

4,1-Benzoxazepin derivatives and their use

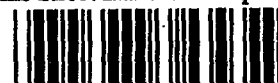
FIELD OF THE INVENTION

5 This invention relates to 4,1-benzoxazepin-2-one derivatives or salts which are useful for inhibiting squalene synthetase and fungal growth, and their use.

BACKGROUND OF THE INVENTION

10 Hypercholesteremia, high blood pressure and smoking are known as three major dangerous factors of causing ischemic diseases. Adequate control of cholesterol concentration in blood is remarkably important for the prophylaxis or therapy of, besides ischemic diseases, coronary sclerosis.

15 As pharmaceutical compositions for lowering cholesterol in blood, attention has been drawn to those for controlling the biosynthesis of cholesterol, besides those of inhibiting its absorption by binding bile acid including, among others, cholestyramine, 20 colestipol (disclosed in, for example, USP 4027009), and those of suppressing the intestinal absorption of cholesterol by inhibiting acyl coenzyme A cholesterol acyl transferase (ACAT) including melinamide (disclosed in French Patent No.1476569). As pharmaceutical 25 preparations for controlling the biosynthesis of cholesterol, lovastatin (disclosed in USP 4231938), simvastatin (disclosed in USP 4444784), pravastatin (USP 4346227), etc., which are capable of inhibiting especially 3-hydroxy-3-methyl glutaryl coenzyme (HMG-CoA) reductase, are provided for medicinal use. 30 However, when HMG-CoA reductase is inhibited, not only the biosynthesis of cholesterol but the biosynthesis of some other components such ubiquinone, dolichol and heme A, which are necessary for the living body, is 35 also inhibited, so that occurrences of undesirable side effects to be caused thereby are feared.



Squalene synthetase is the enzyme involved in the committed step of the de novo cholesterol biosynthetic pathway. This enzyme catalyzes the reductive dimerization of two molecules of farnesyl pyrophosphate to form squalene.

On the other hand, the compounds expected as inhibitors of cholesterol biosynthesis by inhibiting squalene synthetase are disclosed in JPA H1(1989)-213288, JPA H2(1990)-101088, JPA H2(1990)-235820, JPA H2(1990)-235821, JPA H3(1991)-20226, JPA H3(1991)-68591, JPA H3(1991)-48288, USP 5,019,390, Journal of Medicinal Chemistry, 51 (10), p.1869-1871 (1988), USP 5,135,935 and WO 9215579.

Also, the compounds expected as inhibitors of fungal growth by inhibiting squalene synthetase are disclosed in JPA H4 (1992)-279589, EP 475706-A, EP 494622-A and EP 503520-A.

Among 4,1-benzoxazepine derivatives, in 4,1-benzoxazepin-2-one derivatives in which 2-position is substituted with ketone group, those in which one of the hydrogen atoms at 3-position is replaced with a different substituent, are disclosed in JPA S57(1982)-345765 and Chem. Pharm. Bull., 34, 140 (1986).

Ubiquinone, dolichol and heme A have been known as being synthesized from farnesyl pyrophosphate along the cholesterol biosynthesis pathway. Therefore, for avoiding occurrence of side effects due to loss of these substances, it is desirable to inhibit enzymes subsequent to farnesyl pyrophosphate, especially squalene synthetase, in the cholesterol biosynthetic pathway.

SUMMARY OF THE INVENTION

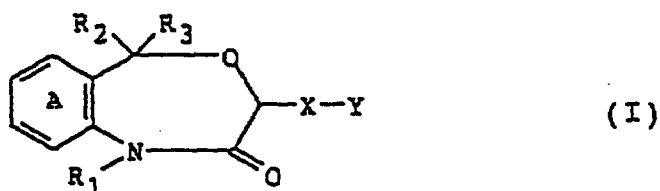
Through intensive investigations from the above viewpoint, the present inventors found that 4,1-benzoxazepin-2-one derivatives exhibit excellent squalene synthetase inhibitory action and antifungal



action, and developed the present invention.

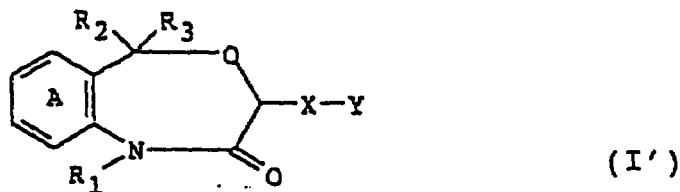
Accordingly, the present invention provides:

(1) 4,1-Benzoxazepin-2-one derivatives represented by the formula (I):



10 , wherein R₁ stands for hydrogen atom or an optionally substituted hydrocarbon group; R₂ and R₃ independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic
15 heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally
20 substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; provided that, when X is methylene and R₁ is not an alkyl group having carbon atoms of more than 4, Y is
25 neither carboxyl group nor alkoxycarbonyl group; and the ring A may optionally be substituted, or salts thereof,

(2) 4,1-Benzoxazepin-2-one derivatives represented by the formula (I'):



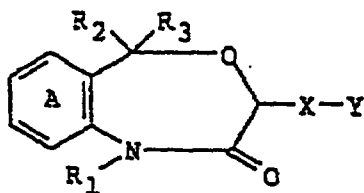
This Sheet Has Been Replaced



35 , wherein R¹ stands for hydrogen atom or an optionally

substituted hydrocarbon group; R_2 and R_3 independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; provided that, when X is methylene, Y is neither carboxyl group nor alkoxycarbonyl group; and the ring A may optionally be substituted, or salts thereof,

(3) a squalene synthetase inhibitor comprising as an active ingredient a 4,1-Benzoxazepin-2-one derivative represented by the formula (I''):



(I'')

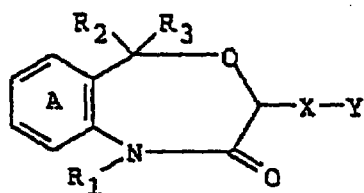
This Sheet Has Been Replaced



, wherein R^1 stands for hydrogen atom or an optionally substituted hydrocarbon group; R_2 and R_3 independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue

having hydrogen atom capable of being deprotonated;
and the ring A may optionally be substituted, or a salt thereof, and

(4) a fungal growth inhibitor comprising as an active ingredient a 4,1-Benzoxazepin-2-one derivative represented by the formula (I''):



, wherein R¹ stands for hydrogen atom or an optionally substituted hydrocarbon group; R₂ and R₃ independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; and the ring A may optionally be substituted, or a salt thereof.

Further, the present invention is to provide a method of producing the novel compounds represented by the formula (I) and (I') or salts thereof.

In the above-mentioned formulae (I), (I') and (I''), as the hydrocarbon group of "optionally substituted hydrocarbon group" shown by R₁, mention is made of aliphatic chain hydrocarbon groups, alicyclic hydrocarbon group and aryl group, among others, with preference given to aliphatic chain hydrocarbon groups.



As the aliphatic chain hydrocarbon group of said hydrocarbon group, mention is made of straight-chain or branched aliphatic hydrocarbon groups, for example, alkyl group, alkenyl group and alkynyl group, with
5 preference given to lower alkyl group, lower alkenyl group and lower alkynyl group. As the lower alkyl group, C_{1-7} lower alkyl groups are preferable, which are exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl,
10 neopentyl, tert-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylpropyl, 3,3-dimethylbutyl, 2-ethylbutyl and 1-ethylpropyl, with preference given to C_{2-5} alkyl groups, more preferably C_{4-5} alkyl groups. As the lower alkenyl
15 group, C_{2-6} lower alkenyl groups are preferable, which are exemplified by vinyl, allyl, 2-methylallyl isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 2-methyl-2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-
20 pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl. Among them, vinyl, allyl, isopropenyl, 2-methylallyl, 2-methyl-1-propenyl, 2-methyl-2-propenyl, and 3-methyl-2-butenyl are especially
25 preferable. As the lower alkynyl group, C_{2-6} lower alkynyl groups are preferable, which are exemplified by ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl
30 and 5-hexynyl. Among them, ethynyl, 1-propynyl and 2-propynyl are especially preferable.

As the alicyclic hydrocarbon group of the said hydrocarbon group, mention is made of saturated or unsaturated alicyclic hydrocarbon groups, which are
35 exemplified by cycloalkyl group, cycloalkenyl group or cycloalkadienyl group. As the cycloalkyl group, C_{3-9}



cycloalkyl groups are preferable, which are exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclononyl. Among them, C₃₋₆ cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl are especially preferable. Examples of the cycloalkenyl group include 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 1-cyclobuten-1-yl and 1-cyclopenten-1-yl. Examples of the cycloalkadienyl group include 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, and 2,5-cyclohexadien-1-yl.

As the aryl group of said hydrocarbon group, mention is made of monocyclic or condensed polycyclic aromatic hydrocarbon groups, which are exemplified by phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl. Among them, phenyl, 1-naphthyl and 2-naphthyl are especially preferable.

As the substituent of "optionally substituted hydrocarbon group" shown by R₁, mention is made of optionally substituted aryl groups, optionally substituted cycloalkyl groups or cycloalkenyl groups, optionally substituted heterocyclic groups, optionally substituted amino groups, optionally substituted hydroxyl groups, optionally substituted thiol groups and halogen atoms (e.g. fluorine, chlorine, bromine and iodine). Number of these optional substituents ranges from 1 to 5 (preferably 1 to 3). As the aryl group of said optionally substituted aryl group, mention is made of phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl. Among them, phenyl, 1-naphthyl and 2-naphthyl are preferable. As the substituent on said optionally substituted aryl group, mention is made of C₁₋₃ alkoxy groups (e.g. methoxy, ethoxy and propoxy), halogen atoms (e.g. fluorine, chlorine bromine and iodine) and C₁₋₃ alkyl groups (e.g. methyl, ethyl and propyl). Number of these optional substituents ranges



from 1 to 2. As the cycloalkyl group of said optionally substituted cycloalkyl group, mention is made of C₃₋₇ cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

5 Kinds and number of the substituents on said optionally substituted cycloalkyl group are the same as those mentioned for the substituents in the above-mentioned optionally substituted aryl groups. As the cycloalkenyl group of said optionally substituted cycloalkenyl
10 group, mention is made of C₃₋₆ cycloalkenyl groups including cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl. Kinds and number of the substituents on said optionally substituted cycloalkenyl group are the same as those mentioned for the substituents in the
15 above-mentioned optionally substituted aryl groups. As the heterocyclic group of said optionally substituted heterocyclic group, mention is made of an aromatic heterocyclic group and a saturated or unsaturated non-aromatic heterocyclic group (aliphatic heterocyclic
20 group) having at least one hetero atom selected from oxygen, sulfur and nitrogen, with preference given to an aromatic heterocyclic group. As said aromatic heterocyclic group, mention is made of aromatic monocyclic heterocyclic groups (e.g. furyl, thienyl,
25 pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl,
30 pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc.) and aromatic condensed heterocyclic groups (e.g. benzofuranyl, isobenzofuranyl, benzo[b] thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl,
35 isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl,





phthalazinyl, naphthylidiny, purinyl, pteridinyl,
carbazolyl, α -carbolinyl, β -carbolinyl, γ -carbolinyl,
acrydiny, phenoxazinyl, phenothiazinyl, phenazinyl,
phenoxthiny, thianthrenyl, phenanthridinyl,
5 phenanthrolinyl, indolidinyl, pyrrolo[1,2-
b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-
a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-
b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-
triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-
10 b]pyridazinyl, etc.), with preference given to furyl,
thienyl, pyridyl, pyrimidinyl, pyrazinyl, indolyl and
isoindolyl. As said non-aromatic heterocyclic group,
mention is made of, for example, oxiranyl, azetidiny,
oxetanyl, thiethanyl, pyrrolidinyl, tetrahydrofuryl,
15 thioranyl, piperidyl, tetrahydropyranyl, morpholinyl,
thiomorpholinyl, piperazinyl, etc. As the substituent
of said optionally substituted heterocyclic group,
mention is made of C_{1-3} alkyl groups (e.g. methyl, ethyl
and propyl). As the substituent of said optionally
20 substituted amino group, optionally substituted
hydroxyl group or optionally substituted thiol group,
mention is made of C_{1-3} alkyl groups (e.g. methyl, ethyl
and propyl). In the case where the hydrocarbon group
in the optionally substituted hydrocarbon group shown
25 by R_1 is an alicyclic hydrocarbon group or aryl group,
it may further have a C_{1-3} alkyl group (e.g. methyl,
ethyl and propyl).

In the above-mentioned formulae (I), (I') and
(I''), as the optionally substituted lower alkyl groups
30 shown by R_2 and R_3 , mention is made of C_{1-6} lower alkyl
groups (e.g. methyl, ethyl, n-propyl, isopropyl, butyl,
isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl,
neopentyl, hexyl and isohexyl), preferably C_{1-4} alkyl
groups such as methyl, ethyl, propyl, isopropyl, butyl
35 and t-butyl. As the substituent of said optionally
substituted lower alkyl group, mention is made of



halogen atoms (e.g. fluorine, chlorine, bromine and iodine), C_{1-4} lower alkoxy groups (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy), among others.

- 5 Substituents of "optionally substituted phenyl group" shown by R_2 and R_3 are independently exemplified by halogen atom (e.g. fluorine, chlorine, bromine or iodine), optionally substituted C_{1-4} lower alkyl groups (e.g. methyl, ethyl, propyl, isopropyl, butyl and t-
- 10 butyl), optionally substituted C_{1-4} lower alkoxy groups (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy), optionally substituted hydroxyl group, nitro group and cyano group, and "optionally substituted phenyl group" may have 1 to 3 of these substituents.
- 15 As the substituent of said optionally substituted lower (C_{1-4}) alkyl group or optionally substituted (C_{1-4}) alkoxy group, mention is made of, among others, halogen atoms (e.g. fluorine, chlorine, bromine, iodine), and 1 to 3 of them may be substituted on optional positions.
- 20 As the substituent of optionally substituted hydroxyl group, mention is made of, among others, lower (C_{1-4}) alkyl groups (e.g. methyl, ethyl, propyl, isopropyl, butyl and t-butyl), C_{3-6} cycloalkyl groups (e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl),
- 25 aryl groups (e.g. phenyl, 1-naphthyl and 2-naphthyl) and aralkyl groups (e.g. benzyl, phenethyl). Further, two adjoining substituents on the phenyl group may cooperate therewith to form a ring. Examples of such rings are the following formulae:

30



35

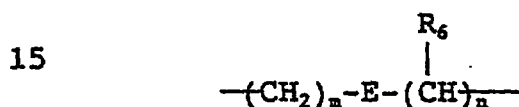
As the aromatic heterocyclic group of "optionally substituted aromatic heterocyclic group shown by R_2 and R_3 , mention is made of the same aromatic heterocyclic



groups as those specified for R_1 . Among them furyl, thienyl, imidazolyl, pyridyl, pyrimidinyl, pyrazinyl, indolyl and isoindolyl are preferred. As the substituent of said aromatic heterocyclic group, mention is made of lower C_{1-3} alkyl groups (e.g. methyl, ethyl and propyl), among others.

As the spacer having a chain length of 1 to 7 atoms shown by X, any one can be exemplified, so long as it is a divalent chain in which the number of atoms constituting the straight chain is 1 to 7, and it may have a side chain.

For example, said spacer includes one represented by the following formula:



wherein m and n denote independently 0, 1, 2 or 3; E stands for a bond or oxygen atom, sulfur atom, sulfoxide, sulfone,



---NHCO--- , ---CON--- or ---NHCONH--- . Herein, R_6 and R_7 independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted aralkyl group or an optionally substituted phenyl group. And, R_5 stands for hydrogen atom, a lower alkyl group, aralkyl group or acyl group.

As the alkyl groups of "optionally substituted lower alkyl groups" shown by R_6 and R_7 , mention is made of C_{1-6} straight-chain or branched lower alkyl groups (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, etc.). As the substituent of said optionally substituted lower alkyl group, mention is made of



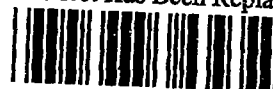
aromatic heterocyclic groups (e.g. furyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl, indolyl, imidazolyl and isoindolyl), optionally substituted amino groups, optionally substituted hydroxyl groups, optionally substituted thiol groups, optionally esterified carboxyl groups and halogen atoms (e.g. fluorine, chlorine, bromine and iodine). As the substituent of optionally substituted amino group, optionally substituted hydroxyl group or optionally substituted thiol group, mention is made of lower (C_{1-3}) alkyl groups (e.g. methyl, ethyl and propyl). As the optionally esterified carboxyl group, mention is made of methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, phenoxycarbonyl, 1-naphtoxycarbonyl, 2-naphtoxycarbonyl, with preference given to methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl.

As the aralkyl groups of "optionally substituted aralkyl groups shown by R_6 and R_7 , mention is made of benzyl, naphthylmethyl, phenylethyl, phenylpropyl, phenylbutyl, etc. As the substituent of said "optionally substituted aralkyl groups", mention is made of halogen atoms (e.g. fluorine, chlorine, bromine, iodine), C_{1-3} alkoxy groups (e.g. methoxy, ethoxy, propoxy, etc.), hydroxyl group, amino group, carboxyl group, sulfhydryl, etc.

As the substituent of the optionally substituted phenyl group shown by R_6 and R_7 , mention is made of halogen atoms (e.g. fluorine, chlorine, bromine and iodine), C_{1-3} alkoxy groups (e.g. methoxy, ethoxy, propoxy, etc.) and C_{1-3} alkyl groups (e.g. methyl, ethyl, propyl, etc.).

R_6 may be different depending on the corresponding methylene chains.

And, examples of "lower alkyl group" and "aralkyl group" shown by R_3 include a C_{1-4} lower alkyl group (e.g. methyl, ethyl, propyl, butyl, t-butyl, etc.), a



C₇₋₁₅ aralkyl group (e.g. benzyl, phenethyl, phenylpropyl, phenylbutyl, naphthylmethyl, etc.).

As the acyl group shown by R₅, mention is made of lower alkanoyl groups (formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isoveleryl, pivaloyl and hexanoyl), lower alkenoyl groups (acryloyl, methacryloyl, crotonoyl and isocrotonoyl), cycloalkanecarbonyl (cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl and cyclohexanecarbonyl), lower alkanesulfonyl groups (mesyl, ethanesulfonyl and propanesulfonyl), aroyl groups (benzoyl, p-toluoyl, 1-naphthoyl and 2-naphthoyl), aryl lower alkanoyl groups (phenylacetyl, phenylpropionyl, hydroatropoyl and phenylbutyryl), aryl lower alkenoyl groups (cinnamoyl and atropoyl) and arenesulfonyl groups (benzenesulfonyl and p-toluenesulfonyl), among others.

Examples of optionally esterified carboxyl group shown by Y include lower alkoxycarbonyl groups (methoxycarbonyl, ethoxycarboxyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, sec-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl and tert-pentyloxycarbonyl) and aryloxycarbonyl groups (phenoxycarbonyl, 1-naphtoxycarbonyl and benzyloxycarbonyl).

Said lower alkoxycarbonyl groups may have 1 or more substituents at any possible positions. Examples of such substituents include optionally substituted hydroxyl groups, optionally esterified carboxyl groups, optionally substituted carbamoyl groups, optionally substituted phenyl groups, optionally substituted C₃₋₆ cycloalkyl groups (e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), lower C₁₋₃ alkenyl groups (e.g. vinyl, allyl, etc.) and 5-membered heterocyclic residue containing one to three of oxygen atom. As the



substituent of said optionally substituted hydroxyl group, mention is made of lower alkanoyl groups (e.g. pivaloyl, etc.) and optionally esterified carboxyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl and cyclohexyloxycarbonyl). As the substituent of said optionally esterified carboxyl group, mention is made of lower C_{1-4} alkoxy carbonyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl tert-butoxycarbonyl and sec-butoxycarbonyl). As the substituent of said optionally carbamoyl group, mention is made of lower C_{1-3} alkyl groups (e.g. methyl, ethyl and propyl), C_{3-6} cycloalkyl groups (e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), phenyl group, benzyl group and optionally esterified carboxyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl). As the substituents of said optionally substituted phenyl group or optionally substituted C_{3-6} cycloalkyl group, mention is made of lower C_{1-3} alkyl groups (e.g. methyl, ethyl and propyl) and lower C_{1-3} alkoxy groups (e.g. methoxy, ethoxy and propoxy). Said 5-membered heterocyclic residue may have 1 or more substituents at any possible positions. Examples of such substituents include lower C_{1-3} alkyl groups (e.g. methyl, ethyl and propyl) and oxo. Further, said heterocyclic group may cooperate with a benzen ring to form a fused ring.

Said aryloxycarbonyl group may have 1 or more substituents at any possible positions. Examples of such substituents include lower C_{1-3} alkyl groups (e.g. methyl, ethyl and propyl), lower C_{1-3} alkoxy groups (e.g. methoxy, ethoxy and propoxy) and optionally esterified carboxyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl).

Also, the optionally esterified carboxyl group



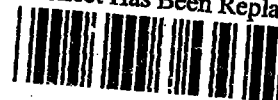
shown by Y may be thioesterified.

Example substituents of optionally substituted hydroxyl group shown by Y include lower C₁₋₄ alkyl groups (e.g. methyl, ethyl, propyl, isopropyl, butyl and t-butyl), C₃₋₆ cycloalkyl groups (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), aryl groups (e.g. phenyl, 1-naphthyl and 2-naphthyl) and aralkyl groups (e.g. benzyl and phenethyl).

Example substituents of optionally substituted amino group shown by Y include lower C₁₋₄ alkyl groups (e.g. methyl, ethyl, propyl, isopropyl, butyl and t-butyl), C₃₋₆ cycloalkyl groups (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), aryl groups (e.g. phenyl, 1-naphthyl and 2-naphthyl) and aralkyl groups (e.g. benzyl and phenethyl). Also, two substituents on a nitrogen atom may cooperate therewith to form a cyclic amino group. Examples of such cyclic amino groups include 1-azetidiny, 1-pyrrolidinyl, piperidino, morpholino, 1-piperazinyl, and 1-piperazinyl having a lower C₁₋₃ alkyl group (e.g. methyl, ethyl, propyl, etc.), an aralkyl group (e.g. benzyl, phenethyl, etc.), an aryl group (e.g. phenyl, etc.) or the like at the 4-position.

Example substituents of optionally substituted phenyl group shown by Y include optionally substituted lower C₁₋₄ alkyl groups (e.g. methyl, ethyl, propyl, isopropyl, butyl and t-butyl), lower C₁₋₄ alkoxy groups (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy), optionally esterified carboxyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl and sec-butoxycarbonyl), optionally substituted phenyl groups, optionally substituted amino groups and a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated.

As the substituent of said optionally lower C₁₋₄ alkyl



group or said optionally substituted phenyl group,
mention is made of optionally esterified carboxyl
groups (e.g. methoxycarbonyl, ethoxycarbonyl,
propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl,
5 tert-butoxycarbonyl and sec-butoxycarbonyl). As the
substituent of said optionally substituted amino group,
mention is made of lower C₁₋₃ alkyl groups (e.g. methyl,
ethyl and propyl). Said N-containing heterocyclic
residue includes tetrazol-5-yl, 2,5-dihydro-5-oxo-1,2,4-
10 oxadiazol-3-yl, 2,5-dihydro-5-oxo-1,2,4-thiadiazol-3-
yl.

Example substituents of optionally substituted
carbamoy group shown by Y include lower C₁₋₄ alkyl
groups (e.g. methyl, ethyl, propyl, isopropyl, butyl
15 and t-butyl), C₃₋₆ cycloalkyl groups (cyclopropyl,
cyclobutyl, cyclopentyl and cyclohexyl), aryl groups
(e.g. phenyl, 1-naphthyl and 2-naphthyl) and aralkyl
groups (e.g. benzyl and phenethyl). Also, two
substituents on a nitrogen atom may cooperate therewith
20 to form a cyclic amino group. Examples of such cyclic
amino groups include 1-azetidiny, 1-pyrrolidinyl,
piperidino, morpholino, 1-piperazinyl, and 1-
piperazinyl having a lower C₁₋₃ alkyl group (e.g.
methyl, ethyl, propyl, etc.), an aralkyl group (e.g.
25 benzyl, phenethyl, etc.), an aryl group (e.g. phenyl,
etc.) optionally substituted with halogen (e.g.
fluorine, chlorine, bromine, iodine) or the like at the
4-position. Further, said piperidino may cooperate
with a benzene ring to form a fused ring.

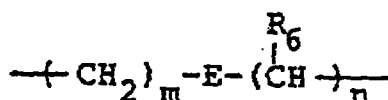
30 Examples of N-containing heterocyclic residue
having hydrogen atom capable of being protonated shown
by Y include tetrazol-5-yl, 2,5-dihydro-5-oxo-1,2,4-
oxadiazol-3-yl, 2,5-dihydro-5-oxo-1,2,4-thiadiazol-3-
yl.

35 As the substituent of ring A, mention is made of
halogen atoms (e.g. fluorine, chlorine, bromine,



iodine), C₁₋₄ optionally substituted lower alkyl groups (e.g. methyl, ethyl, propyl, butyl and tert-butyl), C₁₋₄ optionally substituted lower alkoxy groups (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy), nitro group and cyano group. The ring A may have 1 to 3, preferably one or two, of these substituents. And, these substituents may form a ring with each of the adjacent substituents. As the substituent of said optionally substituted lower alkyl group or optionally substituted lower alkoxy group, mention is made of halogen atoms (e.g. fluorine, chlorine, bromine, iodine), and 1 to 3 of these halogen atoms may be substituted on an optional position.

And, when X is shown by the formula



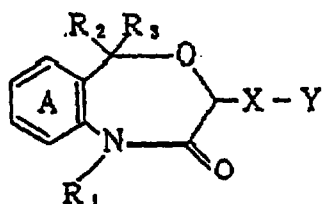
, wherein symbols are of the same meaning as defined above, E is preferably a bond or -CONH-. When E is -CONH-, preferably m=1, n=1 or m=2, n=1, especially m=1, n=1. In this case, R₆ is preferably hydrogen atom benzyl and 3-indolyl methyl, especially hydrogen atom and 3-indolyl methyl. When E is -CONH-, Y is preferably carboxyl group and esterified carboxyl group, especially carboxyl group.

Further, preferable examples of substituents of the ring A include no substituent, lower alkoxy or a halogen atom, and methoxy or chlorine atom is especially preferable.

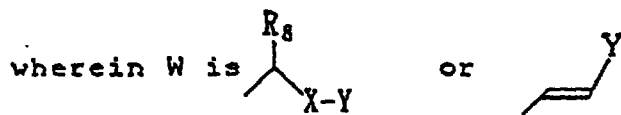
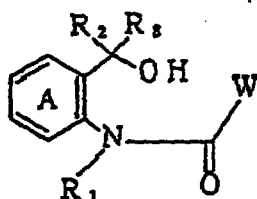
As salts of the compound (I), (I') or (I''), mention is made of pharmacologically acceptable salts including inorganic salts such as hydrochloride, hydrobromide, sulfate, nitrate, phosphate, etc., organic acid salts such as acetate, tartrate, citrate, fumarate, maleate, toluenesulfonate, methanesulfonate, etc., metal salts such as sodium salt, potassium salt,

calcium salt, aluminium salt, etc. and basic salts such as triethylamine salt, guanidine salt, ammonium salt, hydrazine salt, quinine salt, cinchonine salt, etc.

Further, the present invention provides a method of producing a compound represented by the formula (I) or the formula (I'):



wherein each of the symbols is of the same meaning as defined above or a pharmaceutically acceptable salt thereof, by subjecting a compound represented by the following formula:



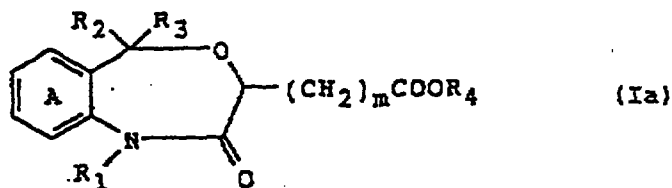
wherein R₃ is halogen (e.g. fluorine, chlorine, bromine and iodine) or -OSO₂CH₃ or other symbols are of the same meaning as defined above, to a cyclization reaction.

This Sheet Has Been Replaced



Methods of producing compounds of this invention are described below:

Among the compounds of formula (I) and (I'), compounds represented by the formula (Ia)



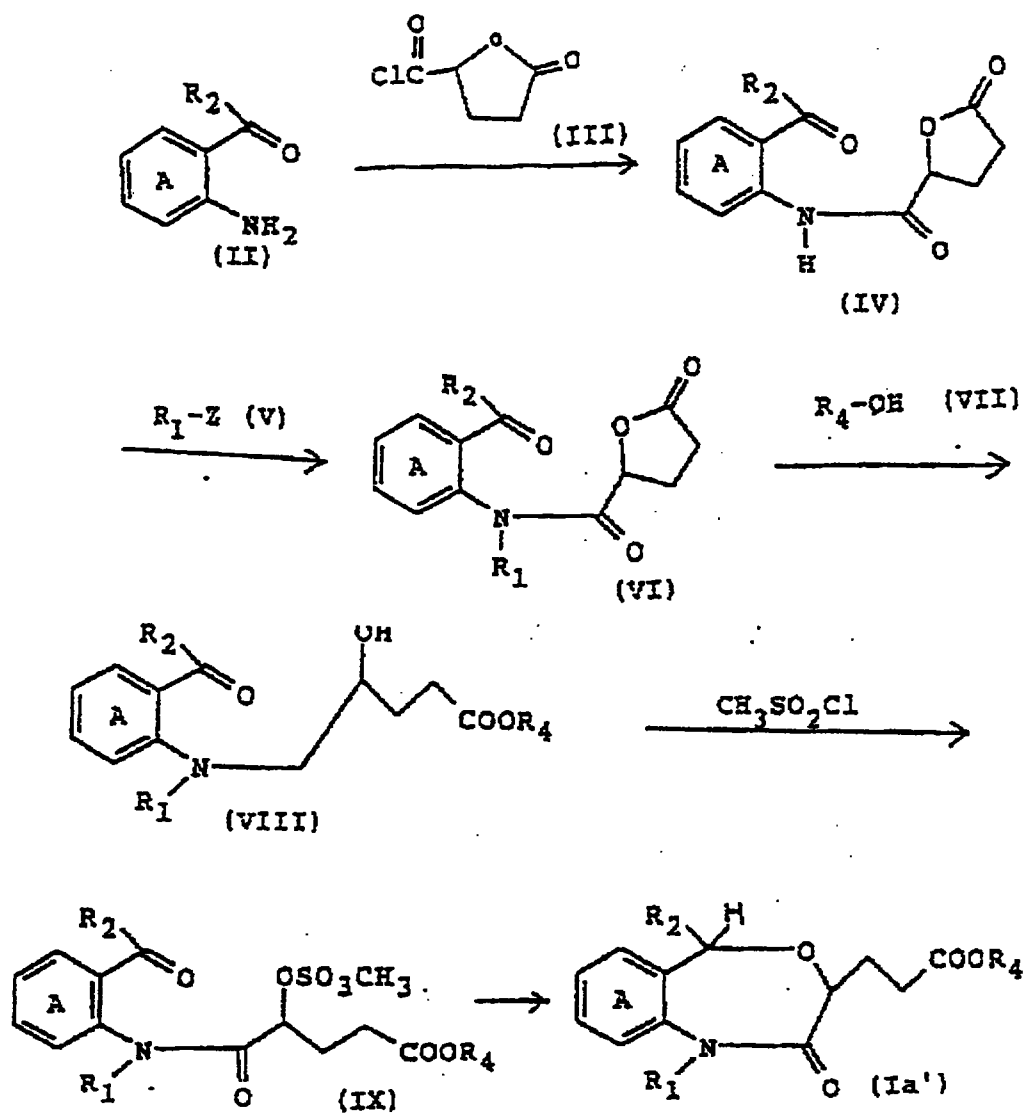
, wherein R_4 stands for a C_{1-8} alkyl group or aralkyl group, and other symbols are of the same meaning as defined above, can be produced by the following methods.

2-aminobenzophenones as the starting material can be synthesized by, or in accordance with, the method described in D.A. Walsh, Synthesis, 677 (1980) or the method cited in said reference.

This Sheet Has Been Replaced



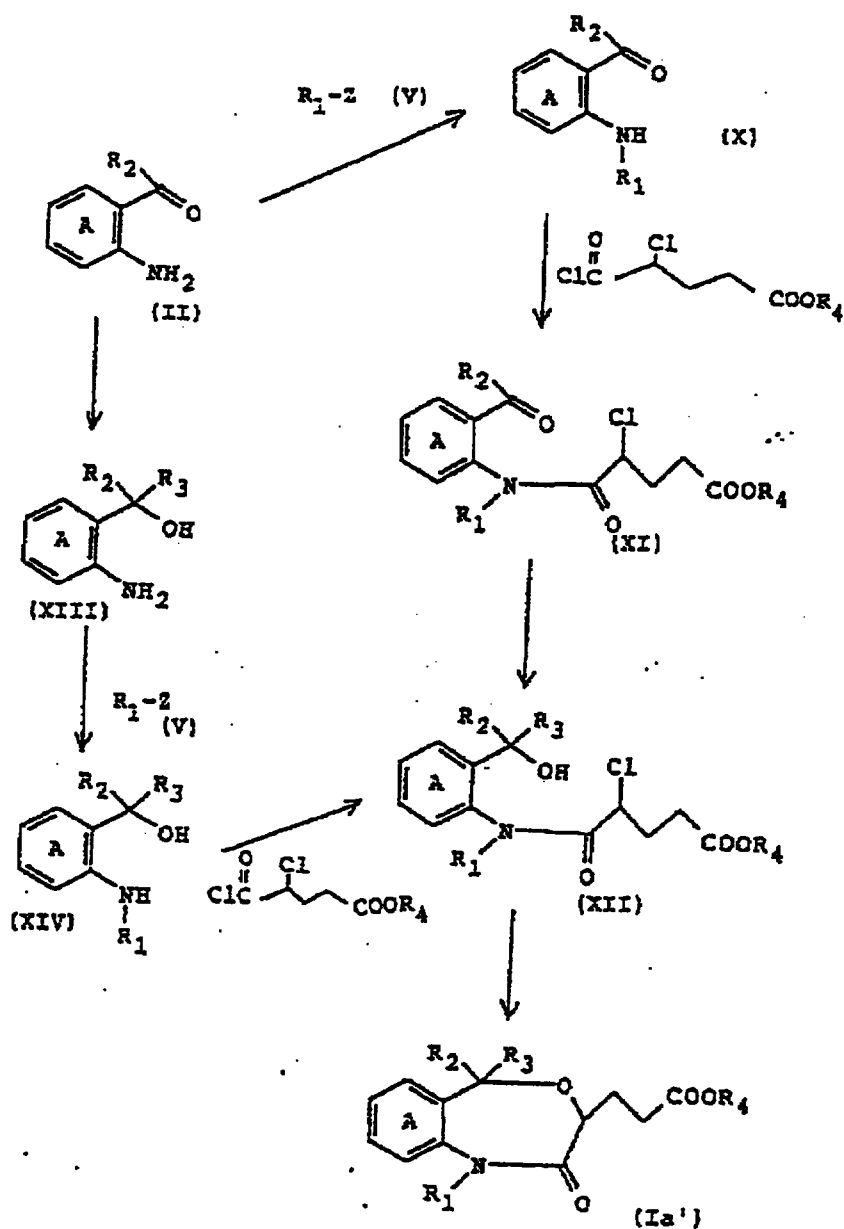
[Method A]



This Sheet Has Been Replaced



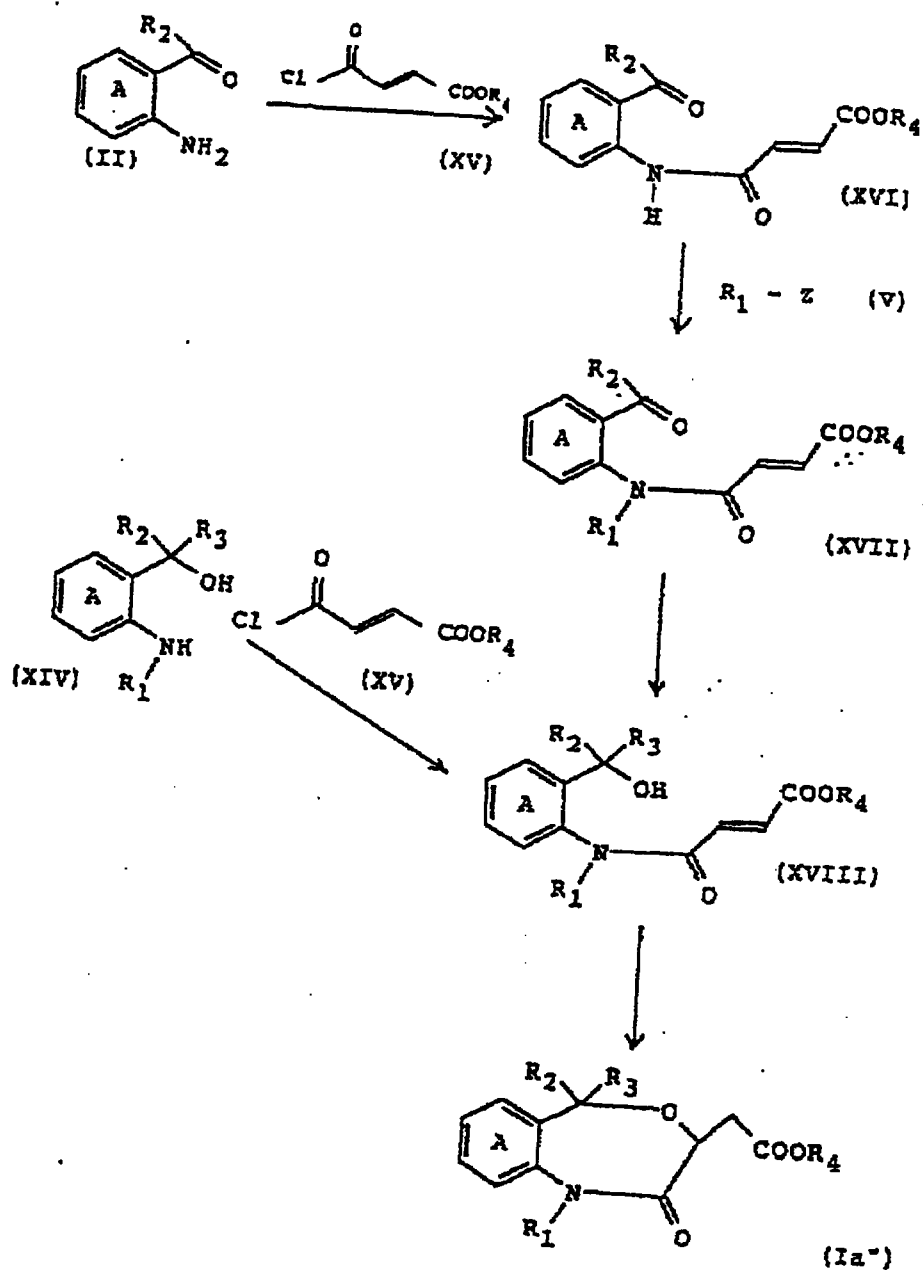
[Method B]



This Sheet Has Been Replaced



[Method C]



This Sheet Has Been Replaced





, wherein Z stands for a halogen atom, and other symbols are of the same meaning as defined above.

The reactions from the formula (II) to the formula (IV) and from the formula (VIII) to the formula (IX) in the above-mentioned [Method A] or those from the formula (X) to the formula (XI) and from the formula (XIV) to the formula (XII) in the above-mentioned [Method B] can be carried out by utilizing a per se known acylation reaction. For example, the acylation reaction of this invention can be conducted in a solvent exemplified by an ether-type solvent such as diethyl ether, tetrahydrofuran, dioxane, etc., a halogen-type solvent such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride, etc., a hydrocarbon-type solvent such as benzene, toluene, hexane, heptane, etc., dimethylformamide, dimethyl sulfoxide, etc., and, depending on necessity, in the presence of water and a base (e.g. an organic base such as 4-dimethylaminopyridine, triethylamine, triethylenediamine, tetramethylethylenediamine, etc. an inorganic base such as sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, etc, sodium hydride, potassium hydride), among others. Relative to one mole of a compound represented by the formulae (II), (VIII), (X) and (XIV), acid chloride and methanesulfonyl chloride by the formula (III) and ester of 4-chloroformyl butyric acid are usually employed in an amount of 1 to 10 mol., preferably 1 to 3 mol. And, the reaction time usually ranges from about 1 to 48 hours, preferably from about 5 to 10 hours. The reaction temperature ranges from -50 to 100°C, preferably from about 0 to 50°C.

And, the reaction from the formula (IV) to the formula (VI) in [Method A] and the reactions from the formula (II) to the formula (X) and from the formula

(XIII) to the formula (XIV) in [Method B] can be carried out in an ether type solvent such as diethyl ether, tetrahydrofuran, dioxane etc., a hydrocarbon type solvent such as benzene, toluene, hexane, heptane etc., an alcohol type solvent such as methanol, ethanol, propanol, butanol etc., acetone or dimethylformamide, and, depending on necessity, in the presence of a base (e.g. sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, sodium hydride, potassium hydride or the like). Relative to one mole of a compound represented by the formula (II), the formula (IV) or the formula (XIII), a compound represented by the formula (V) is employed usually in an amount ranging from 1 to 10 mol., preferably about 1 to 2 mol. The reaction temperature ranges from 0 to 100°C, preferably from about 20 to 50°C. The reaction time ranges usually from 1 to 24 hours, preferably about 3 to 10 hours.

And, the reduction reaction of carbonyl group from the formula (IX) to the formula (Ia') in [Method A], from the formula (II) to the formula (XIII) and from the formula (XI) to the formula (XII) in [Method B] can be conducted in a protonic solvent (e.g. methanol, ethanol, propanol, butanol, etc.) or a non-protonic solvent (e.g. ethyl ether, tetrahydrofuran, dioxane, etc.) in the presence of a metal hydrogen complex (e.g. lithium aluminum hydride, sodium aluminum hydride, sodium triethoxyaluminum hydride, sodium borohydride, etc.). Relative to one each mol. of compounds shown by the formula (IX), the formula (II) and the formula (XI), such a metal hydrogen complex as mentioned above is employed in an amount, usually ranging from 0.3 to 5 mol. equivalents, preferable from 0.5 to 2 mol. equivalents. The reaction temperature ranges from -20 to 100°C, preferably from 20 to 50°C.



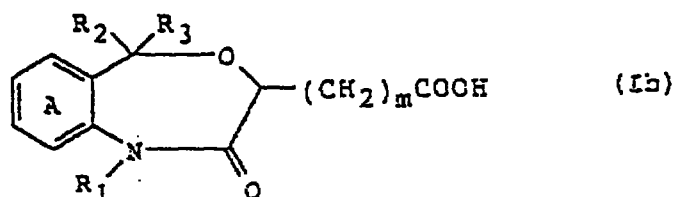
The cyclization reaction to the formula (Ia') from the formula (XII) in [Method B] can be carried out in a solvent, for example, an ether type solvent such as diethyl ether, tetrahydrofuran, dioxane, etc., a hydrocarbon type solvent such as benzene, toluene, hexane, heptane, etc., an alcohol type solvent such as methanol, ethanol, propanol, butanol, etc., acetone, dimethylformamide or the like, in the presence of, depending on necessity, a base (e.g. sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, sodium hydride, potassium hydride, etc.). Relative to one mol. of a compound shown by the formula (XII), a base as exemplified above is employed in an amount usually ranging from 1 to 5 mol., preferable from about 1 to 2 mol. The reaction temperature ranges usually from -20 to 200°C, preferably from 20 to 100°C. The reaction time ranges usually from 1 to 20 hours, preferably from 2 to 5 hours.

The reaction from the formula (VI) to (VIII) in [Method A] can be conducted in an alcohol shown by the formula (VII), and, depending on necessity, in the presence of an inorganic acid such as nitric acid, hydrochloric acid, hydrobromic acid or sulfuric acid, or an organic acid such as toluenesulfonic acid or methanesulfonic acid, at temperatures ranging from -20 to 100°C, preferably from 20 to 50°C. The reaction time ranges from 10 to 100 hours, preferably from 10 to 48 hours.

The compound shown by the formula (Ia'') can be produced in accordance with a conventional method.

Among the compounds shown by the formula (I) and (I'), a compound represented by the formula (Ib)





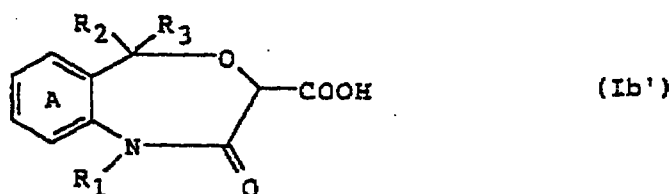
5

, wherein symbols are of the same meaning as defined above, can be produced by subjecting a compound shown by the formula (Ia) to hydrolysis, for example, by processing a compound shown by the formula (Ia) with an acid or a base. More specifically, a compound shown by the formula (Ia) is processed in an aqueous solution of a mineral acid (e.g. nitric acid, hydrochloric acid, hydrobromic acid, iodic acid, sulfuric acid or the like) or an alkali metal hydroxide (sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide) at temperatures ranging from 0 to 150°C, preferably from 20 to 50°C. The strength of the acid or the base ranges usually from 1 to 10 N, preferably from 4 to 10N. The reaction time varies with the reaction temperature, but usually ranges from 1 to 24 hours, preferably from about 2 to 10 hours.

15

20

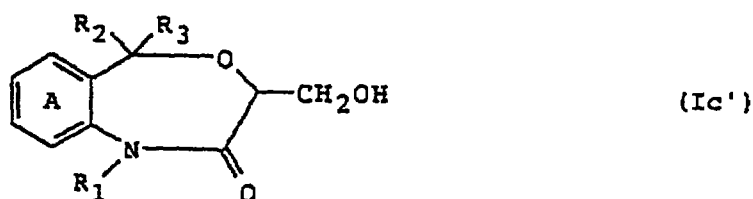
A compound shown by the formula (Ib')



25

, wherein symbols are of the same meaning as defined above, can be produced by subjecting a compound shown by the formula (Ic')

30

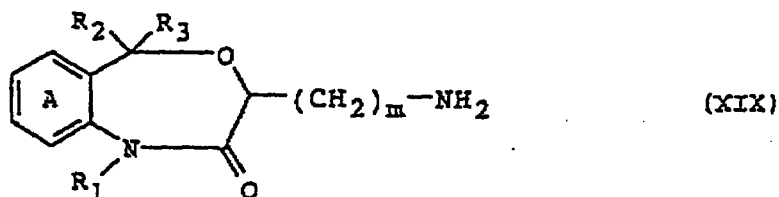


35



, wherein symbols are of the same meaning as defined above, to oxidation. The solvent then to be used may be any one so long as it does not hamper the reaction, which is exemplified by acetone, dioxane,
5 tetrahydrofuran, dichloromethane, dichloroethane or chloroform. As the oxidizing agent, permanganate, chromic acid or nickel peroxide can be used, for example. In this case, the oxidizing agent is used in an amount ranging from 0.5 to 20 mol. equivalents,
10 preferably from 1 to 3 mol. equivalents, relative to one mol. of the compound shown by the formula (Ic'), the reaction temperature ranges from 0 to 100°C, preferably from 15 to 50°C and the reaction time ranges from 0.5 to 5 hours, preferably from about 1 to 2
15 hours.

Among the compounds to be used as intermediates for synthesizing a compound of formula (I) or (I'), a compound shown by the formula (XIX)



25 , wherein symbols are of the same meaning as defined above, can be produced by allowing a compound shown by the formula (Ib) to react with diphenylphosphoryl azide in a solvent in the presence of a base, then by processing the resultant with an acid in a solvent.
30 The solvent to be used in the reaction between a compound shown by the formula (Ib) and diphenylphosphoryl azide may be any one, so long as it does not hamper the reaction, which is exemplified by dimethylformamide, a halogen-type solvent such as
35 dichloromethane, chloroform or dichloroethane and an ether-type solvent such as ether, tetrahydrofuran or

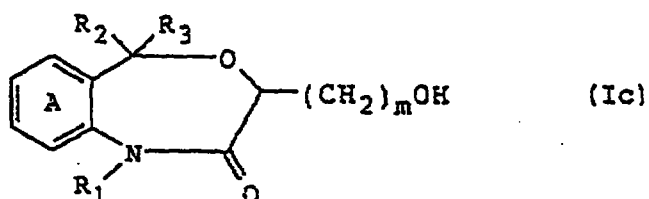




dioxane. Typical examples of the base to be employed include triethylamine, 4-dimethylaminopyridine, triethylenediamine and tetramethylethylenediamine. Relative to 1 mol. of a compound shown by the formula (Ib), 1 to 10 mol. equivalents, preferably about 1.5 to 3 mol. equivalents, of diphenylphosphoryl azide is employed. The reaction temperature ranges from -20 to 50°C, preferably from 0 to 20°C, and the reaction time ranges from 0.5 to 5 hours, preferably from about 1 to 2 hours.

In the case of processing the product obtained by the above-described reactions, the solvent to be used is exemplified by water, dioxane, dimethylformamide etc., and, as the acid to be employed, a mineral acid such as sulfuric acid, hydrochloric acid, nitric acid or hydrobromic acid can be exemplified. The reaction temperature ranges from 20 to 200°C, preferably from about 50 to 100°C, and the reaction time ranges from 0.5 to 5 hours, preferably from about 1 to 2 hours.

Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (Ic)



, wherein symbols are of the same meaning as defined above, can be produced by subjecting a compound shown by the formula (Ia) to reduction. More specifically, the compound shown by the formula (Ic) can be produced by processing the compound shown by the formula (Ia) with a metal hydride complex (e.g. lithium aluminum hydride, sodium aluminum hydride, sodium borohydride) in a protonic solvent (e.g. methanol, ethanol propanol, butanol etc.) or a non-protonic solvent (e.g. ethyl ether, tetrahydrofuran, dioxane etc.) Relative to one

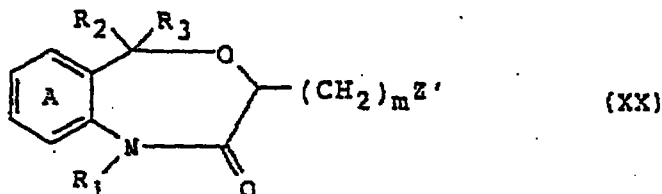
mol. of the compound shown by the formula (Ia), such a metal hydride complex compound is used in an amount ranging usually from 0.3 to 5 mol. equivalents, preferably from 0.5 to 2 mol. equivalents. The reaction temperature ranges from -20°C to 100°C, preferably from 0 to 20°C. The reaction time ranges from 0.5 to 10 hours, preferably from about 1 to 3 hours.

And, a compound shown by the formula (Ic) can be produced also by converting the amine portion of a compound shown by the formula (XIX) into hydroxyl group. For example, a compound of the formula (Ic) can be produced by adding sodium nitrite to a compound of the formula (XIX) in a solvent in the presence of an acid then by processing the resultant azide compound in a solvent in the presence of a base. In the method of azidation, for example, 0.5 to 3, preferably 1 to 1.5, mol. equivalents of sodium nitrite, is employed relative to 1 mol. of a compound of (XIX). As the acid, any one can be employed so long as it does not hamper the reaction, typically exemplified by acetic acid and sulfuric acid. The reaction temperature ranges from -20 to 20°C, preferably 0 to 5°C, and the reaction time ranges from 5 to 60 minutes, preferably about 10 to 30 minutes. The method of converting the azide of thus-obtained azide compound into hydroxyl group comprises, for example, use of, as the base, for example, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide or the like in water or an aqueous organic solvent (e.g. an alcohol-type solvent such as methanol, ethanol, propanol, butanol or the like, an ether-type solvent such as tetrahydrofuran, dioxane or the like, dimethylformamide, etc.). The reaction temperature ranges from 20 to 200°C, preferably from 50 to 100°C,



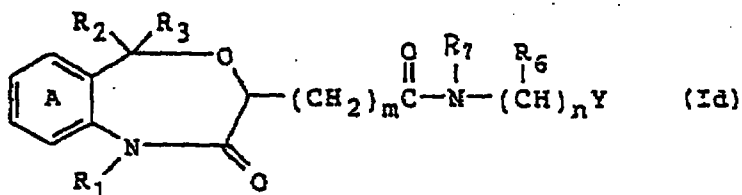
and the reaction time ranges from 5 minutes to 2 hours, preferably from about 15 to 30 minutes.

The compound shown by the formula (XX)

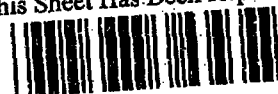


10 , wherein Z' stands for halogen (chlorine, bromine, iodine) and other symbols are of the same meaning as defined above, which is an intermediate for synthesizing the compound of the formula (I), can be produced by, like the method employed in the case of producing the compound (Ic) from the compound (XIX),
15 subjecting a compound shown by the formula (XIX) to diazotization with sodium nitrite in hydrochloric acid, hydrobromic acid or hydroiodic acid, then by heating thus diazotized compound. The reaction temperature
20 ranges from 20 to 200°C, preferably from 50 to 100°C, and the reaction time ranges from 5 minutes to 2 hours, preferably from about 15 to 30 minutes.

Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (Id)



30 , wherein Y' stands for, among the definitions given to Y as above, esterified carboxyl group and hydroxyl group, and other symbols are of the same meaning as defined above, can be produced by subjecting a compound shown by the formula (Ib) to condensation with a
35 compound represented by the formula (XXI)



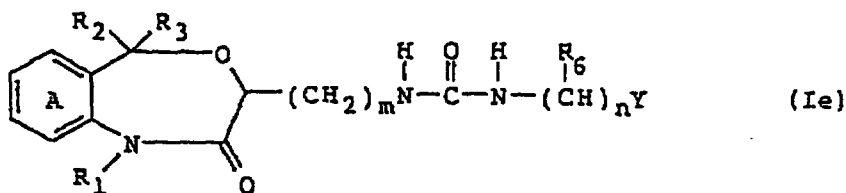


, wherein symbols are of the same meaning as defined
5 above, more specifically, the compound (Ib) and the
compound (XXI) are subjected to condensation in a
solvent by using a condensing agent, and, upon
necessity, in the presence of a base. The solvents to
be employed are exemplified by hydrocarbon-type
10 solvents such as benzene, toluene, hexane, heptane
etc., halogen-type solvents such as dichloromethane,
dichloroethane, chloroform carbon tetrachloride etc.,
ether-type solvents such as ethyl ether,
tetrahydrofuran, dioxane, etc., acetonitrile,
15 dimethylformamide, etc. As the base, use is made of,
among others, triethylamine, 4-dimethyl aminopyridine,
triethylenediamine and tetramethyl ethylenediamine. As
condensing agents, mention is made of those to be
employed for peptide synthesis, which are exemplified
20 by, among others, cyclohexyl carbodiimide, diethyl
cyanophosphate and 1-ethyl-3-(3-
dimethylaminopropyl)carbodiimide. Relative to one mol.
of the compound shown by the formula (Ib), a compound
represented by the formula (XXI) is used in an amount
25 ranging from 0.5 to 2 mol. equivalents, preferably from
1 to 1.2 mol. equivalent, and a condensing agent is
used in an amount ranging from 0.5 to 5 mol.
equivalents, preferably 1 to 2 mol. equivalents. The
reaction temperature ranges from 0 to 100°C, preferably
30 from 20 to 50°C, and the reaction time ranges from 0.5
to 24 hours, preferably from about 1 to 5 hours.

Among the compounds represented by the formula (I)
and (I'), a compound shown by the formula (Ie)

This Sheet Has Been Replaced





5

10

15

20

25

, wherein symbols are of the same meaning as defined above, can be produced by allowing a compound (Ib) to react with diphenyl phosphoryl azide in a solvent in the presence of a base, then by allowing the resultant compound to react with a compound (XXI). As the solvent to be employed in the reaction between the compound (Ib) and diphenyl phosphoryl azide, any one can be used so long as it does not hamper the reaction, which is exemplified by dimethylformamide or a halogen-type solvent such as dichloromethane, chloroform, dichloroethane etc., and an ether-type solvent such as ether, tetrahydrofuran, dioxane etc. The base to be employed is typically exemplified by triethylamine, 4-dimethyl aminopyridine, triethylene diamine or tetramethyl ethylenediamine. Relative to one mol. of the compound shown by the formula (Ib), 1-10, preferably about 1.5 to 3 mol. equivalents of diphenyl phosphoryl azide is employed. The reaction temperature ranges from -20 to 50°C, preferably from 0 to 20°C, and the reaction time ranges from 0.5 to 5 hours, preferably from about 1 to 2 hours.

30

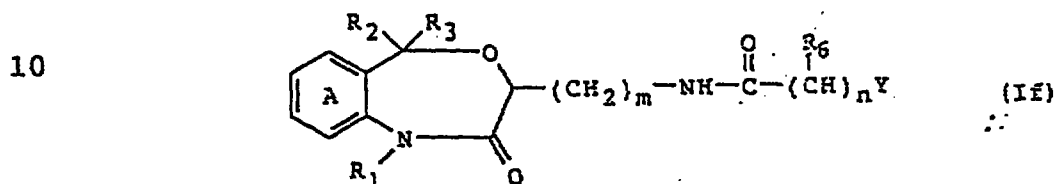
35

The solvent to be employed in the reaction between the compound obtained thus above and a compound shown by the formula (XXI) is exemplified by a halogen-type solvent such as dichloromethane, dichloroethane, chloroform etc., an ether-type solvent such as ether, tetrahydrofuran, dioxane etc., acetonitrile, dimethylformamide, among others. And, depending on necessity, a base is employed. As the base, mentioned is made of an organic base including triethylamine, 4-dimethyl aminopyridine, triethylenediamine and

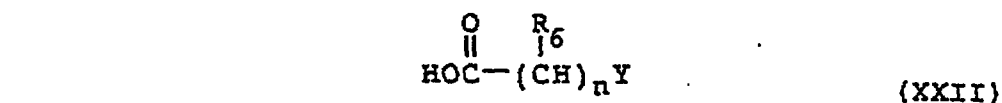


tetramethyl ethylenediamine. Relative to one mol. of the compound (Ib), 0.5 to 3, preferably 1 to 1.5, mol. equivalents of the compound (XXI). The reaction temperature ranges from 0 to 150°C, preferably from 30 to 100°C, and the reaction time ranges from 0.5 to 24, preferably about 1 to 3, hours.

Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (If)

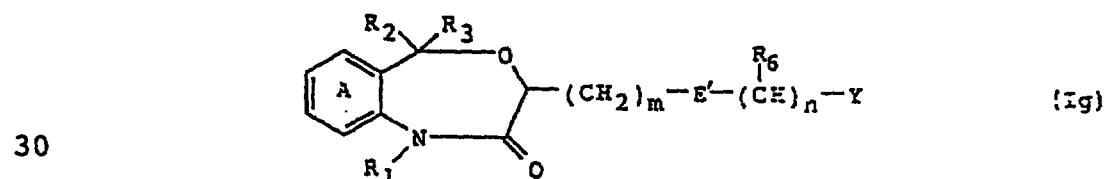


15 , wherein symbols are of the same meaning as defined above, can be produced by subjecting a compound of (XIX) to condensation with a compound represented by the formula (XXII)



, wherein symbols are of the same meaning as defined above. This reaction can be conducted in completely the same manner as in the production of the compound (Id).

25 Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (Ig)



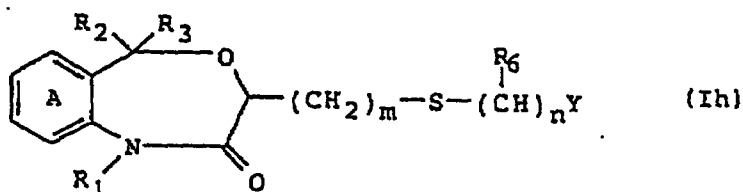
35 , wherein E' stands for, among the definitions given above, oxygen atom or -NH-, and other symbols are of the same meaning as defined above, can be produced by allowing a compound shown by the formula (Ic) or a compound shown by the formula (XIX) to react with a

compound represented by the formula (XXIII)



5 , wherein symbols are of the same meaning as defined above. More specifically, the compound (Ic) or the compound (XIX) is allowed to react with the compound (XXIII) in an alcohol-type solvent such as methanol, ethanol, propanol, butanol etc., an ether-type solvent
10 such as diethyl ether, tetrahydrofuran, dioxane etc. or dimethylformamide, among others, in the presence of a base including an inorganic base such as sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate etc., an organic base
15 such as triethylamine, 4-dimethyl aminopyridine, triethylenediamine, tetramethyl ethylenediamine etc. or sodium hydride. Relative to one mol. of the compound (Ic) or (XIX), 0.5 to 1.5 mol. equivalent of the compound (XXIII) is used, and, relative to one mol. of
20 the compound (Ic) or (XIX), 1 to 5, preferably 1 to 2, mol. equivalents of the base is used. The reaction temperature ranges from 0 to 200°C, preferably from 20 to 100°C, and the reaction time ranges from 0.5 to 24 hours, preferably from about 1 to 3 hours.

25 Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (Ih)



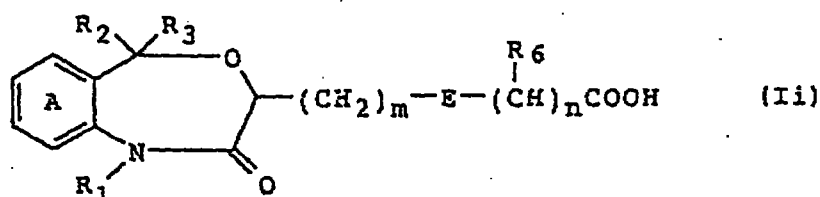
30 , wherein symbols are of the same meaning as defined above, can be produced by allowing a compound (XX) to react with a compound represented by the formula (XXV)



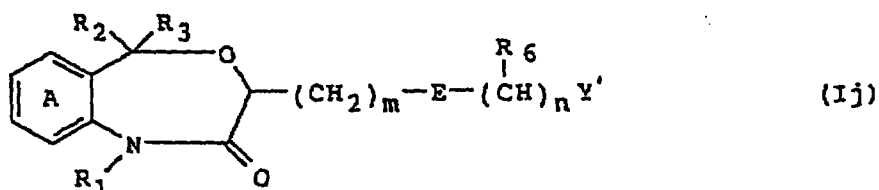


, wherein symbols are of the same meaning as defined above. The solvent to be employed is a non-protonic solvent exemplified by ethyl ether, tetrahydrofuran, dioxane, acetonitrile, dimethylformamide or the like. Depending on necessity, an inorganic base such as sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate or potassium carbonate, an organic base such as triethylamine, 4-dimethyl aminopyridine, triethylenediamine or tetramethyl ethylenediamine, sodium hydride, cesium fluoride or the like may be used. Relative to one mol. of the compound (XX), 0.5 to 5, preferably 1 to 2, mol. equivalents of the compound (XXV) is employed. The reaction temperature ranges from 0 to 200°C, preferably 20 to 100°C, and the reaction time ranges from 10 minutes to 5 hours, preferably from about 30 minutes to 2 hours.

Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (Ii)



, wherein symbols are of the same meaning as defined above, can be produced by subjecting a compound represented by the formula (Ij)



, wherein Y' stands for, among the groups defined by Y as above, esterified carboxyl group, and other symbols

are of the same meaning as defined above, to hydrolysis. More specifically, the hydrolysis is conducted in a solvent such as water, methanol, ethanol, propanol or butanol in the presence of an alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, barium hydroxide or lithium hydroxide), sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate or potassium carbonate, or, in the presence of a mineral acid (e.g. nitric acid, hydrochloric acid, hydrobromic acid, iodic acid or sulfuric acid) or trifluoroacetic acid, at temperatures ranging from 10 to 150°C, preferably from 10 to 50°C. While the reaction time varies with the reaction temperature, it ranges usually from 1 to 24 hours, preferably from about 2 to 10 hours.

While the compound represented by the formula (I") of this invention has a squalene synthetase inhibiting action and an antifungal action, among the compounds used in the present invention, there are compounds capable of inhibiting other enzymes in the pathway of cholesterol biosynthesis. Be the matter as it may, the compound represented by the formula (I") of this invention inhibits biosynthesis of cholesterol, which is useful for the prophylaxis or therapy of hypercholesteremia or coronary sclerosis of mammals (e.g. mouse, rat, rabbit, dog, cat, cow, pig and human being) and, further, for the prophylaxis or therapy of fungus infections.

Said compound (I") can be administered to man orally or non-orally. The orally administrable compositions may be in a solid or liquid form, more specifically tablets (including sugar-coated tablets and film-coated tablets), syrups, emulsions, suspensions or the like. These compositions can be prepared by a per se known method and contain carriers or excipients conventionally used in the field of



pharmaceutical preparation, for example, carriers or excipients such as lactose, starch, sucrose or magnesium stearate for preparing tablets.

5 The non-orally administrable compositions are exemplified by injections and suppositories, and the injections include hypodermic injections, intradermal
10 injections and intramuscular injections. These injections can be prepared by a per se known method, more specifically, by suspending or emulsifying the compound of this invention in a sterile water or oil
15 conventionally used for preparing injectable compositions. The aqueous liquid to be used for preparation of injections include physiological saline solution and isotonic solution, and, depending on
20 necessity, a suitable suspending agent such as sodium carboxymethyl cellulose, a non-ionic surfactant or the like may be jointly used. As the oil, mention is made of sesame oil, soybean oil, etc., and benzyl benzoate, benzyl alcohol etc. as a solubilizer may be jointly
used. Injections thus prepared are, in general, filled in appropriate ampoules.

The compound represented by the formula (I") or a salt thereof can be used safely with low toxicity. Although the daily dose varies depending on the
25 condition and weight of the patient, kind of the compound, route of administration and other factors, for example, in the case of administering the compound of the present invention for the therapy of
hypercholesteremia, a daily oral dosage per adult human
30 is about 1 to 500 mg, preferably about 10 to 200 mg. Within this range, no toxicity is observed at all.

This Sheet Has Been Replaced



The compound of the formula (I") for squalene synthetase inhibition is effectively administered to a mammal, e.g. human, in a therapeutically effective amount which is generally provided with an oral daily dosage per adult of from about 1 to about 500mg, preferably about 10 to about 200mg. In terms of a non-oral daily dosage range such as for an injection or suppository, a therapeutically effective amount is generally in the range of from about 0.1 to about 100mg, preferably about 1 to about 20mg.

The present invention compounds also demonstrate broad spectrum antifungal activity as determined by broth or agar dilution methods.

In case of administering the compound of the present invention for the therapy of fungus infections, generally from 2 to 5 mg/kg should be employed as a unit dosage in an antifungal treatment.

The compound of the formula (I") for fungus treatment is effectively administered to a mammal, e.g. human, in a therapeutically effective amount which is generally provided with an oral daily dosage per adult of from about 0.1 to about 100mg, preferably about 1 to about 50mg. In terms of a non-oral daily dosage range such as for an injection or suppository, a therapeutically effective amount is generally in the range of from about 0.1 to about 100mg, preferably about 1 to about 50mg.

Abbreviations for amino acids, and other used in the present specification are based on abbreviations specified by the IUPAC-IUB Commission on Biochemical Nomenclature or abbreviations in common use in relevant fields. Some examples are given below. When an optical isomer may be present in amino acid, it is of the L-configuration, unless otherwise stated.

This Sheet Has Been Replaced



Trp or Y : Tryptophan
Ser or S : Serine
Asp or D : Aspartic acid
Glu or E : Glutamic acid
Me : Methyl
Et : Ethyl
Ph : Phenyl

[Examples]

The following examples, reference examples, formulation examples and test examples are intended to illustrate the present invention in further detail and should by no means be construed as defining the metes and bounds of the invention.

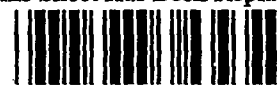
In the following description, two types of racemic diastereomers are obtained depending of the kinds of compounds, which is due to the presence of asymmetric carbon atoms at 3- and 5-positions. Isomers in which the substituents at 3- and 5-positions are oriented in the same direction relative to the face of 7-membered ring are named cis-isomers, while those in which the substituents at 3- and 5-positions are oriented in the adverse directions to each other are named trans-isomers.

Reference Example 1

Trans-7-chloro-5-(2-chlorophenyl)-1,2,3,5-tetrahydro-1-methyl-2-oxo-4,1-benzoxazepine-3-acetic acid ethyl ester

This Sheet Has Been Replaced





(1) Ethyl 3-[N-[2-(2-chlorobenzoyl)-4-chlorophenyl] carbamoyl]acrylate

To a suspension of 5.0 g of 2-amino-5-chloro-2'-chlorobenzophenone and 2.5 g of sodium hydrogencarbonate in 100 ml of methylene chloride was added dropwise 3.3 g of monoethyl ester of fumaric acid semi-chloride in the course of 30 minutes. The mixture was stirred for 2 hours at room temperature, to which was then added water, followed by shaking. The organic layer was separated, which was dried over anhydrous sodium sulfate, followed by distilling off the solvent under reduced pressure to leave 4.8 g of 3-[N-[2-(2-chlorobenzoyl)-4-chlorophenyl] carbamoyl] acrylic acid ethyl ester as crystals, m.p. 113-114°C.

Elemental Analysis for $C_{19}H_{15}Cl_2NO_4$:

Calcd.: C 58.18; H 3.85; N 3.57

Found : C 58.27; H 3.88; N 3.48

(2) Ethyl ester of 3-[N-[2-(2-chlorobenzoyl)-4-chlorophenyl]-N-methylcarbamoyl] acrylic acid

To a suspension of 0.15 g of sodium hydride in 20 ml of N,N-dimethylformamide was added, while stirring under ice-cooling, 3.0 g of the crystals obtained above. The mixture was stirred for 10 minutes at 0°C, to which was added 2.0 g of methyl iodide, then the mixture was stirred for 2 hours at room temperature. The reaction mixture was poured into ice-water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried, from which the solvent was distilled off under reduced pressure to leave 2.8 g of ethyl ester of 3-[N-[2-(2-chlorobenzoyl)-4-chlorophenyl]-N-methyl carbamoyl] acrylic acid as an oily product.

$IR_{\text{max}}^{\text{Neat}}$ cm^{-1} : 1725(C=O), 1670(C=O), 1490, 1370, 1300, 1180, 1115, 920, 740

$^1\text{H-NMR}$ spectrum (200MHz, CDCl_3) δ : 1.27(3H, t, $\text{CH}_2 \text{ CH}_3$),

3.18(3H,s,-N CH₃), 4.18(2H,q, CH₂ CH₃), 6.78(2H,d,-CH=CH-), 7.1-7.7(7H,m)

(3) Ethyl ester of 3-[N-[4-chloro-2-(α -hydroxy-2-chlorobenzyl)phenyl]-N-methylcarbamoyl] acrylic acid

5 In 50 ml of methanol was dissolved 2.8 g of the oily product obtained above, to which was added 0.2 g of sodium borohydride, and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under reduced pressure, which was
10 subjected to extraction with ethyl acetate. The organic layer was washed with water, dried and subjected to distillation under reduced pressure. Crystallization of the residue afforded 2.4 g of ethyl ester of 3-[N-[4-chloro-2-(α -hydroxy-2-
15 chlorobenzyl)phenyl]-N-methylcarbamoyl] acrylic acid, m.p. 128-130°C.

Elemental Analysis for C₂₀H₁₉Cl₂NO₄.1/4H₂O:

Calcd.: C 58.19; H, 4.76; N 3.39

Found : C 58.38; H, 4.79; N 3.31

20 (4) Ethyl trans-7-chloro-5-(2-chlorophenyl)-1,2,3,5-tetrahydro-1-methyl-2-oxo-4,1-benzoxazepine-3-acetate

In 30 ml of ethanol was dissolved 2.2 g of the crystals obtained above, to which was added 1.5 g of potassium carbonate, and the mixture was stirred for 3
25 hours at room temperature. The reaction mixture was concentrated under reduced pressure. To the concentrate was added water, which was subjected to extraction with ethyl acetate. The organic layer was washed with water and dried, followed by distilling off
30 the solvent under reduced pressure. The residue was purified by means of a silica gel chromatography (eluent, hexane:ethyl acetate = 3:1) to afford 1.85 g of ethyl ester of trans-7-chloro-5-(2-chlorophenyl)-
1,2,3,5-tetrahydro-1-methyl-2-oxo-4,1-benzoxazepine-3-
35 acetic acid as crystals, m.p. 147-148°C.

Elemental Analysis for C₂₀H₁₉Cl₂NO₄:





Calcd.: C 58.84; H 4.69; N 3.43

Found : C 58.76; H 4.79; N 3.28

Reference Example 2

Ethyl trans-7-chloro-5-(2-chlorophenyl)-1-cyclohexylmethyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetate

(1) N-cyclohexylmethyl-4-chloro-2-[α -hydroxy-(2-chlorophenyl)methyl]aniline

In 50 ml of glacial acetic acid was dissolved 5.0 g of 4-chloro-2-[α -hydroxy-(2-chlorophenyl)methyl]aniline. To the solution was added 2.5 g of cyclohexane carboxaldehyde. To the mixture was added, while stirring under ice-cooling, 1.06 g of sodium borohydride in the course of 40 minutes. The reaction mixture was poured into ice-water, which was subjected to extraction with ethyl acetate. The organic layer was washed with a dilute aqueous solution of sodium hydroxide, then with water, followed by drying. The solvent was distilled off under reduced pressure to leave 6.2 g of N-cyclohexylmethyl-4-chloro-2-[α -hydroxy-(2-chlorophenyl)methyl]aniline as crystals, m.p. 91-92°C.

Elemental Analysis for $C_{20}H_{23}Cl_2NO$:

Calcd.: C 65.94; H 6.36; N 3.84

Found : C 65.79; H 6.32; N 3.71

(2) Ethyl ester of 3-[N-[4-chloro-2-(α -hydroxy-2-chlorophenylmethyl)phenyl]-N-cyclohexylmethyl-carbamoyl]acrylic acid

In 80 ml of methylene chloride was dissolved 6.0 g the crystals obtained above. To the solution was added dropwise, while stirring under ice-cooling, 2.8 g of monoethyl ester of fumaric acid chloride (a solution in 20 l of methylene chloride) in the course of 30 minutes. The reaction mixture was stirred for 20 minutes at room temperature, which was washed with water, dried and subjected to concentration under

reduced pressure. The concentrate was purified by means of a silica gel chromatography (eluent, hexane:ethyl acetate=3:1) to afford 6.5 g of ethyl ester of 3-[N-[4-chloro-2-(α -hydroxy-2-chlorophenylmethyl)phenyl]-N-cyclohexylmethylcarbamoyl] acrylic acid as an oily product.

IR_{max}^{Neat} cm⁻¹ : 3400(OH), 2940, 1730(C=O), 1660(C=O), 1630, 1300, 1180, 1040

¹H-NMR spectrum (200MHz, CDCl₃) δ : 0.8-2.0(14H, multiplet, CH₂CH₃, -cyclohexane), 2.6-3.5(2H, multiplet, -N CH₂-cyclohexane), 4.0-4.5(2H, multiplet, CH₂ CH₃), 6.05-7.7(10H, multiplet)

(3) Ethyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-cyclohexylmethyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic acid

In 100 ml of ethanol was dissolved 6.5 g of the oily product obtained above, to which was added 5 g of potassium carbonate, and the mixture was stirred for 15 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The concentrate was subjected to extraction with ethyl acetate. The organic layer was washed with water and dried, from which was distilled off the solvent under reduced pressure. The residue was purified by means of a silica gel chromatography (eluent, hexane:ethyl acetate = 8:1) to afford 5.2 g of ethyl ester of 3,5-trans-7-chloro-5-(2-chlorophenyl)-1-cyclohexylmethyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic acid as a powdery product.

IR_{max}^{Neat} cm⁻¹ : 2940, 1740(C=O), 1680(C=O), 1600, 1490, 1380, 1270

Elemental Analysis for C₂₆H₂₉Cl₂NO₄:

Calcd.: C 63.68; H 5.96; N 2.86

Found : C 63.48; H 5.98; N 2.71

Reference Example 3

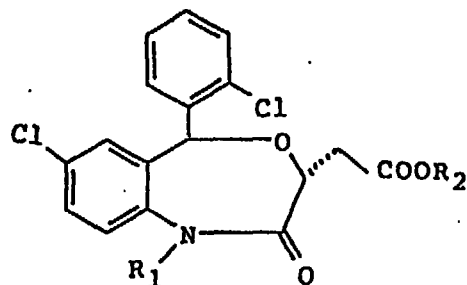


By substantially the same procedure as in Reference Example 2, compounds shown in Table 1 through Table 4 were obtained.

This Sheet Has Been Replaced



Table 1



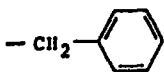
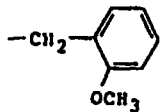
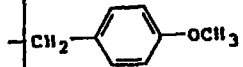
Compd. No.	R ₁	R ₂	m.p. (°C)	Formula	Elemental Analysis (Found)		
					C	H	N
1	H	C ₂ H ₅	148-150	C ₁₉ H ₁₇ Cl ₂ NO ₄	57.88 (57.92)	4.35 (4.60)	3.55 (3.33)
2		C ₂ H ₅	126-127	C ₂₈ H ₂₃ Cl ₂ NO ₄	64.47 (64.67)	4.79 (4.65)	2.89 (2.91)
3		C ₂ H ₅	oil	C ₂₇ H ₂₅ Cl ₂ NO ₅	IR, $\nu_{\text{neat max}}$ cm ⁻¹ : 2980, 1735 (CO), 1680 (CO) 1H-NMR (CDCl ₃) δ : 1.26 (3H, t, CH ₂ CH ₃), 2.82 (1H, dd), 3.13 (1H, dd) 3.67 (3H, s, OCH ₃), 4.16 (2H, q, CH ₂ CH ₃), 4.51 (1H, dd, C ₃ -H)		
4		C ₂ H ₅	135-136	C ₂₇ H ₂₅ Cl ₂ NO ₅	63.04 (62.84)	4.90 (5.02)	2.72 (2.70)

Table 2

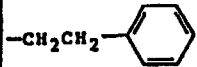
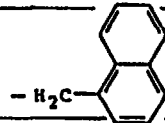
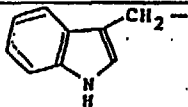
Compd. No.	R ₁	R ₂	m.p. (°C)	Formula	Elemental Analysis (Found) C H N
5		C ₂ H ₅	oil	C ₂₇ H ₂₅ Cl ₂ NO ₄	IR $\nu_{\text{max}}^{\text{neat}}$ cm ⁻¹ : 3000, 1740 (CO), 1680 (CO), 1490, 1170 ¹ H-NMR (CDCl ₃) δ : 1.26 (3H, t, CH ₂ CH ₃), 3.8 (1H, dd, C ₃ -H), 4.15 (2H, q, CH ₂ CH ₃), 6.04 (1H, s, C ₅ -H)
6		C ₂ H ₅	142-143	C ₃₀ H ₂₅ Cl ₂ NO ₄	67.42 4.71 2.62 (67.38) (4.89) (2.45)
7		C ₂ H ₅	oil	C ₂₂ H ₂₃ Cl ₂ NO ₄	IR $\nu_{\text{max}}^{\text{neat}}$ cm ⁻¹ : 2980, 1740 (CO), 1670 (CO) ¹ H-NMR (CDCl ₃) δ : 1.1-1.6 (9H, m, CH ₂ CH ₃ , CH(CH ₃) ₂), 2.77 (1H, dd), 3.07 (1H, dd), 4.13 (2H, q,); 4.33 (1H, t, C ₃ -H), 6.01 (1H, s, C ₅ -H)
8		C ₂ H ₅	186-187	C ₂₈ H ₂₄ Cl ₂ N ₂ O ₄	64.25 4.62 5.35 (64.02) (4.69) (5.39)

Table 3

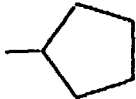
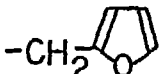
Compd. No.	R ₁	R ₂	m.p. (°C)	Formula	Elemental Analysis (Found)		
					C	H	N
9	-C ₂ H ₅	C ₂ H ₅	119-120	C ₂₁ H ₂₁ Cl ₂ NO ₄	59.73 (59.60)	5.01 (4.95)	3.32 (3.35)
10		C ₂ H ₅	oil	C ₂₄ H ₂₅ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ: 1.25(3H, t, CH ₂ CH ₃), 1.5-2.4(8H, m), 2.78, 3.05(2H, ^{both} dd), 4.15(2H, m), 4.31(1H, dd, C ₃ -H), 4.69(1H, t), 6.01(1H, s, C ₅ -H), 6.50(1H, d, C ₆ -H), 7.2-7.6(6H, m)		
11		C ₂ H ₅	oil	C ₂₄ H ₂₁ Cl ₂ NO ₅	¹ H-NMR(CDCl ₃) δ: 1.24(3H, t, CH ₃), 2.82, 3.10(2H, ^{both} dd), 4.14(2H, q, CH ₂ CH ₃), 4.46(1H, dd, C ₃ -H), 4.85, 5.5(2H, ^{both} d), 5.93(1H, s, C ₅ -H), 6.2-6.5(3H, m), 7.2-7.7(7H, m)		

Table 4

Compd. No.	R ₁	R ₂	m.p. (°C)	Formula	Elemental Analysis (Found)		
					C	H	N
12	$-\text{CH}_2-\text{CH}=\text{C}(\text{CH}_3)_2$	C_2H_5	oil	$\text{C}_{24}\text{H}_{25}\text{Cl}_2\text{NO}_4$	¹ H-NMR (CDCl ₃) δ : 1.25 (3H, t, CH ₃), 1.65 (6H, d, CH ₃ × 2), 2.8, 3.8 (2H, both dd), 4.05-4.3 (3H, m), 4.42 (1H, dd), 4.9-5.4 (2H, m), 6.0 (1H, s, C ₅ -H), 6.49 (1H, d), 7.2-7.7 (6H, m)		
13	$-\text{CH}_2-\text{C}(\text{CH}_3)=\text{CH}_2$	C_2H_5	oil	$\text{C}_{23}\text{H}_{23}\text{Cl}_2\text{NO}_4$	¹ H-NMR (CDCl ₃) δ : 1.25 (3H, t, CH ₃), 1.82 (3H, s, CH ₃), 2.80, 3.13 (2H, both dd), 4.13 (2H, q, CH ₂ CH ₃), 4.40, 4.67 (2H, both d), 4.53 (1H, dd, C ₃ -H), 4.97 (2H, m), 6.05 (1H, s), 6.5 (1H, d), 7.2-7.8 (6H, m)		
14	$-\text{CH}_2-\text{CH}=\text{CH}_2$	C_2H_5	126-127	$\text{C}_{22}\text{H}_{21}\text{Cl}_2\text{NO}_4$	60.84 (60.91)	4.87 (4.90)	3.23 (3.06)
15	$-\text{CH}_2-\text{C}\equiv\text{CH}$	C_2H_5	oil	$\text{C}_{22}\text{H}_{19}\text{Cl}_2\text{NO}_4$	¹ H-NMR (CDCl ₃) δ : 1.25 (3H, t, CH ₃), 2.82, 3.08 (2H, both dd), 4.14 (2H, q, CH ₂ CH ₃), 4.47 (1H, dd, C ₃ -H), 4.55, 4.95 (2H, both dd), 6.10 (1H, s, C ₅ -H), 6.53 (1H, d), 7.3-7.75 (7H, m)		
16	$-\text{CH}_2\text{CH}_2\text{CH}_3$	C_2H_5	oil	$\text{C}_{22}\text{H}_{23}\text{Cl}_2\text{NO}_4$	¹ H-NMR (CDCl ₃) δ : 0.97 (3H, t, CH ₃), 1.25 (3H, t), 1.5-1.9 (2H, m), 2.78, 3.07 (2H, both dd), 3.53 (1H, m), 4.13 (2H, dq), 4.4 (2H, m), 6.03 (1H, s), 6.50 (1H, d), 7.2-7.8 (6H, m)		

This Sheet Has Been Replaced

Example 1

By substantially the same procedure as in Reference Example 2, compounds shown in Table 5 and Table 6 were obtained

5

This Sheet Has Been Replaced



Table 5

Compd. No.	R ₁	R ₂	m.p. (°C)	Formula	Elemental Analysis (Found)		
					C	H	N
1	-(CH ₂) ₈ CH ₃	C ₂ H ₅	80-81	C ₂₈ H ₃₁ Cl ₂ NO ₄	63.42 (63.58)	6.35 (6.58)	2.84 (2.79)
2	-CH ₂ CH(CH ₃) ₂	C ₂ H ₅	oil	C ₂₃ H ₂₅ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ: 0.92, 1.03(6H, ^{both} t, CH ₃), 1.25(3H, ^{both} t, CH ₃), 1.98(1H, m), 2.8, 3.06(2H, dd), 3.45(1H, dd), 4.13(2H, q), 4.2-4.5(2H, m), 6.14(1H, s, C ₅ -H), 6.51(1H, d), 7.2-7.8(6H, m)		
3	-CH ₂ CH(C ₂ H ₅) ₂	C ₂ H ₅	oil	C ₂₅ H ₂₉ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ: 0.85, 0.89(6H, ^{both} t, CH ₃), 1.25(3H, ^{both} t, CH ₃), 1.2-1.7(4H, m), 2.8, 3.05(2H, dd), 4.14(2H, q, CH ₂ CH ₃), 3.45(1H, dd), 4.45(2H, m), 6.11(1H, s, C ₅ -H), 6.51(1H, d), 7.2-7.8(6H, m)		
4	-CH ₂ C(CH ₃) ₃	C ₂ H ₅	101-102	C ₂₄ H ₂₇ Cl ₂ NO ₄	62.07 (62.36)	5.86 (5.87)	3.02 (2.99)
5	-(CH ₂) ₂ CH(CH ₃) ₂	C ₂ H ₅	oil	C ₂₄ H ₂₇ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ: 0.91, 0.92(6H, ^{both} t, CH ₃), 1.25(3H, ^{both} t, CH ₃), 1.4-1.8(3H, m), 2.79, 3.06(2H, dd), 3.55(1H, m), 4.05-4.6(4H, m), 6.01(1H, s, C ₅ -H), 6.51(1H, d), 7.2-7.8(6H, m)		

Table 6

Compd. No.	R ₁	R ₂	m.p. (°C)	Formula	Elemental Analysis (Found)		
					C	H	N
6	-CH(C ₂ H ₅) ₂	C ₂ H ₅	oil	C ₂₃ H ₂₇ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 0.98, 1.04(6H, ^{both} t, CH ₃), 1.24(3H, t), 1.6-2.1(4H, m), 2.76, 3.1(2H, ^{both} dd), 4.13, (2H, q, OCH ₂ CH ₃), 4.2-4.4(2H, m), 6.09(1H, s, C ₅ -H), 6.51(1H, d) 7.2-7.8(6H, m)		
7	-(CH ₂) ₃ CH ₃	C ₂ H ₅	oil	C ₂₃ H ₂₅ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 0.91(3H, t), 1.25(3H, t), 1.3-1.8(4H, m), 2.78, 3.06(2H, both dd), 3.45-3.63(1H, m), 4.13(2H, dq), 4.35-4.55(2H, m), 6.03(1H, s), 6.51(1H, d), 7.2-7.75(6H, m)		



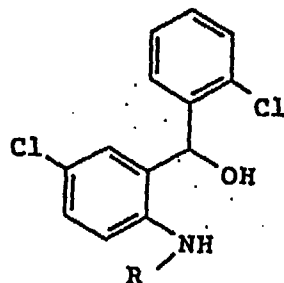
This Sheet Has Been Replaced

In Table 7 through Table 12, physicochemical properties of intermediates obtained in Reference Example 3 and Example 1 are shown.

This Sheet Has Been Replaced

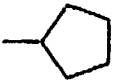


Table 7



R	m.p. (°C)	Formula	Elemental Analysis (Found)		
			C	H	N
	oil	$C_{21}H_{19}Cl_2NO_2$	$^1H-NMR (CDCl_3) \delta : 3.77 (3H, s, OCH_3), 4.29 (2H, s), 6.08 (1H, s), 6.55-7.5 (11H, m)$		
	119-120	$C_{21}H_{19}Cl_2NO$	67.75 (67.83)	5.14 (5.12)	3.76 (3.71)
	oil	$C_{24}H_{19}Cl_2NO$	$^1H-NMR (CDCl_3) \delta : 4.73 (2H, s), 6.09 (1H, s), 6.6-8.0 (14H, m)$		
	oil	$C_{18}H_{17}Cl_2NO$	$NMR (CDCl_3) \delta : 1.12 (3H, d), 1.18 (3H, d), 3.6 (1H, m), 6.07 (1H, m), 6.5-7.5 (7H, m)$		
	oil	$C_{22}H_{18}Cl_2N_2O$	$^1H-NMR (CDCl_3) \delta : 4.45 (2H, s, CH_2-indol), 6.05 (1H, s), 6.5-8.2 (12H, m)$		

Table 8

R	m.p. (°C)	Formula	Elemental Analysis (Found)		
			C	H	N
$-(\text{CH}_2)_6\text{CH}_3$	oil	$\text{C}_{20}\text{H}_{25}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 0.87(3H, t, CH_3), 1.0-1.7 (10H, m), 2.8-3.1(2H, m), 6.1-7.7(8H, m)		
$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	87-88	$\text{C}_{17}\text{H}_{19}\text{Cl}_2\text{NO}$	62.97 (62.97)	5.91 (6.05)	4.32 (4.44)
	oil	$\text{C}_{18}\text{H}_{19}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 1.2-2.2(8H, m), 3.75(1H, m), 6.05(1H, s), 6.5-7.5(7H, m)		
$-\text{CH}_2-$ 	oil	$\text{C}_{18}\text{H}_{15}\text{Cl}_2\text{NO}_2$	$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 3.7(2H, m), 5.9-6.2(3H, m), 6.8-7.5(8H, m)		
$-\text{CH}_2\text{CH}(\text{C}_2\text{H}_5)_2$	oil	$\text{C}_{19}\text{H}_{23}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 0.7-1.6(10H, m), 2.97(2H, d), 6.11(1H, s), 6.6(1H, d), 6.9-7.5(6H, m)		
$-\text{CH}_2\text{C}(\text{CH}_3)_3$	110-111	$\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{NO}$	63.91 (64.12)	6.26 (6.30)	4.14 (4.31)
$-(\text{CH}_2)_2\text{CH}(\text{CH}_3)_2$	oil	$\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 0.90, 0.93(6H, ^d _{both} , CH_3), 1.4-1.8(3H, m), 3.09(2H, t), 6.12(1H, s), 6.60(1H, d), 6.90(1H, d), 7.1-7.5(5H, m)		

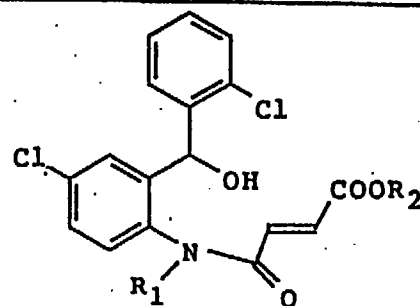
This Sheet Has Been Replaced



Table 9

R	p. m. (°C)	Formula	Elemental Analysis(Found)		
			C	H	N
$-\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$	oil	$\text{C}_{18}\text{H}_{19}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta : 1.66, 1.73 (6\text{H, both s, CH}_3), 3.66(2\text{H, d}), 6.01(1\text{H, s}), 6.59(1\text{H, d}), 8.22(1\text{H, d}), 7.1-7.5(6\text{H, m})$		
$-\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}_2$	oil	$\text{C}_{17}\text{H}_{17}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta : 1.72(3\text{H, s, CH}_3), 3.68(2\text{H, s}), 4.85(2\text{H, m}), 6.15(1\text{H, s}), 6.55(1\text{H, d}), 6.86(1\text{H, d}), 7.05-7.5(5\text{H, m})$		
$-\text{CH}(\text{C}_2\text{H}_5)_2$	oil	$\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta : 0.75(3\text{H, t, CH}_3), 0.88(3\text{H, t, CH}_3), 1.1-1.7(4\text{H, m}), 3.2(1\text{H, m}), 6.1(1\text{H, s}), 6.5-7.5(7\text{H, m})$		
$-\text{CH}_2-\text{CH}=\text{CH}_2$	oil	$\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta : 3.8(2\text{H, m}), 5.1-6.0(3\text{H, m}), 6.16(1\text{H, s}), 6.55-7.5(7\text{H, m}), 6.82(1\text{H, d})$		
$-\text{CH}_2\text{C}\equiv\text{CH}$	oil	$\text{C}_{18}\text{H}_{13}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta : 3.95(2\text{H, d}), 6.14(1\text{H, s}), 6.73(1\text{H, d}), 6.8(1\text{H, d}), 7.1-7.6(6\text{H, m})$		
$-\text{CH}_2\text{CH}_2\text{CH}_3$	oil	$\text{C}_{18}\text{H}_{17}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta : 0.95(3\text{H, t}), 1.65(2\text{H, m}), 3.06(2\text{H, t}), 6.12(1\text{H, s}), 6.55-7.5(7\text{H, m})$		
$-(\text{CH}_2)_3\text{CH}_3$	oil	$\text{C}_{17}\text{H}_{19}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta : 0.92(3\text{H, t}), 1.2-1.7(4\text{H, m}), 3.07(2\text{H, t}), 6.10(1\text{H, s}), 6.59(1\text{H, d}), 6.87(1\text{H, d}), 7.1-7.5(5\text{H, m})$		

Table 10



R ₁	R ₂	m.p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
	-C ₂ H ₅	oil	C ₂₇ H ₂₅ Cl ₂ NO ₅	¹ H-NMR (CDCl ₃) δ : 1.2 (3H, t, CH ₂ CH ₃), 3.5 (3H, s, OCH ₃), 4.06 (2H, q, CH ₂ CH ₃), 4.68 (1H, d), 5.55 (1H, d), 6.0-7.7 (14H, m)		
	-C ₂ H ₅	oil	C ₂₇ H ₂₅ Cl ₂ NO ₅	¹ H-NMR (CDCl ₃) δ : 1.2 (3H, t, CH ₂ CH ₃), 3.76 (3H, s, OCH ₃), 4.05 (2H, q, CH ₂ CH ₃), 4.24 (1H, d), 5.65 (1H, d) 6.1-7.6 (14H, m)		
	-C ₂ H ₅	oil	C ₂₇ H ₂₅ Cl ₂ NO ₄	¹ H-NMR (CDCl ₃) δ : 1.1-1.4 (3H, m), 2.7-4.7 (6H, m), 6.0-7.7 (15H, m)		



This Sheet Has Been Replaced

Table 11

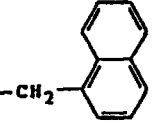
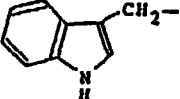
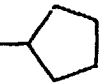
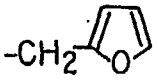
R ₁	R ₂	p. m. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
	- C ₂ H ₅	oil	C ₃₀ H ₂₅ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 1.13(3H, t, CH ₂ CH ₃), 4.1(2H, q, CH ₂ CH ₃), 5.02(1H, d), 5.9-8.2(18H, m)		
	- C ₂ H ₅	oil	C ₂₈ H ₂₄ Cl ₂ N ₂ O ₄	¹ H-NMR(CDCl ₃) δ : 1.1-1.4(3H, m), 3.9-4.3(2H, m), 4.6-5.8(2H, m), 6.0-8.4(15H, m)		
- C ₂ H ₅	- C ₂ H ₅	oil	C ₂₁ H ₂₁ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 0.9-1.5(6H, m), 3.5-4.5(4H, m), 6.0-7.9(10H, m)		
-(CH ₂) ₆ CH ₃	- C ₂ H ₅	oil	C ₂₆ H ₃₁ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 0.85(3H, t, CH ₃), 0.95-1.7(13H, m), 2.7-4.5(4H, m) 6.0-7.7(10H, m)		
-CH ₂ CH(CH ₃) ₂	- C ₂ H ₅	136-138	C ₂₃ H ₂₅ Cl ₂ NO ₄	61.34 (61.26)	5.59 (5.71)	3.11 (3.06)
	- C ₂ H ₅	192-194	C ₂₄ H ₂₅ Cl ₂ NO ₄	62.34 (62.05)	5.45 (5.50)	3.03 (3.07)
	- C ₂ H ₅	oil	C ₂₄ H ₂₁ Cl ₂ NO ₅	¹ H-NMR(CDCl ₃) δ : 1.27(3H, m, CH ₃), 3.6(1H, m), 4.15(2H, m, CH ₂), 5.35(1H, m), 5.9-8.0(13H, m)		

Table 12

R ₁	R ₂	p. m. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
-CH ₂ CH(C ₂ H ₅) ₂	-C ₂ H ₅	oil	C ₂₅ H ₂₉ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 0.6-1.7(14H,m), 2.7-4.6(4H,m), 5.9-7.7(10H,m)		
-CH ₂ C(CH ₃) ₃	-C ₂ H ₅	oil	C ₂₄ H ₂₇ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 0.7-1.4(12H,m), 2.8-4.6(4H,m), 6.1-7.7(10H,m)		
-(CH ₂) ₂ CH(CH ₃) ₂	-C ₂ H ₅	oil	C ₂₄ H ₂₇ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 0.6-1.7(12H,m), 2.6-4.6(4H,m), 5.9-7.7(10H,m)		
-CH ₂ -CH=C(CH ₃) ₂	-C ₂ H ₅	oil	C ₂₄ H ₂₅ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 1.1-1.9(9H,m), 3.9-4.9(4H,m), 6.0-7.7(11H,m)		
-CH ₂ -C(CH ₃)=CH ₂	-C ₂ H ₅	oil	C ₂₃ H ₂₃ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 1.25(3H,m), 1.75(3H,m), 3.0-5.2(6H,m), 5.9-7.9(10H,m)		
-CH(C ₂ H ₅) ₂	-C ₂ H ₅	oil	C ₂₄ H ₂₇ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 0.7-2.1(13H,m), 4.0-4.4(3H,m), 6.0-7.5(10H,m)		
-CH ₂ -CH=CH ₂	-C ₂ H ₅	oil	C ₂₂ H ₂₁ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 1.15-1.4(3H,m, CH ₃), 3.1-6.0(7H,m), 6.1-7.7(10H,m)		
-CH ₂ -C≡CH	-C ₂ H ₅	132- 133	C ₂₂ H ₁₉ Cl ₂ NO ₄	61.12 (61.02)	4.43 (4.67)	3.24 (3.13)
-CH ₂ CH ₂ CH ₃	-C ₂ H ₅	oil	C ₂₂ H ₂₃ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 0.77, 0.86(3H, both d), 1.22, 1.24 (3H, both t), 1.4-1.9(2H,m), 2.6-4.5(4H,m), 6.0-7.6 (10H,m)		
-(CH ₂) ₃ CH ₃	-C ₂ H ₅	oil	C ₂₃ H ₂₅ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 0.7-1.9(10H,m), 2.6-4.5(4H,m), 5.9-7.7(10H,m)		

This Sheet Has Been Replaced



Reference Example 4

Trans-7-chloro-5-(2-chlorophenyl)-1-methyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic acid

5 In a mixture of 10 ml of methanol and 4 ml of water was suspended 0.5 g of ethyl ester of 3,5-trans-7-chloro-5-(2-chlorophenyl)-1-methyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic acid. To the suspension was added 0.8 g of potassium carbonate, and the mixture was stirred for 3 hours at 60°C. The
10 reaction mixture was concentrated under reduced pressure, to which was added water, followed by extraction with ether. The aqueous layer was acidified with dilute hydrochloric acid, followed by extraction with ethyl acetate. The organic layer was washed with
15 water and dried, followed by concentration under reduced pressure. The concentrate was purified by means of a silica gel chromatography to afford 0.21 g of 3,5-trans-7-chloro-5-(2-chlorophenyl)-1-methyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic
20 acid as crystals, m.p. 211-213°C.

Elemental Analysis for $C_{18}H_{15}Cl_2NO_4$:

Calcd.: C 56.86; H 3.98; N 3.68

Found : C 56.86; H 4.24; N 3.53

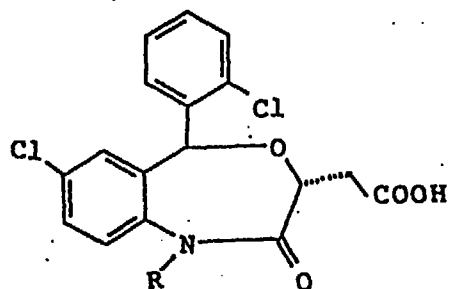
Reference Example 5

25 By substantially the same procedure as in Reference Example 4, compounds shown in Table 13 through Table 15 were obtained.

This Sheet Has Been Replaced



Table 13



Compd. No.	R	m.p. (°C)	Formula	Elemental Analysis (Found)		
				C	H	N
1		175-178	$C_{24}H_{19}Cl_2NO_4$	63.17 (63.18)	4.20 (4.24)	3.07 (3.23)
2		213-214	$C_{25}H_{21}Cl_2NO_5$	61.74 (61.55)	4.35 (4.55)	2.88 (2.79)
3		165-167	$C_{25}H_{21}Cl_2NO_5$	61.74 (61.49)	4.35 (4.47)	2.88 (2.84)



This Sheet Has Been Replaced

Table 14

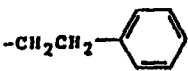
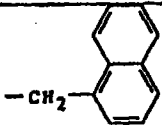
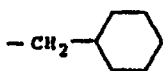
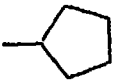
Compd. No.	R	p. m. (°C)	Formula	Elemental Analysis (Found)		
				C	H	N
4		212-214	$C_{25}H_{21}Cl_2NO_4$	63.84 (63.94)	4.50 (4.71)	2.98 (3.17)
5		243-244	$C_{28}H_{21}Cl_2NO_4$	66.41 (66.27)	4.18 (4.05)	2.77 (2.65)
6		241-242	$C_{24}H_{25}Cl_2NO_4$	62.34 (62.27)	5.45 (5.45)	3.03 (3.02)
7	$-CH(CH_3)_2$	208-209	$C_{20}H_{19}Cl_2NO_4$	58.84 (58.78)	4.69 (4.83)	3.43 (3.38)

Table 15

Compd. No.	R	p. m. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
8	-C ₂ H ₅	215- 216	C ₁₉ H ₁₇ Cl ₂ NO ₄	57.88 (57.67)	4.35 (4.27)	3.55 (3.54)
9		224- 225	C ₂₂ H ₂₁ Cl ₂ NO ₄	60.84 (60.64)	4.87 (4.94)	3.22 (3.32)
10	-CH ₂ - 	190- 191	C ₂₂ H ₁₇ Cl ₂ NO ₅	59.21 (58.99)	3.84 (3.78)	3.14 (3.10)
11	-CH ₂ -CH=C(CH ₃) ₂	154- 155	C ₂₂ H ₂₁ Cl ₂ NO ₄	60.84 (60.54)	4.87 (5.15)	3.22 (3.31)
12	-CH ₂ -C(CH ₃)=CH ₂	241- 242	C ₂₁ H ₁₉ Cl ₂ NO ₄	60.01 (59.76)	4.56 (4.73)	3.33 (3.22)
13	-CH ₂ -CH=CH ₂	199- 200	C ₂₀ H ₁₇ Cl ₂ NO ₄	59.13 (58.88)	4.22 (4.30)	3.45 (3.58)
14	-CH ₂ -C≡CH	184- 185	C ₂₀ H ₁₅ Cl ₂ NO ₄	59.42 (59.18)	3.74 (3.75)	3.46 (3.23)
15	-CH ₂ CH ₂ CH ₃	189- 190	C ₂₀ H ₁₉ Cl ₂ NO ₄	58.84 (58.78)	4.69 4.95	3.43 3.60



Example 2

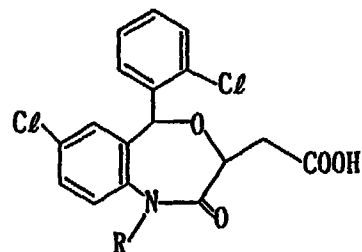
By substantially the same procedure as in Reference Example 4, compounds shown in Table 16, were obtained.

5

This Sheet Has Been Replaced



Table 16



Compd. No.	R	p. m. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
1	$-(CH_2)_6CH_3$	188- 189	$C_{24}H_{27}Cl_2NO_4$	62.07 (62.21)	5.86 (5.83)	3.02 (3.00)
2	$-CH_2CH(CH_3)_2$	220- 221	$C_{21}H_{21}Cl_2NO_4$	59.73 (59.98)	5.01 (5.24)	3.32 (3.14)
3	$-CH_2CH(C_2H_5)_2$	188- 189	$C_{23}H_{25}Cl_2NO_4$	61.34 (61.39)	5.60 (5.74)	3.11 (2.99)
4	$-CH_2-C(CH_3)_3$	247- 248	$C_{22}H_{23}Cl_2NO_4$	60.56 (60.55)	5.31 (5.47)	3.21 (3.11)
5	$-(CH_2)_2CH(CH_3)_2$	166- 167	$C_{22}H_{23}Cl_2NO_4$	60.56 (60.40)	5.31 (5.49)	3.21 (3.22)
6	$-CH(C_2H_5)_2$	220- 221	$C_{22}H_{23}Cl_2NO_4$	60.56 (60.45)	5.31 (5.29)	3.21 (3.20)
7	$-(CH_2)_3CH_3$	195- 196	$C_{21}H_{21}Cl_2NO_4$	59.73 (59.68)	5.01 4.97	3.32 3.54



Reference Example 6

Trans-1-benzyl-7-chloro-5-phenyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

0.3 g of the ethyl ester of trans-1-benzyl-7-chloro-5-phenyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid disclosed in JPA S57(1982)-35576 was subjected to hydrolysis in the manner to be described in the following Reference Example 4 to afford 0.12 g of trans-1-benzyl-7-chloro-5-phenyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as a white powdery product.

Example 3

Ethyl ester of trans-1-isobutyl-2-oxo-5-(o-tolyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

(1) 2-Isobutylamino- α -(o-tolyl)benzyl alcohol

Using 2-amino- α -(o-tolyl)benzyl alcohol (2.5 g) and isobutyl aldehyde (1.17 ml), reaction is conducted in substantially the same manner as in Reference Example 2 (1) to give 2-isobutylamino- α -(o-tolyl)benzyl alcohol (3.1 g) as an oily product.

IR_v^{Neat}_{max} cm⁻¹ : 3400(OH); 1720, 1655, 1630(C=O, C=C)

¹H-NMR(CDCl₃) δ : 0.7-1.1(6H,m), 1.21(3H,t,J=7.0Hz), 1.5-2.0(1H,m), 2.29(3H,s), 2.0-2.3 and 2.9-3.1(1H, each m), 3.9-4.5(3H,m), 5.9-6.4(2H,m), 6.6-6.9(1H,m), 6.95-7.9(8H,m)

(2) Ethyl ester of 3-[N-[2-(α -hydroxy-2-methylbenzyl)phenyl-N-isobutyl]carbamoyl]acrylic acid

In substantially the same manner as in Reference Example 2 (2), 2-isobutylamino- α -(o-tolyl)benzyl alcohol (1.3 g) obtained in (1) above was allowed to react with fumaric acid chloride monoethyl ester to give ethyl ester of 3-[N-[2-(α -hydroxy-2-methylbenzyl)phenyl-N-isobutyl]carbamoyl]acrylic acid (3.1 g) as an oily product.

IR_v^{Neat}_{max} cm⁻¹ : 3400(OH); 1720, 1655, 1630(C=C, C=O)

¹H-NMR spectrum (200MHz, CDCl₃) δ : 0.7-1.1(6H,m),

1.21(3H,t,J=7.0Hz), 1.5-2.0(1H,m), 2.29(3H,s), 2.0-2.3
and 2.9-3.1(1H, each m), 3.9-4.5(3H,m), 5.9-6.4(2H,m),
6.6-6.9(1H,m), 6.95-7.9(8H,m)

(3) Ethyl ester of trans-1-isobutyl-2-oxo-5-(o-tolyl)-
5 1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In the same manner as in Reference Example 2 (3),
ethyl ester of 3-[N-[2-(α -hydroxy-2-methylbenzyl)
phenyl-N-isobutyl]carbamoyl] acrylic acid (1.8 g) was
subjected to reaction. The reaction product was
10 crystallized from water-ethanol to give ethyl ester of
trans-1-isobutyl-2-oxo-5-(o-tolyl)-1,2,3,5-tetrahydro-
4,1-benzoxazepine-3-acetic acid (2.41 g) as prisms,
88°C - 90°C.

IR_v^{KBr}_{max} cm⁻¹ : 1730, 1670(C=O)

15 Elemental Analysis for C₂₄H₂₉NO₄:

Calcd.: C 72.89; H 7.39; N 3.54

Found : C 73.18; H 7.25; N 3.54

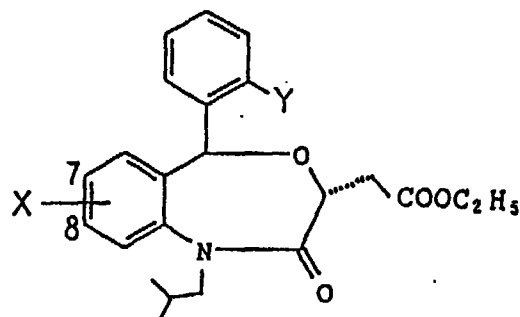
Example 4

By substantially the same synthetic procedure as
20 in Example 3, compounds listed in Table 17 and Table 18
were obtained.

This Sheet Has Been Replaced



Table 17



Compd. No.	X	Y	p. m. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
1	H	Cl	99-100	$C_{23}H_{28}ClNO_4$	66.42 (66.20)	6.30 (6.57)	3.37 (3.42)
2	(7)-CH ₃	Cl	oil	$C_{24}H_{28}ClNO_4$	¹ H-NMR(CDCl ₃) δ : 0.92, 1.03(6H, ^{both} d, CH ₃), 1.25(3H, t, CH ₂ CH ₃), 2.19(3H, s, CH ₃), 2.8, 3.03(2H, ^{both} dd), 3.45 (1H, dd), 4.13(2H, q, CH ₂ CH ₃), 4.2-4.5(2H, m), 6.16(1H, s, C ₅ -H), 6.31(1H, s, C ₆ -H), 7.1-7.8(6H, m)		
3	(7)-Cl	F	oil	$C_{23}H_{25}ClFNO_4$	¹ H-NMR(CDCl ₃) δ : 0.89, 0.97(6H, ^{both} d, CH ₃), 1.26(3H, t, CH ₂ CH ₃), 2.04(1H, m), 2.78, 3.07(2H, ^{both} dd), 3.4 (1H, dd), 4.13(2H, q), 4.2-4.5(2H, m), 6.13(1H, s, C ₅ -H), 6.63(1H, d), 7.0-7.7 (6H, m)		

This Sheet Has Been Replaced

Table 18

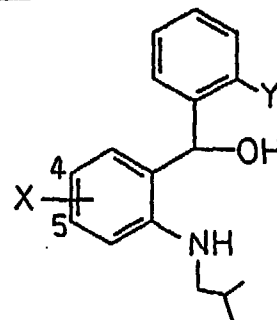
Compd. No.	X	Y	m.p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
4	(7)-CH ₂ CH ₂ CH ₂ -(8)	Cl	oil	C ₂₈ H ₃₀ ClNO ₄	¹ H-NMR(CDCl ₃) δ: 0.93, 1.04(6H, ^{both} d), 1.9-2.2 3H,m), 2.7-3.15(6H,m), 3.48(1H,dd), 4.0-4.5(4H,m), 6.16(1H,s,C ₅ -H), 6.35(1H,s,C ₆ -H), 7.1-7.8(5H,m)		
5	H	F	oil	C ₂₃ H ₂₆ FNO ₄	¹ H-NMR(CDCl ₃) δ: 0.89, (3H,d), 0.98(3H,d), 1.24(3H, t), 1.9-2.2(1H,m), 2.78(1H,dd), 3.06(1H,dd), 3.46 (1H,dd), 4.13(2H,q), 4.25-4.5(2H,m), 6.18(1H,s) 6.67(1H,d), 6.9-7.75(7H,m)		
6	H	OCH ₃	132-133	C ₂₄ H ₂₉ NO ₅	70.05 (70.20)	7.10 (7.13)	3.40 (3.56)

In Table 19 through Table 22, physicochemical properties of intermediates are shown.

This Sheet Has Been Replaced



Table 19



X	Y	m.p. (°C)	Formula	Elemental Analysis (Found)
				C H N
H	Cl	oil	$C_{17}H_{20}ClNO$	$^1H-NMR(CDCl_3) \delta$: 0.8-1.1(6H,m), 1.9(1H,m), 2.95 (2H,d), 5.29(1H, s), 6.17(1H,s), 6.5-7.6(7H,m)
(4)-CH ₃	Cl	oil	$C_{18}H_{22}ClNO$	$^1H-NMR(CDCl_3) \delta$: 0.8-1.1(6H,m), 1.85(1H,m), 2.18(3H,s,CH ₃), 2.91 (2H,d), 6.16(1H,s), 6.55-7.6(7H,m)
(4)-Cl	F	oil	$C_{17}H_{18}ClFNO$	$^1H-NMR(CDCl_3) \delta$: 0.8-1.1(6H,m, CH ₃), 1.85(1H,m), 2.89(2H,d,NHCH ₂), 6.05(1H,s), 6.57(1H,d), 6.9-7.5 (6H,m)

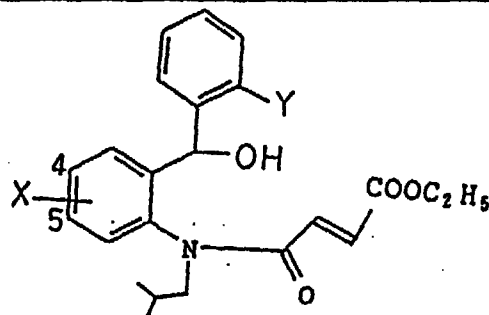
Table 20

X	Y	m.p. (°C)	Formula	Elemental Analysis (Found)		
				C	H	N
(4)-CH ₂ CH ₂ CH ₂ -(5)	Cl	oil	C ₂₀ H ₂₄ ClNO	¹ H-NMR(CDCl ₃) δ: 0.8-1.1(6H,m), 1.7-2.1(3H,m), 2.6-3.0(6H,m), 6.17(1H,s), 6.62(1H,s), 6.68(1H,s), 7.2-7.6(4H,m)		
H	F	oil	C ₁₇ H ₂₀ FNO	¹ H-NMR(CDCl ₃) δ: 0.95(6H,d, J=6.8Hz), 1.8-2.1(1H,m), 2.93(2H,d, J=6.6Hz), 6.11(1H,s), 6.55-6.75 (2H,m), 6.9-7.5(6H,m)		
H	OCH ₃	oil	C ₁₈ H ₂₃ NO ₂	¹ H-NMR(CDCl ₃) δ: 0.94(6H,d, J=6.6Hz), 1.75-2.05(1H,m), 2.94 (2H,d), 3.86(3H,s), 6.02(1H,s), 6.5-6.75(2H,m), 6.85-7.0(3H,m), 7.1-7.4(3H,m) ∴		



This Sheet Has Been Replaced

Table 21



X	Y	m.p. (°C)	Formula	Elemental Analysis (Found)		
				C	H	N
H	Cl	oil	$C_{23}H_{26}ClNO_4$	1H -NMR($CDCl_3$) δ : 0.7-1.4(9H,m), 1.9(1H,m), 2.6-4.5(4H,m), 6.1-7.7 (11H,m)		
(4)- CH_3	Cl	oil	$C_{24}H_{28}ClNO_4$	1H -NMR($CDCl_3$) δ : 0.7-1.4(9H,m), 1.8-3.2(5H,m), 4.0-4.5(3H,m), 6.0-7.6(10H,m)		
(4)-Cl	F	oil	$C_{23}H_{25}ClFNO_4$	1H -NMR($CDCl_3$) δ : 0.7-1.4(9H,m), 1.85(1H,m), 2.5-4.4(4H,m), 5.9- 7.9(10H,m)		

This Sheet Has Been Replaced

Table 22

X	Y	m.p. (°C)	Formula	Elemental Analysis (Found)		
				C	H	N
(4)-CH ₂ CH ₂ CH ₂ -(5)	Cl	oil	C ₂₈ H ₃₀ ClNO ₄	¹ H-NMR(CDCl ₃) δ : 0.7-1.4(9H,m), 1.8-2.3(3H,m), 2.7-3.2(5H,m), 4.0-4.5(3H,m), 5.95-7.7(9H,m),		
H	F	oil	C ₂₃ H ₂₈ FNO ₄	¹ H-NMR(CDCl ₃) δ : 0.75-1.15(6H,m), 1.20(3H,t,J=7.0Hz), 1.5-2.1(1H,m), 2.6-2.8, 2.95-3.15(1H, ^{both} m), 4.0- 4.5(3H,m), 6.0-6.5(2H,m), 6.7- 7.8(9H,m)		
H	OCH ₃	oil	C ₂₄ H ₂₉ NO ₅	¹ H-NMR(CDCl ₃) δ : 0.7-1.1(6H,m), 1.20(3H,t,J=7.1Hz), 1.7-2.0(1H,m), 2.5-3.2(2H,m), 3.74, 3.78(3H, s), 4.0-4.45(3H,m), 6.0-6.5(2H,m), 6.7-7.85(9H,m)		

This Sheet Has Been Replaced



Example 5

Trans-1-isobutyl-2-oxo-5-(o-tolyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

5 In substantially the same manner as in Reference
Example 4, ethyl ester of trans-1-isobutyl-2-oxo-5-(o-
tolyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic
acid (2.0 g) obtained in Example 3 was subjected to
hydrolysis to give trans-1-isobutyl-2-oxo-5-(o-tolyl)-
1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid
10 (1.23 g) as prisms, m.p. 192°C - 195°C.

IR_{max}^{KBr} cm⁻¹ : 1735, 1650(C=O)

Elemental Analysis for C₂₂H₂₅NO₄:

Calcd.: C 71.91; H 6.66; N 3.81

Found : C 71.86; H 6.78; N 3.80

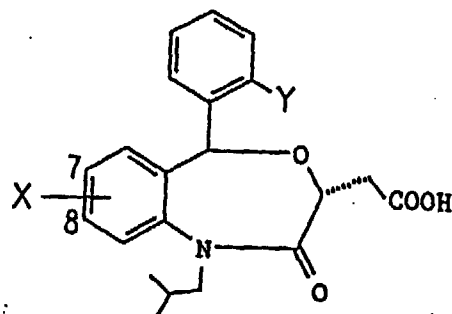
15 Example 6

In substantially the same manner as in Reference
Example 4, using compounds obtained in Example 4,
compounds listed in Table 23 were obtained.

This Sheet Has Been Replaced



Table 23



X	Y	m.p. (°C)	Formula	Elemental Analysis (Found)		
				C	H	N
H	Cl	192-193	$C_{21}H_{22}ClNO_4$	65.03 (64.73)	5.72 (5.63)	3.61 (3.76)
(7)-CH ₃	Cl	166-167	$C_{22}H_{24}ClNO_4$	65.75 (65.78)	6.02 (6.02)	3.49 (3.72)
(7)-Cl	F	153-154	$C_{21}H_{21}ClFNO_4$	62.15 (62.17)	5.22 (5.19)	3.45 (3.50)
(7)-CH ₂ CH ₂ CH ₂ -(8)	Cl	170-171	$C_{24}H_{28}ClNO_4$	66.66 (66.61)	6.18 (6.27)	3.24 (3.12)
H	F	185-187	$C_{21}H_{22}FNO_4$	67.91 (67.93)	5.97 (6.01)	3.77 (3.65)
H	OCH ₃	243-245	$C_{22}H_{26}NO_5$	68.91 (68.89)	6.57 (6.60)	3.65 (3.74)

This Sheet Has Been Replaced



Example 7

Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid
pivaloyloxymethyl ester

5 In N,N-dimethylformamide (10 ml) was dissolved
trans- 7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (0.5
g) obtained in Example 2. To the solution were added
pivaloyloxymethyl chloride (0.43 ml), N,N-diisobutyl
10 ethylamine (0.52 ml) and KI (0.2 g). The mixture was
stirred at room temperature overnight. To the reaction
mixture were added water (100 ml) and ethyl acetate
(100 ml), followed by extraction. The ethyl acetate
layer was washed with an aqueous solution of potassium
15 hydrogensulfate, an aqueous solution of sodium
hydrogencarbonate and water, successively, which was
dried over anhydrous magnesium sulfate. The solvent
was then distilled off under reduced pressure. The
residue was purified by means of a silica gel column
20 chromatography (hexane : ethyl acetate = 10:1 to 5:1)
to afford trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-
2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic
acid pivaloyloxymethyl ester (0.55 g).

IR_{max}^{Neat} cm⁻¹ : 1750, 1675(C=O)

25 Elemental Analysis for C₂₇H₃₁Cl₂NO₆:

Calcd.: C 60.45; H 5.82; N 2.61

Found : C 60.38; H 5.93; N 2.48

Reference Example 7

Ethyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-
30 (2,4-dimethoxybenzyl)-2-oxo-1,2,3,5-tetrahydro-4,1-
benzoxazepine-3-acetic acid

(1) 5-Chloro- α -(2-chlorophenyl)-2-(2,4-
dimethoxybenzyl)aminobenzyl alcohol

To a solution of 2-amino-5-chloro- α -(2-chloro
35 phenyl)benzyl alcohol (5.0 g) and 2,4-dimethoxy
benzaldehyde (3.72 g) in acetic acid (50 ml) was added,



under ice-cooling, sodium borohydride (0.94 g). The mixture was stirred for one hour at room temperature, which was poured into water (200 ml), followed by extraction with ethyl acetate (200 ml x 2). The ethyl acetate layer was washed with 1N sodium hydroxide, which was dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of a silica gel column chromatography (hexane : ethyl acetate = 5:1) to give 5-chloro- α -(2-chlorophenyl)-2-(2,4-dimethoxybenzyl)aminobenzyl alcohol (7.5 g) as an oily product.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.78(3H,s), 3.79(3H,s), 3.65-3.95(1H,m), 4.27(2H,s), 6.15(1H,s), 6.35-7.55(10H,m)
(2) Ethyl ester of 3-[N-[4-chloro-2-(2-chloro- α -hydroxybenzyl)phenyl]-N-(2,4-dimethoxybenzyl)carbamoyl]acrylic acid

A solution of fumaric acid monoethyl ester (2.24 g) and thionyl chloride (3.4 ml) in toluene (10 ml) was stirred for 30 minutes at 90°C. Then the solvent was distilled off under reduced pressure to leave acid chloride of fumaric acid monoethyl ester. This product and 5-chloro- α -(2-chlorophenyl)-2-(2,4-dimethoxybenzyl)aminobenzyl alcohol (5.0 g) obtained in (1) were dissolved in methylene chloride (100 ml). To the solution was added sodium hydrogencarbonate (2.01 g), and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was washed with water and dried over anhydrous magnesium sulfate, then the solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography (hexane : ethyl acetate = 2:1) to give 3-[N-[4-chloro-2-(2-chloro- α -hydroxybenzyl)phenyl]-N-(2,4-dimethoxybenzyl)carbamoyl]acrylic acid ethyl ester (5.5 g) as an oily product.

$\text{IR}_{\text{max}}^{\text{Neat}}$ cm^{-1} : 3390(OH); 1720, 1610(C=O); 1655(C=C)



¹H-NMR spectrum (200 MHz, CDCl₃) δ : 1.2-1.4 (3H, m), 3.4-3.9 (6H, m), 3.95-4.4 (3H, m), 4.45-4.75 (1H, m), 5.25-5.6 (1H, m), 6.0-8.05 (13H, m)

(3) Trans-7-chloro-5-(2-chlorophenyl)-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid ethyl ester

In ethanol (50 ml) was dissolved 3-[N-[4-chloro-2-(2-chloro- α -hydroxybenzyl)phenyl]-N-(2,4-dimethoxybenzyl) carbamoyl]acrylic acid ethyl ester (5.5 g) obtained in (2). To the solution was added potassium carbonate (1.4 g), and the mixture was stirred for 2 hours. To the reaction mixture were added water (200 ml) and ethyl acetate (300 ml). The mixture was subjected to extraction. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate, then the solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography to afford trans-7-chloro-5-(2-chlorophenyl)-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid ethyl ester as an oily product.

IR_{max}^{Neat} cm⁻¹ : 1730, 1675 (C=O)

Elemental Analysis for C₂₈H₂₇Cl₂NO₆:

Calcd.: C 61.77; H 5.00; N 2.57

Found : C 62.06; H 5.26; N 2.61

Reference Example 8

Trans-7-chloro-5-(2-chlorophenyl)-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

To a solution of trans-7-chloro-5-(2-chlorophenyl)-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid ethyl ester (1.0 g) obtained in Reference Example 7 in methanol (20 ml) was added an aqueous solution (10 ml) of potassium carbonate (0.51 g), followed by stirring for one hour



at 60°C. The reaction mixture was acidified with 1N hydrochloric acid (50 ml), which was subjected to extraction with ethyl acetate (100 ml). The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate, then the solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography (hexane : ethyl acetate = 1:1 ~ hexane : methylene chloride : ethanol = 5:5:1) to afford trans-7-chloro-5-(2-chlorophenyl)-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (0.43 g) as a powdery product.

IR_{max}^{KBr} cm^{-1} : 1715, 1670 (C=O)

Elemental Analysis for $\text{C}_{26}\text{H}_{23}\text{Cl}_2\text{NO}_6$:

Calcd.: C 60.48; H 4.49; N 2.71

Found : C 60.21; H 4.73; N 2.72

Example 8

Ethyl ester of 1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid

(1) 2-(5-Oxotetrahydrofuran-2-carbonyl)aminobenzophenone

A mixture of 4.9 g of 5-oxotetrahydrofuran-2-carboxylic acid and 5.5 ml of thionyl chloride was subjected to reflux for 2 hours. Thionyl chloride was then distilled off under reduced pressure to leave 5-oxotetrahydrofuran-2-carbonyl chloride. This product was mixed with 5.0 g of 2-aminobenzophenone, 200 ml of ethyl acetate and 200 ml of a saturated aqueous solution of sodium hydrogencarbonate, which was stirred for one hour at room temperature. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate, then the solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate = 2:1) to give 2-(5-oxotetrahydrofuran-2-carbonyl)aminobenzophenone (6.5 g)



as needles, m.p. 100°C - 102°C.

$\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3300(NH), 1790, 1690, 1640(C=O)

Elemental Analysis for $\text{C}_{18}\text{H}_{15}\text{NO}_4$:

Calcd.: C 69.89; H 4.88; N 4.53

5 Found : C 69.98; H 5.01; N 4.41

(2) 2-[N-benzyl-N-(5-oxotetrahydrofuran-2-carbonyl)]
aminobenzophenone

In 20 ml of N,N-dimethylformamide was dissolved
3.0 g of 2-(5-oxotetrahydrofuran-2-
10 carbonyl)aminobenzophenone obtained in (1). To the
solution were added 1.73 ml of benzyl bromide, 2.67 g
of potassium carbonate and 0.1 g of tetrabutyl ammonium
iodide. The mixture was stirred overnight at room
temperature. The reaction mixture was subjected to
15 extraction with a mixture of 200 ml of ethyl acetate
and 100 ml of water. The ethyl acetate layer was
washed with 0.1N hydrochloric acid and an aqueous
solution of sodium hydrogencarbonate, which was then
dried over anhydrous magnesium sulfate. The solvent
20 was distilled off under reduced pressure. The residue
was purified by means of a silica gel column
chromatography (eluent, hexane : ethyl acetate = 2:1)
to give crystals. Recrystallization from hexane -
ethyl acetate afforded 2-[N-benzyl-N-(5-
25 oxotetrahydrofuran-2-carbonyl)] aminobenzophenone (3.71
g) as needles, m.p. 142-143°C.

$\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 1780, 1660, 1650(C=O)

Elemental Analysis for $\text{C}_{25}\text{H}_{21}\text{NO}_4$:

Calcd.: C 75.17; H 5.30; N 3.51

30 Found : C 75.05; H 5.59; N 3.49

(3) 2-[N-benzyl-N-(4-ethoxycarbonyl-2-hydroxy)butyryl]
aminobenzophenone

In 100 ml of ethanol was dissolved 5.0 g of 2-[N-
benzyl-N-(5-oxotetrahydrofuran-2-
35 carbonyl)]aminobenzophenone obtained in (2). To the
solution was added 0.2 ml of conc. sulfuric acid, and



the mixture was left standing for 7 days. Ethanol was distilled off under reduced pressure. The residue was subjected to extraction with a mixture of 100 ml of water and 200 ml of ethyl acetate. The ethyl acetate layer was washed with an aqueous solution of sodium hydrogencarbonate, which was then dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate = 2:1) to afford 2.8 g of 2-[N-benzyl-N-(4-ethoxycarbonyl-2-hydroxy)butyryl]aminobenzophenone as an oily product.

IR_{max}^{Neat} cm⁻¹ : 3440(OH), 1735, 1670(C=O)

Mass spectrum (m/e) : 445 (M⁺)

¹H-NMR spectrum (200MHz, CDCl₃) δ : 1.20(3H, t, J=7.2Hz), 1.65-2.0(2H, m), 2.2-2.6(2H, m), 3.65-3.7(1H, br), 4.05(2H, q, J=7.2Hz), 4.0-4.35(1H, m), 4.69(1H, d, J=14.4Hz), 4.87(1H, d, J=14.4Hz), 6.9-7.9(14H, m)

(4) 2-[N-benzyl-N-(4-ethoxycarbonyl-2-methanesulfonyloxy)butyryl]aminobenzophenone

2-[N-Benzyl-N-(4-ethoxycarbonyl-2-hydroxy)butyryl]aminobenzophenone (2.8 g) obtained in (3) was dissolved in 30 ml of ethyl acetate. To the solution were added, under ice-cooling, 0.73 ml of methanesulfonyloxy chloride and 1.31 ml of triethylamine. The mixture was stirred for 2 hours at room temperature. The reaction mixture was then washed with 1N HCl and an aqueous solution of sodium hydrogencarbonate, successively, which was dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate = 2:1) to afford 3.2 g of 2-[N-benzyl-N-(4-ethoxycarbonyl-2-methanesulfonyloxy) butyryl]aminobenzophenone as an



oily product.

IR_v^{Neat}_{max} cm⁻¹ : 1730, 1670(C=O)

Mass spectrum (m/e): 523 (M⁺)

¹H-NMR spectrum (200MHz, CDCl₃) δ : 1.1-1.35(3H, m), 2.0-
2.6(4H, m), 3.14+3.38(3H, each s), 3.9-4.7(3H, m),
4.93(d, J=14.2Hz)+5.53(d, J=14.8Hz)(1H), 5.05-
5.15(m) 5.15-5.3(m)(1H), 7.0-7.85(14H, m)

(5) Ethyl-cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-
tetrahydro-4,1-benzoxazepine-3-propionate and ethyl-
trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-
benzoxazepine-3-propionate

In 30 ml of ethanol was dissolved 3.2 g of 2-[N-
benzyl-N-(4-ethoxycarbonyl-2-methanesulfonyloxy)
butyryl]aminobenzophenone obtained in (4). To the
solution was added, under ice-cooling, 0.32 g of sodium
borohydride. The reaction mixture was stirred for 45
minutes at 50°C, followed by cooling the reaction
mixture to room temperature. The reaction mixture was
acidified by the addition of 100 ml of 1N HCl, which
was subjected to extraction with 200 ml of ethyl
acetate. The extract solution was washed with an
aqueous solution of sodium hydrogencarbonate, dried
over magnesium sulfate, then the solvent was distilled
off under reduced pressure. The residue was purified
by means of a silica gel column chromatography (eluent,
hexane : ethyl acetate = 10:1 to 5:1) to afford, as the
first fraction, 0.73 g of ethyl ester of cis-1-benzyl-
2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-
propionic acid as needles, m.p. 107°C - 108°C.

IR_v^{KBr}_{max} cm⁻¹ : 1735, 1670(C=O)

Elemental Analysis for C₂₇H₂₇NO₄:

Calcd.: C 75.50; H 6.34; N 3.26

Found : C 75.21; H 6.44; N 3.27

¹H-NMR spectrum (200MHz, CDCl₃) δ : 1.21(3H, t, J=7.2Hz),
2.2-2.4(2H, m), 2.55(2H, t, J=7.0Hz), 3.72(1H, d, J=16.0Hz),



4.10(2H,q,J=7.2Hz), 4.23(1H,t,J=6.5Hz),
4.70(1H,d,J=16.0Hz), 5.95(1H,s), 7.0-7.5(14H,m)

As the second fraction, 0.3 g of ethyl ester of
trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-
5 benzoxazepine-3-propionic acid as an oily product.

IR_v^{Neat}_{max} cm⁻¹ : 1730, 1670(C=O)

Mass spectrum (m/e) : 429 (M⁺)

¹H-NMR spectrum (200MHz,CDCl₃) δ : 1.17(3H,t,J=7.1Hz),
2.05-2.4(2H,m), 2.49(2H,t,J=7.0Hz), 4.06(2H,q,J=7.1Hz),
10 3.95-4.05(1H,m), 4.86(1H,d,J=14.6Hz), 5.46(1H,s),
5.50(1H,d,J=14.6Hz), 6.53(1H,d,J=7.8Hz), 7.0-
7.45(13H,m)

Example 9

15 Ethyl ester of cis-1-benzyl-7-chloro-5-(2-
chlorophenyl)-2-
oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic
acid

(1) 2',5-Dichloro-2-(5-oxotetrahydrofuran-2-carbonyl)
20 aminobenzophenone

In substantially the same manner as in Example 8
(1), 15 g of 2-amino-2',5-dichlorobenzophenone was
allowed to react with 5-oxotetrahydrofuran-2-carbonyl
chloride to afford 18.1 g of 2',5-dichloro-2-(5-
25 oxotetrahydrofuran-2-carbonyl) aminobenzophenone, m.p.
170°C-173°C.

IR_v^{KBr}_{max} cm⁻¹ : 3250(NH), 1775, 1695, 1640(C=O)

Elemental Analysis for C₁₈H₁₃Cl₂NO₄:

Calcd.: C 57.16; H 3.46; N 3.70

30 Found : C 57.29; H 3.55; N 3.57

(2) 2-[N-benzyl-N-(5-oxotetrahydrofuran-2-
carbonyl)]amino-2',5-dichlorobenzophenone

In substantially the same manner as in Example 8
(2), 20 g of 2',5-dichloro-2-(5-oxotetrahydrofuran-2-
35 carbonyl) aminobenzophenone obtained in (1) was allowed



to react with benzyl bromide to afford 24.5 g of 2-[N-benzyl-N-(5-oxotetrahydrofuran-2-carbonyl)]amino-2',5-dichlorobenzophenone as an oily product.

IR_v^{Neat}_{max} cm⁻¹ : 1780, 1670(C=O)

5 ¹H-NMR spectrum (200MHz,CDCl₃) δ : 2.1-2.55(2H,m), 2.65-3.0(2H,m), 4.01(d,J=14.4Hz)+4.29(d,J=14.4Hz)(1H), 4.75-4.9(1H,m), 5.29(d=14.4Hz)+5.47(d,J=14.4Hz)(1H), 6.6-7.6(13H,m)

(3) 2-[N-benzyl-N-(4-ethoxycarbonyl-2-hydroxy)butyryl]amino-2',5-dichlorobenzophenone

10 23 g of 2-[N-benzyl-N-(5-oxotetrahydrofuran-2-carbonyl)]amino-2',5-dichlorobenzophenone obtained in (2) was subjected to substantially the same reaction as in Example 8 (3) to afford 17 g of 2-[N-benzyl-N-(4-ethoxycarbonyl-2-hydroxy)butyryl]amino-2',5-dichlorobenzophenone.

IR_v^{Neat}_{max} cm⁻¹ : 1730, 1660(C=O)

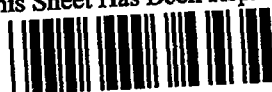
20 ¹H-NMR spectrum (200MHz,CDCl₃) δ : 1.1-1.35(3H,m), 1.6-2.0(2H,m), 2.3-2.8(2H,m), 3.9-4.8(4H,m), 5.34(d,J=14.4Hz)+5.69(d,J=14.4Hz)(1H), 6.8-7.6(12H,m)

(4) 2-[N-benzyl-N-(4-ethoxycarbonyl-2-methanesulfonyloxy)butyryl]amino-2',5-dichlorobenzophenone

25 In substantially the same manner as in Example 8 (4), 17 g of 2-[N-benzyl-N-(4-ethoxycarbonyl-2-hydroxy)butyryl]amino-2',5-dichlorobenzophenone was allowed to react with methanesulfonyl chloride to afford 19 g of 2-[N-benzyl-N-(4-ethoxycarbonyl-2-methanesulfonyloxy)butyryl]amino-2',5-dichlorobenzophenone as an oily product.

30 IR_v^{Neat}_{max} cm⁻¹ : =1730, 1675(C=O)

35 ¹H-NMR spectrum (200MHz,CDCl₃) δ : 1.1-1.35(3H,m), 1.9-2.6(4H,m), 3.17+3.32(3H,each s), 4.85-5.0(m)+5.05-5.15(m)(1H), 5.45(d,J=14.4Hz)+5.72(d,J=14.4Hz)(1H),



6.9-7.6(12H,m)

(5) Ethyl ester of cis-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid and ethyl ester of trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid

19 g of 2-[N-benzyl-N-(4-ethoxycarbonyl-2-methanesulfonyloxy)butyryl]amino-2',5-dichlorobenzophenone was subjected to substantially the same reaction as in Example 8 (5). The reaction mixture was purified by means of a silica gel column chromatography. As the first fraction, 3.1 g of ethyl ester of cis-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid was obtained in the form of an oily product.

$IR_{\text{max}}^{\text{Neat}} \text{ cm}^{-1}$: 1730, 1670(C=O)

As the second fraction, 3.3 g of ethyl ester of trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid as prisms, m.p. 122 C-123°C.

$IR_{\text{max}}^{\text{Neat}} \text{ cm}^{-1}$: 1740, 1670(C=O)

Elemental Analysis for $\text{C}_{27}\text{H}_{25}\text{Cl}_2\text{NO}_4$:

Calcd.: C 65.07; H 5.06; N 2.81

Found : C 65.30; H 5.09; N 2.81

Example 10

Ethyl ester of 7-chloro-5-(2-chlorophenyl)-1-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid

(1) 2',5-Dichloro-2-[N-methyl-N-(5-oxotetrahydrofuran-2-carbonyl)]aminobenzophenone

In 100 ml of acetone was dissolved 15 g of 2',5-dichloro-2-(5-oxotetrahydrofuran-2-carbonyl)aminobenzophenone obtained in Example 9 (1). To the solution were added 4.96 ml of methyl iodide and 11 g of potassium carbonate, and the mixture was stirred for 3



days at room temperature. The reaction mixture was subjected to distillation under reduced pressure. The residue was subjected to extraction by the addition of 200 ml of water and 300 ml of ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate, then the solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel chromatography (eluent, hexane : ethyl acetate = 2:1 to 1:1) to afford 13.5 g of 2',5-dichloro-2-[N-methyl-N-(5-oxotetrahydrofuran-2-carbonyl)]aminobenzophenone as an oily product.

IR_v^{Neat}_{max} cm⁻¹ : 1780, 1675 (C=O)

¹H-NMR spectrum (200MHz, CDCl₃) δ : 2.1-3.0 (4H, m), 3.08+3.14 (3H, each s), 4.75-4.9 (1H, m), 7.1-7.7 (7H, m)
(2) 2',5-Dichloro-2-[N-(4-ethoxycarbonyl-2-hydroxy)butyryl-N-methyl]aminobenzophenone

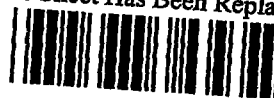
13.5 g of 2',5-dichloro-2-[N-methyl-N-(5-oxotetrahydrofuran-2-carbonyl)]aminobenzophenone was subjected to substantially the same reaction as in Example 8 (3) to afford 9.5 g of 2',5-dichloro-2-[N-(4-ethoxycarbonyl-2-hydroxy)butyryl-N-methyl]aminobenzophenone as an oily product.

IR_v^{Neat}_{max} cm⁻¹ : 1730, 1670, 1660 (C=O)

¹H-NMR spectrum (200MHz, CDCl₃) δ : 1.1-1.4 (3H, m), 1.5-1.9 (2H, m), 2.0-2.75 (2H, m), 3.0-3.5 (3H, m), 3.95-4.5 (4H, m), 7.2-7.7 (7H, m)

(3) 2',5-Dichloro-2-[N-(4-ethoxycarbonyl-2-methanesulfonyloxy)butyryl-N-methyl]aminobenzophenone

In substantially the same manner as in Example 8 (4), 9.5 g of 2',5-dichloro-2-[N-(4-ethoxycarbonyl-2-hydroxy)butyryl-N-methyl]aminobenzophenone obtained in (2) was allowed to react with methanesulfonyl chloride to give 11.0 g of 2',5-dichloro-2-[N-(4-ethoxycarbonyl-2-methanesulfonyloxy)butyryl-N-methyl]aminobenzophenone



as an oily product.

IR_v^{Neat}_{max} cm⁻¹ : 1730, 1680(C=O)

¹H-NMR spectrum (200MHz, CDCl₃) δ : 1.1-1.35(3H,m),
1.9-2.7(4H,m), 3.0-3.7(6H,m), 3.9-4.25(2H,m), 4.9-
5.7(1H,m), 7.3-7.75(7H,m)

(4) Ethyl ester of 7-chloro-5-(2-chlorophenyl)-1-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid

11.0 g of 2',5-dichloro-2-[N-(4-ethoxycarbonyl-2-methanesulfonyloxy)butyryl-N-methyl]aminobenzophenone obtained in (3) was subjected to substantially the same reaction in Example 8 (5), and the reaction product was purified by means of a silica gel column chromatography to give 4.17 g of the mixture of cis- and trans-isomers of ethyl ester of 7-chloro-5-(2-chlorophenyl)-1-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid as an oily product.

IR_v^{Neat}_{max} cm⁻¹ : 1735, 1675(C=O)

¹H-NMR spectrum (200MHz,CDCl₃) δ : 1.19(3H,t,J=7.2Hz),
1.21(3H,t,J=7.2Hz), 2.0-2.4(4H,m), 2.4-2.6(4H,m),
3.15(3H,s), 3.51(3H,s), 3.95-4.2(5H,m),
4.36(1H,t,J=6.6Hz), 5.99(1H,s), 6.16(1H,s),
6.50(1H,d,J=2.4Hz), 7.05-7.8(13H,m)

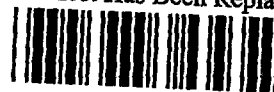
Example 11

Ethyl ester of 1-benzyl-5-(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid
(1) 4'-Methoxy-2-(5-oxotetrahydrofuran-2-carbonyl)amino benzophenone

In substantially the same manner as in Example 8 (1), 8 g of 2-amino-4'-methoxybenzophenone was allowed to react with 5-oxotetrahydrofuran-2-carbonyl chloride to give 12 g of 4'-methoxy-2-(5-oxotetrahydrofuran-2-carbonyl)aminobenzophenone as an oily product.

IR_v^{Neat}_{max} cm⁻¹ : 1780, 1685, 1625(C=O)

¹H-NMR spectrum (200MHz,CDCl₃) δ : 2.3-2.8(4H,m),



3.89(3H,s), 4.9-5.05(1H,m), 6.9-7.85(7H,m), 8.5-8.6(1H,m), 11.2(1H,br)

(2) 2-[N-benzyl-N-(5-oxotetrahydrofuran-2-carbonyl)]amino-4'-methoxybenzophenone

5 In substantially the same manner as in Example 8 (2), 12 g of 4'-methoxy-2-(5-oxotetrahydrofuran-2-carbonyl) aminobenzophenone obtained in (1) was allowed to react with benzyl bromide to give 13.2 g of 2-[N-benzyl-N-(5-oxotetrahydrofuran-2-carbonyl)]amino-4'-methoxybenzo-phenone as prisms, m.p. 137°C-138°C.

10 $\text{IR}_{\text{max}}^{\text{KBr cm}^{-1}}$: 1775, 1660, 1645(C=O)

Elemental Analysis for $\text{C}_{26}\text{H}_{23}\text{NO}_5$:

Calcd.: C 72.71; H 5.40; N 3.26

Found : C 72.98; H 5.46; N 3.22

15 (3) 2-[N-benzyl-N-(4-ethoxycarbonyl-2-hydroxy)butyryl]amino-4'-methoxybenzophenone

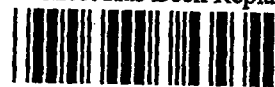
13.0 g of 2-[N-benzyl-N-(5-oxotetrahydrofuran-2-carbonyl)]amino-4'-methoxybenzophenone obtained in (2) was subjected to substantially the same reaction as in Example 8 (3) to give 10.5 g of 2-[N-benzyl-N-(4-ethoxycarbonyl-2-hydroxy)butyryl]amino-4'-methoxybenzophenone as an oily product.

20 $\text{IR}_{\text{max}}^{\text{Neat cm}^{-1}}$: 1730, 1650(C=O)

$^1\text{H-NMR}$ spectrum (200MHz, CDCl_3) δ : 1.1-1.35(3H,m), 1.7-2.1(2H,m), 2.2-2.55(2H,m), 3.88(3H,s), 3.9-4.3(3H,m), 4.52(1H,d,J=14.4Hz), 4.99(1H,d,J=14.4Hz), 6.8-7.9(13H,m)

(4) 2-[N-benzyl-N-(4-ethoxycarbonyl-2-methanesulfonyloxy)butyryl]amino-4'-methoxybenzophenone

30 In substantially the same manner as in Example 8 (4), 10.5 g of 2-[N-benzyl-N-(4-ethoxycarbonyl-2-hydroxy)butyryl]amino-4'-methoxybenzophenone was allowed to react with methanesulfonyl chloride to give 8.5 g of 2-[N-benzyl-N-(4-ethoxycarbonyl-2-methanesulfonyloxy)butyryl]amino-4'-methoxybenzophenone



as an oily product.

IR_v^{Neat}_{max} cm⁻¹ : 1730, 1670, 1660(C=O)

¹H-NMR spectrum (200MHz, CDCl₃) δ : 1.1-1.3(3H, m), 2.0-2.6(4H, m), 3.14+3.38(3H, each s), 3.89+3.91(3H, each s),
5 3.9-4.6(3H, m), 4.9-5.65(2H, m), 6.8-7.9(13H, m)

(5) Ethyl ester of cis-1-benzyl-5-(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid and ethyl ester of trans-1-benzyl-5-(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid
10 benzoxazepine-3-propionic acid

8.5 g of 2-[N-benzyl-N-(4-ethoxycarbonyl-2-methanesulfonyloxy)butyryl]amino-4'-methoxybenzophenone obtained in (4) was subjected to substantially the same reaction as in Example 8 (5) to give a mixture product,
15 which was purified by means of a silica gel column chromatography to give, as the first fraction, 2.0 g of ethyl ester of cis-1-benzyl-5-(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid as needles, m.p. 95-96°C.

IR_v^{KBr}_{max} cm⁻¹ : 1730, 1670(C=O)

Elemental Analysis for C₂₈H₂₉NO₅:

Calcd.: C 73.18; H 6.36; N 3.05

Found : C 73.09; H 6.42; N 3.19

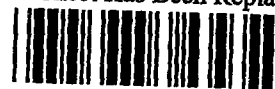
As the second fraction, 0.88 g of ethyl ester of trans-1-benzyl-5-(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid was obtained as an oily product.

IR_v^{Neat}_{max} cm⁻¹ : 1730, 1670(C=O)

¹H-NMR spectrum (200MHz, CDCl₃) δ : 1.17(3H, t, J=7.1Hz),
30 2.1-2.4(2H, m), 2.47(2H, t, J=7.1Hz), 3.82(1H, s), 3.95-4.2(3H, m), 4.87(1H, d, J=14.6Hz), 5.42(1H, s), 6.58(1H, d, J=7.2Hz), 6.8-7.5(12H, m)

Example 12

Methyl ester of 1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid
35



(1) 2-[N-benzyl-N-(2-chloro-4-methoxycarbonyl)butyryl]aminobenzophenone

A mixture of 7.6 g of 2-chloro-4-methoxycarbonyl valeric acid, 9.2 ml of thionyl chloride and 30 ml of toluene was stirred for 30 minutes at 80°C, followed by distilling off the solvent under reduced pressure to leave 2-chloro-4-methoxycarbonyl butyryl chloride. A mixture of this compound, 5.0 g of 2-benzylaminobenzophenone, 100 ml of ethyl acetate and 100 ml of a saturated aqueous solution of sodium hydrogencarbonate was stirred for 30 minutes at room temperature. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate, then the solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate = 5:1) to give 1.2 g of 2-[N-benzyl-N-(2-chloro-4-methoxycarbonyl)butyryl]aminobenzophenone as an oily product.

IR_{max}^{Neat} cm⁻¹ : 1735, 1655(C=O)
Mass spectrum (m/e) : 449 (M⁺)
¹H-NMR spectrum (200MHz, CDCl₃) δ : 2.3-2.8(4H,m), 3.62(3H,s), 4.2-4.3(1H,m), 4.53(1H,d,J=14.4Hz), 4.92(1H,d,J=14.4Hz), 6.9-7.75(14H,m)

(2) 2-[N-benzyl-N-(2-chloro-4-methoxycarbonyl)butyryl]aminodiphenyl methanol
[Method A] In 30 ml of methanol was dissolved 1.2 g of 2-[N-benzyl-N-(2-chloro-4-methoxycarbonyl)butyryl]aminobenzophenone. To the solution was added, under ice-cooling, 0.135 g of sodium borohydride. The mixture was stirred for 30 minutes at room temperature, then the solvent was distilled off under reduced pressure. To the residue was added 100 ml of 1N hydrochloric acid to make the solution acid, which was subjected to extraction with 100 ml of ethyl acetate. The ethyl acetate layer was washed with an aqueous solution of sodium hydrogencarbonate and dried over anhydrous



magnesium sulfate, then the solvent was distilled off. The residue was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate = 2:1) to give 1.1 g of 2-[N-benzyl-N-(2-chloro-4-methoxycarbonyl) butyryl]aminodiphenyl methanol.

IR_v^{Neat}_{max} cm⁻¹ : 3430(OH), 1735, 1660(C=O)

¹H-NMR spectrum (200MHz, CDCl₃) δ : 1.95-2.65(4H,m), 3.2-4.4(6H,m), 5.1-5.5(1H,m), 5.75-6.15(1H,m), 6.5-7.85(14H,m)

[Method B]

A mixture of 6.2 g of 2-chloro-4-methoxycarbonyl valeric acid and 12.6 ml of thionyl chloride was refluxed for 30 minutes, then the solvent was distilled off under reduced pressure to leave 2-chloro-4-methoxycarbonyl butyryl chloride. A mixture of this product, 5.0 g of 2-benzylaminodiphenyl methanol, 100 ml of ethyl acetate and 100 ml of a saturated aqueous solution of sodium hydrogencarbonate was stirred for one hour at room temperature. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. then the solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate = 2:1) to give 5.3 g of 2-[N-benzyl-N-(2-chloro-4-methoxycarbonyl)butyryl]amino-diphenyl methanol as an oily product.

(3) Methyl ester of cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid and methyl ester of trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid

In 20 ml of tetrahydrofuran was dissolved 1.1 g of 2-[N-benzyl-N-(2-chloro-4-methoxycarbonyl)butyryl]aminodiphenyl methanol. To the solution was added 107 mg of sodium hydride (60% in oil), and the mixture was stirred for one hour at room temperature. To the reaction mixture was added 50 ml



of 1N hydrochloric acid to make the solution acid, which was subjected to extraction with 100 ml of ethyl acetate. The ethyl acetate layer was washed with an aqueous solution of sodium hydrogencarbonate and dried
5 over anhydrous magnesium sulfate, then the solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate = 5:1). From the first
10 fraction, 0.4 g of methyl ester of cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid as plates, m.p. 134-136°C

$\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 1740, 1670 (C=O)

Elemental Analysis for $\text{C}_{25}\text{H}_{25}\text{NO}_4$:

Calcd.: C 75.16; H 6.06; N 3.37

15 Found : C 74.74; H 5.97; N 3.38

From the second fraction, 0.18 g of of methyl ester of trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine- 3-propionic acid was obtained as needles, m.p. 116-118°C.

20 $\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 1740, 1670 (C=O)

Elemental Analysis for $\text{C}_{26}\text{H}_{25}\text{NO}_4$:

Calcd.: C 75.16; H 6.06; N 3.73

Found : C 75.22; H 5.94; N 3.58

Example 13

25 Cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid

In 20 ml of methanol was dissolved 0.5 g of ethyl ester of cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid obtained
30 in Example 8. To the solution was added 7 ml of 1N sodium hydroxide, and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was acidified with 100 ml of 1N hydrochloric acid, which was subjected to extraction with 150 ml of ethyl
35 acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. Then the



solvent was distilled off under reduced pressure to leave 0.46 g of cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid as plates, m.p. 112-114°C.

5 IR_v^{KBr}_{max} cm⁻¹ : 1710, 1670(C=O)
Elemental Analysis for C₂₃H₂₃NO₄:

Calcd.: C 74.80; H 5.77; N 3.49

Found : C 74.52; H 5.85; N 4.42

Example 14

10 Trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid

In substantially the same manner as in Example 13, 1.0 g of ethyl ester of trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid
15 obtained in Example 8 was subjected to hydrolysis to give 0.81 g of trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid as plates, m.p. 148-150°C.

IR_v^{KBr}_{max} cm⁻¹ : 1735, 1650(C=O)
20 Elemental Analysis for C₂₃H₂₃NO₄:

Calcd.: C 74.80; H 5.77; N 3.49

Found : C 74.66; H 5.78; N 3.55

In substantially the same manner as above, 0.9 g of methyl ester of trans-1-benzyl-2-oxo-5-phenyl-
25 1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid obtained in Example 12 was subjected to hydrolysis to give 0.86 g of trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid.

Example 15

30 Cis-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid

In substantially the same manner as in Example 13, 3.1 g of ethyl ester of cis-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-
35 benzoxazepine-3-propionic acid obtained in Example 9 was subjected to hydrolysis to give 2.9 g of cis-1-



benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid as prisms, m.p. 135-137°C.

$\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 1725, 1640(C=O)

5 Elemental Analysis for $\text{C}_{25}\text{H}_{21}\text{Cl}_2\text{NO}_4$:

Calcd.: C 63.84; H 4.50; N 2.98

Found : C 64.02; H 4.76; N 2.88

Example 16

10 Trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid

In substantially the same manner as in Example 13, 2.7 g of ethyl ester of trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid obtained in Example 9 was subjected to hydrolysis to give 2.5 g trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid as prisms, m.p. 192-194°C.

$\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 1730, 1640(C=O)

20 Elemental Analysis for $\text{C}_{25}\text{H}_{21}\text{Cl}_2\text{NO}_4$:

Calcd.: C 63.84; H 4.50; N 2.98

Found : C 63.99; H 4.57; N 2.92

Example 17

25 7-Chloro-5-(2-chlorophenyl)-1-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid

In substantially the same manner as in Example 13 4.1 g of ethyl ester of 7-chloro-5-(2-chlorophenyl)-1-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid obtained in Example 10 was subjected to hydrolysis to give 3.7 g of 7-chloro-5-(2-chlorophenyl)-1-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid as an oily product of the mixture of cis- and trans-compounds (1:1).

$\text{IR}_{\text{max}}^{\text{Neat}} \text{cm}^{-1}$: 1705, 1670(C=O)

35 ^1H -NMR spectrum (200MHz, CDCl_3) δ : 2.0-2.4(4H,m), 2.45-



2.7(4H,m), 3.14(3H,s), 3.50(3H,s), 4.00(1H,dd,J=7.2 x
5.4Hz), 4.35(1H,t,J=6.7Hz), 5.99(1H,s), 6.16(1H,s),
6.50(1H,d,J=2.2Hz), 7.0-7.81(13H,m)

Example 18

- 5 Cis-1-benzyl-5-(4-methoxyphenyl)-2-oxo-1,2,3,5-
tetrahydro-4,1-benzoxazepine-3-propionic acid

In substantially the same manner as in Example 13
1.7 g of ethyl ester of cis-1-benzyl-5-(4-
methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-
10 benzoxazepine-3-propionic acid obtained in Example 11
was subjected to hydrolysis to give 1.5 g of cis-1-
benzyl-5-(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-
4,1-benzoxazepine-3-propionic acid as prisms, m.p.
107°C-109°C.

- 15 IR_v^{KBr}_{max} cm⁻¹ : 1715, 1670(C=O)
Elemental Analysis for C₂₆H₂₅NO₃:

Calcd.: C 72.37; H 5.84; N 3.25

Found : C 72.26; H 5.90; N 3.10

Example 19

- 20 Trans-1-benzyl-5-(4-methoxyphenyl)-2-oxo-1,2,3,5-
tetrahydro-4,1-benzoxazepine-3-propionic acid

In substantially the same manner as in Example 13
0.85 g of ethyl ester of trans-1-benzyl-5-(4-
methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-
25 benzoxazepine-3-propionic acid was subjected to
hydrolysis to give 0.78 g of trans-1-benzyl-5-(4-
methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-
benzoxazepine-3-propionic acid as an oily product.

- IR_v^{Neat}_{max} cm⁻¹ : 1710, 1670(C=O)
30 ¹H-NMR spectrum (200MHz,CDCl₃) δ : 2.05-2.35(2H,m),
2.52(2H,t,J=7.1Hz), 3.81(1H,s), 4.00(1H,dd,J=7.3 x
5.7Hz), 4.39(1H,d,J=14.4Hz), 5.40(1H,s),
5.49(1H,d,J=14.4Hz), 6.57(1H,d,J=7.2Hz), 6.8-7.5(12H,m)

Example 20

- 35 Trans-1-benzyl-3-(3-hydroxypropyl)-5-phenyl-1,5-
dihydro-4,1-benzoxazepine-2(3H)-one

The mixture of 0.4 g of methyl ester of trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid obtained in Example 12, 0.16 g of sodium borohydride and 0.16 g of lithium chloride in 15 ml of tetrahydrofuran were stirred for 10 minutes at room temperature. To the resultant was added 30 ml of ethanol, which was stirred for 2 hours at 60°C. To the reaction mixture were added 100 ml of 1N hydrochloric acid and 150 ml of ethyl acetate. The ethyl acetate layer was washed with an aqueous solution of sodium hydrogencarbonate, which was dried over anhydrous magnesium sulfate, then the solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate = 2:1) to give 0.19 g of trans-1-benzyl-3-(3-hydroxypropyl)-5-phenyl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one as needles, m.p. 59-62°C.

IR_v^{KBr}_{max} cm⁻¹ : 1645 (C=O)

Elemental Analysis for C₂₅H₂₅NO₃:

Calcd.: C 77.49; H 6.50; N 3.61

Found : C 77.12; H 6.44; N 3.87

Example 21

Cis-1-benzyl-3-(3-hydroxypropyl)-5-phenyl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one

In substantially the same manner as in Example 20, 0.23 g of methyl ester of cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid obtained in Example 12 was subjected to reduction to give 0.09 g of cis-1-benzyl-3-(3-hydroxypropyl)-5-phenyl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one as needles, m.p. 94-95°C.

IR_v^{KBr}_{max} cm⁻¹ : 1675, 1660 (C=O)

Elemental Analysis for C₂₅H₂₅NO₃:

Calcd.: C 77.49; H 6.50; N 3.61

Found : C 77.44; H 6.49; N 3.76

This Sheet Has Been Replaced



Example 22

N-(cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl)aminoethanol

5 In 5 ml of N,N-dimethylformamide were dissolved
0.3 g of cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-
tetrahydro-4,1-benzoxazepine-3-propionic acid obtained
in Example 13 and 0.054 ml of ethanolamine. To the
solution were added, under ice-cooling, 0.17 g of
10 diethyl phosphorocyanidate and 0.14 ml of
triethylamine. The mixture was stirred for 30 minutes
at room temperature, to which was added 100 ml of
water. The mixture was subjected to extraction with
ethyl acetate (100 ml x 2). The ethyl acetate layer
was washed with 1N hydrochloric acid and an aqueous
15 solution of sodium hydrogencarbonate, successively,
which was then dried over anhydrous magnesium sulfate.
The solvent was distilled off under reduced pressure.
The residue was purified by means of a silica gel
column chromatography (eluent, hexane: methylene
20 chloride:ethanol=5:5:1) to give 0.28 g of N-(cis-1-
benzyl-2-oxo-5-phenyl-1,2,3,5-
tetrahydro-4,1-benzoxazepine-3-propionyl)aminoethanol
as needles, m.p. 117-119°C.

IR_{max}^{KBr} cm⁻¹ : 1670, 1640(C=O)

25 Elemental Analysis for C₂₇H₂₈N₂O₄·0.5H₂O:

Calcd.: C 71.50; H 6.44; N 6.18

Found : C 71.29; H 6.47; N 5.98

This Sheet Has Been Replaced



Example 23

30 N-(trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-
4,1-benzoxazepine-3-propionyl)aminoethanol

In substantially the same manner as in Example 22
0.25 g of trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-
tetrahydro-4,1-benzoxazepine-3-propionic acid obtained
in Example 14 was subjected to condensation with
35 ethanolamine to give 0.20 g of N-(trans-1-benzyl-2-oxo-
5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-



propionyl)aminoethanol

as plates, m.p. 125°C-127°C.

$\text{IR}_{\text{max}}^{\text{KBr cm}^{-1}}$: 1675, 1645(C=O)

Elemental Analysis for $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_4$:

5 Calcd.: C 72.95; H 6.35; N 6.30

Found : C 72.70; H 6.36; N 6.19

Example 24

Methyl ester of N-(cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl)-L-tryptophane

10 In 10 ml of N,N-dimethylformamide were dissolved
0.35 g of cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid obtained
in Example 13 and 0.23 g of L-tryptophane methyl ester
hydrochloride. To the solution were added, under ice-
15 cooling, 0.15 g of diethyl phosphorocyanidate and 0.24
ml of triethylamine. The mixture was stirred for 30
minutes at room temperature, which was subjected to
extraction with the addition of 100 ml of water and 100
ml of ethyl acetate. The ethyl acetate layer was
20 washed with 1N hydrochloric acid and an aqueous
solution of sodium hydrogencarbonate, successively,
which was then dried over anhydrous magnesium sulfate.
The solvent was distilled off, and the residue was
purified by means of a silica gel column chromatography
25 (eluent, hexane:ethyl acetate = 1:1) to give 0.50 g of
methyl ester of N-(cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl)-L-tryptophane
as an oily product.

$\text{IR}_{\text{max}}^{\text{Neat cm}^{-1}}$: 1740, 1665(C=O)

30 $^1\text{H-NMR}$ spectrum (200MHz, CDCl_3) δ : 2.15-2.5(4H,m),

3.27(2H,t,J=4.7Hz), 3.62+3.63(3H,each s),

3.71(1H,d,J=16.0Hz), 4.15-4.3(1H,m),

4.68(1H,d,J=16.0Hz), 4.8-5.0(1H,m), 5.85(1H,s), 6.15-

6.35(1H,m), 6.9-7.6(19H,m), 8.13(1H,br)

35 Example 25

N-(cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-



benzoxazepine-3-propionyl)-L-tryptophane

In 10 ml of methanol was dissolved 0.5 g of methyl ester of N-(cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl)-L-tryptophane obtained in Example 24. To the solution was added 5 ml of 1N sodium hydroxide, and the mixture was stirred for one hour at room temperature. The reaction mixture was made acid by the addition of 100 ml of 1N hydrochloric acid, which was subjected to extraction with 100 ml of ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure to give 0.24 g of N-(cis-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl)-L-tryptophane as a powdery product.

$IR_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$: 1730, 1660(C=O)

Elemental Analysis for $\text{C}_{36}\text{H}_{33}\text{N}_3\text{O}_5$

Calcd.: C 73.58; H 5.66; N 7.15

Found : C 73.56; H 6.07; N 6.79

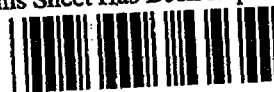
Example 26

Methyl ester of N-(trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl)-L-tryptophane

In substantially the same manner as in Example 24, 0.2 g of trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid obtained in Example 14 was subjected to condensation with L-tryptophane methyl ester hydrochloride to give 0.28 g of methyl ester of N-(trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl)-L-tryptophane as an oily product.

$IR_{\text{max}}^{\text{Neat}} \text{ cm}^{-1}$: 1740, 1670(C=O)

$^1\text{H-NMR}$ spectrum (200MHz, CDCl_3) δ : 2.1-2.4(4H,m), 3.15-3.3(2H,m), 3.6-3.7(3H,m), 3.95-4.15(1H,m), 4.8-5.0(2H,m), 5.45(1H,s), 5.49(1H,d,J=14.2Hz), 6.05-6.2(1H,m), 6.45-6.6(1H,m), 6.9-7.6(18H,m), 8.03(1H,br)



Example 27

N-(trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl)-L-tryptophane

In substantially the same manner as in Example 25,
5 0.28 g of methyl ester of N-(trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl)-L-tryptophane obtained in Example 26 was subjected to hydrolysis to give 0.24 g of N-(trans-1-benzyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl)-L-tryptophane as a powdery
10 product.

IR_{max}^{KBr} cm⁻¹ : 1730, 1660(C=O)

Elemental Analysis for C₃₆H₃₃N₃O₅·0.4H₂O:

Calcd.: C 72.69; H 5.73; N 7.06.

15 Found : C 72.82; H 5.84; N 6.79.

Example 28

Methyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl]-L-tryptophane

20 In substantially the same manner as in Example 24, 0.3 g of trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-2-propionic acid obtained in Example 16 was subjected to condensation with L-tryptophane methyl ester
25 hydrochloride to give 0.41 g of methyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl]-L-tryptophane as an oily product.

IR_{max}^{Neat} cm⁻¹ : 1735, 1660(C=O)

30 ¹H-NMR spectrum (200MHz, CDCl₃) δ : 2.1-2.45(4H,m), 3.2-3.35(2H,m), 3.64+3.66(3H,each s), 3.95-4.15(1H,m), 4.65-4.8(1H,m), 4.8-5.0(1H,m), 5.5-5.65(1H,m), 5.76(1H,s), 6.0-6.2(1H,m), 6.35-6.45(1H,m), 6.9-7.7(16H,m), 8.16(1H,br)

35 Example 29

N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-



1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl]-L-tryptophane

In substantially the same manner as in Example 25, methyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl]-L-tryptophane (0.41 g) obtained in Example 28 was subjected to hydrolysis to give 0.31 g of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl]-L-tryptophane as a powdery product.

IR_{max}^{KBr} cm⁻¹ : 1730, 1660(C=O)

Elemental Analysis for C₃₆H₃₁Cl₂N₃O₅:

Calcd.: C 65.86; H 4.76; N 6.40

Found : C 66.13; H 5.02; N 6.24

Example 30

Ethyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl]-D-tryptophane

In substantially the same manner as in Example 24, 0.3 g of trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionic acid obtained in Example 16 was subjected to condensation with D-tryptophane ethyl ester hydrochloride to give 0.43 g of ethyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl]-D-tryptophane as an oily product.

IR_{max}^{Neat} cm⁻¹ : 1730, 1665(C=O)

¹H-NMR spectrum (200MHz, CDCl₃) δ : 1.1-1.3(3H,m), 2.1-2.45(4H,m), 3.2-3.35(2H,m), 3.95-4.2(3H,m), 4.65-4.8(1H,m), 4.8-5.0(1H,m), 5.5-5.65(1H,m), 5.76(1H,s), 6.0-6.2(1H,m), 6.35-6.45(1H,m), 6.9-7.7(16H,m), 8.13(1H,br)

Example 31

N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl]-D-



tryptophane

In substantially the same manner as in Example 25, 0.43 g of ethyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl]-D-tryptophane obtained in Example 30 was subjected to hydrolysis to give 0.38 g of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-propionyl]-D-tryptophane as a powdery product.

10 $\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 1725, 1660 (C=O)
Elemental Analysis for $\text{C}_{36}\text{H}_{31}\text{Cl}_2\text{N}_3\text{O}_5$:

Calcd.: C 65.86; H 4.76; N 6.40

Found : C 65.90; H 5.15; N 6.03

Example 32

15 Methyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ylacetyl]-L-tryptophane

To a mixture of 0.6 g of trans-7-chloro-5-(2-chlorophenyl)-1-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid obtained in Reference Example 4, 0.42 g of tryptophane methyl ester hydrochloride and 10 ml of dimethylformamide was added, while stirring under ice-cooling, 0.3 g of diethyl phosphorocyanidate. To the resultant was then added 25 0.55 ml of triethylamine. The reaction mixture was stirred for 40 minutes at room temperature, which was poured into ice-water, followed by subjecting the mixture to extraction with ethyl acetate. The organic layer was washed with a dilute aqueous solution of 30 potassium hydrogensulfate, an aqueous solution of sodium hydrogencarbonate and water, successively, dried and concentrated under reduced pressure. The concentrate was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate = 35 1:1 to 1:3). From the first fraction of the eluate, 0.33 g of methyl ester of N-[trans-7-chloro-5-(2-

chlorophenyl)-1-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl acetyl]tryptophane of a crystalline form was obtained, m.p. 236°C-237°C.

5 Elemental Analysis for $C_{30}H_{27}Cl_2N_3O_5$:

Calcd.: C 62.08; H 4.69; N 7.24

Found : C 61.82; H 4.71; N 6.95

From the subsequent fraction of the eluate, 0.28 g of the steric isomer of the above compound was
10 obtained, m.p. 159°C-160°C.

Elemental Analysis for $C_{30}H_{27}Cl_2N_3O_5$:

Calcd.: C 62.08; H 4.69; N 7.24

Found : C 61.94; H 4.50; N 6.96

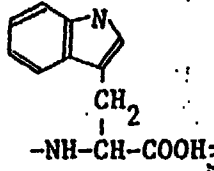
Example 33

15 In substantially the same manner as in Example 32, compounds shown in Table 24 through Table 28 were obtained by using the compounds in Reference Example 5 and Example 2.

This Sheet Has Been Replaced



Table 24

compd. No.	R ₁	R ₂	m.p. (°C)	Formula	Elemental Analysis (Found)		
					C	H	N
1	-CH ₂ - 	-NHCH ₂ COOC ₂ H ₅	153-155	C ₂₈ H ₂₈ Cl ₂ N ₂ O ₅	62.11 (62.05)	4.84 (4.65)	5.17 (4.98)
2	-CH ₂ - 	-NH(CH ₂) ₂ COOC ₂ H ₅	130-131	C ₂₈ H ₂₈ Cl ₂ N ₂ O ₅	62.71 (63.00)	5.08 (5.03)	5.04 (4.99)
3	-CH ₂ - 	Trp·OMe 	amorphous solid	C ₃₆ H ₃₁ Cl ₂ N ₃ O ₅ ·H ₂ O	64.10 (64.32)	4.93 (4.78)	6.23 (6.07)
4	-CH ₂ - 	Trp·OMe	amorphous solid	C ₃₆ H ₃₁ Cl ₂ N ₃ O ₅ ·5/4H ₂ O	63.67 (63.94)	4.97 (4.84)	6.19 (5.90)
5	-CH ₂ - 	D-Trp·OMe	amorphous solid	C ₃₆ H ₃₁ Cl ₂ N ₃ O ₅ ·1/2C ₄ H ₈ O ₂ ·1/2H ₂ O	60.10 (60.11)	4.88 (4.89)	6.78 (6.69)

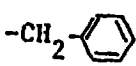
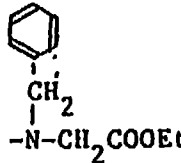
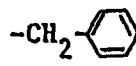
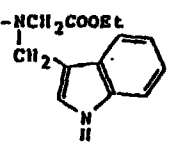
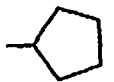
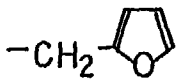
This Sheet Has Been Replaced

Table 25

compd. No.	R ₁	R ₂	m. p. (°C)	Formula	Elemental Analysis (Found)		
					C	H	N
6	-CH ₂ - 	D-Trp·OMe	amorphous solid	C ₃₈ H ₃₁ Cl ₂ N ₃ O ₅ ·1/2C ₄ H ₈ O ₂ ·1/4H ₂ O	60.53 (60.44)	4.84 (4.85)	6.83 (6.83)
7	-CH ₂ - 	Phe·OEt  CH ₂ -NH-CH-COOC ₂ H ₅	amorphous solid	C ₃₅ H ₃₂ Cl ₂ N ₂ O ₅ ·1/4H ₂ O	66.09 (66.10)	5.15 (5.15)	4.41 (4.17)
8	-CH ₂ - 	Phe·OEt	amorphous solid	C ₃₅ H ₃₂ Cl ₂ N ₂ O ₅ ·1/4H ₂ O	66.09 (66.20)	5.15 (5.15)	4.41 (4.17)
9	-CH ₂ - 	D-Phe·OMe	amorphous solid	C ₃₄ H ₃₀ Cl ₂ N ₂ O ₅ ·1/4H ₂ O	65.65 (65.62)	4.94 (5.17)	4.50 (4.51)
10	-CH ₂ - 	D-Phe·OMe	amorphous solid	C ₃₄ H ₃₀ Cl ₂ N ₂ O ₅ ·1/4H ₂ O	65.65 (65.48)	4.94 (5.22)	4.50 (4.31)

This Sheet Has Been Replaced

Table 26

compd. No.	R ₁	R ₂	m. p. (°C)	Formula	Elemental Analysis (Found)		
					C	H	N
1 1			164-165	$C_{35}H_{32}Cl_2N_2O_5 \cdot 1/4H_2O$	66.08 (66.18)	5.17 (5.44)	4.40 (4.13)
1 2			amorphous solid	$C_{37}H_{33}Cl_2N_2O_5 \cdot 2.5H_2O$	62.10 (62.32)	5.35 (5.18)	5.87 (5.63)
1 3	$-C_2H_5$	$-NHCH_2COOC_2H_5$	175-176	$C_{23}H_{24}Cl_2N_2O_5$	57.63 (57.29)	5.05 (4.94)	5.84 (5.90)
1 4	$-(CH_2)_8CH_3$	$-NHCH_2COOC_3H_7$	160-161	$C_{28}H_{34}Cl_2N_2O_5$	61.20 (61.47)	6.24 (6.23)	5.10 (5.39)
1 5	$-CH_2CH(CH_3)_2$	$-NHCH_2COOC_2H_5$	168-170	$C_{25}H_{28}Cl_2N_2O_5$	59.18 (58.97)	5.56 (5.65)	5.52 (5.40)
1 6		$-NHCH_2COOC_2H_5$	206-207	$C_{26}H_{28}Cl_2N_2O_5$	60.12 (60.02)	5.43 (5.51)	5.39 (5.03)
1 7		$-NHCH_2COOC_2H_5$	164-165	$C_{26}H_{24}Cl_2N_2O_6$	58.77 (58.79)	4.55 (4.71)	5.27 (5.19)

This Sheet Has Been Replaced

Table 27

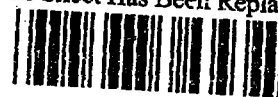
Compd. No.	R ₁	R ₂	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
1 8	$-\text{CH}_2\text{CH}(\text{C}_2\text{H}_5)_2$	$-\text{NHCH}_2\text{COOC}_2\text{H}_5$	142- 143	$\text{C}_{27}\text{H}_{32}\text{Cl}_2\text{N}_2\text{O}_5$	60.56 (60.80)	6.02 (6.06)	5.23 (5.24)
1 9	$-\text{CH}_2\text{C}(\text{CH}_3)_3$	$-\text{NHCH}_2\text{COOC}_2\text{H}_5$	174- 175	$\text{C}_{28}\text{H}_{30}\text{Cl}_2\text{N}_2\text{O}_5$	59.89 (59.97)	5.80 (5.91)	5.37 (5.64)
2 0	$-(\text{CH}_2)_2\text{CH}(\text{CH}_3)_2$	$-\text{NHCH}_2\text{COOC}_2\text{H}_5$	174- 175	$\text{C}_{28}\text{H}_{30}\text{Cl}_2\text{N}_2\text{O}_5$	59.89 (59.69)	5.80 (5.64)	5.37 (5.34)
2 1	$-\text{CH}_2-\text{CH}=\text{C}(\text{CH}_3)_2$	$-\text{NHCH}_2\text{COOC}_2\text{H}_5$	140- 141	$\text{C}_{26}\text{H}_{28}\text{Cl}_2\text{N}_2\text{O}_5$	60.12 (60.14)	5.43 (5.41)	5.39 (5.31)
2 2	$-\text{CH}_2-\text{C}(\text{CH}_3)=\text{CH}_2$	$-\text{NHCH}_2\text{COOC}_2\text{H}_5$	123- 124	$\text{C}_{25}\text{H}_{26}\text{Cl}_2\text{N}_2\text{O}_5$	59.41 (59.11)	5.19 (5.12)	5.54 (5.48)
2 3	$-\text{CH}(\text{C}_2\text{H}_5)_2$	$-\text{NHCH}_2\text{COOC}_2\text{H}_5$	128- 129	$\text{C}_{28}\text{H}_{30}\text{Cl}_2\text{N}_2\text{O}_5$ $\cdot 3/4\text{H}_2\text{O}$	58.37 (58.37)	5.93 (5.85)	5.24 (5.36)
2 4	$-\text{CH}_2-\text{CH}=\text{CH}_2$	$-\text{NHCH}_2\text{COOC}_2\text{H}_5$	191- 192	$\text{C}_{22}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_5$ $\cdot 1/2\text{H}_2\text{O}$	57.61 (57.54)	5.07 (5.16)	5.60 (5.58)
2 5	$-\text{CH}_2\text{C}(\text{CH}_3)_3$	$-\text{NHCH}_2\text{CH}_2\text{COOC}_2\text{H}_5$	172- 173	$\text{C}_{27}\text{H}_{32}\text{Cl}_2\text{N}_2\text{O}_5$	60.56 (60.49)	6.02 6.15	5.23 4.99)



Table 28

compd. No.	R ₁	R ₂	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
2 6	-CH ₂ C(CH ₃) ₃	CH ₂ OH NHCHCOOMe	amorphous solid	C ₂₈ H ₃₀ Cl ₂ N ₂ O ₆	58.10 (57.79)	5.63 5.62	5.21 5.37)
2 7	-CH ₂ C(CH ₃) ₃	CH ₂ OH NHCHCOOMe	amorphous solid	C ₂₈ H ₃₀ Cl ₂ N ₂ O ₆	58.10 (57.91)	5.63 5.62	5.21 5.33)
2 8	-CH ₂ C(CH ₃) ₃	CH ₂ COOMe NHCHCOOMe	amorphous solid	C ₂₈ H ₃₂ Cl ₂ N ₂ O ₇	58.03 (58.19)	5.57 5.64	4.83 4.69)
2 9	-CH ₂ C(CH ₃) ₃	CH(CH ₃) ₂ NHCHCOOMe	190-192	C ₂₈ H ₃₄ Cl ₂ N ₂ O ₅	61.20 (61.25)	6.24 6.28	5.10 5.18)





Example 34

N-[trans-7-chloro-5-(2-chlorophenyl)-1-methyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-ylacetyl]-L-tryptophane

5 0.2 g of ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-methyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-ylacetyl]tryptophane obtained from the first fraction in Example 32 was dissolved in a mixture of 8 ml of methanol and 4 ml of tetrahydrofuran. To
10 the solution were added 200 mg of potassium carbonate and 5 ml of water, and the mixture was stirred for 3 hours at 60°C. The reaction mixture was concentrated under reduced pressure. With 1N hydrochloric acid, the
15 pH of the concentrate was adjusted to 3, followed by extraction with ethyl acetate. The organic layer was washed with water and dried, and the solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent, methylene chloride : methanol : water =
20 100:15:1) to give 0.13 g of N-[trans-7-chloro-5-(2-chlorophenyl)-1-methyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-ylacetyl]-L-tryptophane as a colorless powdery product.

25 $\text{IR}_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$: 3700-2200(COOH), 1660(CO), 1485, 1250, 1110, 740

$^1\text{H-NMR}$ spectrum (200MHz, CDCl_3) δ : 2.2-3.2(4H,m), 3.24(3H,s, N-CH_3), 4.2(1H,m, $\text{C}_3\text{-H}$), 4.63(1H,m), 5.73(1H,s, $\text{C}_5\text{-H}$), 6.34(1H,d, $\text{C}_6\text{-H}$), 6.6-7.7(10H,m)

Elemental Analysis for $\text{C}_{29}\text{H}_{25}\text{Cl}_2\text{N}_3\text{O}_5 \cdot 1/2 \text{C}_4\text{H}_8\text{O}_2 \cdot 1/2 \text{H}_2\text{O}$:

30 Calcd.: C 60.10; H 4.88; N 6.78

Found : C 60.11; H 4.89; N 6.69

0.2 g of the compound subsequently eluted in the silica gel column chromatography was subjected to hydrolysis in substantially the same manner as
35 described above to give 0.11 g of crystals of a steric isomer, m.p. 165°C -167°C.

Elemental Analysis for $C_{29}H_{25}Cl_2N_3O_5 \cdot 1/2C_4H_8O_2 \cdot 1/2H_2O$:

Calcd.: C 60.53; H 4.84; N 6.83

Found : C 60.44; H 4.88; N 6.83

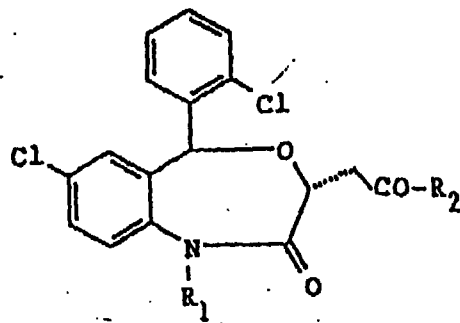
Example 35

- 5 In substantially the same synthetic procedure as in Example 34, compounds shown in Table 29 through Table 33 were obtained.

This Sheet Has Been Replaced

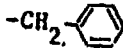
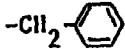
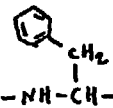
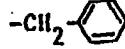
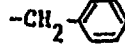
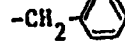
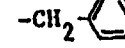
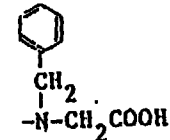
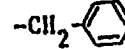
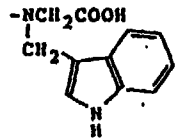


Table 29.



compd. No.	R ₁	R ₂	m. p. (°C)	Formula	Elemental Analysis (Found)		
					C	H	N
1		-NHCH ₂ COOH	130-133	C ₂₆ H ₂₂ Cl ₂ N ₂ O ₅ ·1/2H ₂ O	59.78 (59.81)	4.44 (4.78)	5.36 (4.90)
2		-NH(CH ₂) ₂ COOH	195-197	C ₂₇ H ₂₄ Cl ₂ N ₂ O ₅	61.49 (61.24)	4.59 (4.35)	5.31 (5.27)
3		 Trp-OH -NH-CH-COOH	158-160 [α] _D ^{25°} = -100.3°	C ₃₅ H ₂₉ Cl ₂ N ₃ O ₅ ·1/4H ₂ O	64.97 (64.99)	4.60 (4.82)	6.49 (6.14)
4		Trp-OH	amorphous solid [α] _D ^{25°} = +120.7°	C ₃₅ H ₂₉ Cl ₂ N ₃ O ₅ ·1/4C ₄ H ₈ O ₂	65.06 (65.09)	4.70 (5.08)	6.32 (6.00)
5		D-Trp-OH	157-158 [α] _D ^{25°} = +97.0°	C ₃₅ H ₂₉ Cl ₂ N ₃ O ₅ ·3/2H ₂ O	62.78 (62.77)	4.81 (4.58)	6.28 (6.04)

Table 30

compd. No.	R ₁	R ₂	m. p. (°C)	Formula Elemental Analysis (Found)			
					C	H	N
6		D-Trp-OH	amorphous solid	C ₂₅ H ₂₉ Cl ₂ N ₃ O ₅	62.78	4.81	6.28
			$[\alpha]_D^{25} = -122.9^\circ$	·3/2H ₂ O	(62.51)	(4.98)	(6.02)
7		Phe-OH  -NH-CH-COOH	120-125 $[\alpha]_D^{25} = -109.2^\circ$	C ₂₃ H ₂₅ Cl ₂ N ₂ O ₅ ·1/2H ₂ O	64.71 (64.91)	4.77 (4.70)	4.57 (4.42)
8		Phe-OH	119-122 $[\alpha]_D^{25} = +142.0^\circ$	C ₂₃ H ₂₅ Cl ₂ N ₂ O ₅ ·1/2H ₂ O	64.71 (64.62)	4.77 (4.69)	4.57 (4.41)
9		D-Phe-OH	amorphous solid	C ₂₃ H ₂₅ Cl ₂ N ₂ O ₅ ·3/2H ₂ O	62.86 (62.71)	4.96 (4.66)	4.44 (4.30)
10		D-Phe-OH	amorphous solid	C ₂₃ H ₂₅ Cl ₂ N ₂ O ₅ ·3/2H ₂ O	62.86 (62.89)	4.96 (4.72)	4.44 (4.38)
11		 -N-CH ₂ COOH	193-194	C ₂₃ H ₂₅ Cl ₂ N ₂ O ₅	65.68 (65.81)	4.68 (4.91)	4.64 (4.58)
12		 -NHCH ₂ COOH	amorphous solid	C ₂₇ H ₂₃ Cl ₂ N ₃ O ₅ ·2.5H ₂ O	62.10 (62.32)	5.35 (5.18)	5.87 (5.63)

This Sheet Has Been Replaced

Table 31

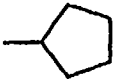
compd. No.	R ₁	R ₂	m. p. (°C)	Formula	Elemental Analysis (Found)		
					C	H	N
13	-C ₂ H ₅	-NHCH ₂ COOH	167-168	C ₂₁ H ₂₀ Cl ₂ N ₂ O ₅ · 1/2H ₂ O	54.79 (54.56)	4.60 (4.57)	6.09 (6.11)
14	-(CH ₂) ₆ CH ₃	-NHCH ₂ COOH	185-186	C ₂₆ H ₃₀ Cl ₂ N ₂ O ₅	59.89 (59.84)	5.80 (5.73)	5.37 (5.53)
15	-CH ₂ CH(CH ₃) ₂	-NHCH ₂ COOH	233-234	C ₂₃ H ₂₄ Cl ₂ N ₂ O ₅	57.63 (57.63)	5.05 (5.23)	5.84 (5.66)
16		-NHCH ₂ COOH	215-216	C ₂₄ H ₂₄ Cl ₂ N ₂ O ₅	58.67 (58.79)	4.92 (5.00)	5.70 (5.96)
17	-CH ₂ - 	-NHCH ₂ COOH	182-183	C ₂₄ H ₂₀ Cl ₂ N ₂ O ₆	57.27 (57.28)	4.01 (4.03)	5.57 (5.53)
18	-CH ₂ CH(C ₂ H ₅) ₂	-NHCH ₂ COOH	110-115	C ₂₅ H ₂₈ Cl ₂ N ₂ O ₅	59.18 (58.32)	5.56 (5.83)	5.52 (5.47)
19	-CH ₂ C(CH ₃) ₃	-NHCH ₂ COOH	235-236	C ₂₄ H ₂₆ Cl ₂ N ₂ O ₅	58.43 (58.57)	5.31 (5.58)	5.68 (5.60)
20	-(CH ₂) ₂ CH(CH ₃) ₂	-NHCH ₂ COOH	114-116	C ₂₄ H ₂₆ Cl ₂ N ₂ O ₅ · 1/2H ₂ O	57.59 (57.24)	5.42 (5.44)	5.58 (5.50)

Table 32

compd. No.	R ₁	R ₂	m. p. (°C)	Formula	Elemental Analysis (Found)		
					C	H	N
21	$-\text{CH}_2-\text{CH}=\text{C}(\text{CH}_3)_2$	$-\text{NHCH}_2\text{COOH}$	146-147	$\text{C}_{24}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_5$	58.67 (58.92)	4.92 (5.05)	5.70 (5.77)
22	$-\text{CH}_2-\text{C}(\text{CH}_3)=\text{CH}_2$	$-\text{NHCH}_2\text{COOH}$	200-201	$\text{C}_{23}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_5$	57.87 (57.87)	4.65 (4.56)	5.87 (6.17)
23	$-\text{CH}(\text{C}_2\text{H}_5)_2$	$-\text{NHCH}_2\text{COOH}$	214-215	$\text{C}_{24}\text{H}_{26}\text{Cl}_2\text{N}_2\text{O}_5$	58.43 (58.56)	5.31 (5.39)	5.68 (5.75)
24	$-\text{CH}_2-\text{CH}=\text{CH}_2$	$-\text{NHCH}_2\text{COOH}$	128-130	$\text{C}_{22}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_5$ $\cdot 1/2\text{H}_2\text{O}$	55.94 (56.09)	4.48 (4.42)	5.93 (5.87)
25	$-\text{CH}_2\text{C}(\text{CH}_3)_3$	$-\text{NHCH}_2\text{CH}_2\text{COOH}$	213-214	$\text{C}_{25}\text{H}_{28}\text{Cl}_2\text{N}_2\text{O}_5$	59.18 (59.12)	5.56 (5.73)	5.52 (5.27)

Table 33

compd. No.	R ₁	R ₂	p. m. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
2 6	-CH ₂ C(CH ₃) ₃	CH ₂ OH NHCHCOOH	amorphous solid	C ₂₅ H ₂₈ Cl ₂ N ₂ O ₆	57.37 (57.54)	5.39 5.67	5.35 5.22)
2 7	-CH ₂ C(CH ₃) ₃	CH ₂ OH NHCHCOOH	143-146	C ₂₅ H ₂₈ Cl ₂ N ₂ O ₆	57.37 (57.34)	5.39 5.47	5.35 5.34)
2 8	-CH ₂ C(CH ₃) ₃	CH ₃ NHCHCOOH	139-141	C ₂₅ H ₂₈ Cl ₂ N ₂ O ₅ 1/2H ₂ O	58.14 (58.36)	5.66 5.89	5.42 5.55)
2 9	-CH ₂ C(CH ₃) ₃	CH ₂ COOH NHCHCOOH	148-150	C ₂₆ H ₂₈ Cl ₂ N ₂ O ₇ 1/2CH ₃ COCH ₃	56.90 (56.88)	5.38 5.66	4.83 4.77)

This Sheet Has Been Replaced



Example 36

[Trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl]methylamine

5 In 5 ml of dimethylformamide was dissolved 1.0 g
of trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid
obtained in Reference Example 5. To the
solution was added 0.3 ml of triethylamine, to which
10 was added dropwise, while stirring under ice-cooling,
0.6 g of diphenylphosphoryl azide. The reaction
mixture was stirred for one hour at room temperature,
which was then poured into ice-water. The mixture was
subjected to extraction with ether. The organic layer
was washed with water and dried, which was then
15 concentrated under reduced pressure. The concentrate
was dissolved in 100 ml of benzene, which was heated
for 30 minutes under reflux. The reaction mixture was
concentrated under reduced pressure. To the
concentrate was added 6 ml of conc. hydrochloric acid,
20 and the mixture was heated for one hour under reflux.
The reaction mixture was concentrated under reduced
pressure. The concentrate was made alkaline by the
addition of a 5% aqueous solution of potassium
carbonate, followed by extraction with ethyl acetate.
25 The organic layer was washed with water and dried, then
the solvent was distilled off under reduced pressure.
To the residue was added an ethanol solution of 4N
hydrochloric acid to lead it to hydrochloride to give
0.85 g of [trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-
30 2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-
yl]methylamine hydrochloride as crystals, m.p. 245-
250°C.

Elemental Analysis for $C_{23}H_{20}Cl_2N_2O_2 \cdot HCl \cdot 3/2H_2O$:

Calcd.: C 56.34; H 4.82; N 5.71
35 Found : C 56.65; H 4.44; N 6.09

Example 37

This Sheet Has Been Replaced

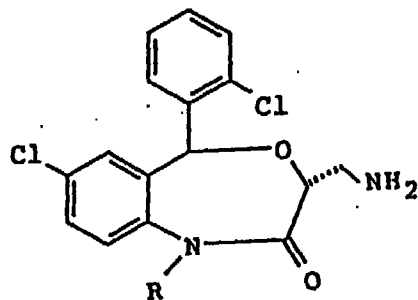


By substantially the same procedure as in Example 36, compounds shown in Table 34 were obtained.

This Sheet Has Been Replaced



Table 34



Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis (Found)		
				C	H	N
1	- CH ₃	114-115	C ₁₇ H ₁₈ Cl ₂ N ₂ O ₂	58.13 (58.16)	4.59 (4.79)	7.98 (7.93)
2	-CH ₂ - 	250-253	C ₂₃ H ₂₈ Cl ₂ N ₂ O ₂ · HCl · 1/4H ₂ O	58.23 (58.08)	5.52 (5.66)	5.91 (5.68)
3	- CH (CH ₃) ₂	136-137	C ₁₉ H ₂₀ Cl ₂ N ₂ O ₂	60.17 (59.93)	5.31 (5.38)	7.39 (7.06)

Example 38

Ethyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl-methylaminocarbonyl]glycine

5 In 4 ml of dimethylformamide was dissolved 0.3 g
of trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid
obtained in Reference Example 5. To the solution was
added 0.15 ml of triethylamine. To the mixture was
10 added, while stirring under ice-cooling, 0.18 g of
diphenylphosphoryl azide. The reaction mixture was
stirred for one hour at room temperature, to which was
added ice-water, followed by extraction with ethyl
acetate. The organic layer was washed with water,
15 dried and concentrated under reduced pressure. To the
concentrate was added 10 ml of benzene, and the mixture
was heated for one hour under reflux while stirring.
To the reaction mixture were added 0.14 g of glycine
ethyl ester hydrochloric acid and 0.15 ml of
20 triethylamine. The mixture was then heated for 3 hours
under reflux. The reaction mixture was concentrated
under reduced pressure. The concentrate was subjected
to extraction with ethyl acetate. The organic layer
was washed with water and dried, then the solvent was
25 distilled off under reduced pressure. Crystals obtained
from the residue were recrystallized from a mixture of
ethyl acetate and hexane to give 0.33 g of the title
compound as white crystals, m.p. 200-201°C.

Elemental Analysis for $C_{28}H_{27}Cl_2N_3O_5$:

30 Calcd.: C 60.44; H 4.89; N 7.55
 Found : C 60.29; H 4.82; N 7.68

This Sheet Has Been Replaced



Example 39

35 In 8 ml of methanol was dissolved 0.2 g of ethyl
ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-
2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl-
methylaminocarbonyl]glycine. To the solution were



added 0.2 g of potassium carbonate and 2 ml of water, and the mixture was stirred for 3 hours at 60°C. The reaction mixture was concentrated under acidified to pressure, to which was added water, followed by
5 extraction with ether. The aqueous layer was acidified to pH 3 with dilute hydrochloric acid, which was subjected to extraction with ethyl acetate. The organic layer was washed with water and dried, then the solvent was distilled off under reduced pressure to
10 leave crystalline residue. Recrystallization from ethyl acetate afforded 0.18 g of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl-methylaminocarbonyl]glycine as colorless needles, m.p. 153-155°C.

15 Elemental Analysis for $C_{26}H_{23}Cl_2N_3O_5 \cdot 1/4H_2O$:

Calcd.: C 58.60; H 4.45; N 7.88

Found : C 58.63; H 4.42; N 7.58

Example 40

Ethyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chloro-
20 phenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]glycine

In 10 ml of acetonitrile was dissolved 0.4 g of trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methylamine
25 obtained in Example 36. To the solution were added 0.15 g of ethyl chloroacetate and 0.5 g of potassium carbonate. The mixture was heated under reflux for 15 hours while stirring. The reaction mixture was concentrated under reduced pressure, and the
30 concentrate was subjected to extraction with ethyl acetate. The organic layer was washed with water and dried, then the solvent was distilled under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent, hexane :
35 ethyl acetate = 3:2 to 1:2) to give 0.28 g of ethyl ester of N-[trans-1-benzyl-7-chloro-5-(2-



chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]glycine as an oily product. This product was made into hydrochloride salt to give white crystals, m.p. 182-184°C.

5 Elemental Analysis for $C_{27}H_{26}Cl_2N_2O_4 \cdot HCl$:

Calcd.: C 58.98; H 4.95; N 5.09

Found : C 58.70; H 4.98; N 5.07

Example 41

10 N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]glycine

In 6 ml of methanol was dissolved 0.15 g of ethyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]glycine obtained in Example 40. To the
15 solution were added 0.4 g of potassium carbonate and 2 ml of water. The mixture was stirred for 2 hours at 50°C. The reaction mixture was concentrated under reduced pressure, whose pH was adjusted to 3 with dilute hydrochloric acid, followed by extraction with
20 methylene chloride. The organic layer was washed with water and dried, then the solvent was distilled off under reduced pressure. From the residue was obtained 0.13 g of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]glycine as crystals, m.p. 224-
25 226°C.

Elemental Analysis for $C_{25}H_{22}Cl_2N_2O_4 \cdot 1/2H_2O$:

Calcd.: C 60.74; H 4.69; N 5.67

Found : C 60.74; H 4.48; N 5.70

30 Example 42

N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]-N-methylglycine

To 0.13 g of ethyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]glycine obtained in Example 40
35



were added 2 ml of formalin and 2 ml of oxalic acid. The mixture was heated at 80°C for 2 hours. The reaction mixture was concentrated under reduced pressure, and the concentrate was subjected to
5 extraction with ethyl acetate. The organic layer was washed with an aqueous solution of sodium hydrogencarbonate, then with water, followed by drying. The solvent was distilled off under reduced pressure. The residue was dissolved in 6 ml of methanol. To the
10 solution were added 0.2 g of potassium carbonate and 2 ml of water. The mixture was stirred for 2 hours at 60°C. The reaction mixture was concentrated under reduced pressure, to which was added water, followed by extraction with ether. The aqueous layer was acidified
15 to pH 4 with dilute hydrochloric acid, followed by extraction with methylene chloride. The organic layer was washed with water and dried, then the solvent was distilled off under reduced pressure. From the residue was obtained 0.1 g of N-[trans-1-benzyl-7-chloro-5-(2-
20 chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]-N-methylglycine as crystals, m.p. 195-197°C.

Elemental Analysis for $C_{26}H_{24}Cl_2N_2O_4 \cdot 1/4H_2O$:

Calcd.: C 61.97; H 4.90; N 5.56
25 Found : C 61.90; H 4.73; N 5.67

Example 43

N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]-N-acetylglycine

30 In 4 ml of methanol was dissolved 60 mg of ethyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]glycine obtained in Example 40. To the solution were added 0.2 ml of acetic anhydride and 0.2
35 ml of triethylamine. The mixture was heated for one hour under reflux while stirring. The reaction mixture



was concentrated under reduced pressure, which was subjected to extraction with ethyl acetate. The organic layer was washed with an aqueous solution of potassium hydrogensulfate, an aqueous solution of sodium hydrogencarbonate and water, which was then dried, followed by distilling off the solvent. The residue was dissolved in 4 ml of methanol, to which was added 2 ml of a 5% aqueous solution of potassium carbonate. The mixture was stirred for 30 minutes at 60°C. The reaction mixture was concentrated under reduced pressure, to which was added 1N hydrochloric acid to acidify the solution, followed by extraction with ethyl acetate. The organic layer was washed with water and dried, then the solvent was distilled off under reduced pressure. From the residue, 45 mg of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]-N-acetyl glycine was obtained as crystals, m.p. 143-145°C.

Elemental Analysis for $C_{27}H_{24}Cl_2N_2O_5 \cdot 1/4H_2O$:

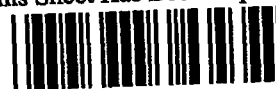
Calcd.: C 60.96; H 4.64; N 5.27

Found : C 60.90; H 4.39; N 5.32

Example 44

N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]-N-benzoylglycine

In 10 ml of methylene chloride was dissolved 0.15 g of ethyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]glycine obtained in Example 40. To the solution were added 90 mg of benzoic anhydride, 0.1 ml of triethylamine and 10 mg of 4-dimethylaminopyridine. The mixture was stirred for 15 hours at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to extraction with ethyl acetate. The



organic layer was washed with water and dried, then the solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate = 3:2) to give an oily product. The oily product was dissolved in a mixture of 5 ml of methanol and 2 ml of tetrahydrofuran. To the solution were added 0.2 g of potassium carbonate and 2 ml of water. The mixture was then stirred for 2 hours at 60°C. The reaction mixture was concentrated under reduced pressure. To the concentrate was added dilute hydrochloric acid to adjust the pH to 2, followed by extraction with ethyl acetate. The organic layer was washed with water and dried, then the solvent was distilled off under reduced pressure. From the residue was obtained 75 mg of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]-N-benzoylglycine as amorphous solid matter.

IR_{max}^{KBr} cm⁻¹ : 3700-2200(COOH), 1740(CO), 1670(CO), 1420, 1250, 1170, 1080, 750

¹H-NMR spectrum (200MHz, CDCl₃) δ : 3.8-5.1(6H, m), 5.75(1H, s, C₅-H), 6.40(1H, s, C₆-H), 7.0-7.8(16H, m)

Elemental Analysis for C₃₂H₂₆Cl₂N₂O₅·2/3H₂O:

Calcd.: C 62.34; H 4.74; N 4.54

Found : C 62.40; H 4.44; N 4.32

Example 45

Trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-3-(3-methoxycarbonylmethylcarbamoyl)methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

To a mixture of 0.25 g of [trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl]methylamine obtained in Example 36, 0.1 g of malonic acid half ester potassium salt and 4 ml of dimethylformamide were added, while stirring under ice-cooling, 0.13 g of diethyl phosphorocyanidate and 0.23 ml of triethylamine. The reaction mixture was



stirred for 40 minutes at room temperature, to which was added ice-water, followed by extraction with ethyl acetate. The organic layer was washed with an aqueous solution of sodium hydrogensulfate, an aqueous solution of sodium hydrogen carbonate and water, successively, which was then dried. The solvent was distilled off, and the residue was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate : ethanol = 10:10:1) to give 0.22 g of trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-3-(3-methoxycarbonylmethylcarbamoyl)methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine as a white powdery product.

$\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3370(NH), 2950, 1745(CO), 1670(CO), 1480, 1420, 1250

$^1\text{H-NMR}$ spectrum (200MHz, CDCl_3) δ : 3.31(2H, s, COCH_2 , CO_2), 3.74(3H, s, OCH_3), 3.7-4.2(3H, m), 4.8(1H, d), 5.6(1H, d), 5.8(1H, s, $\text{C}_5\text{-H}$), 6.42(1H, d, $\text{C}_6\text{-H}$), 7.2-7.8(1H, m)

Elemental Analysis for $\text{C}_{27}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_5 \cdot 1/2\text{H}_2\text{O}$:

Calcd.: C 60.46; H 4.70; N 5.22

Found : C 60.27; H 4.85; N 4.95

In 5 ml of methanol was dissolved 0.15 g of the white powdery product obtained above. To the solution were added 0.2 g of potassium carbonate and 1.5 ml of water, then the mixture was stirred for 2 hours at 50°C . The reaction mixture concentrated under reduced pressure. The concentrate was neutralized with dilute hydrochloric acid, followed by extraction with ethyl acetate. The organic layer was washed with water and dried, then the solvent was distilled off under reduced pressure. From the residue was obtained 0.14 g of Trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-3-(3-hydroxycarbonylmethylcarbamoyl)methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine as a white powdery product.



IR_v^{KBr}_{max} cm⁻¹ : 3700-2200(COOH), 1730(CO), 1670(CO),
1480, 1240

¹H-NMR spectrum (200MHz, CDCl₃) δ : 3.31(2H, s, -CO
CH₂COOH), 3.7-4.2(3H, m), 4.75(1H, d), 5.62(1H, d),

5 5.77(1H, s, C₅-H), 6.44(1H, d, C₆-H), 7.04(1H, t, NH), 7.2-
7.7(11H, m)

Elemental Analysis for C₂₆H₂₂Cl₂N₂O₅·1/2H₂O:

Calcd.: C 59.78; H 4.44; N 5.36

Found : C 59.47; H 4.69; N 5.13

10 Example 46

Trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methanol and
3,5-trans-7-chloro-3-chloromethyl-5-(2-chlorophenyl)-2-
oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

15 In mixture of 12 ml of glacial acetic acid and 10
ml of water was suspended 2.0 g of [trans-1-benzyl-7-
chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-
benzoxazepine-3-yl]methylamine hydrochloride obtained
20 in Example 36. To the suspension was added dropwise,
while stirring under ice-cooling, 1 ml of an aqueous
solution of 1.0 g of sodium nitrite, in the course of
10 minutes. The reaction mixture was stirred for one
hour at room temperature, which was added to ice-water,
followed by extraction with ethyl acetate. The organic
25 layer was washed with an aqueous solution of sodium
hydrogencarbonate and water, successively, which was
then dried, followed by distilling off the solvent
under reduced pressure. The residue was dissolved in
50 ml of methanol, to which was added 5 ml of a 10%
30 aqueous solution of potassium carbonate. The mixture
was stirred for 15 minutes at 60°C. The reaction
mixture was concentrated under reduced pressure. The
concentrate was subjected to extraction with ethyl
acetate. The organic layer was washed with water and
35 dried, then the solvent was distilled off under reduced
pressure. The residue was purified by means of a

silica gel column chromatography (eluent, hexane : ethyl acetate = 4:1 to 1:1). From the preceding portion of the eluate, 0.2 g of trans-7-chloro-3-chloromethyl-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine as colorless prisms, m.p. 177-179°C.

Mass spectrum (m/e) : 445 (M^+)

Elemental Analysis for $C_{23}H_{18}Cl_3NO_2$:

Calcd.: C 61.83; H 4.06; N 3.14

Found : C 62.11; H 4.01; N 3.38

From the subsequent portion of the eluate, 1.05 g of trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methanol as colorless needles, m.p. 158-159°C

Mass spectrum (m/e) : 427, 429 (M^+)

Elemental Analysis for $C_{23}H_{19}Cl_2NO_3$:

Calcd.: C 64.49; H 4.47; N 3.27

Found : C 64.36; H 4.39; N 3.34

Example 47

By substantially the same procedure as in Example 46, compounds shown in Table 35 were obtained.

This Sheet Has Been Replaced

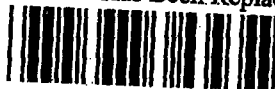
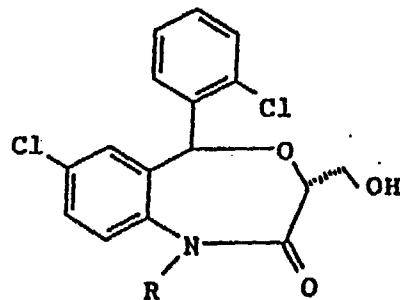


Table 35



compd. No.	R	m. p. (°C)	Formula	Elemental Analysis (Found)		
				C	H	N
1	-CH ₃	208-209	C ₁₇ H ₁₅ Cl ₂ NO ₃	57.97 (58.18)	4.29 (4.46)	3.98 (3.79)
2	-CH ₂ - 	171-172	C ₂₃ H ₂₅ Cl ₂ NO ₃	63.60 (63.60)	5.80 (5.89)	3.22 (3.02)
3	-CH(CH ₃) ₂	154-155	C ₁₉ H ₁₉ Cl ₂ NO ₃	60.01 (59.83)	5.04 (4.91)	3.68 (3.79)

This Sheet Has Been Replaced

Example 48

Trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine-3-carboxylic acid

5 In 20 ml of acetone was dissolved 0.5 g of trans-
1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-
tetrahydro-4,1-benzoxazepine-3-methanol obtained in
Example 46. To the solution was added dropwise, while
stirring at room temperature, 0.5 ml of a Jones'
reagent. The reaction mixture was stirred for one hour
10 at room temperature, which was then concentrated under
reduced pressure. The concentrate was subjected to
extraction with ethyl acetate. The organic layer was
washed with water and dried, then the solvent was
distilled off under reduced pressure. From the residue
15 was obtained 0.23 g of trans-1-benzyl-7-chloro-5-(2-
chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-
benzoxazepine-3-carboxylic acid as white crystals,
m.p. 177-178 C.

Elemental Analysis for $C_{23}H_{17}Cl_2NO_4$:

20 Calcd.: C 62.46; H 3.87; N 3.17
Found : C 62.24; H 3.93; N 3.30

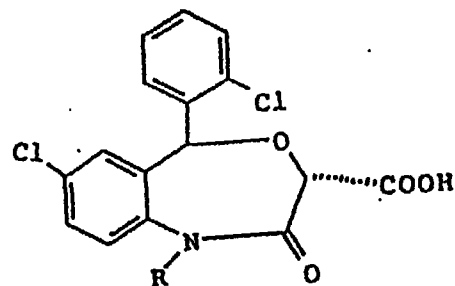
Example 49

By substantially the same synthetic procedure as
in Example 48, compounds listed in Table 36 were
25 obtained.

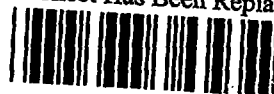
This Sheet Has Been Replaced



Table 36



compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
1	-CH ₃	167-168	C ₁₇ H ₁₃ Cl ₂ NO ₄ · 1/4C ₄ H ₁₀ O · 1/4H ₂ O	55.54 (55.72)	4.14 (4.34)	3.60 (3.34)
2	-CH ₂ - 	189-190	C ₂₃ H ₂₃ Cl ₂ NO ₄	57.88 (57.76)	4.35 (4.55)	3.55 (3.43)
3	-CH(CH ₃) ₂	181-182	C ₁₉ H ₁₇ Cl ₂ NO ₄	61.62 (61.69)	5.17 (5.39)	3.12 (3.39)



Example 50

Ethyl ester of 3-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]thioglycolic acid

5 In 6 ml of acetonitrile was dissolved 0.2 g of
trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-3-
chloromethyl-2-oxo-1,2,3,5-tetrahydro-4,1-
benzoxazepine. To the solution were added 0.08 g of
ethyl thioglycolate and 0.1 g of cesium fluoride. The
10 mixture was heated under reflux for 40 minutes while
stirring. The reaction mixture was concentrated under
reduced pressure. The concentrate was subjected to
extraction with ethyl acetate. The organic layer was
washed with water and dried, then the solvent was
15 distilled off under reduced pressure. The residue was
purified by means of a silica gel column chromatography
(eluent, hexane : ethyl acetate = 4:1) to afford 0.16 g
of ethyl 3-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-
2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]
20 thioglycolate as colorless needles, m.p.153-154°C.
Elemental Analysis for $C_{27}H_{25}Cl_2NO_4S$:

Calcd.: C 61.13; H 4.75; N 2.64

Found : C 61.04; H 4.72; N 2.54

Example 51

25 3-[Trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]glycolic
acid

In a mixture of 4 ml of methanol and 2 ml of
tetrahydrofuran was dissolved 0.11 g of 3-[trans-1-
30 benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-
tetrahydro-4,1-benzoxazepin-3-ylmethyl]thioglycolic
acid ester. To the solution were added 0.2 g of
potassium carbonate and 2 ml of water, then the mixture
was stirred for one hour at 60°C. The reaction mixture
35 was concentrated under reduced pressure. The
concentrate was rendered acid with dilute hydrochloric

acid, which was then subjected to extraction with ethyl acetate. The organic layer was washed with water and dried, then the solvent was distilled off under reduced pressure. From the residue was obtained 90 mg of 3-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]thioglycolic acid as white crystals, m.p. 148-149°C.

Elemental Analysis for $C_{25}H_{21}Cl_2NO_4S$:

Calcd.: C 59.77; H 4.21; N 2.79
Found : C 59.89; H 4.31; N 2.77

Example 52

3-[Trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]glycolic acid

To a suspension of 50 mg of sodium hydride in 4 ml of dimethylformamide was added 0.2 g of trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methanol, while stirring under ice-cooling. The mixture was stirred for 10 minutes at the same temperature, to which was then added 0.1 g of ethyl chloroacetate, followed by stirring for 30 minutes at room temperature. The reaction mixture was poured into ice-water, which was subjected to extraction with ethyl acetate. The organic layer was washed with an aqueous solution of potassium hydrogensulfate, an aqueous solution of sodium hydrogencarbonate and water, successively and dried, then the solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate = 5:1) to give crystals. The crystals were dissolved in 5 ml of methanol. To the solution were added 0.2 g of potassium carbonate and 2 ml of water. The mixture was stirred for 5 hours at 60°C. The reaction mixture was concentrated under reduced





pressure. The concentrate was rendered acid with dilute hydrochloric acid, followed by extraciton with ethyl acetate. The organic layer was washed with water and dried, then the solvent was distilled off under reduced pressure. From the residue was obtained 50 mg of 3-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylmethyl]glycolic acid as white crystals, m.p.92-94°C.

Elemental Analysis for $C_{25}H_{21}Cl_2NO_3 \cdot 1/2C_4H_{10}O \cdot 1/2H_2O$:

10 Calcd.: C 60.91; H 5.11; N 2.63 ..

Found : C 60.95; H 4.99; N 2.77 ..

Example 53

Methyl ester of N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylcarbonyl]tryptophane

15 By substantially the same procedure as in Example 32, 0.4 g of 3,5-trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-carboxylic acid obtained in Example 48 was subjected to the reaction to give a crude product, which was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate : methylene chloride = 9:3:1). From the preceding portion of the eluate, 0.25 g of the product was obtained as a white powdery product.

IR $\nu_{\max}^{KBr}$ cm^{-1} : 3400(NH), 1740(CO), 1690(CO), 1655(CO)

1H -NMR spectrum (200MHz, $CDCl_3$) δ : 3.44(2H,d), 3.64(3H,s, OCH_3), 4.55(1H,s, C_3 -H), 4.70(1H,d, $PhCH_2$), 5.03(1H,m), 5.69(1H,d, $PhCH_2$), 5.79(1H,s, C_3 -H), 6.37(1H,d, C_6 -H), 6.9-8.2(15H,m)

From the subsequent poriton of the eluate, 0.22 g of the title compound as an amorphous solid product.

IR $\nu_{\max}^{KBr}$ cm^{-1} : 3400(NH), 1740(CO), 1695(CO), 1660(CO), 1520, 1480, 1240

35 1H -NMR spectrum (200MHz, $CDCl_3$) δ : 3.2-3.55(2H,m),



3.70(3H,s,OCH₃), 4.53(1H,s,C₃-H), 4.62(1H,d),
5.06(1H,m), 5.63(1H,d), 5.76(1H,s,C₅-H), 6.33(1H,d,C₆-
H), 6.8-8.4(15H,m)

Example 54

5 N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepin-3-
ylcarbonyl]tryptophane

10 N-[trans-1-benzyl-7-chloro-5-(2-chlorophenyl)-2-
oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-
ylcarbonyl]tryptophane ethyl ester obtained in Example
53 was subjected to substantially the same procedure as
in Example 34. From 0.25 g of the compound obtained as
the preceding eluate, 70 mg of a colorless crystalline
product was obtained, m.p.250-155°C (decomp.).

15 Elemental Analysis for C₃₄H₂₇Cl₂N₃O₅.H₂O:

Calcd.: C 63.16; H 4.52; N 6.50

Found : C 63.34; H 4.63; N 6.42

20 From 0.22 g of the compound eluted subsequently,
0.11 g of a colorless amorphous solid product was
obtained

IR_{max}^{KBr} cm⁻¹ : 3700-2200(NH,COOH), 1740(CO), 1680(CO),
1660(CO), 1525, 1240

¹H-NMR spectrum (200MHz,CDCl₃) δ: 3.40(2H,m),
4.54(1H,s), 4.63(1H,d), 5.05(1H,m), 5.63(1H,d),
25 5.70(1H,s,C₅-H), 6.31(1H,d,C₆-H), 6.8-8.4(15H,m)

Elemental Analysis for C₃₄H₂₇Cl₂N₃O₅:

Calcd.: C 64.97; H, 4.33; N 6.67

Found : C 64.70; H, 4.58; N 6.49

Example 55

30 N-(cis-7-chloro-1-isopropyl-5-phenyl-2-oxo-1,2,3,5-
tetrahydro-4,1-benzoxazepin-3-ylacetyl)glycine ethyl
ester

35 In 5 ml of methanol was dissolved 0.3 g of ethyl
ester of 3,5-cis-7-chloro-1-isopropyl-5-phenyl-1,2,3,5-
tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic acid ethyl
ester disclosed in JPA S57(1982)-35576. To the



solution were added 0.3 g of potassium carbonate and 2 ml of water. The mixture was stirred for 8 hours at room temperature. The reaction mixture was concentrated under reduced pressure. To the concentrate was added water, which was subjected to extraction with ether. The aqueous layer was separated, to which was added dilute hydrochloric acid to adjust its pH to 3. The organic layer was washed with water and dried, then the solvent was distilled off under reduced pressure. From the residue was obtained 0.15 g of a powdery product. The product and 0.07 g of glycine ethyl ester hydrochloride were dissolved in 4 ml of dimethylformamide. To the solution were added, while stirring under ice-cooling, 0.1 g of diethyl phosphorocyanidate and, then, 0.2 ml of triethylamine. The reaction mixture was stirred for one hour at room temperature, which was poured into ice-water, followed by extraction with ethyl acetate. The organic layer was washed with an aqueous solution of potassium hydrogensulfate, an aqueous solution of hydrogencarbonate and water, successively, which was then dried. The solvent was distilled off under reduced pressure. The residue was purified by means of a silica gel column chromatography (eluent, hexane : ethyl acetate = 2:1 to 3:2) to afford 0.11 g of N-[cis-7-chloro-1-isopropyl-5-phenyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-ylacetyl]glycine ethyl ester as a crystalline product, m.p. 188°C-190°C.

Elemental Analysis for $C_{24}H_{27}ClN_2O_5$:

Calcd.: C 62.81; H 5.93; N 6.10

Found : C 62.52; H 6.10; N 6.04

Example 56

N-[cis-7-chloro-1-isopropyl-5-phenyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-ylacetyl]glycine

In a mixture of 2 ml of methanol and 1 ml of water was suspended 48 mg of N-(trans-7-chloro-1-isopropyl-5-



phenyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-ylacetyl)glycine ethyl ester obtained in Example 55. To the suspension was added 0.1 g of potassium carbonate. The mixture was stirred for 6 hours at room temperature. The reaction mixture was adjusted to pH 4 with dilute hydrochloric acid, which was subjected to extraction with ethyl acetate. The organic layer was washed with water and dried, then the solvent was distilled off under reduced pressure. Crystals obtained from the residue were recrystallized from ether and hexane to afford 29 mg of N-(cis-7-chloro-1-isopropyl-5-phenyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepin-3-ylacetyl)glycine as white needles.

IR_{max}^{KBr} cm^{-1} : 3700-2200(COOH), 1710(CO), 1680(CO), 1480, 1250, 700

¹H-NMR spectrum (200MHz, CDCl₃) δ : 2.7-3.4(2H, m), 4.4(1H, dd, C₃-H), 4.75(1H, d), 5.34(1H, s, C₅-H), 5.5(1H, d), 6.48(1H, s, C₆-H), 6.9-7.6(12H, m)

Elemental Analysis for C₂₄H₂₀ClNO₄.3/4H₂O:

Calcd.: C 66.20; H 4.98; N 3.22

Found : C 66.12; H 5.19; N 2.97

Example 57

Trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-butyric acid ethyl ester

(1) A solution of oxalyl chloride (0.72 ml) in methylene chloride (10 ml) was cooled to -65°C, to which was added dropwise a solution of dimethyl sulfoxide (0.63 ml) in methylene chloride (2 ml) taking 5 minutes, followed by stirring for 5 minutes. To the mixture was added dropwise, taking 15 minutes, a solution of trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethanol (2.5 g) obtained in Example 47 in methylene chloride (15 ml), which was stirred for 10 minutes. To the resultant mixture was added triethylamine (3.45 ml)



taking 5 minutes, then the cooling bath was removed. The mixture was stirred for 10 minutes at room temperature, to which was then added 1N hydrochloric acid (50 ml), followed by stirring. The methylene chloride layer was dried over anhydrous magnesium sulfate, then the solvent was distilled off under reduced pressure to leave trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetaldehyde (2.3 g) as an oily product.

IR_v^{Neat}_{max} cm⁻¹ : 1720, 1670(C=O)

¹H-NMR spectrum (200MHz, CDCl₃) δ : 1.29(3H,t,J=7.1Hz), 1.29(3H,d,J=7.0Hz), 1.56(3H,d,J=6.8Hz), 2.7-2.85(2H,m), 3.91(1H,t,J=6.5Hz), 4.19(2H,q,J=7.1Hz), 4.75-5.0(1H,m), 5.90(1H,dt,J=15.6, 1.5Hz), 6.01(1H,s), 6.51(1H,d,J=2.4Hz), 6.97(1H,dt,J=15.6, 7.2Hz), 7.2-7.8(6H,m), 9.83(1H,s)

(2) In toluene (20 ml) was dissolved trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetaldehyde (1.5 g). To the solution was added (ethoxycarbonylmethylene)-triphenylphosphorane (2.0 g), and the mixture was stirred for 3 hours at 90°C. The solvent was distilled off, and the residue was purified by means of a silica gel column chromatography (hexane : ethyl acetate = 10:1) to give ethyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-crotonic acid (1.28 g) as prisms, m.p.126-127°C.

IR_v^{KBr}_{max} cm⁻¹ : 1715(C=O), 1670(C=C)

Elemental Analysis for C₂₄H₂₅Cl₂NO₄:

Calcd.: C 62.34; H 5.45; N 3.03

Found : C 62.47; H 5.28; N 3.08

(3) In ethyl acetate (20 ml) was dissolved ethyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-crotonic acid



(0.45 g). To the solution was added 10% palladium carbon (0.1 g), and the mixture was subjected to catalytic reduction at room temperatures under atmospheric pressure. The theoretical amount of hydrogen was allowed to be absorbed, then the catalyst was removed, followed by distilling off ethyl acetate under reduced pressure. The residue was crystallized from a small volume of hexane to give ethyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-butyric acid (0.37 g) as prisms, m.p. 100-101°C.

IR_{max}^{KBr} cm^{-1} : 1730, 1670 (C=O)

Elemental Analysis for $\text{C}_{24}\text{H}_{27}\text{Cl}_2\text{NO}_4$:

Calcd.: C 62.07; H 5.86; N 3.02

Found : C 62.35; H 5.93; N 2.95

Example 58

Trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-butyric acid

In ethanol (5 ml) was dissolved ethyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-butyric acid (0.25 g). To the solution was added 1N sodium hydroxide (4 ml), then the mixture was stirred for 30 minutes at room temperatures. The mixture was acidified with 1N aqueous solution of hydrochloric acid (50 ml), followed by extraction with ethyl acetate (100 ml). The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to leave trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-butyric acid (0.20 g) as prisms, m.p. 158-160°C.

IR_{max}^{KBr} cm^{-1} : 1710, 1670 (C=O)

Elemental Analysis for $\text{C}_{22}\text{H}_{23}\text{Cl}_2\text{NO}_4$:

Calcd.: C 60.56; H 5.31; N 3.21

Found : C 60.62; H 5.18; N 3.23



Example 59

Ethyl ester of N-[trans-1-isobutyl-2-oxo-5-(o-tolyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid

- 5 Trans-1-isobutyl-2-oxo-5-(o-tolyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (0.4 g) obtained in Example 5 and glycine ethyl ester hydrochloride were subjected to substantially the same procedure as in Example 24 to give ethyl ester of N-
- 10 [trans-1-isobutyl-2-oxo-5-(o-tolyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid (0.47 g) as needles, m.p. 137-138°C.

$\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3360(NH), 1745, 1655(C=O)

Elemental Analysis for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_5$:

- 15 Calcd.: C 69.01; H 7.13; N 6.19 .
 Found : C 69.01; H 7.18; N 6.26

Example 60

N-[trans-1-isobutyl-2-oxo-5-(o-tolyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid

- 20 Ethyl ester of N-[trans-1-isobutyl-2-oxo-5-(o-tolyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid (0.3 g) obtained in Example 59 was subjected to hydrolysis in substantially the same manner as in Example 35 to afford N-[trans-1-isobutyl-
- 25 2-oxo-5-(o-tolyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid (0.26 g) as prisms, m.p. 220-223°C.

$\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 1755, 1670, 1630(C=O)

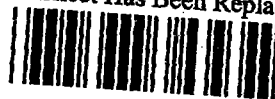
Elemental Analysis for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_5$:

- 30 Calcd.: C 67.91; H 6.65; N 6.60
 Found : C 67.96; H 6.86; N 6.69

Example 61

Ethyl ester of N-[trans-5-(2-fluorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid

- 35 Trans-5-(2-fluorophenyl)-1-isobutyl-2-oxo-1,2,3,5-



tetrahydro-4,1-benzoxazepine-3-acetic acid (0.4 g)
obtained in Example 6 was allowed to react with glycine
ethyl ester hydrochloride in substantially the same
manner as in Example 24 to afford ethyl ester of N-
5 [trans-5-(2-fluorophenyl)-isobutyl-2-oxo-1,2,3,5-
tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid
(0.45 g) as needles, m.p.166-168°C.

IR_{max}^{KBr} cm⁻¹ : 3370(NH), 1750, 1660(C=O)

Elemental Analysis for C₂₅H₂₉FN₂O₅:

10 Calcd.: C 65.78; H 6.40; N 6.14

Found : C 65.89; H 6.34; N 6.15

Example 62

N-[trans-5-(2-fluorophenyl)-1-isobutyl-2-oxo-1,2,3,5-
tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid

15 Ethyl ester of N-[trans-5-(2-fluorophenyl)-1-
isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-
acetyl]aminoacetic acid (0.3 g) obtained in Example 61
was subjected to hydrolysis in substantially the same
manner as in Example 25 to afford N-[trans-5-(2-
20 fluorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-
benzoxazepine-3-acetyl]aminoacetic acid (0.27 g) as
prisms, m.p.201-203°C.

IR_{max}^{KBr} cm⁻¹ : 1755, 1670, 1630(C=O)

Elemental Analysis for C₂₃H₂₅FN₂O₅:

25 Calcd.: C 64.48; H 5.88; N 6.54

Found : C 64.54; H 5.95; N 6.51

Example 63

Ethyl ester of N-[trans-1-isobutyl-5-(2-methoxyphenyl)-
2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]
30 aminoacetic acid

In N,N-dimethylformamide (10 ml) were dissolved
trans-1-isobutyl-5-(2-methoxyphenyl)-2-oxo-1,2,3,5-
tetrahydro-4,1-benzoxazepine-3-acetic acid (0.4 g)
obtained in Example 6 and glycine ethyl ester
35 hydrochloride (0.18 g). To the solution were added,
under ice-cooling, diethyl phosphorocyanidate (0.22 g)

and triethylamine (0.35 ml). The mixture was stirred for 30 minutes at room temperature, to which were then added water (100 ml) and ethyl acetate (100 ml), followed by extraction. The ethyl acetate layer was washed with 1N hydrochloric acid and an aqueous solution of sodium hydrogencarbonate, which was then dried on anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of a silica gel column chromatography (hexane : ethyl acetate = 1:1) to give ethyl ester of N-[trans-1-isobutyl-5-(2-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid (0.45 g) as needles, m.p.135-137°C.

$\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 1750, 1670(C=O)

15 Elemental Analysis for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_6$:

Calcd.: C 66.65; H 6.88; N 5.98

Found : C 66.72; H 6.91; N 5.98

Example 64

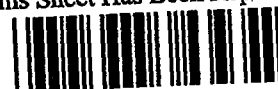
20 N-[trans-1-isobutyl-5-(2-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid

In ethanol (5 ml) was dissolved ethyl ester of N-[trans-1-isobutyl-5-(2-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid (0.3 g) obtained in Example 63. To the solution was added 1N sodium hydroxide, and the mixture was stirred for 15 minutes, which was acidified by the addition of 1N aqueous solution of hydrochloric acid (50 ml), followed by extraction with ethyl acetate (100 ml). The ethyl acetate layer was washed with water, which was then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to leave N-[trans-1-isobutyl-5-(2-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid (0.27 g) as prisms, m.p.210-211°C.

$\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 1760, 1670, 1630(C=O)

This Sheet Has Been Replaced





Elemental Analysis for $C_{24}H_{28}N_2O_6$:

Calcd.: C 65.44; H 6.41; N 6.36

Found : C 65.32; H 6.38; N 6.33

Example 65

5 Trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethanol

In tetrahydrofuran (7 ml) were dissolved trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (0.5 g)
10 obtained in Reference Example 5, and N-methylmorpholine (0.15 ml). To the solution was added ethyl chlorocarbonate (0.13 ml) at -10°C , and the mixture was stirred for 10 minutes. To the mixture was added sodium borohydride (0.15 g), to which was then added
15 dropwise methanol taking 5 minutes, followed by stirring for 30 minutes at 0°C . The reaction mixture was poured into 1N hydrochloric acid (50 ml), followed by extraction with ethyl acetate (100 ml). The ethyl acetate layer was washed with an aqueous solution of
20 sodium hydrogencarbonate, then dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of a silica gel column chromatography to afford trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethanol (0.41 g) as prisms, m.p. $188-189^{\circ}\text{C}$.
25

$\text{IR}_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3430(OH), 1650(C=O)

Elemental Analysis for $C_{20}H_{21}Cl_2NO_3$:

Calcd.: C 60.92; H 5.37; N 3.55

30 Found : C 61.12; H 5.39; N 3.72

Example 66

Ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid

35 In N,N-dimethylformamide (10 ml) were dissolved trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-



1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (0.3 g) and glycine ethyl ester hydrochloride (0.12 g). To the solution were added, under ice-cooling, diethyl phosphorocyanidate (0.15 g) and triethylamine (0.24 ml). The mixture was stirred for 30 minutes at room temperature, to which were added water (100 ml) and ethyl acetate (100 ml), followed by extraction. The ethyl acetate layer was washed with 1N hydrochloric acid and an aqueous solution of sodium hydrogencarbonate, which was then dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of a silica gel column chromatography (hexane : ethyl acetate = 1:1) to afford ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid (0.31 g) as needles, m.p. 197-199°C.

IR_v^{KBr}_{max} cm⁻¹ : 1755, 1670, 1655 (C=O)

Elemental Analysis for C₂₄H₂₆Cl₂N₂O₅:

Calcd.: C 58.43; H 5.31; N 5.68

Found : C 58.73; H 5.33; N 5.80

Example 67

N-[trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid

In ethanol (10 ml) was dissolved ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid (0.2 g) obtained in Example 66. To the solution was added 1N sodium hydroxide (2 ml), and the mixture was stirred for 15 minutes. To the reaction mixture was added 1N aqueous solution of hydrochloric acid (100 ml) to make the solution acid, followed by extraction with ethyl acetate (100 ml). The ethyl acetate layer was washed with water, which

was then dried over anhydrous magnesium sulfate,
followed by distilling off the solvent to leave N-
[trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-
1,2,3,5- tetrahydro-4,1-benzoxazepine-3-
5 acetyl]aminoacetic acid (0.18 g) as crystals, m.p.134-
135°C.

IR_v^{KBr}_{max} cm⁻¹ : 1725, 1650(C=O)

Elemental Analysis for C₂₂H₂₂Cl₂N₂O₃.1/2Et₂O:

Calcd.: C 57.38; H 5.42; N 5.58

10 Found : C 57.48; H 5.59; N 5.58

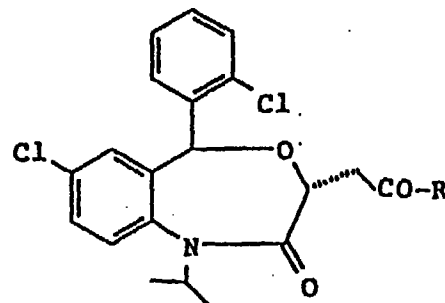
Example 68

By substantially the same synthetic method as in
Example 66, compounds listed in Table 37 and Table 38
were obtained as crystalline or oily products.

This Sheet Has Been Replaced



Table 37



compd. No.	R	m. p. (°C)	Formula	Elemental Analysis (Found)		
				C	H	N
1	NHCH ₂ CH ₂ COOEt	182-183	C ₂₅ H ₂₈ Cl ₂ N ₂ O ₅	59.18 (59.13)	5.56 (5.56)	5.52 (5.45)
2	 -NH-CH-COOCH ₃ (D, L)	160-164	C ₂₉ H ₂₈ Cl ₂ N ₂ O ₅	62.71 (62.55)	5.08 (5.11)	5.04 (4.86)
3	 -NH-CH-COOC ₂ H ₅	187-188	C ₃₁ H ₃₂ Cl ₂ N ₂ O ₅	63.81 (63.97)	5.53 (5.59)	4.80 (4.98)



Table 38

compd. No.	R	IR, ν_{max} cm^{-1}	$^1\text{H-NMR}$ spectrum (200MHZ, CDCl_3)
4	$\begin{array}{c} \text{OH} \\ \\ \text{CH}_2 \\ \\ \text{NH-CH-COOCH}_3 \end{array}$	1745, 1660 (C=O)	1.29(3H, d, J=7.0Hz), 1.54, 1.56(3H, ^{both} d, J=6.6Hz), 2.6-3.05(2H, m), 3.76, 3.77(3H, ^{both} s, OMe), 3.85-4.2(3H, m), 4.25-4.45(1H, m), 4.55-4.7(1H, m), 4.7-4.95(1H, m), 5.99, 6.01(1H, ^{both} s), 6.45-6.55(1H, m), 6.84, 6.92(1H, ^{both} brd, J=7.0Hz), 7.2-7.8(6H, m)
5	$\begin{array}{c} \text{CH}_3\text{OOC} \\ \\ \text{CH}_2 \\ \\ \text{NH-CH-COOCH}_3 \end{array}$	1740, 1670 (C=O)	1.29(3H, d, J=7.0Hz), 1.55, 1.56(3H, ^{both} d, J=6.8Hz), 2.65-3.1(4H, m), 3.6-3.8(6H, m, $\text{CH}_3 \times 2$), 4.25-4.4(1H, m), 4.7-5.0(2H, m), 6.00(1H, s), 6.45-6.55(1H, m), 6.8-7.0(1H, m), 7.2-7.8(6H, m)
6	$\begin{array}{c} \text{COOC}_2\text{H}_5 \\ \\ \text{CH}_2 \\ \\ \text{CH}_2 \\ \\ \text{NH-CH-COOC}_2\text{H}_5 \end{array}$	1735, 1670 (C=O)	1.15-1.4(9H, m), 1.55, 1.56(3H, ^{both} d, J=6.8Hz), 1.9-2.5(4H, m), 2.70(1H, dd, J=14.4, 6.2Hz), 2.85-3.05(1H, m), 4.05-4.4(5H, m), 4.5-4.7(1H, m), 4.7-5.0(1H, m), 6.00, 6.01(1H, ^{both} s), 6.50(1H, d, J=2.4Hz), 6.55, 6.64(1H, ^{both} brd), 7.2-7.8(6H, m)



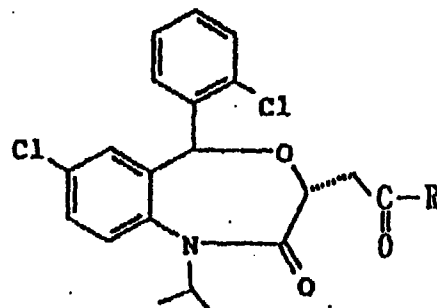
Example 69

By substantially the same synthetic method as in Example 67, compounds listed in Table 39 and Table 40 were obtained.

This Sheet Has Been Replaced



Table 39



compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
1	NHCH ₂ CH ₂ COOH	182-184	C ₂₉ H ₂₄ Cl ₂ N ₂ O ₅	57.63 (57.36)	5.05 (5.08)	5.84 (5.67)
2	 NH-CH-COOH	amorphous solid	C ₂₈ H ₂₆ Cl ₂ N ₂ O ₅	62.11 (62.09)	4.84 (5.02)	5.17 (5.24)
3	 CH ₂ NH-CH-COOH	213-215	C ₂₉ H ₂₈ Cl ₂ N ₂ O ₅	62.71 (62.61)	5.08 (4.96)	5.04 (5.13)

This Sheet Has Been Replaced

Table 40

Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
4	$\begin{array}{c} \text{L-Ser-OH} \\ \text{HO} \\ \\ \text{CH}_2 \\ \\ \text{NH-CH-COOH} \end{array}$	amorphous solid	$\text{C}_{23}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_8$	55.77 (55.88)	4.88 (5.27)	5.66 (5.84)
5	$\begin{array}{c} \text{COOH} \\ \\ \text{CH}_2 \\ \\ \text{NH-CH-COOH} \\ \text{(L)} \end{array}$	amorphous solid	$\text{C}_{24}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_7$	55.07 (54.65)	4.62 (4.98)	5.35 (5.22)
6	$\begin{array}{c} \text{COOH} \\ \\ (\text{CH}_2)_2 \\ \\ \text{NH-CH-COOH} \\ \text{(L)} \end{array}$	198-199	$\text{C}_{25}\text{H}_{26}\text{Cl}_2\text{N}_2\text{O}_7$	55.88 (55.97)	4.88 (5.16)	5.21 (5.16)

This Sheet Has Been Replaced



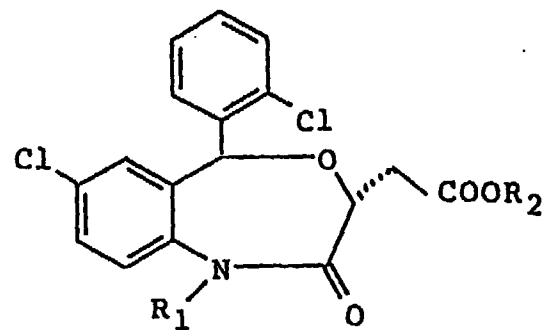
Example 70

By substantially the same synthetic method as in Reference Example 2, a compound listed in Table 41 was obtained.

This Sheet Has Been Replaced



Table 41



R ₁	R ₂	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
		amorphous solid	C ₃₃ H ₂₀ Cl ₂ N ₂ O ₄	IR ν ^{neat} max cm ⁻¹ : 3400(NH), 1740(CO), 1670(CO) ¹ H-NMR(CDCl ₃) δ : 2.9(1H, dd), 3.2(1H,dd), 4.47(1H,dd,C ₃ -H), 5.54(1H,s,C ₅ -H)		

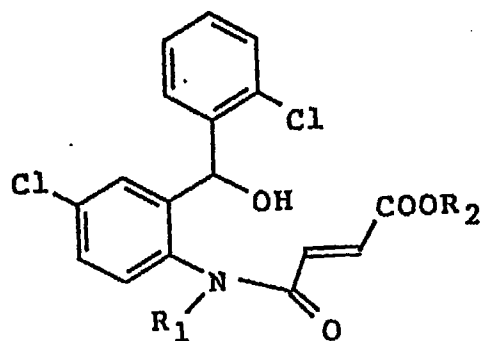
This Sheet Has Been Replaced

Also, physicochemical properties of an intermediate are shown in Table 42.

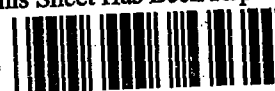
This Sheet Has Been Replaced



Table 42



R ₁	R ₂	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
		amorphous solid	C ₃₃ H ₂₈ Cl ₂ N ₂ O ₄	1H-NMR(CDCl ₃) δ : 4.7(1H, d), 5.03(2H,s,CH ₂ Ph), 5.65(1H,d), 6.0-8.3(20H,m)		



Example 71

Ethyl ester of trans-7-chloro-5-(2,4,6-trimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

- 5 (1) 2-acetylamino-5-chloro-2',4',6'-trimethoxybenzophenone

A solution of 2.41 g of 1,3,5-trimethoxybenzene in 10 ml of dry tetrahydrofuran was cooled to -78°C, and 9.1 ml of n-butyl lithium (1.58 M solution in hexane) was added dropwise over a period of 10 minutes. This solution was added dropwise to a solution of 2.0 g of 6-chloro-4-methyl-4H-3,1-benzoxazin-4-one in 20 ml of dry tetrahydrofuran. After mixture stirring at 0°C for 1 hour, the solvent was removed, after which the residue was acidified with dilute hydrochloric acid and then extracted with ethyl acetate. After the extract was washed with dilute hydrochloric acid and an aqueous solution of sodium hydrogen carbonate, the solvent was removed, and the residue was subjected to silica gel column chromatography to yield 1.28 g of a crystal. Melting point: 159-160°C.

Elemental analysis (for $C_{18}H_{18}ClNO_5$)

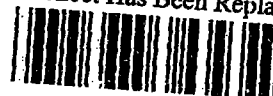
Calcd.: C 59.43; H 4.99; N 3.85

Found : C 59.39; H 4.94; N 3.86

- 25 (2) 2-amino-5-chloro-2',4',-6'-trimethoxybenzophenone

A mixture of 4.7 g of 2-acethylamino-5-chloro-2',4',6'-trimethoxybenzophenone, 50 ml of 6 N hydrochloric acid and 50 ml of ethanol was refluxed for 1 hour while heating. After the solvent was distilled off, the residue was basefied with an aqueous solution of sodium hydrogen carbonate and then extracted with ethyl acetate. After the extract was washed with water and dried, the solvent was removed, and the residue was subjected to silica gel column chromatography to yield 3.75 g of a crystal.

- 35 (3) 2-amino-5-chloro- α -(2,4,6-trimethoxyphenyl)benzyl



alcohol

To a solution of 3.0 g of 2-amino-5-chloro-2',4',6'-trimethoxybenzophenone in 50 ml of tetrahydrofuran, 0.43 g of lithium aluminum hydride was added, followed by stirring for 1 hour. After water was added, the solution was extracted with ethyl acetate and dried over anhydrous sodium sulfate, after which the solvent was removed and the residue was subjected to silica gel column chromatography to yield 2.9 g of a crystal.

(4) 5-chloro- α -(2,4,6-trimethoxyphenyl)-2-(neopentylamino)benzyl alcohol

After a solution of 2.5 g of 2-amino-5-chloro- α -(2,4,6-trimethoxyphenyl)benzyl alcohol, 1.01 ml of trimethylacetaldehyde and 0.56 g of acetic acid in 30 ml of ethanol was stirred at room temperature for 1.5 hours, 0.81 g of sodium cyanoborohydride was added, followed by stirring overnight. After concentration and subsequent dilution with water, the solution was extracted with ethyl acetate. After solvent removal, the residue was subjected to silica gel column chromatography to yield 2.2 g of a crystal.

(5) Ethyl ester of 3-[N-(4-chloro-2-(α -hydroxy-2,4,6-trimethoxybenzyl)phenyl]-N-neopentylcarbamoyl]acrylic acid

2.0 g of 5-chloro- α -(2,4,6-trimethoxyphenyl)-2-(neopentylamino)benzyl alcohol, 0.99 g of monoethyl ester of chlorofumaric acid and 0.85 g of sodium hydrogen carbonate were added to 30 ml of dichloromethane, and this mixture was stirred for 30 minutes. To the reaction mixture was added water, and the organic layer was dried, after which the solvent was removed and the residue was subjected to silica gel column chromatography to yield 2.5 g of an oily compound.

(6) Ethyl ester of trans-7-chloro-5-(2,4,6-

trimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid.

2.5 g of ethyl ester of 3-[N-(4-chloro-2-(α -hydroxy-2,4,6-trimethoxybenzyl)phenyl]-N-

5 neopentylcarbamoyle]acrylic acid and 1.33 g of potassium carbonate were added to 30 ml of ethanol, and this mixture was stirred at room temperature overnight.

After ethyl acetate was added, the mixture was washed with water and dried, after which the solvent was

10 removed and the residue was subjected to silica gel column chromatography to yield 2.0 g of a crystal.

Melting point: 154-155°C.

Elemental analysis (for $C_{27}H_{34}ClNO_7$)

Calcd.: C 62.36; H 6.59; N 2.69

15 Found : C 62.51; H 6.32; N 2.67

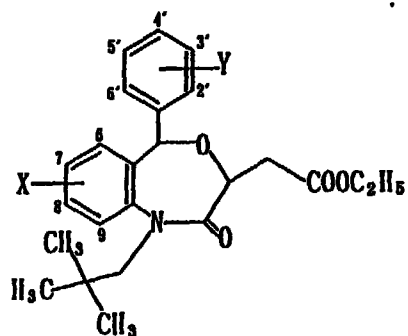
Example 72

By the same procedure as in Example 71, the compounds listed in Tables 43 and 44 were obtained.

This Sheet Has Been Replaced



Table 4 3



Compd. No.	X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
1	7-Cl	2', 4' -OCH ₃	117-119	C ₂₆ H ₃₂ ClNO ₆	63.73 (63.63)	6.58 6.81	2.86 2.83)
2	7-Cl	2', 6' -OCH ₃	175-177	C ₂₆ H ₃₂ ClNO ₆	63.73 (63.54)	6.58 6.49	2.86 2.89)
3	7-Cl	2', 5' -OCH ₃	165-166	C ₂₆ H ₃₂ ClNO ₆	63.73 (63.63)	6.58 6.59	2.86 2.82)
4	7-Cl	2', 3' -OCH ₂ O-	164-167	C ₂₅ H ₂₈ ClNO ₆	63.35 (63.31)	5.95 5.88	2.96 2.92)
5	7-Cl	3', 4' -OCH ₂ O-	133-134	C ₂₅ H ₂₈ ClNO ₆	63.36 (63.13)	5.95 5.96	2.96 2.79)

Table 4 4

Compd. No.	X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
6	8-Cl	2'-Cl	142-143	$C_{24}H_{27}Cl_2NO_4$	62.07 (61.87)	5.86 6.01	3.02 2.89)
7	7, 9-Cl	2'-OCH ₃	167-169	$C_{25}H_{29}Cl_2NO_5$	60.73 (60.73)	5.91 5.97	2.83 2.74)
8	7-Cl	2'-OCH ₃	173-174	$C_{25}H_{30}ClNO_5$	65.28 (65.32)	6.57 6.64	3.05 3.11)
9	7-Cl	2'-Br	128-129	$C_{24}H_{27}BrClNO_4$	56.65 (56.77)	5.35 5.42	2.75 2.76)
10	7-Br	2'-Cl	143-146	$C_{24}H_{27}BrClNO_4$	56.65 (56.50)	5.35 5.23	2.75 2.58)
11	7-Cl	2', 3'-OCH ₃	184-185	$C_{26}H_{32}ClNO_6$	63.73 (63.75)	6.58 6.82	2.86 2.67)



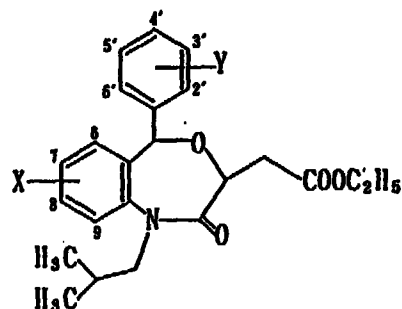
Example 73

By the same procedure as in Example 71 except that isobutyl aldehyde was used in place of trimethylacetaldehyde, the compounds listed in Tables 5 45 through 47 were obtained.

This Sheet Has Been Replaced



Table 45



Compd. No.	X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
1	7-F	2'-Cl	oil	$C_{23}H_{26}ClFNO_4$	1H -NMR($CDCl_3$) δ : 0.93 and 1.03(each 3H, d, J=6.6Hz), 1.25(3H, t, J=7.2Hz), 1.86-2.10 (1H, m), 2.80(1H, dd, J=16.5, 6.2Hz), 3.06(1H, dd, J=16.5, 7.4 Hz), 3.44(1H, dd, J=13.8, 5.4Hz), 4.14(2H, q, J=7.2Hz), 4.32 (1H, dd, J=13.8, 8.4Hz), 4.43(1H, dd, J=7.4, 6.2Hz), 6.15 (1H, s), 6.26(1H, dd, J=9.0, 2.9Hz), 7.12(1H, ddd, J=8.8, 7.6, 2.9Hz), 7.29-7.47(4H, m), 7.66-7.75(1H, m)		
2	7-OCH ₃	2'-Cl	oil	$C_{24}H_{28}ClNO_5$	1H -NMR($CDCl_3$) δ : 0.93(3H, d, J=6.8Hz), 1.03 (3H, d, J=6.6Hz), 1.25(3H, t, J=7.2Hz), 1.98 (1H, m), 2.80(1H, dd, J=6.2, 16.4Hz), 3.04(1H, dd, J=7.2, 16.4Hz), 3.43(1H, dd, J=5.4, 13.6Hz), 3.6 (3H, s), 4.13(2H, q, J=7.2Hz), 4.30(1H, dd, J=8.4, 13.6Hz), 4.44(1H, dd, J=6.2, 7.2Hz), 6.06 (1H, d, J=3.0Hz), 6.16(1H, s), 6.93(1H, dd, J=3.0, 8.6Hz), 7.25-7.74(5H, m)		

Table 46

Compd. No.	X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
3	7-Cl	2', 4'-Cl	amorphous solid	$C_{23}H_{24}Cl_3NO_4$	56.98 (56.92)	4.99 5.00	2.89 2.95
4	7-Cl	2'-CF ₃	120-122	$C_{24}H_{25}ClF_3NO_4$	59.57 (59.57)	5.21 5.18	2.89 2.84
5	7-Cl	2-OCH ₃	124-125	$C_{24}H_{28}ClNO_5$	64.64 (64.54)	6.33 6.34	3.14 3.07
6	7-Cl	2'-Br	oil	$C_{23}H_{25}BrClNO_4$	¹ H-NMR(CDCl ₃) δ: 0.95(3H, d, J=6.8Hz), 1.06(3H, d, J=6.6Hz), 1.25(3H, t, J=7.1Hz), 1.85-2.09(1H, m), 2.80(1H, dd, J=16.6, 6.2Hz), 3.05(1H, dd, J=16.6, 7.4Hz), 3.48(1H, dd, J=13.8, 5.2Hz), 4.14(2H, q, J=7.1Hz), 4.29(1H, dd, J=13.8, 8.8Hz), 4.43(1H, dd, J=7.4, 6.2Hz), 6.07(1H, s), 6.50(1H, d, J=2.2Hz), 7.22-7.75(6H, m)		
7	7-Br	2'-Cl	oil	$C_{23}H_{25}BrClNO_4$	¹ H-NMR(CDCl ₃) δ: 0.93 and 1.02(each 3H, d, J=6.6Hz), 1.25(3H, t, J=7.2Hz), 1.86-2.08(1H, m), 2.79(1H, dd, J=16.6, 6.2Hz), 3.06(1H, dd, J=16.6, 7.4Hz), 3.44(1H, dd, J=13.8, 5.6Hz), 4.13(2H, q, J=7.2Hz), 4.31(1H, dd, J=13.8, 8.4Hz), 4.43(1H, dd, J=7.4, 6.2Hz), 6.13(1H, s), 6.65(1H, d, J=2.4Hz), 7.20-7.75(6H, m)		



Table 4 7

Compd. No.	X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
8	7-Cl	4'-Cl	oil	$C_{23}H_{25}Cl_2NO_4$	1H -NMR($CDCl_3$) δ : 0.91 and 0.98(each 3H, d, J=6.6Hz), 1.24(3H, t, J=7.1Hz), 1.93-2.20(1H, m), 2.76(1H, dd, J=16.6, 6.0Hz), 3.05(1H, dd, J=16.6, 7.6Hz), 3.44(1H, dd, J=13.6, 7.6Hz), 4.12(2H, q, J=7.1Hz), 4.26(1H, dd, J=13.6, 7.6Hz), 4.41(1H, dd, J=7.6, 6.0Hz), 5.84(1H, s), 6.57(1H, s), 7.20-7.50(6H, m)		
9	H	2'-CH ₃	88- 90	$C_{24}H_{29}NO_4$	72.89 (73.18)	7.39 7.25	3.54 3.54
10	7-Cl	3'-Cl	oil	$C_{23}H_{25}Cl_2NO_4$	1H -NMR($CDCl_3$) δ : 0.91(3H, d, J=20Hz), 0.98(3H, d, J=6.6Hz), 1.25(3H, t, J=7.1Hz), 1.95-2.18(1H, m), 2.78(1H, dd, J=16.4, 6.0Hz), 3.05(1H, dd, J=16.4, 7.6Hz), 3.44(1H, dd, J=13.6, 6.4Hz), 4.13(2H, q, J=7.1Hz), 4.26(1H, dd, J=13.6, 7.6Hz), 4.40(1H, dd, J=7.6, 6.0Hz), 5.84(1H, s), 6.59(1H, d, J=2.0Hz), 7.14-7.50(6H, m)		
11	7-CF ₃	H	100-102	$C_{24}H_{26}F_3NO_4$	64.13 (64.44)	5.83 5.85	3.12 2.98
12	7-Cl	H	oil	$C_{23}H_{26}ClNO_4$	1H -NMR($CDCl_3$) δ : 0.91 and 0.99(each 3H, d, J=6.6Hz), 1.24(3H, t, J=7.2Hz), 1.95-2.20(1H, m), 2.78(1H, dd, J=16.6, 5.8Hz), 3.07(1H, dd, J=16.6, 7.8Hz), 3.44(1H, dd, J=13.8, 6.4Hz), 4.13(2H, q, J=7.2Hz), 4.27(1H, dd, J=13.8, 7.6Hz), 4.43(1H, d, J=7.8, 5.8Hz), 5.88(1H, s), 6.61(1H, d, J=2.4Hz), 7.24-7.49(7H, m)		

This Sheet Has Been Replaced



Example 74

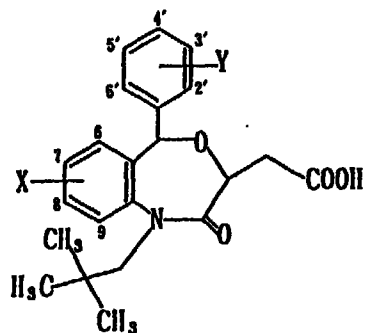
The compounds obtained in Examples 71 and 72 were hydrolyzed by the same procedure as in Reference Examples 5 and Example 2 to yield the compounds listed in Tables 48 and 49.

5

This Sheet Has Been Replaced



Table 48



Compd. No.	X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
1	7-Cl	2', 4' -OCH ₃	260-263	C ₂₄ H ₂₈ ClNO ₆	62.40 (62.27)	6.11 6.26	3.03 2.97)
2	7-Cl	2', 6' -OCH ₃	263-270 (decomp)	C ₂₄ H ₂₈ ClNO ₆ +0.3H ₂ O	61.68 (61.72)	6.17 6.15	3.00 2.90)
3	7-Cl	2', 5' -OCH ₃	230-232	C ₂₄ H ₂₈ ClNO ₆	62.40 (62.31)	6.11 6.13	3.03 3.03)
4	7-Cl	2', 4', 6' -OCH ₃	260-263 (decomp)	C ₂₅ H ₃₀ ClNO ₇	61.04 (60.97)	6.15 6.12	2.85 2.71)
5	7-Cl	2', 3' -OCH ₂ O-	215-218	C ₂₃ H ₂₄ ClNO ₆	61.95 (61.78)	5.42 5.56	3.14 3.31)

This Sheet Has Been Replaced

Table 49

Compd. No.	X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
6	7-Cl	3', 4'-OCH ₂ O-	211-212	C ₂₃ H ₂₄ ClNO ₆	61.95 (61.79)	5.43 5.37	3.14 2.94
7	8-Cl	2'-Cl	186-187	C ₂₂ H ₂₃ Cl ₂ NO ₄	60.56 (60.23)	5.31 5.58	3.21 3.06
8	7, 9-Cl	2'-OCH ₃	265-267	C ₂₃ H ₂₅ Cl ₂ NO ₅ +0.5H ₂ O	58.12 (58.18)	5.51 5.27	2.94 2.69
9	7-Cl	2'-OCH ₃	167-168	C ₂₃ H ₂₆ ClNO ₅	63.96 (63.56)	6.07 6.14	3.24 3.07
10	7-Cl	2'-Br	251-253	C ₂₂ H ₂₃ BrClNO ₄	54.96 (54.97)	4.82 4.85	2.91 2.87
11	7-Br	2'-Cl	247-250	C ₂₂ H ₂₃ BrClNO ₄	54.96 (54.73)	4.82 5.12	2.91 2.82
12	7-Cl	2', 3'-OCH ₃	244-247	C ₂₄ H ₂₈ ClNO ₆ +0.3H ₂ O	61.68 (61.65)	6.17 6.16	3.00 2.89

Example 75

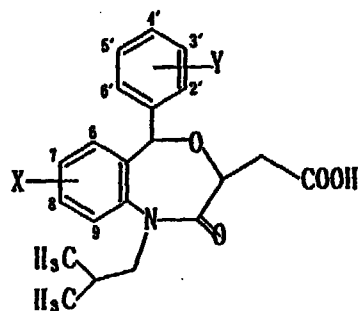
The compounds obtained in Example 73 were hydrolyzed by the same procedure as in Reference Example 5 and Example 2 to yield the compounds listed in Tables 50 and 51.

5

This Sheet Has Been Replaced



Table 50



Compd. No.	X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
1	7-F	2'-Cl	204-206	$C_{21}H_{21}ClFNO_4$	62.15 (61.96)	5.22 5.18	3.45 3.66)
2	7-OCH ₃	2'-Cl	92- 94	$C_{22}H_{24}ClNO_5$ +0.4H ₂ O	62.16 (62.14)	5.88 5.93	3.30 3.28)
3	7-Cl	2', 4'-Cl	236-238	$C_{21}H_{20}Cl_3NO_4$	55.22 (55.12)	4.41 4.45	3.07 3.00)
4	7-Cl	2'-CF ₃	212-225	$C_{22}H_{21}ClF_3NO_4$	57.97 (57.72)	4.64 4.67	3.07 3.05)



Table 51

Compd. No.	X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
5	7-Cl	2'-OCH ₃	219-222	C ₂₂ H ₂₄ ClNO ₅	63.23 (62.88)	5.79 6.09	3.35 3.16)
6	7-Cl	2'-Br	212-216	C ₂₁ H ₂₁ BrClNO ₄	54.04 (53.68)	4.53 4.56	3.00 3.10)
7	7-Br	2'-Cl	194-196	C ₂₁ H ₂₁ BrClNO ₄ +0.2H ₂ O	53.61 (53.44)	4.59 4.49	2.98 2.91)
8	7-Cl	4'-Cl	223-225	C ₂₁ H ₂₁ Cl ₂ NO ₄	59.73 (59.58)	5.01 5.01	3.32 3.23)
9	H	2'-CH ₃	192-195	C ₂₂ H ₂₅ NO ₄	71.91 (71.86)	6.86 6.78	3.81 3.80)
10	7-Cl	3'-Cl	158-160	C ₂₁ H ₂₁ Cl ₂ NO ₄ +0.2H ₂ O	59.22 (59.00)	5.06 5.00	3.29 3.23)
11	7-CF ₃	H	149-151	C ₂₂ H ₂₂ F ₃ NO ₄	62.70 (62.51)	5.26 5.50	3.32 3.14)
12	7-Cl	H	190-192	C ₂₁ H ₂₂ ClNO ₄	65.03 (64.94)	5.72 5.61	3.61 3.48)



This Sheet Has Been Replaced

Example 76

n-butyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

5 A solution of 0.4 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as obtained in Example 2, 0.21 ml of n-butyl iodide and 0.21 ml of triethylamine in 5 ml of dimethylformamide was stirred overnight at
10 room temperature. After ethyl acetate was added, the mixture was washed with dilute hydrochloric acid, an aqueous solution of sodium hydrogen carbonate and water. After the solution was dried, the solvent was removed and the residue was subjected to silica gel
15 column chromatography to yield 0.25 g of a crystal. Melting point: 106-109°C.

Elemental analysis (for $C_{26}H_{31}Cl_2NO_4$)

Calcd.: C 63.42; H 6.35; N 2.84

Found : C 63.42; H 6.39; N 2.71

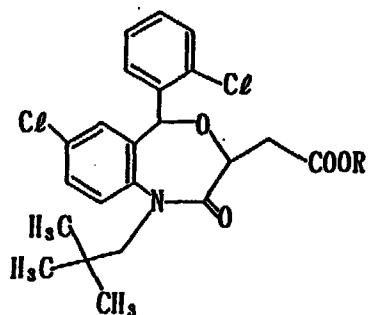
20 Example 77

By the same procedure as in Example 76, the compounds listed in Tables 52 through 54 were synthesized.

This Sheet Has Been Replaced



Table 52



Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found) C H N
1	$\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \parallel \quad \\ -\text{CH}_2\text{OC}-\text{C}-\text{CH}_3 \\ \\ \text{CH}_3 \end{array}$	oil	$\text{C}_{28}\text{H}_{34}\text{Cl}_2\text{NO}_6$	$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 0.93(9H, s, Bu ^t), 1.19(9H, s, Bu ^t), 2.86(1H, dd, J=16.8, 6.4Hz), 3.09(1H, dd, J=16.6, 7.0Hz), 4.27(1H, t, J=6.8Hz), 4.50(1H, d, J=14.0Hz), 5.73(1H, d, J=15.0Hz), 5.79(1H, d, J=15.0Hz), 6.26(1H, s, C ₅ -H), 6.5-6.6(1H, m), 7.3-7.8(6H, m, aromatic)
2	$\begin{array}{c} \text{CH}_3 \quad \text{O} \\ \quad \parallel \\ -\text{CHO} \text{CO}-\text{C}_6\text{H}_{11} \end{array}$	oil	$\text{C}_{31}\text{H}_{37}\text{Cl}_2\text{NO}_7$	$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 0.93(9H, s, Bu ^t), 1.1-1.6 (6H, m), 1.65-2.0(4H, m), 2.75-3.2(2H, m), 3.3-3.5(1H, m), 4.35-4.7(3H, m), 6.25 and 6.28(1H, each s, C ₅ -H), 6.52(1H, s, aromatic), 6.7-6.85(1H, m), 7.3-7.8(6H, m, aromatic)

Table 53

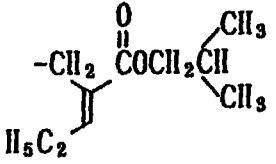
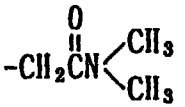
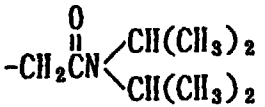
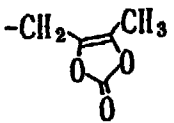
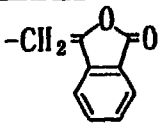
Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
3		oil	$C_{32}H_{39}Cl_2NO_6$	1H -NMR($CDCl_3$) δ : 0.93(6H, d, $J=6.8$ Hz), 0.94(9H, s, Bu'), 1.06(3H, t, $J=7.6$ Hz), 1.85-2.1(1H, m), 2.2-2.4(2H, m), 2.81(1H, dd, $J=16.6, 6.8$ Hz), 3.02(1H, dd, $J=16.6, 6.8$ Hz), 3.39(1H, d, $J=14.0$ Hz), 3.92(2H, d, $J=6.6$ Hz), 4.42(1H, t, $J=6.7$ Hz), 4.50(1H, d, $J=14.0$ Hz), 4.81(1H, d, $J=11.6$ Hz), 4.93(1H, d, $J=11.6$ Hz), 6.25(1H, s, C ₅ -H), 6.52(1H, s), 7.04(1H, t, $J=7.8$ Hz), 7.3-7.8(6H, m)		
4		167-168	$C_{26}H_{30}Cl_2N_2O_5$	59.89 (59.92)	5.80 5.82	5.37 5.15)
5		oil	$C_{30}H_{38}Cl_2N_2O_5$	1H -NMR($CDCl_3$) δ : 0.94(9H, s, Bu'), 1.1-1.5(12H, m), 2.99(1H, dd, $J=16.8, 6.1$ Hz), 3.20(1H, dd, $J=16.8, 7.2$ Hz), 3.39(1H, d, $J=14.0$ Hz), 3.3-3.8(2H, m), 4.4-4.65(3H, m), 4.78(1H, d, $J=14.0$ Hz), 6.27(1H, s), 6.52(1H, s), 7.3-7.8(6H, m)		
6		165-166	$C_{27}H_{27}Cl_2NO_7$	59.13 (59.21)	4.96 5.28	2.55 2.46)
7		191-193	$C_{32}H_{29}Cl_2NO_6$	64.65 (64.67)	4.92 5.27	2.36 2.14)

Table 54

Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
8	-CH ₃	158-159	C ₂₃ H ₂₅ Cl ₂ NO ₄	61.34 (61.48)	5.60 5.78	3.11 2.84)
9	-CH ₂ - 	122-123	C ₂₉ H ₂₉ Cl ₂ NO ₄ •½H ₂ O	65.54 (65.40)	5.69 5.70	2.64 2.43)
10	-CH ₂ COOCH ₃	137-138	C ₂₅ H ₂₇ Cl ₂ NO ₆	59.06 (59.11)	5.35 5.34	2.76 2.60)
11	-CH ₂ CH=CH ₂	108-109	C ₂₅ H ₂₇ Cl ₂ NO ₄	63.03 (63.12)	5.71 5.86	2.94 2.77)
12	-CH ₂ - 	89- 90	C ₂₉ H ₃₅ Cl ₂ NO ₄	65.41 (65.62)	6.62 6.51	2.63 2.42)
13	-CH ₂ COO-C(CH ₃) ₃	140	C ₂₈ H ₃₃ Cl ₂ NO ₆	61.09 (60.87	6.04 6.14	2.54 2.48)

This Sheet Has Been Replaced



Example 78

Phenyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

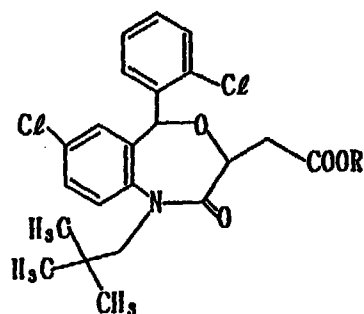
- 5 0.3 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as obtained in Example 2 and 0.072 g of phenol were dissolved in 12 ml of dichloromethane, and 10 ml of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added, followed by stirring at room temperature for 1.5 hours. The reaction mixture was concentrated, ethyl acetate was added and the mixture was washed with water, after which the organic layer was dried and the solvent was distilled off. The residue was subjected to silica gel column chromatography to yield 0.28 g of a crystal. Melting point: 147-148°C. Elemental analysis (for $C_{28}H_{27}Cl_2NO_4$) Calcd.: C 65.63; H 5.31; N 2.73 Found : C 65.55; H 5.45; N 2.46
- 10
- 15
- 20
- Example 79

The compounds obtained in Example 2 were subjected to the same procedure as in Example 78 to yield the compounds listed in Table 55.

This Sheet Has Been Replaced



Table 5 5



Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
1		199-200	$C_{31}H_{31}Cl_2NO_6$	63.70 (63.71)	5.35 (5.63)	2.40 (2.11)
2		100-101	$C_{25}H_{29}Cl_2NO_4$	62.76 (62.91)	6.11 (6.32)	2.93 (2.72)

Example 80

Cyclohexylthio ester of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

5 0.3 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as obtained in Example 2 and 0.09 g of cyclohexylmercaptan were subjected to the same procedure as in Example 78 to yield 0.19 g of a
10 crystalline compound.

Melting point: 157-158°C.

Elemental analysis (for $C_{28}H_{33}Cl_2NO_3S$)

Calcd.: C 62.91; H 6.22; N 2.62

Found : C 62.94; H 6.08; N 2.40

15 Example 81

t-butyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid.

20 To a solution of 1.2 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as obtained in Example 2 in 40 ml of dichloromethane, 10 ml of isobutene and 0.1 ml of concentrate sulfuric acid were added, and the mixture was kept standing at room temperature for 3
25 days. After reaction mixture concentration, ethyl acetate and an aqueous solution of sodium hydrogen carbonate were added, and the organic layer was washed with water and dried, after which the solvent was
30 removed and the residue was subjected to silica gel column chromatography to yield 1.07 g of a crystal.

Melting point: 141-142°C.

Elemental analysis (for $C_{26}H_{31}ClNO_4$)

Calcd.: C 63.42; H 6.35; N 2.84

Found : C 63.52; H 6.37; N 2.80

35 Example 82

Carboxymethyl ester of trans-7-chloro-5-(2-

This Sheet Has Been Replaced





chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

0.3 g of t-butoxycarbonylmethyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as obtained in Example 77 was dissolved in 3 ml of trifluoroacetic acid, and this solution was kept standing at room temperature for 30 minutes. After the solution was concentrated, ethyl acetate was added, followed by washing with water and subsequent drying, after which the solvent was removed and the residue was recrystallized from petroleum ether to yield 0.24 g of a crystal.

Melting point: 186-190°C.

Elemental analysis (for $C_{24}H_{25}Cl_2NO_6 \cdot 1/2H_2O$)

Calcd.: C 57.27; H 5.21; N 2.78

Found : C 57.38; H 5.05; N 2.78

Example 83

Methyl ester of 2-[trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminobenzoic acid

0.35 g of trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as obtained in Reference Example 5 was dissolved in 10 ml of toluene, and 0.63 ml of thionyl chloride was added, followed by stirring for 30 minutes while heating at 90°C. The solution was concentrated and the residue was dissolved in 10 ml of dichloromethane, and 0.13 ml of methyl ester of 2-aminobenzoic acid and 0.14 ml of triethylamine were added, followed by stirring at room temperature for 30 minutes. After the solution was concentrated, ethyl acetate was added, and the mixture was washed with dilute hydrochloric acid, an aqueous solution of sodium hydrogen carbonate and water. The solvent was removed and the residue was subjected to silica gel column

chromatography to yield 0.25 g of a crystal.

Melting point: 188-190°C.

Elemental analysis (for $C_{28}H_{26}Cl_2N_2O_5$)

Calcd.: C 62.11; H 4.91; N 5.24

5 Found : C 61.94; H 4.91; N 5.24

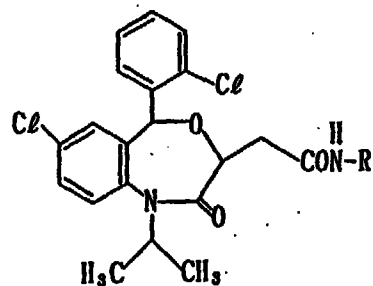
Example 84

By the same procedure as in Example 83, the compounds listed in Tables 56 and 57 were obtained.

This Sheet Has Been Replaced

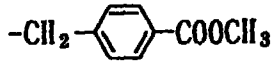
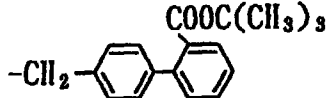


Table 5 6



Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
1		161-163	$C_{29}H_{28}Cl_2N_2O_5$	62.71 (62.62)	5.08 4.96	5.04 5.15)
2		236-238	$C_{29}H_{28}Cl_2N_2O_5$	62.71 (62.67)	5.08 5.26	5.04 5.09)
3		172-174	$C_{29}H_{28}Cl_2N_2O_5$	62.71 (62.63)	5.08 5.00	5.04 5.28)
4		92- 94	$C_{29}H_{28}Cl_2N_2O_5 \cdot \frac{1}{2}H_2O$	61.71 (61.85)	5.18 5.33	4.96 5.10)

Table 57

Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5		139-142	$C_{29}H_{28}Cl_2N_2O_5$	62.71 (62.62)	5.08 5.12	5.04 4.96)
6		oil	$C_{38}H_{38}Cl_2N_2O_5$	1H -NMR($CDCl_3$) δ : 1.27(9H, s, Bu ¹), 1.29(3H, d, J=6.8Hz), 1.54(3H, d, J=6.8Hz), 2.71(1H, dd, J=14.2, 6.0Hz), 2.95(1H, dd, J=14.2, 7.4Hz), 4.38(1H, t, J=6.6Hz), 4.45-4.6(1H, m), 4.7-4.9(2H, m), 6.00(1H, s), 6.3-6.45(1H, m, NH), 6.50(1H, d, J=2.4Hz), 7.2-7.85(14H, m)		



Example 85

2-[trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminobenzoic acid

5 0.15 g of methyl ester of 2-[trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminobenzoic acid as obtained in Example 83 was subjected to the same procedure of ester hydrolysis as in Example 34 to yield 0.11 g of a
10 crystal.

Melting point: 208-211°C.

Elemental analysis (for $C_{27}H_{24}Cl_2N_2O_5$)

Calcd.: C 61.49; H 4.59; N 5.31

Found : C 61.22; H 4.68; N 5.35

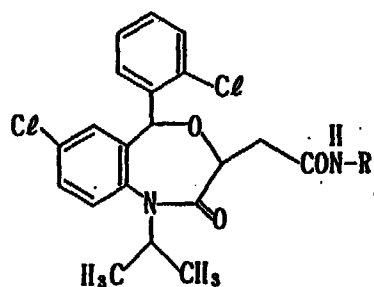
15 Example 86

The compounds obtained in Example 84 were subjected to the same procedure of ester hydrolysis as in Example 34 to yield the compounds listed in Table 58.

This Sheet Has Been Replaced



Table 58



Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
1		149-152	$C_{27}H_{24}Cl_2N_2O_5$	61.49 (61.81)	4.59 4.79	5.31 5.45)
2		>300	$C_{27}H_{24}Cl_2N_2O_5$ $\cdot \frac{1}{2}H_2O$	60.97 (60.97)	4.64 4.76	5.27 5.39)
3		223-225	$C_{28}H_{26}Cl_2N_2O_5$	62.11 (61.96)	4.84 4.82	5.17 5.35)
4		240-244	$C_{28}H_{26}Cl_2N_2O_5$	62.11 (62.13)	4.84 5.00	5.17 5.17)
5		242-244 (decomp)	$C_{28}H_{26}Cl_2N_2O_5$	62.11 (61.96)	4.84 4.85	5.17 5.25)

Example 87

Ethyl ester of 4-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminobenzoic acid

5 0.6 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as obtained in Example 2 and 0.27 g of ethyl ester of 4-aminobenzoic acid were subjected to the same procedure as in Example 83 to yield 0.43 g of
10 a crystal.

Melting point: 218-210°C.

Elemental analysis (for $C_{31}H_{32}Cl_2N_2O_5$)

Calcd.: C 63.81; H 5.53; N 4.80

Found : C 63.79; H 5.38; N 4.70

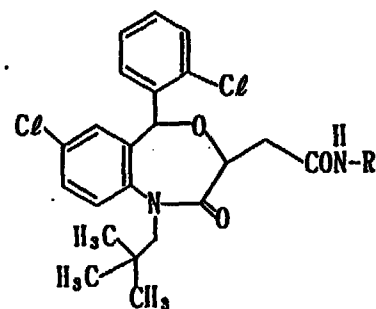
15 Example 88

By the same procedure as in Example 83, the compounds listed in Tables 59 and 60 were synthesized.

This Sheet Has Been Replaced

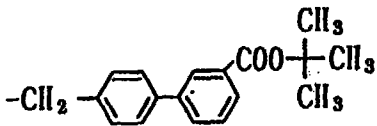


Table 59



Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
1		181-182	$C_{31}H_{32}Cl_2N_2O_5$	63.81 (63.85)	5.53 5.41	4.80 4.66)
2		208-209	$C_{31}H_{32}Cl_2N_2O_5$	63.81 (63.62)	5.53 5.53	4.80 4.79)
3		224-225	$C_{31}H_{32}Cl_2N_2O_5$	63.81 (63.69)	5.53 5.60	4.80 4.54)
4		114-115	$C_{32}H_{34}Cl_2N_2O_5$	64.32 (64.22)	5.74 5.97	4.69 4.43)

Table 60

Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5		oil	1H-NMR(CDC1 ₃) δ: 0.94(9H, s, Bu'), 1.27(9H, s, Bu'), 2.72(1H, dd, J=14.2, 6.0Hz), 2.92(1H, dd, J=14.2, 7.2Hz), 3.40(1H, d, J=14.0 Hz), 4.30-4.7(4H, m), 6.27(1H, s), 5.52(1H, d, J=1.6Hz), 7.1-7.9(14H, m)			

This Sheet Has Been Replaced

Example 89

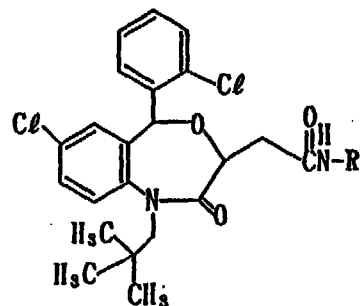
The compounds synthesized in Examples 87 and 88 were subjected to the same procedure as in Examples 24 and 82 to yield the compounds listed in Tables 61 and 62.

5

This Sheet Has Been Replaced



Table 6 1



Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
1		283-286	$C_{29}H_{28}Cl_2N_2O_5$	62.71 (62.95)	5.08 5.39	5.04 5.01)
2		220-223	$C_{30}H_{30}Cl_2N_2O_5$	63.27 (63.24)	5.31 5.23	4.92 4.78)
3		251-253	$C_{30}H_{30}Cl_2N_2O_5$	63.27 (62.98)	5.31 5.43	4.92 4.61)
4		156-158	$C_{30}H_{30}Cl_2N_2O_5$	63.27 (63.39)	5.31 5.21	4.92 4.76)

Table 62

Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5	$-\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_4-\text{COOH}$	143-145	$\text{C}_{31}\text{H}_{32}\text{Cl}_2\text{N}_2\text{O}_5$ $\frac{1}{2}\text{H}_2\text{O}$	62.28 (62.32)	5.61 5.78	4.73 4.49)
6	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{COOH}$	158-161	$\text{C}_{36}\text{H}_{36}\text{Cl}_2\text{N}_2\text{O}_5$	66.77 (66.76)	5.60 5.80	4.33 4.39)



Example 90

Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetamide

1.0 g of trans-7-chloro-5-(2-chlorophenyl)-1-
5 isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-
acetic acid and 0.5 g of ammonium chloride were
dissolved in 8 ml of dimethylformamide, and 0.46 g of
1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
hydrochloride and 0.7 ml of triethylamine were added,
10 followed by stirring at room temperature for 30
minutes. After water was added, the solution was
extracted with ethyl acetate, followed by washing with
water, after which the solvent was removed and the
residue was recrystallized to yield 0.75 g of a
15 crystal.

Melting point: 271-272°C.

Elemental analysis (for $C_{21}H_{22}Cl_2N_2O_3$)

Calcd.: C 59.87; H 5.26; N 6.65

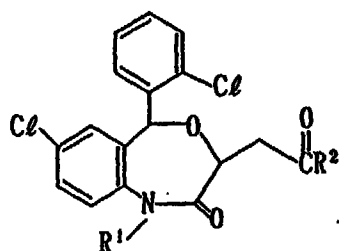
Found : C 59.91; H 5.33; N 6.91

20 Example 91

The compound obtained in Example 2 and Reference
Example 5 and various amines were subjected to the same
procedure as in Example 90 to yield the compounds
listed in Tables 63 through 67.



Table 63



This Sheet Has Been Replaced

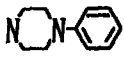
- 187 -

Compd. No.	R ¹	R ²	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
1	CH(CH ₃) ₂	NH ₂	226-227	C ₂₀ H ₂₀ Cl ₂ N ₂ O ₃	58.98 (58.93)	4.95 4.85	6.88 6.75)
2	CH ₃	NH ₂	187-189	C ₁₈ H ₁₆ Cl ₂ N ₂ O ₃	56.34 (56.53)	4.33 4.55	7.30 6.94)
3	-CH ₂ - 	NH ₂	246-248	C ₂₄ H ₂₆ Cl ₂ N ₂ O ₃	62.48 (62.28)	5.68 5.87	6.07 5.86)
4	-CH ₂ - 	NH ₂	185-187	C ₂₄ H ₂₀ Cl ₂ N ₂ O ₃	63.31 : (63.23)	4.43 4.49	6.15 6.10)

Table 64

Compd. No.	R ¹	R ²	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
5	$-\text{CH}_2-\text{C}_6\text{H}_5$	NHCH_3	189-190	$\text{C}_{25}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_3$	63.97 (64.01)	4.72 4.53	5.97 5.90)
6	$-\text{CH}_2-\text{C}_6\text{H}_5$	$\text{N}(\text{CH}_3)_2$	183-184	$\text{C}_{26}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_3$ $\cdot \frac{1}{2}\text{H}_2\text{O}$	64.00 (63.97)	5.06 5.03	5.74 5.81)
7	$-\text{CH}_2-\text{C}_6\text{H}_4\text{OCH}_3$	NHCH_3	104-107	$\text{C}_{26}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_4$ $\cdot \frac{1}{2}\text{H}_2\text{O}$	61.42 (61.65)	4.96 5.05	5.51 5.40)
8	$-\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_5$	NHCH_3	193-195	$\text{C}_{26}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_3$	64.60 (64.42)	5.00 4.99	5.80 5.73)
9	$-\text{CH}_2-\text{C}_6\text{H}_4\text{OCH}_3$	NHCH_3	171-172	$\text{C}_{26}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_4$	62.53 (62.24)	4.84 5.05	5.61 5.34)
10	$-\text{CH}_2-\text{C}_{10}\text{H}_7$	NHCH_3	190-191	$\text{C}_{29}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_3$	67.06 (66.78)	4.66 4.56	5.39 5.26)
11	$\text{CH}_2\text{CH}(\text{CH}_3)_2$	$\text{N}(\text{CH}_3)_2$	134-135	$\text{C}_{23}\text{H}_{26}\text{Cl}_2\text{N}_2\text{O}_3$	61.47 (61.33)	5.83 5.76	6.23 6.18)

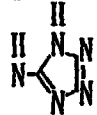
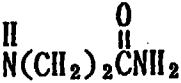
Table 65

Compd. No.	R ¹	R ²	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
12	CH ₂ CH(CH ₃) ₂	$\begin{array}{c} \text{H} \\ \\ \text{N}(\text{CH}_2)_3\text{CH}_3 \end{array}$	135-136	C ₂₅ H ₃₀ Cl ₂ N ₂ O ₃	62.89 (63.15)	6.33 (6.38)	5.87 (5.87)
13	CH ₂ CH(CH ₃) ₂	$\begin{array}{c} \text{H} \\ \\ \text{NCH}_2-\text{C}_6\text{H}_5 \end{array}$	168-169	C ₂₈ H ₂₈ Cl ₂ N ₂ O ₃	65.76 (65.89)	5.52 (5.67)	5.48 (5.57)
14	-CH ₂ -C ₆ H ₅		141-142	C ₃₃ H ₂₈ Cl ₂ N ₂ O ₃ • ½H ₂ O	68.28 (68.33)	5.04 (5.12)	4.83 (4.65)
15	-CH ₂ -C ₆ H ₅	$\begin{array}{c} \text{H} \\ \\ \text{NCH}_2-\text{C}_6\text{H}_4 \\ \\ \text{OCH}_3 \end{array}$	177-178	C ₃₃ H ₂₈ Cl ₂ N ₂ O ₄	66.79 (66.97)	4.90 (4.91)	4.87 (4.83)
16	-CH ₂ -C ₆ H ₅		177-179	C ₃₅ H ₃₃ Cl ₂ N ₃ O ₃	68.40 (68.35)	5.41 (5.57)	6.84 (6.82)
17	CH ₂ C(CH ₃) ₃	NIINH ₂	248-250	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₃	58.67 (58.76)	5.60 (5.90)	9.33 (8.93)
18	CH ₂ C(CH ₃) ₃	NHN(CH ₃) ₂	232-235	C ₂₄ H ₂₉ Cl ₂ N ₃ O ₃	60.25 (60.14)	6.11 (6.20)	8.78 (8.51)

This Sheet Has Been Replaced



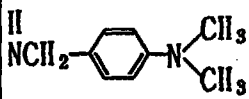
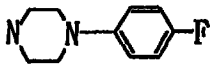
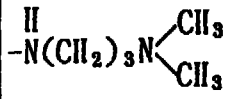
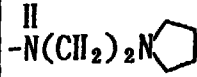
Table 66

Compd. No.	R ¹	R ²	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
19	CH ₂ CH(CH ₃) ₂		270-271	C ₂₂ H ₂₂ Cl ₂ N ₃ O ₃ •½H ₂ O	53.50 (53.63)	4.59 4.43	17.02 16.88
20	CH(CH ₃) ₂		247-248	C ₂₂ H ₂₃ Cl ₂ N ₃ O ₄	56.91 (56.69)	4.99 4.90	9.05 8.96
21	CH ₂ CH(CH ₃) ₂	NH ₂	271-272	C ₂₁ H ₂₂ Cl ₂ N ₂ O ₃	59.87 (59.91)	5.26 5.33	6.65 6.91



This Sheet Has Been Replaced

Table 67

Compd. No.	R ¹	R ²	m. p. (°C)	Formula	Elemental Analysis(Found)		
					C	H	N
22	CH ₂ C(CH ₃) ₃		198-199	C ₃₁ H ₃₅ Cl ₂ N ₃ O ₃	65.49 (65.91)	6.20 6.50	7.39 7.28)
23	CH ₂ C(CH ₃) ₃		132-133	C ₃₂ H ₃₄ Cl ₂ FN ₃ O ₃	64.21 (64.45)	5.73 5.83	7.02 7.13)
24	CH ₂ C(CH ₃) ₃		118-121	C ₂₇ H ₃₅ Cl ₂ N ₃ O ₃ (COOH) ₂ · 1/2H ₂ O	56.22 (56.37)	6.18 6.35	6.78 6.56)
25	CH ₂ C(CH ₃) ₃		179-180	C ₂₈ H ₃₅ Cl ₂ N ₃ O ₃ · 1/4H ₂ O	62.62 (62.66)	6.66 6.54	7.83 7.85)





Example 92

Ethyl ester of 7-chloro-5-(2-chlorophenyl)-1-isobutyl-5-methyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic acid

- 5 (1) 4-chloro-2-[α -hydroxy- α -methyl-(2-chlorophenyl)methyl]aniline

A tetrahydrofuran solution of a Grignard reagent synthesized from 0.45 g of magnesium and 1.2 g of methyl iodide was added dropwise to a solution of 2.0 g
10 of 2-amino-5-chloro-2'-chlorobenzophenone in 20 ml of tetrahydrofuran. After refluxing with heating for 10 minutes, the mixture was cooled with water, and a saturated aqueous solution of ammonium chloride was added, and the mixture was extracted with ethyl
15 acetate. The solvent was distilled off, and the residue was subjected to silica gel column chromatography to yield 1.5 g of an oily compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.04 (3H, s, CH_3), 7.0-7.8 (7H, m)

- 20 (2) N-isobutyl-4-chloro-2-[α -hydroxy- α -methyl-(2-chlorophenyl)methyl]aniline

To a solution of 1.2 g of 4-chloro-2-[α -hydroxy- α -methyl-(2-chlorophenyl)methyl]aniline and 0.32 g of isobutylaldehyde in 8 ml of acetic acid, 0.25 g of sodium borohydride was added, followed by stirring at
25 room temperature for 40 minutes. After water was added, the reaction mixture was extracted with ethyl acetate, after which the solvent was removed and the residue was subjected to silica gel column chromatography to yield 1.4 g of an oily compound

30 $^1\text{H-NMR}$ (CDCl_3) δ : 0.75, 0.80 (6H, each, d, CH_3), 1.67 (1H, m), 1.99 (3H, s, CH_3), 2.74 (2H, d), 7.05-7.8 (7H, m)

- (3) Ethyl ester of 3-[N-[4-chloro-2-[α -hydroxy- α -methyl-(2-chlorophenyl)methyl]phenyl]-N-isobutylcarbamoyl]acrylic acid
35

1.4 g of N-isobutyl-4-chloro-2-[α -hydroxy- α -



methyl-(2-chlorophenyl)methyl]aniline was dissolved in 15 ml of dichloromethane, and 0.7 g of sodium hydrogen carbonate was added, after which a solution of 0.68 g of monomethyl ester of chlorofumaric acid in 4 ml of dichloromethane was added dropwise over a period of 20 minutes. After the mixture was washed with water and dried, the solvent was removed and the residue was subjected to silica gel column chromatography to yield 0.65 g of a crystal.

Melting point: 153-154°C.

Elemental analysis (for $C_{24}H_{27}Cl_2NO_4$)

Calcd.: C 62.07; H 5.86; N 3.02

Found : C 62.19; H 5.86; N 2.90

(4) Ethyl ester of 7-chloro-5-(2-chlorophenyl)-1-isobutyl-5-methyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic acid

1.0 g of ethyl ester of 3-[N-[4-chloro-2-(α -hydroxy- α -methyl-(2-chlorophenylmethyl)phenyl]-N-isobutylcarbamoyl]acrylic acid was dissolved in 10 ml of ethanol, and 0.35 g of potassium carbonate was added, followed by stirring for 12 hours. After water was added, the reaction mixture was extracted with ethyl acetate and dried, after which the solvent was removed and the residue was subjected to silica gel column chromatography to yield 0.8 g of a crystal.

Melting point: 119-120°C.

Elemental analysis (for $C_{24}H_{27}Cl_2NO_4$)

Calcd.: C 62.07; H 5.86; N 3.02

Found : C 62.08; H 5.93; N 2.98

Example 93

7-chloro-5-(2-chlorophenyl)-1-isobutyl-5-methyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic acid

0.3 g of ethyl ester of 7-chloro-5-(2-chlorophenyl)-1-isobutyl-5-methyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic acid was dissolved in 10



ml of methanol, and 2 ml of a 10% aqueous solution of potassium carbonate was added, followed by stirring for 40 minutes with heating at 70°C. After acidification with dilute hydrochloric acid, the reaction mixture was
5 extracted with ethyl acetate. After the extract was dried, the solvent was removed and the residue was recrystallized from ethyl acetate-hexane to yield 0.16 g of a crystal.

Melting point: 153-154°C.

10 Elemental analysis (for $C_{22}H_{23}Cl_2NO_4$)

Calcd.: C 60.56; H 5.31; N 3.21

Found : C 60.59; H 5.32; N 2.92

Reference Example 9

Ethyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-
15 (2,2,2-trifluoroethyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic acid

(1) 5-chloro- α -(2-chlorophenyl)-2-(trifluoroacetylamino)benzyl alcohol

To a solution of 1.0 g of 2-amino-5-chloro- α -(2-chlorophenyl)benzyl alcohol in 12 ml of
20 dichloromethane, a solution of 0.8 g of anhydrous trifluoroacetic acid in 2 ml of dichloromethane was added. After reaction, an aqueous solution of sodium hydrogen carbonate was added, and the organic layer was
25 dried, after which the solvent was removed and the residue was recrystallized from hexane to yield 1.3 g of a crystal.

(2) 5-chloro- α -(2-chlorophenyl)-2-(2,2,2-trifluoroethylamino)benzyl alcohol

30 To a suspension of 0.25 g of lithium aluminum hydride in 20 ml of absolute ethyl ether, a solution of 1.2 g of 5-chloro- α -(2-chlorophenyl)-2-(trifluoroacetylamino)benzyl alcohol in 5 ml of tetrahydrofuran was added dropwise. After mixture
35 stirring at room temperature for 1 hour, water was added, and the organic layer was dried, after which the

solvent was removed and the residue was subjected to silica gel column chromatography to yield 1.0 g of an oily compound.

5 (3) Ethyl ester of 3-[N-[4-chloro-2-(α -hydroxy-2-chlorophenylmethyl)phenyl]-N-(2,2,2-trifluoroethyl)carbamoyl]acrylic acid

10 5-chloro- α -(2-chlorophenyl)-2-(2,2,2-trifluoroethylamino)benzyl alcohol and monomethyl ester of chlorofumaric acid were subjected to the same procedure as in Reference Example 1 to yield an oily compound.

(4) Ethyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic acid

15 Ethyl ester of 3-[N-[4-chloro-2-(α -hydroxy-2-chlorophenylmethyl)phenyl]-N-(2,2,2-trifluoroethyl)carbamoyl]acrylic acid was subjected to the same procedure as in Reference Example 2 to yield a crystal.

20 Melting point: 163-164°C.

Elemental analysis (for $C_{21}H_{18}Cl_2F_3NO_4$)

Calcd.: C 52.96; H 3.81; N 2.94

Found : C 52.93; H 3.88; N 2.91

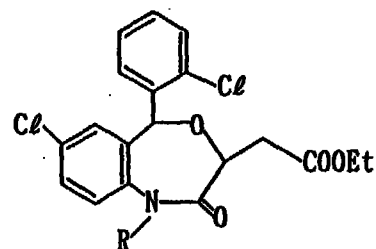
Reference Example 10

25 By the same procedure as in Reference Examples 2 and 9, the compounds listed in Table 68 were synthesized.

This Sheet Has Been Replaced



Table 68



Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
1	$\text{CH}_2\text{CF}_2\text{CF}_3$	oil	$^1\text{H-NMR}(\text{CDCl}_3)\delta: 1.25(3\text{H}, \text{t}), 2.8, 3.1(2\text{H}, \text{各dd}), 4.0-4.3(3\text{H}, \text{m}), 4.48(1\text{H}, \text{dd}), 5.1-5.35(1\text{H}, \text{m}), 6.18(1\text{H}, \text{s}), 6.56(1\text{H}, \text{d}), 7.2-7.8(6\text{H}, \text{m})$			
2	CH_2 	106-107	$\text{C}_{23}\text{H}_{23}\text{Cl}_2\text{NO}_4$	61.62 (61.66)	5.17 5.31	3.12 3.16)



This Sheet Has Been Replaced

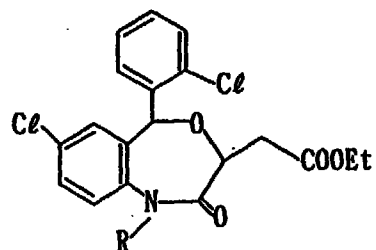
Example 94

By the same procedure as in Reference Examples 2 and 9, the compounds listed in Table 69 were synthesized.

This Sheet Has Been Replaced



Table 69



Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
1	$\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_3$	oil	$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 0.94(9H, s), 1.25(3H, t), 1.3-1.8(2H, m), 2.8, 3.08(2H, 各dd), 3.54(1H, dt), 4.13(2H, dq), 4.35-4.6(2H, m), 6.0(1H, s), 6.52(1H, d), 7.1-7.8(6H, m)			

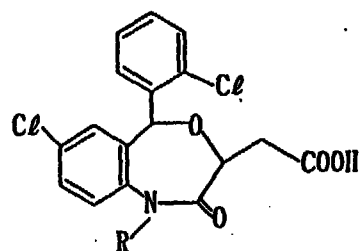
Reference Example 11

The compounds obtained in Reference Examples 9 and 10 were subjected to the same procedure as in Reference Example 4 to yield the compounds listed in Table 70.

This Sheet Has Been Replaced



Table 70



Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
1	$\text{CH}_2\text{CF}_2\text{CF}_3$	186-187	$\text{C}_{20}\text{H}_{14}\text{Cl}_2\text{F}_5\text{NO}_4$	48.21 (47.91)	2.83 2.82	2.81 2.95
2	CH_2 — 	230-232	$\text{C}_{21}\text{H}_{19}\text{Cl}_2\text{NO}_4$	60.01 (59.74)	4.56 4.55	3.33 3.29
3	CH_2CF_3	213-215	$\text{C}_{19}\text{H}_{14}\text{Cl}_2\text{F}_3\text{NO}_4$	50.91 (50.97)	3.15 3.26	3.12 3.05



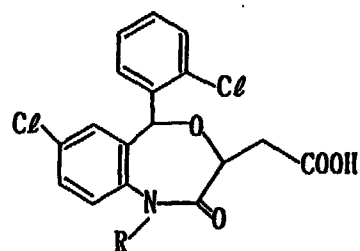
Example 95

The compounds obtained in Example 94 were subjected to the same procedure as in Reference Example 4 to yield the compounds listed in Table 71.

This Sheet Has Been Replaced



Table 71



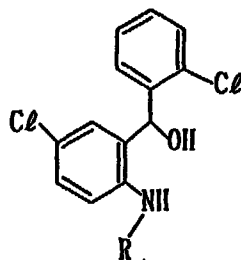
Compd. No.	R	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
1	CH ₂ CH ₂ C(CH ₃) ₃	176-177	C ₂₃ H ₂₅ Cl ₂ NO ₄	61.34 (61.45	5.60 5.68	3.11 3.25)

Also, physicochemical properties of intermediates of compounds obtained in Reference Examples 9 and 10 and Example 94 are shown in Tables 72 and 73.

This Sheet Has Been Replaced

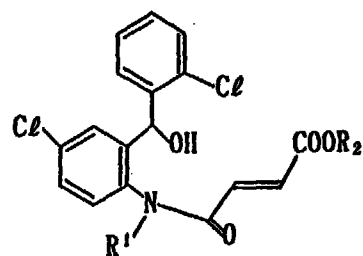


Table 72



R	m. p. (°C)	Formula	Elemental Analysis(Found)		
			C	H	N
$\text{CH}_2\text{CF}_2\text{CF}_3$	oil	$\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{F}_5\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta : 3.82(2\text{H}, \text{dt}), 6.17(1\text{H}, \text{s}), 6.69(1\text{H}, \text{d}), 6.84(1\text{H}, \text{d}), 7.1-7.5(5\text{H}, \text{m})$		
$\text{CH}_2-\triangle$	oil	$\text{C}_{17}\text{H}_{17}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta : 0.1-0.6(4\text{H}, \text{m}), 1.0-1.2(1\text{H}, \text{m}), 2.92(2\text{H}, \text{d}), 6.16(1\text{H}, \text{s}), 6.57(1\text{H}, \text{d}), 6.91(1\text{H}, \text{d}), 7.1-7.6(5\text{H}, \text{m})$		
$\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_3$	oil	$\text{C}_{19}\text{H}_{23}\text{Cl}_2\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta : 0.94(9\text{H}, \text{s}), 1.4-1.6(2\text{H}, \text{m}), 3.1(2\text{H}, \text{m}), 6.10(1\text{H}, \text{s}), 6.62(1\text{H}, \text{d}), 6.83(1\text{H}, \text{d}), 7.1-7.5(5\text{H}, \text{m})$		
CH_2CF_3	oil	$\text{C}_{15}\text{H}_{12}\text{Cl}_2\text{F}_3\text{NO}$	$^1\text{H-NMR}(\text{CDCl}_3) \delta : 2.68(2\text{H}, \text{d}), 5.23(1\text{H}, \text{m}), 6.15(1\text{H}, \text{d}), 6.7(1\text{H}, \text{d}), 6.83(1\text{H}, \text{d}), 7.1-7.6(5\text{H}, \text{m})$		

Table 73



R	R	m. p. (°C)	Formula	Elemental Analysis(Found)
				C H N
CH ₂ CF ₂ CF ₃	-C ₂ H ₅	oil	C ₂₂ H ₁₈ Cl ₂ F ₅ NO ₄	¹ H-NMR(CDCl ₃) δ : 1.15-1.4(3H, m), 3.2-5.45(4H, m), 6.0-7.6(10H, m)
CH ₂ - 	-C ₂ H ₅	oil	C ₂₃ H ₂₃ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 0.1-0.55(4H, m), 0.9-1.4(4H, m), 2.4-4.4(4H, m), 6.0-7.7(10H, m)
CH ₂ CH ₂ CH(CH ₃) ₃	-C ₂ H ₅	oil	C ₂₅ H ₃₀ Cl ₂ NO ₄	¹ H-NMR(CDCl ₃) δ : 0.76, 0.91(9H, both s), 1.1-1.8(2H, m), 2.6-4.5(4H, m), 5.95-7.7(10H, m)
CH ₂ CF ₃	-C ₂ H ₅	oil	C ₂₁ H ₁₈ Cl ₂ F ₃ NO ₄	¹ H-NMR(CDCl ₃) δ : 1.17-1.4(3H, m), 3.2-5.3(4H, m), 6.0-7.6(10H, m)



This Sheet Has Been Replaced

Example 96

Ethyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-propionic acid.

- 5 (1) Trans-7-chloro-5-(2-chlorophenyl)-3-(2-cyanoethyl)-1-neopentyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine

0.3 g of 7-chloro-3-(2-chloroethyl)-5-(2-chlorophenyl)-1-neopentyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine and 0.1 g of sodium cyanide were
10 suspended in 6 ml of dimethylsulfoxide, followed by stirring at 100°C for 1 hour. Water was added and the suspension was extracted with ethyl acetate, after which the solvent was removed and the residue was
15 subjected to silica gel column chromatography to yield 0.25 g of a crystal.

Melting point: 194-195°C.

Elemental analysis (for $C_{23}H_{24}Cl_2N_2O_2$)

Calcd.: C 64.04; H 5.61; N 6.49

20 Found : C 63.96; H 5.56; N 6.66

- (2) Ethyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-propionic acid

To 0.2 g of trans-7-chloro-5-(2-chlorophenyl)-3-(2-cyanoethyl)-1-neopentyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine, 6 ml of an ethanol solution of 6 N
25 hydrogen chloride was added, followed by refluxing with heating for 6 hours. After solvent removal, ethyl acetate and water were added, the organic layer was
30 dried, the solvent was removed, and the residue was subjected to silica gel column chromatography to yield 0.18 g of a crystal.

Melting point: 130-131°C.

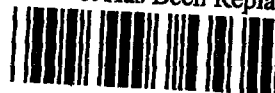
Elemental analysis (for $C_{25}H_{29}Cl_2NO_4$)

35 Calcd.: C 62.76; H 6.11; N 2.93

Found : C 62.78; H 6.12; N 2.68

This Sheet Has Been Replaced





Example 97

Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-propionic acid

90 mg of ethyl ester of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-propionic acid as obtained in Example 96 was subjected to the same procedure as in Reference Example 4 to yield 80 mg of a crystal.

Melting point: 225-227°C.

Elemental analysis (for $C_{23}H_{25}Cl_2NO_4$)

Calcd.: C 61.34; H 5.60; N 3.11

Found : C 61.34; H 5.65; N 2.89

Example 98

Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-ethanol

Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetic acid as obtained in Example 2 was subjected to the same procedure as in Example 65 to yield 1.5 g of a crystal.

Example 99

Ethyl ester of 3-[trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ylethyl]thioglycolic acid

(1) Trans-7-chloro-3-(2-chloroethyl)-5-(2-chlorophenyl)-1-isobutyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine

1.0 g of trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-ethanol as obtained in Example 98 was dissolved in 25 ml of toluene, and 0.1 ml of pyridine and 0.4 ml of thionyl chloride were added, followed by stirring for 30 minutes with heating at 100°C. After solvent removal under reduced pressure, the residue was dissolved in ethyl acetate and washed with a saturated aqueous solution of sodium hydrogen carbonate and dried, after which the solvent was removed and the

residue was subjected to silica gel column chromatography to yield 0.8 g of a crystal.

Melting point: 138-140°C.

Elemental analysis (for $C_{21}H_{22}Cl_3NO_2$)

5 Calcd.: C 59.10; H 5.20; N 3.28

Found : C 59.17; H 5.22; N 2.25

(2) Ethyl ester of 3-[trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ylethyl]thioglycolic acid

10 0.15 g of trans-7-chloro-3-(2-chloroethyl)-5-(2-chlorophenyl)-1-isobutyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine, 0.08 g of ethyl ester of thioglycolic acid and 0.1 g of cesium fluoride were added to 5 ml of acetonitrile, followed by refluxing with heating for 40
15 minutes. After ice water was added and the mixture was extracted with ethyl acetate, the organic layer was dried, after which the solvent was removed and the residue was subjected to silica gel column chromatography to yield 0.17 g of an oily compounds.

20 1H -NMR ($CDCl_3$) δ : 0.93, 1.03 (6H, each, d), 1.26 (3H, t), 1.8-2.4 (3H, m), 2.8 (2H, m), 3.19 (2H, s), 3.42 (1H, dd), 4.0-4.4 (4H, m), 6.12 (1H, s), 6.51 (1H, d), 7.2-7.8 (6H, m)

Example 100

25 3-[trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ylethyl]thioglycolic acid

30 0.17 g of ethyl ester of 3-[trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ylethyl]thioglycolic acid as obtained in Example 99 was subjected to the same procedure as in Example 51 to yield 0.18 g of a crystal.

Melting point: 194-195°C.

Elemental analysis (for $C_{23}H_{25}Cl_2NO_4S$)

35 Calcd.: C 57.26; H 5.22; N 2.90

Found : C 57.27; H 5.20; N 2.96

This Sheet Has Been Replaced





Example 101

3-[trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ylethyl]sulfonylacetic acid

5 0.18 g of ethyl ester of 3-[trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ylethyl]thioglycolic acid as obtained in Example 99 was dissolved in 8 ml of dichloromethane, and 0.25 g of m-chloroperbenzoic acid was added,
10 followed by stirring for 1 hour. To the reaction mixture was added an aqueous solution of sodium hydrogen carbonate, followed by washing and the organic layer was dried and the solvent was removed, after which the residue was subjected to silica gel column
15 chromatography to yield 0.18 g of an oily compound, which was then subjected to the same procedure of ethyl ester hydrolysis as in Example 51 to yield 0.13 g of a crystal.

Melting point: 171-172°C.

20 Elemental analysis (for $C_{23}H_{25}Cl_2NO_6S$)

Calcd.: C 53.70; H 4.90; N 2.72

Found : C 53.62; H 4.95; N 2.68

Example 102

25 Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-3-[3-(tetrazol-5-yl)phenylaminocarbonylmethyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

(1) Trans-7-chloro-5-(2-chlorophenyl)-3-(3-cyanophenylaminocarbonylmethyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

30 To a solution of 0.5 g of trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as obtained in Example 2 and 0.15 g of m-cyanoaniline in 10 ml of dichloromethane, 0.35 g of 1-ethyl-3-
35 (dimethylaminopropyl)carbodiimide hydrochloride and 20 mg of dimethylaminopyridine were added, followed by

stirring at room temperature for 4 hours. The solution was concentrated, and the residue was dissolved in ethyl acetate, followed by washing with water, after which the solvent was removed and the residue was
5 subjected to silica gel column chromatography to yield 0.48 g of a crystal.

Melting point: 213-214°C.

Elemental analysis (for $C_{29}H_{27}Cl_2N_3O_3$)

Calcd.: C 64.93; H 5.07; N 7.83

10 Found : C 64.68; H 4.96; N 7.90

(2) Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-3-[3-(tetrazol-5-yl)phenylaminocarbonylmethyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

A solution of 0.2 g of trans-7-chloro-5-(2-chlorophenyl)-3-(3-cyanophenylaminocarbonylmethyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine
15 and 80 mg of sodium azide in 5 ml of dimethylformamide was stirred at 90°C for 60 hours. After water was added, the mixture was washed with water, after which
20 the solvent was removed and the residue was subjected to silica gel column chromatography to yield 0.11 g of a crystal.

Melting point: 218-220°C.

Elemental analysis (for $C_{29}H_{28}Cl_2N_6O_3$)

25 Calcd.: C 59.64; H 4.92; N 14.39

Found : C 59.44; H 4.87; N 14.30

Example 103

Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-3-[4-(tetrazol-5-yl)phenylaminocarbonylmethyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine. The title
30 compound was synthesized by the same procedure as in Example 102.

(1) Trans-7-chloro-5-(2-chlorophenyl)-3-(4-cyanophenylaminocarbonylmethyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine
35

Melting point: 257-259°C.



Elemental analysis (for $C_{29}H_{27}Cl_2N_3O_3 \cdot 1/4H_2O$)

Calcd.: C 64.39; H 5.12; N 7.77

Found : C 64.33; H 5.13; N 7.64

(2) Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-3-
5 [4-(tetrazol-5-yl)phenylaminocarbonylmethyl]-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine

Melting point: 206-210°C

Elemental analysis (for $C_{29}H_{28}Cl_2N_6O_3 \cdot 1/4H_2O$)

Calcd.: C 59.64; H 4.92; N 14.39

10 Found : C 59.71; H 4.96; N 14.34

Example 104

Trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-3-
[(tetrazol-5-yl)methylaminocarbonylmethyl]-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine

15 (1) Trans-7-chloro-5-(2-chlorophenyl)-3-
(cyanomethylaminocarbonylmethyl)-1-isopropyl-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine

0.3 g of trans-7-chloro-5-(2-chlorophenyl)-1-
isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-
20 acetic acid as obtained in Reference Example 5 and 0.1
g of aminoacetonitrile sulfuric acid salt were
dissolved in 5 ml of dimethylformaldehyde, and 0.18 g
of diethyl phosphorocyanidate and 0.17 ml of
triethylamine were added, followed by stirring at room
25 temperature for 1 hour. After water was added, the
mixture was extracted with ethyl acetate, washed with
water and then dried. After solvent removal, the
residue was subjected to silica gel column
chromatography to yield 0.31 g of a crystal.

30 Melting point: 216-217°C.

Elemental analysis (for $C_{22}H_{21}Cl_2N_3O_3$)

Calcd.: C 59.20; H 4.74; N 9.41

Found : C 58.92; H 4.68; N 9.12

(2) Trans-7-chloro-5-(2-chlorophenyl)-1-isopropyl-3-
35 [(tetrazol-5-yl)methylaminocarbonylmethyl]-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine



Trans-7-chloro-5-(2-chlorophenyl)-3-(cyanomethylaminocarbonylmethyl)-1-isopropyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine and sodium azide were subjected to the same procedure as in Example 102 to yield a crystal.

Melting point: 253-254°C.

Elemental analysis (for $C_{22}H_{22}Cl_2N_6O_3$)

Calcd.: C 54.00; H 4.53; N 17.17

Found : C 53.85; H 4.68; N 17.02

Example 105

Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-3-[(tetrazol-5-yl)methylaminocarbonylmethyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as obtained in Example 2 was subjected to the same procedure as in Examples 102 and 104 to yield a crystalline compound.

(1) Trans-7-chloro-5-(2-chlorophenyl)-3-(cyanomethylaminocarbonylmethyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

Melting point: 168-169°C.

Elemental analysis (for $C_{23}H_{23}Cl_2N_3O_3$)

Calcd.: C 60.01; H 5.04; N 9.13

Found : C 60.11; H 5.28; N 9.15

(2) Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-3-[(tetrazol-5-yl)methylaminocarbonylmethyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

Melting point: 234-235°C.

Elemental analysis (for $C_{23}H_{24}Cl_2N_6O_3$)

Calcd.: C 54.88; H 4.81; N 16.69

Found : C 55.07; H 4.84; N 16.92

Example 106

Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-3-[(tetrazol-5-yl)methyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

This Sheet Has Been Replaced





(1) Trans-7-chloro-5-(2-chlorophenyl)-3-cyanomethyl-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

0.5 g of Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetamide as obtained in Example 91, 0.38 g of carbonyldiimidazole and 1.14 g of allyl bromide were dissolved in 10 ml of acetonitrile, followed by refluxing with heating for 4 hours. The solution was concentrated and ethyl acetate was added, followed by washing with water, after which the solvent was removed and the residue was subjected to silica gel column chromatography to yield 0.44 g of a crystal.

Melting point: 158-159°C.

Elemental analysis (for $C_{21}H_{20}Cl_2N_2O_2$)

Calcd.: C 62.54; H 5.00; N 6.95

Found : C 62.68; H 5.13; N 7.22

(2) Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-3-[tetrazol-5-yl)methyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

0.2 g of trans-7-chloro-5-(2-chlorophenyl)-3-cyanomethyl-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine was subjected to the same procedure as in Example 102 and to yield 90 mg of a crystal.

Melting point: 202-203°C.

Elemental analysis (for $C_{21}H_{21}Cl_2N_5O_2$)

Calcd.: C 56.51; H 4.74; N 15.69

Found : C 56.29; H 4.70; N 15.67

Example 107

Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-3-[2-(tetrazol-5-yl)ethyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

(1) Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-3-(2-cyanoethyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

0.5 g of trans-7-chloro-3-(2-chloroethyl)-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-



benzoxazepine as obtained in Example 99 and 0.4 g of sodium cyanide were added to 8 ml of dimethylsulfoxide, followed by stirring at 100°C for 40 minutes. After water was added, the reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and dried, after which the solvent was removed and the residue was subjected to silica gel column chromatography to yield 0.45 g of an oily substance.

¹H-NMR (CDCl₃) δ: 0.93, 1.03 (6H, each, d), 1.85-2.4 (3H, m), 2.59 (2H, t), 3.43 (1H, dd), 4.05 (1H, dd), 4.33 (1H, dd), 6.14 (1H, s), 6.53 (1H, d), 7.3-7.8 (6H, m)

(2) Trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-3-[2-(tetrazol-5-yl)ethyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

Trans-7-chloro-5-(2-chlorophenyl)-3-(2-cyanoethyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine was subjected to the same procedure as in Example 102 to yield 0.22 g of a crystal.

Melting point: 125-127°C.

Elemental analysis (for C₂₂H₂₃Cl₂N₅O₂)

Calcd.: C 57.40; H 5.04; N 15.21

Found : C 57.15; H 5.26; N 14.97

Example 108

Trans-7-chloro-5-(2-chlorophenyl)-3-[2-(4,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)ethyl]-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

0.25 g of trans-7-chloro-5-(2-chlorophenyl)-3-(2-cyanoethyl)-1-isobutyl-1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine as obtained in Example 107, 120 mg of hydroxylamine hydrochloride and 0.23 g of sodium carbonate were added to 5 ml of ethanol, followed by refluxing with heating for 18 hours. After solvent removal, ethyl acetate was added, and the mixture was washed with water and dried, after which the solvent was

removed and the residue was recrystallized from ethyl acetate.

Melting point: 212-214°C.

Elemental analysis (for $C_{22}H_{25}Cl_2N_3O_3$)

5 Calcd.: C 58.67; H 5.60; N 9.33

Found : C 58.84; H 5.68; N 9.24

0.1 g of this amidoxime, 0.1 g of carbonyldiimidazole and 0.05 ml of triethylamine were added to 5 ml of ethyl acetate, followed by refluxing with heating for 24 hours. The solution was concentrated and the residue was dissolved in ethyl acetate, washed with water and dried, after which the solvent was removed and the residue was recrystallized from ethyl acetate to yield 85 mg of a crystal.

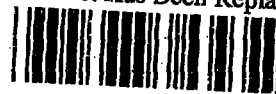
15 Melting point: 241-242°C.

Elemental analysis (for $C_{22}H_{23}Cl_2N_3O_4$)

Calcd.: C 57.99; H 4.87; N 8.82

Found : C 57.79; H 5.07; N 9.00





Example 109

Tert-butyl ester of N-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine; and tert-butyl ester of N-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine

In 20 ml of N,N-dimethylformamide were dissolved 0.5 g of trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 2, and 0.26 g of L-alanine tert-butyl ester hydrochloride; under ice-cooling, to this solution were added 0.26 g of diethyl phosphorocyanidate and 0.41 ml of triethylamine. After stirring for 30 minutes at room temperature, extraction was conducted with the addition of 100 ml of water and 150 ml of ethyl acetate. The ethyl acetate layer was washed with 5% aqueous solutions of potassium hydrogen sulfate and sodium bicarbonate, and after drying over anhydrous magnesium sulfate, it was distilled off under reduced pressure. The residue was then purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 2 : 1) to obtain, as the first fraction, 0.17 g of tert-butyl ester of N-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine as plate crystals, m.p. 146 to 147°C.

Elemental Analysis for $C_{28}H_{34}Cl_2N_2O_5$:

Calcd.: C 61.20; H 6.24; N 5.10

Found: C 61.20; H 6.33; N 5.15

Also, as the second fraction, 0.22 g of tert-butyl ester of N-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine was obtained as an oily product.

$IR_{\max}^{\text{neat}} \text{ cm}^{-1}$: 3330 (NH); 1730, 1670 (C = O)

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 0.93 (3H, d, $J = 6.8$ Hz), 1.03 (3H, d, $J = 6.8$ Hz), 1.34 (3H, t, $J = 7.0$ Hz), 1.46 (9H, s, Bu^t), 1.85-2.1 (1H, m), 2.71 (1H, dd, $J = 14.6, 6.2$ Hz), 2.89 (1H dd, $J = 14.6, 7.2$ Hz), 3.43 (1H, dd, $J = 14.0, 5.4$ Hz), 4.25-4.55 (3H, m), 6.13 (1H, s), 6.31 (1H, brd, NH), 6.51 (1H, d, $J = 2.2$ Hz), 7.2-7.85 (6H, m)

Example 110

N-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine

In 10 ml of a 4N solution of hydrochloric acid in dioxane was dissolved 0.16 g of tert-butyl ester of N-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-



2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine, as obtained in Example 109, and the solution was stirred overnight at room temperature. After distillation under reduced pressure, it was crystallized with hexane-diethylether to form 0.12 g of N-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine as a powdery product.

Elemental Analysis for $C_{24}H_{26}Cl_2N_2O_5$:

Calcd.: C 58.43; H 5.31; N 5.68

Found: C 58.43; H 5.65; N 5.54

1H -NMR spectrum (200 MHz, d_6 -DMSO) δ : 0.89 (3H, d, J = 6.8 Hz), 0.94 (3H, d, J = 6.6 Hz), 1.25 (3H, d, J = 7.2 Hz), 1.7-1.9 (1H, m), 2.4-2.55 (2H, m), 3.58 (1H, dd, J = 14.0, 5.0 Hz), 4.1-4.4 (3H, m), 5.99 (1H, s), 6.30 (1H, d, J = 2.4 Hz), 7.45-7.8 (4H, m), 8.33 (1H, d, J = 7.6 Hz), 12.53 (1H, br, NH)

Example 111

N-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine

In 10 ml of a 4N solution of hydrochloric acid in dioxane was dissolved 0.2 g of tert-butyl ester of N-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine, as obtained in Example 109, and the mixture was stirred for 4 hours at room temperature. After distillation under reduced pressure, it was crystallized from hexane-diethylether to form 0.17 g of N-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine as plate crystals, m.p. 120 to 124°C.

Elemental Analysis for $C_{24}H_{26}Cl_2N_2O_5 \cdot 1/2H_2O$:

Calcd.: C 57.37; H 5.42; N 5.57

Found: C 57.37; H 5.69; N 5.48

Example 112

Methyl ester of (R)-O-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid; and methyl ester of (R)-O-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid.

In 50 ml of methylene chloride were dissolved 2.0 g of trans-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 2, and 0.59 g of methyl ester of (R)-lactic acid; to this solution were added 1.09 g of 1-ethyl-3-(3-dimethylaminopropyl)



carbodiimide hydrochloride and 0.2 g of 4-dimethylaminopyridine; the mixture was stirred for 1.5 hours at room temperature. The reaction mixture was washed with 1N aqueous solutions of hydrochloric acid and sodium bicarbonate, and after drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was separated and purified by means of silica gel column chromatography (eluent, hexane : diethyl ether = 3 : 1) to yield, as the first fraction, 0.46 g of methyl ester of (R)-O-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid as an oily product.

IR $\nu_{\max}^{\text{neat}}$ cm $^{-1}$: 1740, 1675 (C = O)

$^1\text{H-NMR}$ (200 MHz, CDCl $_3$) δ : 0.93 (3H, d, J = 6.8 Hz), 1.02 (3H, d, J = 6.6 Hz), 1.49 (3H, d, J = 7.2 Hz), 1.85-2.1 (1H, m), 2.91 (1H, dd, J = 17.0, 5.4 Hz), 3.19 (1H, dd, J = 17.0, 8.0 Hz), 3.44 (1H, dd, J = 13.8, 5.4 Hz), 3.72 (3H, s), 4.31 (1H, dd, J = 13.8, 8.4 Hz), 4.44 (1H, dd, J = 8.0, 5.4 Hz), 5.07 (1H, q, J = 7.2 Hz), 6.14 (1H, s), 6.52 (1H, d, J = 2.2 Hz), 7.2-7.8 (6H, m)

As the second fraction, 0.63 g of methyl ester of (R)-O-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid was obtained as an oily product.

IR $\nu_{\max}^{\text{neat}}$ cm $^{-1}$: 1740, 1675 (C = O)

$^1\text{H-NMR}$ (200 MHz, CDCl $_3$) δ : 0.93 (3H, d, J = 6.8 Hz), 1.03 (3H, d, J = 6.6 Hz), 1.48 (3H, d, J = 7.0 Hz), 1.85-2.1 (1H, m), 2.93 (1H, dd, J = 16.8, 7.2 Hz), 3.10 (1H, dd, J = 16.8, 6.2 Hz), 3.43 (1H, dd, J = 13.8, 5.4 Hz), 3.28 (3H, s), 4.34 (1H, dd, J = 13.8, 5.4 Hz), 4.45 (1H, t, J = 6.6 Hz), 5.12 (1H, q, J = 7.0 Hz), 6.16 (1H, s), 6.52 (1H, d, J = 2.2 Hz), 7.2-7.8 (6H, m)

Example 113

(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In 20 ml of methanol was dissolved 0.45 g of methyl ester of (R)-O-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid, as obtained in Example 112, to which was added 10 ml of an aqueous solution containing 0.37 g of potassium carbonate; this mixture was stirred for 40 minutes at 60°C. The mixture was concentrated under reduced pressure, and the concentrate subjected to extraction with the addition of 50 ml of 1N hydrochloric acid and 100 ml of ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and distilled off under reduced pressure. The

residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 3 : 1; eluent, hexane : methylene chloride : ethanol = 5 : 5 : 1) to yield 53 mg of (3S, 5R)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as prism crystals, m.p. 183 to 186°C.

$[\alpha]_D^{20} + 223.7^\circ$ ($c = 0.47$, methanol)

Elemental Analysis for $C_{21}H_{21}Cl_2NO_4$:

Calcd.: C 59.73; H 5.01; N 3.32

Found: C 59.36; H 5.09; N 3.19

Example 114

(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In 20 ml of methanol was dissolved 0.6 g of methyl ester of (R)-O-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid, as obtained in Example 112, to which was added 10 ml of an aqueous solution containing 0.49 g of potassium carbonate; this mixture was stirred for 40 minutes at 60°C. The mixture was concentrated under reduced pressure, and the concentrate subjected to extraction with the addition of 50 ml of 1N hydrochloric acid and 100 ml of ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 3 : 1; eluent, hexane : methylene chloride : ethanol = 5 : 5 : 1) to yield 54 mg of (3R,5S)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as prism crystals, m.p. 182 to 185°C.

$[\alpha]_D^{20} - 215.3^\circ$ ($c = 0.43$, methanol)

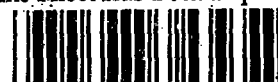
Elemental Analysis for $C_{21}H_{21}Cl_2NO_4 \cdot 1/4H_2O$:

Calcd.: C 59.10; H 5.08; N 3.28

Found: C 59.05; H 5.07; N 3.53

Example 115

Methyl ester of (R)-O-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid; and methyl ester of (R)-O-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid





In 50 ml of methylene chloride were dissolved 2.0 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 2, and 0.57 g of methyl ester of (R)-lactic acid. To the solution were added 1.05 g of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and 0.2 g of 4-dimethylaminopyridine; the mixture was stirred for 3 hours at room temperature. The reaction mixture was washed with 1N solutions of hydrochloric acid and sodium bicarbonate and dried over anhydrous magnesium sulfate; then the solvent was distilled off under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, hexane : diethylether = 3 : 1) to yield, as the first fraction, 0.48 g of methyl ester of (R)-O-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid as prism crystals, m.p. 155 to 157°C.

$[\alpha]_D^{20} + 222.6^\circ$ (c = 1.0, methanol)

Elemental Analysis for $C_{26}H_{29}Cl_2NO_6$:

Calcd.: C 59.78; H 5.60; N 2.68

Found: C 59.87; H 5.75; N 2.41

As the second fraction, 0.6 g of methyl ester of (R)-O-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid was recovered as an oily product.

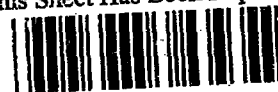
IR $_{\text{max}}^{\text{neat}}$ cm^{-1} : 1745, 1675 (C = O)

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 0.94 (9H, s, Bu^t), 1.47 (3H, d, $J = 7.0$ Hz), 2.92 (1H, dd, $J = 16.8, 7.2$ Hz), 3.08 (1H, dd, $J = 16.8, 6.0$ Hz), 3.39 (1H, d, $J = 14.0$ Hz), 3.72 (3H, s), 4.45 (1H, dd, $J = 7.2, 6.0$ Hz), 4.52 (1H, d, $J = 14.0$ Hz), 5.11 (1H, q, $J = 7.0$ Hz), 6.28 (1H, s), 6.52 (1H, s), 7.3 - 7.8 (6H, m)

Example 116

Methyl ester of (S)-O-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid; and methyl ester of (S)-O-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid.

In 150 ml of methylene chloride were dissolved 10 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 2, and 4.77 g of methyl ester of (S)-lactic acid. To the solution were added, under ice-cooling, 5.27 g of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and 0.3 g of 4-dimethylaminopyridine. The mixture was stirred for 2 hours at room



temperature, followed by washing with 1N aqueous solutions of hydrochloric acid and sodium bicarbonate, drying over magnesium sulfate. The solvent was then distilled off under reduced pressure. The residue was separated and purified by means of silica gel column chromatography (eluent, hexane : diethylether = 3 : 1) to yield, as the first fraction, 2.7 g of methyl ester of (S)-O-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid as prism crystals, m.p. 155 to 157°C.

$[\alpha]_D^{20} - 227.1^\circ$ (c = 0.94, methanol)

Elemental Analysis for $C_{26}H_{29}Cl_2NO_6$:

Calcd.: C 59.78; H 5.60; N 2.68

Found: C 59.82; H 5.69; N 2.51

As the second fraction, 2.8 g of methyl ester of (S)-O-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid was recovered as prism crystals, m.p. 119 to 120°C.

$[\alpha]_D^{20} + 160.1^\circ$ (c = 0.7, methanol)

Elemental Analysis for $C_{26}H_{29}Cl_2NO_6$:

Calcd.: C 59.78; H 5.60; N 2.68

Found: C 59.69; H 5.63; N 2.67

Example 117

(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In 20 ml of methanol was dissolved 0.4 g of methyl ester of (R)-O-[(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid, as obtained in Example 115. To the solution was added 10 ml of an aqueous solution containing 0.32 g of potassium carbonate; the reaction mixture was then stirred for 2 hours at 60°C and concentrated under reduced pressure, followed by extraction by the addition of 50 ml of 1N hydrochloric acid and 50 ml of ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, then distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 2 : 1; methylene chloride : methanol = 3 : 1) to yield 0.15 g of (3S,5R)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as needles, m.p. 241 to 245°C.

$[\alpha]_D^{20} + 244.8^\circ$ (c = 0.52, methanol)

Elemental Analysis for $C_{22}H_{23}Cl_2NO_4 \cdot 1/4H_2O$:

This Sheet Has Been Replaced



Calcd.: C 59.94; H 5.37; N 3.18

Found: C 60.19; H 5.47; N 2.97

Example 118

(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (1); and ethyl ester of (3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (2)

In 45 ml of methanol was dissolved 2.2 g of methyl ester of (S)-O-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid, as obtained in Example 116, to which was added 15 ml of an aqueous solution containing 1.75 g of potassium carbonate; the mixture was then stirred for 2 hours at 60°C, concentrated under reduced pressure and subjected to extraction with the addition of 100 ml of 1N hydrochloric acid and 100 ml of ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, then distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 2 : 1; methylene chloride : methanol = 3 : 1) to yield crystals. Recrystallization from hexane-ethanol yielded 0.85 g of (3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as needles, m.p. 250 to 252°C.

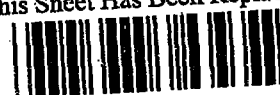
$[\alpha]_D^{20} - 252.0^\circ$ (c = 0.5, methanol)

Elemental Analysis for $C_{22}H_{23}Cl_2NO_4$:

Calcd.: C 59.94; H 5.37; N 3.28

Found: C 59.84; H 5.28; N 3.31

The filtrate was distilled off under reduced pressure; the residue was then dissolved in 30 ml of ethanol, to which 0.3 ml of concentrated sulfuric acid was added; the mixture was then stirred for 2 days. Distillation under reduced pressure was followed by extraction with the addition of 100 ml of water and 100 ml of ethyl acetate. The ethyl acetate layer was washed with aqueous sodium bicarbonate and with water, dried over anhydrous magnesium sulfate, and distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 5 : 1) to yield 0.63 g of ethyl ester of (3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as prism crystals, m.p. 120 to 121°C.



$[\alpha]_D^{20} - 235.5^\circ$ ($c = 0.51$, methanol)

Elemental Analysis for $C_{24}H_{27}Cl_2NO_4$:

Calcd.: C 62.07; H 5.86; N 3.02

Found: C 62.10; H 5.95; N 2.93

Also, in substantially the same manner as above, the hydrolysis of 0.6 g of methyl ester of (R)-O-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]lactic acid yielded 0.37 g of (3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid.

Example 119

Ethyl ester of N-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid

In 5 ml of N,N-dimethylformamide were dissolved 0.15 g of (3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 118, and 58 mg of glycine ethylester hydrochloride. To the solution were added, under ice-cooling, 71 mg of diethyl phosphorocyanidate and 0.12 ml of triethylamine. After the reaction mixture was stirred for 30 minutes at room temperature, it was subjected to extraction with the addition of 50 ml of water and 50 ml of ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid and an aqueous solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, and distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 1 : 1) to yield 0.16 g of ethyl ester of N-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid as plate crystals, m.p. 138 to 139°C.

$[\alpha]_D^{20} - 220.8^\circ$ ($c = 0.45$, methanol)

Elemental Analysis for $C_{26}H_{30}Cl_2N_2O_5$:

Calcd.: C 59.89; H 5.80; N 5.37

Found: C 59.86; H 5.94; N 5.12

Example 120

N-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid

In 5 ml of ethanol was dissolved 0.12 g of ethyl ester of N-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid, as obtained in Example 119, to



which was added 2 ml of 1N sodium hydroxide. The reaction mixture was stirred for 15 minutes at room temperature, after which was subjected to extraction with the addition of 50 ml of 1N hydrochloric acid and 50 ml of ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and distilled off under reduced pressure to leave 0.10 g of N-[(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid as a powdery product.

$[\alpha]_D^{20} - 229.8^\circ$ ($c = 0.46$, methanol)

Elemental Analysis for $C_{24}H_{26}Cl_2N_2O_5$:

Calcd.: C 58.43; H 5.31; N 5.68

Found: C 58.56; H 5.63; N 5.57

Example 121

(3S,5R)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid; and (3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In ethanol were dissolved 10 g of 7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 2, and quinine of equal molarity. After this mixture was concentrated, 150 ml of ethyl ether was added, and crystallization was allowed to occur under ice-cooling. The crystals thus obtained were dissolved in a mixture of ethanol and ethyl ether and allowed to recrystallize. The mother liquor was removed from the crystals thus formed, and was concentrated, leaving a residue. This residue underwent recrystallization using hexane, and the crystals thus formed were dissolved in ethyl acetate. The quinine in this solution was removed with dilute hydrochloric acid. The residue after removal of the solvent underwent recrystallization using hexane, resulting in (3S,5R)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as crystals. The solvent was then removed from the mother liquor remaining from the very first crystallization. The residue was dissolved in ethyl acetate, and the quinine was removed with dilute hydrochloric acid. The solvent was removed, leaving a residue which was recrystallized using a mixture solvent of ethanol and ethyl ether. After removal of the crystals thus formed, the mother liquor was concentrated, and the residue recrystallized using hexane, resulting in

(3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as crystals.

Example 122

Ethyl ester of (3S,5R)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid; and ethyl ester of (3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

To ethyl iodide in dimethyl formamide as a solvent, and under the presence of potassium carbonate, were added, as separate reactions, (3S,5R)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid and (3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 121, resulting in the above compounds. Ethyl ester of (3S,5R)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, m.p. 117 to 118°C.

$[\alpha]_D^{20} + 224.6^\circ$ (c = 0.5, MeOH)

Elemental Analysis for $C_{24}H_{27}Cl_2NO_4$:

Calcd.: C 62.07; H 5.86; N 3.02

Found: C 62.01; H 5.88; N 2.97

Example 123

Ethyl ester of trans-7-chloro-5-(2-ethoxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

(1) 2-amino-5-chloro-2'-hydroxybenzophenone

A mixture of 2.15 g of 2-amino-5-chloro-2'-methoxybenzophenone and 20 ml of 47% hydrogen bromide was heated for 1 hour under reflux. The solution was rendered neutral with sodium bicarbonate, and subjected to extraction with 100 ml of ethyl acetate. The extract solution was washed with water and dried over anhydrous magnesium sulfate; the solvent was then distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 10 : 1) to yield 1.9 g of 2-amino-5-chloro-2'-hydroxybenzophenone as needles, m.p. 51 to 52°C.

Elemental Analysis for $C_{13}H_{10}ClNO_2$:

Calcd.: C 63.04; H 4.07; N 5.66

Found: C 62.90; H 4.04; N 5.61

This Sheet Has Been Replaced



A mixture of 10 g of 2-acetylamino-5-chloro-2'-methoxybenzophenone and 100 ml of 47% hydrogen bromide was heated for 2 hours under reflux. The solution was rendered neutral with sodium hydroxide, and was subjected to extraction with 200 ml of ethyl acetate. The extract solution was washed with water and dried over anhydrous magnesium sulfate; the solvent was then distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 5 : 1) to yield 8.0 g of 2-amino-5-chloro-2'-hydroxybenzophenone as needles.

(2) 2-amino-5-chloro-2'-ethoxybenzophenone

In 10 ml of N,N-dimethylformamide was dissolved 1.5 g of 2-amino-5-chloro-2'-hydroxybenzophenone, as obtained in (1), to which were added 1.26 g of potassium carbonate and 0.63 ml of ethyl iodide. The reaction mixture was stirred for 3 hours at room temperature, after which it was subjected to extraction with 100 ml of water and 100 ml of ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 5 : 1) to yield 1.6 g of 2-amino-5-chloro-2'-ethoxybenzophenone as an oily product.

IR $\nu_{\max}^{\text{neat}}$ cm^{-1} : 3460, 3340 (NH); 1610 (C=O)

^1H -NMR spectrum (200 MHz, CDCl_3) δ : 1.21 (3H, t, $J = 7.0$ Hz), 4.04 (2H, q, $J = 7.0$ Hz), 6.1-6.5 (2H, br, NH_2), 6.65 (1H, d, $J = 8.8$ Hz), 6.9-7.1 (2H, m), 7.15-7.35 (3H, m), 7.35-7.5 (1H, m)

(3) 2-amino-5-chloro- α -(2-ethoxyphenyl)benzyl alcohol

In 30 ml of ethanol was dissolved 1.5 g of 2-amino-5-chloro-2'-ethoxybenzophenone, as obtained in (2), to which was added 0.34 g of sodium borohydride. The reaction mixture was stirred overnight at room temperature. After the ethanol was distilled off under reduced pressure and after dissociation by the addition of an aqueous solution of hydrochloric acid, 50 ml of 1N sodium hydroxide was added to render the solution neutral, and extraction was carried out with 100 ml of ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 3 : 1) to yield 1.35 g of 2-amino-5-chloro- α -(2-ethoxyphenyl)benzyl alcohol as prism crystals, m.p. 80 to 81°C.

Elemental Analysis of $\text{C}_{15}\text{H}_{16}\text{ClNO}_2$:

This Sheet Has Been Replaced



Calcd.: C 64.87; H 5.81; N 5.04

Found: C 64.77; H 5.81; N 4.85

(4) 5-chloro- α -(2-ethoxyphenyl)-2-isobutylaminobenzyl alcohol

In 10 ml of acetic acid were dissolved 1.3 g of 2-amino-5-chloro- α -(2-ethoxyphenyl)benzyl alcohol, as obtained in (3), and 0.47 ml of isobutylaldehyde, to which was added, under ice-cooling, 0.24 g of sodium borohydride. The reaction mixture was stirred for 30 minutes at room temperature, after which it was subjected to extraction with the addition of 100 ml of water and 100 ml of ethyl acetate. The ethyl acetate layer was washed with 1N sodium hydroxide, dried over anhydrous magnesium sulfate, and then distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 20 : 1 to 5 : 1) to yield 1.5 g of 5-chloro- α -(2-ethoxyphenyl)-2-isobutylaminobenzyl alcohol as an oily product.

IR $\nu_{\max}^{\text{neat}}$ cm^{-1} : 3520, 3410 (NH, OH)

$^1\text{H-NMR}$ spectrum (200 MHz, CDCl_3) δ : 0.90 (3H, d, $J = 6.8$ Hz), 0.91 (3H, d, $J = 6.6$ Hz), 1.41 (3H, t, $J = 7.0$ Hz), 1.7-2.0 (1H, m), 2.89 (2H, d, $J = 6.8$ Hz), 3.2-3.6 (1H, br), 4.13 (2H, q, $J = 7.0$ Hz), 4.7-5.1 (1H, br), 5.97 (1H, s), 6.55 (1H, d, $J = 8.6$ Hz), 6.85-7.4 (6H, m)

(5) Ethyl ester of 3-[N-[4-chloro-2-[2-ethoxy- α -hydroxybenzyl]phenyl]-N-isobutylcarbamoyl]acrylic acid

A solution containing 0.84 g of monoethyl ester of fumaric acid and 1.28 ml of thionyl chloride in 10 ml of toluene was stirred for 30 minutes at 90°C. The solvent was distilled off under reduced pressure, leaving monoethyl ester acid chloride of fumaric acid. This product and 1.5 g of 5-chloro- α -(2-methoxyphenyl)-2-isobutylaminobenzyl alcohol, as obtained in (4), were then dissolved in 30 ml of methylene chloride, to which 0.75 g of sodium bicarbonate was added; the mixture was then stirred for 30 minutes at room temperature. The reaction mixture was washed with water and dried over anhydrous magnesium sulfate; the solvent was then distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 4 : 1) to yield 1.95 g of ethyl ester of 3-[N-[4-chloro-2-[2-ethoxy- α -hydroxybenzyl]phenyl]-N-isobutylcarbamoyl]acrylic acid as an oily product.

IR $\nu_{\max}^{\text{neat}}$ cm^{-1} : 3400 (OH); 1720, 1660, 1630 (C = C, C = O)



¹H-NMR spectrum (200 MHz, CDCl₃) δ: 0.65-1.0 (6H, m), 1.15-1.5 (6H, m), 1.6-2.0 (1H, m), 2.3-3.0 (2H, m), 3.9-4.4 (5H, m), 5.8-6.3 (3H, m), 6.6-8.05 (7H, m)

(6) Ethyl ester of trans-7-chloro-5-(2-ethoxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In 30 ml of ethanol was dissolved 1.95 g of ethyl ester of 3-[N-[4-chloro-2-[2-ethoxy- α -hydroxybenzyl]phenyl]-N-isobutylcarbamoyl]acrylic acid, as obtained in (5), to which was added 1.17 g of potassium carbonate, and the mixture was stirred overnight. The reaction mixture was subjected to extraction with 100 ml of water and 100 ml of ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 5 : 1) to yield 1.55 g of ethyl ester of trans-7-chloro-5-(2-ethoxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as prism crystals, m.p. 129 to 130°C.

Elemental Analysis for C₂₅H₃₀ClNO₅:

Calcd.: C 65.28; H 6.57; N 3.05

Found: C 65.38; H 6.44; N 2.91

Example 124

Trans-7-chloro-5-(2-ethoxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In 30 ml of methanol was dissolved 1.25 g of ethyl ester of trans-7-chloro-5-(2-ethoxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 123, to which was added 10 ml of an aqueous solution containing 0.75 g of potassium carbonate; the mixture was then stirred for 3 hours at 60°C. After the reaction mixture was concentrated under reduced pressure, it was rendered acid by the addition of 50 ml of 1N hydrochloric acid, and subjected to extraction with 100 ml of ethyl acetate. The extract solution was washed with water and dried over anhydrous magnesium sulfate; the solvent was then distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 2 : 1; eluent, hexane : dichloromethane : ethanol = 5 : 5 : 1) to yield 0.66 g of trans-7-chloro-5-(2-ethoxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as prism crystals, m.p. 190 to 192 °C.



Elemental Analysis for $C_{23}H_{26}ClNO_5$:

Calcd.: C 63.96; H 6.07; N 3.24

Found: C 63.64; H 5.96; N 3.58

Example 125

Ethyl ester of trans-5-(2-benzyloxyphenyl)-7-chloro-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

(1) 2-amino-2'-benzyloxy-5-chlorobenzophenone

In 30 ml of N,N-dimethylformamide was dissolved 5.0 g of 2-amino-5-chloro-2'-hydroxybenzophenone, as obtained in Example 123 (1), to which were added 4.2 g of potassium carbonate and 2.9 ml of benzyl bromide; the mixture was then stirred for 2 hours at room temperature. The mixture was subjected to extraction with 150 ml of water and 200 ml of ethyl acetate, and the ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 10 : 1 to 5 : 1) to yield 6.4 g of 2-amino-2'-benzyloxy-5-chlorobenzophenone as prism crystals, m.p. 110 to 111 °C.

Elemental Analysis for $C_{20}H_{16}ClNO_2$:

Calcd.: C 71.11; H 4.77; N 4.15

Found: C 71.34; H 4.80; N 4.23

(2) 2-amino- α -(2-benzyloxyphenyl)-5-chlorobenzyl alcohol

In 50 ml of methanol was dissolved 6.0 g of 2-amino-2'-benzyloxy-5-chlorobenzophenone, as obtained in (1), to which was added 1.12 g of sodium borohydride; the mixture was then stirred for 4 hours at room temperature. After ethanol was distilled off under reduced pressure, with dissociation by the addition of an aqueous solution of hydrochloric acid, the reaction mixture was rendered neutral by the addition of 50 ml of 1N sodium hydroxide and subjected to extraction with 200 ml of ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, then distilled off under reduced pressure to leave 5.9 g of 2-amino- α -(2-benzyloxyphenyl)-5-chlorobenzyl alcohol as plate crystals, m.p. 120 to 121 °C.

Elemental Analysis for $C_{20}H_{18}ClNO_2$:

Calcd.: C 70.69; H 5.34; N 4.12

Found: C 70.85; H 5.16; N 4.24

(3) α -(2-benzyloxyphenyl)-5-chloro-2-isobutylaminobenzyl alcohol





In 50 ml of acetic acid were dissolved 5.0 g of 2-amino- α -(2-benzyloxyphenyl)-5-chlorobenzyl alcohol, as obtained in (2), and 1.47 ml of isobutylaldehyde. To the solution was added, under ice-cooling, 0.74 g of sodium borohydride. The reaction mixture was stirred for 30 minutes at room temperature, and, after addition of 150 ml of water, was subjected to extraction with 200 ml of ethyl acetate. The extract solution was washed with 1N sodium hydroxide and dried over anhydrous magnesium sulfate; then the solvent was distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 20 : 1 to 5 : 1) to yield 5.6 g of α -(2-benzyloxyphenyl)-5-chloro-2-isobutylaminobenzyl alcohol as prism crystals, m.p. 79 to 80 °C.

Elemental Analysis for $C_{24}H_{26}ClNO_2$:

Calcd.: C 72.81; H 6.62; N 3.54

Found: C 72.95; H 6.62; N 3.62

(4) Ethyl ester of 3-[N-[4-chloro-2-[2-benzyloxy- α -hydroxybenzyl]phenyl]-N-isobutylcarbamoyl]acrylic acid

A solution comprised of 2.65 g of monoethyl ester of fumaric acid and 4.0 ml of thionyl chloride in 30 ml of toluene was stirred for 1 hour at 90°C. It was then distilled under reduced pressure, leaving monoethyl ester acid chloride of fumaric acid. This product and 5.6 g of α -(2-benzyloxyphenyl)-5-chloro-2-isobutylaminobenzyl alcohol, as obtained in (3), were dissolved in 100 ml of methylene chloride; after the addition of 2.38 g of sodium bicarbonate, the mixture was stirred for 30 minutes at room temperature. The reaction mixture was washed with water and dried over anhydrous magnesium sulfate; then the solvent was distilled off under reduced pressure to yield 6.4 g ethyl ester of 3-[N-[4-chloro-2-[2-benzyloxy- α -hydroxybenzyl]phenyl]-N-isobutylcarbamoyl]acrylic acid as prism crystals, m.p. 169 to 171°C.

Elemental Analysis for $C_{30}H_{32}ClNO_5$:

Calcd.: C 69.02; H 6.18; N 2.68

Found: C 69.24; H 6.04; N 2.71

(5) Ethyl ester of trans-5-(2-benzyloxyphenyl)-7-chloro-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In 150 ml of ethanol was dissolved 6.0 g of ethyl ester of 3-[N-[4-chloro-2-[2-benzyloxy- α -hydroxybenzyl]phenyl]-N-isobutylcarbamoyl]acrylic acid, as obtained in (4), to which was added 3.18 g of potassium carbonate; the

mixture was then stirred overnight. The solvent was distilled off under reduced pressure, and the residue was subjected to extraction with 150 ml of water and 200 ml of ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate, then distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 5 : 1) to yield 5.8 g of ethyl ester of trans-5-(2-benzyloxyphenyl)-7-chloro-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as prism crystals, m.p. 146 to 147°C.

Elemental Analysis for $C_{30}H_{32}ClNO_5$:

Calcd.: C 69.02; H 6.18; N 2.68

Found: C 69.20; H 6.21; N 2.95

Example 126

Trans-5-(2-benzyloxyphenyl)-7-chloro-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In a mixture of 20 ml of methanol and 10 ml of tetrahydrofuran was dissolved 0.5 g of ethyl ester of trans-5-(2-benzyloxyphenyl)-7-chloro-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 125. To this solution was added 10 ml of an aqueous solution containing 0.66 g of potassium carbonate, and the mixture was stirred for 6 hours at 60°C. The reaction mixture was concentrated under reduced pressure, rendered acid by the addition of 50 ml of 1N hydrochloric acid, and subjected to extraction with 100 ml of ethyl acetate. The extract solution was washed with water and dried over anhydrous magnesium sulfate; then the solvent was distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 3 : 1; eluent, hexane : dichloromethane : ethanol = 5 : 5 : 1) to yield 0.21 g of trans-5-(2-benzyloxyphenyl)-7-chloro-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as prism crystals, m.p. 194 to 197°C.

Elemental Analysis for $C_{28}H_{28}ClNO_5$:

Calcd.: C 68.08; H 5.71; N 2.84

Found: C 68.07; H 5.75; N 2.85

Example 127

Ethyl ester of trans-7-chloro-5-(2-hydroxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid



In 50 ml of ethyl acetate was dissolved 3.5 g of ethyl ester of trans-5-(2-benzyloxyphenyl)-7-chloro-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 125. To this solution was added 1.0 g of 10% palladium carbon and hydrogenolysis was then allowed to occur at normal temperature and pressure. After the calculated amount of hydrogen was absorbed, the catalyst was removed, and the ethyl acetate was distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 3 : 1) to yield 2.8 g of ethyl ester of trans-7-chloro-5-(2-hydroxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as an oily product.

IR $\nu_{\max}^{\text{neat}}$ cm^{-1} : 3380 (OH); 1730, 1670, 1650 (C = O)

$^1\text{H-NMR}$ spectrum (200 MHz, CDCl_3) δ : 0.90 (3H, d, $J = 6.6$ Hz), 0.99 (3H, d, $J = 6.6$ Hz), 1.24 (3H, t, $J = 7.2$ Hz), 1.9-2.2 (1H, m), 2.85 (1H, dd, $J = 17.8, 5.0$ Hz), 2.97 (1H, d, $J = 17.8, 8.2$ Hz), 3.41 (1H, dd, $J = 13.8, 6.4$ Hz), 4.16 (2H, q, $J = 7.2$ Hz), 4.30 (1H, dd, $J = 13.8, 7.8$ Hz), 4.49 (1H, dd, $J = 8.2, 4.8$ Hz), 5.97 (1H, s), 6.85 (1H, d, $J = 2.4$ Hz), 6.85-7.5 (6H, m), 7.54 (1H, br, OH)

Example 128

Trans-7-chloro-5-(2-hydroxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In 10 ml of methanol was dissolved 0.4 g of ethyl ester of trans-7-chloro-5-(2-hydroxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 127, to which was added 5 ml of an aqueous solution containing 0.51 g of potassium carbonate; the mixture was then stirred for 1 hour at 60°C . The reaction mixture was condensed under reduced pressure, rendered acid by the addition of 50 ml of 1N hydrochloric acid, and subjected to extraction with 100 ml of ethyl acetate. The extract solution was washed with water and dried over anhydrous magnesium sulfate; the solvent was then distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 2 : 1; eluent, hexane : dichloromethane : ethanol = 5 : 5 : 2) to yield 0.11 g of trans-7-chloro-5-(2-hydroxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as prism crystals, m.p. 238 to 242°C (decomposition).

Elemental Analysis for $\text{C}_{21}\text{H}_{22}\text{ClNO}_5$:

This Sheet Has Been Replaced



Calcd.: C 62.45; H 5.49; N 3.47

Found: C 62.55; H 5.68; N 3.41

Example 129

Ethyl ester of trans-7-chloro-1-isobutyl-5-(2-isopropoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In 10 ml of N,N-dimethylformamide was dissolved 0.7 g of ethyl ester of trans-7-chloro-5-(2-hydroxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 127, to which was added 0.34 g of potassium carbonate and 0.24 ml of isopropyl iodide; the mixture was then stirred overnight at room temperature. The mixture was subjected to extraction with 100 ml of water and 150 ml of ethyl acetate, after which the ethyl acetate layer was washed with 1N hydrochloric acid and sodium bicarbonate, dried over anhydrous magnesium sulfate, and distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 3 : 1) to yield 0.55 g of ethyl ester of trans-7-chloro-1-isobutyl-5-(2-isopropoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as needles, m.p. 135 to 137°C.

Elemental Analysis for $C_{26}H_{32}ClNO_5$:

Calcd.: C 65.88; H 6.80; N 2.96

Found: C 66.09; H 6.83; N 3.24

Example 130

Trans-7-chloro-1-isobutyl-5-(2-isopropoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In 20 ml of methanol was dissolved 0.4 g of ethyl ester of trans-7-chloro-5-(2-isopropoxyphenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, as obtained in Example 129. To this solution was added 10 ml of an aqueous solution containing 0.23 g of potassium carbonate; the mixture was then stirred for 3 hours at 80°C. The reaction mixture was concentrated under reduced pressure, rendered acid by the addition of 50 ml of 1N hydrochloric acid, and subjected to extraction with 100 ml of ethyl acetate. The extract solution was washed with water and dried over anhydrous magnesium sulfate, the solvent was then distilled off under reduced pressure. The residue was purified by means of silica gel column chromatography (eluent, hexane : ethyl acetate = 3 : 1; eluent, hexane : dichloromethane : ethanol = 5 : 5 : 1) to yield 0.24 g of trans-7-chloro-1-





isobutyl-5-(2-isopropoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as prism crystals, m.p. 146 to 149°C.

Elemental Analysis for $C_{24}H_{28}ClNO_5 \cdot 0.2H_2O$:

Calcd.: C 64.12; H 6.37; N 3.11

Found: C 64.18; H 6.37; N 3.28

Example 131

Ethyl trans-7-bromo-1-neopentyl-2-oxo-5-(2-pyridyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate

(1) 2-Amino-5-bromo- α -(2-pyridyl)benzyl alcohol

In 100 ml of methanol was dissolved 10 g of 2-amino-5-bromophenyl-2-pyridylketone. To the solution was added 1.7 g of sodium borohydride and stirred for 30 minutes. The solvent methanol was evaporated off under reduced pressure. The residue was treated with an aqueous solution of hydrochloric acid. The decomposed residue was then neutralized with 200 ml of a sodium bicarbonate aqueous solution, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 2:1) to give 2-amino-5-bromo- α -(2-pyridyl)benzyl alcohol (9.0 g) as prisms, m.p. 104 - 105°C

Elementary analysis for $C_{12}H_{11}BrN_2O$

Calcd.: C 51.64; H 3.97; N 10.04

Found: C 51.61; H 3.93; N 10.04

(2) 5-Bromo-2-neopentylamino- α -(2-pyridyl)benzyl alcohol

In 20 ml of acetic acid was dissolved 2.0 g of 2-amino-5-bromo- α -(2-pyridyl)benzyl alcohol obtained in (1) together with 0.86 ml of trimethylacetaldehyde. To the solution was added 0.36 g of sodium borohydride under ice-cooling. The reaction mixture was stirred for 30 minutes at room temperature and then subjected to extraction with a mixture of 100 ml of water and 150 ml of ethyl acetate. The ethyl acetate layer was washed with 1N sodium hydroxide, dried over anhydrous magnesium sulfate, and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 5:1) to afford 5-bromo-2-neopentylamino- α -(2-pyridyl)benzyl alcohol (2.4 g) as an oily product.

IR ν ^{Neat} _{Max} cm^{-1} : 3390, 3280 (NH, OH)



¹H-NMR spectrum (200MHz, CDCl₃) δ: 0.80 (9H, s, But), 2.68 (2H, s), 5.69 (1H, s), 6.48 (1H, d, J = 8.4Hz), 7.1-7.35 (4H, m), 7.55-7.7 (1H, m), 8.5-8.6 (1H, m).

(3) Ethyl 3-[N-[4-bromo-2-[α-(2-pyridyl) hydroxymethyl]phenyl]-N-neopentylcarbamoyl]acrylate

In 50 ml of dichloromethane was dissolved 2.4 g of 5-bromo-2-neopentylamino-α-(2-pyridyl)benzyl alcohol obtained in (2). To the solution were added 1.15 g of sodium borohydride and 1.23 g of monomethyl fumarate acid chloride. After stirring for 2 hours at room temperature, the reaction mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure. The residue was purified by column chromatography using silica gel (eluent, hexane : ethyl acetate = 2:1) to give ethyl 3-[N-[4-bromo-2-[α-(2-pyridyl) hydroxymethyl]phenyl]-N-neopentylcarbamoyl]acrylate as prisms, m.p. 165 - 166°C.

Elementary analysis for C₂₃H₂₇BrN₂O₄:

Calcd.: C 58.11; H 5.72; N 5.89

Found: C 58.21; H 5.65; N 6.14

(4) Ethyl trans-7-bromo-1-neopentyl-5-(2-pyridyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate

In 30 ml of ethanol was dissolved 2.0 g of ethyl 3-[N-[4-bromo-2-[α-(2-pyridyl) hydroxymethyl]phenyl]-N-neopentylcarbamoyl]acrylate obtained in (3). To the solution was added 1.16 g of potassium carbonate and the mixture was stirred overnight at room temperature. The solvent was evaporated off under reduced pressure. The residue was then extracted with 100 ml of water and 100 ml of ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified on a silica gel column (eluent, hexane : ethyl acetate = 3:1) to give 1.9 g of ethyl trans-7-bromo-1-neopentyl-5-(2-pyridyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate as an oily product.

IR ν_{Neat} cm⁻¹: 1730, 1675 (C=O)
ν_{Max}

¹H-NMR (CDCl₃) δ: 0.94(9H,s,But), 1.25(3H,t,J=7.2Hz), 2.80(1H,dd,J=16.6,5.8Hz), 3.07(1H,dd,J=16.6,7.8Hz), 3.31(1H,d,J=13.8Hz), 4.13(2H,q,J=7.2Hz), 4.44(1H,dd,J=7.8,5.8Hz), 4.49(1H,d,J=13.8Hz), 6.07 (1H,s), 6.59(1H,d,J=2.2Hz), 7.2-7.9 (5H,m), 8.6-8.7(1H,m)

Example 132

Trans-7-bromo-1-neopentyl-5-(2-pyridyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In 20 ml of methanol was dissolved 1.9 g of ethyl trans-7-bromo-1-neopentyl-5-(2-pyridyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate obtained in Example 131. To the solution was added 10 ml of an aqueous solution containing 1.1 g of potassium carbonate. The mixture was heated and refluxed for 30 minutes, and then concentrated under reduced pressure. The concentrate was crystallized by the addition of 30 ml of a hydrochloric acid aqueous solution. The product was collected by filtration and recrystallized from hexane and ethanol to give 1.25 g of trans-7-bromo-1-neopentyl-5-(2-pyridyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as prisms, m.p. $> 263^{\circ}\text{C}$ (decomp.)
Elementary analysis for $\text{C}_{21}\text{H}_{23}\text{BrN}_2\text{O}_4$

Calcd.: C 56.39; H, 5.18; N 6.26

Found : C 56.39; H, 5.18; N 6.10

Example 133

Ethyl N-benzyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetate

In 10 ml of dimethylformamide were dissolved 0.3 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid obtained in Example 2 and 0.27 g of N-benzylglycine ethyl ester. To the solution was added 0.24 g of diethyl phosphorocyanidate together with 0.19 ml of triethylamine under ice-cooling. The mixture was stirred for 30 minutes at room temperature and then subjected to extraction with a mixture of 100 ml of water and 100 ml of ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid and with a sodium bicarbonate aqueous solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 3:1) to afford ethyl N-benzyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]amino acetate (0.56 g) as prisms, m.p. $195 - 197^{\circ}\text{C}$

Elementary Analysis for $\text{C}_{33}\text{H}_{36}\text{Cl}_2\text{N}_2\text{O}_5$

Calcd.: C 64.81; H 5.93; N, 4.58

Found : C 64.84; H 5.97; N 4.45

This Sheet Has Been Replaced



Example 134

N-Benzyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]amino acetic acid

In 15 ml of methanol was dissolved 0.3 g of ethyl N-benzyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]amino acetate obtained in Example 133. To the solution was added 4 ml of sodium hydroxide and the mixture was stirred for 20 minutes. The reaction mixture, after acidified with 50 ml of 1N HCl, was subjected to extraction with 100 ml of ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to yield N-benzyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]amino acetic acid as prisms, m.p. 190 - 192°C.

Elementary Analysis for $C_{31}H_{32}Cl_2N_2O_5$:

Calcd.: C 63.81; H 5.53; N 4.80

Found: C 64.02; H 5.85; N 4.81

Example 135

Methyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-N-phenyl aminoacetate

A mixture of 0.6 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid obtained in Example 2, 10 ml of thionyl chloride and 10 ml of toluene was stirred for 30 minutes at 90°C, and then concentrated under reduced pressure. The concentrate trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl chloride was dissolved in 10 ml of methylene chloride. To the solution were added 0.27 g of N-phenylglycine methyl ester and 0.23 ml of triethylamine. The mixture was stirred for one hour at room temperature, and then subjected to extraction with 100 ml of ethyl acetate. The organic layer was washed with 1N HCl and with a sodium bicarbonate aqueous solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure.

The residue was purified on a silica gel column (eluent, hexane : ethyl acetate = 3:1) to give methyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-N-phenyl amino acetate (0.35 g) as prisms, m.p. 226 - 228°C



This Sheet Has Been Replaced



Elementary Analysis for $C_{31}H_{32}Cl_2N_2O_5$:

Calcd.: C 63.81; H 5.53; N 4.80

Found : C 63.78; H 5.59; N 4.60

Example 136

N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-N-phenylamino acetic acid

In 3 ml of methanol was dissolved 0.25 g of methyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-N-phenyl amino acetate obtained in Example 135. To the solution was added 2 ml of 1N sodium hydroxide. The mixture was stirred for 1.5 hours at 60°C and then acidified with 50 ml of 1N HCl for extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 0.23 g of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-N-phenylaminoacetic acid (0.23 g) as prisms, m.p. 238 - 240°C.

Elementary Analysis for $C_{30}H_{30}Cl_2N_2O_5$:

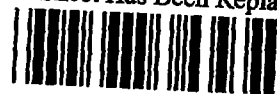
Calcd.: C 63.27; H 5.31; N 4.92

Found : C 63.46; H 5.54; N 4.70

Example 137

Ethyl N-[trans-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]amino acetate

In 10 ml of dimethylformamide were dissolved 0.3 g of trans-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid obtained in Example 74 and 0.12 g of glycine ethyl ester hydrochloride. To the solution were added 0.14 g of diethyl phosphorocyanidate and 0.24 ml of triethylamine under ice-cooling. The mixture was stirred for 30 minutes at room temperature and then subjected to extraction with 100 ml of water and 100 ml of ethyl acetate. The ethyl acetate layer was washed with 1N HCl and with a sodium bicarbonate aqueous solution and dried over anhydrous magnesium sulfate. Ethyl acetate was evaporated off under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 1:1) to yield ethyl N-[trans-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]amino acetate (0.33 g) as needles, m.p. 233 - 236°C.



Elementary Analysis for $C_{27}H_{33}ClN_2O_6$

Calcd.: C 62.72; H 6.43; N 5.42

Found : C 62.54; H 6.47; N 5.28

Example 138

N-[Trans-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid

In 5 ml of ethanol was dissolved 0.25 g of ethyl N-[trans-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetate obtained in Example 137. To the solution was added 2 ml of 1N NaOH. After stirring for 15 minutes, the reaction mixture was acidified with 100 ml of 1N HCl and subjected to extraction with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. Ethyl acetate was evaporated off under reduced pressure to afford N-[trans-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminoacetic acid as prisms, m.p. 239 - 242°C

Elementary Analysis for $C_{25}H_{29}ClN_2O_5$

Calcd.: C 61.41; H 5.98; N 5.73

Found : C 61.38; H 5.91; N 5.83

Example 139

Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methylamine hydrochloride

In the same manner as done in Example 36 was treated 1.0 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid obtained in Example 2. The product was 0.90 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methylamine hydrochloride as plate crystals, m.p. 173 - 175°C

Elementary Analysis for $C_{21}H_{24}Cl_2N_2O_2 \cdot HCl \cdot H_2O$

Calcd.: C 54.62; H 5.89; N 6.06

Found : C 54.77; H 5.95; N 5.83

Example 140

Methyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]carbamoyl acetate

In 10 ml of N,N-dimethylformamide were dissolved 0.3 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-

benzoxazepine-3-methylamine hydrochloride obtained in Example 139 and 0.12 g of monomethyl malonate potassium salt. To the solution was added 0.13 g of diethyl phosphorocyanate together with 0.11 ml of triethylamine under ice-cooling. After stirring for 30 minutes at room temperature, the reaction mixture was subjected to extraction with 100 ml of water and 100 ml of ethyl acetate. The ethyl acetate layer was washed with 1N HCl and with a sodium bicarbonate aqueous solution, and dried over anhydrous magnesium sulfate. The solvent ethyl acetate was then evaporated off under reduced pressure. The residue was purified by silica-gel column chromatography (eluent, hexane : ethyl acetate = 1:1) to give 0.28 g of methyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]carbamoyl acetate as an oily product.

IR ν ^{Neat} _{Max} cm⁻¹: 3330(NH); 1740, 1670 (C=O)

¹H-NMR (200MHz, CDCl₃) δ : 0.94 (9H,s,But), 3.28 (2H,s), 3.38 (1H,d,J=13.9Hz), 3.74(3H,s), 3.7-3.85(2H,m), 3.99(1H,t,J=6.1Hz), 4.54(1H,d,J=13.9Hz), 6.25(1H,s), 6.52(1H,d,J=1.9Hz), 7.2-7.9(7H,m,NH).

Example 141

N-[Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]carbamoyl acetic acid

In 5 ml of ethanol was dissolved 0.28 g of methyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]carbamoyl acetate obtained in Example 140. To the solution was added 2 ml of 1N sodium hydroxide and the mixture was stirred for 10 minutes at room temperature. The reaction mixture was acidified with 50 ml of 1N hydrochloric acid and then subjected to extraction with 50 ml of ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to afford 0.23 g of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]carbamoyl acetic acid as plate crystals, m.p. 135 - 138°C

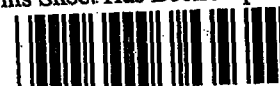
Elementary analysis for C₂₄H₂₆Cl₂N₂O₅:

Calcd.: C 58.43; H 5.31; N 5.68

Found : C 58.48; H 5.42; N 5.52

Example 142

Tert-butyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine 3-methyl]aminoacetate



A mixture of 2.5 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methylamine hydrochloride obtained in Example 139, 0.93 ml of ethyl chloroacetate, 1.87 g of potassium carbonate, and 50 ml of acetonitrile was heated and refluxed overnight. The reaction mixture was concentrated under reduced pressure and the concentrate was extracted with 100 ml of water and 150 ml of ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. Ethyl acetate was evaporated under reduced pressure to give 1.95 g of tert-butyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminoacetate as an oily product.

IR ν ^{Neat} _{Max} cm⁻¹: 3330 (NH); 1735, 1675 (C=O)

¹H-NMR (200MHz, CDCl₃) δ : 0.94 (9H,s,But), 1.44 (9H,s, But), 3.00 (1H,dd,J=12.2,6.4Hz), 3.11 (1H,dd,J=12.2,6.2Hz), 3.33(2H,s), 3.36(1H,d,J=14.0Hz), 4.04(1H,t,J=6.3Hz), 4.52(1H,d,J=14.0Hz), 6.26(1H,s), 6.52(1H,d,J=1.8Hz), 7.2-7.85(6H,m)

Example 143

N-[Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminoacetic acid hydrochloride

In 15 ml of 4N HCl-dioxane solution was dissolved 0.3 mg of tert-butyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminoacetate obtained in Example 142. After stirring for 8 hours at room temperature, the reaction mixture was concentrated under reduced pressure. The addition of hexane and ethyl acetate to the residue yielded 0.23 g of powdered N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminoacetic acid hydrochloride.

Elementary analysis for C₂₃H₂₆Cl₂N₂O₄·HCl

Calcd.: C 55.05; H 5.42; N 5.58

Found: C 55.38; H 5.77; N 5.39

¹H-NMR spectrum (200MHz, d₆-DMSO) δ : 0.89(9H,s,But), 3.2-3.55(2H,m), 3.68(1H,d,J=14.0Hz), 3.88(2H,s), 4.32(1H,d,J=14.0Hz), 4.3-4.5(1H,m), 6.19(1H, s), 6.39(1H,d,J=2.4Hz), 7.5-8.1(6H,m).

Example 144

This Sheet Has Been Replaced





Tert-butyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-methanesulfonylaminoacetate

In 5 ml of N,N-dimethylformamide was dissolved 0.44 g of tert-butyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminoacetate obtained in Example 142. To the solution was added 0.072 ml of methanesulfonyl chloride and 0.14 ml of triethylamine under ice-cooling. After stirring for 30 minutes at room temperature, the reaction mixture was subjected to extraction with 100 ml of water and 100 ml of ethyl acetate. The ethyl acetate layer was washed with 5% potassium bisulfate solution and with a sodium bicarbonate aqueous solution and dried over anhydrous magnesium sulfate. Ethyl acetate was evaporated off under reduced pressure. The residue was purified by silica gel column chromatography (hexane : acetate = 3:1) to afford 0.37 g of tert-butyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-methanesulfonylaminoacetate as prisms, m.p. 178 - 180°C.

Elementary analysis for $C_{28}H_{36}Cl_2N_2O_6S$

Calcd.: C 56.09; H 6.05; N 4.67

Found : C 55.92; H 6.06; N 4.47

Example 145

N-[Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-methanesulfonylaminoacetic acid

In 20 ml of 4N HCl-dioxane solution was dissolved 0.25 g of tert-butyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-methanesulfonylaminoacetate obtained in Example 144. After stirring for 8 hours at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was treated with hexane and ethyl acetate to give 0.21 g of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl] N-methanesulfonylaminoacetic acid as prisms, m.p. 236 - 238°C.

Elementary analysis for $C_{24}H_{28}Cl_2N_2O_6S$

Calcd.: C 53.04; H 5.19; N 5.15

Found : C 53.32; H 5.42; N 5.02

Example 146

Tert-butyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-(p-toluensulfonyl)aminoacetate

In 10 ml of N,N-dimethylformamide was dissolved 0.5 g of tert-butyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl] aminoacetate obtained in Example 142. To the solution was added 0.22 g of p-toluenesulfonyl chloride together with 0.16 ml of triethylamine under ice-cooling.

The mixture was stirred for one hour at room temperature and then subjected to extraction with 100 ml of water and 100 ml of ethyl acetate. The ethyl acetate layer was washed with 5% potassium bisulfate solution and with sodium bicarbonate aqueous solution, dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure. The residue was purified by column chromatography using silica gel (eluent, hexane : ethyl acetate = 5:1) to afford tert-butyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-(p-toluenesulfonyl)aminoacetate as an oily product.

IR ν ^{Neat} _{Max} cm⁻¹: 1740, 1670 (C=O)

¹H-NMR (200MHz, CDC₁₃) δ : 0.92 (9H,s,But), 2.39(3H,s), 3.36(1H,d,J=14.0Hz), 3.66(1H,dd,J=15.6,6.4Hz), 3.84(1H,dd, J=15.6,5.9Hz), 3.98(1H,d,J=18.4Hz), 4.2-4.3(1H,m), 4.29(1H, d,J=18.4Hz), 4.45(1H,d,J=14.0Hz), 6.20(1H,s), 6.46(1H,s, J=2.1Hz), 7.15-7.7(10H,m).

Example 147

N-[Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-(p-toluenesulfonyl)aminoacetic acid

In 15 ml of 4N HCl-dioxane solution was dissolved 0.5 g of tert-butyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-(p-toluenesulfonyl)aminoacetate obtained in Example 146. After stirring for 4 hours at room temperature, the reaction solution was concentrated under reduced pressure. The residue was treated with hexane and diethyl ether to afford 0.41 g of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-(p-toluenesulfonyl)aminoacetic acid as needles, m.p.132 - 134°C.

Elementary analysis for C₃₀H₃₂Cl₂N₂O₆S:

Calcd.: C 58.16; H 5.21; N 4.52

Found : C 58.01; H 5.32; N 4.55

Example 148

This Sheet Has Been Replaced



Tert-butyl N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminoacetate.

In 10 ml of N, N-dimethylformamide was dissolved 0.5 g of tert-butyl N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminoacetate obtained in Example 142. To the solution was added 0.082 ml of acetyl chloride and 0.16 ml of triethylamine under ice-cooling.

The mixture was stirred for 30 minutes at room temperature and then subjected to extraction with 100 ml of water and 100 ml of ethyl acetate. The ethyl acetate layer was washed with 5% potassium bisulfate solution and with a sodium bicarbonate aqueous solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified on a silica gel column (eluent, hexane : ethyl acetate = 1:1) to give 0.5 g of tert-butyl N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminoacetate as an oily product.

IR ν _{Neat} cm^{-1} : 1740, 1670 (C=O)
IR ν _{Max}

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ : 0.92 and 0.94 (9H, each s, But), 1.95 and 2.15 (3H, each s, But), 3.35 and 3.38 (1H, each d, $J = 14.0\text{Hz}$), 3.7-4.3 (5H, m), 4.45 and 4.48 (1H, each d, $J = 14.0\text{Hz}$), 6.23 and 6.28 (1H, each s), 6.45-6.55 (1H, m), 7.3-7.8 (6H, m).

Example 149

N-Acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminoacetic acid

In 20 ml of 4N HCl-dioxane solution was dissolved 0.5 g of tert-butyl N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminoacetate obtained in Example 148. After stirring overnight at room temperature, the mixture was concentrated under reduced pressure. The concentrate was treated with hexane and diethylether to afford 0.37 g of powdery N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminoacetic acid.

Elementary analysis for $\text{C}_{25}\text{H}_{28}\text{Cl}_2\text{N}_2\text{O}_5$:

Calcd.: C 59.18; H 5.56; N 5.52

Found: C 59.36; H 5.70; N 5.50

This Sheet Has Been Replaced



¹H-NMR spectrum (200 MHz, CDCl₃) δ: 0.92 and 0.94 (9H, each s, Bu^t), 2.00 and 2.20 (3H, each s), 3.3-3.5 (1H, m), 3.7-4.5 (6H, m), 6.22 and 6.28 (1H, each s), 6.45-6.55 (1H, m), 7.3-7.8 (6H, m).

Example 150

Methyl ester of 4-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminomethylbenzoic acid

(A) In 30 ml of acetonitrile was mixed 1.0 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methylamine hydrochloride obtained in Example 139 with 0.6 g of methyl 4-bromomethylbenzoate and 0.75 g of potassium carbonate. The mixture was refluxed by heating for 2 hours. After the addition of 0.2 g of methyl 4-bromomethylbenzoate, reflux was continued by heating for 5 hours, followed by concentration under reduced pressure. The concentrate was extracted with 100 ml of water and 150 ml of ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure and the residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 10 : 1 - 1 : 2) to yield 0.15 g of methyl ester of 4-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminomethylbenzoic acid as prisms, m.p. 171 to 173°C.

Elementary analysis for C₃₀H₃₂Cl₂N₂O₄:

Calcd.: C 64.87; H 5.81; N 5.04

Found: C 64.88; H 5.97; N 4.76

(B) In 20 ml of ethanol was dissolved 0.45 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methylamine hydrochloride obtained in Example 139. To the solution was added 0.19 g of terephthalaldehydic acid methyl ester together with 0.5 ml of acetic acid. After stirring for 30 minutes at room temperature, 82 mg of sodium cyanoborohydride was added to the mixture. After further stirring for 2 hours at room temperature, the mixture was concentrated under reduced pressure and the concentrate was extracted with 100 ml of water and 100 ml of ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The organic solvent was evaporated off under reduced pressure and the residue was purified by column chromatography using silica gel (eluent, hexane : ethyl acetate = 1 : 1) to yield 0.31 g of methyl





ester of 4-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminomethylbenzoic acid.

Example 151

Methyl ester of 4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-methanesulfonyl]aminomethylbenzoic acid

In 5 ml of N,N-dimethylformamide was dissolved 0.3 g of methyl ester of 4-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]aminomethylbenzoic acid obtained in Example 150. To the solution were added 0.05 ml of methanesulfonyl chloride and 0.09 ml of triethylamine. After stirring for one hour at room temperature, the reaction mixture was subjected to extraction with 100 ml of water and 100 ml of ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid and with a sodium bicarbonate aqueous solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 2 : 1) to afford 0.27 g of methyl ester of 4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-methanesulfonyl]aminomethylbenzoic acid as needles, m.p. 173 to 174°C.

Elementary analysis for $C_{31}H_{34}Cl_2N_2O_6S$:

Calcd.: C 58.77; H 5.41; N 4.42

Found: C 58.59; H 5.68; N 4.19

Example 152

4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-methanesulfonyl]aminomethylbenzoic acid

In 10 ml of methanol was dissolved 0.17 g of methyl ester of 4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-methanesulfonyl]aminomethylbenzoic acid obtained in Example 151. After the addition of 4 ml of 1N sodium hydroxide the solution was stirred for one hour at 60°C. The reaction mixture was then acidified with 50 ml of 1N hydrochloric acid and subjected to extraction with 50 ml of ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.16 g of 4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-



1,2,3,5-tetrahydro-4,1-benzoxazepine-3-methyl]-N-methanesulfonyl]aminomethylbenzoic acid as prisms, m.p. 235 to 237°C.

Elementary analysis for $C_{30}H_{32}Cl_2N_2O_6S$:

Calcd.: C 58.16; H 5.21; N 4.52

Found: C 58.25; H 5.49; N 4.29

Example 153

Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethanol

In 200 ml of tetrahydrofuran was dissolved 14.7 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid obtained in Example 2 and 4.51 ml of N-methylmorpholine. To the solution was added 3.92 ml of ethyl chlorocarbonate at -10°C; the mixture was then stirred for 15 minutes. After the addition of 3.86 g of sodium borohydride, 200 ml of methanol was added dropwise to the solution. The mixture was stirred for one hour at room temperature and then concentrated. After the addition of 200 ml of 1N hydrochloric acid, the concentrate was extracted with 200 ml of ethyl acetate. The organic layer was washed with a saturated sodium bicarbonate aqueous solution and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 1 : 1) to yield 14.2 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethanol as colorless crystals, m.p. 157 to 159 °C.

Elementary analysis for $C_{22}H_{25}Cl_2NO_3$:

Calcd.: C 62.56; H 5.97; N 3.32

Found: C 62.30; H 6.02; N 3.17

Example 154

Ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminoacetic acid

(1) Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetaldehyde

To 25 ml of dichloromethane solution containing 0.70 ml of oxalyl chloride was added 5 ml of dichloromethane solution containing 0.71 ml of dimethylsulfoxide at -78°C, followed by stirring for 5 minutes. To the solution was slowly added 10 ml of dichloromethane solution containing 1.69 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-

benzoxazepine-3-ethanol obtained in Example 160, followed by stirring for 15 minutes at -78°C . To the reaction mixture was added 2.79 ml of triethylamine and the mixture was further stirred for one hour at 0°C and for 1.5 hours at room temperature. After the addition of 100 ml of water, extraction was performed with 100 ml of dichloromethane. The dichloromethane layer was washed with saturated saline and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure. The residue was purified by column chromatography using silica gel (eluent, hexane : ethyl acetate = 1 : 1) to give 1.08 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetaldehyde as light-yellow crystals, m.p. 173 to 176°C .

Elementary analysis for $\text{C}_{22}\text{H}_{23}\text{Cl}_2\text{NO}_3 \cdot 0.5\text{H}_2\text{O}$:

Calcd.: C 61.55; H 5.63; N 3.26

Found: C 61.27; H 5.49; N 3.17

(2) Ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminoacetic acid

To 40 ml of ethanol containing 1.12 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetaldehyde obtained in Example 161 (1) and 0.56 g of glycine ethyl ester hydrochloride was added 10 ml of ethanol containing 0.13 g of sodium cyanoborohydride dropwise over 1.5 hours. After additional 3-hour stirring, the reaction mixture was subjected to extraction with 200 ml of water and 200 ml of ethyl acetate. The ethyl acetate layer was washed with saturated saline and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure and the residue was purified by silica gel column chromatography (eluent, ethyl acetate) to afford 0.75 g of amorphous solid ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminoacetic acid.

Elementary analysis for $\text{C}_{26}\text{H}_{32}\text{Cl}_2\text{N}_2\text{O}_4$:

Calcd.: C 61.54; H 6.36; N 5.52

Found: C 61.16; H 6.29; N 5.56

$^1\text{H-NMR}$ (CDCl_3) δ : 0.93 (9H, s, Bu^t), 1.26 (3H, t, $J = 7.2$ Hz), 1.90-2.15 (3H, m), 2.76 (2H, dd, $J = 7.2, 6.6$ Hz), 3.38 (1H, d, $J = 13.9$ Hz), 3.38 (2H, s), 4.03 (1H, dd, $J = 6.6, 6.2$ Hz), 4.17 (2H, q, $J = 7.2$ Hz), 4.51 (1H, d, $J = 13.9$ Hz), 6.24 (1H, s), 6.51 (1H, d, $J = 1.6$ Hz), 7.30-7.50 (5H, m), 7.70-7.80 (1H, m)

Example 155

This Sheet Has Been Replaced





Ethyl ester of N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminoacetic acid

In 5 ml of N,N-dimethylformamide was dissolved 0.15 g of ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminoacetate obtained in Example 154. To the solution were added 0.031 ml of acetyl chloride and 0.050 ml of triethylamine under ice-cooling. After stirring for 30 minutes under ice-cooling, the reaction mixture was subjected to extraction with 40 ml of water and 40 ml of ethyl acetate. The ethyl acetate layer was washed with saturated saline and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure. The residue was purified by column chromatography using silica gel (eluent, hexane : ethyl acetate = 1 : 3) to give 0.15 g of amorphous solid ethyl ester of N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminoacetic acid.

Elementary analysis for $C_{28}H_{34}Cl_2N_2O_5 \cdot 0.4H_2O$:

Calcd.: C 60.41; H 6.30; N 5.03

Found: C 60.44; H 6.43; N 4.96

1H -NMR ($CDCl_3$) δ : 0.93 and 0.94 (9H, each s, Bu^t), 1.20-1.32 (3H, m), 1.95-2.20 (2H, m), 1.95 and 2.13 (total 3H, each s), 3.32-3.68 (3H, m), 3.90-4.27 (5H, m), 4.48 and 4.50 (total 1H, each d, $J = 13.8$ Hz), 6.22 and 6.24 (total 1H, each s), 6.50 and 6.53 (total 1H, each d, $J = 2.0$ Hz), 7.29-7.50 (5H, m), 7.65-7.80 (1H, m)

Example 156

N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminoacetic acid

To 5 ml of methanol containing 0.11 g of ethyl ester of N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminoacetate obtained in Example 155 was added 1 ml of 0.5M potassium carbonate aqueous solution. After stirring for 30 minutes at 60°C, the reaction mixture was acidified with 0.5 ml of 1N hydrochloric acid and subjected to extraction with 20 ml of water and 20 ml of ethyl acetate. The ethyl acetate layer was washed with saturated saline and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure. The residue was treated with ether to yield 0.07 g of

white powdery N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminoacetic acid, m.p. 210 to 212°C.

Elementary analysis for $C_{26}H_{30}Cl_2N_2O_5$:

Calcd.: C 59.89; H 5.80; N 5.37

Found: C 59.78; H 5.85; N 5.13

Example 157

Ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-methanesulfonylaminoacetic acid

In 5 ml of N,N-dimethylformamide was dissolved 0.15 g of ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminoacetate obtained in Example 154. To the solution were added 0.028 ml of methanesulfonyl chloride and 0.050 ml of triethylamine under ice-cooling. After stirring for 30 minutes under ice-cooling, extraction was performed with 40 ml of water and 40 ml of ethyl acetate. The ethyl acetate layer was washed with saturated saline and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure, and the residue was purified on a silica gel column chromatography (eluent, hexane : ethyl acetate = 2 : 1) to afford 0.12 g of ethyl ester of N-trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-methanesulphonylaminoacetic acid as a white powdery product, m.p. 134 to 135°C.

Elementary analysis for $C_{27}H_{34}Cl_2N_2O_6S$:

Calcd.: C 55.38; H 5.85; N 4.78

Found: C 55.66; H 5.98; N 4.61

Example 158

N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-methanesulfonylaminoacetic acid

In the same manner as in Example 156 was hydrolyzed 0.12 g of ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-methanesulfonylaminoacetic acid obtained in Example 157 to give 0.10 g of white powdery N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-methanesulfonylaminoacetic acid, m.p. 135 to 137°C.

Elementary analysis for $C_{25}H_{30}Cl_2N_2O_6S \cdot 0.5H_2O$:



Calcd.: C 53.00; H 5.52; N 4.94

Found: C 53.25; H 5.78; N 4.71

Example 159

Ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-(p-toluensulfonyl)aminoacetic acid

In 5 ml of N,N-dimethylformamide was dissolved 0.15 g of ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminoacetic acid obtained in Example 154. To the solution was added 0.069 g of p-toluenesulfonyl chloride together with 0.050 ml of triethylamine under ice-cooling. After stirring for 30 minutes under ice-cooling, the reaction mixture was subjected to extraction with 40 ml of water and 40 ml of ethyl acetate. The ethyl acetate layer was washed with saturated saline and dried over anhydrous magnesium sulfate. Ethyl acetate was evaporated off under reduced pressure. The residue was purified by column chromatography using silica gel (eluent, hexane : ethyl acetate = 3 : 1) to yield 0.17 g of amorphous ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-p-toluenesulfonylaminoacetic acid.

Elementary analysis for $C_{33}H_{38}Cl_2N_2O_6S$:

Calcd.: C 59.91; H 5.79; N 4.23

Found: C 60.25; H 6.01; N 4.04

1H -NMR ($CDCl_3$) δ : 0.94 (9H, s, Bu^t), 1.15 (3H, t, $J = 7.2$ Hz), 1.90-2.30 (2H, m), 2.41 (3H, s), 3.20-3.60 (2H, m), 3.41 (1H, d, $J = 140$ Hz), 3.97-4.18 (5H, m), 4.50 (1H, d, $J = 14.0$ Hz), 6.23 (1H, s), 6.52 (1H, s), 7.21-7.50 (7H, m), 7.62-7.80 (3H, m)

Example 160

N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-p-toluensulfonylaminoacetic acid

In the same manner as in Example 156, 0.15 g of ethyl ester of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-p-toluensulfonylaminoacetic acid was hydrolyzed to yield 0.11 g of N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-p-toluensulfonylaminoacetic acid as white powder, m.p. 274 to 277°C.

Elementary analysis for $C_{31}H_{34}Cl_2N_2O_6S$:

This Sheet Has Been Replaced



Calcd.: C 58.77; H 5.41; N 4.42

Found: C 58.70; H 5.59; N 4.13

Example 161

Methyl ester of 4-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminomethylbenzoic acid

A mixture of 0.42 g of trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetaldehyde obtained in Example 154 (1), 0.30 g of 4-aminomethylbenzoic acid methyl ester hydrochloric acid salt, and 30 ml of ethanol was stirred for 2 hours at room temperature. Subsequently 5 ml of ethanol containing 0.06 g of sodium cyanoborohydride was slowly added dropwise to the mixture. After stirring for 2 hours, the reaction mixture was subjected to extraction with 100 ml of water and 100 ml of ethyl acetate. The ethyl acetate layer was washed with saturated saline and dried over anhydrous magnesium sulfate. The organic solvent was evaporated off under reduced pressure. The residue was purified by column chromatography using silica gel (eluent, ethyl acetate) to give amorphous methyl ester of 4-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminomethylbenzoic acid.

Elementary analysis for $C_{31}H_{34}Cl_2N_2O_4$:

Calcd.: C 65.38; H 6.02; N 4.92

Found: C 64.99; H 6.11; N 5.19

1H -NMR($CDCl_3$) δ : 0.94 (9H, s, Bu^t), 1.98-2.26 (3H, m), 2.65-2.90 (2H, m), 3.38 (1H, d, $J = 14.0$ Hz), 3.83 (2H, s), 3.91 (3H, s), 4.06 (1H, t, $J = 6.2$ Hz), 4.49 (1H, d, $J = 14.0$ Hz), 6.21 (1H, s), 5.51 (1H, d, $J = 2.0$ Hz), 7.26-7.62 (8H, m), 7.92-8.02 (2H, m)

Example 162

Methyl ester of 4-[N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]]aminomethylbenzoic acid

In the same manner as in Example 155, 0.13 g of methyl ester of 4-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminomethylbenzoic acid obtained in Example 161 was treated to yield 0.13 g of amorphous methyl ester of 4-[N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]]aminomethylbenzoic acid.



Elementary analysis for $C_{33}H_{36}Cl_2N_2O_5$:

Calcd.: C 64.81; H 5.93; N 4.58

Found: C 65.14; H 6.12; N 4.11

1H -NMR ($CDCl_3$) δ : 0.93 (9H, s, Bu^t), 2.00-2.20 (2H, m), 2.02 and 2.18 (total 3H, each s), 3.20-3.60 (3H, m), 3.78-4.00 (1H, m), 3.91 and 3.93 (total 3H, each s), 4.42-4.76 (3H, m), 6.21 (1H, s), 6.50 (1H, d, $J = 1.8$ Hz), 7.17-7.70 (8H, m), 7.95 (1H, d, $J = 8.0$ Hz), 8.02 (1H, d, $J = 8.2$ Hz)

Example 163

4-[N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]]aminomethylbenzoic acid

In the same manner as in Example 156, 0.10 g of methyl ester of 4-[N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]]aminomethylbenzoic acid obtained in Example 162 was hydrolyzed to afford 0.08 g of white powdery 4-[N-acetyl-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]]aminomethylbenzoic acid, m.p. 242 to 244°C.

Elementary analysis for $C_{32}H_{34}Cl_2N_2O_5$:

Calcd.: C 64.32; H 5.74; N 4.69

Found: C 64.34; H 5.87; N 4.66

Example 164

Methyl ester of 4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-methanesulfonyl]aminomethylbenzoic acid

In the same manner as in Example 157, 0.13 g of methyl ester of 4-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminomethylbenzoic acid obtained in Example 161 was treated to give 0.12 g of methyl ester of 4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-methanesulfonyl]aminomethylbenzoic acid as colorless crystals, m.p. 172 to 174°C.

Elementary analysis for $C_{32}H_{36}Cl_2N_2O_6S$:

Calcd.: C 59.35; H 5.60; N 4.33

Found: C 59.15; H 5.79; N 4.16

Example 165

This Sheet Has Been Replaced





4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-methanesulfonyl]aminomethylbenzoic acid

In the same manner as in Example 156, 0.09 g of methyl ester of 4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-methanesulfonyl]aminomethylbenzoic acid obtained in Example 164 was hydrolyzed to afford 0.06 g of 4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-methanesulfonyl]aminomethylbenzoic acid as colorless crystals, m.p. 185 to 187°C.

Elementary analysis for $C_{31}H_{34}Cl_2N_2O_6S \cdot 0.5H_2O$:

Calcd.: C 57.95; H 5.49; N 4.36

Found: C 58.30; H 5.83; N 4.19

Example 166

Methyl ester of 4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-p-toluenesulfonyl]aminomethylbenzoic acid

In the same manner as in Example 159, 0.13 g of methyl ester of 4-N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]aminomethylbenzoic acid obtained in Example 161 was treated to give 0.14 g of methyl ester of 4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-p-toluenesulfonyl]aminomethylbenzoic acid as colorless crystals, m.p. 145 to 147°C.

Elementary analysis for $C_{38}H_{40}Cl_2N_2O_6S$:

Calcd.: C 63.07; H 5.57; N 3.87

Found: C 63.09; H 5.50; N 3.93

Example 167

4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-p-toluenesulfonyl]aminomethylbenzoic acid

In the same manner as in Example 156, 0.12 g of methyl ester of 4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-ethyl]-N-p-toluenesulfonyl]aminomethylbenzoic acid obtained in Example 166 was hydrolyzed to afford 0.09 g of 4-[N-[trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-

benzoxazepine-3-ethyl]-N-p-toluenesulfonylaminomethylbenzoic acid as colorless powder, m.p. 265 to 268°C.

Elementary analysis for $C_{37}H_{38}Cl_2N_2O_6S$:

Calcd.: C 62.62; H 5.40; N 3.95

Found: C 62.67; H 5.36; N 3.96

Example 168

Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-3-[(tetrazol-5-yl)methylaminocarbonylmethyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine

In the same manner as in Examples 104, trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid obtained in Example 2 was treated to afford the following crystalline compounds:

(1) Trans-7-chloro-5-(2-chlorophenyl)-3-(cyanomethylaminocarbonylmethyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine, m.p. 171 to 172°C.

Elementary analysis for $C_{24}H_{25}Cl_2N_3O_3$:

Calcd.: C 60.77; H 5.31; N 8.86

Found: C 60.68; H 5.24; N 8.62

(2) Trans-7-chloro-5-(2-chlorophenyl)-1-neopentyl-3-[(tetrazol-5-yl)methylaminocarbonylmethyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine, m.p. 251 to 252°C.

Elementary analysis for $C_{24}H_{26}Cl_2N_6O_3$:

Calcd.: C 55.71; H 5.06; N 16.24

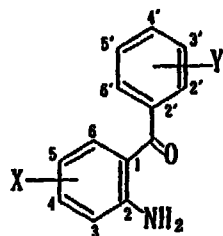
Found: C 55.38; H 5.22; N 16.03

Materials and intermediate compounds included in Examples are listed in Tables 74 to 88.

2-aminobenzophenones as the starting material can be synthesized by, or in accordance with, the method described in D.A. Walsh, Synthesis, 677 (1980) or the method cited in said reference.



Table 7 4



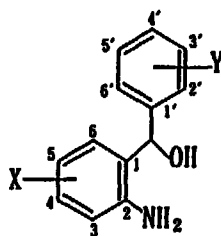
X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5-F	2'-Cl		subjected to the next procedure without isolating			
5-MeO	2'-Cl	oil	¹ H-NMR(CDCl ₃) δ: 3.59(3H, s), 5.88(2H, br), 6.51-7.52(7H, m)			
5-Cl	2', 4'-Cl	81- 84	C ₁₃ H ₈ Cl ₃ NO	51.95 (51.98)	2.68 2.51	4.66 4.83)
5-Cl	2', 4'-OMe	102-103	C ₁₅ H ₁₄ ClNO ₃	61.76 (61.79)	4.84 4.88	4.80 4.72)
5-Cl	2', 6'-OMe	172	C ₁₅ H ₁₄ ClNO ₃	61.76 (61.54)	4.84 4.72	4.80 4.87)

Table 7 5

X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5-Cl	2', 5'-OMe	oil	¹ H-NMR(CDCl ₃) δ: 3. 72(3H, s), 3. 78(3H, s), 6. 39(2H, br s), 6. 64 (1H, d, J=8. 6Hz), 6. 80(1H, d, J=2. 6Hz), 6. 87-7. 28(4H, m)			
5-Cl	2', 4', 6'-OMe	188-189	C ₁₆ H ₁₆ ClNO ₄	59. 73 (59. 93)	5. 01 5. 00	4. 35 4. 30)
5-Cl	2', 3'-OCH ₂ O-	119-120	C ₁₄ H ₁₆ ClNO ₃	60. 99 (60. 81)	3. 66 3. 43	5. 08 5. 07)
5-Cl	3', 4'-OCH ₂ O-	oil	¹ H-NMR(CDCl ₃) δ: 6. 06(2H, s), 6. 67(1H, d), 6. 86(1H, d), 7. 15-7. 5(4H, m)			
4-Cl	2'-Cl	112-113	C ₁₃ H ₉ Cl ₂ NO	58. 67 (58. 47)	3. 41 3. 45	5. 26 5. 16)
3, 5-Cl	2'-OMe	88- 90	C ₁₄ H ₁₁ Cl ₂ NO	60. 02 (59. 96)	3. 96 3. 85	5. 00 4. 96)
5-Cl	2', 3'-OMe	91- 92	C ₁₅ H ₁₄ ClNO ₃	61. 76 (61. 59)	4. 84 4. 87	4. 80 4. 79)



Table 76



X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
4, 5-(CH ₂) ₃ -	2'-Cl	oil	¹ H-NMR(CDCl ₃) δ: 1.8-2.1(2H, m), 2.7-3.0(4H, m), 6.16(1H, s), 6.6-7.5(6H, m)			
5-F	2'-Cl	77- 79	C ₁₃ H ₁₁ ClFNO	62.04 (62.10	4.41 4.40	5.57 5.57)
5-MeO	2'-Cl	oil	¹ H-NMR(CDCl ₃) δ: 3.67(3H, s), 6.23(1H, br s), 6.50-6.54(7H, m)			
5-Cl	2', 4'-Cl	104-106	C ₁₃ H ₁₀ Cl ₃ NO +0.7H ₂ O	49.54 (49.59	3.65 3.48	4.44 4.34)
5-Cl	2', 4'-OMe	oil	¹ H-NMR(CDCl ₃) δ: 3.81(3H, s), 3.85(3H, s), 5.94(1H, s), 6.4-6.7(3H, m), 6.95-7.1(3H, m)			

Table 77

X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5-Cl	2', 6' -OMe	130-135	C ₁₅ H ₁₆ ClNO ₃	61.33 (61.26)	5.49 5.46	4.77 4.71
5-Cl	2', 5' -OMe	177-178	C ₁₅ H ₁₆ ClNO ₃	61.33 (61.22)	5.49 5.54	4.77 4.72
5-Cl	2', 4', 6' -OMe	163-164	C ₁₆ H ₁₈ ClNO ₄	59.35 (59.57)	5.60 5.63	4.33 4.39
5-Cl	2', 3' -OCH ₂ O-	119-120	C ₁₄ H ₁₂ ClNO ₃	60.55 (60.49)	4.36 4.20	5.04 5.10
5-Cl	3', 4' -OCH ₂ O-	136-137	C ₁₄ H ₁₂ ClNO ₃	60.55 (60.41)	4.36 4.48	5.04 4.96
4-Cl	2' -Cl	oil	¹ H-NMR(CDCl ₃) δ: 6.06(1H, s), 6.55-6.75(3H, m), 7.2-7.5(5H, m)			
5-Cl	2', 3' -OMe	124-126	C ₁₅ H ₁₆ ClNO ₃	61.33 (61.25)	5.49 5.58	4.77 4.66
3, 5-Cl	2' -OMe	84- 86	C ₁₄ H ₁₃ Cl ₂ NO ₂	56.40 (56.06)	4.39 4.35	4.70 4.59
H	2' -Cl	oil	¹ H-NMR(CDCl ₃) δ: 5.30(1H, s), 6.17(1H, s), 6.5-7.6(7H, m) ∴			



Table 7 8

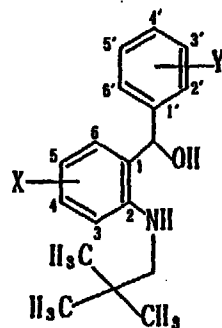
X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5-CH ₃	2'-Cl	oil	¹ H-NMR(CDCl ₃) δ: 2.17(3H, s), 6.16(1H, s), 6.6-7.6(7H, m)			
5-Cl	2'-F	100-101	C ₁₃ H ₁₁ ClFNO	62.03 (61.86)	4.41 4.62	5.57 5.51
H	2'-F	106-107	C ₁₃ H ₁₂ FNO	71.87 (71.76)	5.57 5.59	6.45 6.36
H	2'-OMe	105-106	C ₁₄ H ₁₅ NO ₂	73.34 (73.11)	6.59 6.63	6.11 6.19
5-Cl	2'-CF ₃	127-129	C ₁₄ H ₁₁ ClF ₃ NO	55.74 (55.66)	3.68 3.64	4.64 4.70
5-Cl	2'-OMe	81- 82	C ₁₄ H ₁₄ ClNO ₂	63.76 (63.83)	5.35 5.56	5.31 5.32
5-Cl	2'-Br	87- 88	C ₁₃ H ₁₁ BrClNO	49.95 (50.03)	3.55 3.71	4.48 4.44
5-Br	2'-Cl	97- 99	C ₁₃ H ₁₁ BrClNO	49.95 (49.87)	3.55 3.76	4.48 4.37
5-Cl	4'-Cl	127-128	C ₁₃ H ₁₁ Cl ₂ NO	58.23 (58.47)	4.13 4.17	5.22 5.19

Table 79

X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
II	2'-Me	110-111	$C_{14}H_{15}NO$	78.84 (78.67)	7.09 6.87	6.57 6.60
5-Cl	3'-Cl	136-138	$C_{13}H_{11}Cl_2NO$	58.23 (58.36)	4.13 4.23	5.22 5.14
5-CF ₃	II	86- 87	$C_{14}H_{12}F_3NO$	62.92 (62.84)	4.53 4.55	5.24 5.11
5-Cl	II	107-109	$C_{13}H_{12}ClNO$	66.81 (66.80)	5.18 5.19	5.99 5.97



Table 80

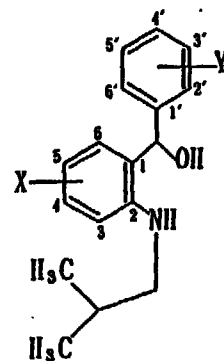


X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5-Cl	2', 4'-OCH ₃	oil	C ₂₀ H ₂₆ ClNO ₃	¹ H-NMR(CDCl ₃) δ: 0.92(9H, s, Bu ¹), 2.82(2H, s), 2.9-3.3(1H, br), 3.81(3H, s), 3.86(3H, s), 4.6-5.0(1H, br), 5.92(1H, s), 6.4-6.6(3H, m), 6.95-7.2(3H, m)		
5-Cl	2', 6'-OCH ₃	oil	C ₂₀ H ₂₆ ClNO ₃	¹ H-NMR(CDCl ₃) δ: 1.06(9H, s), 2.87(1H, d, J=11.4Hz), 2.96(1H, d, J=11.4Hz), 3.80(6H, s), 4.28, 5.61(each 1H, br), 6.26(1H, br), 6.53(1H, d, J=2.6Hz), 6.60(1H, d, J=8.6Hz), 6.66(2H, d, J=8.4Hz), 7.09(1H, dd, J=2.4, 8.6Hz), 7.31(1H, t, J=8.4Hz)		
5-Cl	2', 5'-OCH ₃	126-128	C ₂₀ H ₂₆ ClNO ₃	66.02 (66.18	: : 7.20 7.18	3.85 3.83)

Table 8 1

X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5-Cl	2', 4', 6'-OCH ₃	150-151	C ₂₁ H ₂₃ ClNO ₄	64.03 (64.19	7.16 7.00	3.56 3.48)
5-Cl	2', 3'-OCH ₂ O-		subjected to the next procedure without isolating			
5-Cl	3', 4'-OCH ₂ O-	oil	C ₁₉ H ₂₂ ClNO ₃	¹ H-NMR(CDCl ₃) δ: 0.86(9H, s, Bu'), 2.75 (2H, s), 5.67(1H, s), 5.95(2H, s), 6.5-7.3 (6H, m)		
4-Cl	2'-Cl	oil	C ₁₈ H ₂₁ Cl ₂ NO	¹ H-NMR(CDCl ₃) δ: 0.94(9H, s, Bu'), 2.84 (2H, s), 6.12(1H, s), 6.5-7.5(7H, m)		
3, 5-Cl	2'-OCH ₃	oil	C ₁₉ H ₂₃ Cl ₂ NO ₂	¹ H-NMR(CDCl ₃) δ: 0.98(9H, s, Bu'), 2.75 (2H, s), 3.84(3H, s), 4.05(1H, br s), 6.28 (1H, s), 6.9-7.4(6H, m)		
5-Cl	2'-OCH ₃	oil	C ₁₉ H ₂₄ ClNO ₂	¹ H-NMR(CDCl ₃) δ: 0.92(9H, s, Bu'), 2.83 (2H, s), 3.1-3.5(1H, br), 3.89(3H, s), 4.6- 5.0(1H, br), 5.99(1H, s), 6.59(1H, d, J=8.8Hz), 6.9-7.4(6H, m)		
5-Cl	2'-Br	99-100	C ₁₈ H ₂₁ BrClNO	56.49 (56.69	5.53 5.50	3.66 3.42)
5-Br	2'-Cl	105-107	C ₁₈ H ₂₁ BrClNO	56.49 (56.48	5.53 5.50	3.66 3.59)
5-Cl	2', 3'-OMe	120-121	C ₂₀ H ₂₆ ClNO ₃	66.02 (65.74	7.20 7.01	3.85 3.71)

Table 82

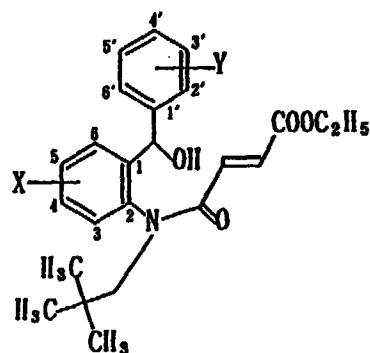


X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5-F	2'-Cl	84- 86	C ₁₇ H ₁₉ ClFNO	66.34 (66.21)	6.22 6.22	4.55 4.50
5-OCH ₃	2'-Cl	oil	C ₁₈ H ₂₂ ClNO ₂	¹ H-NMR(CDCl ₃) δ: 0.85, 0.87 (each 3H, each d, J=6.6Hz), 1.80(1H, m), 2.86(2H, d, J=6.6Hz), 3.68(3H, s), 6.24(1H, s), 6.50-7.55(7H, m)		
5-Cl	2', 4'-Cl	104-106	C ₁₇ H ₁₃ Cl ₃ NO	56.93 (56.96)	5.06 4.85	3.90 3.66
5-Cl	2'-CF ₃	72- 74	C ₁₈ H ₁₉ ClF ₃ NO	60.42 (59.96)	5.35 5.37	3.91 3.83
5-Cl	2'-OCH ₃	oil	C ₁₈ H ₂₂ ClNO ₂	¹ H-NMR(CDCl ₃) δ: 0.92(6H, d, J=6.6Hz), 1.75-2.0(1H, m), 2.89(1H, d, J=6.8Hz), 3.1-3.4(1H, Br), 3.88(3H, s), 4.7-5.1(1H, br), 5.97(1H, s), 6.56(1H, d, J=8.8Hz), 6.9-7.4(6H, m)		

Table 83

X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5-Cl	2'-Br	96- 98	$C_{17}H_{19}BrClNO$	55.38 (55.55)	5.19 5.20	3.80 3.74
5-Br	2'-Cl	oil	$C_{17}H_{19}BrClNO$	$^1H-NMR(CDCl_3)\delta$: 0.91(6H, d, $J=6.6Hz$), 1.7-2.0(1H, m), 2.89(2H, d, $J=6.6Hz$), 6.11(1H, s), 6.53(1H, d, $J=8.6Hz$), 7.05(1H, d, $J=2.4Hz$), 7.14-7.46(5H, m)		
5-Cl	4'-Cl	oil	$C_{17}H_{19}Cl_2NO$	$^1H-NMR(CDCl_3)\delta$: 0.828(3H, d, $J=6.8Hz$), 0.834(3H, d, $J=6.8Hz$), 1.64-1.86(1H, m), 2.2-2.8(1H, br), 2.80(2H, d, $J=6.8Hz$), 4.2-4.7(1H, br), 5.73(1H, s), 6.54(1H, d, $J=8.6Hz$), 6.98(1H, d, $J=2.4Hz$), 7.14(1H, dd, $J=8.6, 2.4Hz$), 7.31(4H, s)		
H	2'-CH ₃	oil	$C_{18}H_{23}NO$	$^1H-NMR(CDCl_3)\delta$: 0.95(6H, d, $J=6.6Hz$), 1.8-2.0(1H, m), 2.21(3H, s), 2.94(2H, d, $J=6.6Hz$), 5.98(1H, s), 6.5-6.8(2H, m), 7.1-7.35(3H, m), 7.1-7.35(3H, m), 7.4-7.55(1H, m)		
5-Cl	3'-Cl	73- 74	$C_{17}H_{19}Cl_2NO$	62.97 (62.81)	5.91 5.88	4.32 4.19
5-CF ₃	H	60- 62	$C_{18}H_{20}F_3NO$	66.86 (66.89)	6.23 6.27	4.33 4.22
5-Cl	H	56- 59	$C_{17}H_{20}ClNO$	70.46 (70.45)	6.96 7.11	4.83 4.90

Table 84



X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5-Cl	2', 4' -OCH ₃	oil	C ₂₆ H ₃₂ ClNO ₆	¹ H-NMR(CDCl ₃) δ: 0.82 and 0.93(9H, each s, Bu ¹), 1.22(3H, t, J=7.2Hz), 2.35-3.1(2H, m), 3.65-3.9(6H, m), 4.0-4.5(3H, m), 5.9-6.55(5H, m), 6.75-7.9(4H, m)		
5-Cl	2', 6' -OCH ₃	oil	C ₂₆ H ₃₂ NO ₆ Cl	¹ H-NMR(CDCl ₃) δ: 0.90, 0.95(9H, each s, Bu ¹), 1.19-1.30(3H, m), 2.88-3.10(1H, m), 3.72-3.82(6H, m), 4.04-4.28(2H, m), 4.44-4.57(1H, m), 6.02-7.88(9H, m)		
5-Cl	2', 5' -OCH ₃	140-142	C ₂₆ H ₃₂ ClNO ₆	63.73 (63.67)	6.58 6.50	2.86 2.81
5-Cl	2', 4', 6' -OCH ₃	oil	C ₂₇ H ₃₄ ClNO ₇	¹ H-NMR(CDCl ₃) δ: 0.90 and 0.94(9H, each s, Bu ¹), 1.15-1.35(3H, m), 2.8-3.1(1H, m), 3.4-4.3(12H, m), 4.35-4.6(1H, m), 5.9-6.45(5H, m), 6.8-7.95(3H, m)		

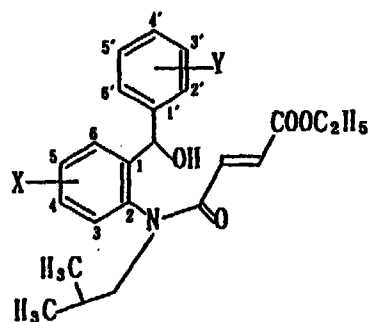
This Sheet Has Been Replaced

Table 85

X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5-Cl	2', 3'-OCH ₂ O-	oil	C ₂₅ H ₂₈ ClNO ₆	¹ H-NMR(CDCl ₃) δ: 0.92 and 1.07(9H, each s, Bu ^t), 1.18-1.33(3H, m), 2.85-3.04(1H, m), 4.05-4.34(2H, m), 4.46-4.54(1H, m), 5.87(2H, s), 6.05-7.89(9H, m)		
5-Cl	3', 4'-OCH ₂ O-	125-126	C ₂₅ H ₂₈ ClNO ₆	63.36 (63.26)	5.95 5.72	2.96 2.76
4-Cl	2'-Cl	152-153	C ₂₄ H ₂₇ Cl ₂ NO ₄	62.07 (61.78)	5.86 5.93	3.02 2.88
3, 5-Cl	2'-OCH ₃	162-164	C ₂₅ H ₂₉ Cl ₂ NO ₅	60.73 (60.84)	5.91 5.89	2.83 2.70
5-Cl	2'-OCH ₃	oil	C ₂₅ H ₃₀ ClNO ₅	¹ H-NMR(CDCl ₃) δ: 0.84 and 0.93(9H, each s, Bu ^t), 1.15-1.3(2H, m), 2.5-3.2(2H, m), 3.73 and 3.82(3H, each s), 4.0-4.25(2H, m), 4.25-4.6(1H, m), 6.0-6.5(3H, m), 6.7-7.85(7H, m)		
5-Cl	2'-Br	168-169	C ₂₄ H ₂₇ BrClNO ₄	56.65 (56.71)	5.35 5.21	2.75 2.47
5-Br	2'-Cl	171-174	C ₂₄ H ₂₇ BrClNO ₄	56.65 (56.68)	5.35 5.39	2.75 2.68
5-Cl	2', 3'-OCH ₃	137-139	C ₂₆ H ₃₂ ClNO ₆	63.73 (63.66)	6.58 6.50	2.86 2.94



Table 86



X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5-F	2'-Cl	148-151	C ₂₃ H ₂₅ ClFNO ₄	63.67 (63.56)	5.81 5.73	3.23 3.38)
5-OCH ₃	2'-Cl	oil	C ₂₄ H ₂₈ NO ₅ Cl	¹ H-NMR(CDCl ₃)δ: 0.73-1.25(total 9H, m), 1.78(1H, m), 2.35-3.10(2H, m), 3.70, 3.75 (3H, each s), 4.10-4.38(4H, m), 5.89-7.73(10H, m)		
5-Cl	2', 4'-Cl	167-168	C ₂₃ H ₂₄ Cl ₃ NO ₄	56.98 (56.85)	4.99 4.84	2.89 2.63)
5-Cl	2'-CF ₃	164-165	C ₂₄ H ₂₅ ClF ₃ NO ₄	59.57 (59.55)	5.21 5.22	2.89 2.83)
5-Cl	2'-OCH ₃	oil	C ₂₄ H ₂₈ ClNO ₅	¹ H-NMR(CDCl ₃)δ: 0.7-1.15(6H, m), 1.15- 1.4(3H, m), 1.6-2.1(1H, m), 2.4-3.1(2H, m), 3.76 and 3.80(3H, each s), 4.0-4.45(4H, m), 5.9-6.45(3H, m), 6.7-7.9(7H, m)		

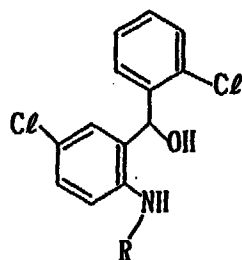
Table 87

X	Y	m. p. (°C)	Formula	Elemental Analysis(Found)		
				C	H	N
5-Cl	2'-Br	158-160	$C_{23}H_{25}BrClNO_4$	55.83 (55.89)	5.09 5.10	2.83 2.89)
5-Br	2'-Cl	157-159	$C_{23}H_{25}BrClNO_4$	55.83 (55.42)	5.09 5.18	2.83 2.65)
5-Cl	4'-Cl	amorphous solid	$C_{23}H_{25}Cl_2NO_4$ +0.2H ₂ O	60.85 (60.85)	5.64 5.62	3.09 3.00)
H	2'-CH ₃	oil	$C_{24}H_{29}NO_4$	¹ H-NMR(CDCl ₃) δ: 0.7-1.1(6H, m), 1.21(3H, t, J=7.0Hz), 1.5-2.0(1H, m), 2.29(3H, s), 2.0-2.3 and 2.9-3.1(1H, each m), 3.9-4.5(3H, m), 5.9-6.4(2H, m), 6.6-6.9(1H, m), 6.95-7.9(8H, m)		
5-Cl	3'-Cl	105-108	$C_{23}H_{25}Cl_2NO_4$	61.34 (61.37)	5.60 5.53	3.11 3.08)
5-CF ₃	H	amorphous solid	$C_{24}H_{26}F_3NO_4$	64.13 (64.28)	5.83 5.80	3.12 3.00)
5-Cl	H	110-113	$C_{23}H_{26}ClNO_4$	66.42 (66.05)	6.30 6.29	3.37 3.35)

This Sheet Has Been Replaced



Table 88



R	m. p. (°C)	Formula	Elemental Analysis(Found)		
			C	H	N
$\begin{array}{c} \text{O} \\ \parallel \\ \text{CCF}_2\text{CF}_3 \end{array}$	101-103	$\text{C}_{16}\text{H}_{10}\text{Cl}_2\text{F}_5\text{NO}_2$	46.40 (46.28)	2.43 2.42	3.38 3.47
$\begin{array}{c} \text{O} \\ \parallel \\ \text{C} \end{array}$ 	115-116	$\text{C}_{17}\text{H}_{15}\text{Cl}_2\text{NO}_2$	60.73 (60.61)	4.50 4.72	4.17 4.03
$\begin{array}{c} \text{O} \\ \parallel \\ \text{CCH}_2\text{C}(\text{CH}_3)_3 \end{array}$	109-110	$\text{C}_{19}\text{H}_{21}\text{Cl}_2\text{NO}_2$	62.30 (62.57)	5.78 5.79	3.82 3.73
$\begin{array}{c} \text{O} \\ \parallel \\ \text{CCF}_3 \end{array}$	155-156	$\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{F}_3\text{NO}_2$	49.47 (49.22)	2.77 2.86	3.85 3.71



Experimental Example 1

Assay Method of Squalene Synthetase Inhibitory Activity

The squalene synthetase inhibitory activity was assayed as follows with the enzyme solutions described in the subsequent Experimental Examples 1 and 2.

5 More specifically, an enzyme solution (protein content 0.8 ug) prepared in Experimental Example 1 or 2 was added to a solution (total volume 50 ul)) containing 5 uM [1-³H] farnesyl pyrophosphate (specific
10 activity 25 uCi/mole), 1 mM NADPH, 5 mM MgCl₂, 6 mM glutathione, a 100 mM buffer solution of potassium phosphate (pH 7.4) and a test drug (used as an aqueous solution or a DMSO solution), then the reaction was allowed to proceed at 37°C for 45 minutes. To the
15 reaction mixture was added 150 ul of a mixture of chloroform and methanol (1:2) to suspend the reaction, followed by adding 50 ul of chloroform and 50 ul of a 3N aqueous solution of sodium hydroxide. 50 ul of the chloroform layer (lower layer) containing the reaction
20 mixture having squalene as the principal component and 3 ml of toluene-based liquid scintillator were mixed, and its radioactivity was determined by means of a liquid scintillation counter.

The squalene synthetase inhibitory activity was
25 expressed in terms of the concentration inhibiting by 50% the radioactivity taken into the chloroform layer (IC₅₀, molar concentration (M)).

Experimental Example 2

Preparation of rat-derived enzyme

30 An SD male rat (6 week old) was killed by bleeding, and its liver was excised. About 10 g of the liver was washed with a physiological saline solution cooled with ice, which was then homogenized in 15 ml of an ice-cooled buffer solution [100 mM potassium
35 phosphate (pH 7.4), 15 mM nicotinamide, 2 mM MgCl₂], followed by centrifugation for 20 minutes (4°C) with

10000 Xg. The supernatant layer was separated and subjected to further centrifugation for 90 minutes (4°C) with 105000 Xg. The sediment was then suspended in an ice-cooled 100 mM phosphate buffer solution (pH 7.4), which was again subjected to centrifugation for 90 minutes (4°C) with 105000 Xg. The sediment thus obtained (microsome fraction) was suspended in an ice-cooled 100 mM potassium phosphate buffer (pH 7.4) (about 40 mg/ml protein concentration, determined with BCA protein assay kit of Pias Co., Ltd.). This suspension was used as the enzyme solution.

Experimental Example 3

Preparation of human-derived enzyme

Human hepatic carcinoma cells HepG2 (about 1×10^9 cells) obtained by incubation on a Dulbecco-modified Eagle's medium (37°C in the presence of 5% CO₂) were suspended in 10 ml of an ice-cooled buffer solution [100 mM potassium phosphate buffer (pH 7.4), 30 mM nicotinamide and 2.5 mM MgCl₂]. The cells were crashed by means of ultrasonication (for 30 seconds, twice). From the sonicate thus obtained, the microsome fraction was obtained by the same procedure as in Experiment Example 1, which was suspended in an ice-cooled 100 mM potassium phosphate buffer (pH 7.4) (about 4 mg/ml protein concentration). This suspension was used as the enzyme solution. The results are shown in Table 74.

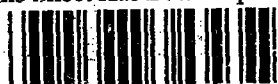


Table 74

	Compd. No.	Rat Enzyme ($10^{-7}M$)	Man Enzyme ($10^{-7}M$)
5	Ref.Ex. 5-1	83	68
	-2	47	51
	-3	40	38
	-4	63	64
	-7	5.4	7.1
	-8	5.3	-
	-12	2.3	-
10	W. Ex. 2-2	0.61	0.34
	-4	0.72	0.24
	33-2	49	38
	35-1	72	53
	-5	43	43
15	-6	34	33
	-11	26	21
	-12	40	35
	-15	0.35	0.12
	-19	0.28	0.30
20	-23	0.94	0.28
	74-5	0.54	0.22
	-9	0.49	0.40
	-11	0.79	0.14
	-12	0.38	0.18
25	105	0.65	0.34
	114	0.43	0.11
	118(1)	0.42	0.16
	120	0.16	0.06
	138	0.42	0.21
30	168	0.67	0.18
	117	>100	-

This Sheet Has Been Replaced





Experimental Example 4

Effects

The antifungal activities of the Compounds (I") were evaluated by the following method: a sheet of filter paper disc (manufactured by Toyo Seisakusho, 8 mm in diameter) soaked in a 1000µg/ml solution of a compound (I") in methanol was placed on an agar plate, which was incubated at 28°C for 2 days, and the diameter of the growth inhibition zone around the filter paper disc was measured. The following culture media were used:

A: yeast nitrogen base agar medium (pH 7.0)

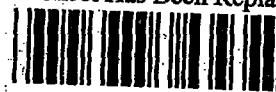
B: peptone-yeast extract-glucose agar medium (pH 7.0)

The antifungal spectra of the compound (I") are shown in Table 90.

The below mentioned test fungi are deposited at the Institute for Fermentation, Osaka, Japan (IFO). Their accession numbers are shown in Table 90.

Table 90. Antifungal spectra

Test fungi	Media	Inhibition zone diameter (mm)		
		Example 75-7	Example 75-6	Example 74-10
Candida albicans IFO 0583	A	16	14	18
Aspergillus niger IFO 4066	A	30	24	0
Cryptococcus neoformans IFO 0410	A	19	13	14
Trichophyton rubrum IFO 6467	B	16	13	20
Trichophyton mentagrophytes IFO 7522	B	12	12	12
Microsporum gypseum IFO 6076	B	13	12	13



Experimental Example 5

In vivo cholesterogenesis in the liver

Six-week-old, male Sprague-Dawley rats were given 5%-cholestylamine as a dietary admixture for 4 days.

5 They were administered compound at a dose of 30 mg/kg as a suspension of 0.5%-methylcellulose solution and were intravenously given 2 uCi of [14 C]acetate 1 hour after the administration. One hour later, rats were sacrificed and livers were removed. Hepatic sterols
10 were extracted with petroleum ether after saponification, and the radioactivity of digitonin-precipitable fraction was measured. Example 1-(4) inhibited the hepatic cholesterogenesis by 38% compared to the control group given only 5%-methylcellulose
15 solution.

Formulation Examples

A squalene synthetase inhibiting agents containing, as its effective component, a 4,1-benzoxazepin-2-one derivative shown by the formula (I)
20 of this invention or a salt thereof, in the case where it is used as a therapeutic agent of hypercholesteremia, can be formulated in accordance with, for example, the following prescriptions.

1. Capsules

25	(1) Compound obtained in Example 28-19	10 mg
	(2) Lactose	90 mg
	(3) Microcrystalline cellulose	70 mg
	(4) Magnesium stearate	10 mg
	One capsule	180 mg

30 (1), (2) and (3) and one half of (4) were blended and the the mixture was granulated, to which was added the balance of (4). The mixture was filled in a gelatin capsule.

2. Tablets

35	(1) Compound obtained in Example 28-19	10 mg
	(2) Lactose	35 mg



(3) Corn starch	150 mg
(4) Microcrystalline cellulose	30 mg
(5) Magnesium stearate	5 mg
One tablet	230 mg

5 (1), (2) and (3) and two thirds of (4) and one half of (5) were blended and the mixture was granulated, to which were added the balance of (4) and (5). The mixture was subjected to compression-molding to provide tablets.

10 3. Injections

(1) Sodium salt of the compound obtained in Example 28-19	10 mg
(2) Inositol	100 mg
(3) Benzyl alcohol	20 mg
One ampoule	130 mg

(1), (2) and (3) were dissolved in distilled water for injection to make the whole volume 2 ml, which was put in an ampoule, and the ampoule was sealed. All the processes were conducted under sterilized conditions.

20 4. Capsules

(1) Compound obtained in Example 1-4	10 mg
(2) Lactose	90 mg
(3) Microcrystalline cellulose	70 mg
(4) Magnesium stearate	10 mg
One capsule	180 mg

(1), (2) and (3) and one half of (4) were blended and the the mixture was granulated, to which was added the balance of (4). The mixture was filled in a gelatin capsule.

30 5. Tablets

(1) Compound obtained in Example 1-4	10 mg
(2) Lactose	35 mg
(3) Corn starch	150 mg
(4) Microcrystalline cellulose	30 mg
(5) Magnesium stearate	5 mg
One tablet	230 mg

(1), (2) and (3) and two thirds of (4) and one half of (5) were blended and the mixture was granulated, to which were added the balance of (4) and (5). The mixture was subjected to compression-molding to provide tablets.

5

6. Injections

(1) Sodium salt of the compound

obtained in Example 1-4 10 mg.

(2) Inositol 100 mg

10 (3) Benzyl alcohol 20 mg

One ampoule 130 mg

(1), (2) and (3) were dissolved in distilled water for injection to make the whole volume 2 ml, which was put in an ampoule, and the ampoule was sealed. All the processes were conducted under sterilized conditions.

15

This Sheet Has Been Replaced.



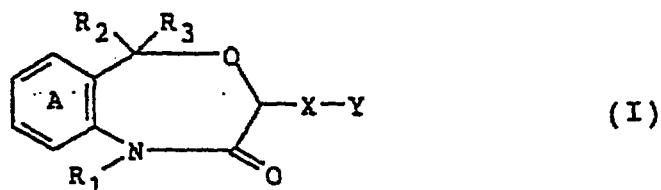


5

CLAIMS

What is claimed is:

1. A 4,1-Benzoxazepin-2-one derivative represented by the formula (I):



, wherein R₁ stands for hydrogen atom or an optionally substituted hydrocarbon group; R₂ and R₃ independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; provided that, when X is methylene and R₁ is not an alkyl group having carbon atoms of more than 4, Y is neither carboxyl group nor alkoxycarbonyl group; and the ring A may optionally be substituted, or a salt thereof.

2. The 4,1-Benzoxazepin-2-one derivative according to claim 1, R₁ stands for an aliphatic chain hydrocarbon group.
3. The 4,1-Benzoxazepin-2-one derivative according to claim 2, R₁ stands for an alkyl group.
4. The 4,1-Benzoxazepin-2-one derivative according to claim 3, R₁ stands for a lower C₁₋₇ alkyl group.
5. The 4,1-Benzoxazepin-2-one derivative according to claim 4, R₁ stands for a C₄₋₅ alkyl group.

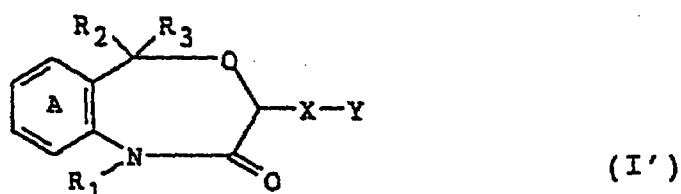




6. The 4,1-Benzoxazepin-2-one derivative according to claim 1, R_2 or R_3 stands for an optionally substituted phenyl group.

7. The 4,1-Benzoxazepin-2-one derivative according to claim 1, Y stands for an optionally esterified carboxyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated.

8. A 4,1-Benzoxazepin-2-one derivative represented by the formula (I'):



, wherein R^1 stands for hydrogen atom or an optionally substituted hydrocarbon group; R_2 and R_3 independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; provided that, when X is methylene, Y is neither carboxyl group nor alkoxycarbonyl group; and the ring A may optionally be substituted, or a salt thereof.

9. The 4,1-Benzoxazepin-2-one derivative according to claim 8, R_1 stands for an aliphatic chain hydrocarbon group.

10. The 4,1-Benzoxazepin-2-one derivative according to claim 9, R_1 stands for an alkyl group.

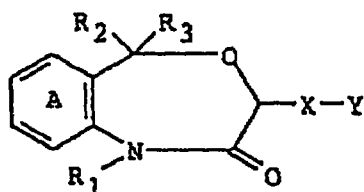




11. The 4,1-Benzoxazepin-2-one derivative according to claim 10, R_1 stands for a lower C_{1-7} alkyl group.
12. The 4,1-Benzoxazepin-2-one derivative according to claim 8, R_2 or R_3 stands for an optionally substituted phenyl group.
13. The 4,1-Benzoxazepin-2-one derivative according to claim 8, Y is an optionally esterified carboxyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated.
14. A pharmaceutical composition for inhibiting a squalene synthetase which comprises a therapeutically effective amount of a 4,1-Benzoxazepin-2-one derivative according to claim 1 or a salt thereof, and a pharmaceutical acceptable carrier.
15. A pharmaceutical composition for inhibiting a squalene synthetase which comprises a therapeutically effective amount of a 4,1-Benzoxazepin-2-one derivative according to claim 8 or a salt thereof, and a pharmaceutical acceptable carrier.
16. A pharmaceutical composition for inhibiting a fungal growth which comprises a therapeutically effective amount of a 4,1-Benzoxazepin-2-one derivative according to claim 1 or a salt thereof, and a pharmaceutical acceptable carrier.
17. A pharmaceutical composition for inhibiting a fungal growth which comprises a therapeutically effective amount of a 4,1-Benzoxazepin-2-one derivative according to claim 8 or a salt thereof, and a pharmaceutical acceptable carrier.
18. Use of a 4,1-Benzoxazepin-2-one derivative represented by the formula (I"):



This Sheet Has Been Replaced



(I'')

, wherein R^1 stands for hydrogen atom or an optionally substituted hydrocarbon group; R_2 and R_3 independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; and the ring A may optionally be substituted, or a salt thereof, for the manufacture of a medicament to be used as a squalene synthetase inhibitor.

19. The use according to claim 18, R_1 stands for an aliphatic chain hydrocarbon group.

20. The use according to claim 19, R_1 stands for an alkyl group.

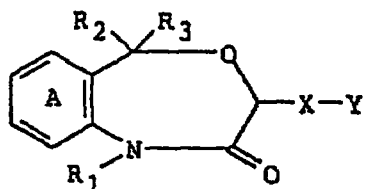
21. The use according to claim 20, R_1 stands for a lower C_{1-7} alkyl group.

22. The use according to claim 18, R_2 or R_3 stands for an optionally substituted phenyl group.

23. The use according to claim 18, Y stands for an optionally esterified carboxyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated.

24. Use of a 4,1-Benzoxazepin-2-one derivative represented by the formula (I''):





(I'')

, wherein R¹ stands for hydrogen atom or an optionally substituted hydrocarbon group; R₂ and R₃ independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; and the ring A may optionally be substituted, or a salt thereof, for the manufacture of a medicament to be used as a fungal growth inhibitor.

