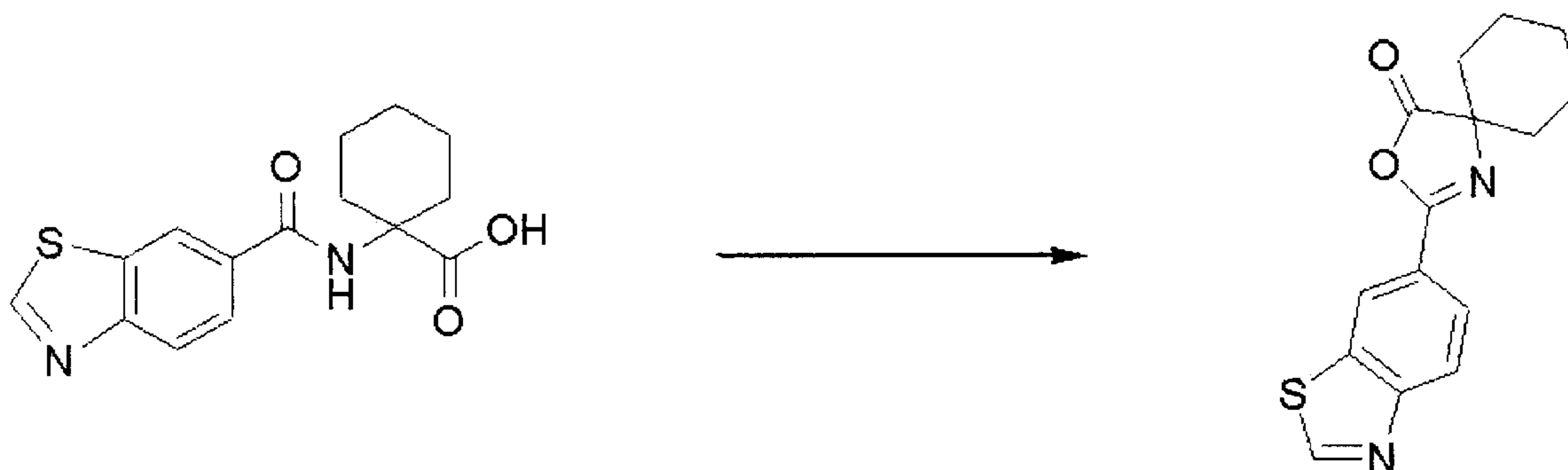
(98%) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.24-1.38 (3H, m), 1.44-1.56 (3H, m), 1.56-1.63 (3H, m), 1.63-1.84 (9H, m), 1.92-2.00 (2H, m), 2.43-2.49 (1H, m)

5 [0376]

Reference Example 143

2-(6-Benzothiazolyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0377]

10 365 mg (1.2 mmol) of 1-[(6-benzothiazolylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-

[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 287 mg

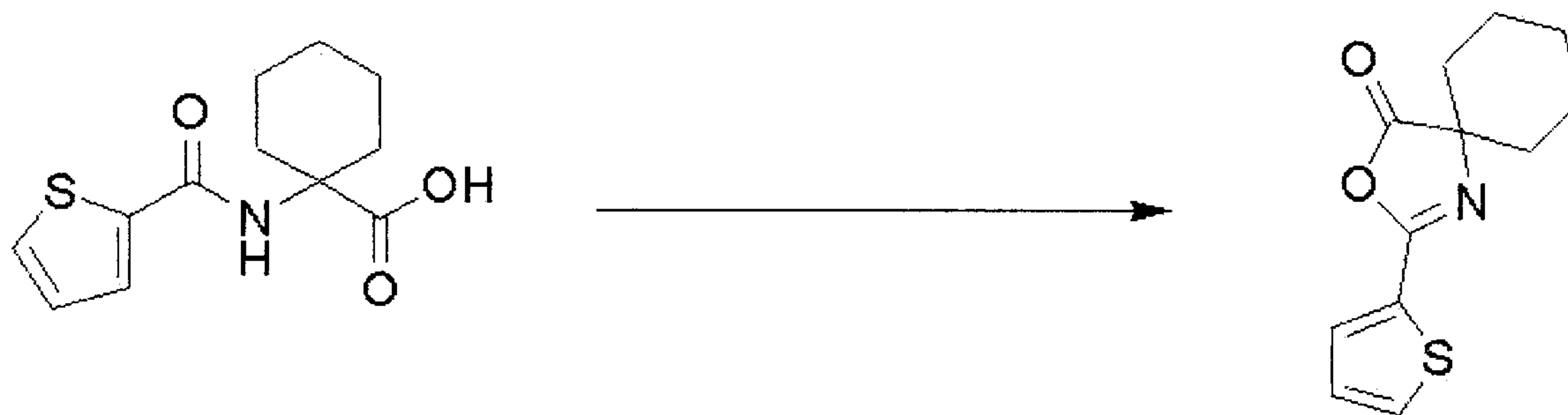
15 (83%) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.53-1.62 (4H, m), 1.68-1.79 (2H, m), 1.81-1.92 (4H, m), 8.19 (1H, dd, $J=9\text{Hz}$, 2Hz), 8.22 (1H, dd, $J=9\text{Hz}$, 1Hz), 8.65 (1H, dd, $J=2\text{Hz}$, 1Hz), 9.15 (1H, s)

[0378]

20 Reference Example 144

2-(2-Thienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0379]

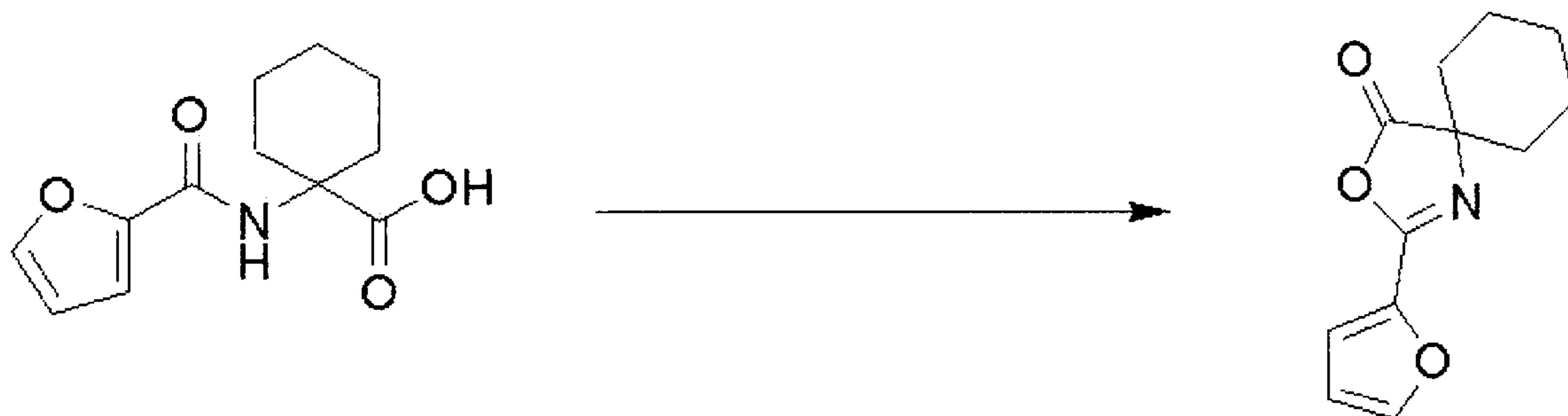
5.0 g (20 mmol) of 1-[(2-thienylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 4.46 g (96%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.51-1.59 (1H, m), 1.61-1.69 (1H, m), 1.71-1.88 (8H, m), 7.14 (1H, dd, J=5Hz, 4Hz), 7.57 (1H, dd, J=5Hz, 1Hz), 7.70 (1H, dd J=4Hz, 1Hz)

10 [0380]

Reference Example 145

2-(2-Furanyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0381]

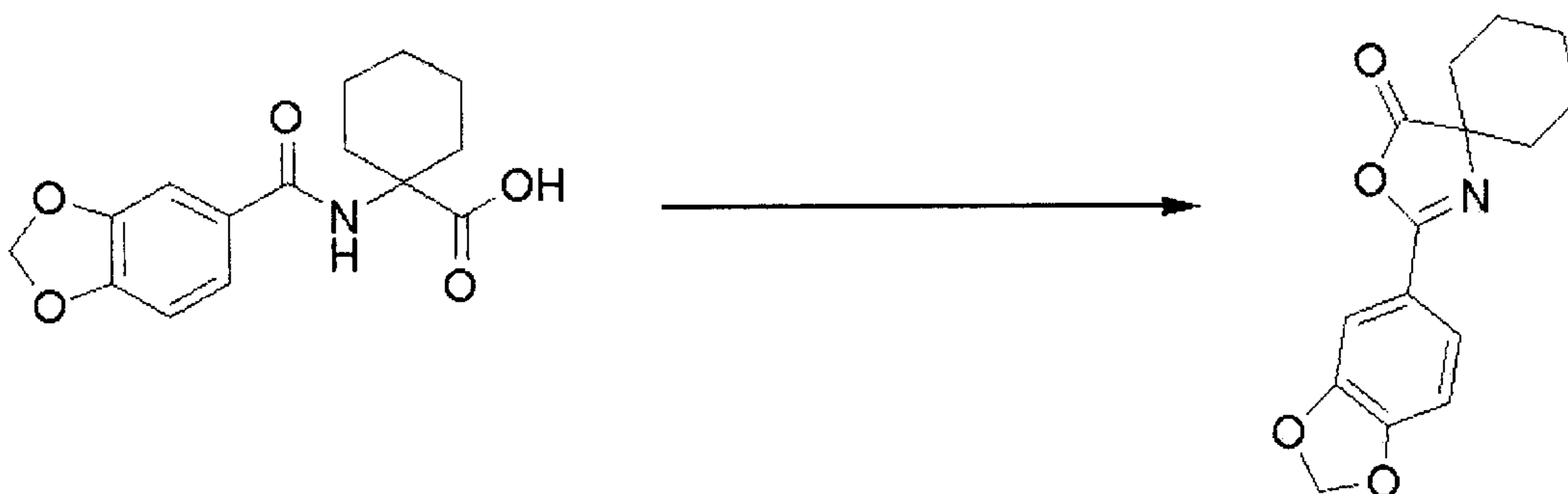
15 6.0 g (44 mmol) of isobutyl chloroformate was added dropwise to a solution of 10 g (42 mmol) of 1-[(2-furanylcarbonyl)amino]cyclohexanecarboxylic acid obtained in Reference Example 14 and 6.1 ml (44 mmol) of triethylamine in tetrahydrofuran (80 ml), and the mixture was stirred at room temperature for 1 hour. The precipitated crystal was removed by filtration, and the filtrate was concentrated. The obtained crystal was washed with water to obtain 8.95 g (97%) of the title compound.

25 ¹H-NMR (CDCl₃, δ): 1.53-1.57 (1H, m), 1.66-1.86 (9H, m), 6.58 (1H, dd, J=4Hz, 2Hz), 7.09 (1H, dd, J=4Hz, 1Hz), 7.65 (1H, dd, J=2Hz, 1Hz)

[0382]

Reference Example 146

2-(1,3-Benzodioxol-5-yl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0383]

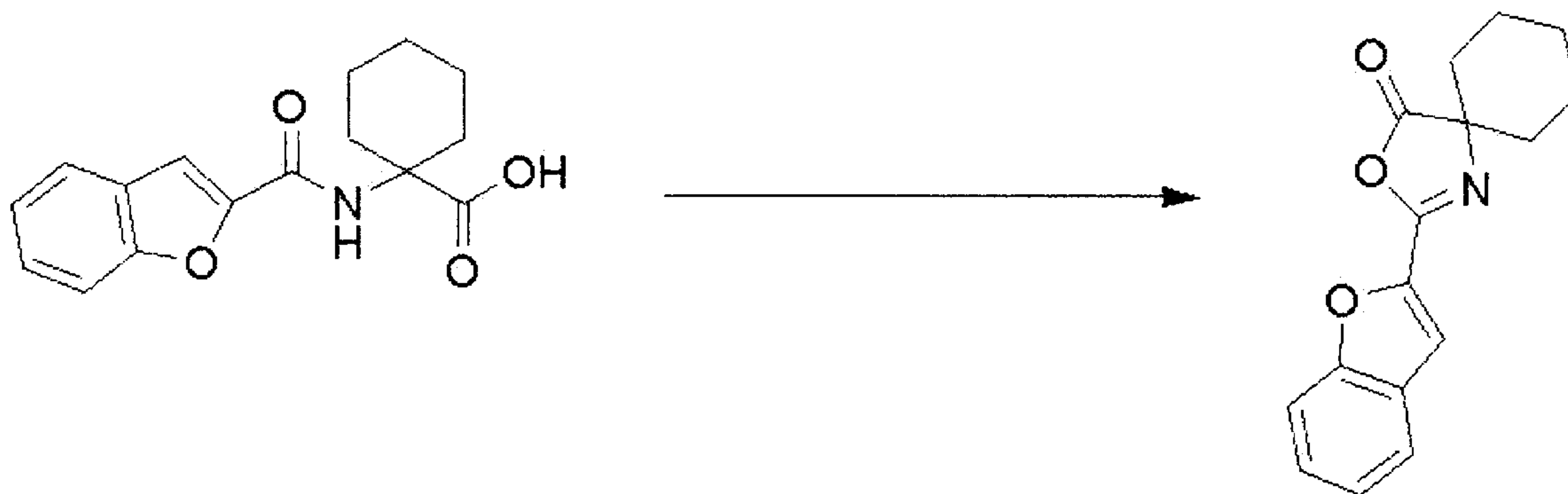
5 5.8 g (20 mmol) of 1-[[[(1,3-benzodioxole)-5-carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 4.9 g (90%) of the title compound.

10 ¹H-NMR (CDCl₃, δ): 1.51-1.57 (1H, m), 1.63-1.75 (3H, m), 1.76-1.88 (6H, m), 6.05 (2H, s), 6.87 (1H, d, J=8Hz), 7.46 (1H, d, J=2Hz), 7.55 (1H, dd, J=8Hz, 2Hz)

[0384]

Reference Example 147

15 2-(2-Benzofuranyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0385]

3.8 g (13 mmol) of 1-[[[(2-benzofuranyl)carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 3.4 g

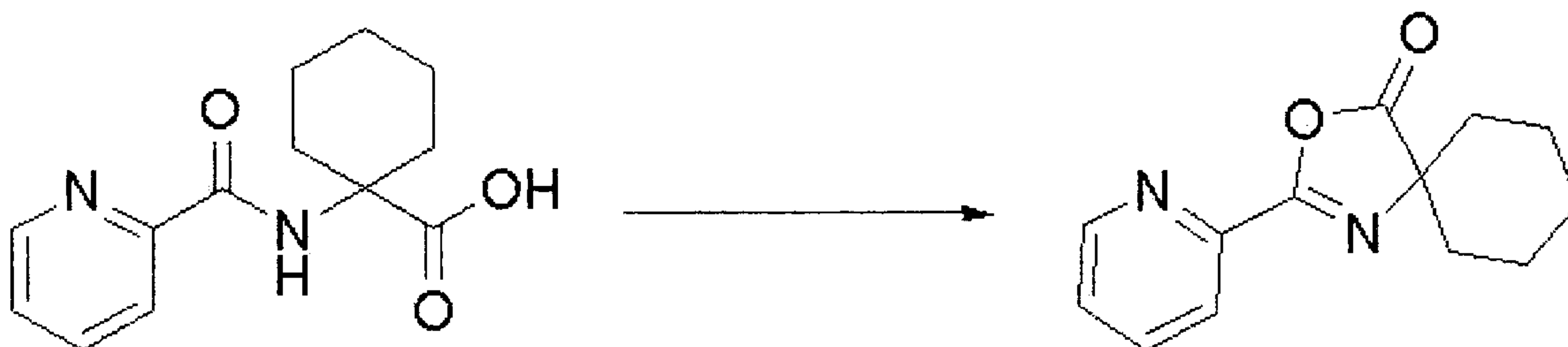
(96%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.51-1.74 (2H, m), 1.78-1.94 (8H, m),
7.33 (1H, ddd, J=8Hz, 7Hz, 1Hz), 7.44 (1H, d, J=1Hz), 7.46
(1H, ddd, J=8Hz, 7Hz, 1Hz), 7.63 (1H, ddd, J=8Hz, 2Hz,
5 1Hz), 7.70 (1H, ddd, J=8Hz, 2Hz, 1Hz)

[0386]

Reference Example 148

2-(2-Pyridinyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



10 [0387]

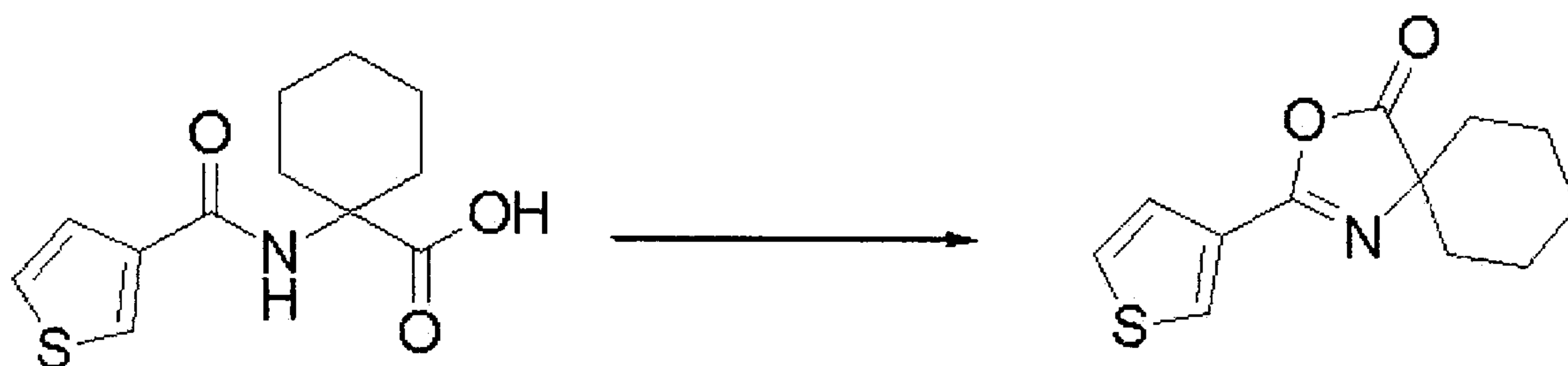
511 mg (2 mmol) of 1-[(2-pyridinylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to
15 obtain 405 mg (85%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.54-1.77 (3H, m), 1.78-1.92 (7H, m),
7.62 (1H, ddd, J=7Hz, 5Hz, 2Hz), 7.87 (1H, dt, J=7Hz, 2Hz),
8.04 (1H, dd, J=5Hz, 2Hz), 8.82 (1H, dd, J=5Hz, 2Hz)

[0388]

20 Reference Example 149

2-(3-Thienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0389]

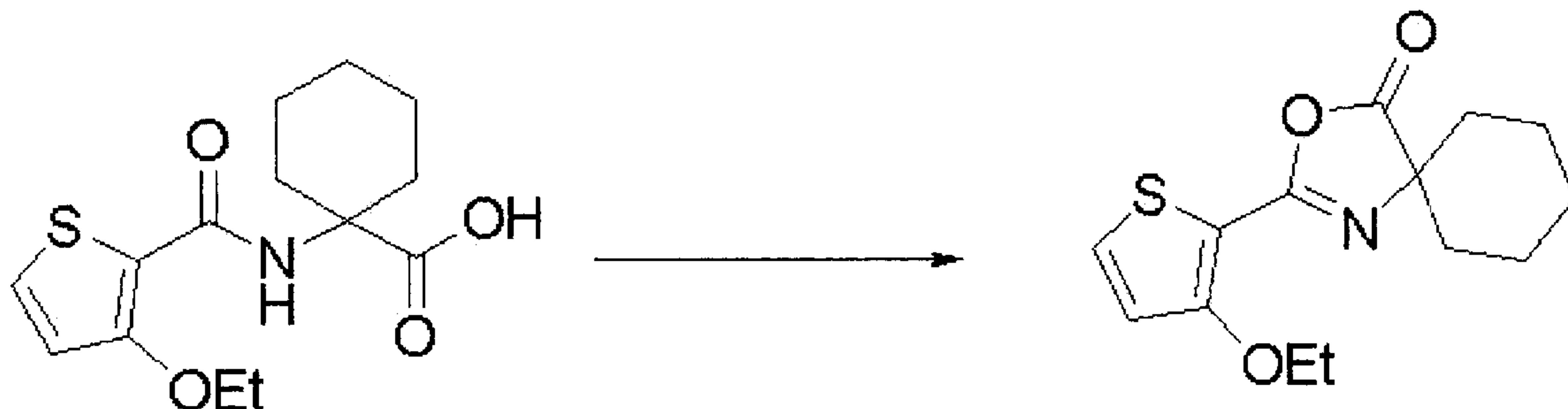
253 mg (1 mmol) of 1-[(3-thienylcarbonyl)amino]cyclohexanecarboxylic acid was used

instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 234 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.52-1.87 (10H, m), 7.40 (1H, dd, J=5Hz, 3Hz), 7.60 (1H, dd, J=5Hz, 1Hz), 8.00 (1H, dd, J=3Hz, 1Hz)
[0390]

Reference Example 150

2-(3-Ethoxy-2-thienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



10 [0391]

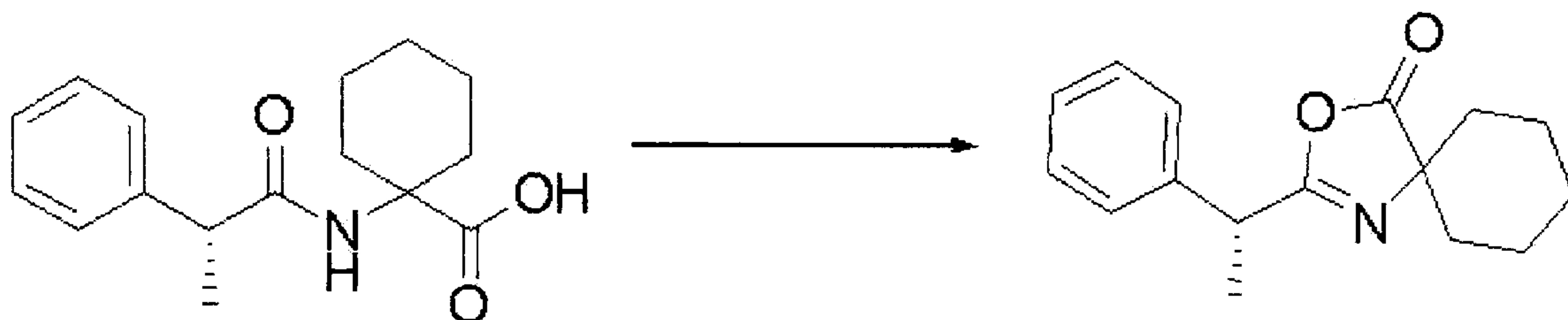
327 mg (1 mmol) of 1-[[3-ethoxy-2-thienyl)carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 307 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.46 (3H, t, J=7Hz), 1.49-1.84 (10H, m), 4.22 (2H, q, J=7Hz), 6.86 (1H, d, J=6Hz), 7.42 (1H, d, J=6Hz)

[0392]

20 Reference Example 151

2-[2-[(S)-1-Phenylethyl]]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0393]

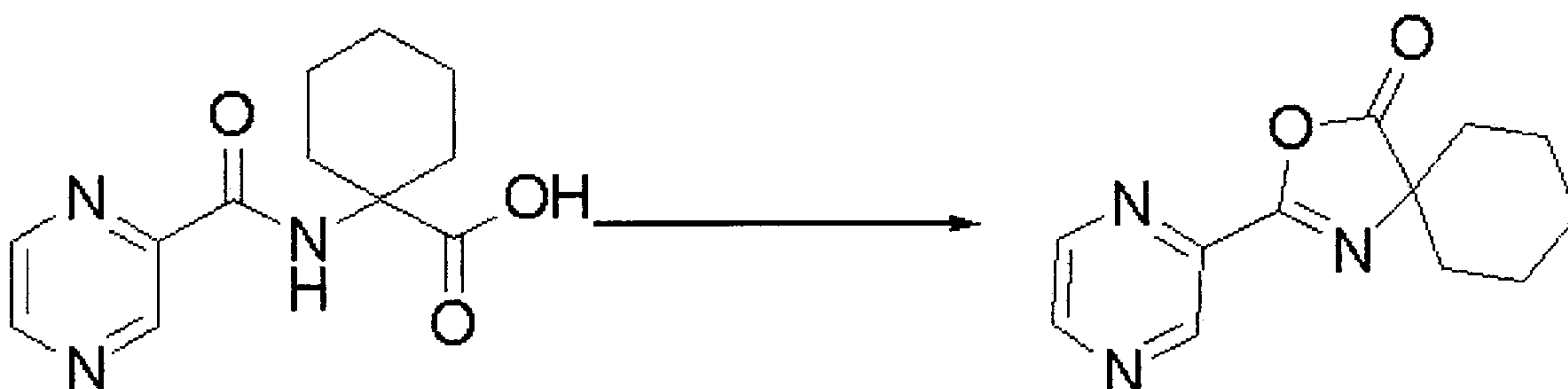
275 mg (1 mmol) of 1-[[*(S)*-1-oxo-2-phenylpropyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 257 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.51-1.78 (13H, m), 3.89 (1H, q, J=7Hz), 7.26-7.35 (5H, m)

[0394]

Reference Example 152

2-(2-Pyrazinyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0395]

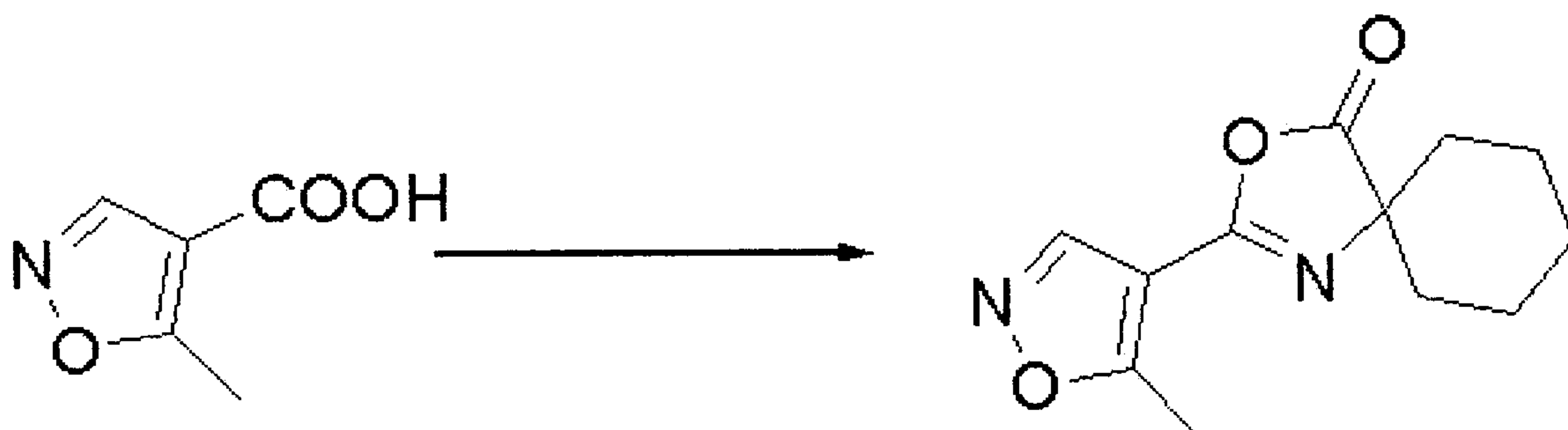
249 mg (1 mmol) of 1-[(2-pyrazinylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 231 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.56-1.93 (10H, m), 8.78 (2H, m), 9.28 (1H, t, J=3Hz)

[0396]

Reference Example 153

2-(5-Methylisoxazol-4-yl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0397]

1 g (7.87 mmol) of 5-methylisoxazole-4-carboxylic acid was added to 3 ml of thionyl chloride, and the mixture was stirred overnight. Under reduced pressure, the reaction solution was concentrated, and the obtained residue was added to a solution of 1.13 g (7.87 mmol) of 1-aminocyclohexanecarboxylic acid and 6.6 g (79 mmol) of sodium hydrogencarbonate in 30 ml of toluene-30 ml of water. After the mixture was stirred at room temperature overnight, the toluene layer was separated. The aqueous layer was neutralized by potassium hydrogensulfate, and it was extracted with ethyl acetate. After the obtained organic layer was washed with saturated brine, it was dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, methylene chloride was added thereto, and under ice-cooling, 332 mg (1.73 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added. After the mixture was stirred at room temperature overnight, under reduced pressure, the reaction solution was concentrated, ethyl acetate was added thereto, and the mixture was successively washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by drying with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 295 mg (16%) of the title compound.

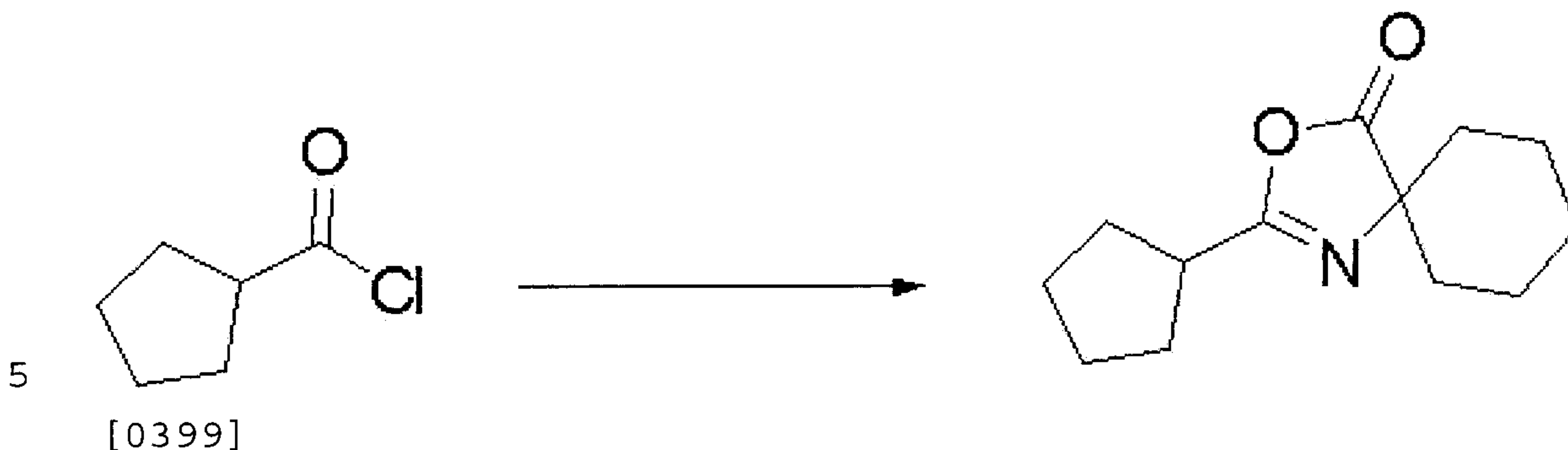
$^1\text{H-NMR}$ (CDCl_3 , δ): 1.50-1.59 (1H, m), 1.64-1.72 (2H, m),

1.76-1.83 (7H, m), 2.75 (3H, s), 8.55 (1H, s)

[0398]

Reference Example 154

2-Cyclopentyl-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



1.98 g (15 mmol) of cyclopentanecarbonyl chloride was added to a solution of 2.16 g (15 mmol) of 1-aminocyclohexanecarboxylic acid and 4.8 g (45 mmol) of sodium carbonate in 50 ml of ethyl acetate-50 ml of water under ice-cooling. After the mixture was stirred at room temperature overnight, ethyl acetate was added thereto, and the mixture was washed with a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium bicarbonate solution and then saturated brine. After the obtained organic layer was washed with saturated brine, it was dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, methylene chloride was added thereto, and under ice-cooling, 1.59 g (8.3 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added. After the mixture was stirred at room temperature overnight, under reduced pressure, the reaction solution was concentrated, ethyl acetate was added thereto, and the mixture was successively washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by drying with anhydrous sodium sulfate. The solvent was distilled off under reduced

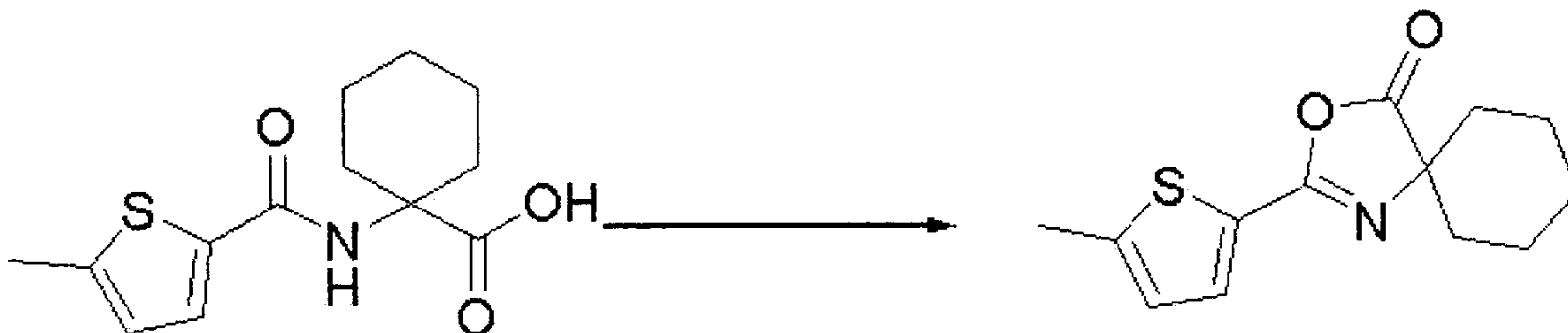
pressure to obtain 1.41 g (42%) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.53-1.65 (5H, m), 1.67-1.76 (4H, m),
1.86-1.95 (8H, m), 2.80-2.89 (2H, m)

[0400]

5 Reference Example 155

2-(5-Methyl-2-thienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0401]

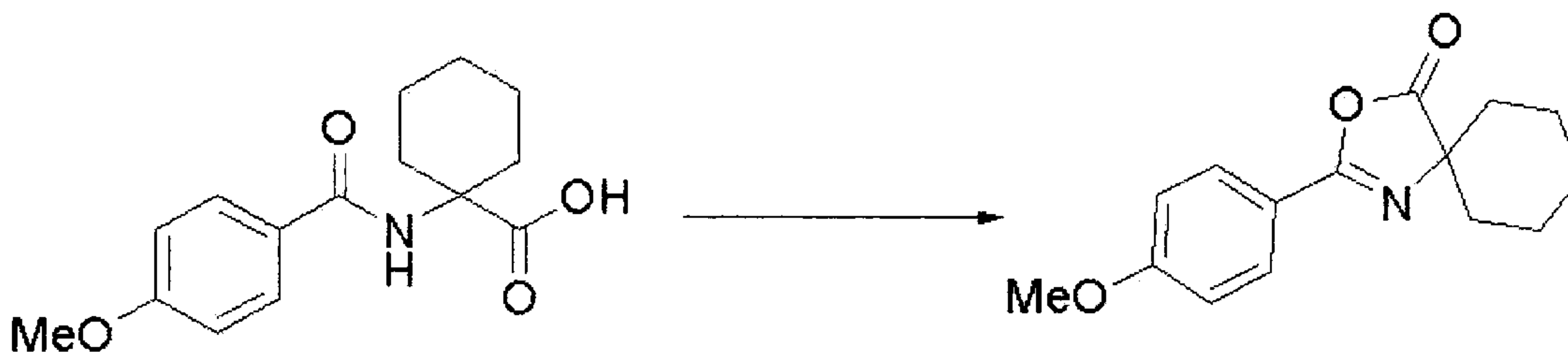
294 mg (1.1 mmol) of 1-[[[(5-methyl-2-
10 thienyl)carbonyl]amino]cyclohexanecarboxylic acid was used
instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic
acid in the process according to Reference Example 132 to
obtain 273 mg (quantitative) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.53-1.62 (3H, m), 1.71-1.84 (7H, m),
15 2.55 (3H, s), 6.79 (1H, d, $J=3\text{Hz}$), 7.50 (1H, d, $J=3\text{Hz}$)

[0402]

Reference Example 156

2-(4-Methoxyphenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



20 [0403]

305 mg (1.1 mmol) of 1-[[[(4-
methoxyphenyl)carbonyl]amino]cyclohexanecarboxylic acid was
used instead of 1-

[(phenylacetyl)amino]cyclohexanecarboxylic acid in the
25 process according to Reference Example 132 to obtain 288 mg

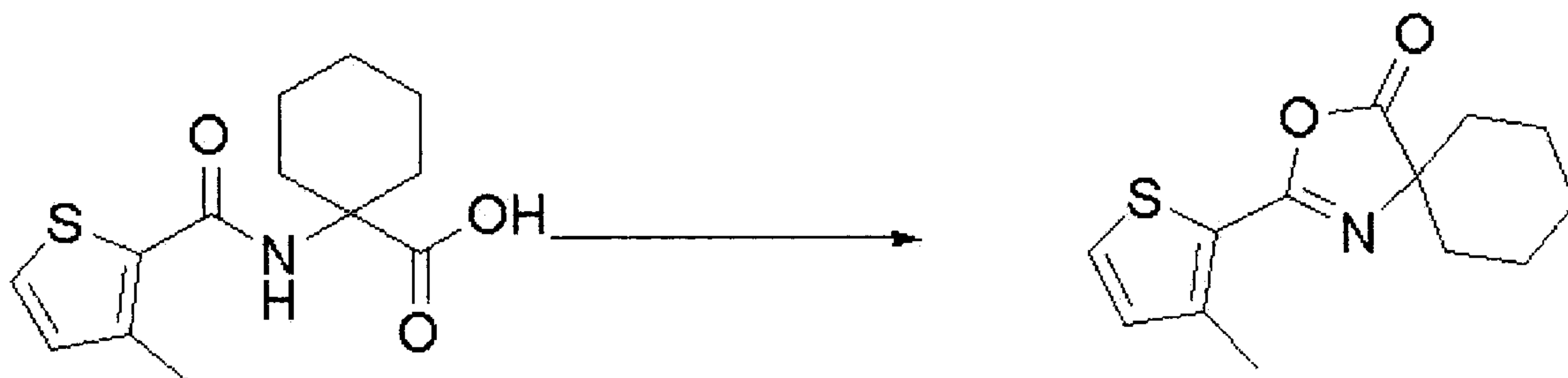
(90%) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.51-1.60 (1H, m), 1.61-1.73 (3H, m), 1.76-1.90 (6H, m), 3.87 (3H, s), 6.96 (2H, dd, $J=7\text{Hz}$, 2Hz), 7.94 (2H, dd, $J=7\text{Hz}$, 2Hz)

5 [0404]

Reference Example 157

2-(3-Methyl-2-thienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0405]

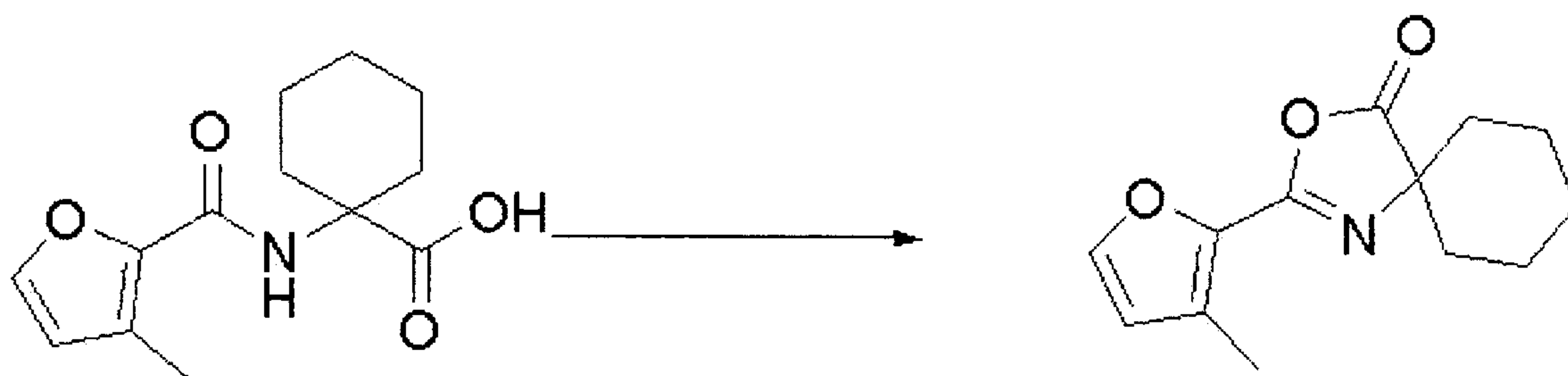
10 249 mg (1.1 mmol) of 1-[[3-methyl-2-thienyl]carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 249 mg (quantitative) of the title compound.

15 $^1\text{H-NMR}$ (CDCl_3 , δ): 1.50-1.60 (1H, m), 1.65-1.78 (3H, m), 1.78-1.90 (6H, m), 2.58 (3H, s), 6.95 (1H, d, $J=5\text{Hz}$), 7.42 (1H, d, $J=5\text{Hz}$)

[0406]

Reference Example 158

20 2-(3-Methyl-2-furanyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0407]

902 mg (3.59 mmol) of 1-[[3-methyl-2-furanyl]carbonyl]amino]cyclohexanecarboxylic acid was used

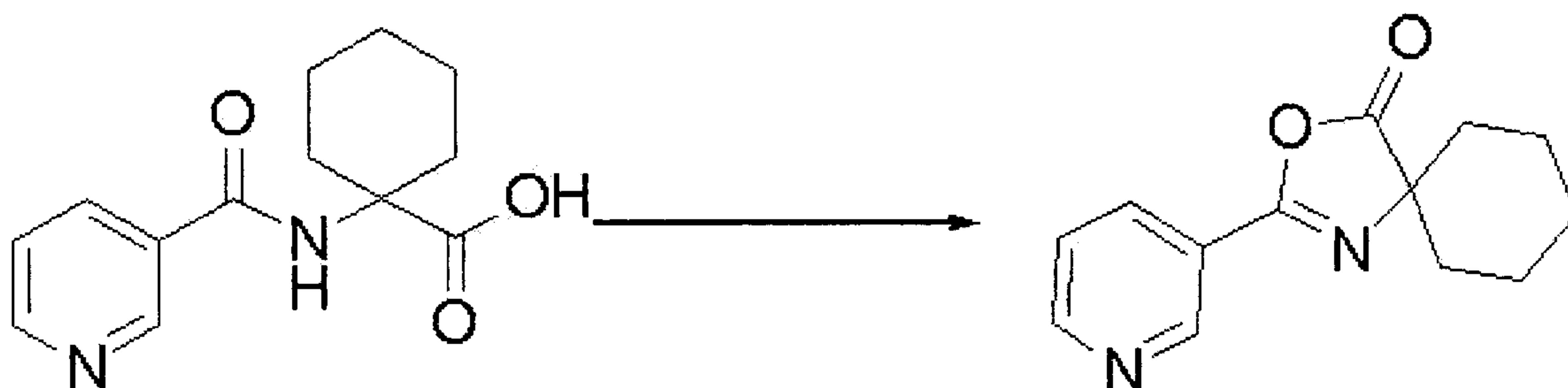
instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 233 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.48-1.61 (1H, m), 1.62-1.89 (9H, m),
 5 2.36 (3H, s), 6.40 (1H, d, J=1Hz), 7.52 (1H, d, J=1Hz)

[0408]

Reference Example 159

2-(3-Pyridinyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



10 [0409]

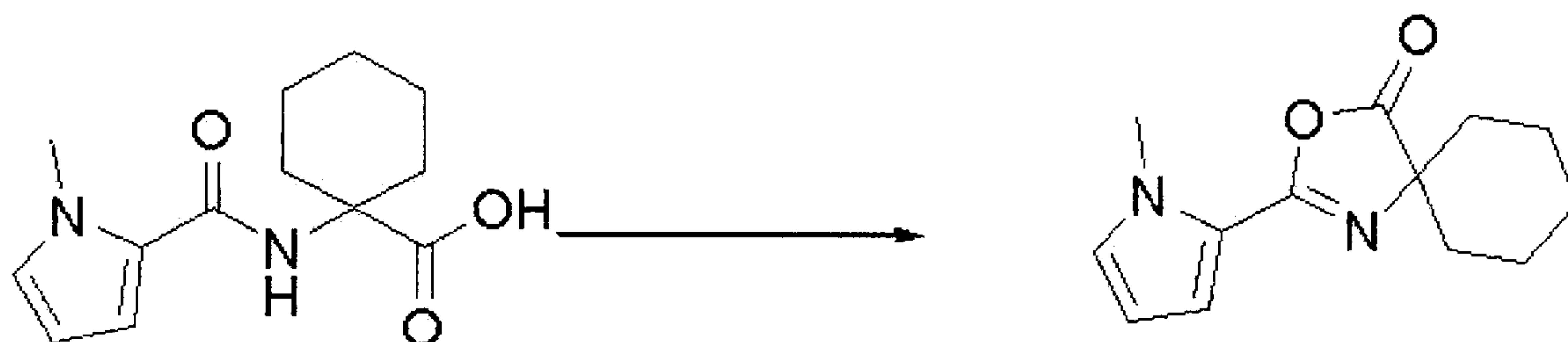
523 mg (2.11 mmol) of 1-[(3-pyridinylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to
 15 obtain 486 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.50-1.90 (10H, m), 7.42 (1H, dd, J=8Hz, 5Hz), 8.27 (1H, d, J=8Hz), 8.78 (1H, d, J=5Hz), 9.00 (1H, s)

[0410]

20 Reference Example 160

2-(1-Methyl-1H-pyrrol-2-yl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0411]

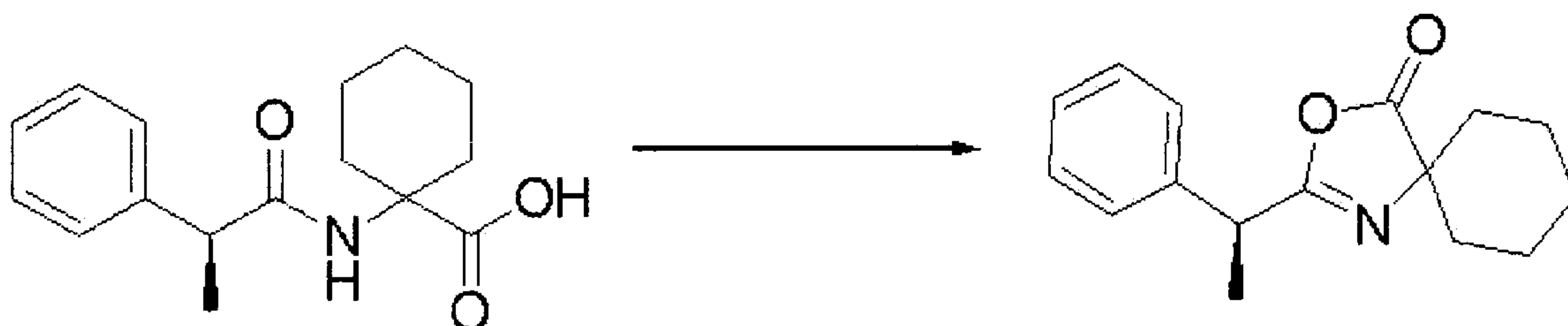
187 mg (0.75 mmol) of 1-[[1-methyl-1H-pyrrol-2-yl)carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 172 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.44-1.85 (10H, m), 3.40 (3H, s), 6.18 (1H, dd, J=4Hz, 3Hz), 6.82-6.86 (2H, m)

[0412]

Reference Example 161

2-[(R)-1-Phenylethyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0413]

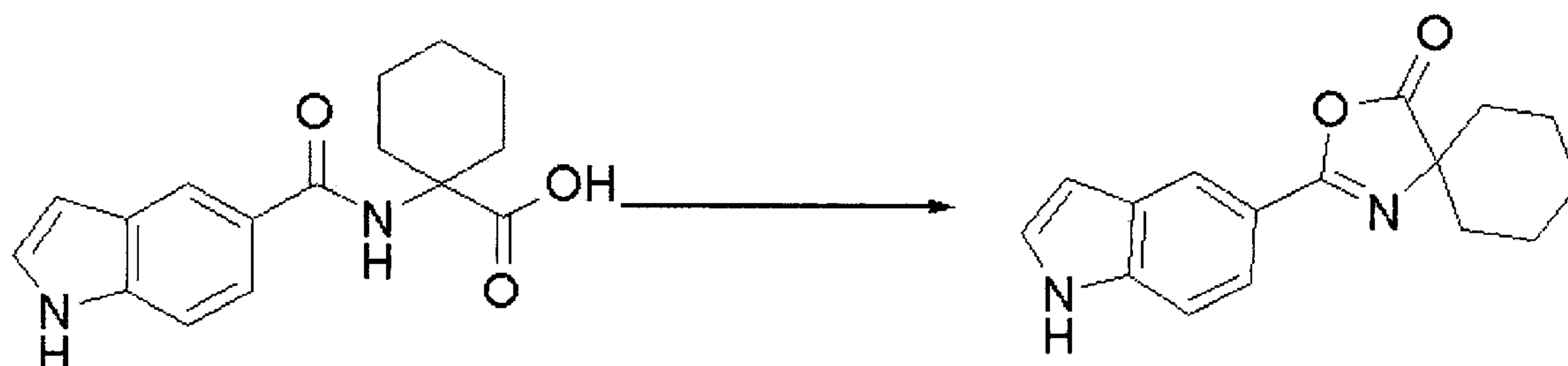
303 mg (1.1 mmol) of 1-[(R)-1-oxo-2-phenylpropyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 257 mg (90%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.45-1.65 (7H, m), 1.67-1.80 (6H, m), 3.89 (1H, q, J=7Hz), 7.26-7.34 (5H, m)

[0414]

Reference Example 162

2-(1H-Indol-5-ylcarbonyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0415]

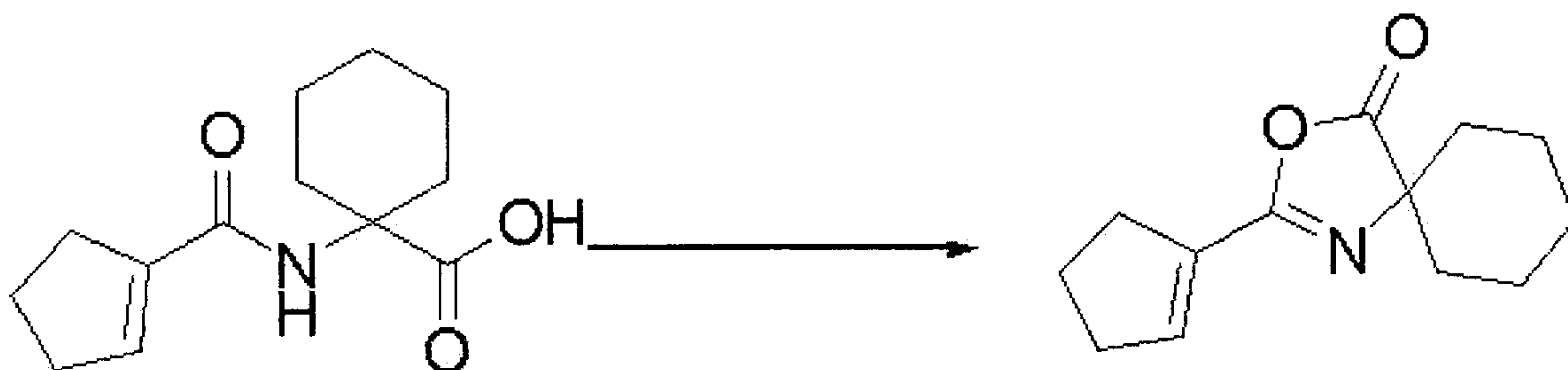
329 mg (1.2 mmol) of 1-[(1H-indol-5-ylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 258 mg (80%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.56-1.89 (10H, m), 6.65 (1H, dd, J=3Hz, 2Hz), 7.26-7.36 (1H, m), 7.46 (1H, d, J=9Hz), 7.88 (1H, dd, J=9Hz, 2Hz), 8.32 (1H, s), 8.35 (1H, br-s)

[0416]

10 Reference Example 163

2-(1-Cyclopentenylcarbonyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0417]

15 237 mg (1 mmol) of 1-[(1-cyclopentenylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-

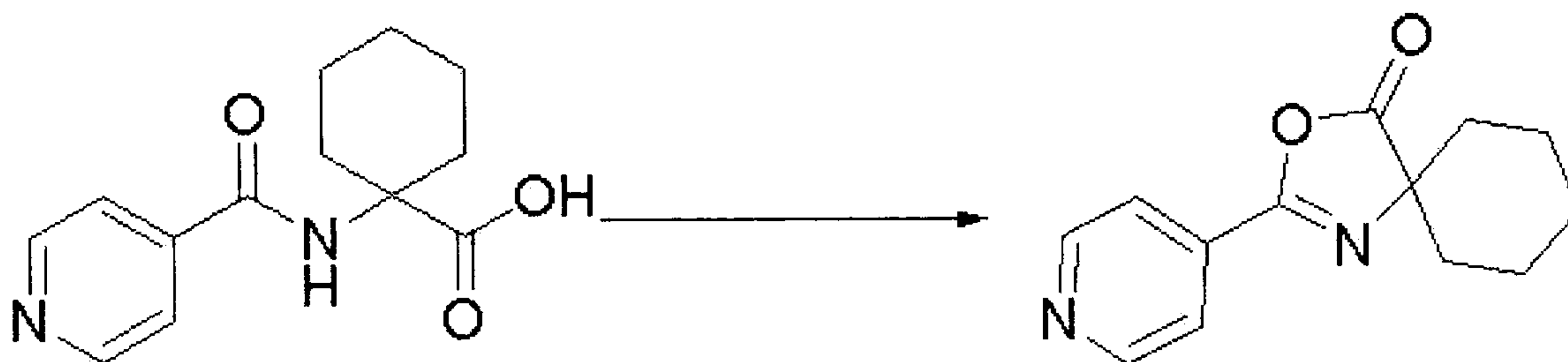
[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 219 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.53-1.82 (10H, m), 1.99-2.10 (2H, m), 2.55-2.69 (2H, m), 2.69-2.80 (2H, m), 6.65-6.67 (1H, m)

[0418]

Reference Example 164

25 2-(4-Pyridinyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0419]

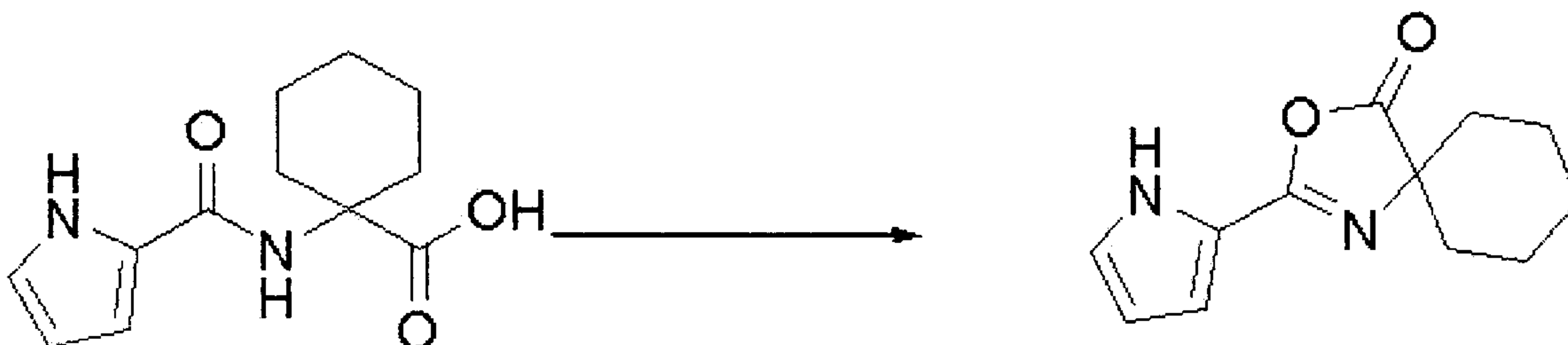
552 mg (2.2 mmol) of 1-[(4-pyridinylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 450 mg (88%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.50-1.92 (10H, m), 7.85 (2H, dd, J=5Hz, 2Hz), 8.80 (2H, dd, J=5Hz, 2Hz)

10 [0420]

Reference Example 165

2-(1H-Pyrrol-2-yl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0421]

15 200 mg (0.85 mmol) of 1-[(1H-pyrrol-2-yl)carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 184 mg (quantitative) of the title compound.

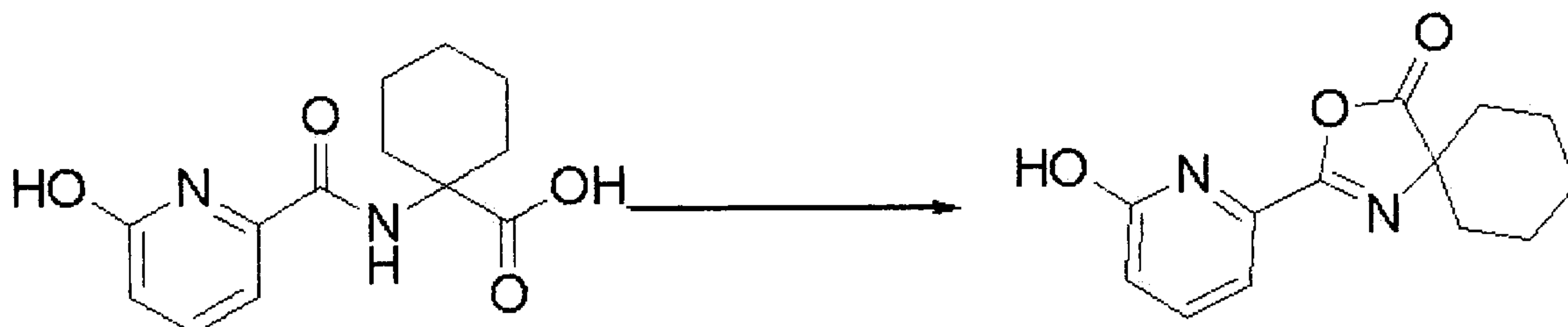
20 ¹H-NMR (CDCl₃, δ): 1.51-1.65 (1H, m), 1.65-1.86 (9H, m), 6.32 (1H, dd, J=4Hz, 2Hz), 6.87 (1H, dd, J=4Hz, 2Hz), 7.01 (1H, dd, J=4Hz, 2Hz), 9.37 (1H, br-s)

[0422]

Reference Example 166

25 2-(6-Hydroxy-2-pyridinyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-

one



[0423]

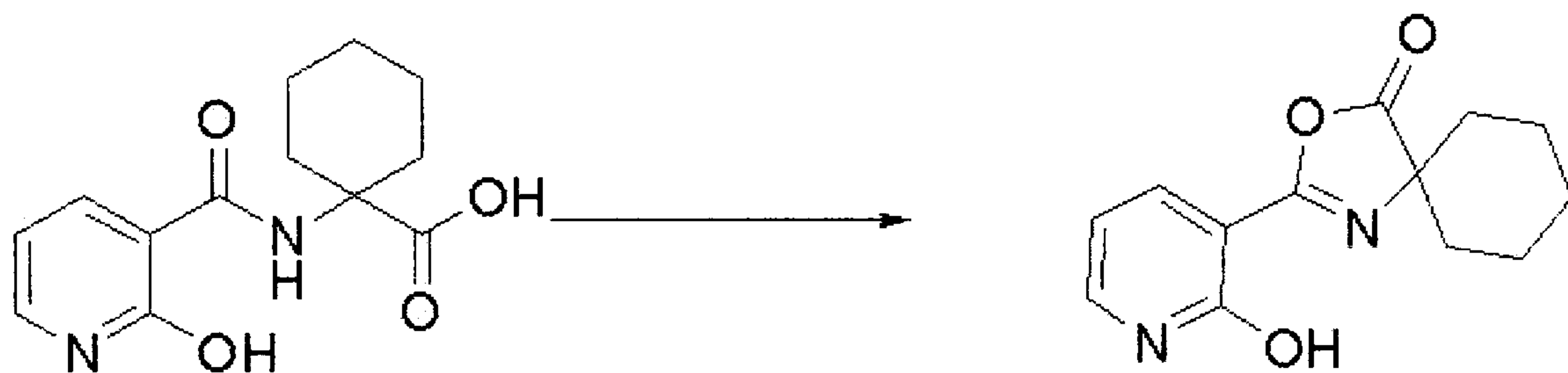
278 mg (1 mmol) of 1-[[[(6-hydroxy-2-pyridinyl)carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 250 mg (97%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.52 (1H, m), 1.78 (9H, m), 6.85-6.79 (2H, m), 7.50 (1H, dd, J=9Hz, 7Hz)

[0424]

Reference Example 167

2-(2-Hydroxy-3-pyridinyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0425]

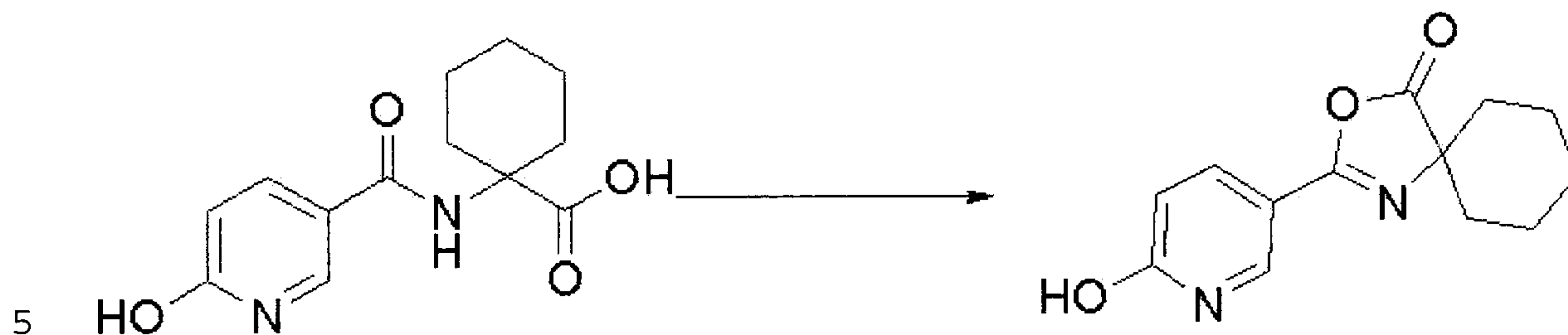
278 mg (1 mmol) of 1-[[[(2-hydroxy-3-pyridinyl)carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 257 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.04-2.21 (10H, m), 6.40-6.50 (1H, m), 7.69-7.82 (1H, m), 8.28-8.35 (1H, m)

[0426]

Reference Example 168

2-(6-Hydroxy-3-pyridinyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0427]

278 mg (1 mmol) of 1-[[[6-hydroxy-3-pyridinyl]carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-

10 [(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 257 mg (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 1.45-1.86 (10H, m), 6.66 (1H, d, J=10Hz), 8.02 (1H, d, J=2Hz), 8.05 (1H, dd, J=10Hz, 2Hz)

15 [0428]

Reference Example 169

2-[2-(2-Furanyl)ethyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0429]

20 1.7 ml of 2N aqueous NaOH solution was added to a solution of 478 mg (1.7 mmol) of 1-[[[1-oxo-3-(2-furanyl)propyl]amino]cyclohexanecarboxylic acid methyl ester obtained in Reference Example 64 in 2 ml of tetrahydrofuran, and the mixture was heated under reflux

25 for 3 hours. Ether was added to the reaction solution to wash it. After the separated aqueous layer was neutralized

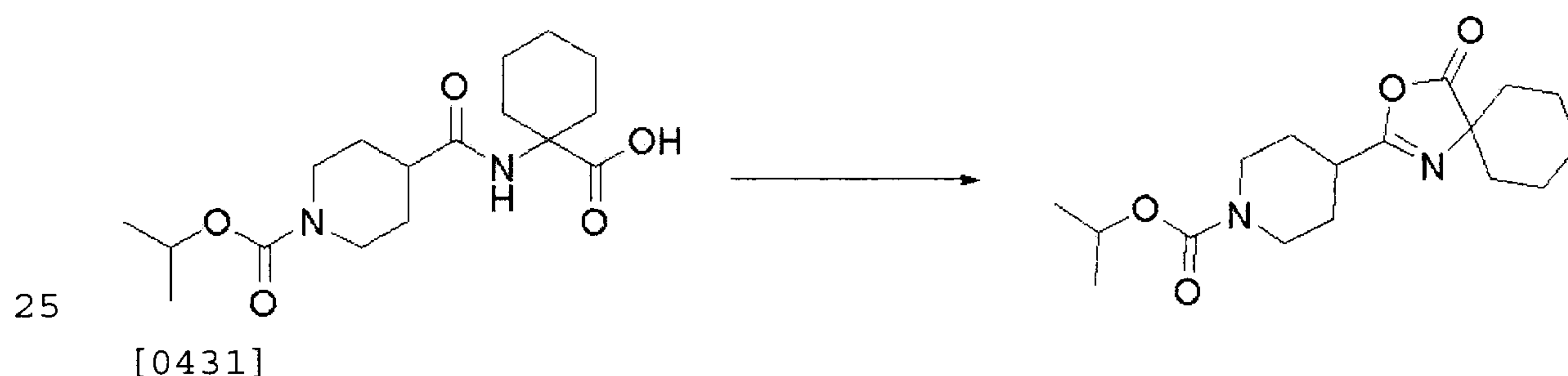
by concentrated hydrochloric acid, it was extracted with ethyl acetate. After the obtained organic layer was washed with saturated brine, it was dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. Then, 10 ml of methylene chloride and 377 mg (1.82 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride were added to the residue, and the mixture was stirred at room temperature overnight. The solvent was distilled off under reduced pressure, ethyl acetate was added thereto, and the mixture was washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and then saturated brine, followed by drying with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 198 mg (47%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.43-1.60 (4H, m), 1.60-1.80 (6H, m), 2.84 (2H, t, J=7Hz), 3.05 (2H, t, J=7Hz), 6.06 (1H, dd, J=2Hz, 1Hz), 6.27 (1H, dd, J=2Hz, 1Hz), 7.31 (1H, dd, J=2Hz, 1Hz)

[0430]

Reference Example 170

2-[1-[(2-Propoxy)carbonyl]piperidin-4-yl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



940 mg (2.76 mmol) of 1-[[[1-(2-propoxycarbonyl)piperidin-4-yl]carbonyl]amino]cyclohexanecarboxylic acid was used

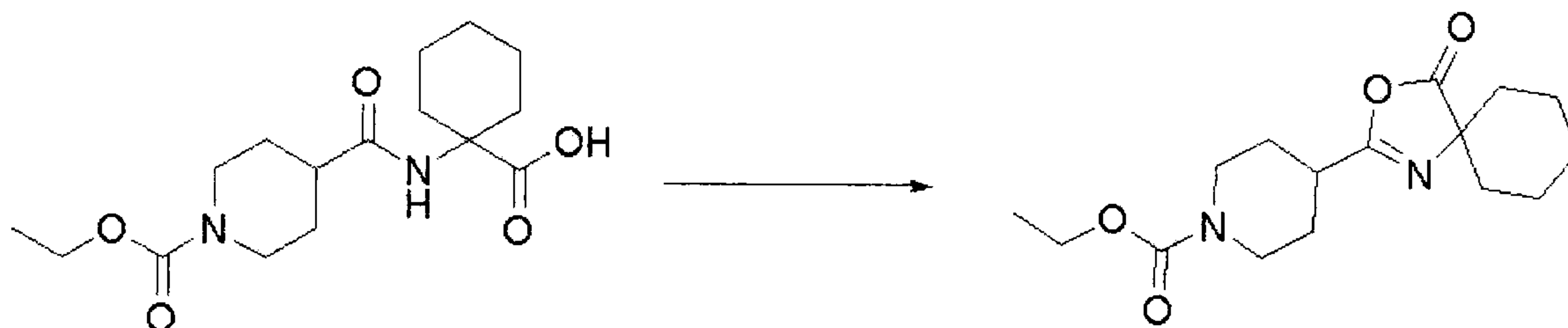
instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 818 mg (92%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.24 (6H, d, J=6Hz), 1.44-1.79 (12H, m),
 5 1.90-1.98 (2H, m), 2.62-2.69 (1H, m), 2.89-2.99 (2H, m),
 4.03-4.19 (2H, m), 4.88-4.97 (1H, m)

[0432]

Reference Example 171

2-[1-(Ethoxycarbonyl)piperidin-4-yl]-3-oxa-1-
 10 azaspiro[4.5]dec-1-en-4-one



[0433]

935 mg (2.86 mmol) of 1-[[[1-(ethoxycarbonyl)piperidin-4-

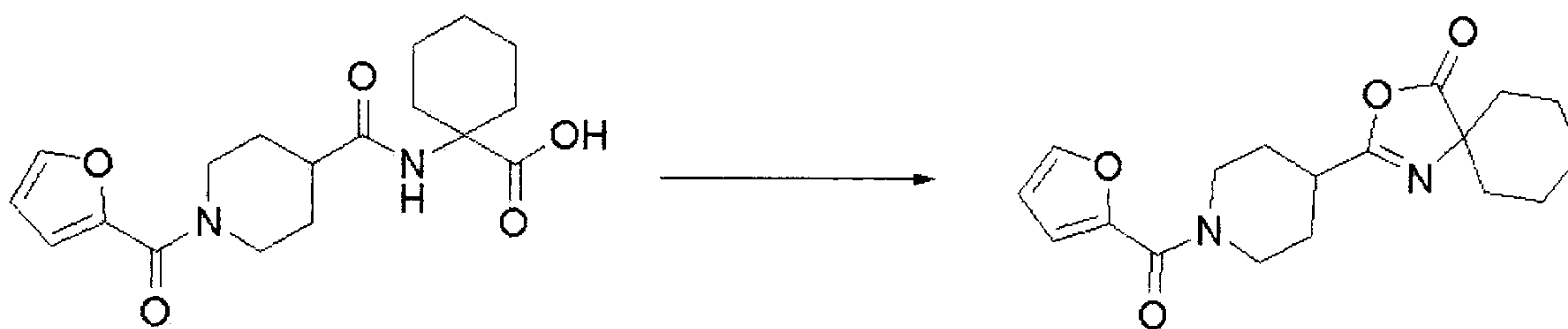
15 yl]carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 730 mg (83%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 1.45-1.80 (12H, m),
 20 1.92-1.99 (2H, m), 2.62-2.70 (1H, m), 2.90-3.03 (2H, m),
 4.03-4.20 (4H, m)

[0434]

Reference Example 172

2-[1-(2-Furanylcarbonyl)piperidin-4-yl]-3-oxa-1-
 25 azaspiro[4.5]dec-1-en-4-one



[0435]

196 mg (0.56 mmol) of 1-[[[1-(2-furanylcarbonyl)piperidin-4-

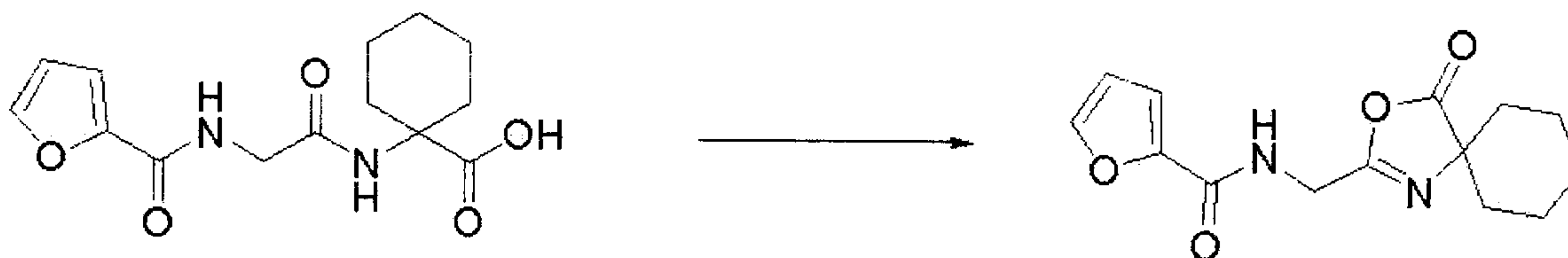
5 yl]carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 185 mg (quantitative) of the title compound.

1H-NMR (CDCl₃, δ): 1.49-1.68 (5H, m), 1.68-1.80 (5H, m),
 10 1.80-1.92 (2H, m), 2.03-2.10 (2H, m), 2.75-2.83 (1H, m),
 3.05-3.31 (2H, m), 4.28-4.40 (2H, m), 6.48 (1H, dd, J=3Hz,
 1Hz), 7.00 (1H, dd, J=3Hz, 1Hz), 7.48 (1H, dd, J=3Hz, 1Hz)

[0436]

Reference Example 173

15 2-[[[(2-Furanylcarbonyl)amino]methyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0437]

249 mg (1 mmol) of 1-[[[1-(2-furanylcarbonyl)amino]acetyl]amino]cyclohexanecarboxylic
 20 acid was used instead of 1-[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 276 mg (quantitative) of the title compound.

25 1H-NMR (CDCl₃, δ): 1.50-1.80 (10H, m), 4.45 (2H, d, J=6Hz),
 6.53 (1H, dd, J=3Hz, 1Hz), 6.90 (1H, br-s), 7.18 (1H, ddd,

J=3Hz, 2Hz, 1Hz), 7.50 (1H, dd, J=2Hz, 1Hz)

[0438]

Reference Example 174

2-[(Benzoylamino)methyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0439]

724 mg (2.26 mmol) of 1-

[[(benzoylamino)acetyl]amino]cyclohexanecarboxylic acid was used instead of 1-

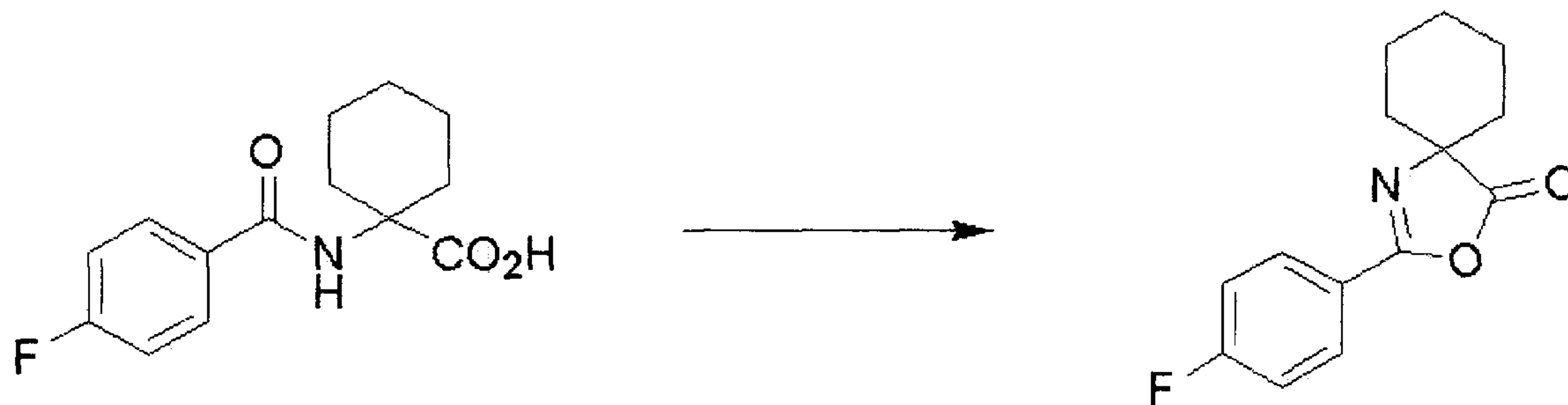
[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 631 mg (97%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.48-1.58 (1H, m), 1.63-1.80 (9H, m), 4.49 (2H, d, J=5Hz), 6.76 (1H, br-s), 7.48 (2H, m), 7.55 (1H, m), 7.83 (2H, m)

[0440]

Reference Example 175

2-(4-Fluorophenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0441]

After a suspension of 13.3 g (50 mmol) of 1-[(4-fluorobenzoyl)amino]cyclohexanecarboxylic acid in 30 ml of acetic anhydride was stirred at 100°C for 30 minutes, the reaction solution was concentrated under reduced pressure.

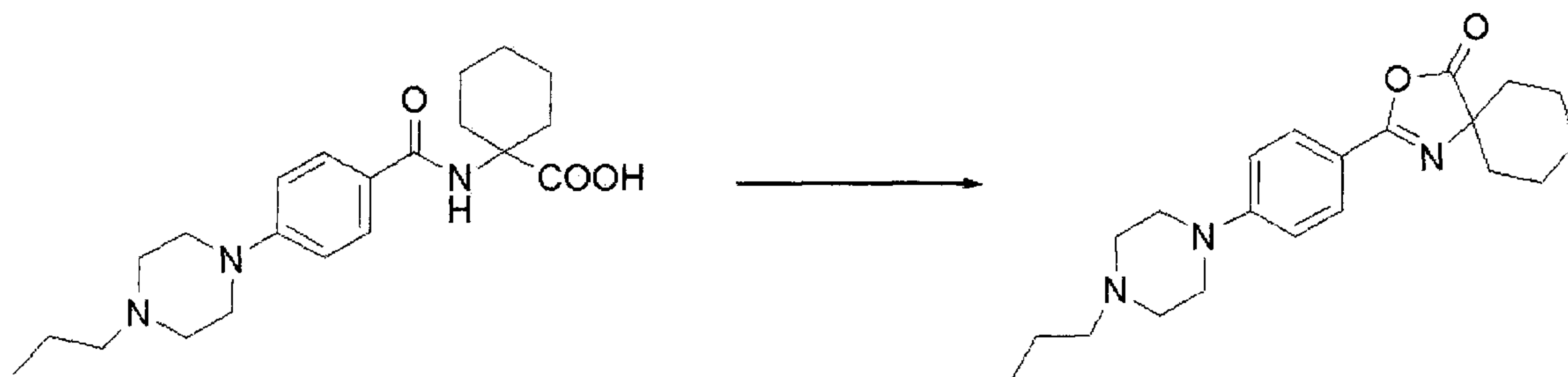
Toluene was added to the residue, and the mixture was washed with water, a saturated aqueous sodium hydrogencarbonate solution and then saturated brine. After the organic layer was dried with anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to obtain 8.5 g (69%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.49-1.60 (1H, m), 1.63-1.90 (9H, m), 7.13-7.20 (2H, m), 8.00-8.05 (2H, m)

10 [0442]

Reference Example 176

2-[4-(4-Propylpiperazin-1-yl)phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



15 [0443]

1.43 g (3.86 mmol) of 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid was used instead of 1-

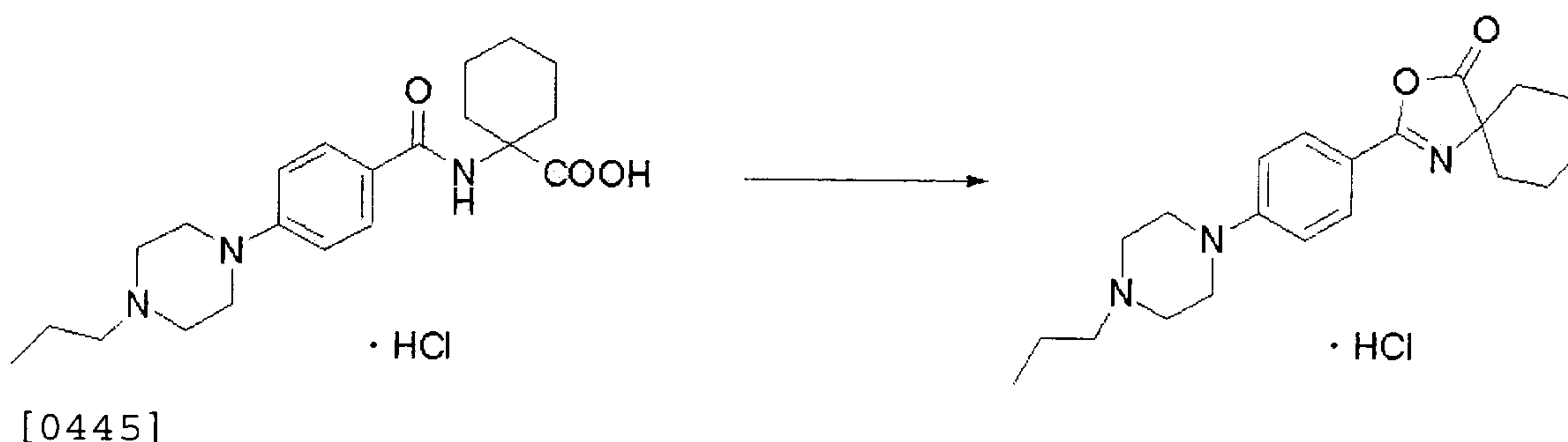
[(phenylacetyl)amino]cyclohexanecarboxylic acid in the process according to Reference Example 132 to obtain 1.33 g (98%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.94 (3H, t, J=8Hz), 1.50-1.61 (3H, m), 1.61-1.69 (1H, m), 1.69-1.76 (2H, m), 1.79-1.84 (6H, m), 2.35 (1H, t, J=6Hz), 2.36 (1H, t, J=6Hz), 2.59 (4H, t, J=5Hz), 3.35 (4H, t, J=5Hz), 6.91 (2H, dd, J=2Hz, 7Hz), 7.86 (2H, dd, J=2Hz, 7Hz)

[0444]

Reference Example 177

2- [4- (4-Propylpiperazin-1-yl)phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one hydrochloride

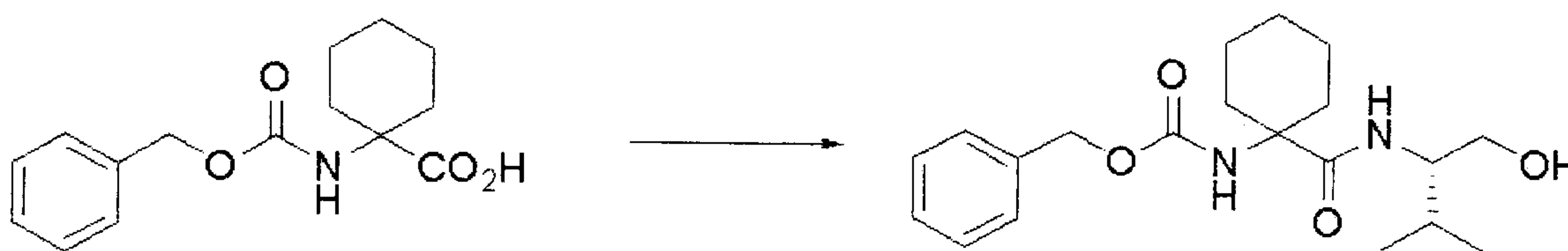


5 After a suspension of 631 mg (1.54 mmol) of 1-[[[4-(4-propylpiperazin-1-yl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid hydrochloride in 18 ml of acetic anhydride was stirred at 100°C for 1 hour, the reaction solution was concentrated under reduced pressure. Toluene was added to the obtained residue, it was distilled off under reduced pressure three times, and acetic anhydride was removed by azeotropic distillation to obtain 500 mg (83%) of the title compound. 1H-NMR (CDCl₃, δ): 1.05 (3H, t, J=8Hz), 1.50-1.87 (10H, m), 1.95-2.06 (2H, m), 2.86-3.01, (4H, m), 3.59-3.68 (2H, m), 3.79-3.90 (4H, m), 6.91 (2H, dd, 2Hz, 7Hz), 7.91 (2H, dd, J=2Hz, 7Hz)

[0446]

Reference Example 178

20 N-[[[1-[(Phenylmethoxy)carbonyl]amino]cyclohexyl]carbonyl]-L-valinol



[0447]

Under ice-cooling, 422 mg (2.2 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added to a solution of 555 mg (2 mmol) of 1-

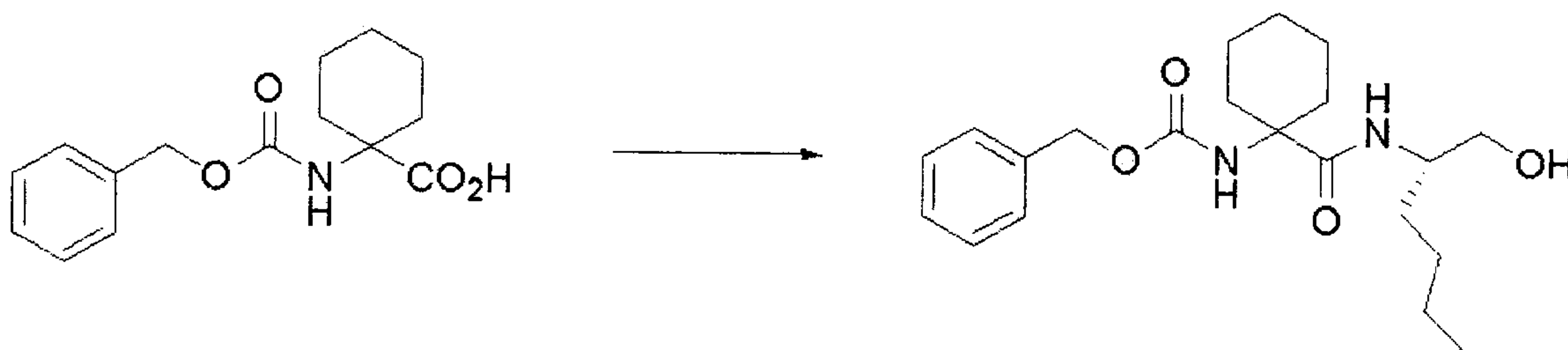
[[(phenylmethoxy) carbonyl] amino] cyclohexanecarboxylic acid, 322 mg (2.1 mmol) of 1-hydroxybenzotriazole and 206 mg (2 mmol) of L-valinol in 20 ml of methylene chloride, and thereafter the mixture was stirred at room temperature for 18 hours. The reaction solution was concentrated under reduced pressure, ethyl acetate was added to the residue, and the mixture was washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and then saturated brine. The organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to obtain 662 mg (91%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.87 (3H, d, J=7Hz), 0.92 (3H, d, J=7Hz), 1.28-1.46 (3H, m), 1.52-1.70 (3H, m), 1.73-1.82 (1H, m), 1.85-2.03 (4H, m), 2.76 (1H, br-s), 3.42-4.47 (1H, m), 3.65-3.74 (2H, m), 5.02-5.16 (3H, m), 6.36 (1H, d, J=8Hz), 7.30-7.40 (5H, m)

[0448]

Reference Example 179

N- [[1- [[(Phenylmethoxy) carbonyl] amino] cyclohexyl] carbonyl] - L-norleucinol



[0449]

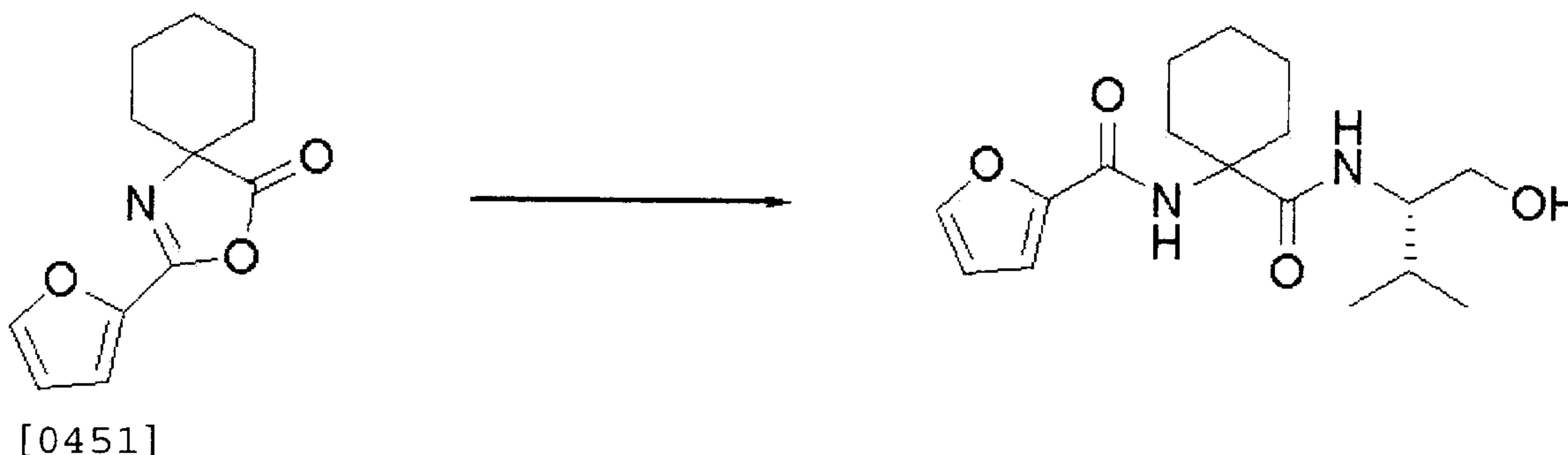
234 mg (2 mmol) of L-norleucinol was used instead of L-valinol in the process according to Reference Example 178 to obtain 350 mg (75%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.88 (3H, t, J=7Hz), 1.23-1.52 (9H, m),

1.58-1.70 (3H, m), 1.83-2.04 (4H, m), 2.83 (1H, br-s),
 3.34-3.40 (1H, m), 3.70 (1H, br-s), 3.89 (1H, br-s), 5.02-
 5.13 (3H, m), 6.26 (1H, d, J=8Hz), 7.31-7.40 (5H, m)
 [0450]

5 Reference Example 180

N-[[1-[(2-Furanylcarbonyl)amino]cyclohexyl]carbonyl]-L-
 valinol



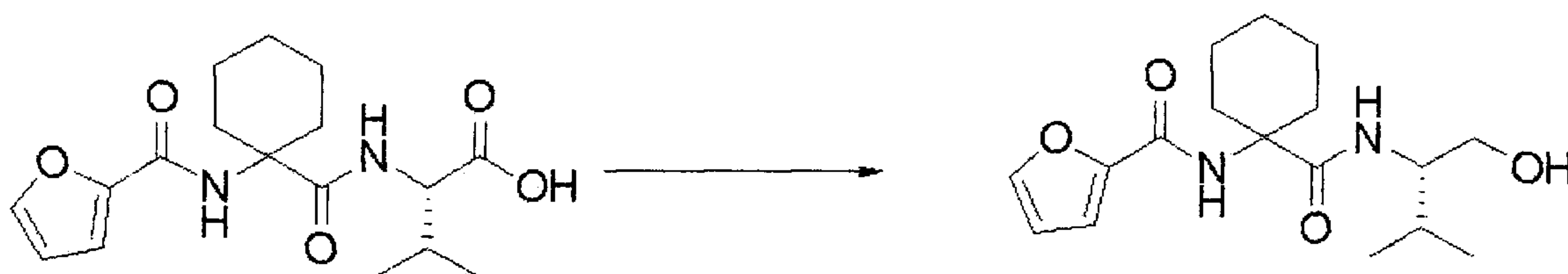
10 A solution of 8.81 ml (50.6 mmol) of N,N-
 diisopropylethylamine and 2.09 g (20.2 mmol) of L-valinol
 in 10 mL of methylene chloride was added to a solution of
 3.71 g (16.9 mmol) of 2-(2-furanyl)-3-oxa-1-
 azaspiro[4.5]dec-1-en-4-one in 100 ml of toluene, and the
 15 mixture was heated under reflux for 14 hours. The reaction
 solution was concentrated under reduced pressure, ethyl
 acetate was added to the residue, and the mixture was
 washed with water, a 10% aqueous potassium hydrogensulfate
 solution, a saturated aqueous sodium hydrogencarbonate
 20 solution and then saturated brine. The organic layer was
 dried with anhydrous sodium sulfate, and the solvent was
 distilled off under reduced pressure. Ethyl acetate was
 added to the residue, and the mixture was stirred
 overnight. The obtained crystal was collected by
 25 filtration to obtain 4.06 g (74.7%) of the title compound.
¹H-NMR (CDCl₃, δ): 0.93 (3H, d, J=7Hz), 0.95 (3H, d,
 J=7Hz), 1.32-1.56 (3H, m), 1.58-1.76 (3H, m), 1.80-1.90
 (1H, m), 1.96-2.08 (2H, m), 2.14-2.24 (2H, m), 3.00-3.06

(1H, m), 3.52-3.58 (1H, m), 3.68-3.78 (2H, m), 6.49 (1H, s), 6.53 (1H, dd, J=4Hz, 2Hz), 6.75-6.77 (1H, m), 7.14 (1H, dd, J=4Hz, 1Hz), 7.49 (1H, dd, J=2Hz, 1Hz)

[0452]

5 Reference Example 181

N-[[1-[(2-Furanylcarbonyl)amino]cyclohexyl]carbonyl]-L-valinol



[0453]

10 Under an argon atmosphere, 72 mg (0.59 mmol) of isopropyl chlorocarbonate was added to a solution of 200 mg (0.59 mmol) of N-[[1-[(2-furanylcarbonyl)amino]cyclohexyl]carbonyl]-L-valine and 60 mg (0.59 mmol) of triethylamine in 2 ml of tetrahydrofuran
15 under ice-cooling. After the mixture was stirred at 0°C for 2 hours, the reaction solution was filtered and poured to a solution of 45 mg (1.2 mmol) of sodium borohydride in 1 ml of water, and the mixture was stirred overnight. Ethyl acetate was added to the reaction solution, and the
20 mixture was successively washed with a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by drying with sodium sulfate. After the solvent was distilled off under reduced pressure, the obtained
25 crystal was washed with ether to obtain 30 mg (16%) of the title compound.

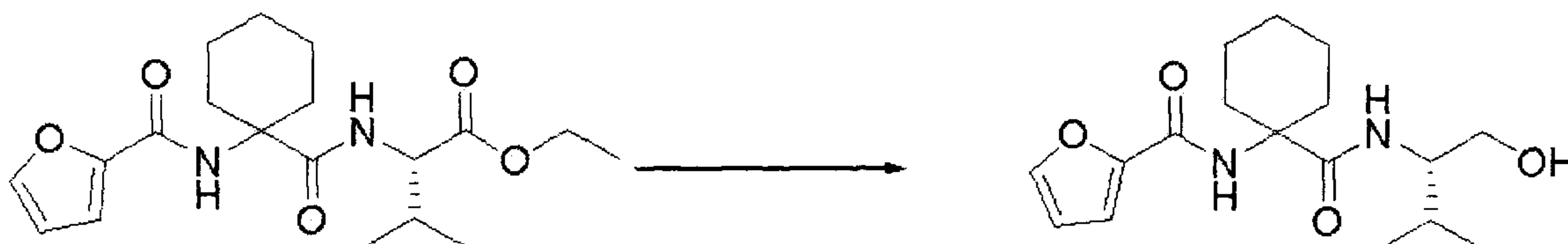
1H-NMR (CDCl₃, δ): 0.93 (3H, d, J=7Hz), 0.95 (3H, d, J=7Hz), 1.32-1.56 (3H, m), 1.58-1.76 (3H, m), 1.80-1.90 (1H, m), 1.96-2.08 (2H, m), 2.14-2.24 (2H, m), 3.00-3.06
30 (1H, m), 3.52-3.58 (1H, m), 3.68-3.78 (2H, m), 6.49 (1H,

s), 6.53 (1H, dd, J=4Hz, 2Hz), 6.75-6.77 (1H, m), 7.14 (1H, dd, J=4Hz, 1Hz), 7.49 (1H, dd, J=2Hz, 1Hz)

[0454]

Reference Example 182

5 N-[[1-[(2-Furanylcarbonyl)amino]cyclohexyl]carbonyl]-L-valinol



[0455]

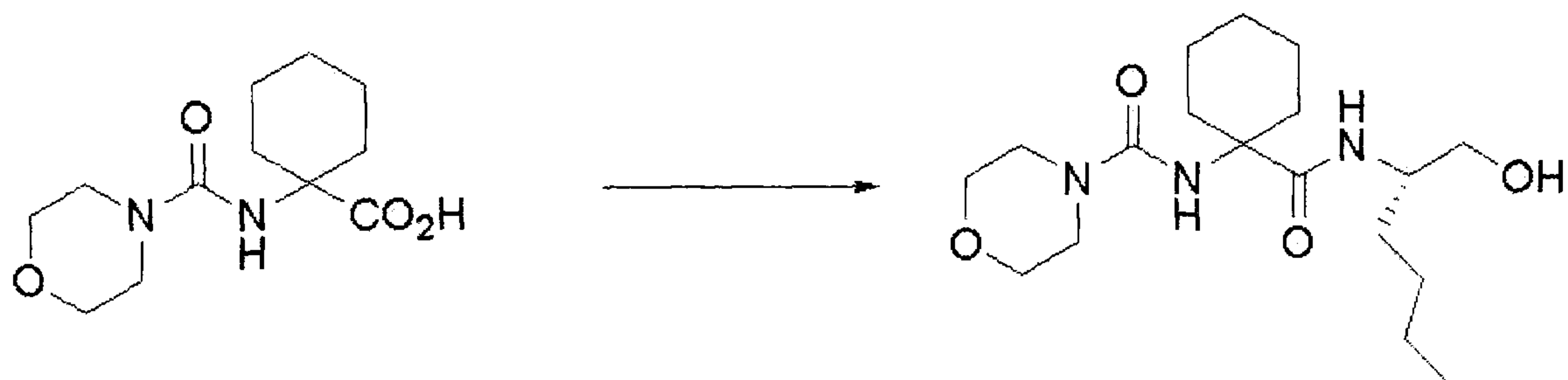
Under an argon atmosphere, 31 mg (0.82 mmol) of
10 lithium aluminum hydride was added to 1 ml of diethyl ether placed in a flask. Under ice-cooling, a solution of 0.3 g (0.82 mmol) of the above compound in 1 ml of tetrahydrofuran was added to the flask, and the mixture was stirred for 1 hour and 30 minutes. Ice-water was added to
15 the reaction solution. Ethyl acetate was added thereto, and the mixture was successively washed with a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and then saturated brine. After it was dried with sodium sulfate, the solvent was
20 distilled off under reduced pressure. The obtained crystal was washed with ether to obtain 155 mg (60%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.93 (3H, d, J=7Hz), 0.95 (3H, d, J=7Hz), 1.32-1.56 (3H, m), 1.58-1.76 (3H, m), 1.80-1.90
25 (1H, m), 1.96-2.08 (2H, m), 2.14-2.24 (2H, m), 3.00-3.06 (1H, m), 3.52-3.58 (1H, m), 3.68-3.78 (2H, m), 6.49 (1H, s), 6.53 (1H, dd, J=4Hz, 2Hz), 6.75-6.77 (1H, m), 7.14 (1H, dd, J=4Hz, 1Hz), 7.49 (1H, dd, J=2Hz, 1Hz)

[0456]

30 Reference Example 183

N-[[1-[(4-Morpholinylcarbonyl)amino]cyclohexyl]carbonyl]-L-norleucinol



[0457]

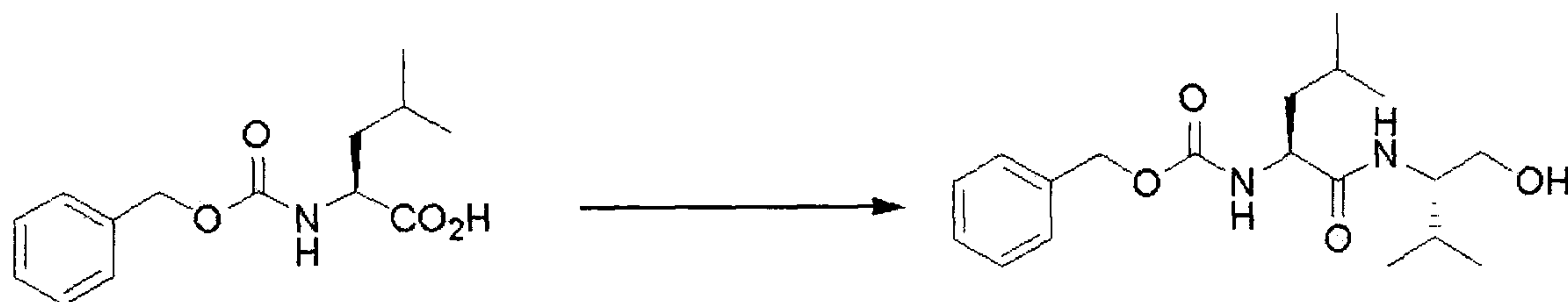
5 513 mg (2 mmol) of 1-[(4-morpholinylcarbonyl)amino]cyclohexanecarboxylic acid was used instead of 1-[[[(phenylmethoxy)carbonyl]amino]cyclohexanecarboxylic acid in the process according to Reference Example 179 to obtain
10 215 mg (30%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.89 (3H, t, J=7Hz), 1.26-1.56 (9H, m), 1.60-1.73 (3H, m), 1.85-2.05 (4H, m), 3.33-3.43 (5H, m), 3.54 (1H, t, J=7Hz), 3.66-3.73 (4H, m), 3.76-3.82 (1H, m), 3.83-3.93 (1H, m), 4.64 (1H, br-s), 6.35 (1H, d, J=8Hz)

15 [0458]

Reference Example 184

N-[N-[(Phenylmethoxy)carbonyl]-L-leucyl]-L-valinol



[0459]

20 N-[(phenylmethoxy)carbonyl]-L-leucine was used instead of 1-[[[(phenylmethoxy)carbonyl]amino]cyclohexanecarboxylic acid in the process according to Reference Example 178 to obtain 659 mg (94%) of the title compound.

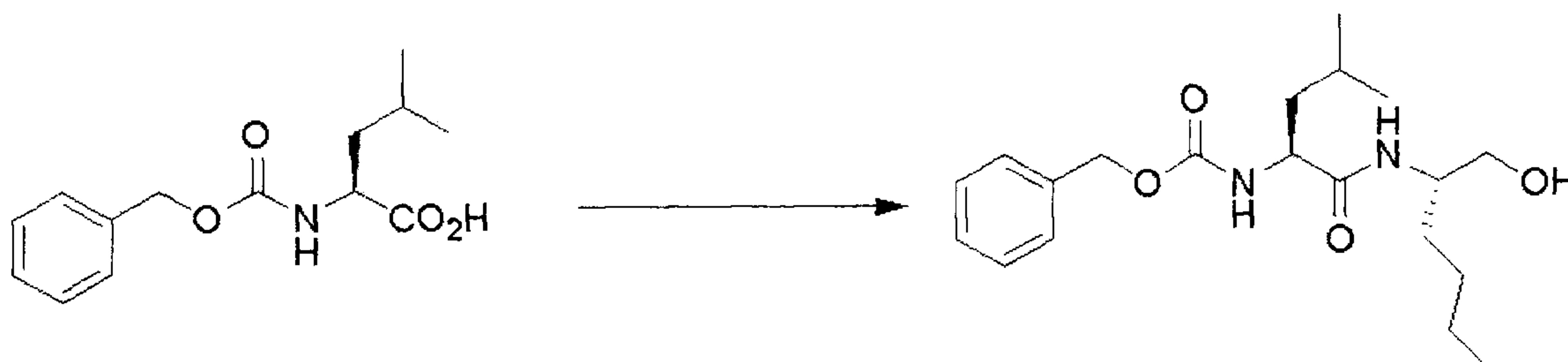
25 ¹H-NMR (CDCl₃, δ): 0.83-0.99 (12H, m), 1.46-1.74 (3H, m),

1.78-1.90 (1H, m), 2.42 (1H, br-s), 3.57-3.72 (3H, m),
4.10-4.17 (1H, m), 5.04-5.17 (3H, m), 6.22 (1H, d, J=7Hz),
7.27-7.39 (5H, m)

[0460]

5 Reference Example 185

N- [N- [(Phenylmethoxy) carbonyl] -L-leucyl] -L-norleucinol



[0461]

N- [(phenylmethoxy) carbonyl] -L-leucine was used

10 instead of 1-

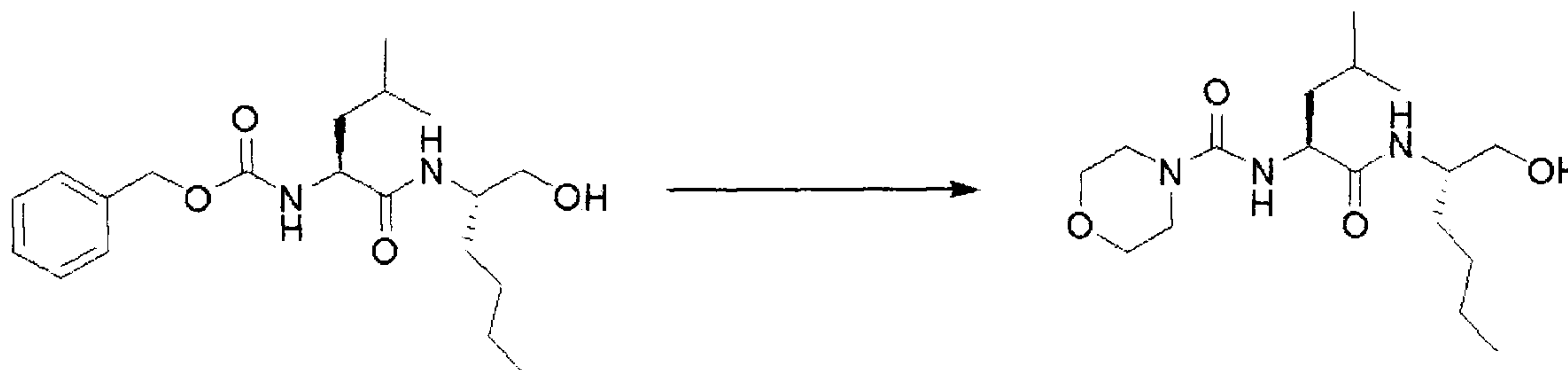
[[(phenylmethoxy) carbonyl] amino] cyclohexanecarboxylic acid,
and L-norleucinol was used instead of L-valinol in the
process according to Reference Example 178 to obtain 421 mg
(58%) of the title compound.

15 ¹H-NMR (CDCl₃, δ): 0.88 (3H, t, J=7Hz), 0.95 (6H, d,
J=7Hz), 1.23-2.72 (9H, m), 2.44 (1H, br-s), 3.47-3.71 (2H,
m), 3.89 (1H, br-s), 4.10-4.17 (1H, m), 5.08-5.16 (3H, m),
6.10 (1H, d, J=6Hz), 7.31-7.39 (5H, m)

[0462]

20 Reference Example 186

N- [N- (4-Morpholinyl carbonyl) -L-leucyl] -L-norleucinol



[0463]

70 mg of 10% palladium-carbon was added to a solution

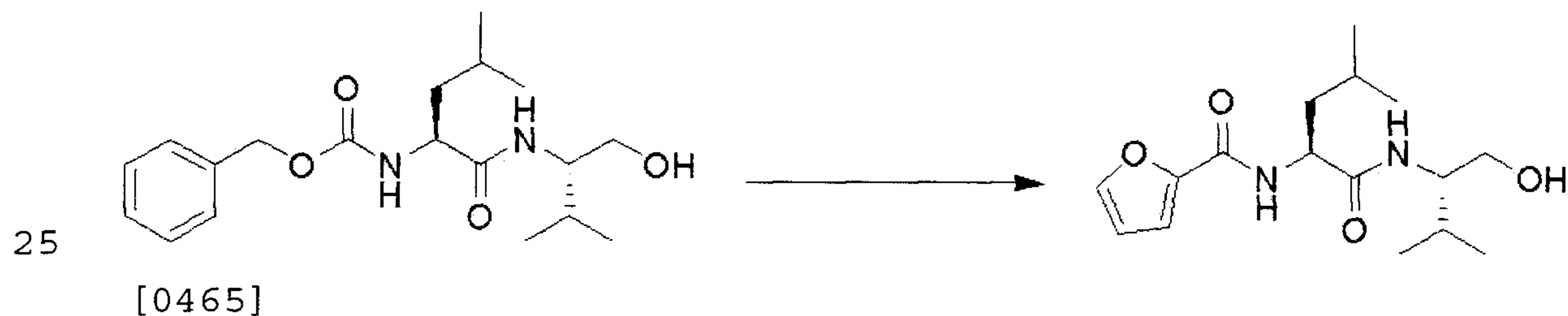
of 700 mg (2 mmol) of N-[N-[(phenylmethoxy)carbonyl]-L-leucyl]-L-norleucinol obtained in Reference Example 185 in 10 ml of methanol, and the mixture was stirred under a hydrogen atmosphere at room temperature overnight. After the reaction solution was filtered, the filtrate was concentrated under reduced pressure. 20 ml of methylene chloride and 404 mg (4 mmol) of triethylamine were added to the residue. Under ice-cooling, a solution of 299 mg (2 mmol) of 4-morpholinecarbonyl chloride in 3 ml of methylene chloride was added to the mixture solution. The reaction solution was returned to room temperature and was stirred overnight. After the reaction solution was washed with water and then saturated brine, it was dried with anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. Ether was added to the residue to wash it to obtain 488 mg (71%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.89 (3H, t, J=7Hz), 0.94 (3H, d, J=7Hz), 0.96 (3H, d, J=7Hz), 1.23-1.37 (4H, m), 1.43-1.72 (5H, m), 2.67 (1H, br-s), 3.31-3.44 (4H, m), 3.52-3.60 (1H, m), 3.65-3.73 (5H, m), 3.82-3.89 (1H, m), 4.24-4.32 (1H, m), 4.82 (1H, d, J=8Hz), 6.31 (1H, d, J=8Hz)

[0464]

Reference Example 187

N-[N-(2-Furanylcabonyl)-L-leucyl]-L-valinol



30 mg of 10% palladium-carbon was added to a solution of 350 mg (1 mmol) of N-[N-[(phenylmethoxy)carbonyl]-L-leucyl]-L-valinol obtained in Reference Example 184 in 10 ml of methanol, and the mixture was stirred under a

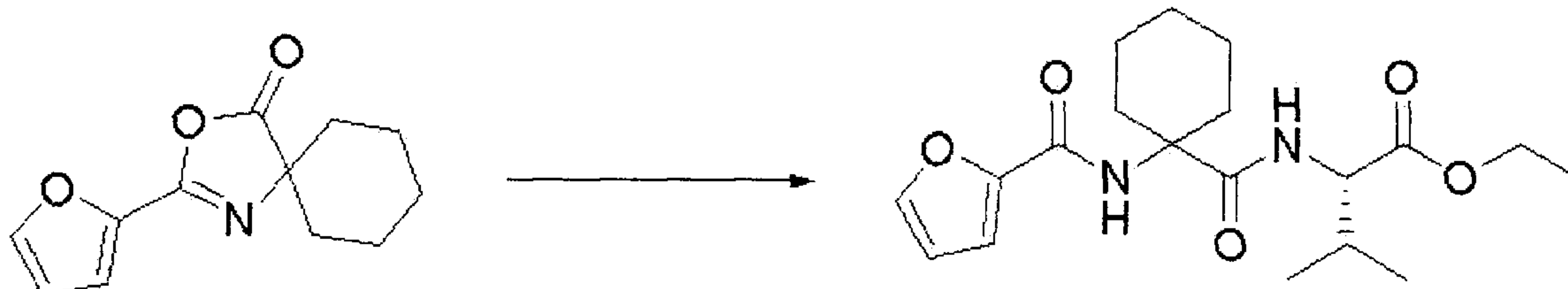
hydrogen atmosphere at room temperature overnight. After the reaction solution was filtered, the filtrate was concentrated under reduced pressure. 10 ml of ethyl acetate, 10 ml of water and further 159 mg (1.5 mmol) of sodium carbonate were added to the residue. Under ice-cooling, a solution of 131 mg (1 mmol) of 2-furancarboxyl chloride in 3 ml of ethyl acetate was added to the mixture solution. The reaction solution was returned to room temperature and was stirred overnight. The aqueous layer of the reaction solution was separately collected and extracted with ethyl acetate. The organic layer was combined and after it was washed with a 10% potassium hydrogensulfate and then saturated brine, it was dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and ether was added to the residue to wash the crystal to obtain 268 mg (86%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.91 (3H, t, J=7Hz), 0.93 (3H, t, J=7Hz), 0.97 (3H, t, J=7Hz), 0.99 (3H, t, J=7Hz), 1.65-1.94 (4H, m), 2.47 (1H, t, J=5Hz), 3.63-3.74 (3H, m), 4.54-4.62 (1H, m), 6.42 (1H, d, J=7Hz), 6.52 (1H, dd, J=4Hz, 2Hz), 6.68 (1H, d, J=8Hz), 7.14 (1H, dd, J=4Hz, 1Hz), 7.47 (1H, dd, J=2Hz, 1Hz)

[0466]

Example 1

N-[[1-[(2-Furanylcarbonyl)amino]cyclohexyl]carbonyl]-L-valine ethyl ester



[0467]

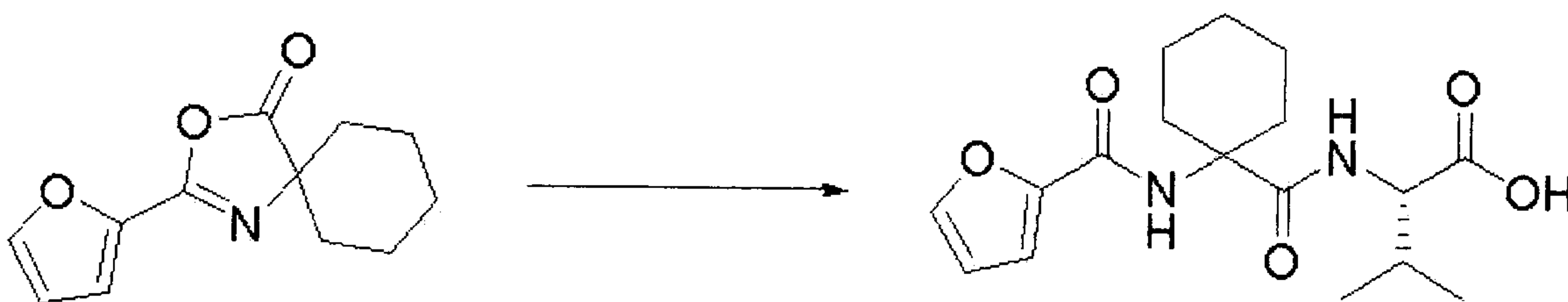
30 ml of dimethylformamide was added to a flask placed with 5 g (27 mmol) of L-valine ethyl ester hydrochloride and 5 g (22.8 mmol) of 2-(2-furanyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one. Then, 3.53 g (27.4 mmol) of diisopropylethylamine was added thereto, and the mixture was stirred for 3 days. After the solvent was distilled off under reduced pressure, ethyl acetate was added thereto, and the mixture was successively washed with a 10% aqueous potassium hydrogensulfate solution and saturated brine, followed by drying with sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by silica gel chromatography to obtain 8.3 g (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 0.89 (3H, d, J=7Hz), 0.94 (3H, d, J=7Hz), 1.25 (3H, t, J=7Hz), 1.35-1.70 (6H, m), 1.98-2.01 (2H, m), 2.19-2.23 (2H, m), 2.31-2.39 (1H, m), 4.11-4.19 (2H, m), 4.49 (1H, dd, J=9Hz, 5Hz), 6.34 (1H, s), 6.53 (1H, dd, J=3Hz, 1Hz), 7.15 (1H, dd, J=3Hz, 1Hz), 7.48 (1H, dd, J=2Hz, 1Hz), 7.58 (1H, d, J=9Hz)

[0468]

Reference Example 188

N-[[1-[(2-Furanylcarbonyl)amino]cyclohexyl]carbonyl]-L-valine



[0469]

10 ml of N-methylmorpholine was added to 1.0 g (9.1 mmol) of L-valine and 2.0 g (9.1 mmol) of 2-(2-furanyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, and the mixture was stirred and heated under reflux overnight. Under reduced

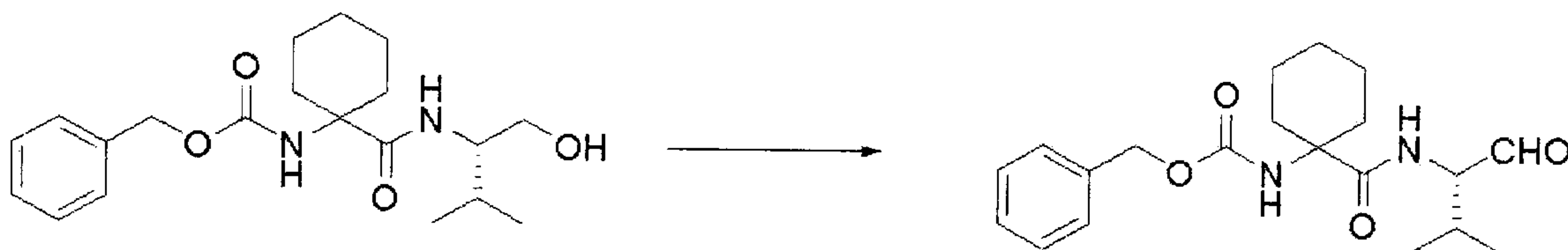
pressure, the reaction mixture was distilled off, ethyl acetate was added thereto, and the mixture was washed with a 10% aqueous potassium hydrogensulfate solution and then saturated brine, followed by drying with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography to obtain 384 mg (12.5%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.93 (3H, d, J=7Hz), 0.97 (3H, d, J=7Hz), 1.33-1.48 (3H, m), 1.64-1.73 (3H, m), 1.98 (2H, dt, J=14Hz, 4Hz), 2.22-2.30 (3H, m), 4.46 (1H, m), 6.43 (1H, s), 6.53 (1H, dd, J=3Hz, 2Hz), 7.17 (1H, dd, J=3Hz, 1Hz), 7.48 (1H, dd, J=2Hz, 1Hz), 7.55 (1H, d, J=8Hz)

[0470]

Reference Example 189

N-[[1-[[(Phenylmethoxy) carbonyl] amino] cyclohexyl] carbonyl]-L-valinal



[0471]

Under an argon gas atmosphere, 1.22 g (9.44 mmol) of N,N-diisopropylethylamine was added dropwise to a solution of 1.50 g (9.44 mmol) of sulfur trioxide-pyridine complex in 10 ml of anhydrous dimethyl sulfoxide and 5 ml of anhydrous methylene chloride under ice-cooling, and the mixture was stirred for 15 minutes. Further, under ice-cooling, a solution of 570 mg (1.57 mmol) of N-[[1-[[(phenylmethoxy) carbonyl] amino] cyclohexyl] carbonyl]-L-valinol in 3 ml of anhydrous dimethyl sulfoxide was added to the reaction solution, and the mixture was stirred at the same temperature for 2 hours. The reaction solution

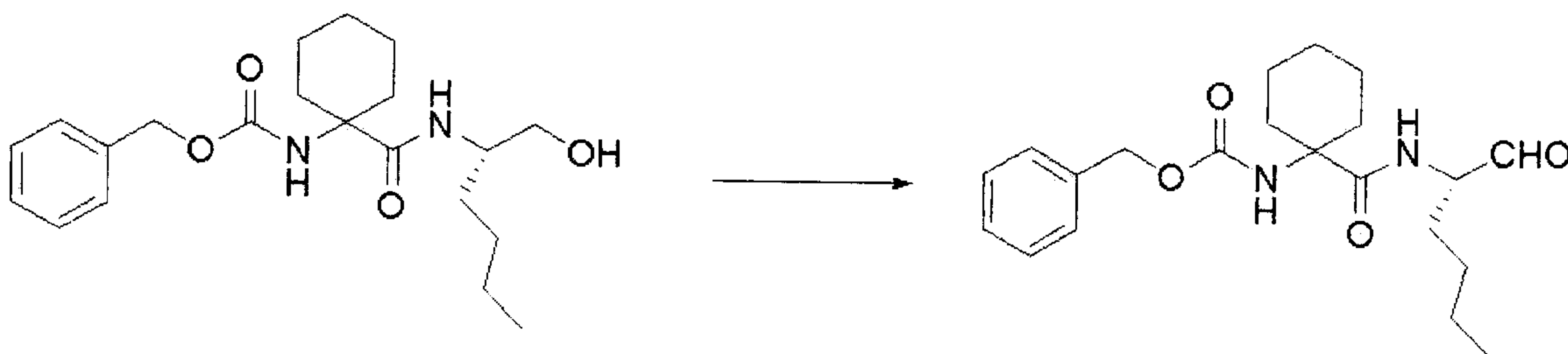
was poured to ice-water and extracted with ethyl acetate twice. After the organic layer was washed with a 10% aqueous citric acid solution, a saturated aqueous sodium hydrogencarbonate solution and then saturated brine and dried with anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. 20 ml of diisopropyl ether was added to the residue, and the mixture was stirred at room temperature for 18 hours. The obtained crystal was collected by filtration to obtain 435 mg (77%) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 0.88 (3H, d, $J=7\text{Hz}$), 0.97 (3H, d, $J=7\text{Hz}$), 1.22-1.44 (3H, m), 1.59-1.70 (3H, m), 1.85-2.15 (4H, m), 2.22-2.34 (1H, m), 4.48 (1H, s), 4.96 (1H, s), 5.11 (2H, s), 7.10-7.41 (6H, m), 9.59 (1H, s)

[0472]

Reference Example 190

N-[[1-[[(Phenylmethoxy) carbonyl] amino] cyclohexyl] carbonyl] - L-norleucinal



[0473]

465 mg (1.24 mmol) of N-[[1-[[(phenylmethoxy) carbonyl] amino] cyclohexyl] carbonyl] - L-norleucinol was used instead of N-[[1-[[(phenylmethoxy) carbonyl] amino] cyclohexyl] carbonyl] - L-valinol in the process according to Reference Example 189 to obtain 350 mg (75%) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 0.88 (3H, d, $J=7\text{Hz}$), 1.19-1.43 (7H, m), 1.51-1.70 (4H, m), 1.82-2.13 (5H, m), 4.42 (1H, br-s), 4.95 (1H, s), 5.10 (2H, s), 7.10 (1H, br-s), 7.29-7.42 (5H, m),

9.53 (1H, s)

[0474]

Reference Example 191

N-[[1-[(2-Furanylcarbonyl)amino]cyclohexyl]carbonyl]-L-
5 valinal



[0475]

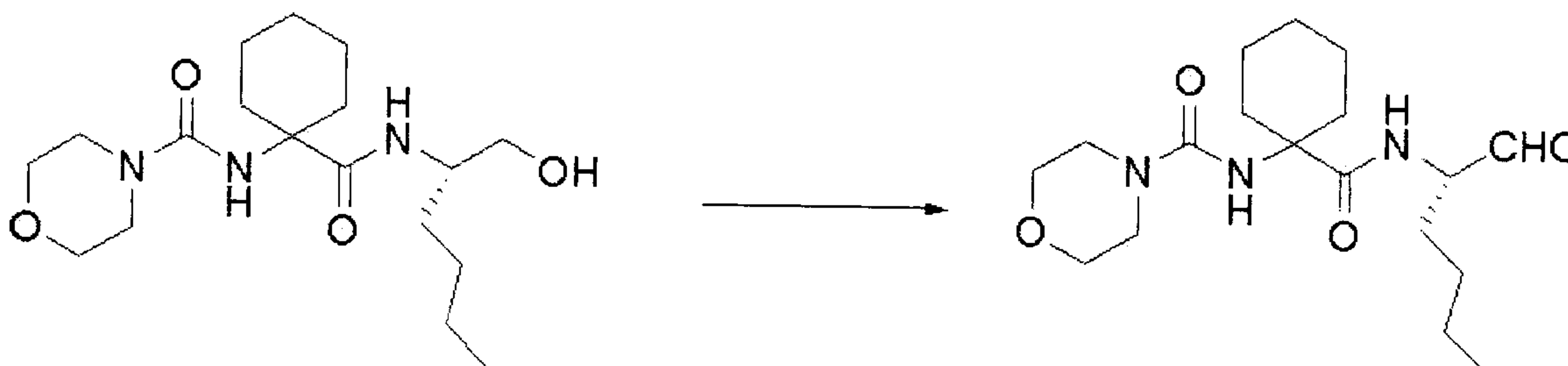
3.50 g (10.9 mmol) of N-[[1-[(2-furanylcarbonyl)amino]cyclohexyl]carbonyl]-L-valinol was
10 used instead of N-[[1-[[[(phenylmethoxy)carbonyl]amino]cyclohexyl]carbonyl]-L-valinol in the process according to Reference Example 189 to obtain 3.14 g (90.3%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.94 (3H, d, J=7Hz), 1.01 (3H, d, J=7Hz), 1.30-1.40 (1H, m), 1.41-1.54 (2H, m), 1.62-1.76 (3H, m), 1.95-2.04 (2H, m), 2.20-2.26 (1H, m), 2.28-2.36 (2H, m), 4.44 (1H, dd, J=8Hz, 5Hz), 6.38 (1H, br-s), 6.54 (1H, dd, J=4Hz, 2Hz), 7.15 (1H, dd, J=4Hz, 1Hz), 7.49 (1H, dd, J=2Hz, 1Hz), 7.68 (1H, d, J=8Hz), 9.60 (1H, s)

20 [0476]

Reference Example 192

N-[[1-[(4-Morpholinylcarbonyl)amino]cyclohexyl]carbonyl]-L-norleucinal



25 [0477]

205 mg (0.58 mmol) of N-[[1-[(4-

morpholinylcarbonyl)amino]cyclohexyl]carbonyl]-L-norleucinol was used instead of N-[[1-
 [(phenylmethoxy)carbonyl]amino]cyclohexyl]carbonyl]-L-valinol in the process according to Reference Example 189
 5 to obtain 125 mg (61%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.89 (3H, t, J=7Hz), 1.23-1.42 (7H, m), 1.52-1.71 (4H, m), 1.83-1.98 (3H, m), 2.05-2.18 (2H, m), 3.34-3.42 (4H, m), 3.65-3.76 (4H, m), 4.37 (1H, dt, J=7Hz, 7Hz), 4.48 (1H, s), 7.81 (1H, d, J=7Hz), 9.55 (1H, s)

10 [0478]

Reference Example 193

N-[N-[(Phenylmethoxy)carbonyl]-L-leucyl]-L-valinal



[0479]

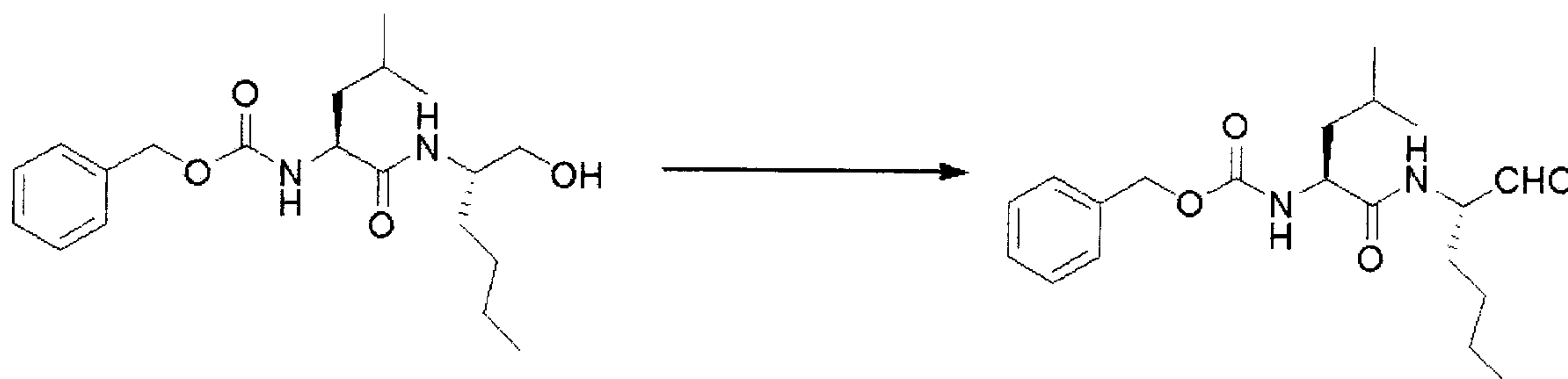
15 280 mg (0.8 mmol) of N-[N-[(phenylmethoxy)carbonyl]-L-leucyl]-L-valinol was used instead of N-[[1-
 [(phenylmethoxy)carbonyl]amino]cyclohexyl]carbonyl]-L-valinol in the process according to Reference Example 189
 to obtain 278 mg (quantitative) of the title compound.

20 ¹H-NMR (CDCl₃, δ): 0.83-1.01 (12H, m), 1.48-1.59 (1H, m), 1.62-1.74 (2H, m), 2.28-2.37 (1H, m), 4.19-4.28 (1H, m), 4.51-4.56 (1H, m), 5.05-5.17 (3H, m), 6.51 (1H, d, J=7Hz), 7.27-7.39 (5H, m), 9.64 (1H, s)

[0480]

25 Reference Example 194

N-[N-[(Phenylmethoxy)carbonyl]-L-leucyl]-L-norleucinal



[0481]

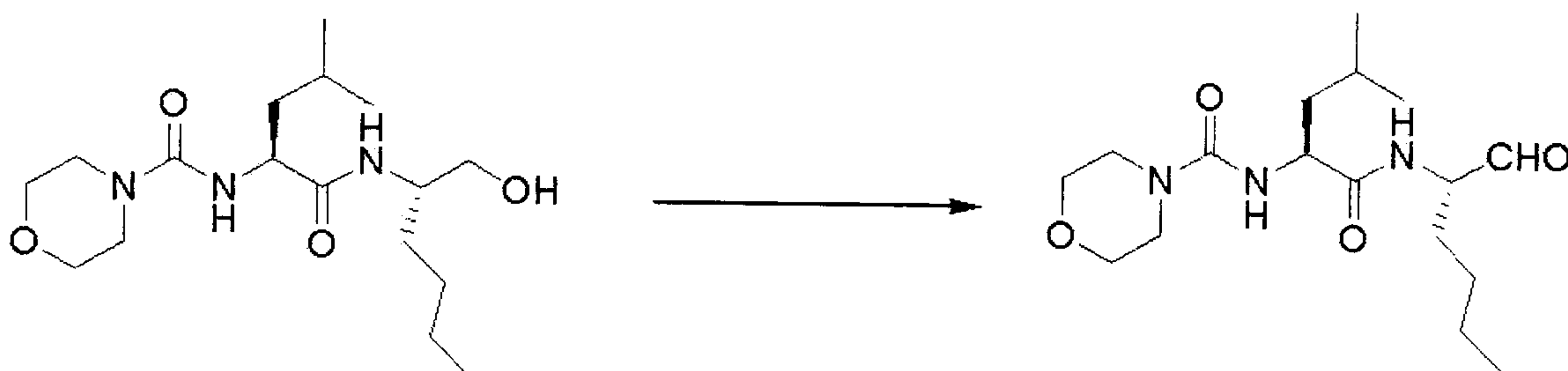
253 mg (0.7 mmol) of N-[N-[(phenylmethoxy)carbonyl]-L-leucyl]-L-norleucinol was used instead of N-[[1-
 5 [[(phenylmethoxy)carbonyl]amino]cyclohexyl]carbonyl]-L-valinol in the process according to Reference Example 189 to obtain 195 mg (78%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.89 (3H, t, J=7Hz), 0.95 (6H, d, J=7Hz), 1.22-1.39 (4H, m), 1.47-1.72 (4H, m), 1.83-1.97
 10 (1H, m), 4.19-4.26 (1H, m), 4.45-4.53 (1H, m), 5.08-5.17 (3H, m), 6.46 (1H, br-s), 7.29-7.39 (5H, m), 9.57 (1H, s)

[0482]

Reference Example 195

N-[N-(4-Morpholinylcarbonyl)-L-leucyl]-L-norleucinal



15

[0483]

473 mg (1.4 mmol) of N-[N-(4-morpholinylcarbonyl)-L-leucyl]-L-norleucinol was used instead of N-[[1-
 [[(phenylmethoxy)carbonyl]amino]cyclohexyl]carbonyl]-L-valinol in the process according to Reference Example 189
 20 to obtain 315 mg (67%) of the title compound.

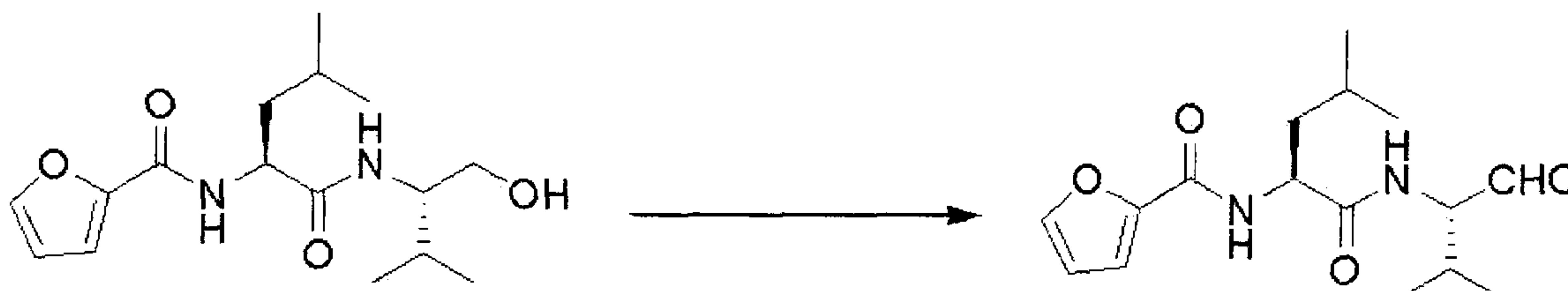
¹H-NMR (CDCl₃, δ): 0.90 (3H, t, J=7Hz), 0.96 (3H, d, J=6Hz), 0.97 (3H, d, J=6Hz), 1.23-1.39 (4H, m), 1.50-1.76
 (4H, m), 1.85-1.96 (1H, m), 3.32-3.43 (4H, m), 3.63-3.72

(4H, m), 4.37-4.46 (2H, m), 4.86 (1H, d, J=8Hz), 6.69 (1H, d, J=7Hz), 9.56 (1H, s)

[0484]

Reference Example 196

5 N- [N- (2-Furanylcabonyl) -L-leucyl] -L-valinal



[0485]

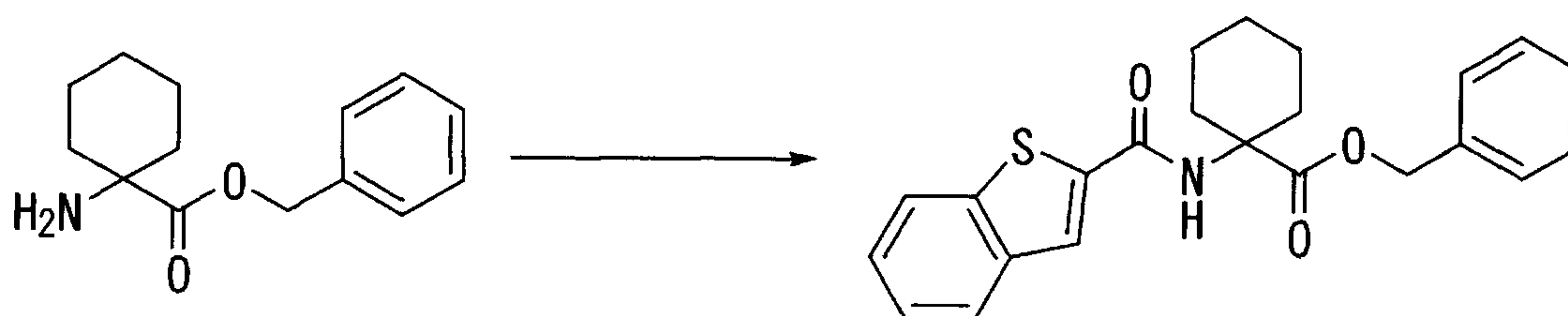
256 mg (0.8 mmol) of N- [N- (2-furanylcabonyl) -L-leucyl] -L-valinol was used instead of N- [[1-
10 [[(phenylmethoxy)carbonyl]amino]cyclohexyl]carbonyl] -L-valinol in the process according to Reference Example 189 to obtain 175 mg (72%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.90-1.02 (12H, m), 1.64-1.82 (3H, m), 2.29-2.36 (1H, m), 4.52 (1H, dd, J=8Hz, 5Hz), 4.67 (1H, td, J=8Hz, 6Hz), 6.51 (1H, dd, J=4Hz, 2Hz), 6.67-6.73 (2H, m), 7.14 (1H, dd, J=4Hz, 1Hz), 7.46 (1H, dd, J=2Hz, 1Hz), 9.65 (1H, s)

[0486]

Reference Example 197

20 1- [(2-Benzothienylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester



[0487]

Under ice-cooling, 5.9 g (31 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added to
25 a solution of 5 g (28 mmol) of 2-benzothiophenecarboxylic

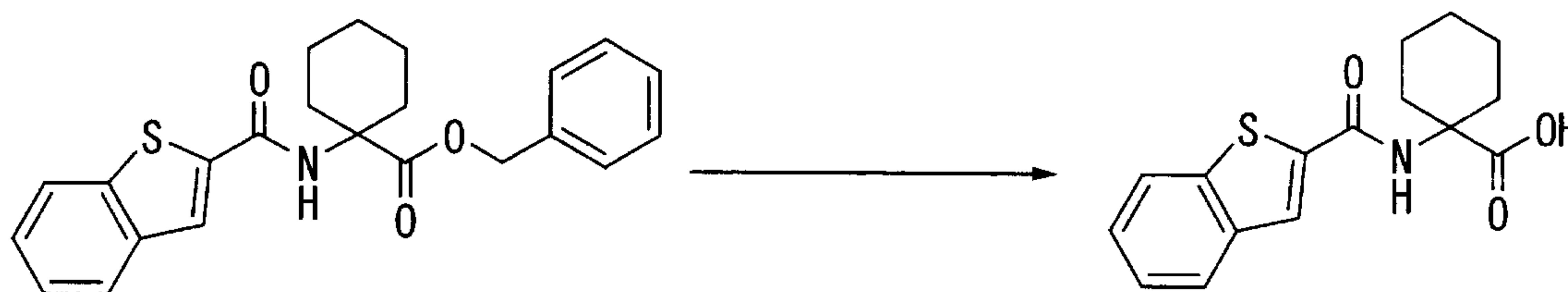
acid, 6.5 g (28 mmol) of 1-aminocyclohexanecarboxylic acid phenylmethyl ester and 4.5 g (29 mmol) of 1-hydroxybenzotriazole in methylene chloride. After the mixture was stirred at room temperature overnight, the reaction solvent was distilled off under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate twice. The obtained organic layer was washed with a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and then saturated brine, and it was dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, diethyl ether was added to the obtained residue, and the mixture was stirred overnight. The crystal was collected by filtration and heated/dried under reduced pressure to obtain 10 g (91%) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.25-1.78 (6H, m), 1.93-2.05 (2H, m), 2.12-2.25 (2H, m), 5.18 (2H, s), 6.24 (1H, s), 7.20-7.38 (5H, m), 7.38-7.51 (2H, m), 7.77 (1H, s), 7.80-7.91 (2H, m)

[0488]

Reference Example 198

1-[(2-Benzothienylcarbonyl)amino]cyclohexanecarboxylic acid



[0489]

42 ml of 2N aqueous sodium hydroxide solution was added to a solution of 10 g (24 mmol) of 1-[(2-benzothienylcarbonyl)amino]cyclohexanecarboxylic acid phenylmethyl ester in 20 ml of tetrahydrofuran, and the mixture was heated under reflux for 3 days. After ether

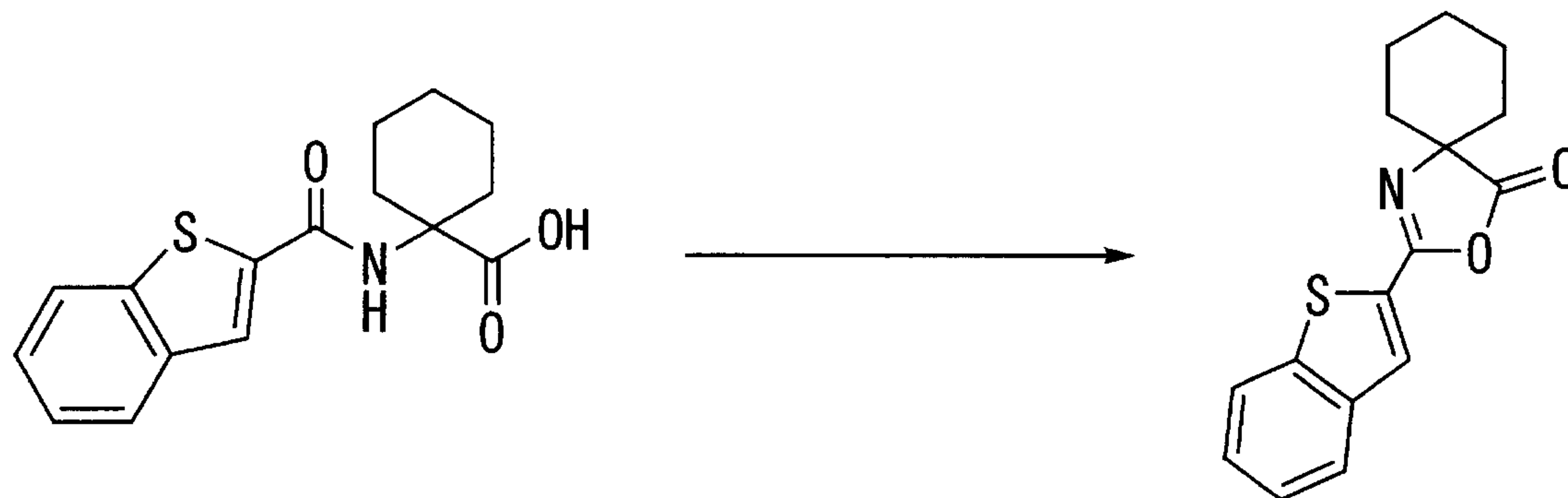
was added to the reaction solution to wash it, the aqueous layer was neutralized by concentrated hydrochloric acid, and the precipitated crystal was collected by filtration. The obtained crystal was dried under reduced pressure to
5 obtain 6.1 g (80%) of the title compound.

¹H-NMR (CDCl₃, δ): 1. H 31-1.85 (6H, m), 1.91-2.08 (2H, m), 2.21-2.35 (2H, m), 6.22 (1H, s), 7.38-7.53 (2H, m), 7.80-7.93 (3, m)

[0490]

10 Reference Example 199

2-(2-Benzothienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0491]

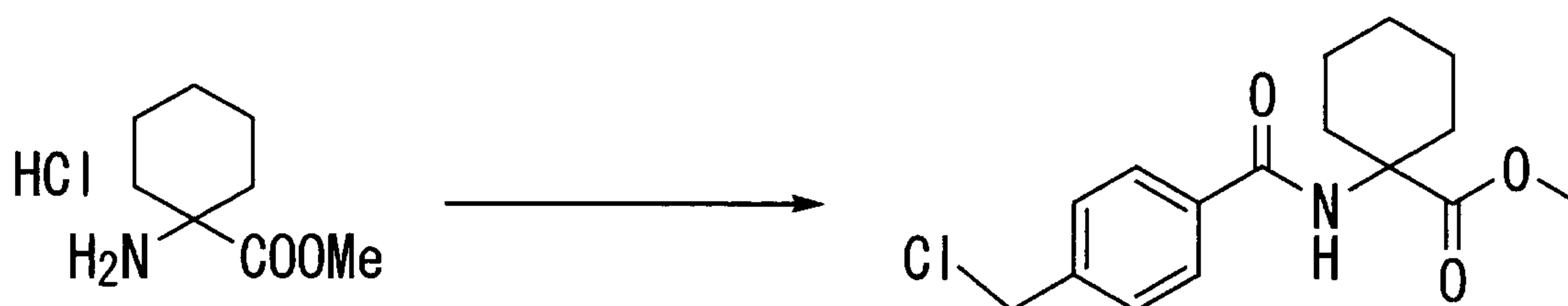
4.1 g (21 mmol) of 1-ethyl-3-(3-
15 dimethylaminopropyl)carbodiimide hydrochloride was added to a solution of 5 g (16 mmol) of 1-[(2-benzothienylcarbonyl)amino]cyclohexanecarboxylic acid in 50 ml of methylene chloride. After the mixture was stirred at room temperature for 4 hours, the reaction solution was
20 concentrated under reduced pressure, ethyl acetate was added thereto, and the mixture was successively washed with water, a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and saturated brine. The organic layer was dried with
25 anhydrous sodium sulfate and the solvent was distilled off under reduced pressure to obtain 3.5 g (75%) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.45-1.98 (10H, m), 7.38-7.51 (2H, m),
7.80-7.91 (2H, m), 7.93 (1H, s)

[0492]

Reference Example 200

- 5 1-[[[4-(Chloromethyl)phenyl]carbonyl]amino]cyclohexanecarboxylic
acid methyl ester



[0493]

- 10 Under ice-cooling, 9.96 g (52 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added to
a solution of 8.8 g (52 mmol) of 4-(chloromethyl)benzoic
acid, 10 g (52 mmol) of 1-aminocyclohexanecarboxylic acid
methyl ester hydrochloride, 15 g (152 mmol) of
15 triethylamine and 8.63 g (56 mmol) of 1-
hydroxybenzotriazole in methylene chloride. After the
mixture was stirred at room temperature overnight, the
reaction solvent was distilled off under reduced pressure.
Water was added to the residue, and the mixture was
20 extracted with ethyl acetate twice. The obtained organic
layer was washed with a 10% aqueous potassium
hydrogensulfate solution, a saturated aqueous sodium
hydrogencarbonate solution and then saturated brine, and it
was dried with anhydrous sodium sulfate. The obtained
25 residue was purified by silica gel column chromatography to
obtain 8.5 g (53%) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.25-1.73 (6H, m), 1.83-2.00 (2H, m),
2.08-2.21 (2H, m), 3.71 (3H, s), 5.56 (2H, s), 6.30 (1H,
s), 7.44 (2H, dd, $J=8\text{Hz}$, 2Hz), 7.75 (2H, dd, $J=8\text{Hz}$, 2Hz)

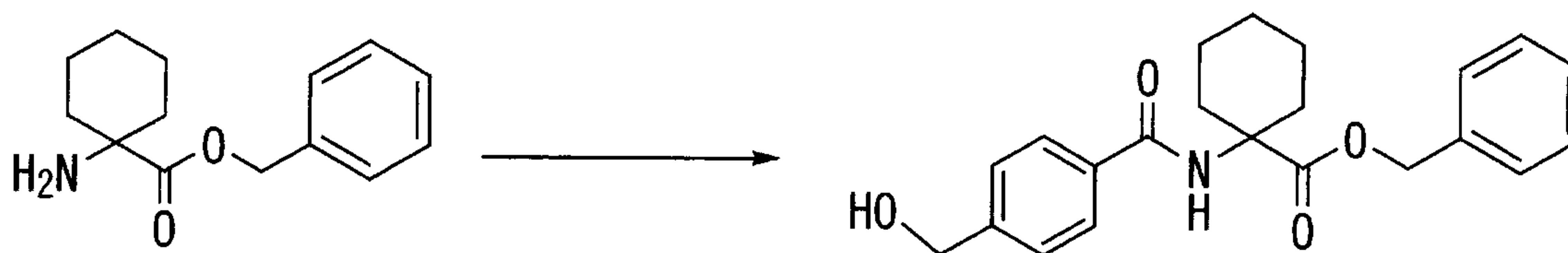
[0494]

Reference Example 201

1-[[[4-

(Hydroxymethyl)phenyl]carbonyl]amino]cyclohexanecarboxylic

5 acid phenylmethyl ester



[0495]

Under ice-cooling, 6.94 g (36 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added to a solution of 5 g (33 mmol) of 4-(hydroxymethyl)benzoic acid, 7.7 g (33 mmol) of 1-aminocyclohexanecarboxylic acid phenylmethyl ester and 5.29 g (35 mmol) of 1-hydroxybenzotriazole in methylene chloride. After the mixture was stirred at room temperature overnight, the reaction solvent was distilled off under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate twice. The obtained organic layer was washed with a 10% aqueous potassium hydrogensulfate solution, a saturated aqueous sodium hydrogencarbonate solution and then saturated brine, and it was dried with anhydrous sodium sulfate. The obtained residue was purified by silica gel column chromatography to obtain 6.83 g (56%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.23-1.79 (6H, m), 1.82-2.23 (4H, m), 4.73 (2H, m), 5.16 (2H, s), 6.25 (1H, s), 7.20-7.32 (5H, m), 7.32-7.43 (2H, m), 7.62-7.79 (2H, m)

[0496]

Reference Example 202

1-[[[4-

30 [(Dimethylamino)methyl]phenyl]carbonyl]amino]cyclohexancar

boxylic acid methyl ester



[0497]

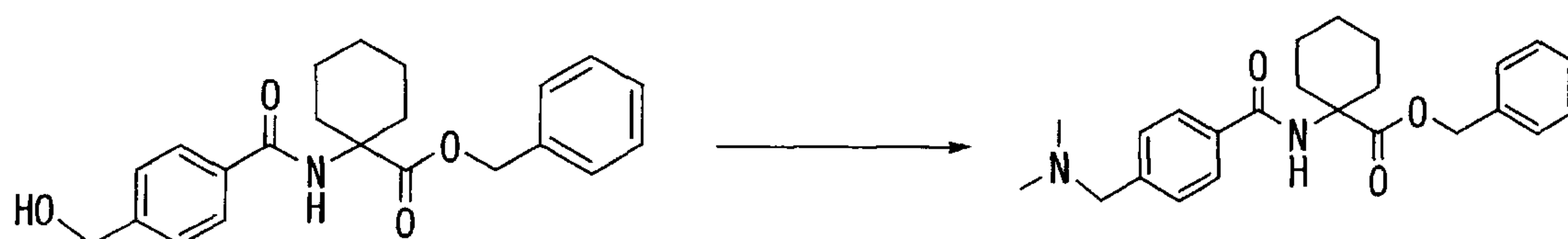
30 ml of 40% aqueous dimethylamine solution was added
 5 to 4.5 g (14.5 mmol) of 1-[[[4-(chloromethyl)phenyl]carbonyl]amino]cyclohexanecarboxylic
 acid methyl ester, and the mixture was heated under reflux
 for 3 hours. The reaction mixture was distilled off under
 reduced pressure, a saturated aqueous sodium bicarbonate
 10 solution was added thereto, and the mixture was extracted
 with ethyl acetate. The organic layer was washed with
 saturated brine and dried with anhydrous sodium sulfate.
 The solvent was distilled off under reduced pressure,
 diisopropyl ether was added to the residue, and the mixture
 15 was stirred overnight. The precipitated solid was
 collected by filtration to obtain 2.3 g (50%) of the title
 compound.

¹H-NMR (CDCl₃, δ): 1.30-2.19 (10H, m), 2.24 (6H, s), 3.46
 (2H, s), 3.76 (3H, s), 6.22 (1H, s), 7.38 (2H, d, J=9Hz),
 20 7.73 (2H, d, J=9Hz)

[0498]

Reference Example 203

1-[[[4-(
 [(Dimethylamino)methyl]phenyl]carbonyl]amino]cyclohexanecar
 25 boxylic acid phenylmethyl ester



[0499]

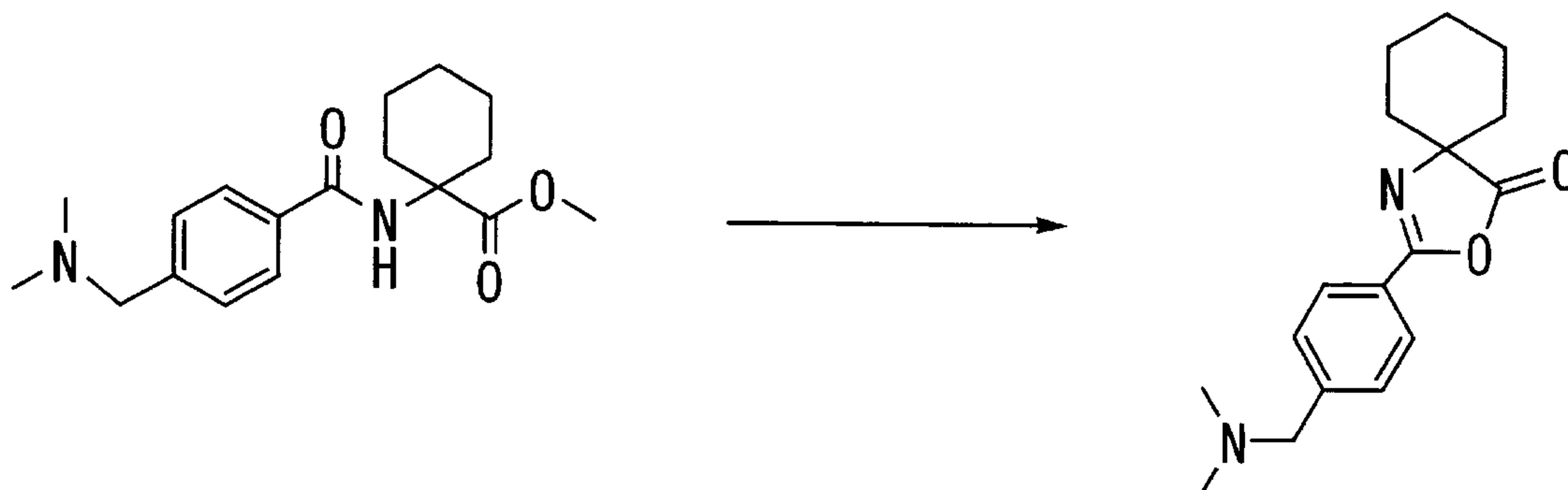
Under ice-cooling, 1 g (9 mmol) of methanesulfonyl chloride was added dropwise to a solution of 3 g (8 mmol) of 1-[[[4-(hydroxymethyl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester and 2.46 g (24 mmol) of triethylamine in methylene chloride. After the mixture was stirred at room temperature for 1 hour, 20 ml of 2N dimethylamine-tetrahydrofuran solution was added thereto, and the mixture was stirred overnight. The reaction mixture was distilled off under reduced pressure, and a saturated aqueous sodium bicarbonate solution was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was purified by silica gel column chromatography to obtain 700 mg (22%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.30-2.01 (9H, m), 2.12-2.28 (1H, m), 2.24 (6H, s), 3.46 (2H, s), 5.17 (2H, s), 6.25 (1H, s), 7.21-7.32 (5H, m), 7.37 (2H, dd, J=9Hz, 2Hz), 7.10 (2H, dd, J=9Hz, 2Hz)

[0500]

Reference Example 204

2-[4-[(Dimethylamino)methyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0501]

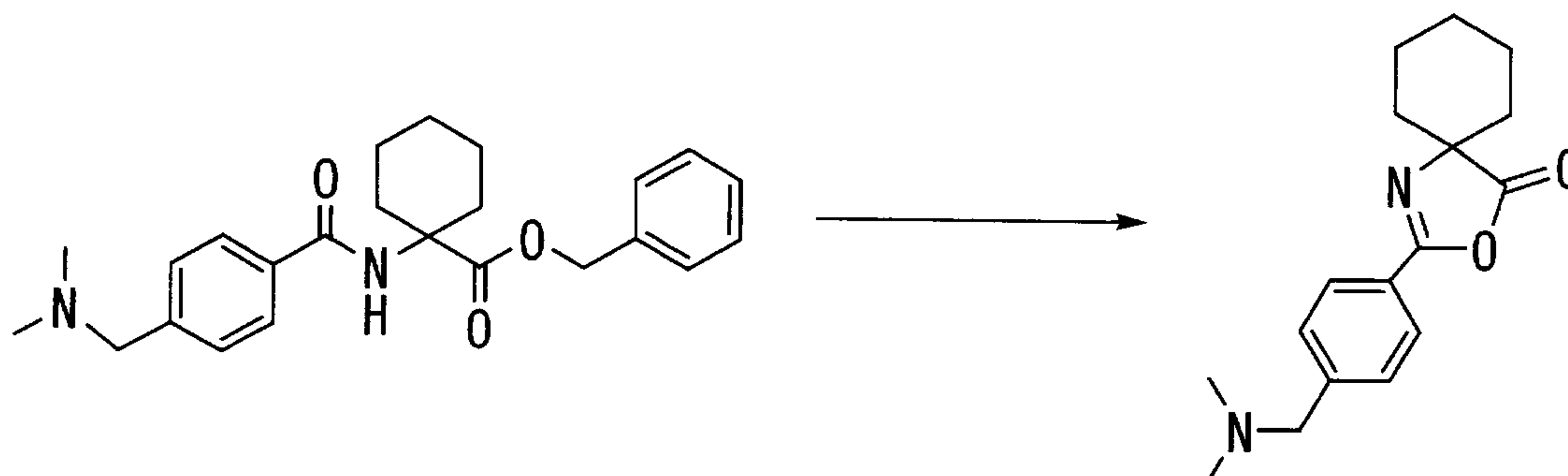
29 ml of 2N aqueous sodium hydroxide solution was added to a solution of 1.85 g (5.8 mmol) of 1-[[[4-[(dimethylamino)methyl]phenyl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester in 29 ml of tetrahydrofuran, and the mixture was heated under reflux overnight. After the reaction solution was neutralized by concentrated hydrochloric acid, the reaction mixture was distilled off under reduced pressure. 30 ml of methylene chloride, 1.76 g (17 mmol) of triethylamine and 1.67 g (8.7 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride were added to the residue, and the mixture was stirred for 1 hour. The reaction mixture was distilled off under reduced pressure, a saturated aqueous sodium bicarbonate solution was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 1.33 g (80%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.50-1.88 (10H, m), 2.25 (6H, s), 3.48 (2H, s), 7.43 (2H, dd, J=9Hz, 2Hz), 7.96 (2H, dd, J=9Hz, 2Hz)

[0502]

Reference Example 205

2-[4-[(Dimethylamino)methyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0503]

0.7 ml of 2N aqueous sodium hydroxide solution was added to a solution of 100 mg (0.25 mmol) of 1-[[[4-
 5 [(dimethylamino)methyl]phenyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in 1 ml of tetrahydrofuran, and the mixture was heated under reflux overnight. After the reaction mixture was neutralized by concentrated hydrochloric acid, the reaction mixture was distilled off under reduced pressure. 3 ml of methylene chloride, 126 mg
 10 (1.25 mmol) of triethylamine and 96 mg (0.5 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride were added to the residue, and the mixture was stirred for 1 hour. The reaction solution was distilled off under reduced pressure, a saturated aqueous sodium bicarbonate solution was added thereto, and the mixture was extracted
 15 with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 52 mg (68%) of the
 20 title compound.

¹H-NMR (CDCl₃, δ): 1.50-1.88 (10H, m), 2.25 (6H, s), 3.48 (2H, s), 7.43 (2H, dd, J=9Hz, 2Hz), 7.96 (2H, dd, J=9Hz, 2Hz)

[0504]

25 Reference Example 206

1-[[[4-(4-

Morpholinylmethyl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester



30 [0505]

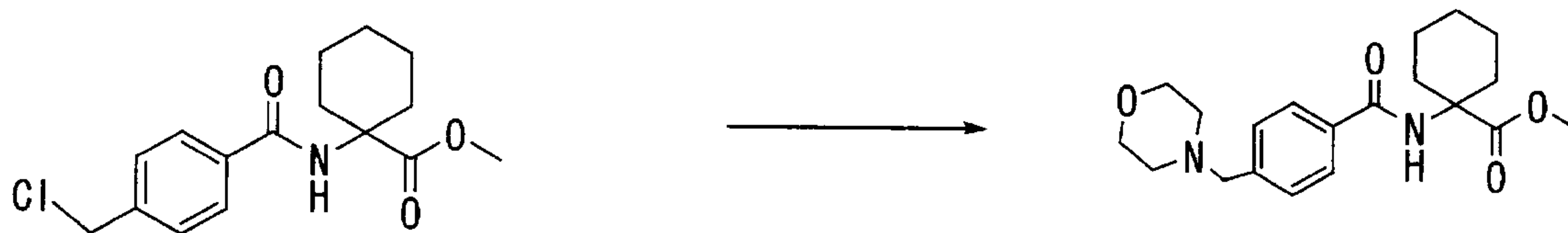
Under ice-cooling, 628 mg (5.5 mmol) of methanesulfonyl chloride was added dropwise to a solution of 1.83 g (5 mmol) of 1-[[[4-(hydroxymethyl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester and 1.52 g (15 mmol) of triethylamine in methylene chloride. After the mixture was stirred at room temperature for 1 hour, 5 ml of morpholine was added thereto, and the mixture was stirred overnight. The reaction solution was distilled off under reduced pressure, a saturated aqueous sodium bicarbonate solution was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was purified by silica gel column chromatography to obtain 1 g (57%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.25-1.79 (6H, m), 1.89-2.03 (2H, m), 2.15-2.29 (2H, m), 2.43 (4H, t, J=5Hz), 3.53 (2H, s), 3.70 (4H, t, J=5Hz), 5.17 (2H, s), 6.21 (1H, s), 7.21-7.38 (5H, m), 7.39 (2H, d, J=8Hz), 7.71 (2H, d, J=8Hz)

[0506]

Reference Example 207

1-[[[4-(4-(morpholinylmethyl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester



[0507]

30 ml of morpholine was added to 4 g (13 mmol) of 1-[[[4-(chloromethyl)phenyl]carbonyl]amino]cyclohexanecarboxylic

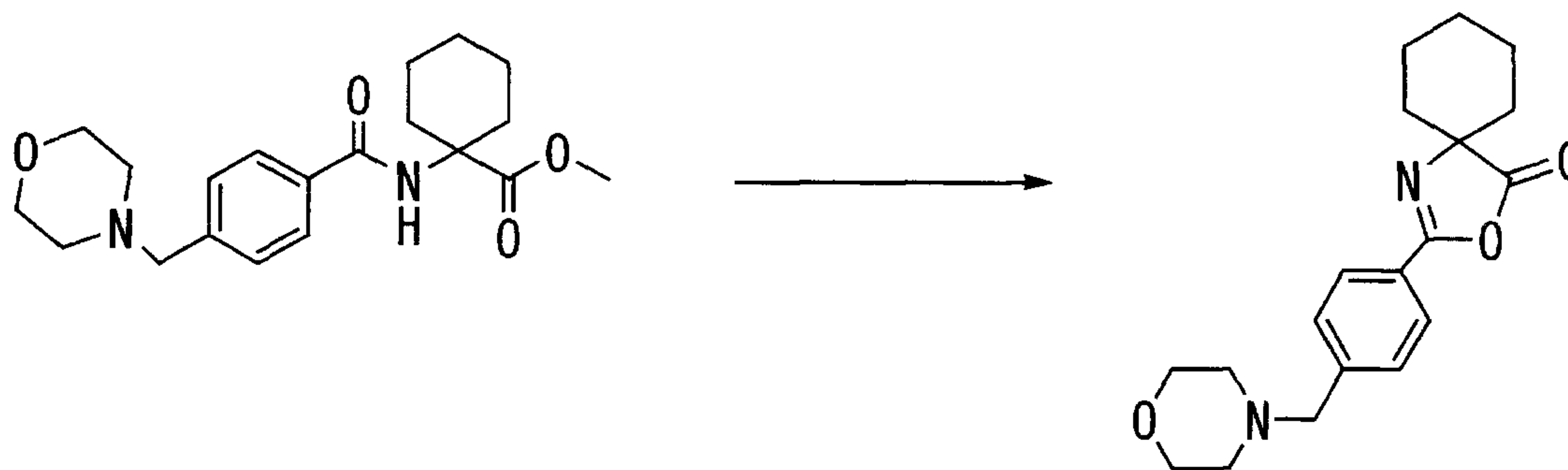
acid methyl ester, and the mixture was heated under reflux for 1 hour. The reaction solution was distilled off under reduced pressure, a saturated aqueous sodium bicarbonate solution was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, diethyl ether was added to the residue, and the mixture was stirred overnight. The precipitated solid was collected by filtration to obtain 3.8 g (83%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.28-1.80 (6H, m), 1.80-1.99 (2H, m), 2.11-2.21 (2H, m), 2.38-2.49 (4H, m), 3.54 (2H, s), 3.63-3.74 (4H, m), 3.73 (3H, s), 6.22 (1H, s), 7.41 (2H, d, J=8Hz), 7.73 (2H, d, J=8Hz)

[0508]

Reference Example 208

2-[4-(4-Morpholinylmethyl)phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0509]

18 ml of 2N aqueous sodium hydroxide solution was added to a solution of 2.07 g (5.7 mmol) of 1-[[[4-(4-morpholinylmethyl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester in 18 ml of tetrahydrofuran, and the mixture was heated under reflux overnight. After the reaction solution was neutralized by concentrated hydrochloric acid, the reaction solution was distilled off

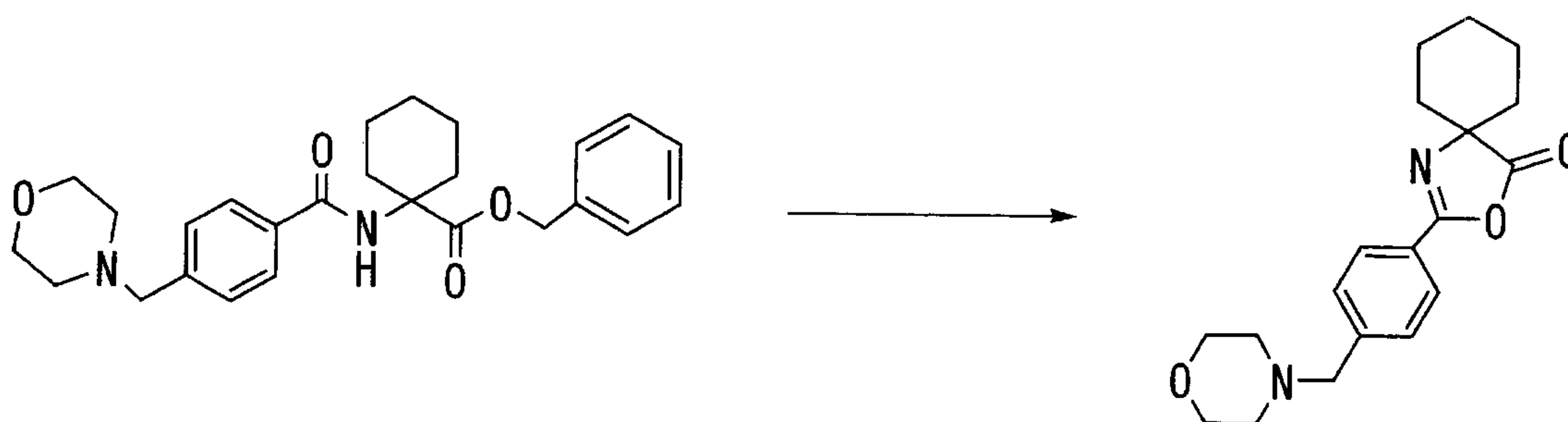
under reduced pressure. 30 ml of methylene chloride, 1.74 g (17 mmol) of triethylamine and 1.65 g (8.6 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride were added to the residue, and the mixture was stirred for 1 hour. The reaction solution was distilled off under reduced pressure, a saturated aqueous sodium bicarbonate solution was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 1.27 g (60%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.42-1.80 (10H, m), 2.44 (4H, t, J=5Hz), 3.56 (2H, s), 3.71 (4H, t, J=5Hz), 7.45 (2H, d, J=8Hz), 7.96 (2H, d, J=8Hz)

[0510]

Reference Example 209

2-[4-(4-Morpholinylmethyl)phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0511]

2 ml of 2N aqueous sodium hydroxide solution was added to a solution of 300 mg (0.69 mmol) of 1-[[[4-(4-morpholinylmethyl)phenyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester in 2 ml of tetrahydrofuran, and the mixture was heated under reflux overnight. After the reaction solution was neutralized by concentrated hydrochloric acid, the reaction solution was distilled off

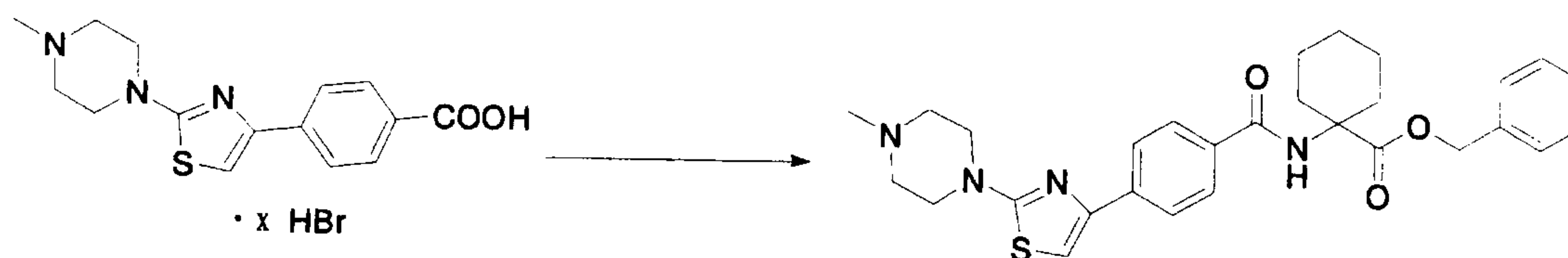
under reduced pressure. 3 ml of methylene chloride, 698 mg (6.9 mmol) of triethylamine and 264 mg (1.38 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride were added to the residue, and the mixture was stirred for 1 hour. The reaction solution was distilled off under reduced pressure, a saturated aqueous sodium bicarbonate solution was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 191 mg (80%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.42-1.80 (10H, m), 2.44 (4H, t, J=5Hz), 3.56 (2H, s), 3.71 (4H, t, J=5Hz), 7.45 (2H, d, J=8Hz), 7.96 (2H, d, J=8Hz)

[0512]

Reference Example 210

1-[[[4-[2-(4-Methyl-1-piperazinyl)-4-thiazolyl]phenyl]carbonyl]amino]cyclohexanecarboxylic acid phenylmethyl ester



[0513]

Under ice-cooling, 5.29 g (374 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added to a solution of 8.84 g (23.0 mmol) of 4-[2-(4-methyl-1-piperazinyl)-4-thiazolyl]benzoic acid hydrobromide, 4.19 g (27.6 mmol) of 1-hydroxybenzotriazole, 6.44 g (27.6 mmol) of 1-aminocyclohexanecarboxylic acid phenylmethyl ester and 11.9 g (92 mmol) of N,N-diisopropylethylamine in 120 ml of dimethylformamide. After the mixture was stirred at room

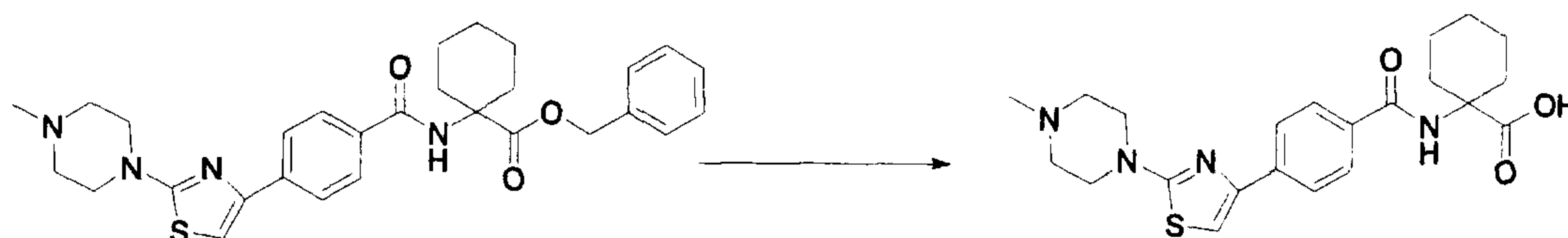
temperature overnight, the reaction solution was concentrated under reduced pressure, ethyl acetate was added thereto, and the mixture was successively washed with water, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, ether was added to the residue to wash the crystal to obtain 11.8 g (quantitative) of the title compound.

1H-NMR (CDCl₃, δ): 1.30-1.42 (1H, m), 1.45-1.61 (2H, m), 1.62-1.75 (3H, m), 1.91-2.01 (2H, m), 2.18-2.24 (2H, m), 2.37 (3H, s), 2.56 (4H, t, J=5Hz), 3.59 (4H, t, J=5Hz), 5.18 (2H, s), 6.23 (1H, br-s), 6.88 (1H, s), 7.25-7.34 (5H, m), 7.76 (2H, dd, J=8Hz, 2Hz), 7.90 (2H, dd, J=8Hz, 2Hz)

[0514]

Reference Example 211

1-[[[4-[2-(4-Methyl-1-piperazinyl)-4-thiazolyl]phenyl]carbonyl]amino]cyclohexanecarboxylic acid



[0515]

35 ml of 2N aqueous sodium hydroxide solution was added to a solution of 11.8 g (23.0 mmol) of 1-[[[4-[2-(4-methyl-1-piperazinyl)-4-

thiazolyl]phenyl]carbonyl]amino]cyclohexanecarboxylic acid

phenylmethyl ester in 120 ml of tetrahydrofuran, and the mixture was heated under reflux for 15 hours. Ether was added to the reaction solution to separate the aqueous layer. Concentrated hydrochloric acid was added to the separated aqueous layer to neutralize it, and the

precipitated crystal was collected by filtration to obtain

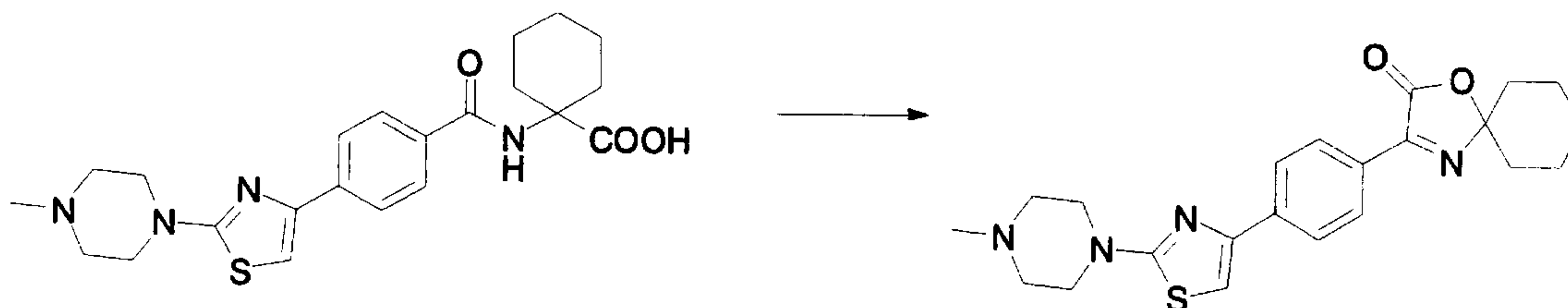
6.60 g (67%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.28-1.38 (1H, m), 1.40-1.51 (2H, m),
1.58-1.73 (3H, m), 1.85-2.00 (2H, m), 2.10-2.21 (2H, m),
2.47 (3H, s), 2.66-2.75 (4H, m), 3.54-4.04 (4H, m), 6.38
5 (1H, br-s), 6.83 (1H, s), 7.69 (2H, d, J=8Hz), 7.76 (2H, d,
J=8Hz)

[0516]

Reference Example 212

2-[4-[2-(4-Methyl-1-piperazinyl)-4-thiazolyl]phenyl]-3-oxa-
10 1-azaspiro[4.5]dec-1-en-4-one



[0517]

450 mg (2.5 mmol) of 1-ethyl-3-(3-
dimethylaminopropyl)carbodiimide hydrochloride was added to
15 a solution of 910 mg (2.1 mmol) of 1-[[[4-[2-(4-methyl-1-
piperazinyl)-4-
thiazolyl]phenyl]carbonyl]amino]cyclohexanecarboxylic acid
in 20 ml of dimethylformamide. After the mixture was
stirred at room temperature for 4 hours, the reaction
20 solution was concentrated under reduced pressure, ethyl
acetate was added thereto, and the mixture was successively
washed with water, a saturated aqueous sodium
hydrogencarbonate solution and saturated brine, followed by
drying with anhydrous sodium sulfate. The solvent was
25 distilled off under reduced pressure to obtain 577 mg (67%)
of the title compound.

¹H-NMR (CDCl₃, δ): 1.51-1.62 (1H, m), 1.62-1.71 (1H, m),
1.71-1.78 (2H, m), 1.78-1.90 (6H, m), 2.37 (3H, s), 2.56
(4H, t, J=5Hz), 3.60 (4H, t, J=5Hz), 6.92 (1H, s), 7.94

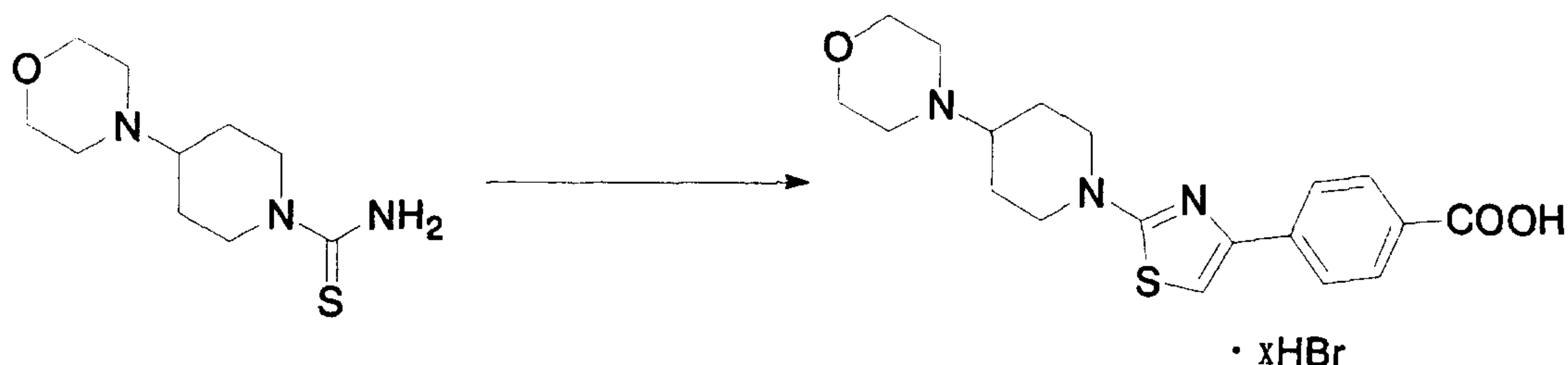
(2H, d, J=8Hz), 8.00 (2H, d, J=8Hz)

[0518]

Reference Example 213

4-[[2-(4-Morpholinyl)-1-piperazinyl]-4-thiazolyl]benzoic

5 acid hydrobromide



[0519]

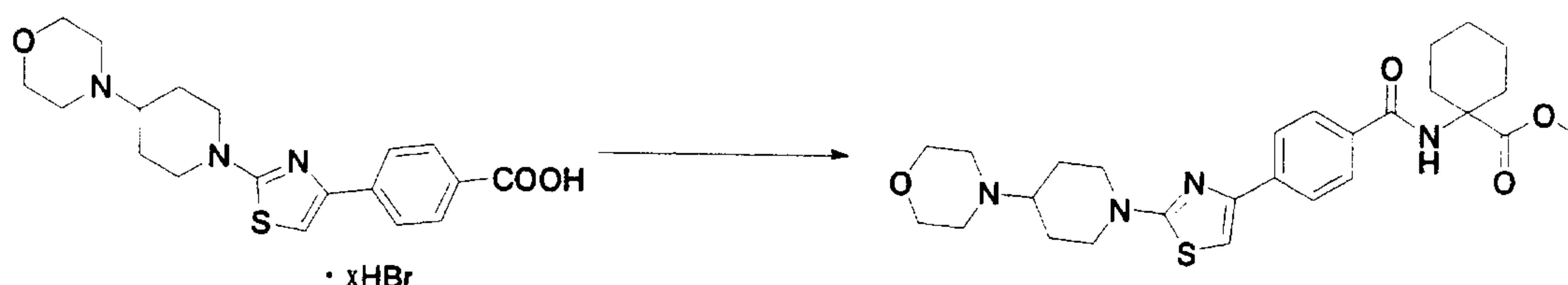
After a solution of 2.47 g (16.9 mmol) of 4-(4-morpholinyl)piperidine-1-thiocarboxamide and 4.08 g (16.9 mmol) of 4-(bromoacetyl)benzoic acid in 150 ml of ethanol was heated under reflux for 2 hours, the mixture was left to be cooled to room temperature. After 150 ml of ether was added to the reaction solution and the mixture was stirred at 4°C overnight, the precipitated crystal was collected by filtration to obtain 4.64 g (95%) of the title compound.

¹H-NMR (DMSO-d₆, δ): 1.68-1.80 (2H, m), 2.17-2.25 (2H, m), 3.07-3.20 (4H, m), 3.21-3.63 (5H, m), 3.64-3.78 (1H, m), 3.98-4.10 (1H, m), 4.10-4.18 (2H, m), 7.51 (1H, s), 7.95-7.99 (4H, m)

[0520]

Reference Example 214

1-[[[4-[2-[4-(4-Morpholinyl)-1-piperazinyl]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester



[0521]

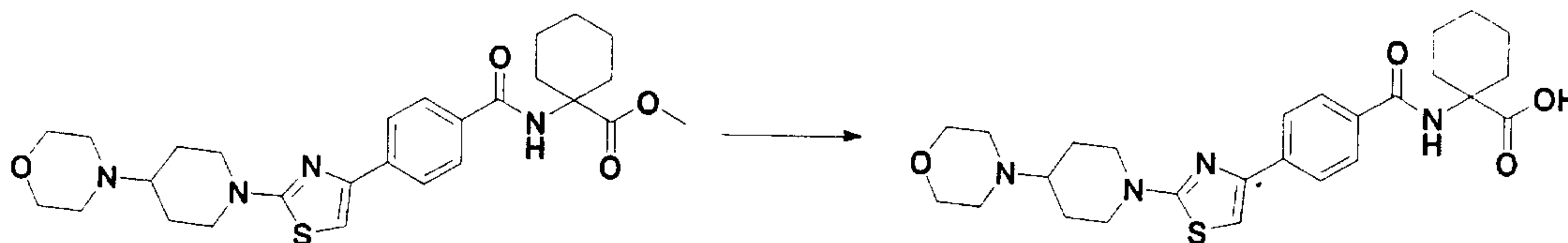
4.50 g (9.90 mmol) of 4-[2-[4-(4-morpholinyl)-1-piperazinyl]-4-thiazolyl]benzoic acid hydrobromide was used instead of 4-[2-(4-methyl-1-piperazinyl)-4-thiazolyl]benzoic acid hydrobromide, and 1.57 g (9.90 mmol) of 1-aminocyclohexanecarboxylic acid methyl ester was used instead of 1-aminocyclohexanecarboxylic acid phenylmethyl ester in the process according to Reference Example 210 to obtain 5.08 g (quantitative) of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.32-1.42 (1H, m), 1.45-1.74 (7H, m), 1.93-2.01 (4H, m), 2.14-2.21 (2H, m), 2.41-2.50 (1H, m), 2.58 (4H, t, $J=5\text{Hz}$), 3.07 (2H, dd, $J=13\text{Hz}$, 13Hz), 3.73 (4H, t, $J=5\text{Hz}$), 3.74 (3H, s), 4.13 (2H, d, $J=13\text{Hz}$), 6.25 (1H, br-s), 6.86 (1H, s), 7.78 (2H, dd, $J=8\text{Hz}$, 2Hz), 7.90 (2H, dd, $J=8\text{Hz}$, 2Hz)

[0522]

Reference Example 215

1-[[[4-[2-[4-(4-Morpholinyl)-1-piperazinyl]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexanecarboxylic acid



[0523]

5.08 g (9.90 mmol) of 1-[[[4-[2-[4-(4-morpholinyl)-1-piperazinyl]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexanecarboxylic acid methyl ester was used instead of 1-[[[4-[2-(4-methyl-1-

piperazinyl)-4-

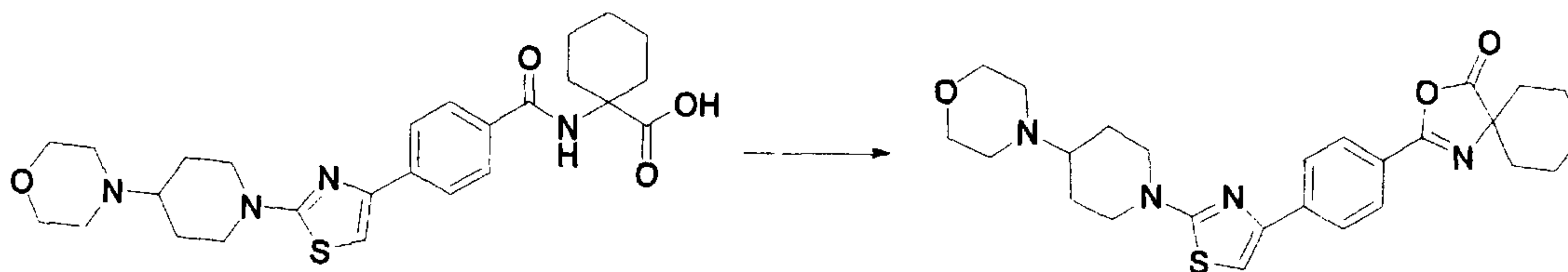
thiazolyl]phenyl]carbonyl]amino]cyclohexanecarboxylic acid
phenylmethyl ester in the process according to Reference
Example 211 to obtain 4.93 g (quantitative) of the title
5 compound.

¹H-NMR (CDCl₃, δ): 1.32-1.45 (1H, m), 1.46-1.60 (2H, m),
1.61-1.77 (5H, m), 1.90-2.03 (4H, m), 2.15-2.25 (2H, m),
2.44-2.52 (1H, m), 2.62 (4H, t, J=5Hz), 3.08 (2H, dd,
J=13Hz, 13Hz), 3.78 (4H, t, J=5Hz), 4.14 (2H, d, J=13Hz),
10 6.70 (1H, br-s), 6.88 (1H, s), 7.79 (2H, d, J=8Hz), 7.90
(2H, d, J=8Hz)

[0524]

Reference Example 216

2-[4-[2-[4-(4-Morpholinyl)-1-piperidinyl]-4-
15 thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one



[0525]

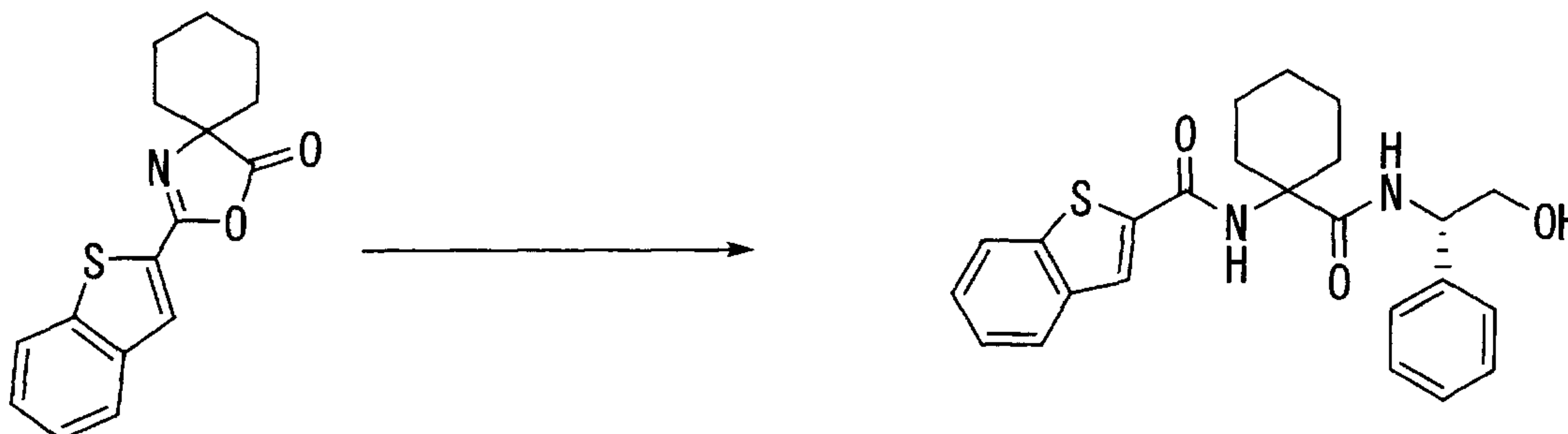
4.93 g (9.90 mmol) of 1-[[[4-[2-[4-(4-morpholinyl)-1-
piperazinyl]-4-
20 thiazolyl]phenyl]carbonyl]amino]cyclohexanecarboxylic acid
was used instead of 1-[[[4-[2-(4-methyl-1-piperazinyl)-4-
thiazolyl]phenyl]carbonyl]amino]cyclohexanecarboxylic acid
in the process according to Reference Example 212 to obtain
3.00 g (63%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.50-1.61 (1H, m), 1.61-1.71 (3H, m),
1.71-1.79 (2H, m), 1.79-1.89 (5H, m), 1.91-2.00 (2H, m),
2.40-2.48 (1H, m), 2.59 (4H, t, J=5Hz), 3.09 (2H, d,
J=12Hz), 3.74 (4H, t, J=5Hz), 4.13 (2H, d, J=12Hz), 6.90
(1H, s), 7.96 (2H, dd, J=7Hz, 2Hz), 8.00 (2H, dd, J=7Hz,
30 2Hz)

[0526]

Reference Example 217

N-[[1-[(2-Benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-
L-phenylglycinol



5

[0527]

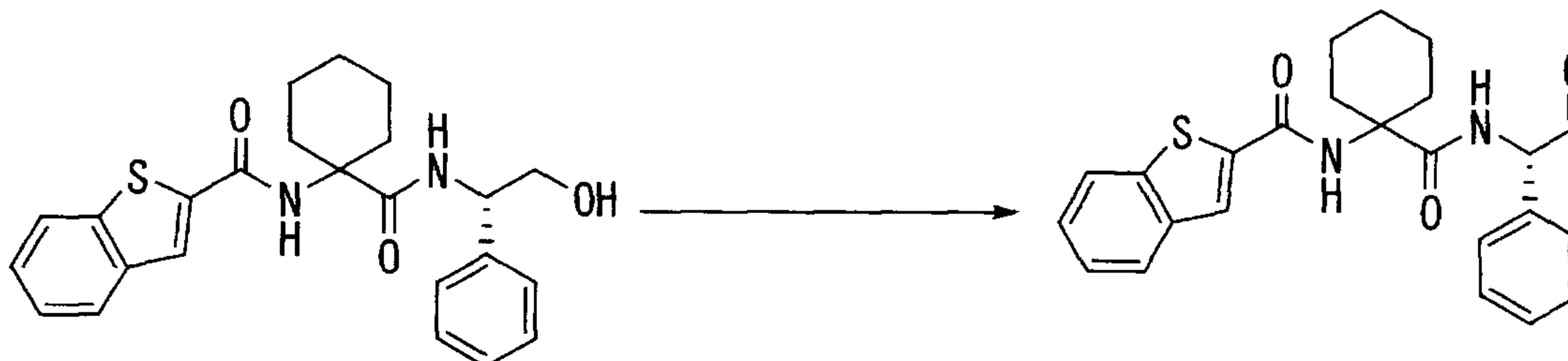
288 mg (2 mmol) of L-phenylglycinol was added to a solution of 500 mg (1.75 mmol) of 2-(2-benzothienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one in 3 ml of N,N-dimethylformamide, and the mixture was stirred overnight. Water was slowly added thereto and the precipitated crystal was collected by filtration. The obtained crystal was dried under reduced pressure to obtain 730 mg (98%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.29-1.80 (6H, m), 1.91-2.12 (2H, m), 2.19-2.38 (2H, m), 2.91 (1H, br-s), 3.73-3.83 (1H, m), 3.89-4.02 (1H, m), 5.07-5.20 (1H, m), 6.26 (1H, s), 7.20-7.49 (8H, m), 7.83 (1H, s), 7.84-7.92 (2H, m)

[0528]

20 Reference Example 218

N-[[1-[(2-Benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-
L-phenylglycinal



[0529]

Under ice-cooling, 585 mg (1.38 mmol) of Des Martin periodinane was added to a solution of 100 mg (0.23 mmol) of N-[[1-[(2-

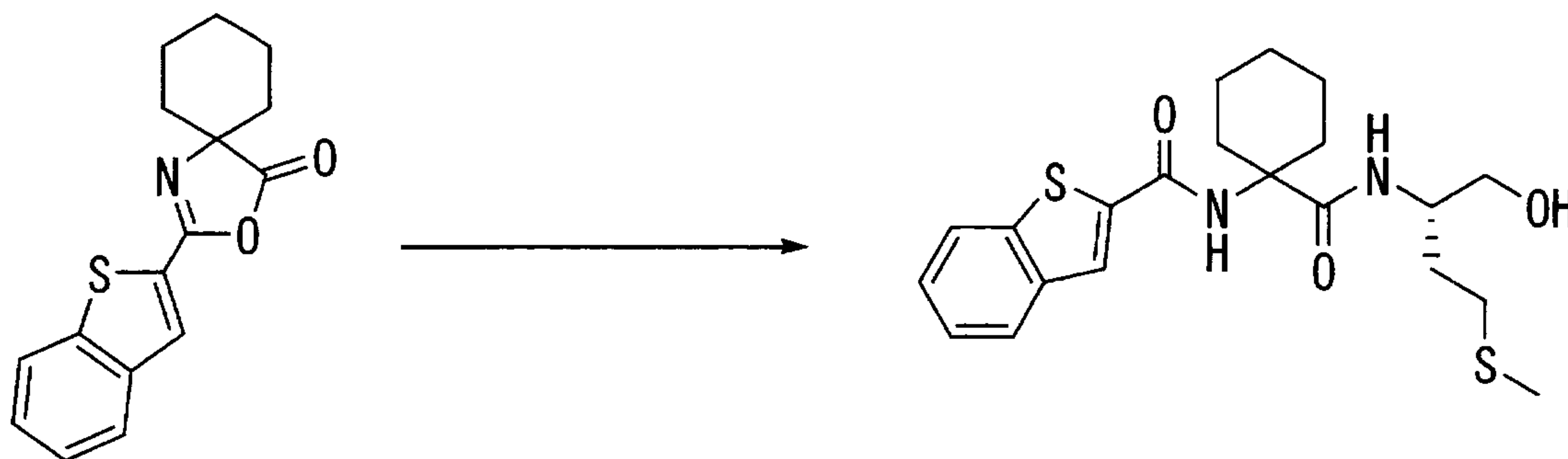
5 benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-L-phenylglycinol in 5 ml of methylene chloride, and the mixture was stirred for 1 hour. At the same temperature, 10 ml of ethyl acetate and 10 ml of a saturated aqueous sodium bicarbonate solution were added to the reaction
10 solution. Sodium thiosulfate was added until the solution became transparent, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and saturated brine, and dried with anhydrous sodium sulfate. The
15 solvent was distilled off under reduced pressure, ethyl acetate was added to the obtained residue, and the mixture was stirred for 1 hour. The precipitated solid was collected by filtration to obtain 55 mg (57%) of the title compound.

20 ¹H-NMR (CDCl₃, δ): 1.21-1.80 (6H, m), 1.83-2.18 (2H, m), 2.23-2.40 (2H, m), 5.51 (1H, d, J=5Hz), 6.10 (1H, s), 7.21-7.52 (7H, m), 7.83 (1H, s), 7.84-7.96 (2H, m), 8.18 (1H, d, J=5Hz), 9.55 (1H, s)

[0530]

25 Reference Example 219

N-[[1-[(2-Benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-L-methioninol



[0531]

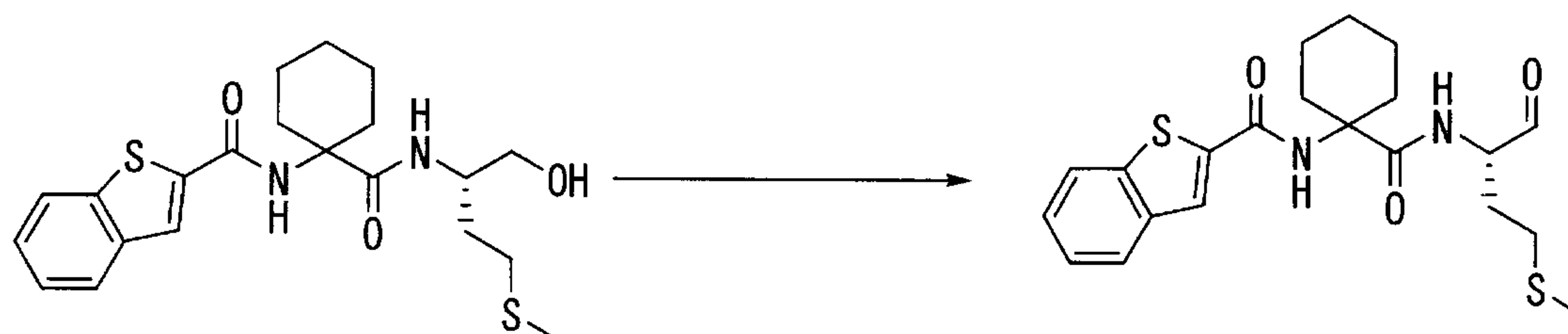
284 mg (2.1 mmol) of L-methioninol was added to a solution of 500 mg (1.75 mmol) of 2-(2-benzothienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one in 3 ml of N,N-dimethylformamide, and the mixture was stirred overnight. Water was slowly added and the precipitated crystal was collected by filtration. The obtained crystal was dried under reduced pressure to obtain 722 mg (98%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.31-2.29 (16H, m), 2.45-2.63 (1H, m), 3.06 (1H, br-s), 3.45-3.61 (1H, m), 3.73-3.82 (1H, m), 3.97-4.05 (1H, m), 6.29 (1H, s), 6.85 (1H, br-s), 7.38-7.50 (2H, m), 7.82 (1H, s), 7.83-7.90 (2H, m)

[0532]

Reference Example 220

N-[[1-[(2-Benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-L-methioninal



[0533]

Under an argon gas atmosphere, 245 mg (1.9 mmol) of N,N-diisopropylethylamine was added dropwise to a solution of 297 mg (1.9 mmol) of sulfur trioxide-pyridine complex in

10 ml of anhydrous dimethyl sulfoxide and 5 ml of anhydrous methylene chloride under ice-cooling, and the mixture was stirred for 15 minutes. Further, under ice-cooling, 100 mg (0.23 mmol) of N-[[1-[(2-

5 benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-L-methioninol was added to the reaction solution, and the mixture was stirred at the same temperature for 2 hours. The reaction solution was poured to ice-water and extracted with ethyl acetate twice. The organic layer was washed
10 with a 10% aqueous citric acid solution, a saturated aqueous sodium hydrogencarbonate solution and then saturated brine, and it was dried with anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. 20 ml of diisopropyl ether was added to the
15 residue, and the mixture was stirred at room temperature for 18 hours. The obtained crystal was collected by filtration to quantitatively obtain the title compound.

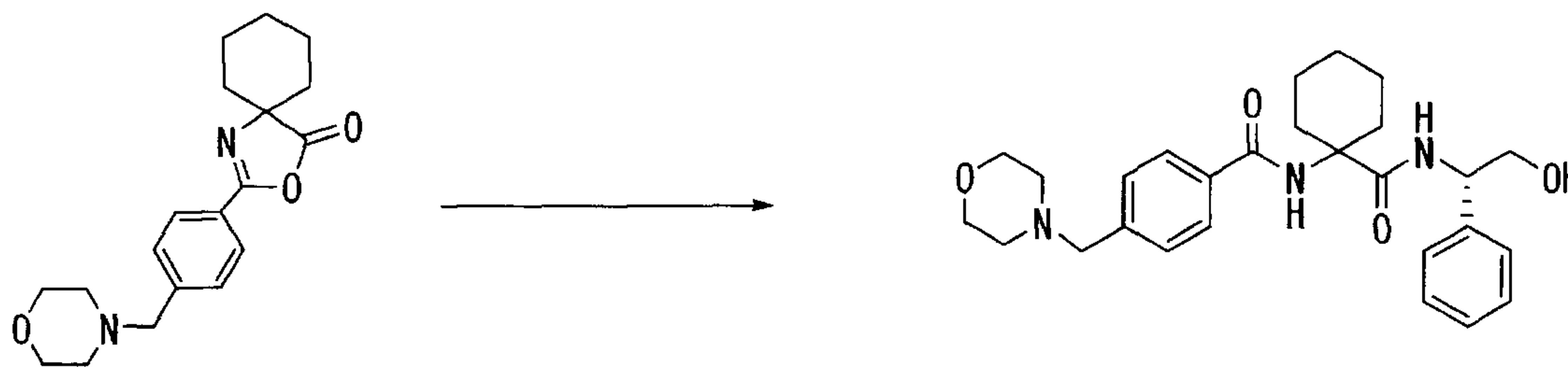
¹H-NMR (CDCl₃, δ): 1.36-1.80 (9H, m), 1.91-2.09 (5H, m), 2.20-2.35 (2H, m), 2.50-2.63 (1H, m), 4.43-4.59 (1H, m),
20 6.19 (1H, s), 7.38-7.52 (2H, m), 7.67 (1H, d, J=7Hz), 7.71 (1H, s), 7.80-7.89 (2H, m), 9.61 (1H, s)

[0534]

Reference Example 221

N-[[1-[[[4-(4-

25 Morpholinylmethyl)phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycinol



[0535]

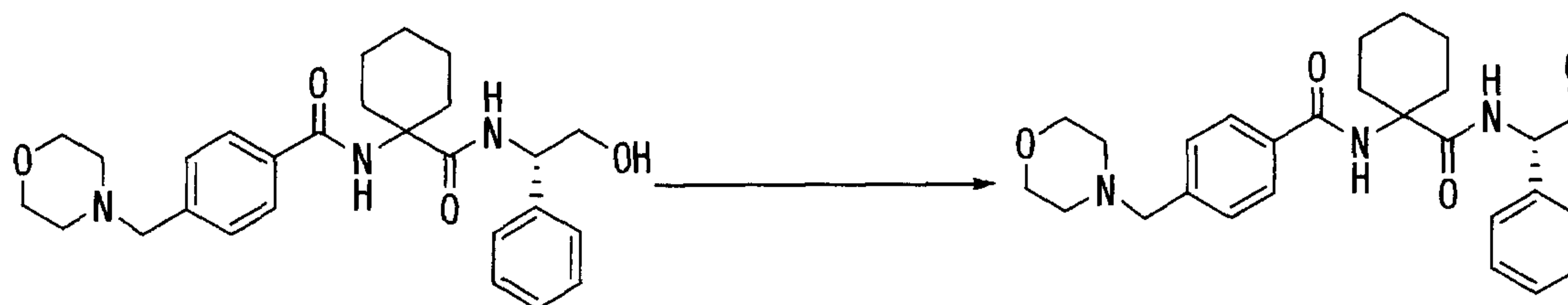
44 mg (0.32 mmol) of L-phenylglycinol was added to a solution of 100 mg (0.29 mmol) of 2-[4-(4-morpholinylmethyl)phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one in 3 ml of N,N-dimethylformamide, and the mixture was stirred overnight. Water was slowly added thereto and the precipitated crystal was collected by filtration. The obtained crystal was dried under reduced pressure to obtain 46 mg (34%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.25-1.80 (6H, m), 1.92-2.10 (2H, m), 2.18-2.32 (2H, m), 2.37-2.50 (4H, m), 2.99 (1H, br-s), 3.55 (2H, s), 3.62-3.71 (4H, m), 3.71-3.83 (1H, m), 3.91-4.02 (1H, m), 5.05-5.18 (1H, m), 6.24 (1H, s), 7.17-7.37 (6H, m), 7.44 (2H, d, J=8Hz), 7.73 (2H, d, J=8Hz)

[0536]

15 Reference Example 222

N-[[1-[[[4-(4-morpholinylmethyl)phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycinal



20 [0537]

Under ice-cooling, 254 mg (0.6 mmol) of Des Martin periodinane was added to a solution of 46 mg (0.1 mmol) of N-[[1-[[[4-(4-morpholinylmethyl)phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycinol in 5 ml of methylene chloride, and the mixture was stirred for 1 hour. At the same temperature, 10 ml of ethyl acetate and 10 ml of a saturated aqueous sodium bicarbonate solution were added to the reaction solution. Sodium thiosulfate was added thereto until the

solution became transparent, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and saturated brine, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, ethyl acetate was added to the obtained residue, and the mixture was stirred for 1 hour. The precipitated solid was collected by filtration to obtain 30 mg (60%) of the title compound.

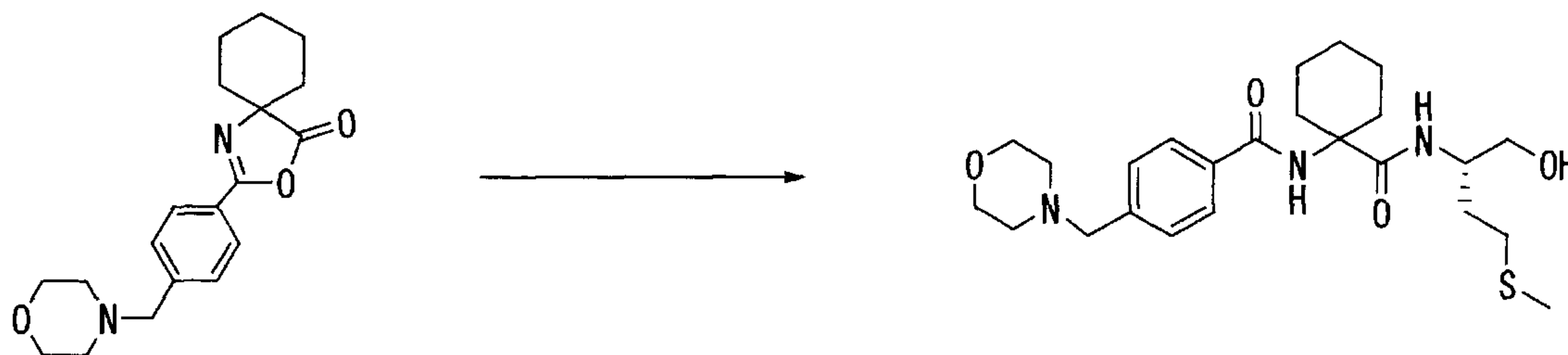
¹H-NMR (CDCl₃, δ): 1.20-2.37 (10H, m), 2.37-2.60 (4H, m), 3.55 (2H, s), 3.61-3.80 (4H, m), 5.49 (1H, d, J=6Hz), 6.16 (1H, s), 7.20-7.58 (7H, m), 7.75 (2H, d, J=8Hz), 8.27 (1H, d, J=6Hz), 9.54 (1H, s)

[0538]

Reference Example 223

N-[[1-[[[4-(4-

Morpholinylmethyl)phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-methioninol



[0539]

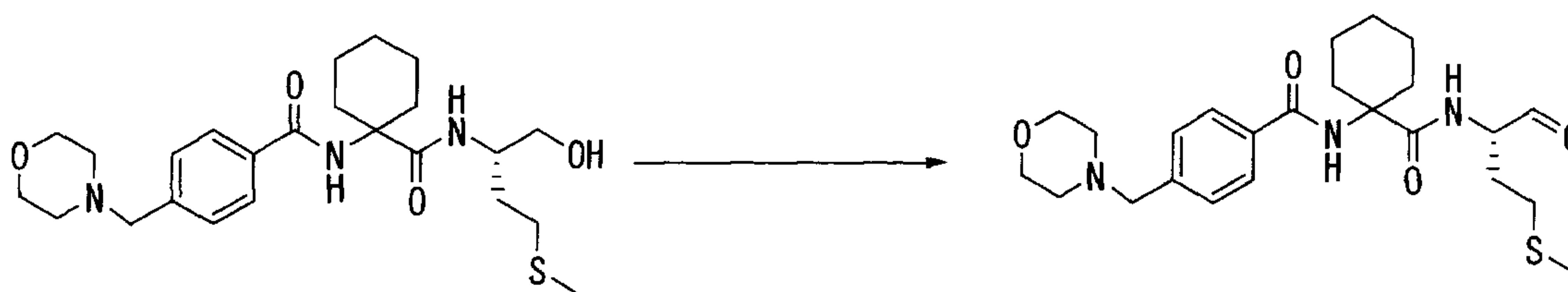
43 mg (0.32 mmol) of L-methioninol was added to a solution of 100 mg (0.29 mmol) of 2-[4-(4-morpholinylmethyl)phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one in 3 ml of N,N-dimethylformamide, and the mixture was stirred overnight. Water was slowly added thereto and the precipitated crystal was collected by filtration. The obtained crystal was dried under reduced pressure to obtain 65 mg (49%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.31-2.23 (15H, m), 2.35-2.45 (4H, m),

2.45-2.62 (2H, m), 3.12 (1H, br-s), 3.40-3.60 (3H, m),
 3.60-3.82 (5H, m), 3.95-4.05 (1H, m), 6.28 (1H, s), 6.80
 (1H, d, J=8Hz), 7.43 (2H, d, J=8Hz), 7.72 (2H, d, J=8Hz)
 [0540]

5 Reference Example 224

N-[[[1-[[[4-(4-morpholinylmethyl)phenyl]carbonyl]amino]cyclohexyl]carbonyl]
]-L-methioninal



10 [0541]

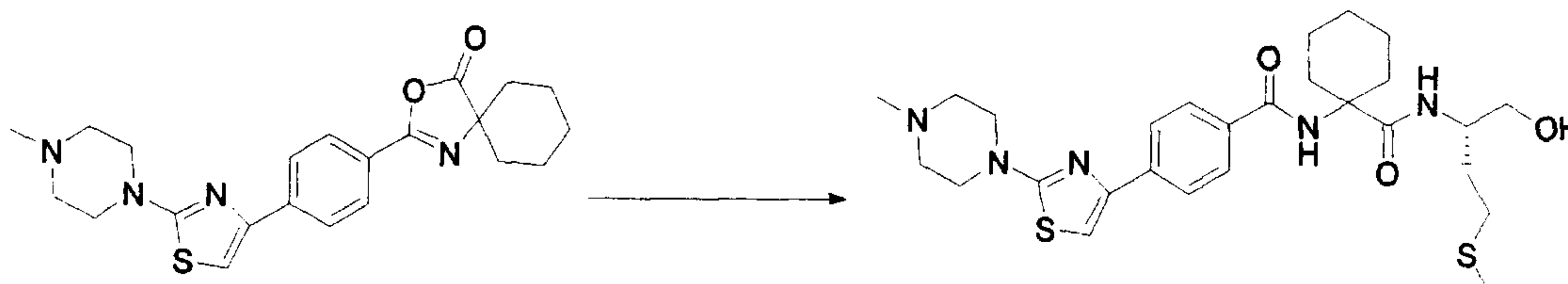
Under ice-cooling, 356 mg (0.84 mmol) of Des Martin
 periodinane was added to a solution of 65 mg (0.14 mmol) of
 N-[[[1-[[[4-(4-morpholinylmethyl)phenyl]carbonyl]amino]cyclohexyl]carbonyl]
]-L-methioninol in 5 ml of methylene chloride, and the
 mixture was stirred for 1 hour. At the same temperature,
 10 ml of ethyl acetate and 10 ml of a saturated aqueous
 sodium bicarbonate solution were added to the reaction
 solution. Sodium thiosulfate was added thereto until the
 solution became transparent, and the mixture was extracted
 with ethyl acetate. The organic layer was washed with a
 saturated aqueous sodium bicarbonate solution and saturated
 brine, and dried with anhydrous sodium sulfate. The
 solvent was distilled off under reduced pressure to obtain
 55 mg (85%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.20-2.80 (21H, m), 3.56 (2H, s), 3.60-
 3.81 (4H, m), 4.40-4.58 (1H, m), 5.12 (1H, d, J=7Hz), 6.18
 (1H, s), 7.44 (2H, d, J=8Hz), 7.73 (2H, d, J=8Hz), 9.59
 (1H, s)

[0542]

Reference Example 225

N-[[1-[[[4-[2-(4-Methyl-1-piperazinyl)-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-methioninol



[0543]

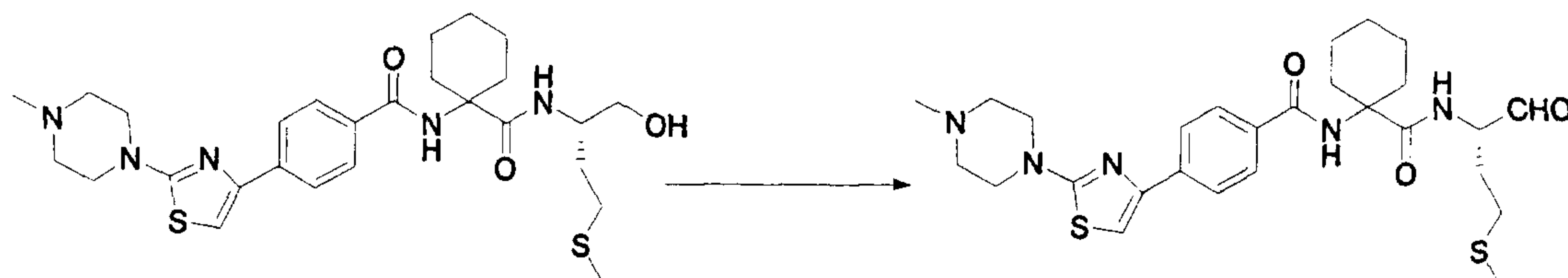
100 mg (0.74 mmol) of L-methioninol was added to a solution of 250 mg (0.68 mmol) of 2-[4-[2-(4-methyl-1-piperazinyl)-4-thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one in 20 ml of dimethylformamide. After the mixture was stirred at 80°C for 15 hours, the reaction solution was concentrated under reduced pressure, ethyl acetate was added thereto, and the mixture was successively washed with water, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, diisopropyl ether was added to the residue to wash the crystal to obtain 319 mg (86%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.37-1.61 (3H, m), 1.65-1.80 (3H, m), 1.80-1.86 (2H, m), 1.96-2.05 (2H, m), 2.07 (3H, s), 2.15-2.29 (2H, m), 2.37 (3H, s), 2.51-2.60 (2H, m), 2.56 (4H, t, J=5Hz), 3.14-3.21 (1H, m), 3.50-3.56 (1H, m), 3.59 (4H, t, J=5Hz), 3.77-3.84 (1H, m), 4.00-4.06 (1H, m), 6.30 (1H, br-s), 6.85 (1H, d, J=7Hz), 6.90 (1H, s), 7.76 (2H, dd, J=8Hz, 2Hz), 7.92 (2H, dd, J=8Hz, 2Hz)

[0544]

Reference Example 226

N-[[1-[[[4-[2-(4-Methyl-1-piperazinyl)-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-methioninal



5 [0545]

Under an argon gas atmosphere, 453 mg (3.5 mmol) of N,N-diisopropylethylamine was added dropwise to a solution of 658 mg (3.5 mmol) of sulfur trioxide-pyridine complex in 10 ml of anhydrous dimethyl sulfoxide and 5 ml of anhydrous methylene chloride under ice-cooling, and the mixture was stirred for 15 minutes. Further, under ice-cooling, a solution of 319 mg (0.58 mmol) of N-[[1-[[[4-[2-(4-methyl-1-piperazinyl)-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-methioninol in 3 ml of anhydrous dimethyl sulfoxide was added to the reaction solution, and the mixture was stirred at the same temperature for 2 hours. The reaction solution was poured to ice-water and extracted with ethyl acetate twice. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and then saturated brine, and after it was dried with anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. 20 ml of diisopropyl ether was added to the residue, and the mixture was stirred at room temperature for 18 hours. The obtained crystal was collected by filtration to obtain 203 mg (64%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.36-1.78 (6H, m), 1.98-2.08 (3H, m), 2.02 (3H, s), 2.21-2.57 (3H, m), 2.38 (3H, s), 2.55 (4H, t,

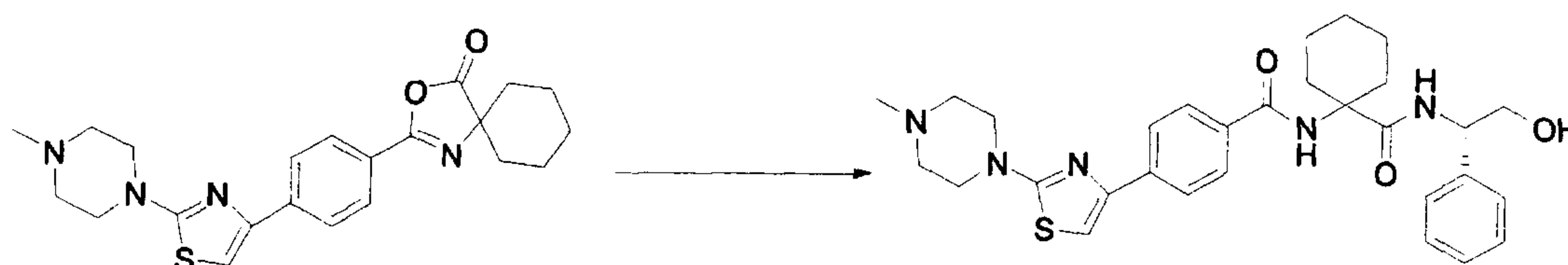
J=5Hz), 2.56 (2H, m), 3.61 (4H, t, J=5Hz), 4.49 (1H, dt, J=8Hz, 5Hz), 6.17 (1H, br-s), 6.90 (1H, s), 7.78 (2H, d, J=8Hz), 7.84 (1H, d, J=8Hz), 7.92 (2H, d, J=8Hz), 9.62 (1H, s)

5 [0546]

Reference Example 227

N-[[[1-[[[4-[2-(4-Methyl-1-piperazinyl)-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycinol

10



[0547]

96 mg (0.7 mmol) of L-phenylglycinol was used instead of L-methioninol in the process according to Reference Example 225 to obtain 220 mg (57%) of the title compound.

15 ¹H-NMR (CDCl₃, δ): 1.34-1.43 (1H, m), 1.42-1.61 (2H, m), 1.61-1.79 (3H, m), 1.96-2.10 (2H, m), 2.20-2.29 (1H, m), 2.30-2.36 (1H, m), 2.37 (3H, s), 2.56 (4H, t, J=5Hz), 3.01-3.08 (1H, m), 3.60 (4H, t, J=5Hz), 3.76-3.85 (1H, m), 3.92-4.01 (1H, m), 5.09-5.15 (1H, m), 6.27 (1H, br-s), 6.90 (1H, s), 7.24-7.30 (3H, m), 7.31-7.36 (2H, m), 7.37 (1H, d, J=7Hz), 7.78 (2H, d, J=8Hz), 7.92 (2H, d, J=8Hz)

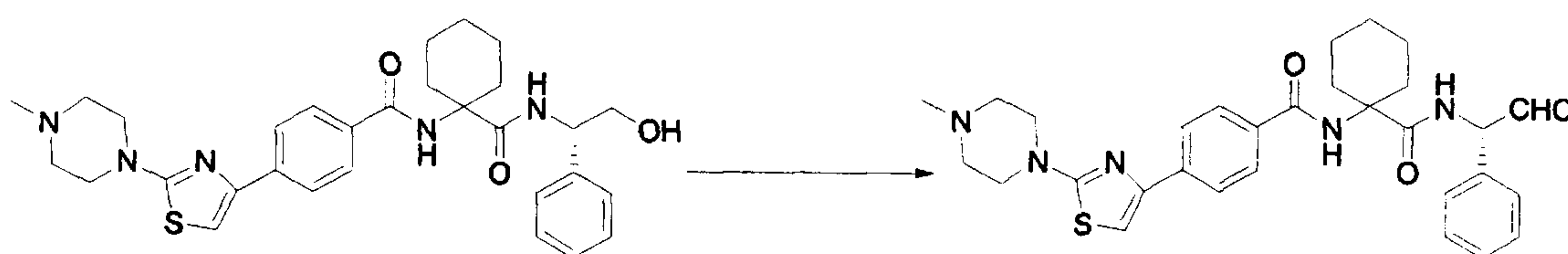
20

[0548]

Reference Example 228

N-[[[1-[[[4-[2-(4-Methyl-1-piperazinyl)-4-

25 thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycinal



[0549]

Under an argon gas atmosphere, 310 mg (2.4 mmol) of N,N-diisopropylethylamine was added dropwise to a solution of 382 mg (2.4 mmol) of sulfur trioxide-pyridine complex in 10 ml of anhydrous dimethyl sulfoxide and 5 ml of anhydrous methylene chloride under ice-cooling, and the mixture was stirred for 15 minutes. Further, under ice-cooling, a solution of 220 mg (0.4 mmol) of N-[[1-[[[4-[2-(4-methyl-1-piperazinyl)-4-

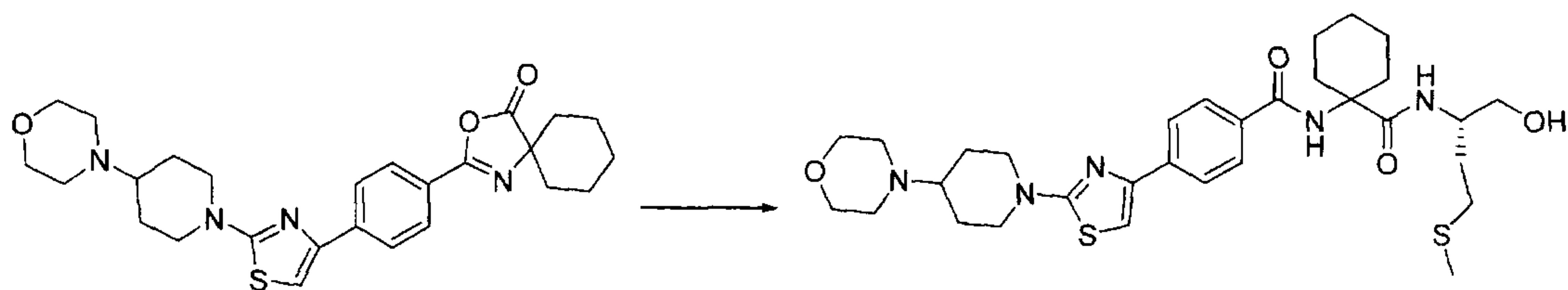
thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycinol in 3 ml of anhydrous dimethyl sulfoxide was added to the reaction solution, and the mixture was stirred at the same temperature for 30 minutes. After the completion of the reaction, under ice-cooling, 200 ml of water was added to the reaction solution, and thereafter the mixture was stirred at room temperature for 3 hours. The precipitated crystal was washed with diethyl ether again to obtain 67 mg (31%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.35-1.82 (6H, m), 2.25-2.39 (2H, m), 2.50-2.59 (1H, m), 2.62 (3H, s), 2.75 (4H, t, J=5Hz), 3.06-3.15 (1H, m), 3.72 (4H, t, J=5Hz), 5.51 (1H, d, J=6Hz), 6.16 (1H, br-s), 6.91 (1H, s), 7.21-7.38 (5H, m), 7.38 (1H, d, J=6Hz), 7.79 (2H, d, J=8Hz), 7.92 (2H, d, J=8Hz), 9.56 (1H, s)

[0550]

Reference Example 229

N-[[1-[[[4-[2-[4-(4-Morpholinyl)-1-piperazinyl]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-methioninol



[0551]

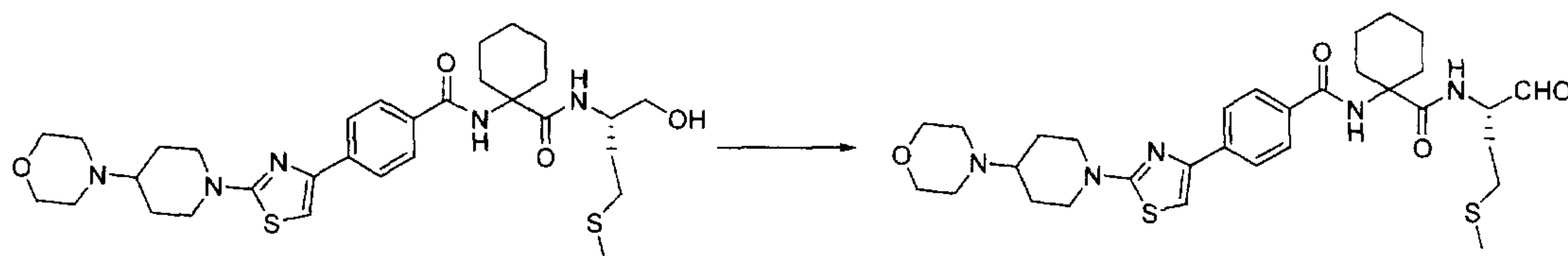
481 mg (1.00 mmol) of 2-[4-[2-[4-(4-morpholinyl)-1-piperidinyl]-4-thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one was used instead of 2-[4-[2-(4-methyl-1-piperazinyl)-4-thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one in the process according to Reference Example 225 to obtain 501 mg (81%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.35-1.80 (7H, m), 1.81-1.89 (2H, m), 1.92-2.09 (4H, m), 2.07 (3H, s), 2.15-2.23 (3H, m), 2.41-2.49 (1H, m), 2.54 (2H, t, J=6Hz), 2.57 (4H, t, J=5Hz), 3.08 (2H, dd, J=13Hz, 13Hz), 3.18 (1H, t, J=7Hz), 3.50-3.58 (1H, m), 3.74 (4H, t, J=5Hz), 3.77-3.85 (1H, m), 4.00-4.08 (1H, m), 4.12 (2H, d, J=13Hz), 6.30 (1H, br-s), 6.83 (1H, d, J=8Hz), 6.88 (1H, s), 7.77 (2H, d, J=8Hz), 7.96 (2H, d, J=8Hz)

[0552]

Reference Example 230

N-[[1-[[[4-[2-[4-(4-Morpholinyl)-1-piperazinyl]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-methioninal



[0553]

501 mg (0.81 mmol) of N-[[1-[[[4-[2-[4-(4-morpholinyl)-1-piperazinyl]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-methioninol was used instead of N-[[1-[[[4-[2-(4-methyl-1-

piperaziny]-4-

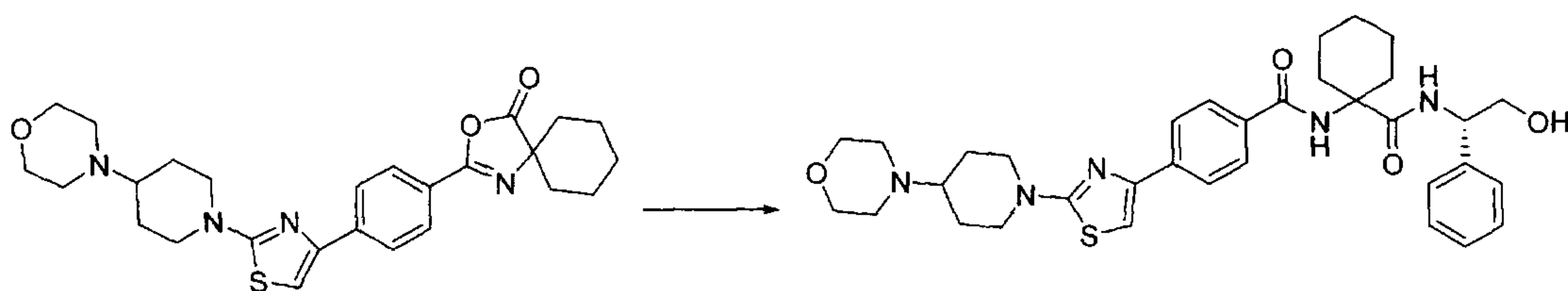
thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-methioninol in the process according to Reference Example 226 to obtain 100 mg (20%) of the title compound.

5 ¹H-NMR (CDCl₃, δ): 1.36-1.56 (3H, m), 1.61-1.79 (6H, m), 1.93-2.07 (5H, m), 2.02 (3H, s), 2.04-2.15 (2H, m), 2.40 (2.49 (1H, m), 2.45 (2H, t, J=6Hz), 2.58 (4H, t, J=5Hz), 3.08 (2H, dd, J=12Hz, 12Hz), 3.74 (4H, t, J=5Hz), 4.12 (2H, d, J=12Hz), 4.49 (1H, dd, J=8Hz, 5Hz), 6.15 (1H, br-s), 6.88 (1H, s), 7.78 (2H, d J=8Hz), 7.85 (1H, d, J=8Hz), 7.93 (2H, d, J=8Hz), 9.62 (1H, s)

[0554]

Reference Example 231

N-[[1-[[[4-[2-[4-(4-Morpholinyl)-1-piperaziny]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycinol



[0555]

481 mg (1.00 mmol) of 2-[4-[2-[4-(4-morpholinyl)-1-piperidiny]-4-thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one was used instead of 2-[4-[2-(4-methyl-1-piperaziny)-4-thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, and 137 mg (1.00 mmol) of L-phenylglycinol was used instead of L-methioninol in the process according to Reference Example 225 to obtain 324 mg (52%) of the title compound.

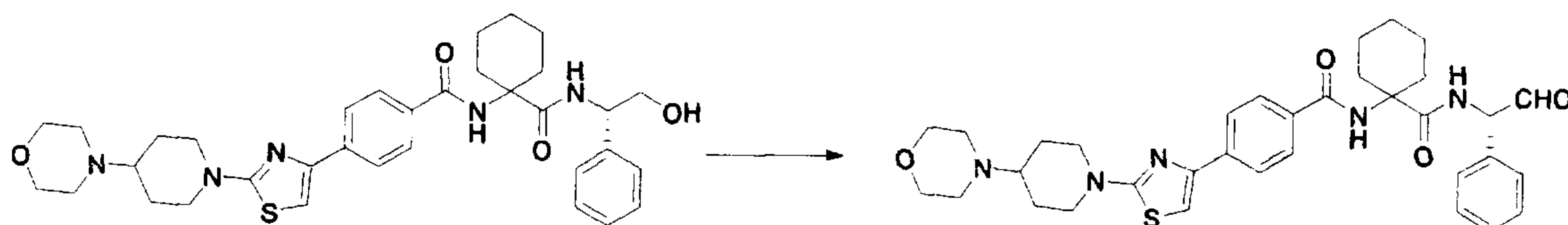
¹H-NMR (CDCl₃, δ): 1.32-1.78 (9H, m), 1.95-2.11 (4H, m), 2.20-2.27 (1H, m), 2.29-2.36 (1H, m), 2.40-2.49 (1H, m), 2.59 (4H, t, J=5Hz), 3.09 (2H, dd, J=13Hz, 13Hz), 3.74 (4H,

t, J=5Hz), 3.78-3.82 (1H, m), 3.96-4.00 (1H, m), 4.12 (2H, d, J=13Hz), 5.09-5.14 (1H, m), 6.28 (1H, br-s), 6.88 (1H, s), 7.25-7.30 (1H, m) 7.30-7.35 (4H, m), 7.78 (1H, d, J=8Hz), 7.78 (2H, dd, J=7Hz, 2Hz), 7.92 (2H, dd, J=7Hz, 2Hz)

[0556]

Reference Example 232

N-[[[1-[[[4-[2-[4-(4-Morpholinyl)-1-piperazinyl]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycinal



[0557]

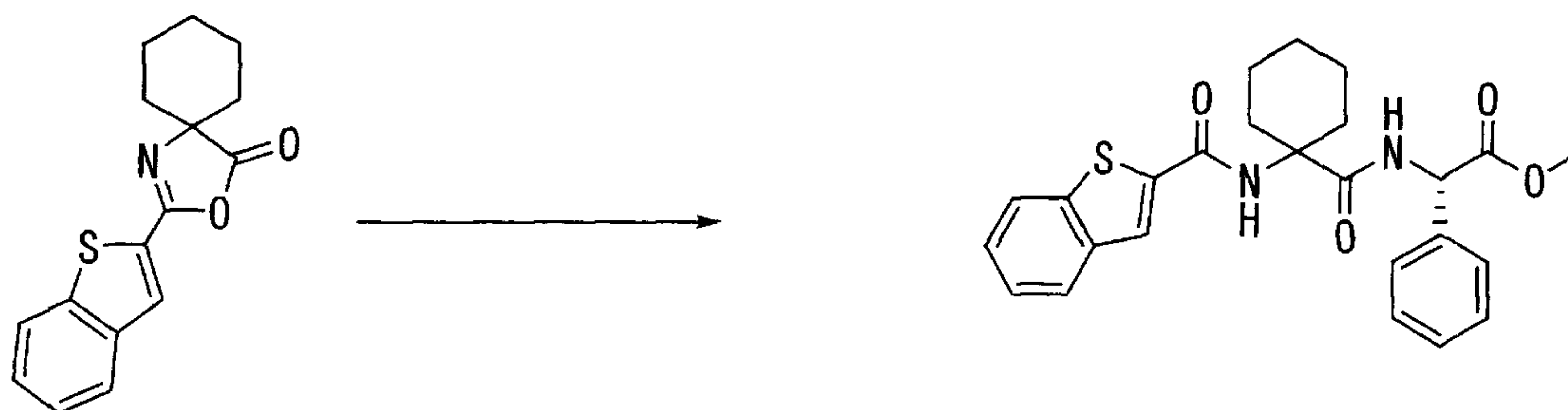
324 mg (0.52 mmol) of N-[[[1-[[[4-[2-[4-(4-morpholinyl)-1-piperazinyl]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycinol was used instead of N-[[[1-[[[4-[2-(4-methyl-1-piperazinyl)-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-methioninol in the process according to Reference Example 226 to obtain 128 mg (40%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.30-1.85 (8H, m), 1.92-2.13 (4H, m), 2.25-2.50 (3H, m), 2.59 (4H, t, J=5Hz), 3.08 (2H, dd, J=12Hz, 12Hz), 3.74 (4H, t, J=5Hz), 4.13 (2H, d, J=12Hz), 5.51 (1H, d, J=6Hz), 6.14 (1H, br-s), 6.88 (1H, s), 7.30-7.41 (5H, m), 7.79 (2H, d, J=8Hz), 7.93 (2H, d, J=8Hz), 8.34 (1H, d, J=6Hz), 9.56 (1H, s)

[0558]

Example 2

N-[[[1-[(2-Benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-L-phenylglycine methyl ester



[0559]

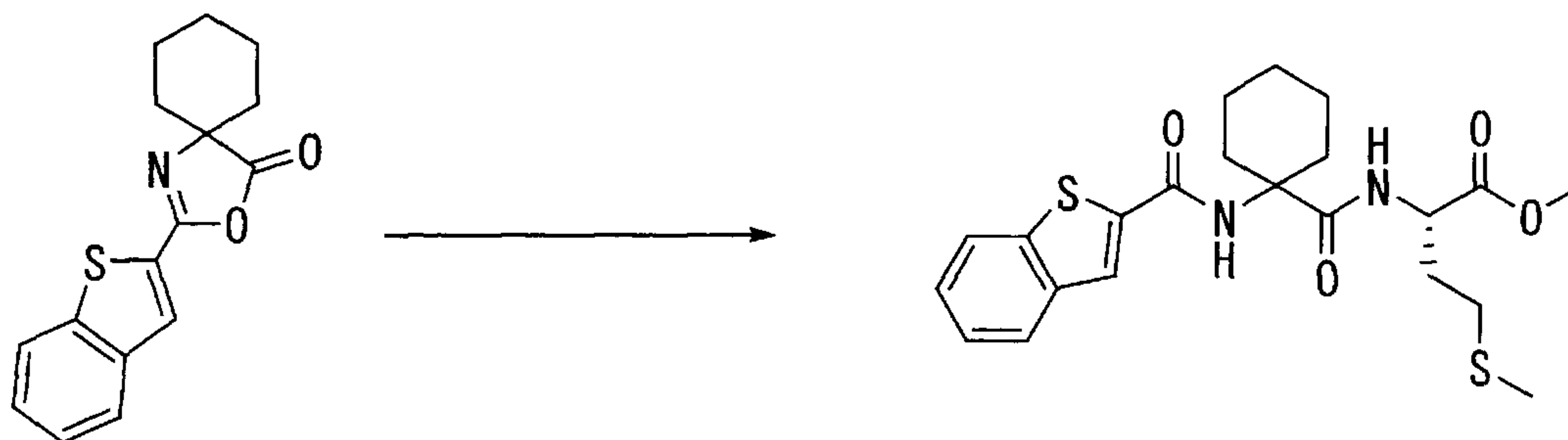
679 mg (5.3 mmol) of diisopropylethylamine was added to a suspension of 423 mg (2 mmol) of L-phenylglycine methyl ester hydrochloride and 500 mg (1.75 mmol) of 2-(2-benzothienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one in 10 ml of toluene, and the mixture was heated under reflux overnight. After the solvent was distilled off under reduced pressure, ethyl acetate was added thereto, and the mixture was washed with a 10% aqueous potassium hydrogensulfate solution and saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, diethyl ether was added, and the mixture was stirred overnight. The precipitated solid was collected by filtration and dried under reduced pressure to obtain 670 mg (91%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.25-1.80 (6H, m), 1.90-2.08 (2H, m), 2.23-2.40 (2H, m), 3.69 (3H, s), 5.53 (1H, d, J=7Hz), 6.10 (1H, s), 7.23-7.49 (7H, m), 7.81 (1H, s), 7.83-7.91 (2H, m), 8.13 (1H, d, J=7Hz)

[0560]

Example 3

N-[[1-[(2-Benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-L-methionine methyl ester



[0561]

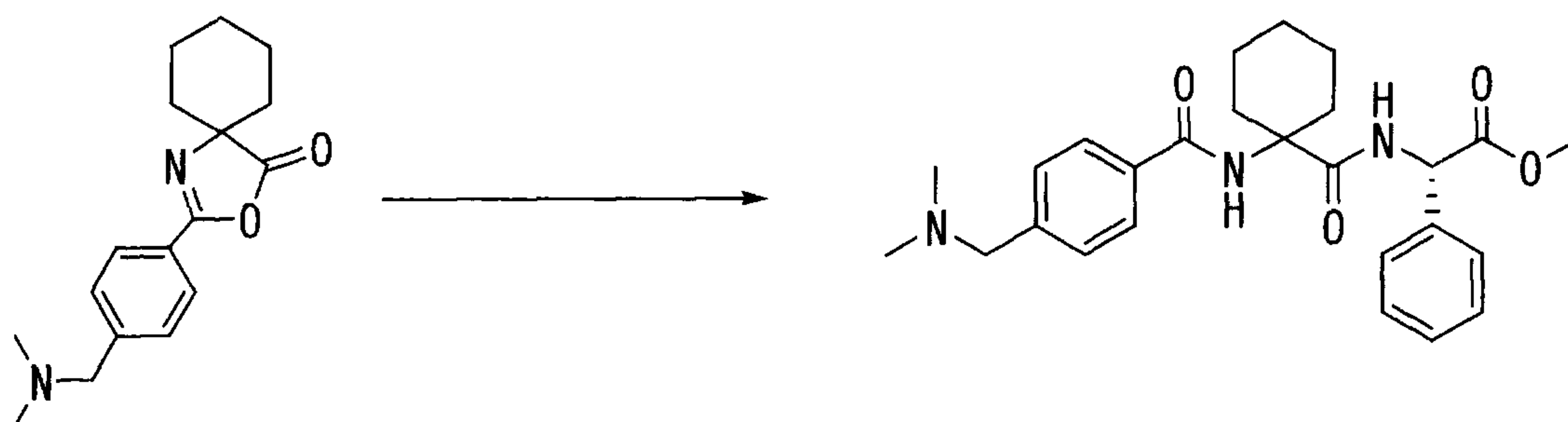
679 mg (5.3 mmol) of diisopropylethylamine was added to a suspension of 419 mg (2 mmol) of L-methionine methyl ester hydrochloride and 500 mg (1.75 mmol) of 2-(2-benzothienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one in 10 ml of toluene, and the mixture was heated under reflux overnight. After the solvent was distilled off under reduced pressure, ethyl acetate was added thereto, and the mixture was washed with a 10% aqueous potassium hydrogensulfate solution and saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, diethyl ether was added, and the mixture was stirred overnight. The precipitated solid was collected by filtration and dried under reduced pressure to obtain 678 mg (86%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.30-1.81 (8H, m), 1.95-2.09 (5H, m), 2.11-2.39 (2H, m), 2.43-2.61 (2H, m), 3.71 (3H, s), 4.61-4.73 (1H, m), 6.16 (1H, s), 7.38-7.45 (2H, m), 7.59 (1H, d, J=8Hz), 7.80 (1H, s), 7.82-7.90 (2H, m)

[0562]

Example 4

N-[[1-[[[4-[(Dimethylamino)methyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycine methyl ester



[0563]

129 mg (1 mmol) of diisopropylethylamine was added to a suspension of 85 mg (0.42 mmol) of L-phenylglycine methyl ester hydrochloride and 100 mg (0.35 mmol) of 2-[4-
 5 [(dimethylamino)methyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one in 3 ml of toluene, and the mixture was heated under reflux overnight. After the solvent was distilled off under reduced pressure, ethyl acetate was added
 10 thereto, and the mixture was washed with saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, diethyl ether was added thereto, and the mixture was stirred overnight. The precipitated solid was collected by
 15 filtration and dried under reduced pressure to obtain 62 mg (39%) of the title compound.

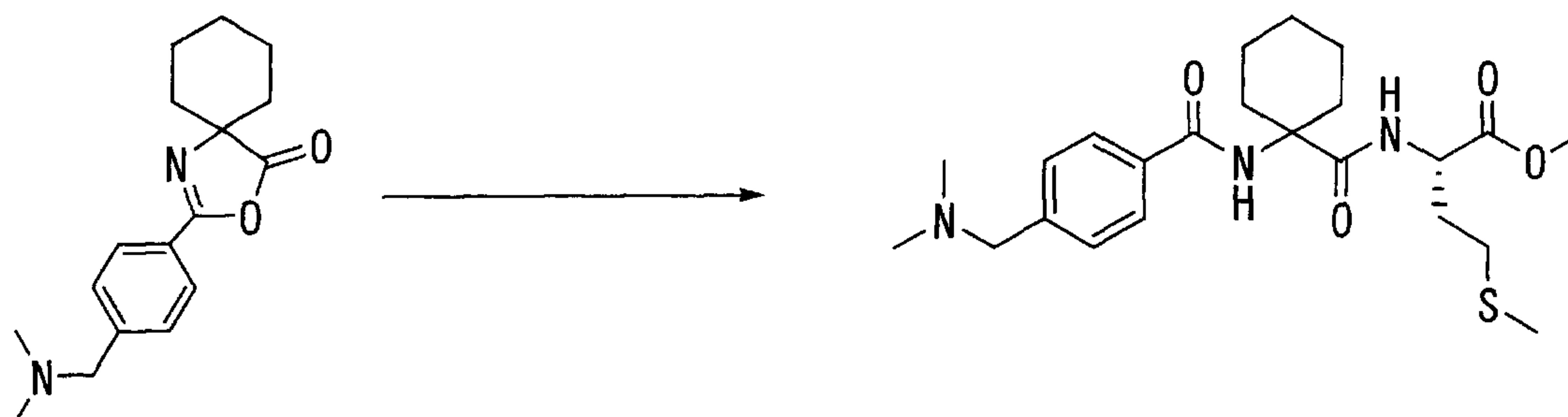
¹H-NMR (CDCl₃, δ): 1.27-1.80 (7H, m), 1.83-2.09 (2H, m), 2.18-2.39 (1H, m), 2.25 (6H, s), 3.47 (2H, s), 3.69 (3H, s), 5.53 (1H, d, J=7Hz), 6.07 (1H, s), 7.10-7.25 (7H, m),
 20 7.73 (2H, d, J=8Hz), 8.28 (1H, d, J=7Hz)

[0564]

Example 5

N-[[1-[[[4-

[(Dimethylamino)methyl]phenyl]carbonyl]amino]cyclohexyl]car
 25 bonyl]-L-methionine methyl ester



[0565]

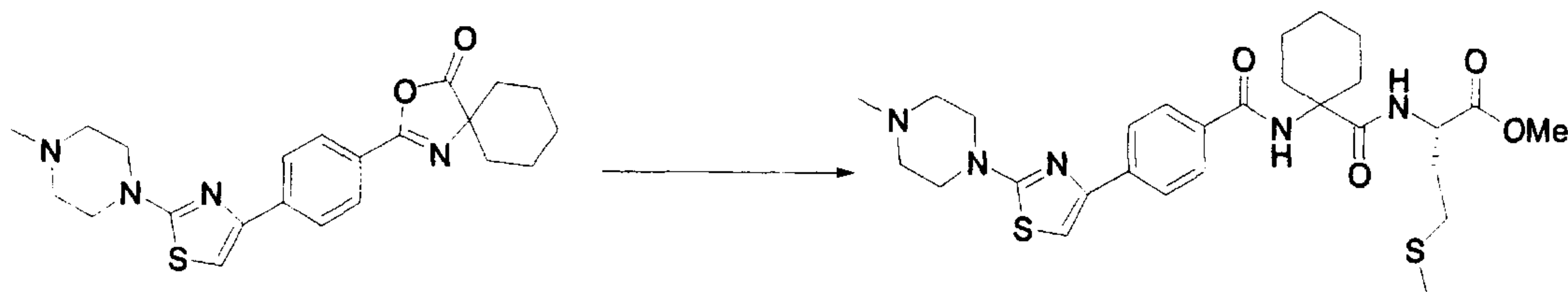
129 mg (1 mmol) of diisopropylethylamine was added to a suspension of 84 mg (0.42 mmol) of L-methionine methyl ester hydrochloride and 100 mg (0.35 mmol) of 2-[4-
 5 [(dimethylamino)methyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one in 3 ml of toluene, and the mixture was heated under reflux overnight. After the solvent was distilled off under reduced pressure, ethyl acetate was added
 10 thereto, and the mixture was washed with saturated brine, followed by drying with sodium sulfate. After the solvent was distilled off under reduced pressure, diethyl ether was added thereto, and the mixture was stirred overnight. The precipitated solid was collected by filtration and dried
 15 under reduced pressure to obtain 93 mg (59%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.29-1.58 (4H, m), 1.58-1.79 (4H, m), 1.92-2.35 (7H, m), 2.25 (6H, s), 2.43-2.59 (2H, m), 3.47 (2H, s), 3.71 (3H, s), 4.61-4.72 (1H, m), 6.10 (1H, s),
 20 7.41 (2H, d, J=8Hz), 7.69 (1H, d, J=8Hz), 7.73 (2H, d, J=8Hz)

[0566]

Example 6

N-[[1-[[[4-[2-(4-Methyl-1-piperazinyl)-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-methionine methyl ester
 25



[0567]

200 mg (1.00 mmol) of L-methionine methyl ester hydrochloride was added to a solution of 411 mg (1.00 mmol) of 2-[4-[2-(4-methyl-1-piperazinyl)-4-thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one and 258 mg (2.00 mmol) of N,N-diisopropylethylamine in 20 ml of dimethylformamide.

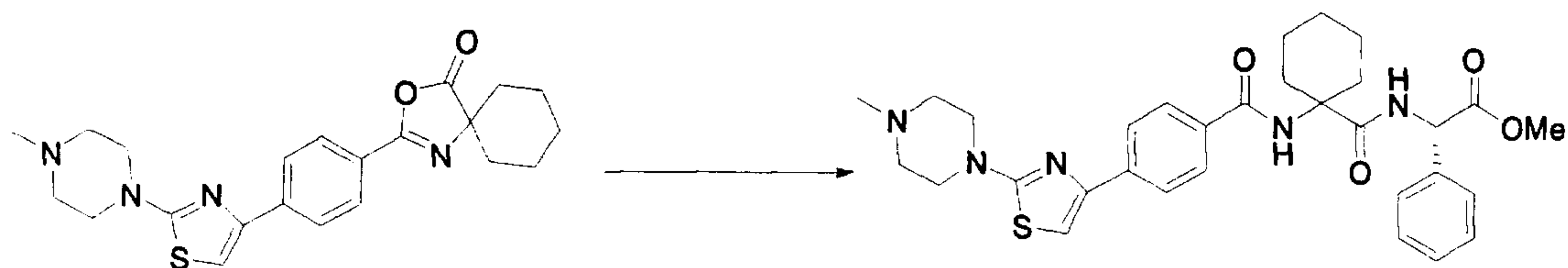
After the mixture was stirred at 80°C for 15 hours, the reaction solution was concentrated under reduced pressure, ethyl acetate was added thereto, and the mixture was successively washed with water, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography to obtain 191 mg (33%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.33-1.60 (3H, m), 1.63-1.78 (3H, m), 1.97-2.05 (3H, m), 2.05 (3H, s), 2.15-2.35 (3H, m), 2.37 (3H, s), 2.50-2.58 (2H, m), 2.56 (4H, t, J=5Hz), 3.59 (4H, t, J=5Hz), 3.71 (3H, s), 4.69 (1H, dt, J=7Hz, 5Hz), 6.13 (1H, br-s), 6.90 (1H, s), 7.72 (1H, d, J=7Hz), 7.78 (2H, dd, J=8Hz, 2Hz), 7.92 (2H, dd, J=8Hz, 2Hz)

[0568]

Example 7

N-[[1-[[[4-[2-(4-Methyl-1-piperazinyl)-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycine methyl ester



[0569]

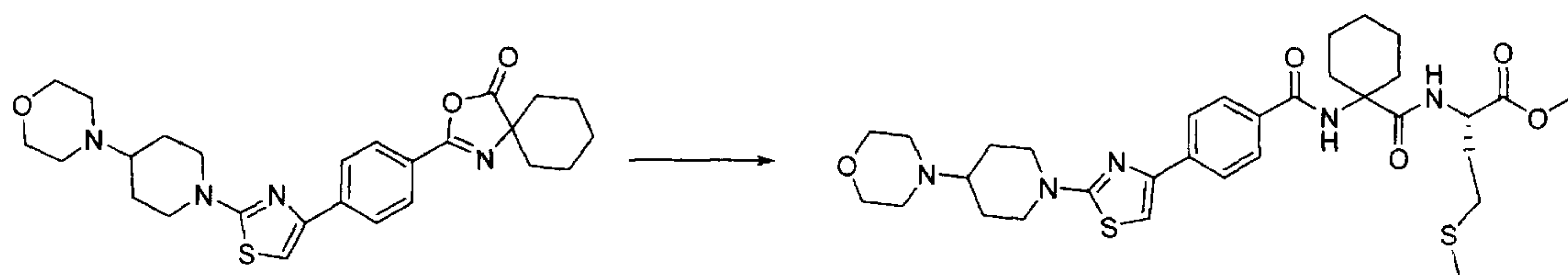
202 mg (1.00 mmol) of L-phenylglycine methyl ester hydrochloride was used instead of L-methionine methyl ester hydrochloride in the process according to Example 6 to obtain 156 mg (24%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.25-1.41 (1H, m), 1.41-1.55 (2H, m), 1.60-1.76 (3H, m), 1.94-2.05 (2H, m), 2.25-2.40 (2H, m), 2.37 (3H, s), 2.56 (4H, t, J=5Hz), 3.59 (4H, t, J=5Hz), 3.69 (3H, s), 5.54 (1H, d, J=7Hz), 6.08 (1H, br-s), 6.89 (1H, s), 7.26-7.35 (3H, m), 7.38-7.41 (2H, m), 7.78 (2H, d, J=8Hz), 7.92 (2H, d, J=8Hz), 8.29 (1H, d, J=7Hz)

[0570]

Example 8

15 N-[[[1-[[[4-[2-[4-(4-Morpholinyl)-1-piperidinyl]-4-thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-methionine methyl ester



[0571]

20 481 mg (1.00 mmol) of 2-[4-[2-[4-(4-morpholinyl)-1-piperidinyl]-4-thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one was used instead of 2-[4-[2-(4-methyl-1-piperazinyl)-4-thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-1-en-4-one in the process according to Example 6 to obtain 439 mg (68%) of the title compound.

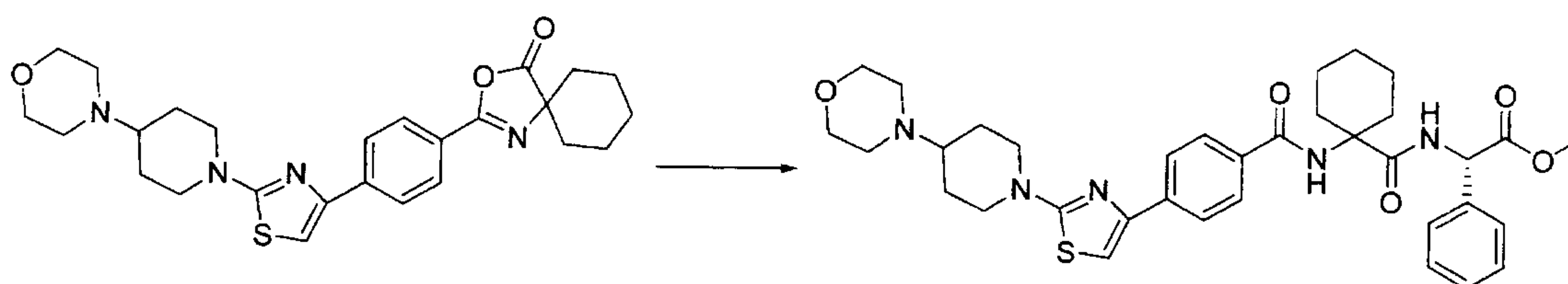
¹H-NMR (CDCl₃, δ): 1.31-1.79 (8H, m), 1.92-2.05 (5H, m),

2.05 (3H, s), 2.15-2.34 (3H, m), 2.40-2.49 (1H, m), 2.53
 (2H, t, J=7Hz), 2.59 (4H, t, J=5Hz), 3.08 (2H, dd, J=12Hz,
 12Hz), 3.71 (3H, s), 3.74 (4H, t, J=5Hz), 4.13 (2H, d,
 J=12Hz), 4.69 (1H, dt, J=8Hz, 5Hz), 6.12 (1H, br-s), 6.88
 5 (1H, s), 7.72 (1H, d, J=8Hz), 7.78 (2H, d, J=8Hz), 7.92
 (2H, d, J=8Hz)

[0572]

Example 9

N-[[1-[[[4-[2-[4-(4-Morpholinyl)-1-piperidinyl]-4-
 10 thiazolyl]phenyl]carbonyl]amino]cyclohexyl]carbonyl]-L-
 phenylglycine methyl ester



[0573]

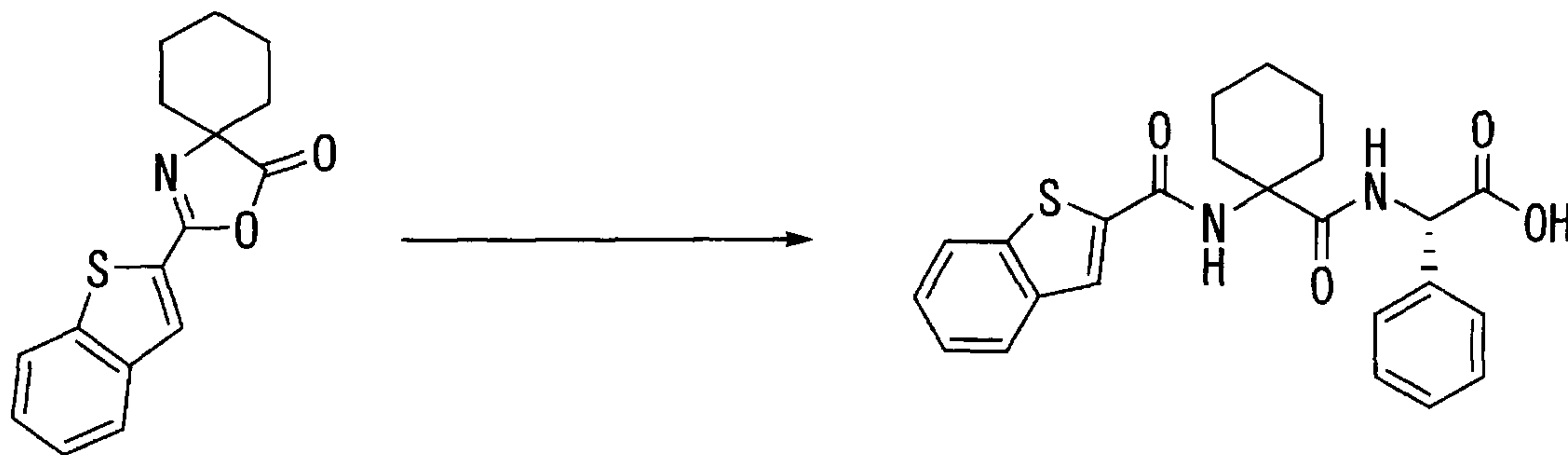
481 mg (1.00 mmol) of 2-[4-[2-[4-(4-morpholinyl)-1-
 15 piperidinyl]-4-thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-
 1-en-4-one was used instead of 2-[4-[2-(4-methyl-1-
 piperazinyl)-4-thiazolyl]phenyl]-3-oxa-1-azaspiro[4.5]dec-
 1-en-4-one, and 202 mg (1.00 mmol) of L-phenylglycine
 methyl ester hydrochloride was used instead of L-methionine
 20 methyl ester hydrochloride in the process according to
 Example 6 to obtain 156 mg (24%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.30-1.41 (1H, m), 1.42-1.60 (3H, m),
 1.61-1.77 (4H, m), 1.92-2.08 (4H, m), 2.25-2.37 (2H, m),
 2.40-2.49 (1H, m), 2.59 (4H, t, J=5Hz), 3.08 (2H, dd,
 25 J=12Hz, 12Hz), 3.69 (3H, s), 3.74 (4H, t, J=5Hz), 4.12 (2H,
 d, J=12H), 5.54 (1H, d, J=7Hz), 6.07 (1H, br-s), 6.87 (1H,
 s), 7.26-7.36 (3H, m), 7.37-7.42 (2H, m), 7.77 (2H, d,
 J=8Hz), 7.91 (2H, d, J=8Hz), 8.30 (1H, d, J=8Hz)

[0574]

Reference Example 233

N-[[1-[(2-Benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-
L-phenylglycine



5 [0575]

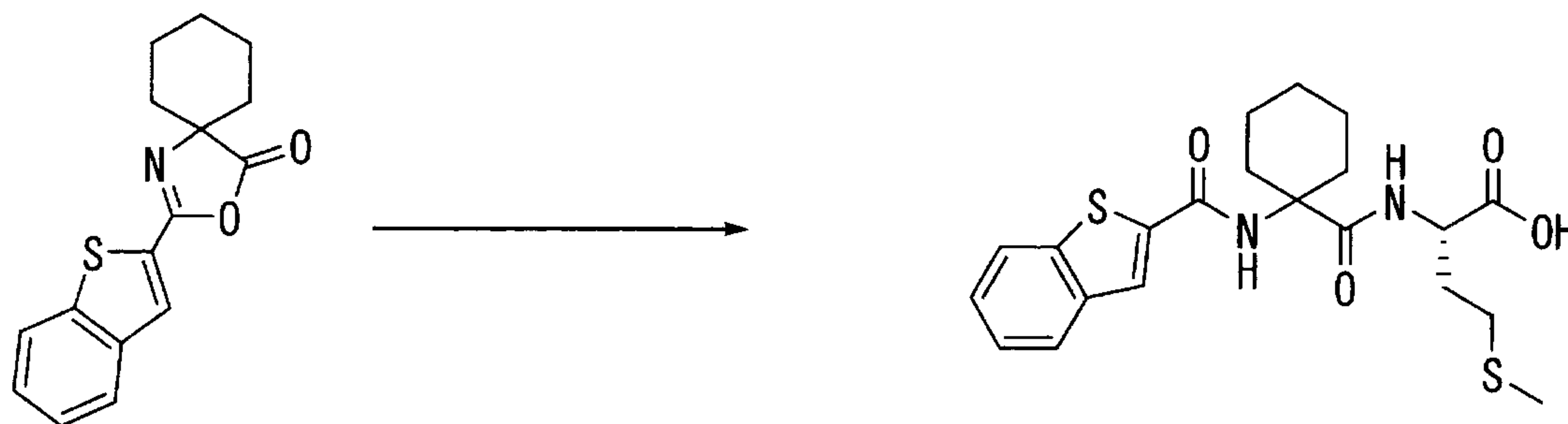
10 ml of N-methylmorpholine was added to 530 mg (3.5 mmol) of L-phenylglycine and 500 mg (1.75 mmol) of 2-(2-benzothienyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, and the mixture was stirred and heated under reflux overnight. The reaction solution was distilled off under reduced pressure, a 10% aqueous potassium hydrogensulfate solution was added thereto, and the mixture was extracted with methylene chloride three times. The obtained organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. Ethyl acetate was added to the obtained residue, and the mixture was stirred overnight. The precipitated solid was collected by filtration and dried under reduced pressure to obtain 259 mg (34%) of the title compound.

20 ¹H-NMR (CDCl₃, δ): 1.25-1.80 (6H, m), 1.83-2.03 (2H, m), 2.12-2.40 (2H, m), 4.47 (1H, d, J=5Hz), 6.11 (1H, s), 7.18-7.55 (8H, m), 7.79 (1H, s), 7.80-7.91 (2H, m)

[0576]

Reference Example 234

25 N-[[1-[(2-Benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-
L-methionine



[0577]

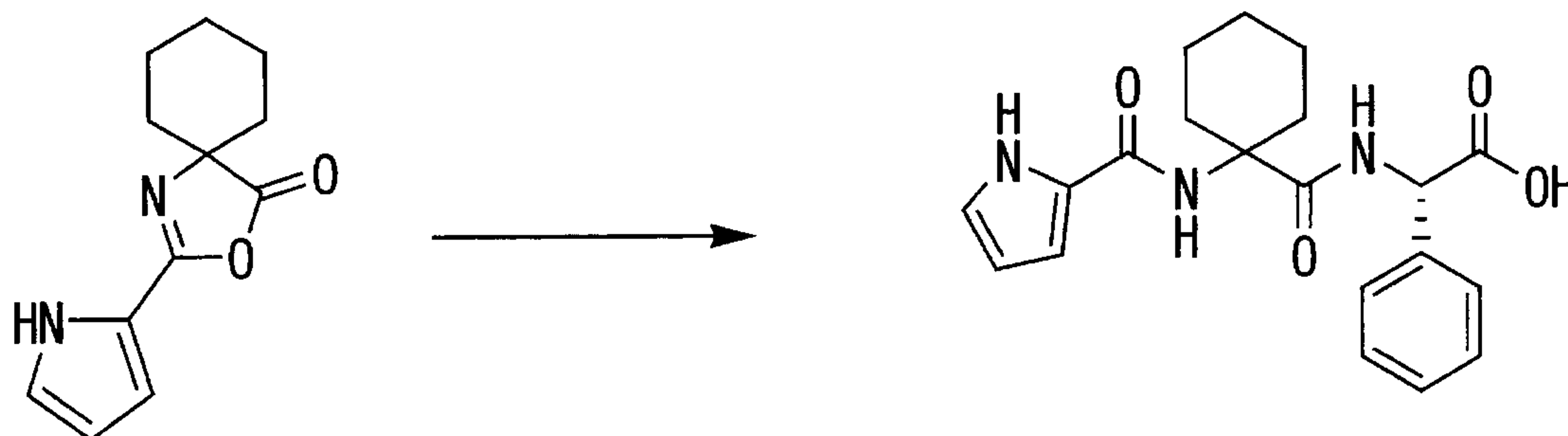
10 ml of N-methylmorpholine was added to 522 mg (3.5 mmol) of L-methionine and 500 mg (1.75 mmol) of 2-(2-benzothiophenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, and the mixture was stirred and heated under reflux overnight. The reaction solution was distilled off under reduced pressure, a 10% aqueous potassium hydrogensulfate solution was added thereto, and the mixture was extracted with methylene chloride three times. The obtained organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. Ethyl acetate was added to the obtained residue, and the mixture was stirred overnight. The precipitated solid was collected by filtration and dried under reduced pressure to obtain 170 mg (22%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.21-2.99 (17H, m), 4.51-4.68 (1H, m), 6.42 (1H, s), 6.75-6.85 (1H, m), 7.32-7.50 (2H, m), 7.74-7.98 (3H, m)

[0578]

Reference Example 235

N-[[[1-[(1H-Pyrrol-2-yl)carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycine



[0579]

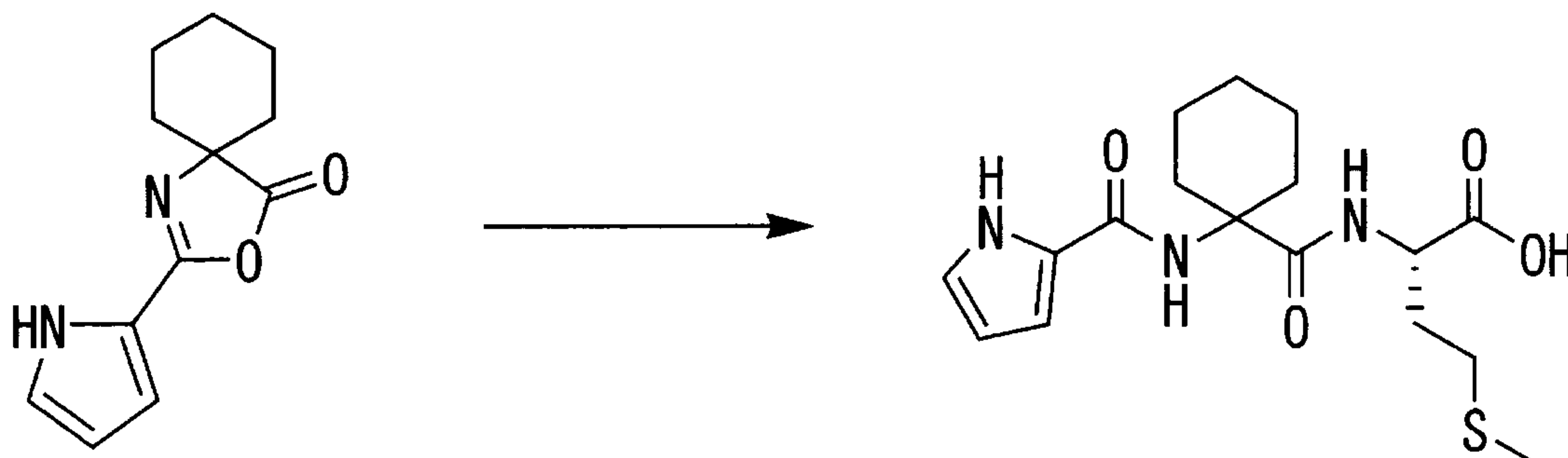
10 ml of N-methylmorpholine was added to 583 mg (3.9 mmol) of L-phenylglycine and 500 mg (1.9 mmol) of 2-(1H-pyrrol-2-yl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, and the mixture was stirred and heated under reflux overnight. The reaction solution was distilled off under reduced pressure, a 10% aqueous potassium hydrogensulfate solution was added thereto, and the mixture was extracted with methylene chloride three times. The obtained organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 120 mg (17%) of the title compound.

1H-NMR (CDCl₃, δ): 1.18-2.08 (9H, m), 2.18-2.30 (1H, m), 5.63 (1H, d, J=7Hz), 6.16-6.23 (1H, m), 6.25 (1H, s), 6.61-6.83 (2H, m), 7.17-7.35 (3H, m), 7.41 (2H, d, J=8Hz), 7.83 (1H, d, J=7Hz), 10.92 (1H, s)

[0580]

Reference Example 236

N-[[[1-[(1H-Pyrrol-2-yl)carbonyl]amino]cyclohexyl]carbonyl]-L-methionine



[0581]

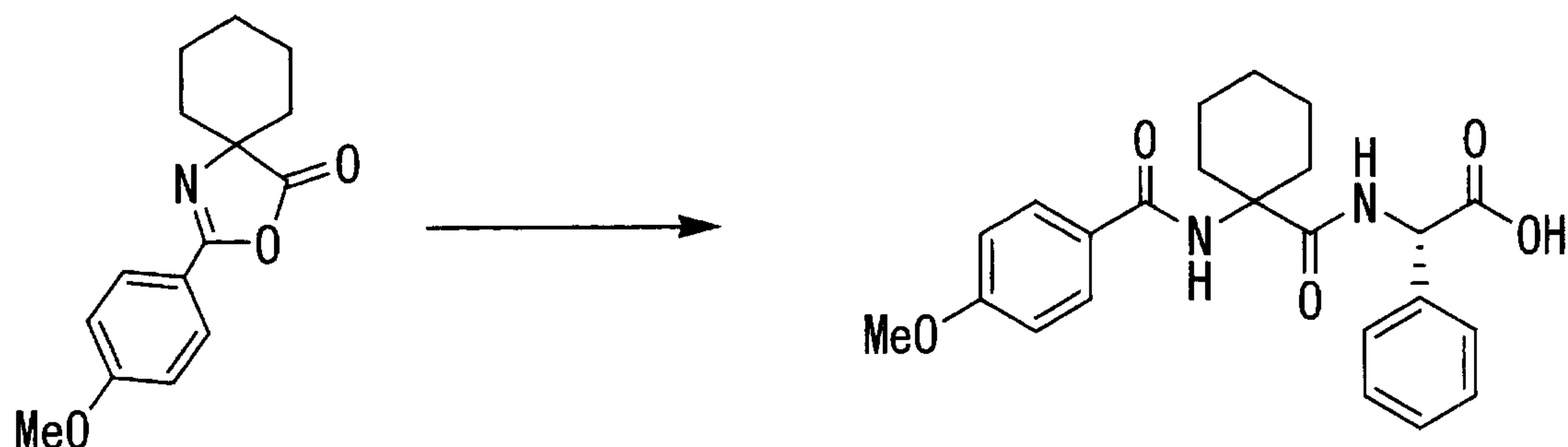
10 ml of N-methylmorpholine was added to 575 mg (3.9 mmol) of L-methionine and 500 mg (1.9 mmol) of 2-(1H-pyrrol-2-yl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, and the mixture was stirred and heated under reflux overnight. The reaction solution was distilled off under reduced pressure, a 10% aqueous potassium hydrogensulfate solution was added thereto, and the mixture was extracted with methylene chloride three times. The obtained organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. Ethyl acetate was added to the obtained residue, and the mixture was stirred overnight. The precipitated solid was collected by filtration and dried under reduced pressure to obtain 503 mg (72%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.20-2.33 (15H, m), 2.42-2.61 (2H, m), 4.58-4.72 (1H, m), 6.21 (1H, dd, J=5Hz, 3Hz), 6.28 (1H, s), 6.69 (1H, d, J=3Hz), 6.78 (1H, d, J=5Hz), 7.29 (1H, d, J=8Hz)

[0582]

Reference Example 237

N-[[[1-[(4-Methoxyphenyl)carbonyl]amino]cyclohexyl]carbonyl]-L-phenylglycine



[0583]

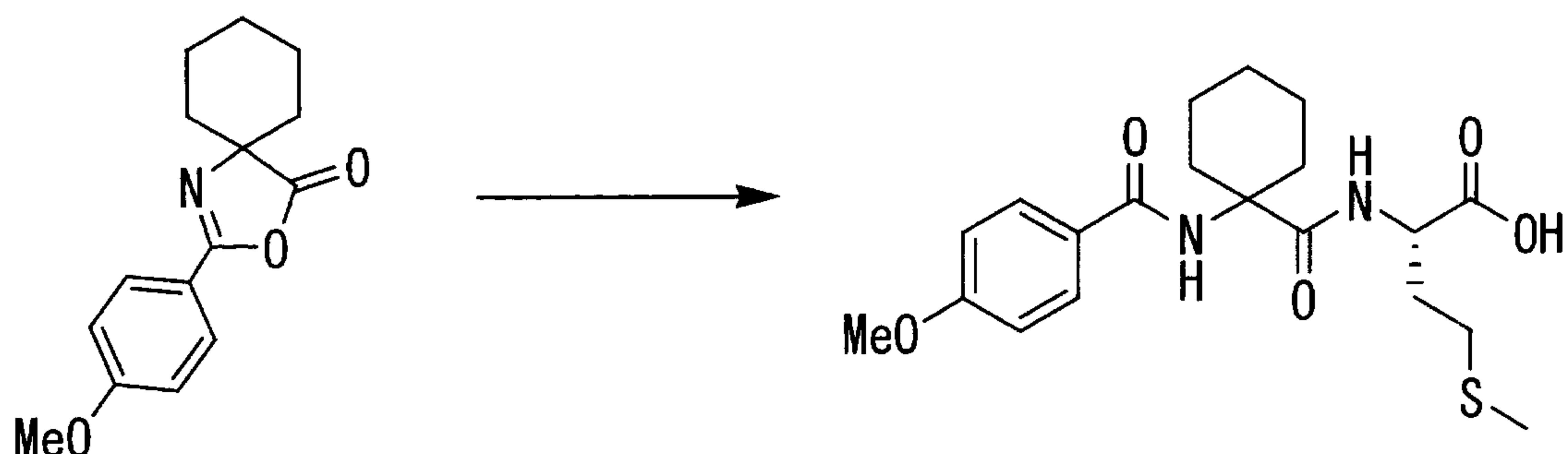
10 ml of N-methylmorpholine was added to 583 mg (3.9 mmol) of L-phenylglycine and 500 mg (1.9 mmol) of 2-(4-methoxyphenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, and the mixture was stirred and heated under reflux overnight. The reaction solution was distilled off under reduced pressure, a 10% aqueous potassium hydrogensulfate solution was added thereto, and the mixture was extracted with methylene chloride three times. The obtained organic layer was dried with anhydrous sodium hydrogensulfate and the solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 92 mg (22%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.25-1.58 (3H, m), 1.60-1.81 (3H, m), 1.85-2.05 (2H, m), 2.17-2.39 (2H, m), 3.86 (3H, s), 4.45 (1H, d, J=6Hz), 6.01 (1H, s), 6.82-7.00 (3H, m), 7.19-7.38 (4H, m), 7.57-7.83 (3H, m)

[0584]

Reference Example 238

N-[[1-[[[(4-Methoxyphenyl)carbonyl]amino]cyclohexyl]carbonyl]-L-methionine



[0585]

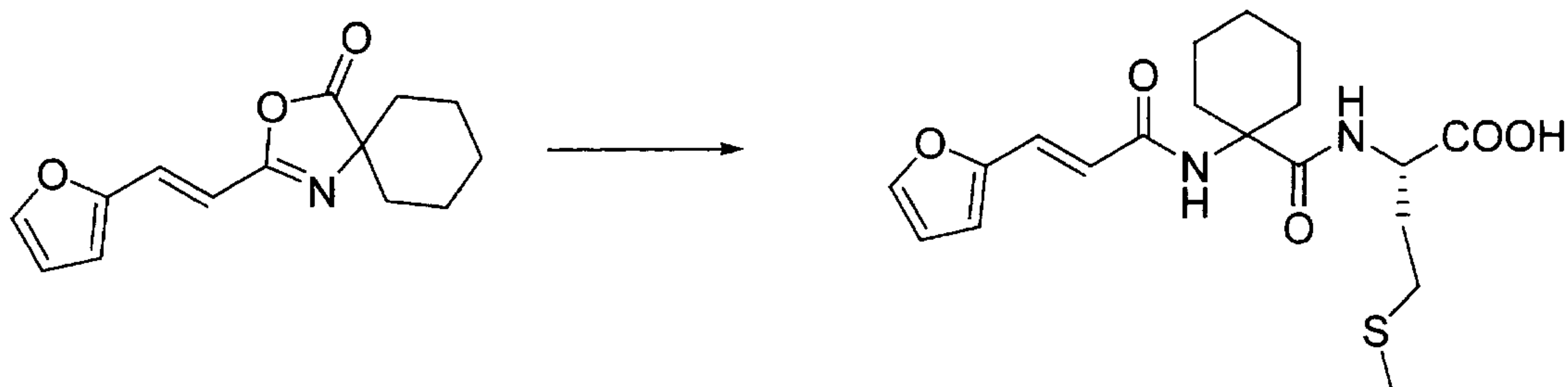
10 ml of N-methylmorpholine was added to 298 mg (2 mmol) of L-methionine and 259 mg (1 mmol) of 2-(4-methoxyphenyl)-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, and the mixture was stirred and heated under reflux overnight. The reaction solution was distilled off under reduced pressure, a 10% aqueous potassium hydrogensulfate solution was added thereto, and the mixture was extracted with methylene chloride three times. The obtained organic layer was dried with anhydrous sodium hydrogensulfate and the solvent was distilled off under reduced pressure. Ethyl acetate was added to the obtained residue, and the mixture was stirred overnight. The precipitated solid was collected by filtration and dried under reduced pressure to obtain 52 mg (13%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.20-2.62 (17H, m), 3.86 (3H, s), 4.56-4.71 (1H, m), 6.27 (1H, s), 6.95 (2H, d, J=9Hz), 7.75 (2H, d, J=9Hz), 7.86 (1H, d, J=8Hz)

[0586]

Reference Example 239

N-[[1-[[[(E)-3-(2-Furanyl)-1-oxo-2-propenyl]amino]cyclohexyl]carbonyl]-L-methionine



[0587]

A solution of 491 mg (2 mmol) of 2-[(E)-2-(2-furanylmethoxy)ethenyl]-3-oxo-1-azaspiro[4.5]dec-1-en-4-one and 597 mg (4 mmol) of L-methionine in 20 ml of N-methylmorpholine was heated under reflux for 15 hours. After ethyl acetate and water were added to the reaction solution, the mixture was acidified using concentrated hydrochloric acid. The organic layer was separated and successively washed with water and saturated brine, followed by drying with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by silica gel chromatography to obtain 74 mg (9%) of the title compound.

¹H-NMR (CDCl₃, δ): 1.24-1.48 (3H, m), 1.59-1.71 (3H, m), 1.87-1.98 (2H, m), 2.00-2.25 (4H, m), 2.05 (3H, s), 2.51-2.63 (2H, m), 4.63 (1H, dt, J=8Hz, 5H), 6.00 (1H, br-s), 6.40 (1H, d, J=15Hz), 6.46 (1H, dd, J=3Hz, 2Hz), 6.59 (1H, d, J=3Hz), 7.40 (1H, d, J=15Hz), 7.45 (1H, d, J=2Hz), 7.76 (1H, d, J=8Hz)

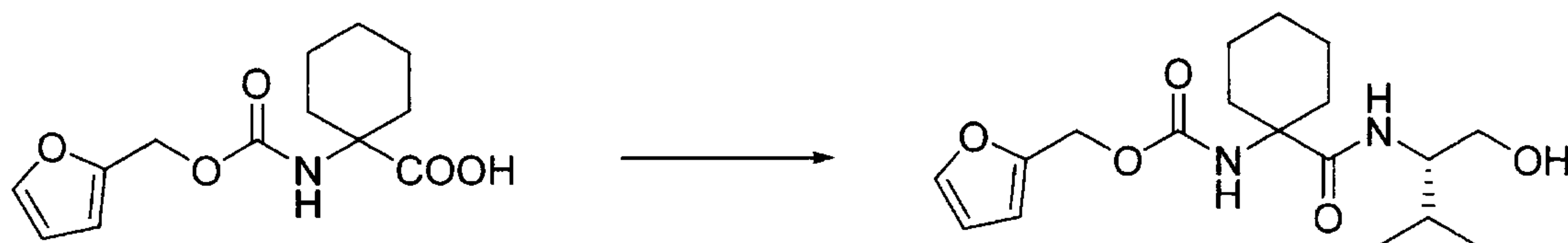
[0588]

Reference Example 240

N-[[1-[[2-(2-

Furanylmethoxy)carbonyl]amino]cyclohexyl]carbonyl]-L-

25 valinol



[0589]

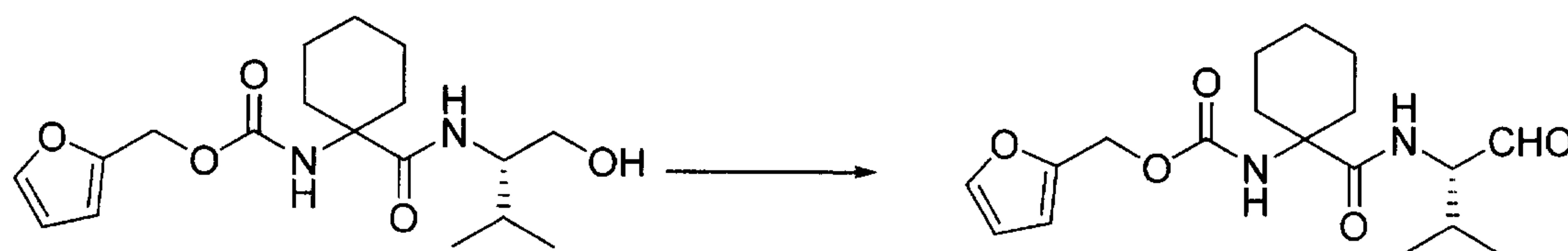
2.00 g (7.48 mmol) of 1-[[[(2-furanylmethoxy)carbonyl]amino]cyclohexanecarboxylic acid
 5 was used instead of 2-benzothiophenecarboxylic acid, and
 772 mg (7.48 mmol) of L-valinol was used instead of 1-
 aminocyclohexanecarboxylic acid phenylmethyl ester in the
 process according to Reference Example 197 to obtain 2.67 g
 (quantitative) of the title compound and 2.64 g
 10 (quantitative) of the title compound.

¹H-NMR (CDCl₃, δ): 0.90 (3H, d, J=7Hz), 0.95 (3H, d,
 J=7Hz), 1.29-1.46 (3H, m), 1.56-1.72 (3H, m), 1.78-1.85
 (1H, m), 1.88-1.96 (2H, m), 1.96-2.06 (2H, m), 2.75-2.90
 (1H, br-s), 3.48-3.55 (1H, m), 3.68-3.78 (2H, m), 5.06 (1H,
 15 br-s), 5.00 (1H, d, J=13Hz), 5.10 (1H, d, J=13Hz), 6.35
 (1H, br-s), 6.37 (1H, dd, J=3Hz, 2Hz), 6.43 (1H, dd, J=3Hz,
 1Hz), 7.43 (1H, dd, J=2Hz, 1Hz)

[0590]

Reference Example 241

20 N-[[[1-[[[(2-furanylmethoxy)carbonyl]amino]cyclohexyl]carbonyl]-L-
 valinal



[0591]

25 2.67 g of the above obtained N-[[[1-[[[(2-furanylmethoxy)carbonyl]amino]cyclohexyl]carbonyl]-L-
 valinol was used instead of N-[[[1-[(2-

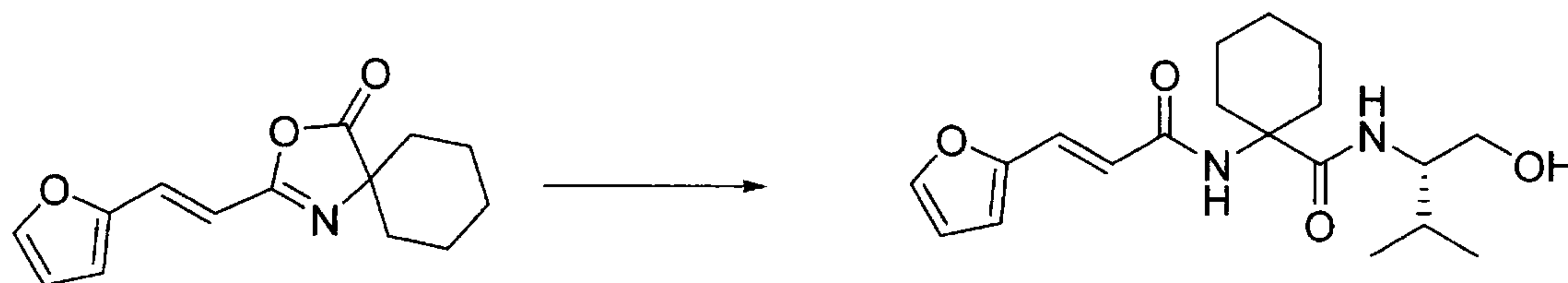
benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-L-phenylglycinol in the process according to Reference Example 218 to obtain 2.08 g (83.7%, 2 steps) of the title compound.

5 ¹H-NMR (CDCl₃, δ): 0.92 (3H, d, J=7Hz), 1.00 (3H, d, J=7Hz), 1.26-1.46 (3H, m), 1.52-1.70 (3H, m), 1.86-1.96 (2H, m), 1.96-2.04 (1H, m), 2.05-2.14 (1H, m), 2.28-2.36 (1H, m), 4.46-4.52 (1H, m), 4.92-4.99 (1H, br-s), 5.04 (1H, d, J=13Hz), 5.09 (1H, d, J=13Hz), 6.36 (1H, dd, J=3Hz, 2Hz), 6.41 (1H, d, J=3Hz), 7.04-7.16 (1H, m), 7.42 (1H, d, J=2Hz), 9.61 (1H, s)

[0592]

Reference Example 242

N-[[1-[(E)-3-(2-Furanyl)-1-oxo-2-propenyl]amino]cyclohexyl]carbonyl]-L-valinol



[0593]

1.07 ml (6.12 mmol) of DIPEA was added to a solution of 252 mg (2.45 mmol) of L-valinol and 500 mg (2.04 mmol) of 2-[(E)-2-(2-furanyl)ethenyl]-3-oxo-1-azaspiro[4.5]dec-1-en-4-one in 15 ml of toluene, and the mixture was stirred and heated under reflux for 4 days. The reaction solution was distilled off under reduced pressure, the residue was purified by silica gel chromatography to obtain 481 mg (67.7%) of the title compound.

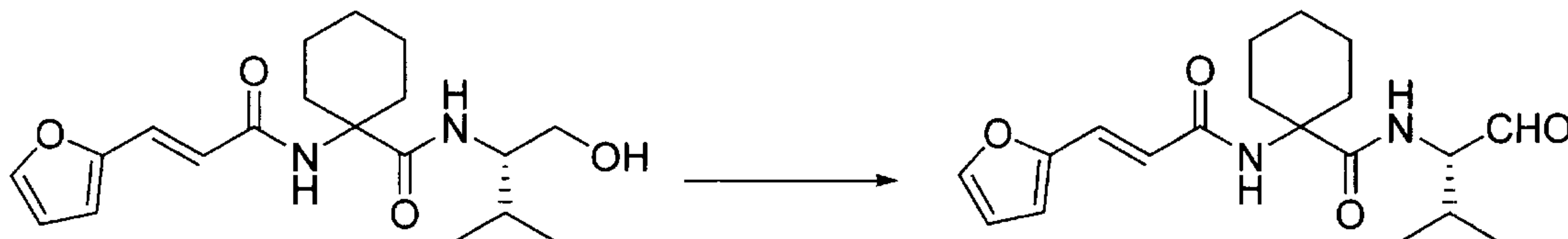
¹H-NMR (CDCl₃, δ): 0.93 (3H, d, J=7Hz), 0.95 (3H, d, J=7Hz), 1.34-1.52 (3H, m), 1.60-1.74 (3H, m), 1.80-1.88 (1H, m), 1.94-2.06 (2H, m), 2.08-2.18 (2H, m), 3.16-3.21 (1H, m), 3.51-3.57 (1H, m), 3.68-3.78 (2H, m), 5.72 (1H,

br-s), 6.35 (1H, d, 15Hz), 6.47 (1H, dd, J=3Hz, 2Hz), 6.58 (1H, dd, J=3Hz, 1Hz), 6.73 (1H, br-d, J=9Hz), 7.41 (1H, d, J=15Hz), 7.46 (1H, dd, J=2Hz, 1Hz)

[0594]

5 Reference Example 243

N-[[1-[[[(E)-3-(2-Furanyl)-1-oxo-2-propenyl]amino]cyclohexyl]carbonyl]-L-valinal



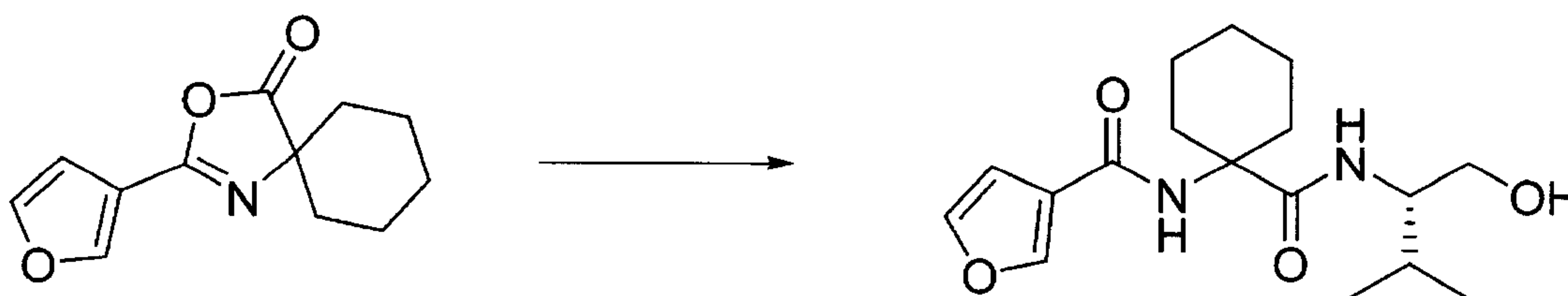
[0595]

10 481 mg (1.38 mmol) of N-[[1-[[[(E)-3-(2-furanyl)-1-oxo-2-propenyl]amino]cyclohexyl]carbonyl]-L-valinol was used instead of N-[[1-[(2-benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-L-phenylglycinol in the process according to Reference
15 Example 218 to obtain 449 mg (93.9%) of the title compound.
1H-NMR (CDCl₃, δ): 0.95 (3H, d, J=7Hz), 1.01 (3H, d, J=7Hz), 1.30-1.74 (6H, m), 1.92-2.02 (2H, m), 2.14-2.22 (1H, m), 2.22-2.30 (1H, m), 2.28-2.36 (1H, m), 4.42 (1H, ddd, J=8Hz, 5Hz, 1Hz), 5.55 (1H, br-s), 6.38 (1H, d, J=15Hz), 6.47 (1H, dd, J=3Hz, 2Hz), 6.58 (1H, d, J=3Hz, 1Hz), 7.42 (1H, d, J=15Hz), 7.46 (1H, dd, J=2Hz, 1Hz), 7.83 (1H, d, J=8Hz), 9.59 (1H, d, 1Hz)

[0596]

Reference Example 244

25 N-[[1-[(3-Furanylcarbonyl)amino]cyclohexyl]carbonyl]-L-valinol



[0597]

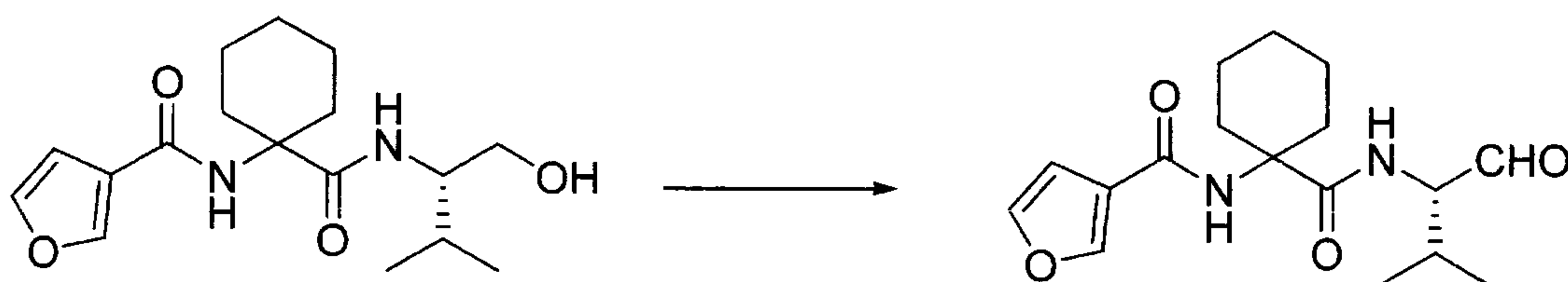
0.52 ml (3.01 mmol) of DIPEA was added to a solution of 124 mg (1.20 mmol) of L-valinol and 222 mg (1.00 mmol) of 2-(3-furanyl)-3-oxo-1-azasprio[4.5]dec-1-en-4-one in 10 ml of toluene, and the mixture was stirred and heated under reflux for 4 days. The reaction solution was distilled off under reduced pressure and the residue was purified by silica gel chromatography to obtain 340 mg (quantitative) of the title compound.

1H-NMR (CDCl₃, δ): 0.93 (3H, d, J=7Hz), 0.96 (3H, d, J=7Hz), 1.35-1.54 (3H, m), 1.56-1.76 (3H, m), 1.82-1.90 (1H, m), 1.96-2.06 (2H, m), 2.13-2.20 (2H, m), 3.05 (1H, br-s), 3.54-3.59 (1H, m), 3.69-3.78 (2H, m), 5.88 (1H, br-s), 6.60 (1H, dd, J=2Hz, 1Hz), 6.80 (1H, br-d, J=8Hz), 7.46 (1H, dd, J=2Hz, 2Hz), 7.96 (1H, dd, J=2Hz, 1Hz)

[0598]

Reference Example 245

N-[[1-[(3-Furanylcarbonyl)amino]cyclohexyl]carbonyl]-L-valinal



[0599]

340 mg of the above obtained N-[[1-[(3-furanylcarbonyl)amino]cyclohexyl]carbonyl]-L-valinol was used instead of N-[[1-[(2-benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-L-phenylglycinol in the process according to Reference Example 218 to obtain 282 g (87.6%, 2 steps) of the title compound.

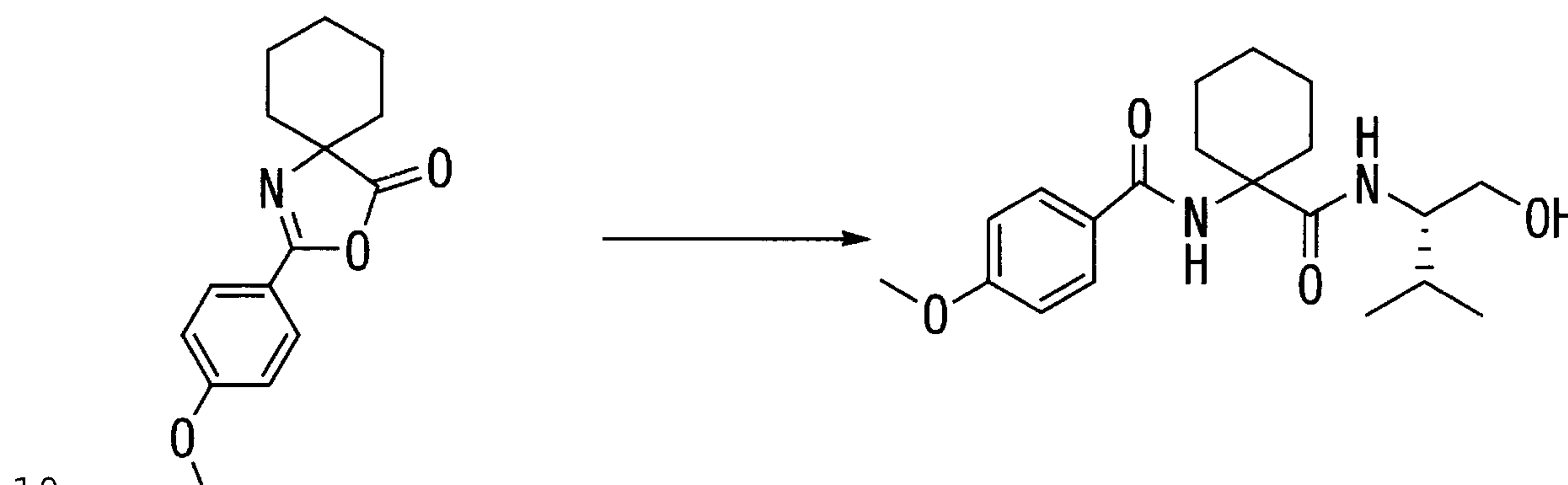
1H-NMR (CDCl₃, δ): 0.95 (3H, d, J=7Hz), 1.02 (3H, d,

J=7Hz), 1.32-1.52 (3H, m), 1.60-1.76 (3H, m), 1.95-2.06 (2H, m), 2.18-2.24 (1H, m), 2.26-2.36 (2H, m), 4.46 (1H, ddd, J=8Hz, 5Hz, 1Hz), 5.74 (1H, br-s), 6.62 (1H, dd, J=2Hz, 1Hz), 7.47 (1H, dd, J=2Hz, 1Hz), 7.71 (1H, d, J=8Hz), 7.97 (1H, dd, J=1Hz, 1Hz), 9.61 (1H, d, J=1Hz)
[0600]

Reference Example 246

N-[[1-[(4-

Methoxyphenyl)carbonyl]amino]cyclohexyl]carbonyl]-L-valinol



[0601]

260 mg (1.00 mmol) of 2-(4-methoxyphenyl)-3-oxo-1-azaspiro[4.5]dec-1-en-4-one was added to a solution of 252 mg (2.45 mmol) of L-valinol in 5 ml of ethyl acetate, and the mixture was stirred at room temperature for 4 days. The reaction solution was distilled off under reduced pressure, and the residue was washed with diethyl ether to obtain 243.5 mg (66.7%) of the title compound.

1H-NMR (CDCl₃, δ): 0.93 (3H, d, J=7Hz), 0.96 (3H, d, J=7Hz), 1.36-1.80 (7H, m), 1.80-1.88 (1H, m), 1.98-2.10 (2H, m), 2.16-2.26 (2H, m), 3.55 (1H, dd, J=11Hz, 6Hz), 3.69-3.74 (1H, m), 3.77 (1H, dd, J=11Hz, 3Hz), 3.86 (3H, s), 6.17 (1H, br-s), 6.84 (1H, br-d, J=9Hz), 6.95 (2H, dd, J=7Hz, 2Hz), 7.74 (2H, dd, J=7Hz, 2Hz)

[0602]

Reference Example 247

N-[[1-[(4-

Methoxyphenyl) carbonyl] amino] cyclohexyl] carbonyl] -L-valinal



[0603]

5 243 mg (0.67 mmol) of N-[[1-[(4-methoxyphenyl) carbonyl] amino] cyclohexyl] carbonyl] -L-valinol was used instead of N-[[1-[(2-

benzothienyl carbonyl] amino] cyclohexyl] carbonyl] -L-phenylglycinol in the process according to Reference

10 Example 218 to obtain 240 mg (98.9%) of the title compound.

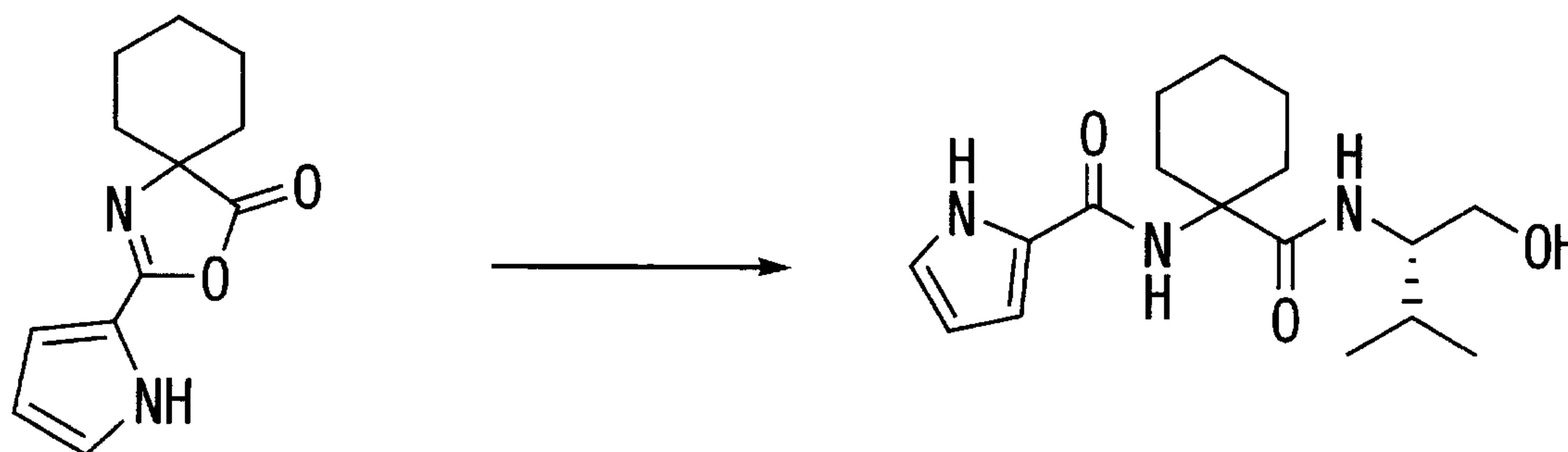
¹H-NMR (CDCl₃, δ): 0.95 (3H, d, J=7Hz), 1.02 (3H, d, J=7Hz), 1.34-1.54 (3H, m), 1.63-1.78 (3H, m), 1.96-2.05 (2H, m), 2.24-2.37 (3H, m), 3.87 (3H, s), 4.43 (1H, ddd, J=8Hz, 5Hz, 1Hz), 6.03 (1H, br-s), 6.96 (2H, dd, J=7Hz, 2Hz), 7.75 (2H, dd, J=7Hz, 2Hz), 7.87 (1H, d, J=8Hz), 9.60 (1H, s)

[0604]

Reference Example 248

N-[[1-[(1H-Pyrrol-2-

20 yl) carbonyl] amino] cyclohexyl] carbonyl] -L-valinol



[0605]

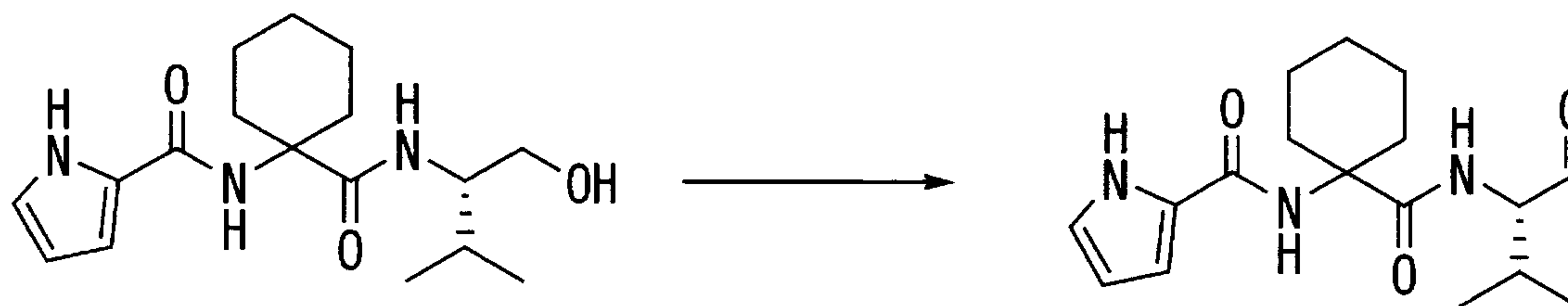
220 mg (1.01 mmol) of 2-(1H-pyrrol-2-yl)-3-oxo-1-azaspiro[4.5]dec-1-en-4-one was added to a solution of 252

mg (2.45 mmol) of L-valinol in 5 ml of ethyl acetate, and the mixture was stirred at room temperature for 4 days. The reaction solution was distilled off under reduced pressure and the residue was purified by silica gel chromatography to obtain 247 mg (76.4%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.93 (3H, d, J=7Hz), 0.94 (3H, d, J=7Hz), 1.34-1.52 (3H, m), 1.62-2.14 (8H, m), 2.16-2.22 (1H, m), 3.51 (1H, dd, J=12Hz, 7Hz), 3.69-3.76 (2H, m), 6.03 (1H, br-s), 6.27 (1H, ddd, J=4Hz, 3Hz, 3Hz), 6.60-6.66 (2H, m), 6.97 (1H, ddd, J=3Hz, 3Hz, 1Hz), 9.48 (1H, br-s) [0606]

Reference Example 249

N-[[1-[[1H-Pyrrol-2-yl)carbonyl]amino]cyclohexyl]carbonyl]-L-valinal



[0607]

247 mg (0.77 mmol) of N-[[1-[[1H-pyrrol-2-yl)carbonyl]amino]cyclohexyl]carbonyl]-L-valinol was used instead of N-[[1-[(2-benzothienylcarbonyl)amino]cyclohexyl]carbonyl]-L-phenylglycinol in the process according to Reference Example 218 to obtain 217 mg (88.2%) of the title compound.

¹H-NMR (CDCl₃, δ): 0.93 (3H, d, J=7Hz), 1.00 (3H, d, J=7Hz), 1.32-1.52 (3H, m), 1.60-1.76 (3H, m), 1.94-2.03 (2H, m), 2.18-2.25 (1H, m), 2.26-2.34 (2H, m), 4.45 (1H, dd, J=8Hz, 5Hz), 5.84 (1H, br-s), 6.28 (1H, ddd, J=4Hz, 3Hz, 3Hz), 6.63 (1H, ddd, J=4Hz, 3Hz, 1Hz), 6.96 (1H, ddd, J=3Hz, 3Hz, 1Hz), 7.75 (1H, br-d, J=8Hz), 9.33 (1H, br-s),

9.59 (1H, s)

[0608]

Test Example 1 Measurement of Cathepsin K Inhibitory Activity

5 Active enzyme was produced by expressing cathepsin K in the form of a proenzyme in a cell culture from a baculovirus expression system using Sf21 insect cells, followed by incubating for 1 hour at 40°C¹⁾. Cathepsin K activity was measured based on decomposition of the
10 fluorescent substrate Z-Gly-Pro-Arg-MCA (Peptide Institute, Inc.) in compliance with the method of Aibe, et al.²⁾. Namely, the decomposition of 20 mM Z-Gly-Pro-Arg-MCA by cathepsin K was measured in 100 mM sodium/potassium phosphate, 1 mM EDTA and 8 mM cysteine at pH 6.0. The
15 reaction was carried out for 30 minutes at 37°C, and stopped by the addition of 2×10^{-5} M CalpeptinTM. After stopping the reaction, fluorescent intensity was measured at an excitation wavelength of 355 nm and measurement wavelength of 460 nm. Inhibition of cathepsin K by the
20 compounds was examined using the reaction system described above. The 50% inhibitory concentrations on cathepsin K of the compounds of the reference examples are shown in Table 1.

[0609]

25 Test Example 2 Measurement of Cathepsin B Inhibitory Activity

Human cathepsin B (Calbiochem Corp.) was used for measurement. Activity was measured based on decomposition of the fluorescent substrate Z-Arg-Arg-MCA (Peptide
30 Institute, Inc.) in compliance with the method of Barrett, et al.³⁾. Namely, the decomposition of 20 mM Z-Arg-Arg-MCA by cathepsin B was measured in 100 mM sodium/potassium phosphate, 1 mM EDTA, 8 mM cysteine and 0.005% Brij35 at pH

6.0. The reaction was carried out for 30 minutes at 30°C, and stopped by the addition of 2×10^{-5} M Calpeptin. After stopping the reaction, fluorescent intensity was measured at an excitation wavelength of 355 nm and measurement wavelength of 460 nm. Inhibition of cathepsin B by the compounds was examined using the reaction system described above. The 50% inhibitory concentrations on cathepsin B of the compounds of the reference examples are shown in Table 1.

10 [0610]

Test Example 3 Measurement of Cathepsin L Inhibitory Activity

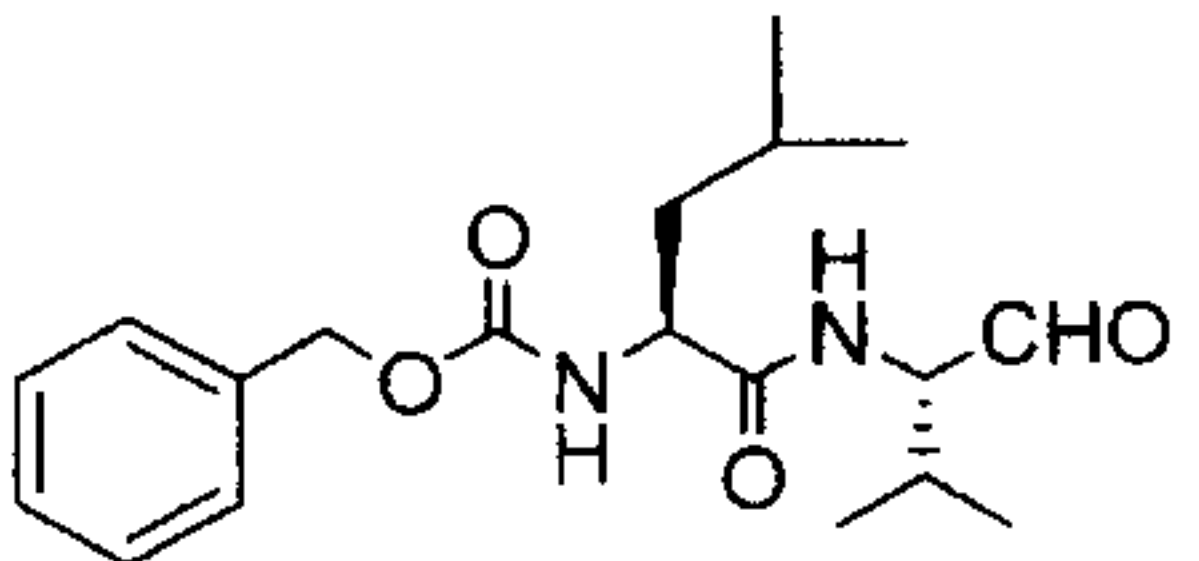
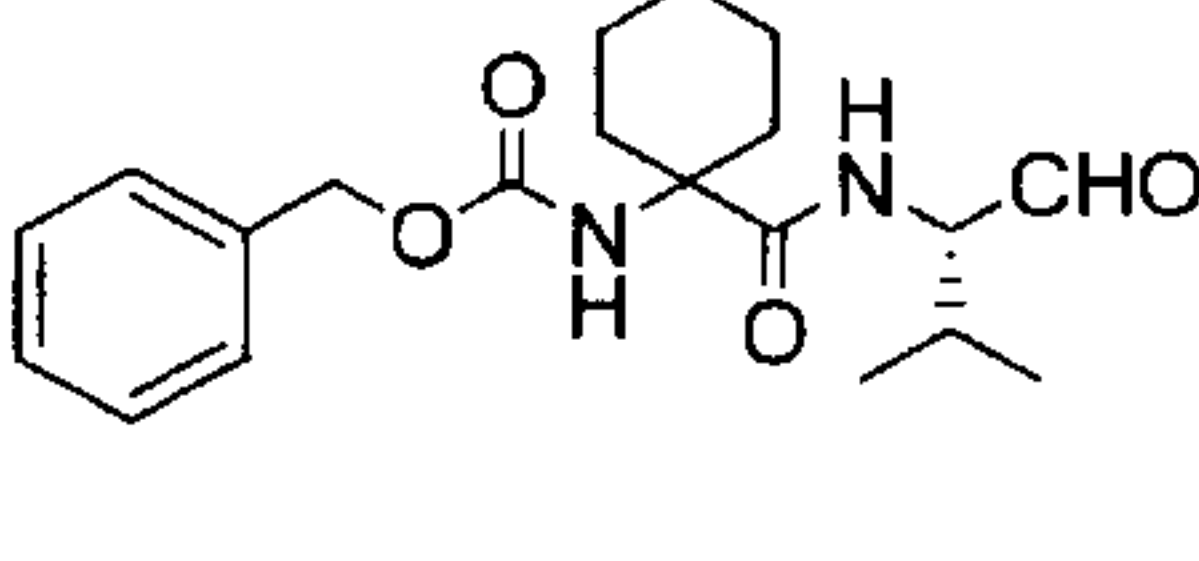
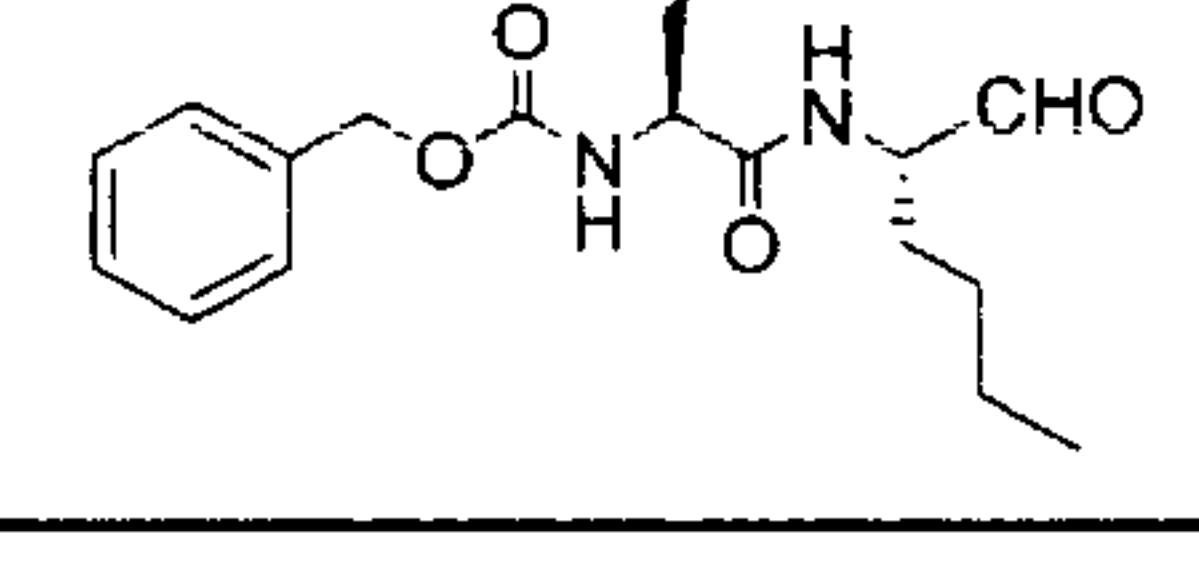
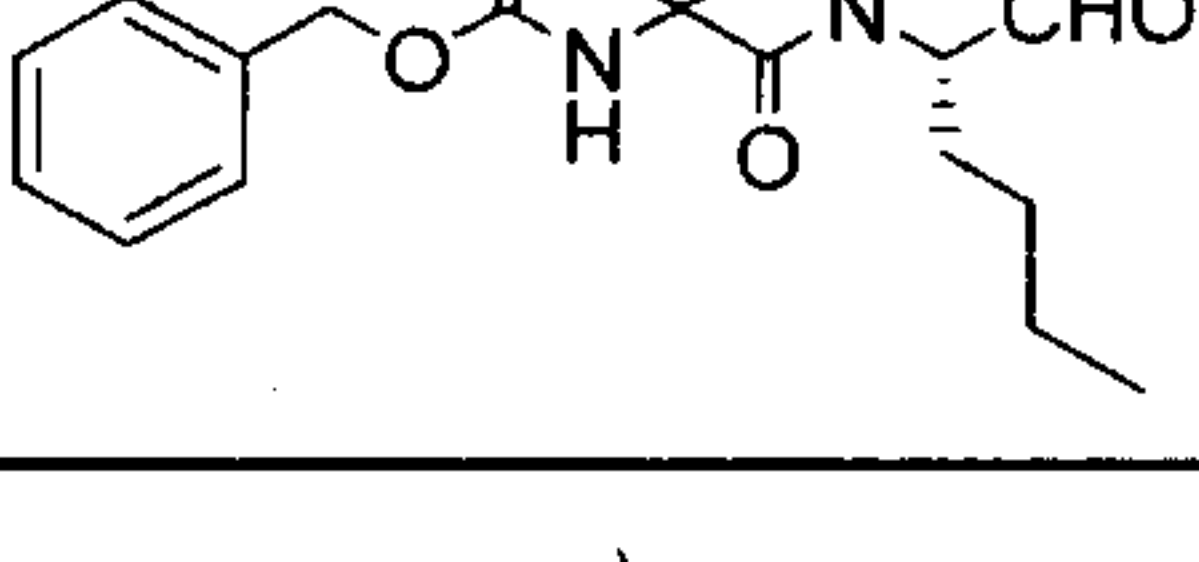
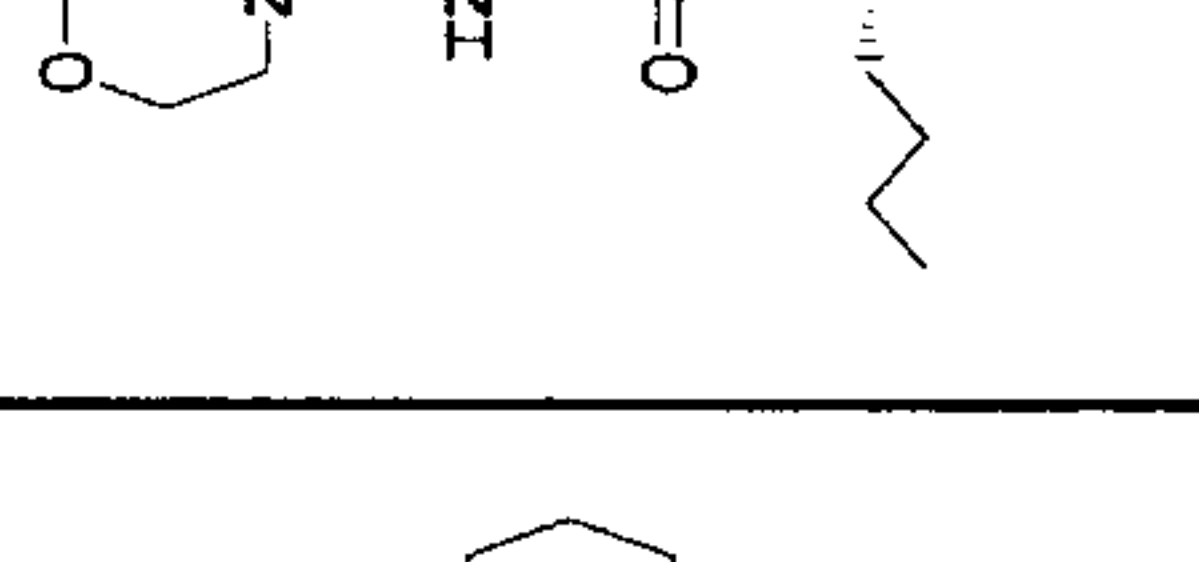
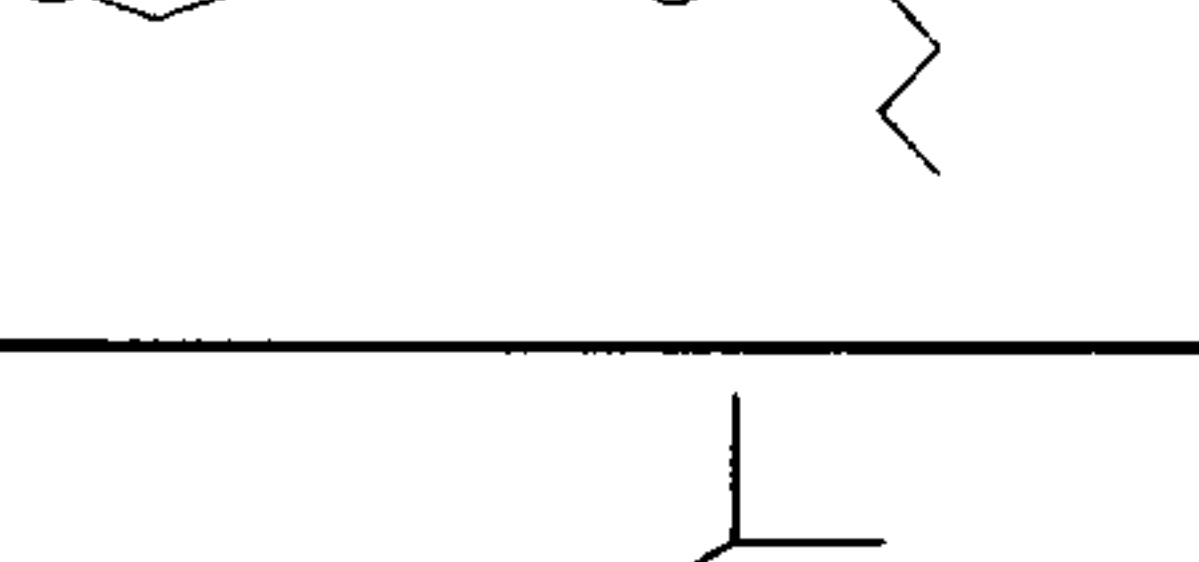
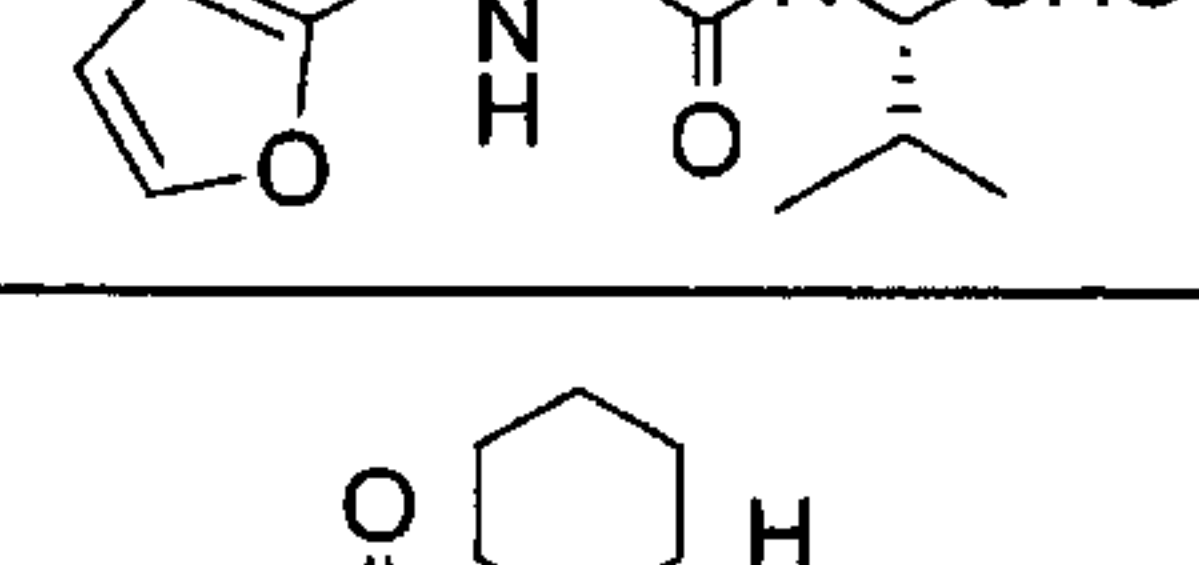
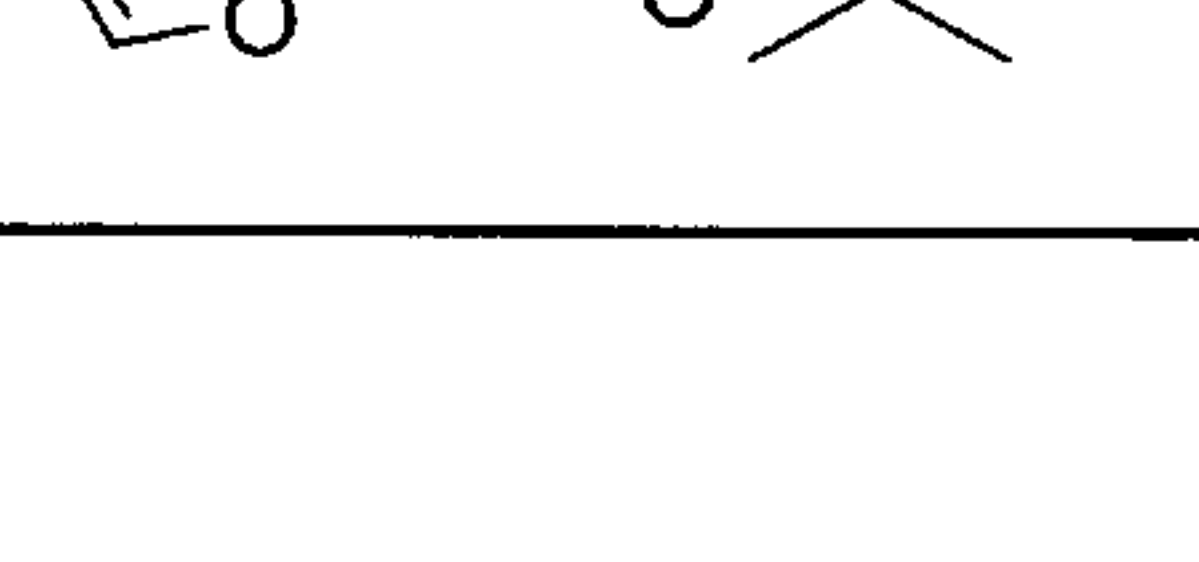
Human cathepsin L (Calbiochem Corp.) was used for measurement. Activity was measured based on decomposition of the fluorescent substrate Z-Phe-Arg-MCA (Peptide Institute, Inc.) in compliance with the method of Barrett, et al.³⁾. Namely, the decomposition of 20 mM Z-Phe-Arg-MCA by cathepsin L was measured in 100 mM sodium acetate, 5 mM EDTA, 4 mM urea, 8 mM cysteine and 0.005% Brij35 at pH 5.5. The reaction was carried out for 30 minutes at 30°C, and stopped by the addition of 2×10^{-5} M Calpeptin. After stopping the reaction, fluorescent intensity was measured at an excitation wavelength of 355 nm and measurement wavelength of 460 nm. Inhibition of cathepsin L by the compounds was examined using the reaction system described above. The 50% inhibitory concentrations on cathepsin L of the compounds of the reference examples are shown in Table 1.

References

- 30 • Tezuka et al., J. Biol.Chem., 269, 1106-1109 (1994)
• Aibe et al., Biol. Pharm. Bull., 19, 1026-1031 (1996)
• Barrett, A.J. & Kirschke, H. Methods Enzymol. 80, 535-

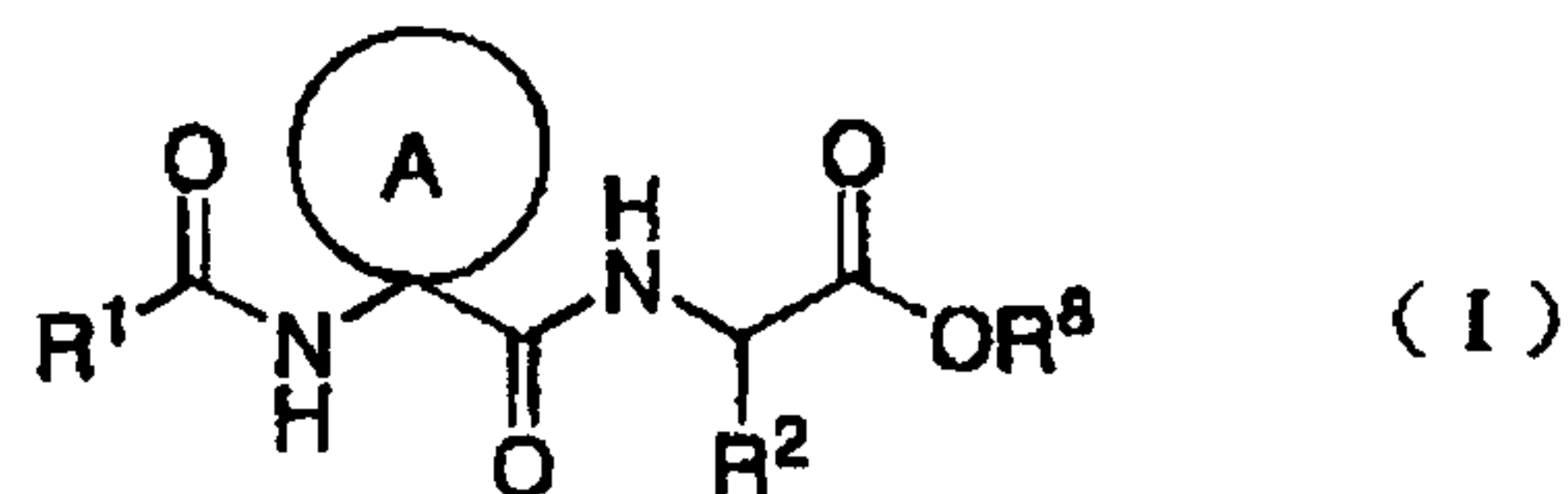
561 (1981)

[0611]

Compound No.	Structural Formula	IC ₅₀ (M)		
		Cathepsin K	human Cathepsin B	human Cathepsin L
Reference Example 193		1.9×10^{-9}	1.1×10^{-7}	1.4×10^{-7}
Reference Example 189		1.7×10^{-9}	3.9×10^{-7}	6.8×10^{-7}
Reference Example 194		3.5×10^{-9}	4.0×10^{-8}	5.3×10^{-8}
Reference Example 190		4.0×10^{-9}	1.4×10^{-7}	2.0×10^{-7}
Reference Example 195		3.0×10^{-9}	1.3×10^{-8}	2.2×10^{-8}
Reference Example 192		2.2×10^{-8}	2.6×10^{-7}	4.7×10^{-7}
Reference Example 196		1.9×10^{-9}	5.7×10^{-8}	6.7×10^{-8}
Reference Example 191		5.4×10^{-10}	4.7×10^{-8}	2.0×10^{-7}

We Claim:

1. A cycloalkylcarbonylamino acid ester derivative
 represented by formula (I) or a pharmaceutically acceptable
 5 salt thereof:



- wherein, R¹ represents a substituted or unsubstituted alkyl
 group, substituted or unsubstituted alkenyl group,
 substituted or unsubstituted alkynyl group, substituted or
 10 unsubstituted aromatic hydrocarbon group, substituted or
 unsubstituted heterocyclic group, group represented by
 R⁴O-, group represented by R⁵S- or group represented by
 R⁶(R⁷)N-, wherein R⁴, R⁵, R⁶ and R⁷ respectively and
 independently represent a substituted or unsubstituted
 15 alkyl group, substituted or unsubstituted alkenyl group,
 substituted or unsubstituted alkynyl group, substituted or
 unsubstituted aromatic hydrocarbon group, or substituted or
 unsubstituted heterocyclic group, furthermore R⁶ and R⁷ may
 together form a ring; R² represents a primary or secondary
 20 substituted or unsubstituted alkyl group, substituted or
 unsubstituted alkenyl group, substituted or unsubstituted
 alkynyl group, substituted or unsubstituted aromatic
 hydrocarbon group or substituted or unsubstituted
 heterocyclic group; ring A represents a cyclic alkylidene
 25 group having 6 or 7 carbon atoms; and, R⁸ represents a
 substituted or unsubstituted alkyl group having 1 to 6
 carbon atoms; provided that, in the case R² is a
 carbamoylmethyl group or hydroxymethyl group, R⁸ is not a
 t-butyl group, in the case R² is a benzyl group, 2,2-
 30 dimethylpropyl group, 2-propyl group or 1-hydroxyethyl

group, R^8 is not a benzyl group, and in the case R^2 is a 1,1-dimethylethyl group, benzyl group, 2-(methylthio)ethyl group, 2-methylpropyl group, p-hydroxyphenylmethyl group or methyl group, R^8 is not a methyl group provided that the compounds, Z-Ac7c-L-Ala-OMe, Z-L-Ala-Ac7c-L-Ala-OMe, Z-(Ac7c)₂-L-Ala-OMe, Z-Ac7c-L-Val-OMe and Boc-L-Leu-Ac7c-L-Val-OMe, wherein Z represents benzyloxycarbonyl, Ac7c represents 1-aminocycloheptane-1-carbonyl and Boc represents t-butoxycarbonyl, are not encompassed herein.

10

2. The cycloalkylcarbonylamino acid ester derivative or pharmaceutically acceptable salt thereof according to claim 1, wherein the alkyl group in the groups represented by R^1 , R^2 , R^4 , R^5 , R^6 and R^7 in the formula (I) is a linear, branched or cyclic alkyl group having 1 to 12 carbon atoms, the alkenyl group is a linear, branched or cyclic alkenyl group having 2 to 12 carbon atoms, the alkynyl group is a linear, branched or cyclic alkynyl group having 2 to 12 carbon atoms, the aromatic hydrocarbon group is a monocyclic or polycyclic aromatic hydrocarbon group having 6 to 18 carbon atoms, and the heterocyclic group is a heterocyclic group of a 3- to 7-membered ring containing at least one nitrogen atom, oxygen atom or sulfur atom as a ring-composing atom.

25

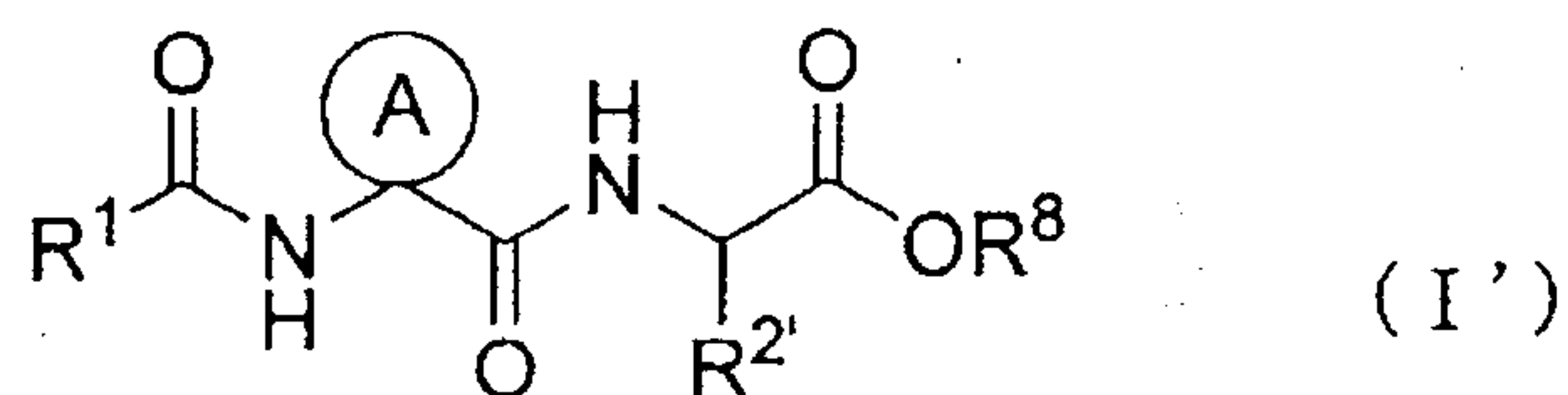
3. The cycloalkylcarbonylamino acid ester derivative or pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein substituents of alkyl groups in the groups represented by R^1 , R^2 , R^4 , R^5 , R^6 , R^7 and R^8 in the formula (I) are respectively and independently groups selected from a hydroxyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group,

30

alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, amido group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group, alkoxycarbonylamino group and $R_x(R_y)N$ group, wherein, R_x and R_y respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group; and,

substituents of alkenyl groups, alkynyl groups, aromatic hydrocarbon groups or heterocyclic groups in the groups represented by R^1 , R^2 , R^4 , R^5 , R^6 and R^7 are respectively and independently groups selected from a hydroxyl group, alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, amido group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group, alkoxycarbonylamino group and $R_x(R_y)N$ group, wherein, R_x and R_y respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group.

4. A cycloalkylcarbonylamino acid ester derivative represented by formula (I') or a pharmaceutically acceptable salt thereof:



wherein, R^1 represents a substituted or unsubstituted alkyl group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group, substituted or unsubstituted heterocyclic group, group represented by R^4O- , group represented by R^5S- or group represented by $R^6(R^7)N$, wherein R^4 , R^5 , R^6 and R^7 respectively and independently represent a substituted or unsubstituted alkyl group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group, or substituted or unsubstituted heterocyclic group, furthermore R^6 and R^7 may together form a ring; $R^{2'}$ represents an alkyl group represented by $Ra(Rb)CH-$, wherein, Ra and Rb respectively and independently represent a hydrogen atom, substituted or unsubstituted alkyl group, substituted or unsubstituted aromatic hydrocarbon group, or substituted or unsubstituted heterocyclic group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group, or substituted or unsubstituted heterocyclic group; ring A represents a cyclic alkylidene group having 6 or 7 carbon atoms; and, R^8 represents a substituted or unsubstituted alkyl group having 1 to 6 carbon atoms;

a substituent of an alkenyl group, alkynyl group or aromatic hydrocarbon group of R^1 , and a substituent of an alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group of $R^{2'}$, R^4 , R^5 , R^6 and R^7 are respectively and independently a group selected from a hydroxyl group,

alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, amido group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group, alkoxycarbonylamino group and Rx(Ry)N group, wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group;

a substituent of an alkyl group of R⁴, R⁵, R⁶, R⁷, R⁸, Ra and Rb is respectively and independently a group selected from a hydroxyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, amido group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group, alkoxycarbonylamino group and Rx(Ry)N group, wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group;

a substituent of an alkyl group of R¹ is respectively and independently a group selected from a hydroxyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group,

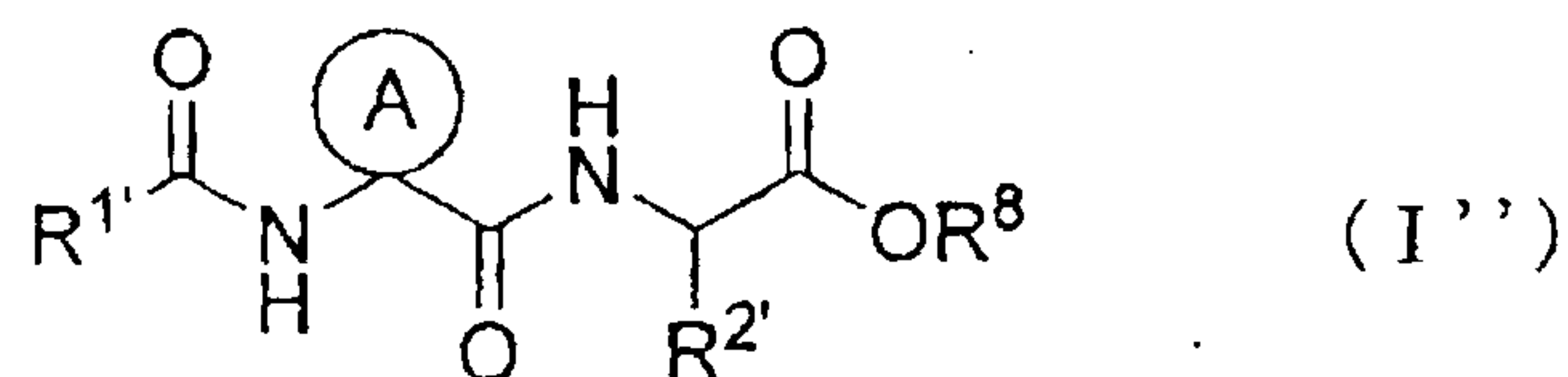
aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group and Rx(Ry)N group, wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group, provided that Rx and Ry are not simultaneously hydrogen atoms;

a substituent of a heterocyclic group of R¹ is a group selected from a hydroxyl group, alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, aryloxy group, arylthio group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group and Rx(Ry)N group, wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group; and,

a substituent of an aromatic hydrocarbon group or heterocyclic group of Ra and Rb is respectively and independently a group selected from a hydroxyl group, alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido

group, sulfonamido group, mercapto group,
 alkoxycarbonylamino group and Rx(Ry)N group, wherein, Rx and
 Ry respectively and independently represent a hydrogen
 atom, alkyl group, alkenyl group, alkynyl group, aromatic
 5 hydrocarbon group or heterocyclic group, provided that R⁴
 and R⁸ are not respectively t-butyl groups, and R^{2'}, R⁴ and
 R⁸ are not simultaneously benzyl groups provided that the
 compounds, Z-Ac7c-L-Ala-OMe, Z-L-Ala-Ac7c-L-Ala-OMe, Z-
 (Ac7c)₂-L-Ala-OMe, Z-Ac7c-L-Val-OMe and Boc-L-Leu-Ac7c-L-
 10 Val-OMe, wherein Z represents benzyloxycarbonyl, Ac7c
 represents 1-aminocycloheptane-1-carbonyl and Boc
 represents t-butoxycarbonyl, are not encompassed herein.

5. A cycloalkylcarbonylamino acid ester derivative
 15 represented by formula (I'') or a pharmaceutically
 acceptable salt thereof:



wherein, R^{1'} represents a substituted or unsubstituted
 alkyl group, substituted or unsubstituted alkenyl group,
 20 substituted or unsubstituted alkynyl group, substituted or
 unsubstituted aromatic hydrocarbon group, substituted or
 unsubstituted heterocyclic group, group represented by R⁵S-
 or group represented by R⁶(R⁷)N-, wherein R⁵, R⁶ and R⁷
 respectively and independently represent a substituted or
 25 unsubstituted alkyl group, substituted or unsubstituted
 alkenyl group, substituted or unsubstituted alkynyl group,
 substituted or unsubstituted aromatic hydrocarbon group or
 substituted or unsubstituted heterocyclic group, or R⁶ and
 R⁷ may together form a ring); R^{2'} represents an alkyl group
 30 represented by Ra(Rb)CH-, wherein, Ra and Rb respectively

and independently represent a hydrogen atom, substituted or unsubstituted alkyl group, substituted or unsubstituted aromatic hydrocarbon group, or substituted or unsubstituted heterocyclic group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heterocyclic group; ring A represents a cyclic alkylidene group having 6 or 7 carbon atoms; and, R⁸ represents a substituted or unsubstituted alkyl group having 1 to 6 carbon atoms;

a substituent of an alkenyl group, alkynyl group or aromatic hydrocarbon group of R^{1'}, and a substituent of an alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group of R^{2'}, R⁵, R⁶ and R⁷ are respectively and independently a group selected from a hydroxyl group, alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, amido group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group, alkoxycarbonylamino group and Rx(Ry)N group, wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group;

a substituent of an alkyl group of R⁵, R⁶, R⁷, R⁸, Ra and Rb is respectively and independently a group selected from a hydroxyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group,

alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, amido group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group, alkoxycarbonylamino group and Rx(Ry)N group, wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group;

a substituent of an alkyl group of R^{1'} is a group selected from a hydroxyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, alkoxycarbonyl group, aryloxy group, arylthio group, acyl group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group, acyloxy group, azido group, sulfonamido group, mercapto group and Rx(Ry)N group, wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group, provided that Rx and Ry are not simultaneously hydrogen atoms; and,

a substituent of a heterocyclic group of R^{1'} is a group selected from a hydroxyl group, alkyl group, alkenyl group, alkynyl group, halogen atom, aromatic hydrocarbon group, heterocyclic group, alkoxy group, guanidino group, alkylthio group, aryloxy group, arylthio group, sulfonyl group, heterocyclyloxy group, heterocyclylthio group, ureido group, carboxyl group, carbamoyl group, oxo group, sulfamoyl group, sulfo group, cyano group, nitro group,

acyloxy group, azido group, sulfonamido group, mercapto group and Rx(Ry)N group wherein, Rx and Ry respectively and independently represent a hydrogen atom, alkyl group, alkenyl group, alkynyl group, aromatic hydrocarbon group or heterocyclic group provided that the compounds, Z-Ac7c-L-Ala-OMe, Z-L-Ala-Ac7c-L-Ala-OMe, Z-(Ac7c)₂-L-Ala-OMe, Z-Ac7c-L-Val-OMe and Boc-L-Leu-Ac7c-L-Val-OMe, wherein Z represents benzyloxycarbonyl, Ac7c represents 1-aminocycloheptane-1-carbonyl and Boc represents t-butoxycarbonyl, are not encompassed herein.

6. The cycloalkylcarbonylamino acid ester derivative or pharmaceutically acceptable salt thereof according to claim 4 or 5, wherein in the formula (I') as defined in claim 4 or (I'') as defined in claim 5, the alkyl group in the groups represented by R¹ or R^{1'}, R⁴, R⁵, R⁶, R⁷, Ra, Rb, Rx and Ry is a linear, branched or cyclic alkyl group having 1 to 12 carbon atoms, the aromatic hydrocarbon group in the groups represented by R¹ or R^{1'}, R^{2'}, R⁴, R⁵, R⁶, R⁷, Ra, Rb, Rx and Ry is a monocyclic or polycyclic aromatic hydrocarbon group having 6 to 18 carbon atoms, the heterocyclic group is a heterocyclic group of a 3- to 7-membered ring containing at least one nitrogen atom, oxygen atom or sulfur atom as a ring-composing atom, the alkenyl group in the groups represented by R¹ or R^{1'}, R^{2'}, R⁴, R⁵, R⁶, R⁷, Rx and Ry is a linear, branched or cyclic alkenyl group having 2 to 12 carbon atoms, and the alkynyl group is a linear, branched or cyclic alkynyl group having 2 to 12 carbon atoms.

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7. The cycloalkylcarbonylamino acid ester derivative or pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, wherein in the formula (I), (I') or

(I'') above, R^2 or $R^{2'}$ is a substituted or unsubstituted alkyl group, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heterocyclic group.

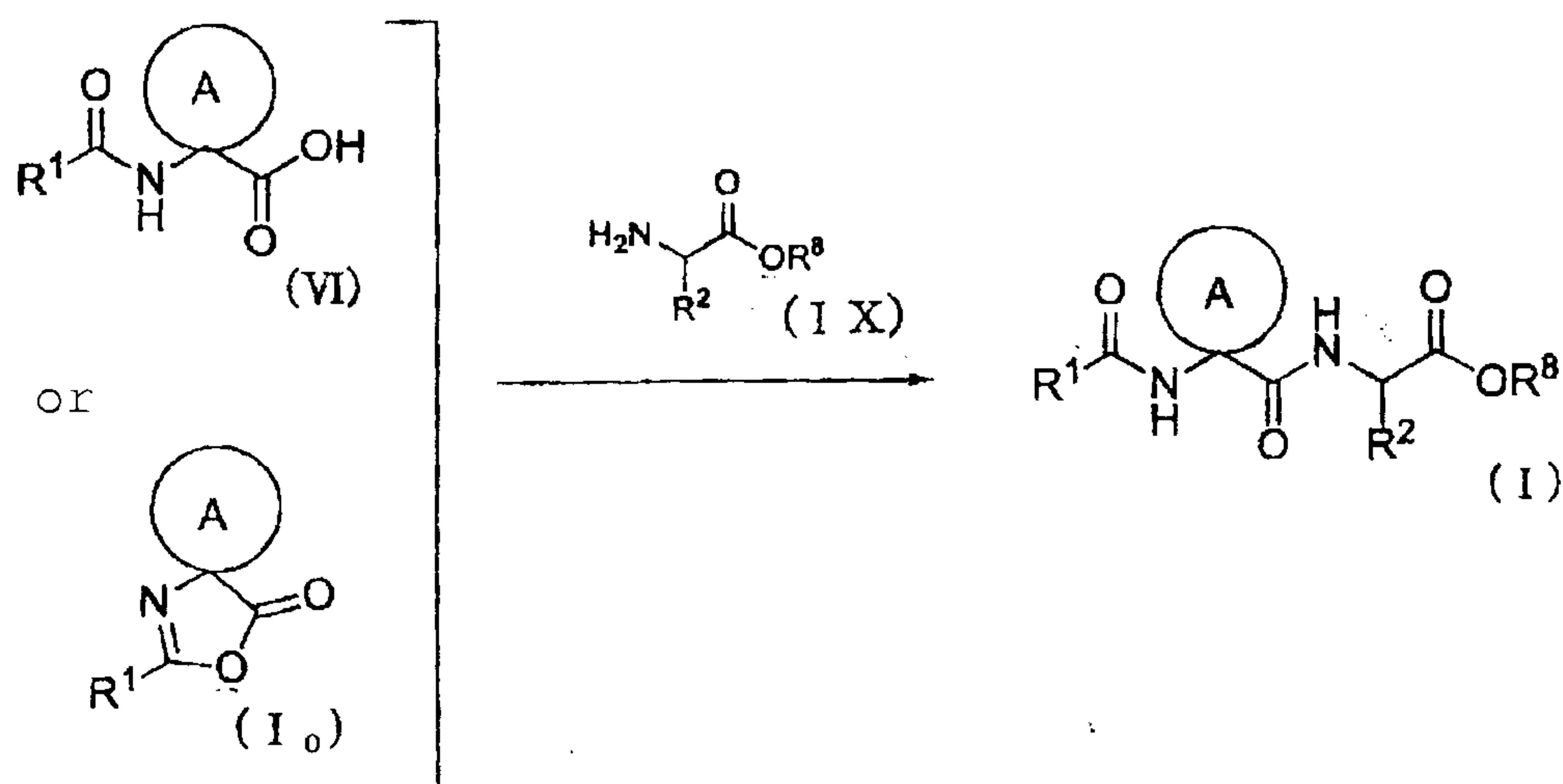
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8. The cycloalkylcarbonylamino acid ester derivative or pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, wherein in the formula (I), (I') or (I''), the substituted or unsubstituted alkyl group represented by R^2 or $R^{2'}$, alkyl group represented by $R^a(R^b)CH-$, wherein R^a and R^b respectively and independently represent a hydrogen atom, substituted or unsubstituted alkyl group, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heterocyclic group, substituted or unsubstituted alkenyl group, substituted or unsubstituted alkynyl group, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heterocyclic group is a group derived from an α -amino acid, and said α -amino acid is an α -amino acid selected from alanine, arginine, asparagine, aspartic acid, isoasparagine, γ -carboxyglutamic acid, cysteine, cystine, glutamine, glutamic acid, histidine, homoarginine, homocysteine, homocystine, homoserine, homophenylalanine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, phenylalanine, phenylglycine, serine, threonine, tryptophan, tyrosine, valine, 3,4-dihydroxyphenylalanine, allylglycine, neopentylglycine, allothreonine, homolysine, naphthylalanine, α -aminoadipic acid, thienylglycine, pyridylalanine and cyclohexylalanine.

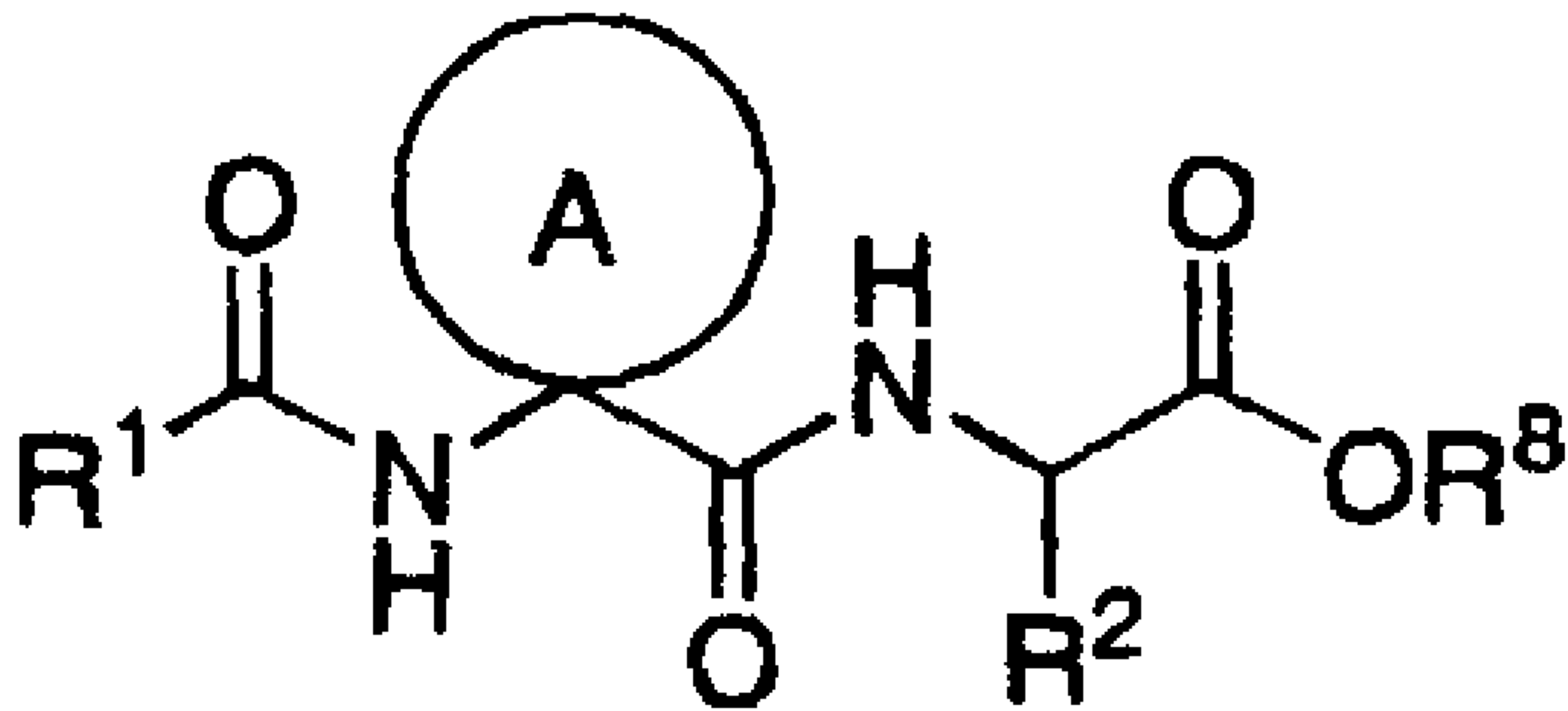
9. The cycloalkylcarbonylamino acid ester derivative or

pharmaceutically acceptable salt thereof according to any one of claims 1 to 8, wherein in the formula (I), (I') or (I'') above, R^1 or $R^{1'}$ represents a 3- to 7-membered substituted or unsubstituted heterocyclic group containing at least one nitrogen atom, oxygen atom or sulfur atom as a ring-composing atom, or a substituted aromatic hydrocarbon group, R^2 or $R^{2'}$ represents an alkyl group having 1 to 4 carbon atoms, R^8 represents an alkyl group having 1 to 6 carbon atoms, and ring A represents a cyclohexylidene group.

10. A process for producing a cycloalkylcarbonylamino acid ester derivative represented by formula (I) comprising: reacting a carboxylic acid derivative represented by the following formula (VI) or an oxazolone derivative represented by the following formula (I₀) with an amino acid ester derivative represented by the following formula (IX):



20 wherein, R^1 , R^2 , R^8 and ring A are the same as previously defined in claim 1.



(I)