



(86) Date de dépôt PCT/PCT Filing Date: 2000/04/28

(87) Date publication PCT/PCT Publication Date: 2000/11/16

(85) Entrée phase nationale/National Entry: 2001/11/05

(86) N° demande PCT/PCT Application No.: JP 2000/002825

(87) N° publication PCT/PCT Publication No.: 2000/068203

(30) Priorité/Priority: 1999/05/07 (11/127724) JP

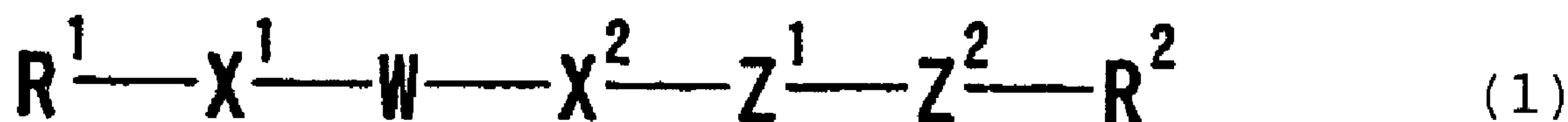
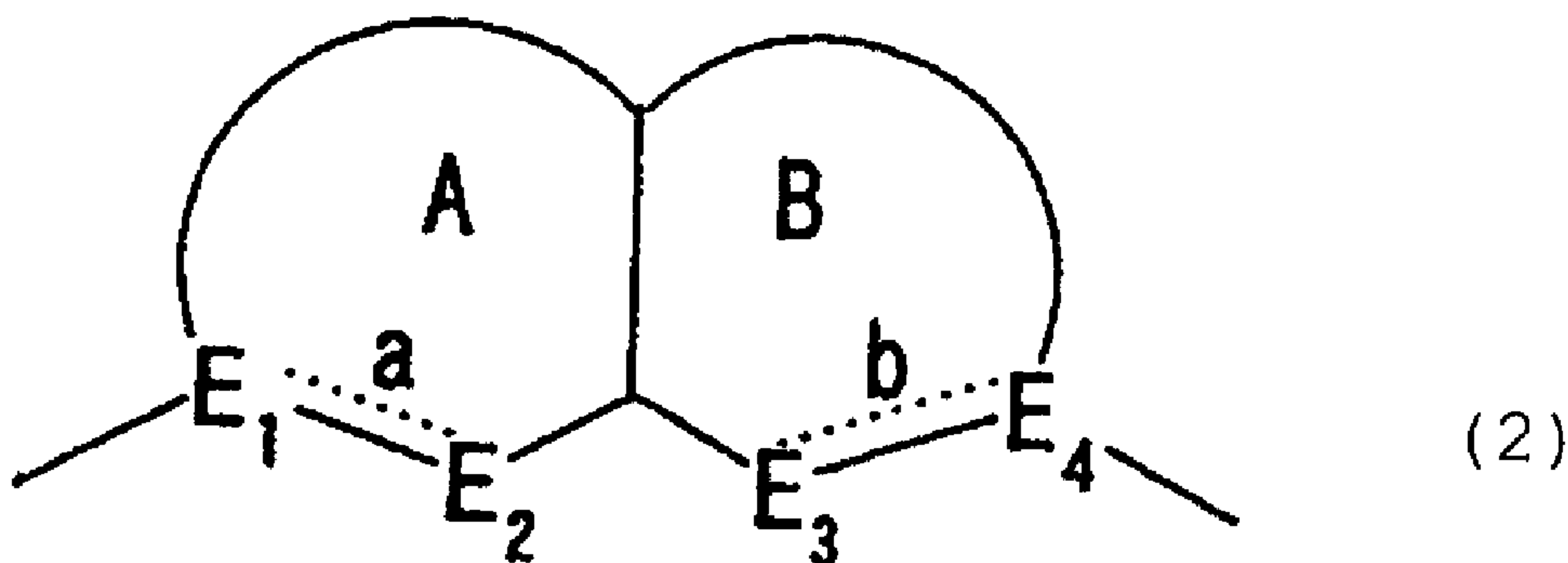
(51) Cl.Int.⁷/Int.Cl.⁷ C07D 217/06, A61K 31/661, A61K 31/4725, A61K 31/4709, A61K 31/44, A61K 31/4025, A61K 31/381, A61K 31/352, A61K 31/351, A61P 31/18, C07D 409/14, C07D 309/14, C07D 409/12, C07D 407/12, C07D 405/12, C07D 401/12, C07F 9/655

(71) Demandeur/Applicant:
TAKEDA CHEMICAL INDUSTRIES, LTD., JP

(72) Inventeurs/Inventors:
SHIRAISHI, MITSURU, JP;
BABA, MASANORI, JP;
SETO, MASAKI, JP;
KANZAKI, NAOYUKI, JP;
NISHIMURA, OSAMU, JP

(54) Titre : COMPOSES CYCLIQUES ET LEURS UTILISATIONS

(54) Title: CYCLIC COMPOUNDS AND USES THEREOF



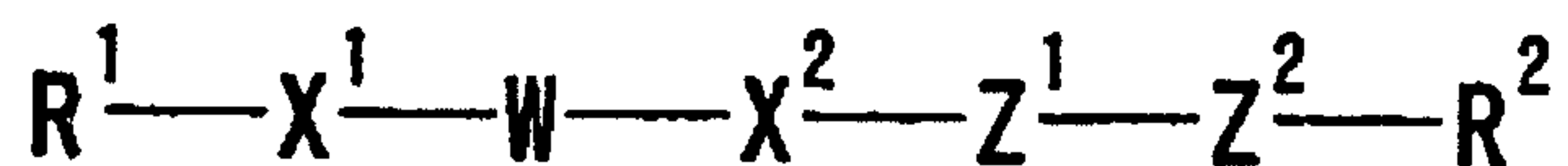
(57) Abrégé/Abstract:

Compounds of general formula (1) or salts thereof, exhibiting preventive and therapeutic effects against HIV infections wherein R^1 is an optionally substituted five- or six-membered ring group; X^1 is a free valency or the like; W is a divalent group represented by, e.g., general formula (2) (wherein A and B are each an optionally substituted five- to seven-membered ring; E_1 and E_4 are each optionally substituted carbon or the like; E_2 and E_3 are each oxygen or the like; and a and b are each a single bond or a double bond); X^2 is a divalent group constituting a straight chain moiety; Z^1 is a divalent cyclic group or the like; Z^2 is a free valency or the like; and R^2 is optionally substituted amino or the like.

(74) **Agent:** FETHERSTONHAUGH & CO.

Abstract of the disclosure:

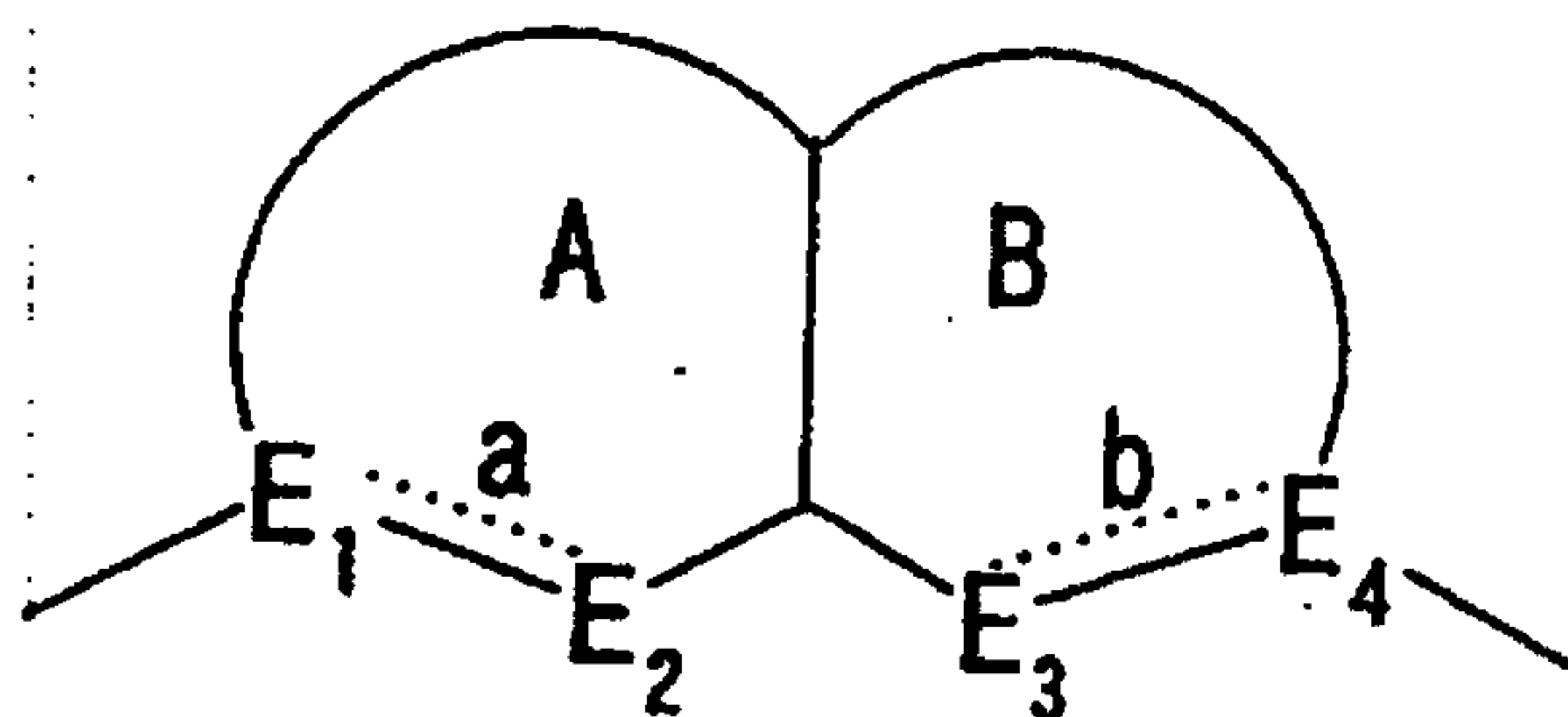
Compounds of general formula (1)



5

or salts thereof, exhibiting preventive and therapeutic effects against HIV infectious diseases wherein R^1 is an optionally substituted five- or six-membered ring group; X^1 is a free valency or the like; W is a divalent group represented by, e. g., general formula (2)

10



(wherein A and B are each an optionally substituted five- to seven-membered ring; E_1 and E_4 are each optionally substituted carbon or the like; E_2 and E_3 are each oxygen or the like; and a and b are each a single bond or a double bond); X^2 is a divalent group constituting a straight chain moiety; Z^1 is a divalent cyclic group or the like; Z^2 is a free valency or the like; and R^2 is optionally substituted amino or the like.

15

20

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

CYCLIC COMPOUNDS AND USES THEREOF

Technical Field

5 The present invention relates to novel cyclic ring compounds, which possess CCR antagonistic actions, particularly a CCR5 antagonistic action, and uses thereof.

Background Art

10 In recent years, inhibitors of HIV (human immunodeficiency virus) protease have been developed as therapeutic agents against AIDS (acquired immunodeficiency syndrome), and the use of these drugs in combination with the two HIV reverse transcriptase inhibitors, which have
15 been heretofore employed, have brought a remarkable progress in the treatment of AIDS, whereas this progress is not yet sufficient for eradicating AIDS, whereby the development of new anti-AIDS drugs, which act by still another mechanism, has been desired.

20 CD4 has been known for some time as a receptor through which HIV enters the target cells, while G-protein-coupled, seven trans-membrane chemokine receptors called CCR5 and CXCR4 have recently been found out as the second group of receptors for macrophage-trophic HIV and T-cell-
25 trophic HIV, respectively, and it is speculated that these

chemokine receptors play essential roles in the establishment of infection and transmission of HIV. In fact, there is a report that people who remained resistant to HIV infection in spite of repeated exposures were found to have homozygous deletion in CCR5 gene. Therefore, CCR5 antagonists are expected to be new anti-HIV drugs, and examples of synthesizing new anilide derivatives possessing the CCR5-antagonistic activity are described in patent applications such as PCT/JP98/05708 (WO99/32100), Japanese Patent Application No. 1998-234388 (WO00/10965) and Japanese Patent Application No. 1998-363404 (PCT/JP99/07148), whereas there have so far been no report on commercialization of CCR5 antagonists as the therapeutic agents against AIDS.

Disclosure of the Invention

The present invention is to provide novel bicyclic ring compounds, which are useful as the prophylactic and therapeutic agents against HIV infectious diseases, particularly AIDS, on the basis of CCR antagonistic actions, particularly a CCR5 antagonistic action.

As a result of intensive investigations on compounds possessing a CCR5 antagonistic action, the present inventors have found that compounds represented by

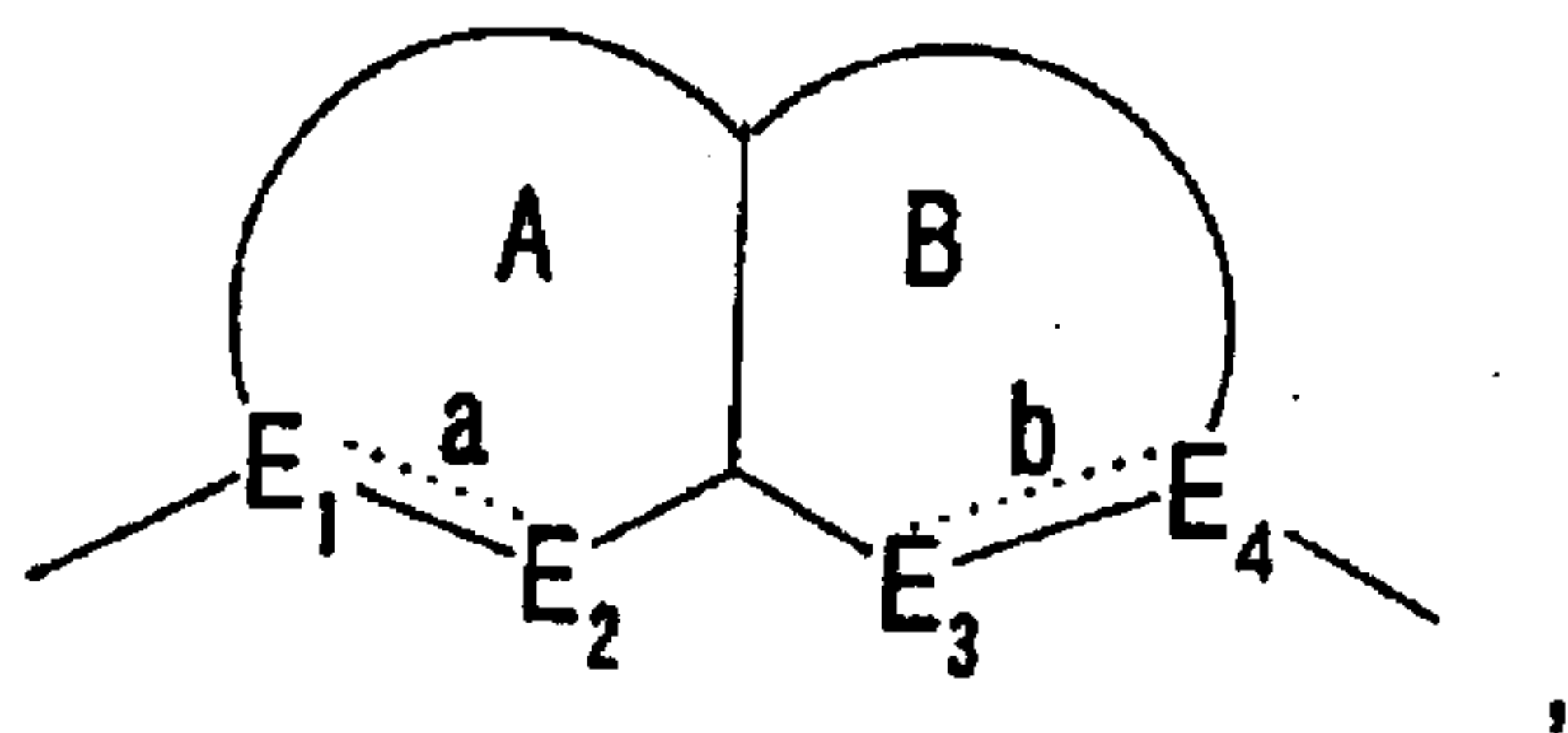
the following formula (I) or salts thereof (hereinafter,
 may be designated as compounds (I)) possess clinically
 desirable, medicinal effects such as exhibition of CCR
 antagonistic actions, particularly an excellent CCR5
 5 antagonistic action, and the like, completing the present
 invention on the basis of this finding.

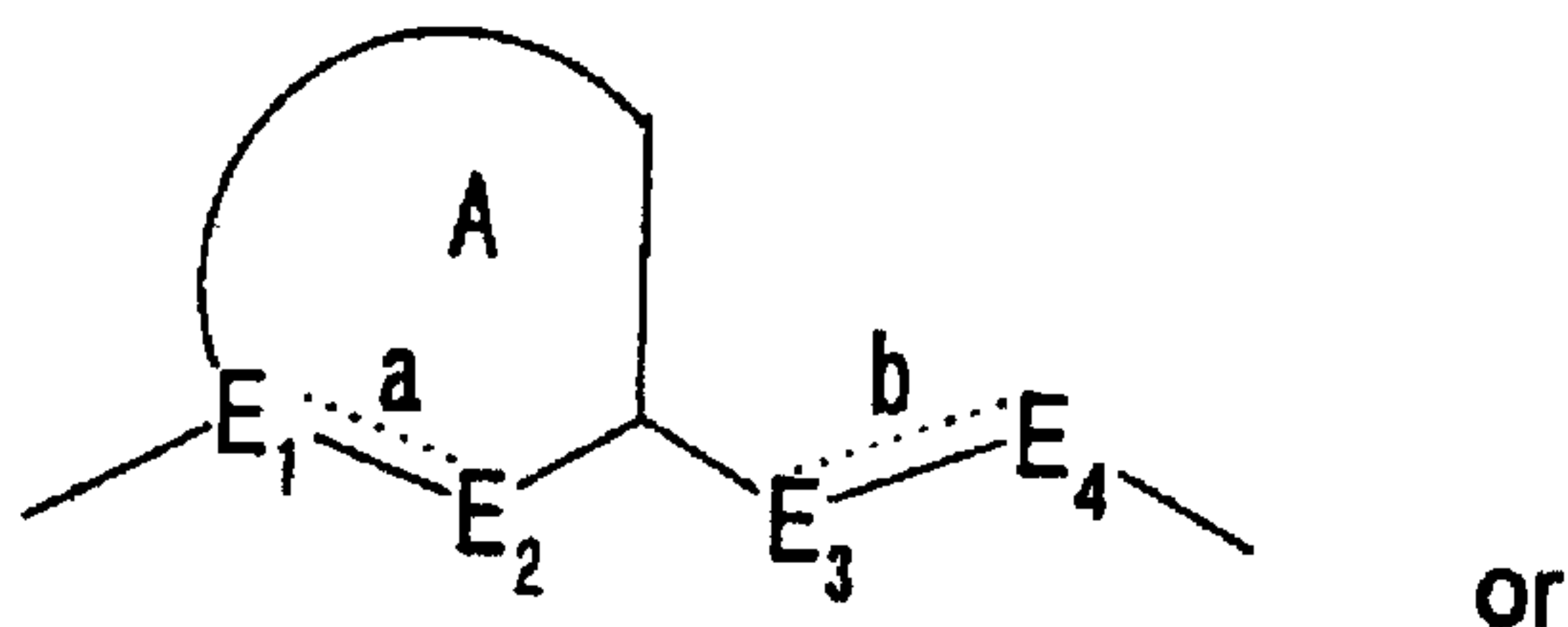
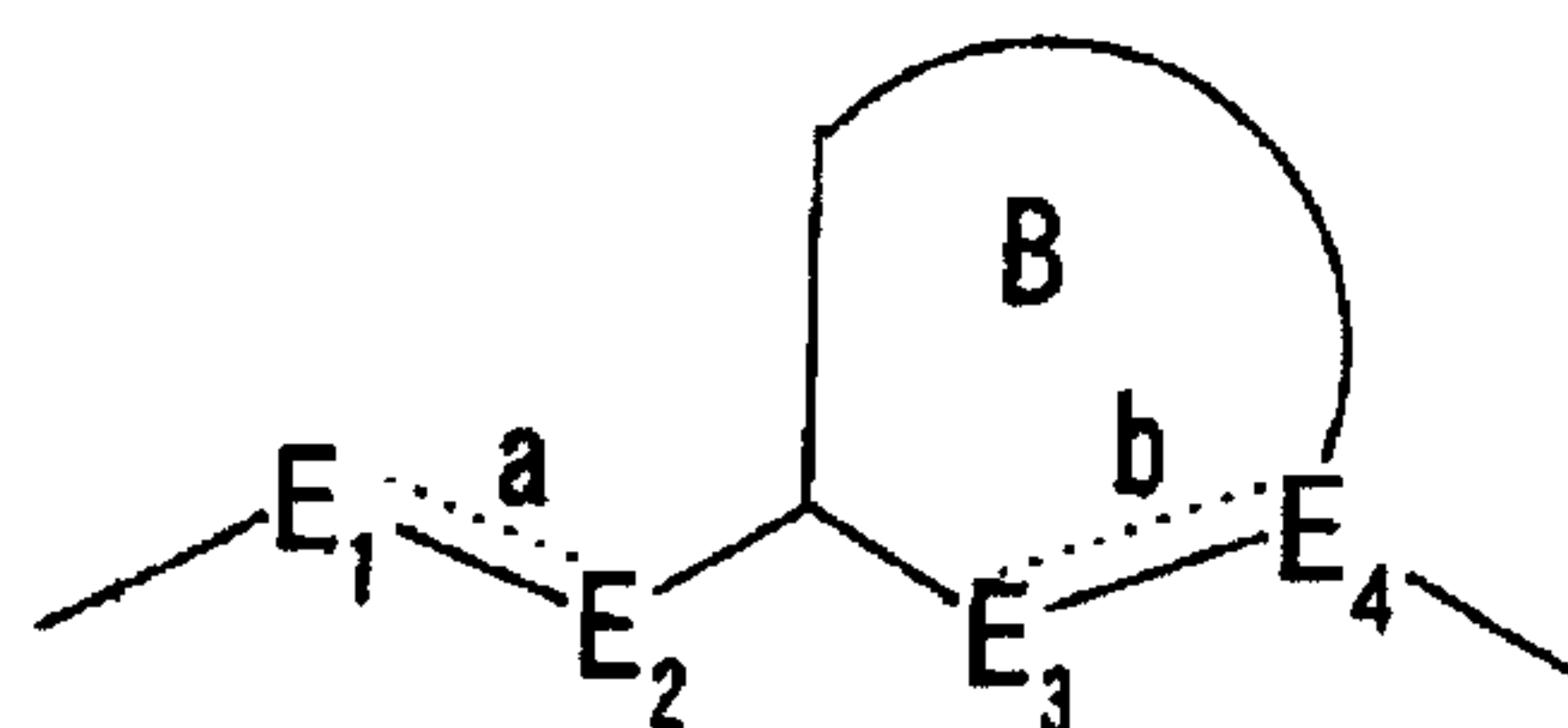
In other words, the present invention relates to:

(1) A compound represented by formula (I)



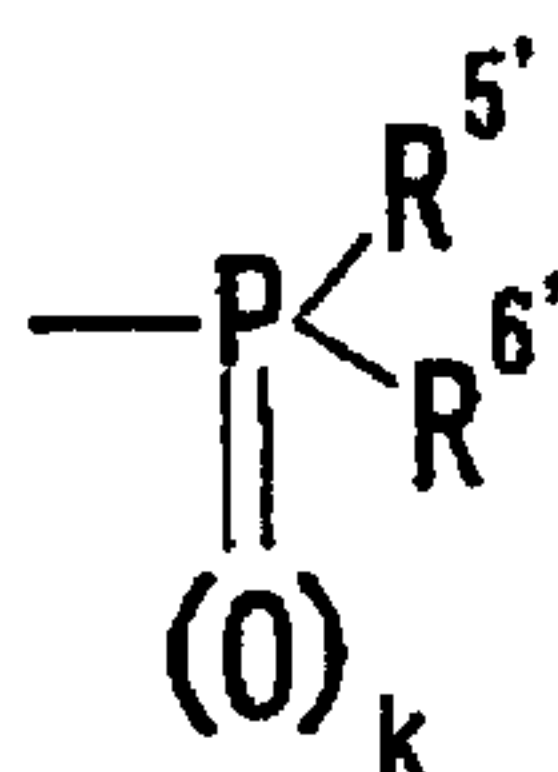
[wherein R^1 indicates a 5- to 6-membered cyclic ring group
 that may be substituted, X^1 indicates a bond or a bivalent
 group, in which the number of atoms constituting the
 15 straight-chain portion is 1 to 4, W indicates a bivalent
 group that is represented by formula





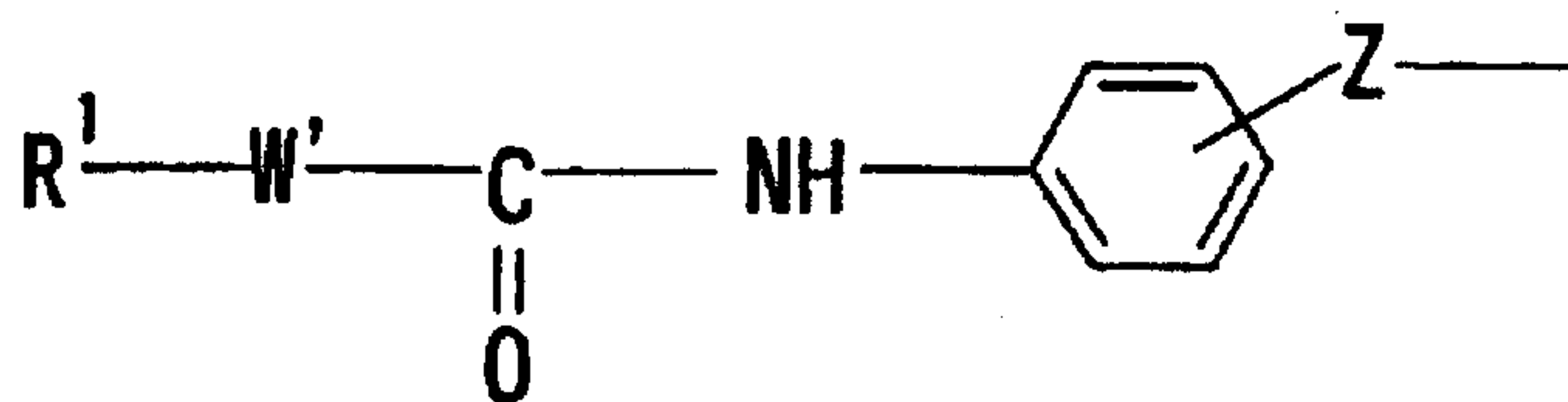
- 5 (wherein each of ring A and ring B indicates a 5- to 7-
 membered cyclic ring group that may be substituted, each of
 E₁ and E₄ indicates the carbon atom that may be substituted
 or the nitrogen atom that may be substituted, each of E₂
 and E₃ indicates the carbon atom that may be substituted or
 10 the nitrogen atom that may be substituted, the sulfur atom
 that may be oxidized or the oxygen atom and each of a and b
 indicates to be a single bond or a double bond), X²
 indicates a bivalent group, in which the number of atoms
 constituting the straight-chain portion is 1 to 4, Z¹
 15 indicates a bond or a bivalent cyclic ring group, Z²
 indicates a bond or a bivalent cyclic ring group, in which
 the number of atoms constituting the straight-chain portion
 is 1 to 4, and R² indicates (1) an amino group that may be
 substituted, where the nitrogen atom may be converted into

a quaternary ammonium or the N-oxide, (2) a nitrogen-containing, heterocyclic ring group that may be substituted and may contain the sulfur atom or the oxygen atom as a ring-constituting atom, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide, (3) a group that is bonded via the sulfur atom, (4) a group represented by formula



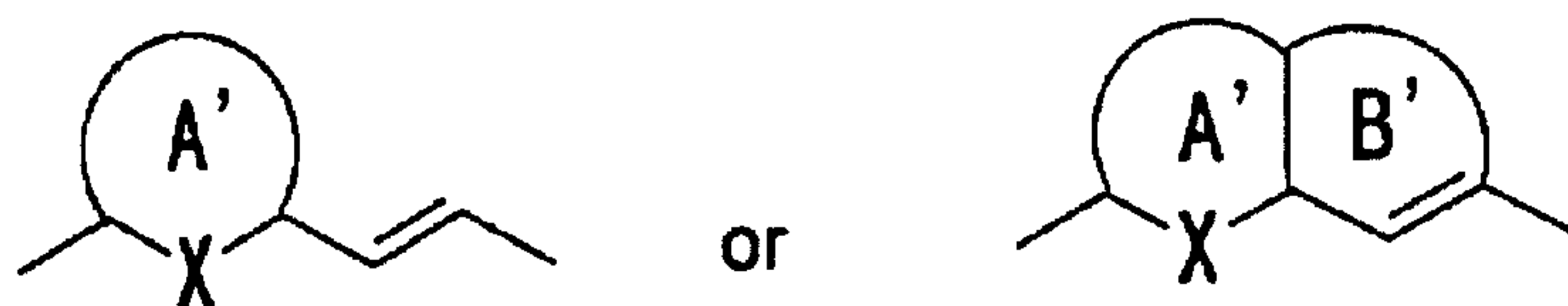
(wherein k indicates 0 or 1, the phosphorus atom may form a phosphonium salt when k is 0, and each of R^{5'} and R^{6'} indicates the hydrocarbon atom that may be substituted, the hydroxyl group that may be substituted or an amino group that may be substituted (preferably, the hydrocarbon atom that may be substituted or an amino group that may be substituted; more preferably the hydrocarbon atom that may be substituted) and R^{5'} and R^{6'} may bind each other to form a cyclic ring group together with the adjacent phosphorus atom), (5) an amidino group that may be substituted or (6) a guanidino group that may be substituted] [provided that, when a group represented by formula R¹-X¹-W-X²-Z¹-Z²- indicates a group represented by formula

6

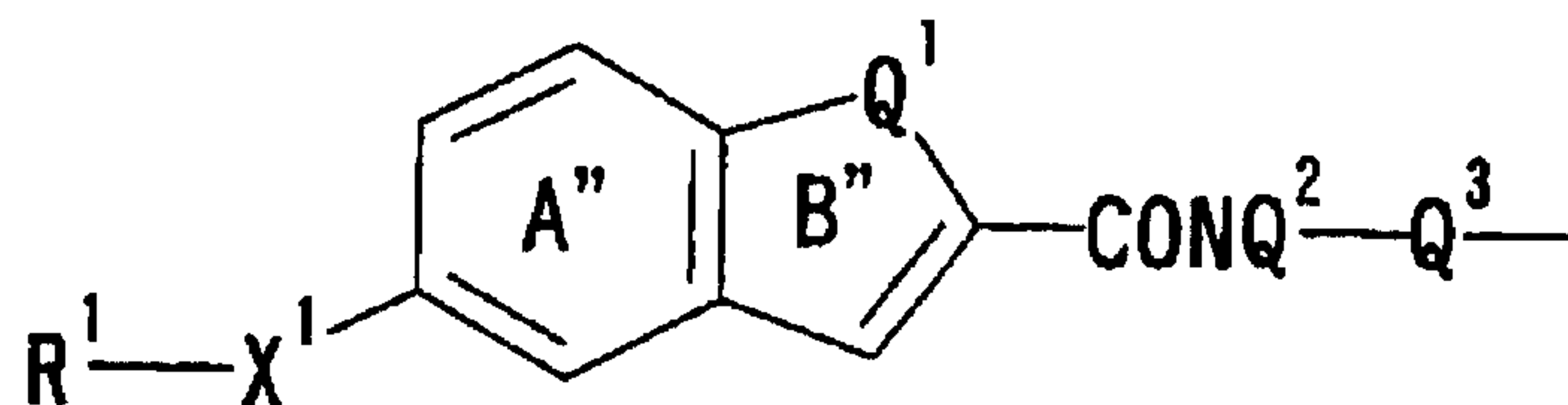


(wherein R^1 indicates the same meaning as described above,
 W' indicates a bivalent group represented by formula

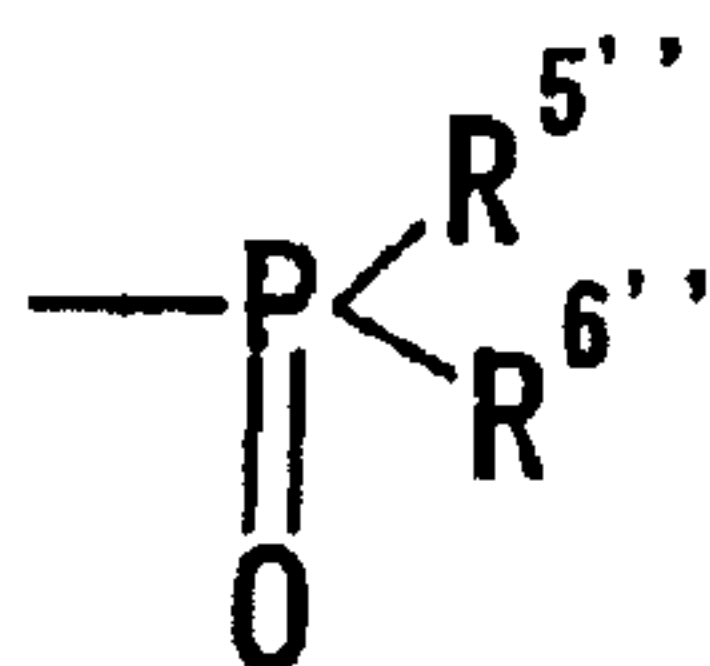
5



(wherein ring A' indicates a 5- to 6-membered aromatic ring
that may be substituted, X indicates the carbon atom that
may be substituted, the nitrogen atom that may be
substituted, the sulfur atom or the oxygen atom and ring B'
indicates a 5- to 7-membered ring that may be substituted)
and Z indicates a bivalent group, in which the number of
atoms constituting the straight-chain portion is 1 to 4, R^2
indicates an amidino group that may be substituted or a
guanidino group that may be substituted; when a group
represented by formula $R^1 - X^1 - W - X^2 - Z^1 - Z^2 -$ indicates a group
represented by formula



(wherein R^1 and X^1 indicate the same meanings as described above, ring A'' indicates a benzene ring that may be substituted, Q^1 indicates a bivalent group, in which ring B'' forms a 5- to 7-membered ring, Q^2 indicates the hydrogen atom, a hydrocarbon group that may be substituted, a heterocyclic ring group that may be substituted and Q^3 indicates a bond or a bivalent group), R^2 does not indicate a group represented by formula



(wherein each of $R^{5''}$ and $R^{6''}$ indicates the hydroxyl group that may be substituted and $R^{5''}$ and $R^{6''}$ may bind each other to form a cyclic ring group together with the adjacent phosphorus atom)], or salts thereof;

(2) A prodrug of the compound or the salt thereof as described in the above-mentioned item (1);

(3) The compound as described in the above-mentioned item (1), wherein R^1 is a group that is formed by

removing one hydrogen atom from benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine or tetrahydrofuran, each of which may be substituted;

5 (4) The compound as described in the above-mentioned item (1), wherein X^1 is a phenyl that may be substituted;

(5) The compound as described in the above-mentioned item (1), wherein R^1 is a bond, $-(CH_2)_{a'}-$ [a' indicates an integer of 1 to 4], $-(CH_2)_{b'}-X^3-$ [b' indicates an integer of 0 to 3 and X^3 indicates an imino group that may be substituted, the carbonyl group, the oxygen atom or the sulfur atom that may be oxidized], $-CH=CH-$, $-C\equiv C-$, $-CO-NH-$ or $-SO_2-NH-$;

10

15 (6) The compound as described in the above-mentioned item (1), wherein X^1 is a bond;

(7) The compound as described in the above-mentioned item (1), wherein X^1 is $-(CH_2)_{b'}-X^3-$ [b' indicates an integer of 0 to 3, and X^3 indicates an imino group that may be substituted, the carbonyl group, the oxygen atom or the sulfur atom that may be oxidized];

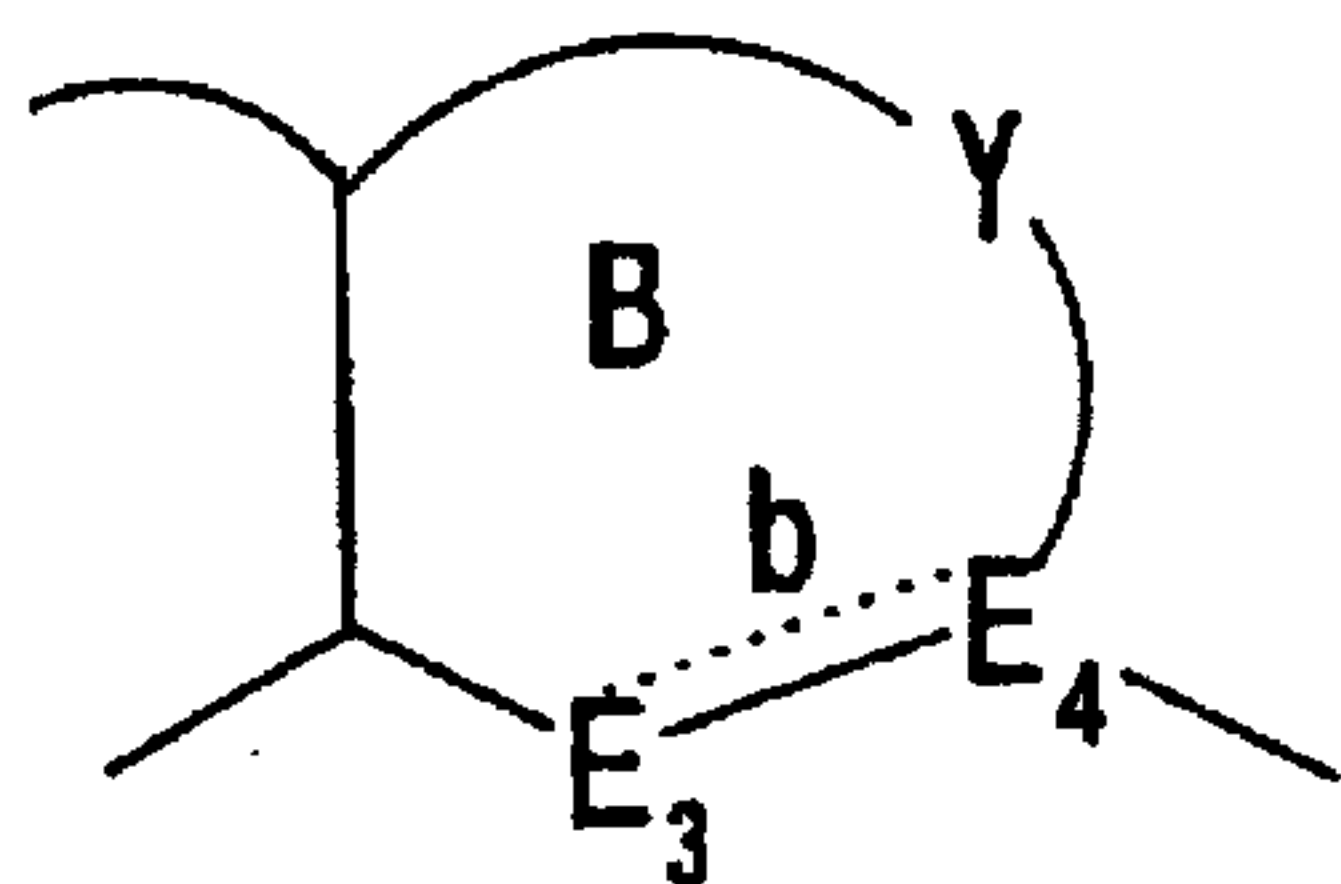
20

(8) The compound as described in the above-mentioned item (1), wherein ring A is furan, thiophene, pyrrole, pyridine, pyran or benzene, each of which may be substituted;

25

(9) The compound as described in the above-mentioned item (1), wherein ring A is a benzene that may be substituted;

(10) The compound as described in the above-mentioned item (1), wherein ring B is a 5- to 7-membered ring that may be substituted at a substitutable optional position, which is represented by formula



10

[wherein E_3 indicates the carbon atom that may be substituted or the nitrogen atom that may be substituted, E_4 indicates the carbon atom that may be substituted or the nitrogen atom, b indicates a single bond or a double bond and Y indicates $-Y'-(CH_2)_m-$ (Y' indicates $-S(O)_m-$ (m indicates an integer of 0 to 2), $-O-$, $-NH-$ or $-CH_2-$, and m' indicates an integer of 0 to 2), $-CH=$, $-CH=CH-$ or $-N=CH-$];

(11) The compound as described in the above-mentioned item (10), wherein Y indicates $-Y'-(CH_2)_2-$ [Y' indicates $-S(O)_m-$ (m indicates an integer of 0 to 2), $-O-$, $-NH-$ or $-CH_2-$];

(12) The compound as described in the above-

mentioned item (1), wherein E_3 indicates the carbon atom that may be substituted, E_4 indicates the carbon atom that may be substituted and b indicates a double bond;

(13) The compound as described in the above-mentioned item (1), wherein X^2 is $-(CH_2)_{a'}-$ [a' indicates an integer of 1 to 4], $-(CH_2)_{b'}-X^3-$ [b' indicates an integer of 0 to 3, and X^3 indicates an imino group that may be substituted, the carbonyl group, the oxygen atom or the sulfur atom that may be oxidized], $-CH=CH-$, $-C\equiv C-$, $-CO-NH-$ or $-SO_2-NH-$;

(14) The compound as described in the above-mentioned item (1), wherein X^2 is $-CO-NH-$;

(15) The compound as described in the above-mentioned item (1), wherein Z^1 is (1) a bond or (2) a bivalent cyclic ring group that is formed by removing two hydrogen atoms from benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine or tetrahydropyran, each of which may be substituted;

(16) The compound as described in the above-mentioned item (1), wherein Z^1 is (1) a bond or (2) a bivalent cyclic ring group that is formed by removing two hydrogen atoms from benzene, cyclohexane or piperidine, each of which may be substituted;

(17) The compound as described in the above-

mentioned item (1), wherein Z^1 is a phenylene that may be substituted;

(18) The compound as described in the above-mentioned item (1), wherein Z^2 is a bond or a C_{1-3} alkylene that may be substituted;

(19) The compound as described in the above-mentioned item (1), wherein Z^2 is a bivalent group that has a skeleton represented by $-Z'-(CH_2)_n-$ [Z' indicates $-CH(OH)-$, $-C(O)-$ or $-CH_2-$, and n indicates an integer of 0 to 2] and may have a substituent at an optional methylene group;

(20) The compound as described in the above-mentioned item (1), wherein Z^2 is a bond or a methylene;

(21) The compound as described in the above-mentioned item (1), wherein Z^1 is a 6-membered, bicyclic ring group, and Z^2 is substituted at the para position of X^2 ;

(22) The compound as described in the above-mentioned item (1), wherein R^2 is (1) an amino group that may be substituted, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide, (2) a nitrogen-containing, heterocyclic ring group that may be substituted and may contain the sulfur atom or the oxygen atom as a ring-constituting atom, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide,

(3) an amidino group that may be substituted or (4) a guanidino group that may be substituted;

(23) The compound as described in the above-mentioned item (1), wherein R^2 is an amino group that may
5 be substituted;

(24) The compound as described in the above-mentioned item (1), wherein R^2 is an amidino group that may be substituted or a guanidino group that may be substituted;

10 (25) N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[2-(4-propoxyphenyl)ethoxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(3-propoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide,
15 carboxamide, N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(2-propoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(4-propoxyphenyl)methoxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide,
20 benzothiepine-4-carboxamide, N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(4-propoxyethoxyphenyl)methoxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[3-(4-propoxyphenyl)propoxy]-1,1-dioxo-2,3-dihydro-1-

25

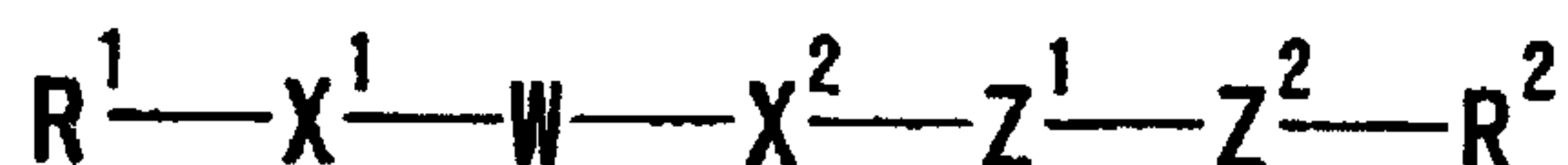
benzothiepine-4-carboxamide, or salts thereof;

(26) A prodrug of the compound or salt thereof as described in the above-mentioned item (25);

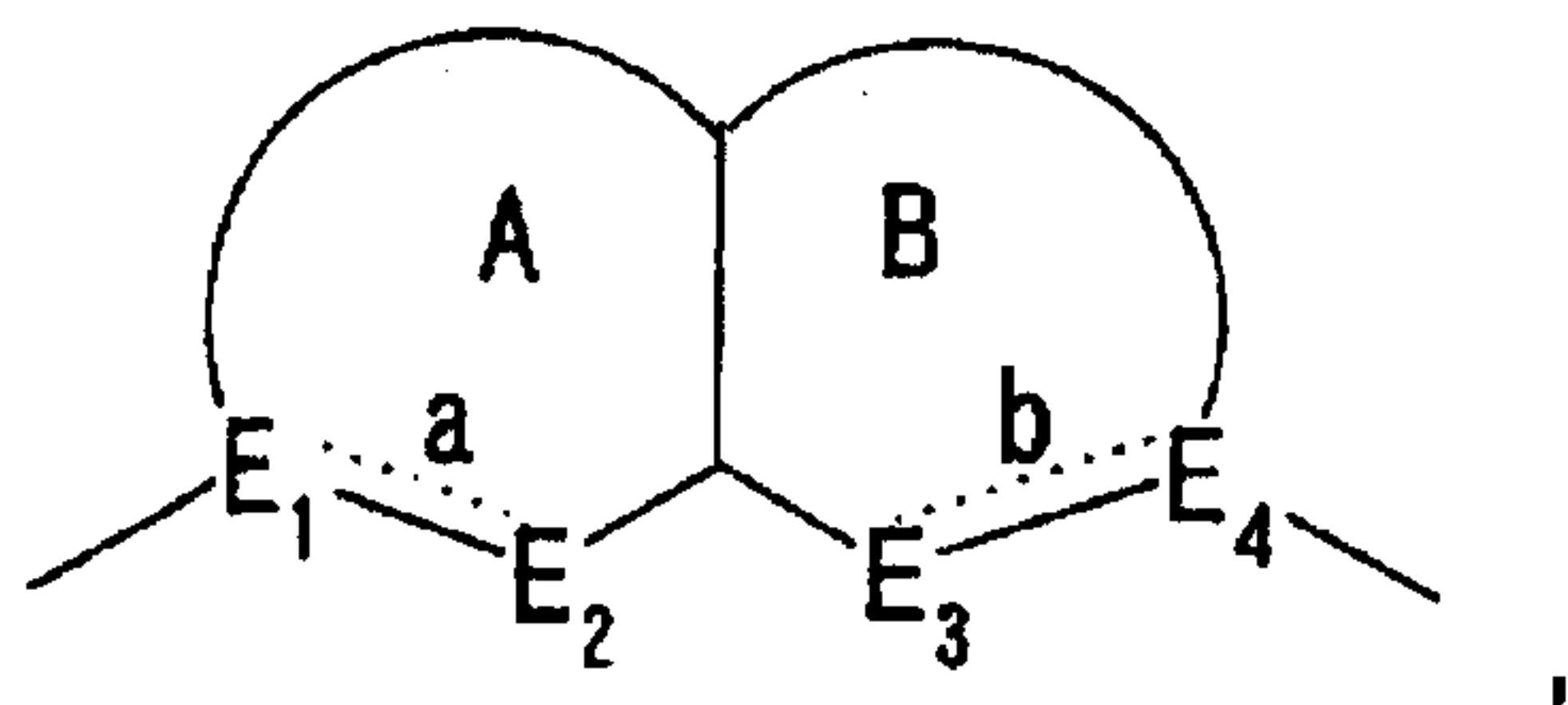
(27) A pharmaceutical composition comprising the
5 compounds or salt thereof as described in the above-mentioned item (1);

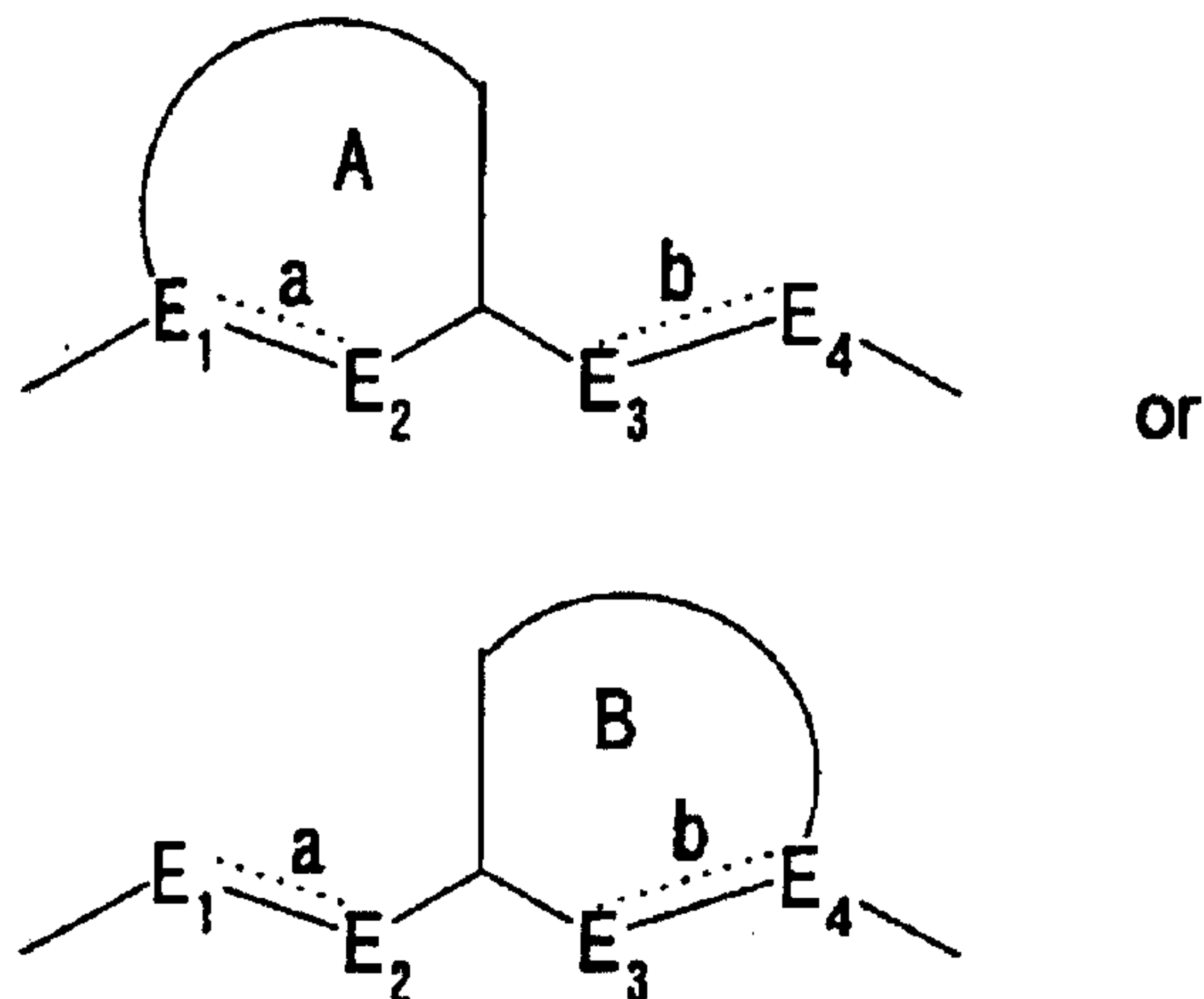
(28) A pharmaceutical composition for CCR antagonisms (preferably, a CCR5 antagonism) which comprises a compound represented by formula

10



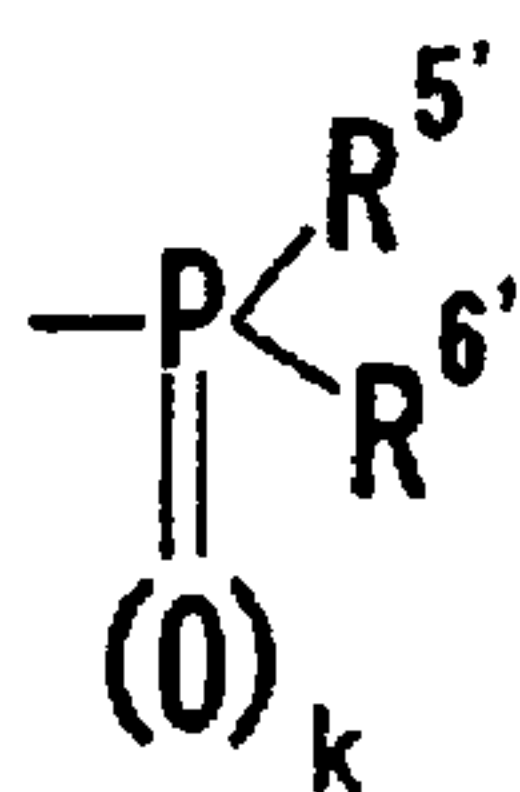
[wherein R^1 indicates a 5- to 6-membered cyclic ring group that may be substituted, X^1 indicates a bond or a bivalent group, in which the number of atoms constituting the
15 straight-chain portion is 1 to 4, W indicates a bivalent group that is represented by formula



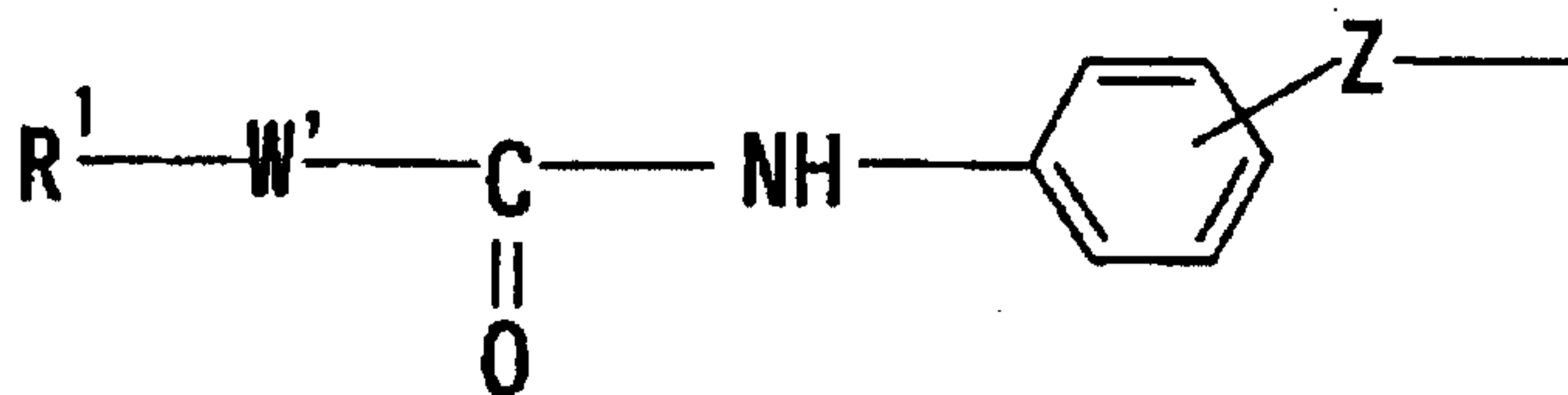


(wherein each of ring A and ring B indicates a 5- to 7-
 5 membered cyclic ring group that may be substituted, each of
 E_1 and E_4 indicates the carbon atom that may be substituted
 or the nitrogen atom that may be substituted, each of E_2
 and E_3 indicates the carbon atom that may be substituted or
 the nitrogen atom that may be substituted, the sulfur atom
 10 that may be oxidized or the oxygen atom and each of a and b
 indicates to be a single bond or a double bond), X^2
 indicates a bivalent group, in which the number of atoms
 constituting the straight-chain portion is 1 to 4, Z^1
 indicates a bond or a bivalent cyclic ring group, Z^2
 15 indicates a bond or a bivalent cyclic ring group, in which
 the number of atoms constituting the straight-chain portion
 is 1 to 4, and R^2 indicates (1) an amino group that may be
 substituted, where the nitrogen atom may be converted into
 a quaternary ammonium or the N-oxide, (2) a nitrogen-

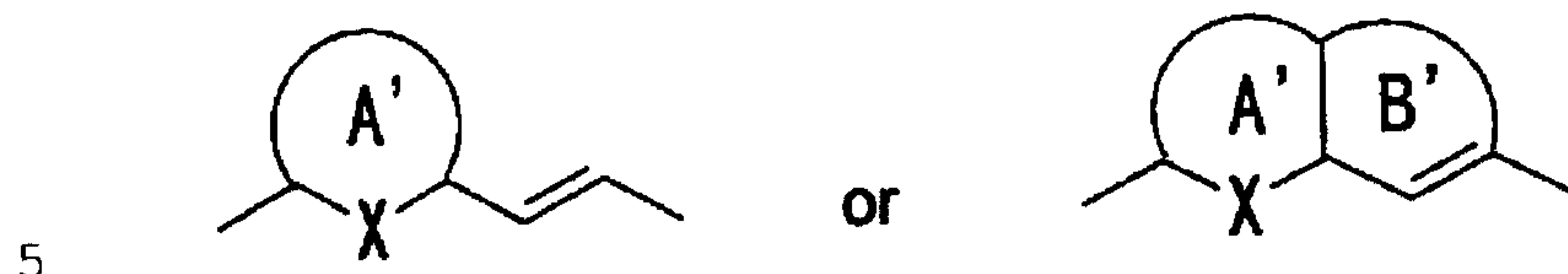
containing, heterocyclic ring group that may be substituted and may contain the sulfur atom or the oxygen atom as a ring-constituting atom, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide, (3) a group that bonded via the sulfur atom, (4) a group represented by formula



(wherein k indicates 0 or 1, the phosphorus atom may form a phosphonium salt when k is 0, and each of R^{5'} and R^{6'} indicates the hydrocarbon atom that may be substituted, the hydroxyl group that may be substituted or an amino group that may be substituted and R^{5'} and R^{6'} may bind each other to form a cyclic ring group together with the adjacent phosphorus atom), (5) an amidino group that may be substituted or (6) a guanidino group that may be substituted] [provided that, when a group represented by formula R¹-X¹-W-X²-Z¹-Z²- indicates a group represented by formula



(wherein R^1 indicates the same meaning as described above,
 W' indicates a bivalent group represented by formula



(wherein ring A' indicates a 5- to 6-membered aromatic ring
 that may be substituted, X indicates the carbon atom that
 may be substituted, the nitrogen atom that may be
 substituted, the sulfur atom or the oxygen atom and ring B'
 10 indicates a 5- to 7-membered ring that may be substituted)
 and Z indicates a bivalent group, in which the number of
 atoms constituting the straight-chain portion is 1 to 4),
 R^2 indicates an amidino group that may be substituted or a
 guanidino group that may be substituted], or salts thereof;

15 (29) The composition as described in the above-
 mentioned item (28) which is a prophylactic/therapeutic
 agent of HIV infectious diseases;

(30) The composition as described in the above-
 mentioned item (28) which is a prophylactic/therapeutic
 20 agent of AIDS;

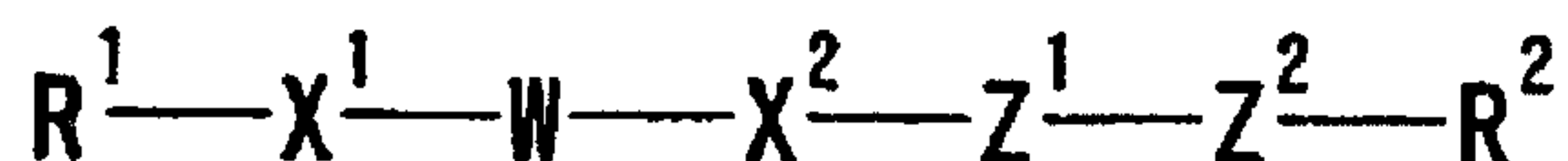
(31) The composition as described in the above-
 mentioned item (28) which is a depressant against the
 pathologic progress of AIDS;

(32) The composition as described in the above-mentioned item (29) which is in combination with a protease inhibitor and/or a reverse transcriptase inhibitor;

(33) The composition as described in the above-mentioned item (32), wherein the reverse transcriptase inhibitor is zidovudine, didanosine, zalcitabine, lamivudine, stavudine, nevirapine, delavirdine, efavirenz or abacavir;

(34) The composition as described in the above-mentioned item (32), wherein the protease inhibitor is saquinavir, ritonavir, indinavir, amprenavir or nelfinavir;

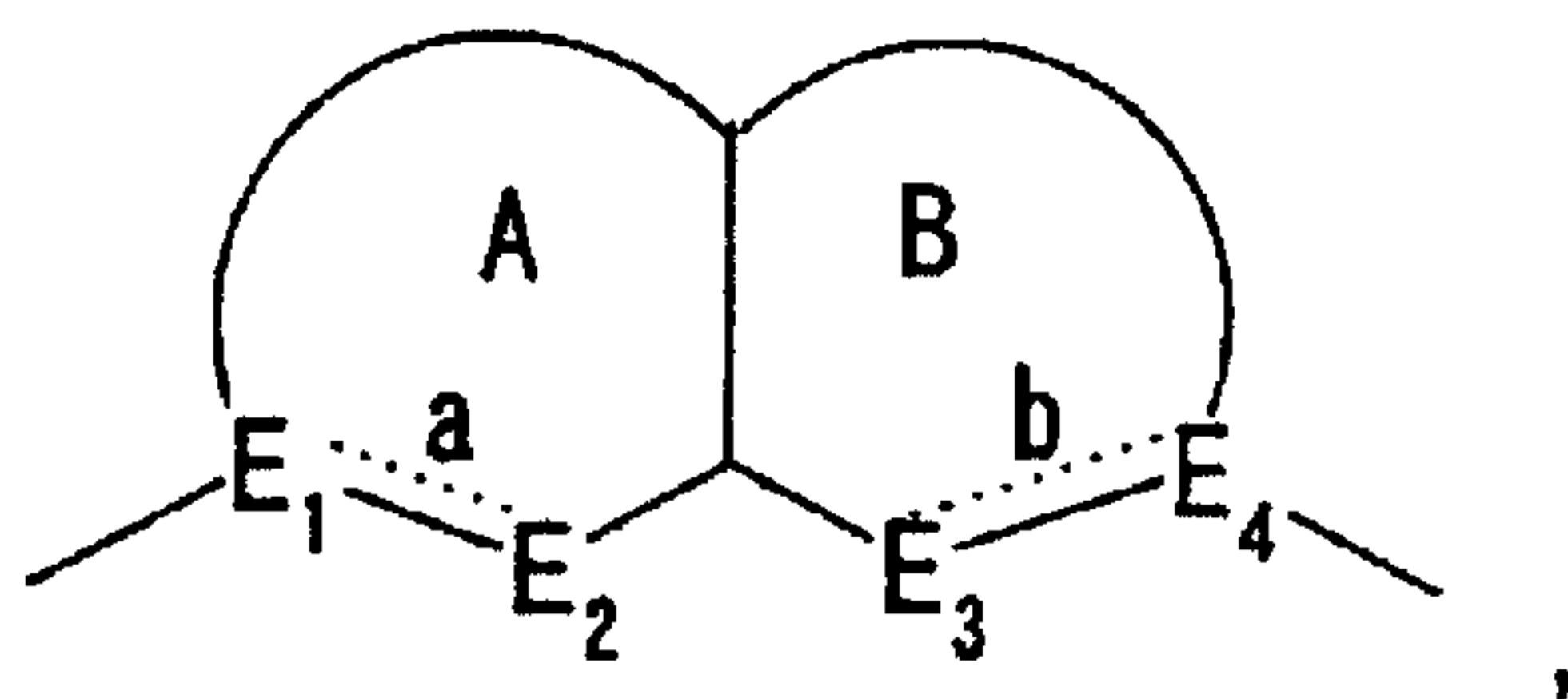
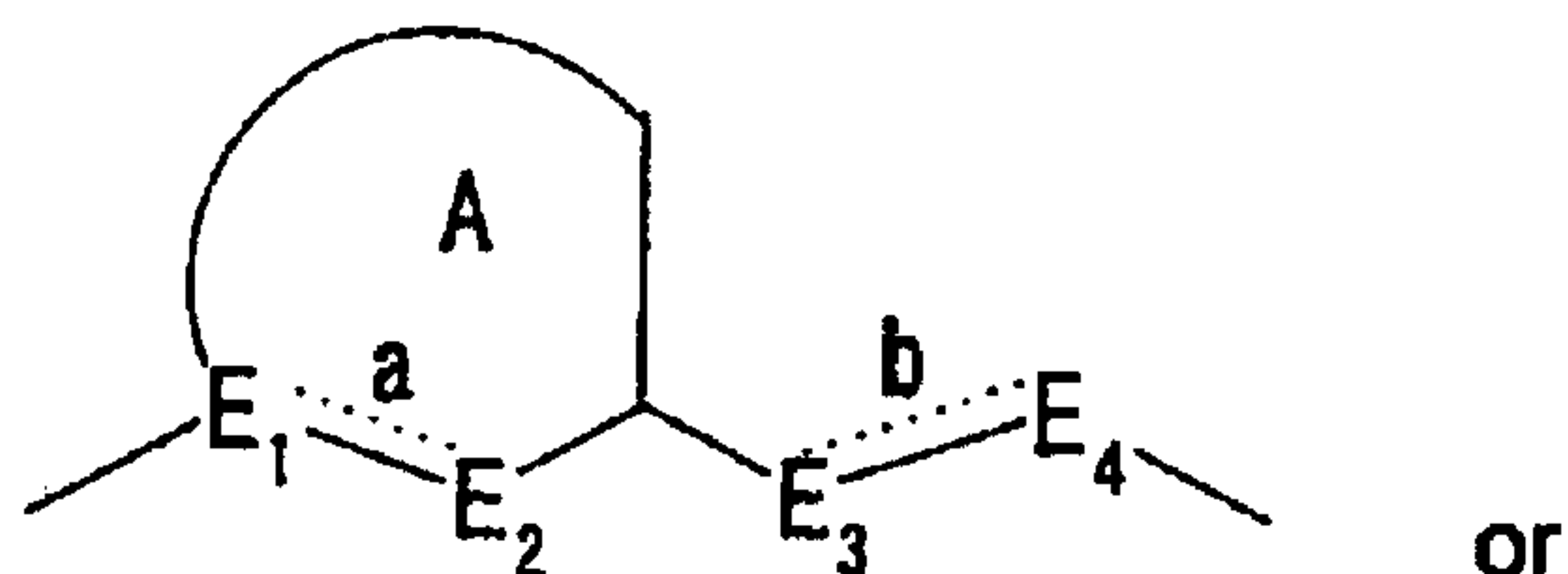
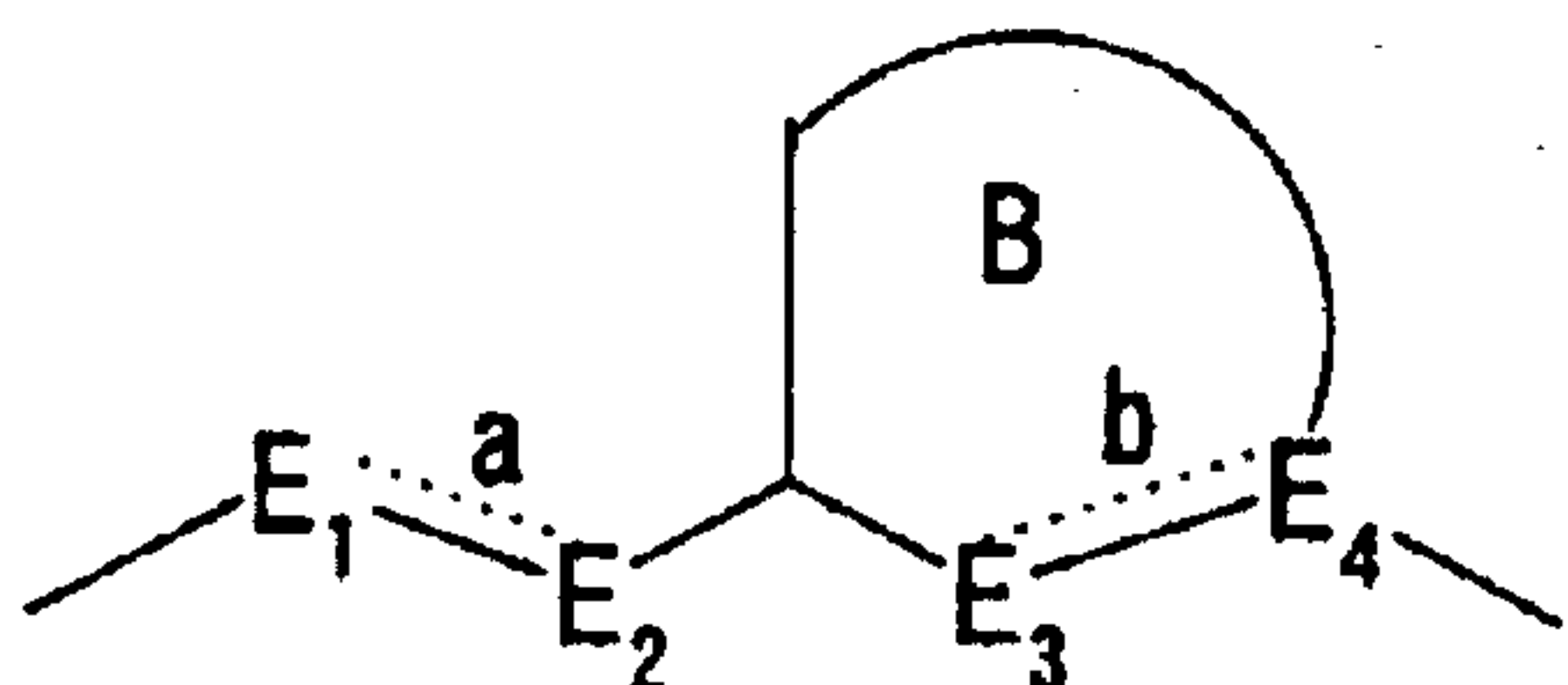
(35) Use of a compound represented by formula



15

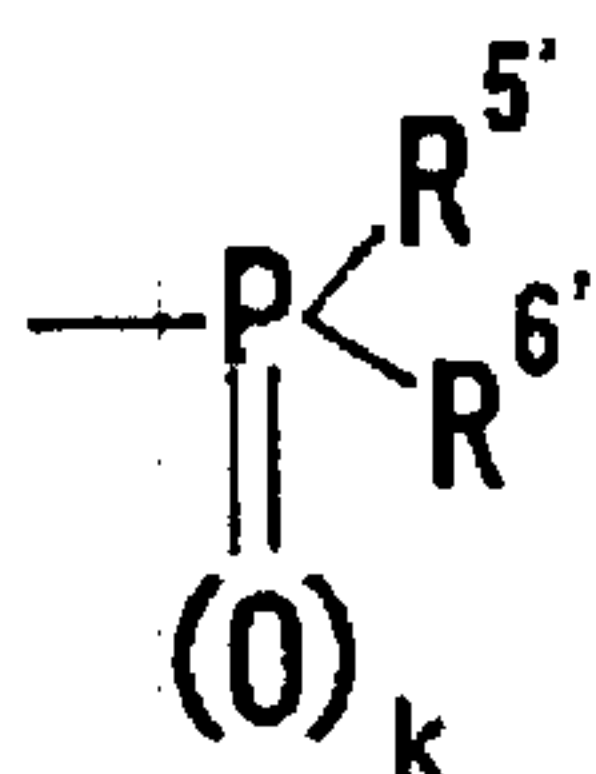
[wherein R^1 indicates a 5- to 6-membered cyclic ring group that may be substituted, X^1 indicates a bond or a bivalent group, in which the number of atoms constituting the straight-chain portion is 1 to 4, W indicates a bivalent group that is represented by formula

20



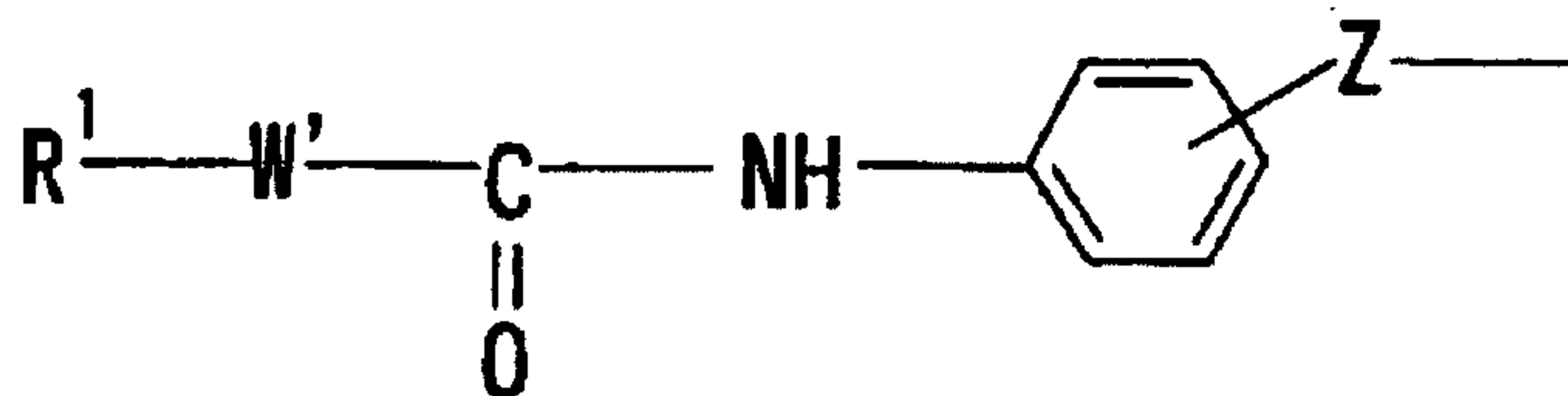
- 5 (wherein each of ring A and ring B indicates a 5- to 7-
 membered cyclic ring group that may be substituted, each of
 E₁ and E₄ indicates the carbon atom that may be substituted
 or the nitrogen atom that may be substituted, each of E₂
 and E₃ indicates the carbon atom that may be substituted or
 10 the nitrogen atom that may be substituted, the sulfur atom
 that may be oxidized or the oxygen atom and each of a and b
 indicates to be a single bond or a double bond), X²
 indicates a bivalent group, in which the number of atoms
 constituting the straight-chain portion is 1 to 4, Z¹
 15 indicates a bond or a bivalent cyclic ring group, Z²

indicates a bond or a bivalent cyclic ring group, in which the number of atoms constituting the straight-chain portion is 1 to 4, and R^2 indicates (1) an amino group that may be substituted, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide, (2) a nitrogen-containing, heterocyclic ring group that may be substituted and may contain the sulfur atom or the oxygen atom as a ring-constituting atom, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide, (3) a group that bonded via the sulfur atom, (4) a group represented by formula

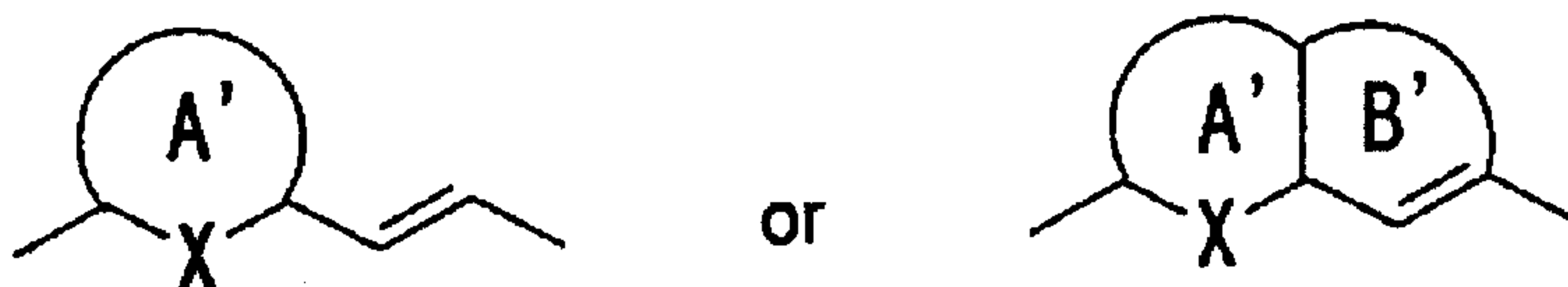


(wherein k indicates 0 or 1, the phosphorus atom may form a phosphonium salt when k is 0, and each of $R^{5'}$ and $R^{6'}$ indicates the hydrocarbon atom that may be substituted, the hydroxyl group that may be substituted or an amino group that may be substituted and $R^{5'}$ and $R^{6'}$ may bind each other to form a cyclic ring group together with the adjacent phosphorus atom), (5) an amidino group that may be substituted or (6) a guanidino group that may be substituted] [provided that, when a group represented by formula $R^1-X^1-W-X^2-Z^1-Z^2-$ indicates a group represented by

formula



- 5 (wherein R¹ indicates the same meaning as described above, W' indicates a bivalent group represented by formula



- 10 (wherein ring A' indicates a 5- to 6-membered aromatic ring that may be substituted, X indicates the carbon atom that may be substituted, the nitrogen atom that may be substituted, the sulfur atom or the oxygen atom and ring B' indicates a 5- to 7-membered ring that may be substituted)
- 15 and Z indicates a bivalent group, in which the number of atoms constituting the straight-chain portion is 1 to 4), R² indicates an amidino group that may be substituted or a guanidino group that may be substituted], or salts thereof,
- 20 together with a protease inhibitor and/or a reverse transcriptase inhibitor for preventing and/or treating HIV infectious diseases;

(36) A method for antagonizing CCR (preferably, a method for antagonizing CCR5), which comprises administering an effective dose of the compound or a salt thereof as described in the above-mentioned item (28) to the mammals;

(37) Use of the compound or a salt thereof as described in the above-mentioned item (28) for manufacturing a medicine for the CCR antagonism (preferably, the CCR5 antagonism); and the like.

10

"A 5- to 6-membered cyclic ring" of "a 5- to 6-membered cyclic ring group that may be substituted", which is indicated by R^1 in the above-mentioned formula (I), is exemplified by a group that is formed by removing one hydrogen atom from a 6-membered aromatic hydrocarbon such as benzene or the like, a 5- to 6-membered aliphatic hydrocarbon such as cyclopentane, cyclohexane, cyclopentene, cyclohexene, cyclopentadiene, cyclohexadiene or the like, a 5- to 6-membered, aromatic heterocyclic ring, which contains 1 to 4 heteroatoms of 1 to 2 kinds selected from the nitrogen atom, the sulfur atom and the oxygen atom, such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole or the like, a 5- to 6-membered, non-aromatic heterocyclic ring,

which contains 1 to 4 heteroatoms of 1 to 2 kinds selected from the nitrogen atom, the sulfur atom and the oxygen atom, such as tetrahydrofuran, tetrahydrothiophene, dithiolan, oxathiolan, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran, tetrahydropyran, tetrahydrothiopyran or the like, or the like, where as for "a 5- to 6-membered cyclic ring" is preferably benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, tetrahydropyran (preferably, a 6-membered cyclic ring) or the like, particularly benzene.

Examples of "a substituent" that may be possessed by "a 5- to 6-membered cyclic ring" of "a 5- to 6-membered cyclic ring group that may be substituted", which is indicated by R^1 in the above-mentioned formula (I), to be used include a halogen atom, nitro, cyano, an alkyl that may be substituted, a cycloalkyl that may be substituted, the hydroxyl group that may be substituted, the thiol group that may be substituted (the sulfur atom may be oxidized to form a sulfinyl group that may be substituted or a sulfonyl group that may be substituted), an amino group that may be substituted, an acyl that may be substituted, the carboxyl group that may be substituted, an aromatic group that may

be substituted and the like.

A halogen as a substituent of R^1 is exemplified by fluorine, chlorine, bromine, iodine or the like, where fluorine and chlorine are particularly preferable.

5 An alkyl for an alkyl that may be substituted as a substituent of R^1 is exemplified by a straight-chain or branched alkyl having a carbon number of 1 to 10, for example, a C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 10 isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl or the like, preferably a lower (C_{1-6}) alkyl. A substituent in said alkyl that may be substituted is exemplified by a halogen (for example, fluorine, chlorine, bromine, iodine or the like), nitro, cyano, the hydroxyl group, the thiol 15 group that may be substituted (for example, thiol, a C_{1-4} alkylthio or the like), an amino group that may be substituted (for example, amino, a mono- C_{1-4} alkylamino, a di- C_{1-4} alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, 20 morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C_{1-4} alkoxycarbonyl, carbamoyl, a mono- C_{1-4} alkylcarbamoyl, a di- C_{1-4} alkylcarbamoyl or the like), a C_{1-4} alkoxyl that may be 25 halogenated (for example, methoxy, ethoxy, propoxy, butoxy,

trifluoromethoxy, trifluoroethoxy or the like), a C₁₋₄ alkoxy-C₁₋₄ alkoxyl that may be halogenated (for example, methoxymethoxy, methoxyethoxy, ethoxyethoxy, trifluoromethoxyethoxy, trifluoroethoxyethoxy or the like),
5 formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like) or the like, where the number of the substituents is preferably 1 to 3.

A cycloalkyl for a cycloalkyl that may be
10 substituted as a substituent of R¹ is exemplified by, for example, a C₃₋₇ cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like. A substituent in said cycloalkyl that may be substituted is exemplified by a halogen (for example, fluorine, chlorine,
15 bromine, iodine or the like), nitro, cyano, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 6-membered cyclic
20 ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-
25 C₁₋₄ alkylcarbamoyl or the like), a C₁₋₄ alkoxyl that may be

halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like), a C₁₋₄ alkoxy-C₁₋₄ alkoxyl that may be halogenated (for example, methoxymethoxy, methoxyethoxy, ethoxyethoxy, trifluoromethoxyethoxy, trifluoroethoxyethoxy or the like), formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like) or the like, where the number of the substituents is preferably 1 to 3.

A substituent for the hydroxyl group that may be substituted as a substituent of R¹ is exemplified by a substituent such as (1) an alkyl that may be substituted (for example, a C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl or the like, preferably a lower (C₁₋₆) alkyl, or the like is exemplified);

(2) a cycloalkyl that may be substituted and may contain heteroatoms (for example, a C₃₋₇ cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like; a saturated, 5- to 6-membered heterocyclic ring group containing 1 to 2 heteroatoms such as tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrazolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydrothiopyranyl

or the like (preferably, tetrahydropyranyl or the like); or the like is exemplified);

(3) an alkenyl that may be substituted (for example, an alkenyl that has the carbon number of 2 to 10 such as allyl, 5 crotyl, 2-pentenyl, 3-hexenyl or the like, preferably a lower (C_{2-6}) alkenyl, or the like is exemplified);

(4) a cycloalkenyl that may be substituted (for example, an cycloalkenyl that has the carbon number of 3 to 7 such as 2-cyclopentenyl, 2-cyclohexenyl 2-cyclopentenylmethyl, 2- 10 cyclohexenylmethyl or the like, or the like is exemplified);

(5) an aralkyl that may be substituted (for example, a phenyl- C_{1-4} alkyl (for example, benzyl, phenethyl or the like) or the like is exemplified);

15 (6) formyl or an acyl that may be substituted (for example, an alkanoyl that has the carbon number of 2 to 4 (for example, acetyl, propionyl, butyryl, isobutyryl or the like), an alkylsulfonyl that has the carbon number of 1 to 4 (for example, methanesulfonyl, ethanesulfonyl or the 20 like) or the like is exemplified); and

(7) an aryl that may be substituted (for example, phenyl, naphthyl or the like is exemplified),

where examples of the substituents that may be possessed by

(1) an alkyl that may be substituted, (2) a cycloalkyl that 25 may be substituted, (3) an alkenyl that may be substituted,

(4) a cycloalkenyl that may be substituted, (5) an aralkyl that may be substituted, (6) an acyl that may be substituted and (7) an aryl that may be substituted, which are described above, include a halogen (for example, 5 fluorine, chlorine, bromine, iodine or the like), nitro, cyano, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 10 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, 15 a di-C₁₋₄ alkylcarbamoyl or the like), a C₁₋₄ alkyl that may be halogenated (for example, trifluoromethyl, methyl, ethyl or the like), a C₁₋₆ alkoxy that may be halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like; preferably, a C₁₋₄ alkoxy that 20 may be halogenated), formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like), a 5- to 6-membered, aromatic heterocyclic ring that may be substituted [for example, an aromatic heterocyclic ring, 25 which contains 1 to 4 heteroatoms of 1 to 2 kinds selected

from the nitrogen atom, the sulfur atom and the oxygen atom, such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole or the like; the substituent that may be possessed by said heteroaromatic ring is exemplified by a halogen (for example, fluorine, chlorine, bromine, iodine or the like), nitro, cyano, the hydroxyl group, the thiol group, an amino group, the carboxyl group, a C₁₋₄ alkyl that may be halogenated (for example, trifluoromethyl, methyl, ethyl or the like), a C₁₋₆ alkoxyl that may be halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like), formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like), where the number of the substituents is preferably 1 to 3.], or the like, where the number of the substituents is preferably 1 to 3.

A substituent for the thiol group that may be substituted as a substituent of R¹ is exemplified by a substituent similar to "a substituent for the hydroxyl group that may be substituted as a substituent of R^{1''}", among which preferable is

(1) an alkyl that may be substituted (for example, a C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl,

isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl or the like, preferably a lower (C_{1-6}) alkyl, or the like is exemplified);

5 (2) a cycloalkyl that may be substituted and may contain heteroatoms (for example, a C_{3-7} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like is exemplified);

(3) an aralkyl that may be substituted (for example, a
10 phenyl- C_{1-4} alkyl (for example, benzyl, phenethyl or the like) or the like is exemplified); and

(4) an aryl that may be substituted (for example, phenyl, naphthyl or the like is exemplified),

where examples of the substituents that may be possessed by

15 (1) an alkyl that may be substituted, (2) a cycloalkyl that may be substituted, (3) an aralkyl that may be substituted and (4) an aryl that may be substituted, which are described above, include a halogen (for example, fluorine, chlorine, bromine, iodine or the like), nitro, cyano, the
20 hydroxyl group, the thiol group that may be substituted (for example, thiol, a C_{1-4} alkylthio or the like), an amino group that may be substituted (for example, amino, a mono- C_{1-4} alkylamino, a di- C_{1-4} alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine,
25 piperidine, morpholine, thiomorpholine, pyrrole, imidazole

or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxy-carbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-C₁₋₄ alkylcarbamoyl or the like), a C₁₋₄ alkoxy that may be
5 halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like), a C₁₋₄ alkoxy-C₁₋₄ alkoxy that may be halogenated (for example, methoxymethoxy, methoxyethoxy, ethoxyethoxy, trifluoromethoxyethoxy, trifluoroethoxyethoxy or the like),
10 formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like), where the number of the substituents is preferably 1 to 3.

A substituent for an amino group that may be
15 substituted as a substituent of R¹ is exemplified by an amino group that may have 1 to 2 substituents similar to "a substituent for the hydroxyl group that may be substituted as a substituent of R^{1''}", among which preferable is (1) an alkyl that may be substituted (for example, a C₁₋₁₀ alkyl
20 such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl or the like, preferably a lower (C₁₋₆) alkyl, or the like is exemplified);
(2) a cycloalkyl that may be substituted and may contain
25 heteroatoms (for example, a C₃₋₇ cycloalkyl such as

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like);

(3) an alkenyl that may be substituted (for example, an alkenyl that has the carbon number of 2 to 10 such as allyl, crotyl, 2-pentenyl, 3-hexenyl or the like, preferably a lower (C_{2-6}) alkenyl, or the like is exemplified);

(4) a cycloalkenyl that may be substituted (for example, an cycloalkenyl that has the carbon number of 3 to 7 such as 2-cyclopentenyl, 2-cyclohexenyl 2-cyclopentenylmethyl, 2-cyclohexenylmethyl or the like, or the like is exemplified);

(5) formyl, or an acyl that may be substituted (for example, an alkanoyl that has the carbon number of 2 to 4 (for example, acetyl, propionyl, butyryl, isobutyryl or the like), an alkylsulfonyl that has the carbon number of 1 to 4 (for example, methanesulfonyl, ethanesulfonyl or the like) or the like is exemplified); and

(6) an aryl that may be substituted (for example, phenyl, naphthyl or the like is exemplified),

where examples of the substituents that may be possessed by

(1) an alkyl that may be substituted, (2) a cycloalkyl that may be substituted, (3) an alkenyl that may be substituted, (4) a cycloalkenyl that may be substituted, (5) an acyl that may be substituted and (6) an aryl that may be substituted, which are described above, include a halogen

(for example, fluorine, chlorine, bromine, iodine or the like), nitro, cyano, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxy-carbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-C₁₋₄ alkylcarbamoyl or the like), a C₁₋₆ alkoxy that may be halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like), formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like), where the number of the substituents is preferably 1 to 3.

Also, as for the substituents for an amino group that may be substituted as a substituent of R¹, the substituents for the amino group may bind together to form a cyclic ring amino group (for example, a cyclic ring amino group that is formed by removing one hydrogen from the nitrogen atom constituting the ring of a 5- to 6-membered cyclic ring such as tetrahydropyrrole, piperazine,

piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, and has a bond on the nitrogen atom). Said cyclic ring amino group may have substituents, and such substituents are exemplified by a halogen (for example, 5 fluorine, chlorine, bromine, iodine or the like), nitro, cyano, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 10 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, 15 a di-C₁₋₄ alkylcarbamoyl or the like), a C₁₋₆ alkoxy that may be halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like), a C₁₋₄ alkoxy-C₁₋₄ alkoxy that may be halogenated (for example, methoxymethoxy, methoxyethoxy, ethoxyethoxy, 20 trifluoromethoxyethoxy, trifluoroethoxyethoxy or the like), formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like), where the number of the substituents is preferably 1 to 3.

25 An acyl that may be substituted as a substituent

of R¹ is exemplified by a group, wherein the carbonyl group or the sulfonyl group is bonded with

(1) hydrogen,

(2) an alkyl that may be substituted (for example, a C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl or the like, preferably a lower (C₁₋₆) alkyl, or the like is exemplified);

(3) a cycloalkyl that may be substituted and may contain heteroatoms (for example, a C₃₋₇ cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like);

(4) an alkenyl that may be substituted (for example, an alkenyl that has the carbon number of 2 to 10 such as allyl, crotyl, 2-pentenyl, 3-hexenyl or the like, preferably a lower (C₂₋₆) alkenyl, or the like is exemplified);

(5) a cycloalkenyl that may be substituted (for example, a cycloalkenyl that has the carbon number of 3 to 7 such as 2-cyclopentenyl, 2-cyclohexenyl 2-cyclopentenylmethyl, 2-cyclohexenylmethyl or the like, or the like is exemplified); or

(6) a 5- to 6-membered, monocyclic ring aromatic group (for example, phenyl, pyridyl or the like is exemplified) that is bonded with the carbonyl group or the sulfonyl group,

(for example, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl, nicotinoyl, methanesulfonyl, ethanesulfonyl or the like), where examples of the substituents that may be possessed by (2) an alkyl that may be substituted, (3) a cycloalkyl that may be substituted, (4) an alkenyl that may be substituted, (5) a cycloalkenyl that may be substituted and (6) a 5- to 6-membered, monocyclic ring aromatic group that may be substituted, which are described above, include a halogen (for example, fluorine, chlorine, bromine, iodine or the like), nitro, cyano, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-C₁₋₄ alkylcarbamoyl or the like), a C₁₋₆ alkoxy that may be halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like), a

C₁₋₄ alkoxy-C₁₋₄ alkoxyl that may be halogenated (for example, methoxymethoxy, methoxyethoxy, ethoxyethoxy, trifluoromethoxyethoxy, trifluoroethoxyethoxy or the like), formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like), where the number of the substituents is preferably 1 to 3.

The carbonyl group that may be esterified as a substituent of R¹ is exemplified by a group, wherein the carbonyloxy group is bonded with

- (1) hydrogen,
- (2) an alkyl that may be substituted (for example, a C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl or the like, preferably a lower (C₁₋₆) alkyl, or the like is exemplified);
- (3) a cycloalkyl that may be substituted and may contain heteroatoms (for example, a C₃₋₇ cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like);
- (4) an alkenyl that may be substituted (for example, an alkenyl that has the carbon number of 2 to 10 such as allyl, crotyl, 2-pentenyl, 3-hexenyl or the like, preferably a lower (C₂₋₆) alkenyl, or the like is exemplified);

(5) a cycloalkenyl that may be substituted (for example, an cycloalkenyl that has the carbon number of 3 to 7 such as 2-cyclopentenyl, 2-cyclohexenyl 2-cyclopentenylmethyl, 2-cyclohexenylmethyl or the like, or the like is exemplified); or

(6) an aryl that may be substituted (for example, phenyl, naphthyl or the like is exemplified), preferably carboxyl, a lower (C_{1-6}) alkoxycarbonyl and an aryloxycarbonyl (for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, phenoxycarbonyl, naphthoxycarbonyl or the like), where examples of the substituents that may be possessed by (2) an alkyl that may be substituted, (3) a cycloalkyl that may be substituted, (4) an alkenyl that may be substituted, (5) a cycloalkenyl that may be substituted and (6) an aryl that may be substituted, which are described above, include a halogen (for example, fluorine, chlorine, bromine, iodine or the like), nitro, cyano, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C_{1-4} alkylthio or the like), an amino group that may be substituted (for example, amino, a mono- C_{1-4} alkylamino, a di- C_{1-4} alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C_{1-4} alkoxycarbonyl,

carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-C₁₋₄ alkylcarbamoyl or the like), a C₁₋₆ alkoxy that may be halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like), a C₁₋₄ alkoxy-C₁₋₄ alkoxy that may be halogenated (for example, methoxymethoxy, methoxyethoxy, ethoxyethoxy, trifluoromethoxyethoxy, trifluoroethoxyethoxy or the like), formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like), where the number of the substituents is preferably 1 to 3.

The aromatic group for an aromatic group that may be substituted as a substituent of R¹ is exemplified by a 5- to 6-membered, same element or heterocyclic ring, aromatic group such as phenyl, pyridyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isooxazolyl, tetrazolyl, pirazinyl, pyrimidinyl, pyridazinyl, triazinyl or the like, a condensed, heterocyclic ring aromatic group such as benzofuran, indole, benzothiophene, benzoxazole, benzthiazole, indazole, benzimidazole, quinoline, isoquinoline, quinoxaline, phthalazine, quinazoline, cinnoline or the like, or the like. Examples of the substituents for these aromatic groups include a halogen (for example, fluorine, chlorine, bromine, iodine or the

like), nitro, cyano, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-C₁₋₄ alkylcarbamoyl or the like), a C₁₋₄ alkyl that may be halogenated (for example, trifluoromethyl, methyl, ethyl or the like), a C₁₋₆ alkoxy that may be halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like), formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like), where the number of the substituents is preferably 1 to 3.

Such a substituent of R¹ may be substituted at any position of 1 to 4 (preferably, 1 to 2) of the same or different cyclic rings. Also, in the case where "a 5- to 6-membered cyclic ring" of "a 5- to 6-membered cyclic ring that may be substituted", which is indicated by R¹, has 2 or more substituents, 2 substituents of them may be bonded

together to form, for example, a lower (C_{1-6}) alkylene (for
 example, trimethylene, tetramethylene or the like), a lower
 (C_{1-6}) alkyleneoxy (for example, $-CH_2-O-CH_2-$, $-O-CH_2-CH_2-$, $-$
 $O-CH_2-CH_2-CH_2-$, $-O-CH_2-CH_2-CH_2-CH_2-$, $-O-C(CH_3)(CH_3)-CH_2-CH_2-$ or
 5 the like), a lower (C_{1-6}) alkylenethio (for example, $-CH_2-S-$
 CH_2- , $-S-CH_2-CH_2-$, $-S-CH_2-CH_2-CH_2-$, $-S-CH_2-CH_2-CH_2-CH_2-$, $-S-$
 $C(CH_3)(CH_3)-CH_2-CH_2-$ or the like), a lower (C_{1-6})
 alkylenedioxy (for example, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-O-$
 $CH_2-CH_2-CH_2-O-$ or the like), a lower (C_{1-6}) alkylenedithio
 10 (for example, $-S-CH_2-S-$, $-S-CH_2-CH_2-S-$, $-S-CH_2-CH_2-CH_2-S-$ or
 the like), an oxy-lower (C_{1-6}) alkylenamino (for example, $-$
 $O-CH_2-NH-$, $-O-CH_2-CH_2-NH-$ or the like), an oxy-lower (C_{1-6})
 alkylenethio (for example, $-O-CH_2-S-$, $-O-CH_2-CH_2-S-$ or the
 like), a lower (C_{1-6}) alkylenamino (for example, $-NH-CH_2-CH_2-$,
 15 $-NH-CH_2-CH_2-CH_2-$ or the like), a lower (C_{1-6}) alkylenediamino
 (for example, $-NH-CH_2-NH-$, $-NH-CH_2-CH_2-NH-$ or the like), a
 thia-lower (C_{1-6}) alkylenamino (for example, $-S-CH_2-NH-$, $-S-$
 CH_2-CH_2-NH- or the like), a lower (C_{2-6}) alkenylene (for
 example, $-CH_2-CH=CH-$, $-CH_2-CH_2-CH=CH-$, $-CH_2-CH=CH-CH_2-CH_2-$ or
 20 the like), a lower (C_{4-6}) alkadienylene (for example, $-$
 $CH=CH-CH=CH-$ or the like) or the like.

Furthermore, the bivalent group that is formed by
 binding each other 2 substituents of R^1 may have 1 to 3
 substituents similar to "the substituent" that may be
 25 possessed by "a 5- to 6-membered cyclic ring" of "a 5- to

6-membered cyclic ring that may be substituted", which is indicated by R^1 , (a halogen atom, nitro, cyano, an alkyl that may be substituted, a cycloalkyl that may be substituted, the hydroxyl group that may be substituted, the thiol group that may be substituted (the sulfur atom may be oxidized to form a sulfinyl group that may be substituted or a sulfonyl group that may be substituted), an amino group that may be substituted, an acyl that may be substituted, the carboxyl group that may be esterified or amidated, an aromatic group that may be substituted and the like).

"The substituent" that may be possessed by "a 5- to 6-membered cyclic ring" of "a 5- to 6-membered cyclic ring that may be substituted", which is indicated by R^1 , is exemplified particularly by a lower (C_{1-4}) alkyl that may be halogenated or alkoxyated with a lower (C_{1-4}) (for example, methyl, ethyl, t-butyl, trifluoromethyl, methoxymethyl, ethoxymethyl, propoxymethyl, butoxymethyl, methoxyethyl, ethoxyethyl, propoxyethyl, butoxyethyl, or the like), a lower (C_{1-4}) alkoxy that may be halogenated or alkoxyated with a lower (C_{1-4}) (for example, methoxy, ethoxy, propoxy, butoxy, t-butoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, propoxymethoxy, butoxymethoxy, methoxyethoxy, ethoxymethoxy, propoxyethoxy, butoxyethoxy, methoxypropoxy, ethoxypropoxy, propoxypropoxy, butoxypropoxy or the like),

a halogen (for example, fluorine, chlorine or the like),
nitro, cyano, an amino group that may be substituted with 1
to 2 of a lower (C_{1-4}) alkyl, formyl or a lower (C_{1-4})
alkanoyl (for example, amino, methylamino, dimethylamino,
5 formylamino, acetylamino or the like), a 5- to 6-membered
cyclic ring amino group (for example, 1-pyrrolidinyl, 1-
piperazinyl, 1-piperidinyl, 4-morpholino, 4-thiomorpholino,
1-imidazolyl, 4-tetrahydropyranyl or the like) or the like.

"A bivalent group, in which the number of atoms
10 constituting the straight-chain portion is 1 to 4",
indicated by X^1 and X^2 , is exemplified by, for example, -
(CH_2)_a-, [a' indicates an integer of 1 to 4 (preferably, an
integer of 1 to 2)], -(CH_2)_b-, X^3 -, [b' indicates an integer
of 0 to 3 (preferably, an integer of 0 to 1) and X^3
15 indicates an imino group that may be substituted (for
example, an imino group that may be substituted with a
lower (C_{1-6}) lower alkyl, a lower (C_{3-7}) cycloalkyl, formyl,
a lower (C_{2-7}) lower alkanoyl, a lower (C_{1-6}) lower
alkoxycarbonyl or the like), the carbonyl group, the oxygen
20 atom, the sulfur atom that may be oxidized by the oxygen
atom (for example, -S(O)_m- (m indicates an integer of 0 to
2) or the like)], -CH=CH-, -C≡C-, -CO-NH-, -SO₂-NH- or the
like. Although these groups may be bonded with W through
either of the left or right bond, it is preferable to be
25 bonded with W through the right hand in the case of X^1 ,

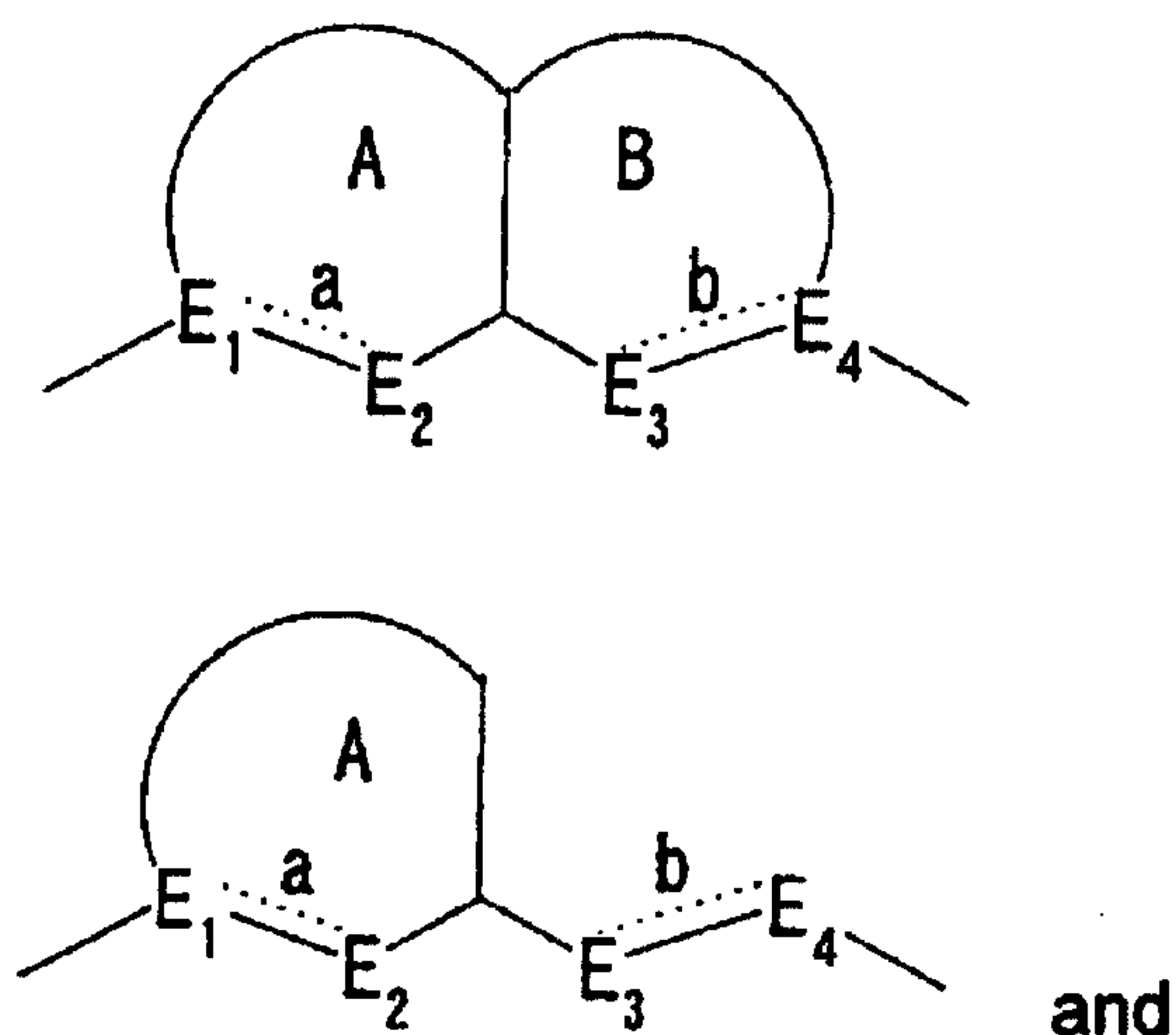
whereas it is preferable to be bonded with W through the left hand in the case of X^2 .

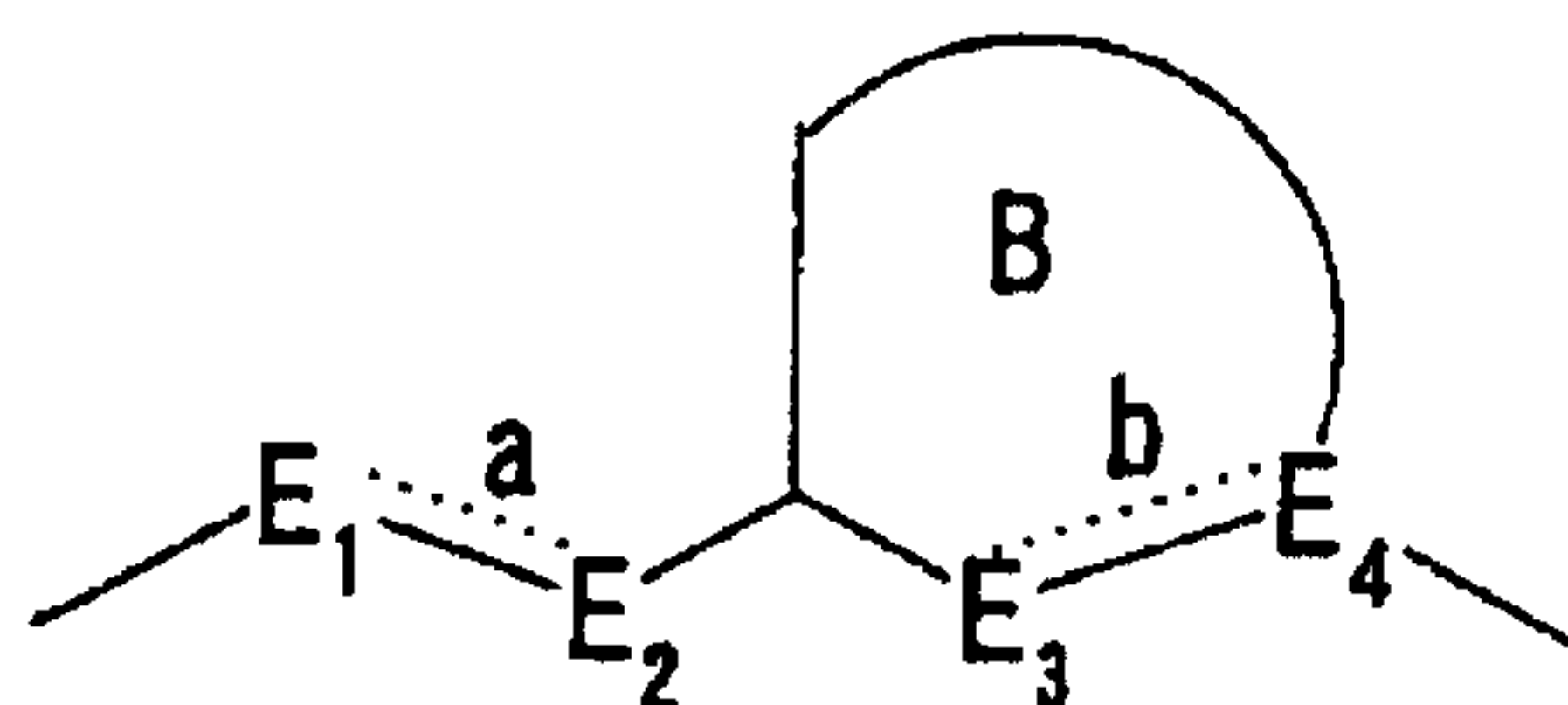
As for X^1 , a bond, $-(CH_2)_{b'}-O-$ [b' indicates an integer of 0, 1 or 2 (preferably, an integer of 0 to 1), $-C\equiv C-$ or the like is preferable, and a bond is more preferable.

As for X^2 , $-(CH_2)_{a'}-$ [a' indicates an integer of 1 to 2], $-(CH_2)_{b'}-X^3-$ [b' indicates an integer of 0 to 1 and X^3 indicates an imino group that may be substituted, the carbonyl group, the oxygen atom, the sulfur atom that may be oxidized by the oxygen atom], $-CH=CH-$, $-CO-NH-$, $-SO_2-NH-$ or the like is preferable, and $-CO-NH-$ is more preferable.

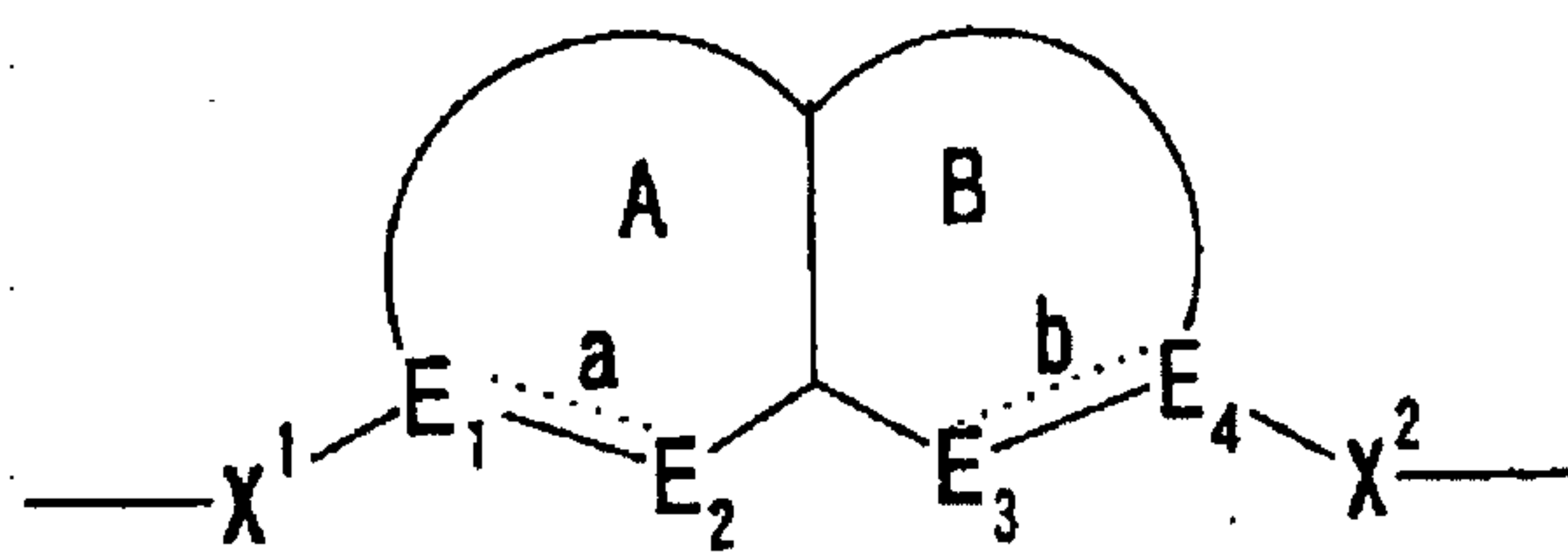
In the above-mentioned formula (I), a bivalent group that is represented by formula indicated by W

15

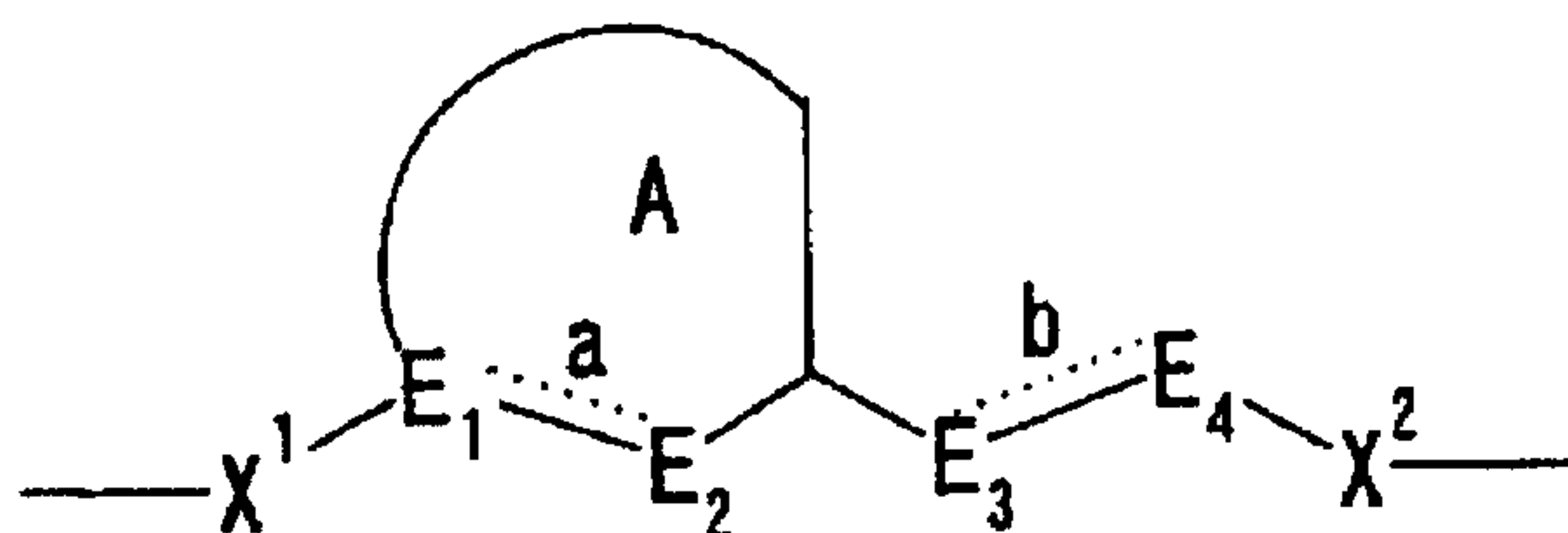




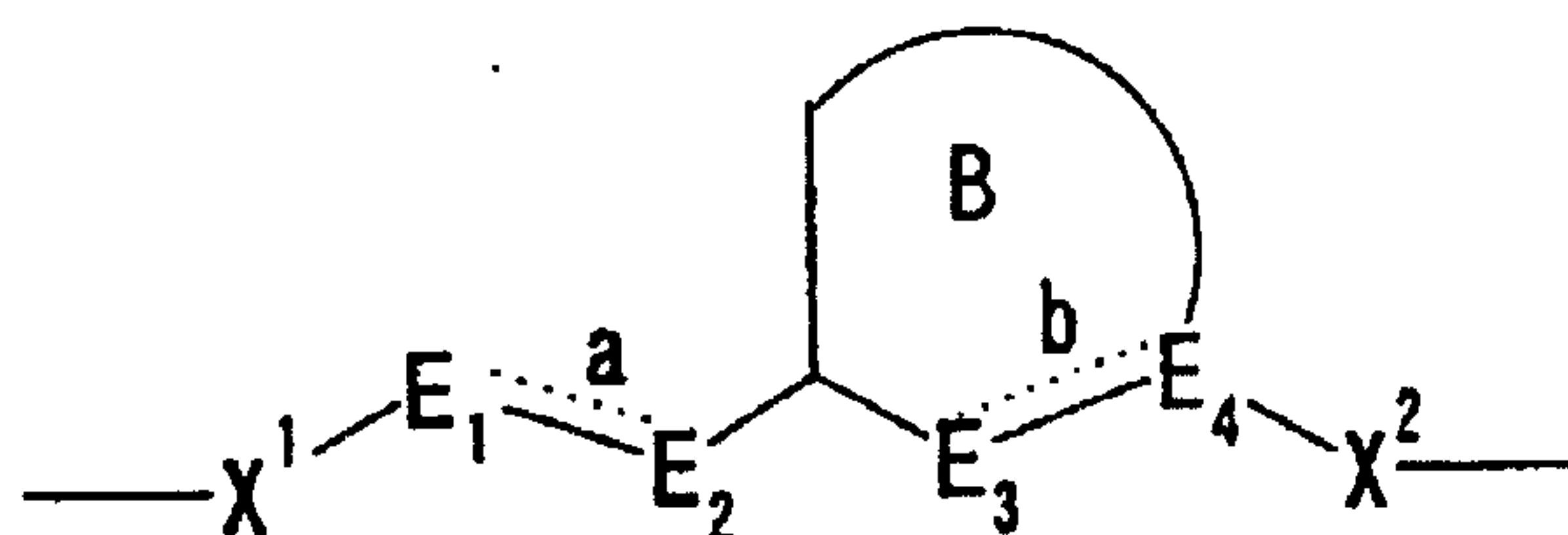
(wherein each of ring A and ring B indicates a 5- to 7-
 membered cyclic ring group that may be substituted, each of
 5 E₁ and E₄ indicates the carbon atom that may be substituted
 or the nitrogen atom that may be substituted, each of E₂
 and E₃ indicates the carbon atom that may be substituted or
 the nitrogen atom that may be substituted, the sulfur atom
 that may be oxidized (for example, -S(O)_m- (m indicates an
 10 integer of 0 to 2) or the like) or the oxygen atom and each
 of a and b indicates to be a single bond or a double bond)
 indicates that the bonding with adjacent X¹ and X² is made
 in a mode that is shown respectively by



15



and



(wherein each of the symbols has the same meaning as that described hereinabove).

5 In the above-mentioned formula (I), "a 5- to 7-membered cyclic ring" of "a 5- to 7-membered cyclic ring that may be substituted", which is indicated by A, is exemplified by a 5- to 7-membered (preferably, 5- to 6-membered, saturated or unsaturated alicyclic hydrocarbon
10 such as a C₅₋₇ cycloalkane (for example, cyclopentane, cyclohexane, cycloheptane or the like), a C₅₋₇ cycloalkene (for example, 1-cyclopentene, 2-cyclopentene, 3-cyclopentene, 2-cyclohexene, 3-cyclohexene or the like), a C₅₋₆ cycloalkadiene (for example, 2,4-cyclopentadiene, 2,4-cyclohexadiene, 2,5-cyclohexadiene or the like); a 6-
15 membered aromatic hydrocarbon such as benzene; a 5- to 7-membered, aromatic heterocyclic ring, a saturated or unsaturated non-aromatic heterocyclic ring (aliphatic heterocyclic ring) or the like, which contains at least one
20 (preferably, 1 to 4, more preferably 1 to 2) of heteroatoms of 1 to 3 kinds (preferably, 1 to 2 kinds) selected from the oxygen atom, the sulfur atom and the nitrogen atom; or

the like.

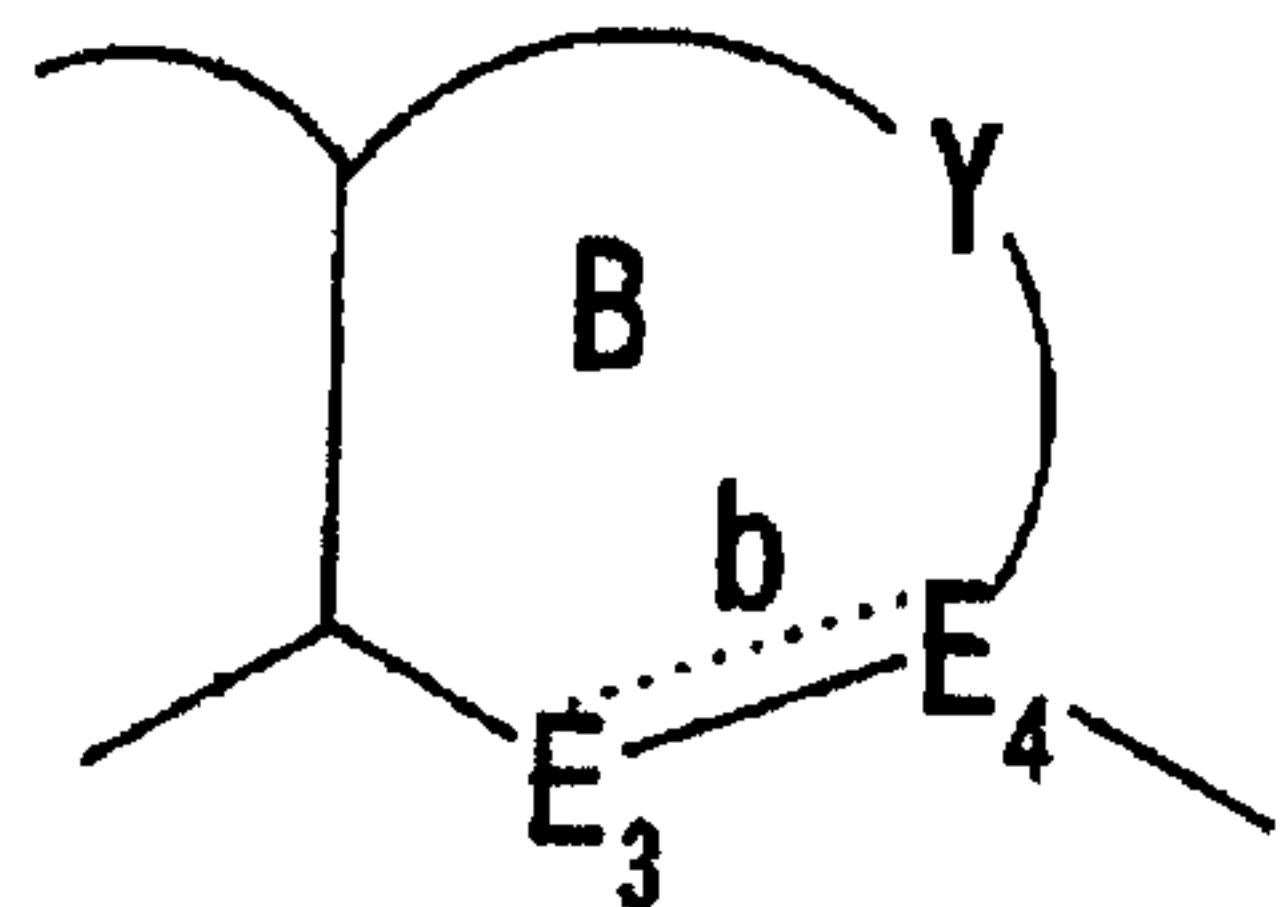
Herein, "an aromatic heterocyclic ring" is exemplified by a 5- to 7-membered, aromatic monocyclic, heterocyclic ring (for example, furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, furazane, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine or the like) or the like, and "a non-aromatic heterocyclic ring" is exemplified by, for example, a 5- to 7-membered (preferably, 5- to 6-membered), saturated or unsaturated non-aromatic heterocyclic ring (aliphatic heterocyclic ring) such as pyrrolidine, tetrahydrofuran, thiolan, piperidine, tetrahydropyran, morpholine, thiomorpholine, piperazine, pyran, oxepine, azepine or the like, a 5- to 6-membered, non-aromatic heterocyclic ring, where a part or all of the double bonds in the above-mentioned aromatic monocyclic heterocyclic ring are saturated, or the like.

As for "a 5- to 7-membered cyclic ring" of "a 5- to 7-membered cyclic ring that may be substituted", which is indicated by A, a 5- to 6-membered, aromatic ring is preferable, and further benzene, furan, thiophene, pyrrole, pyridine (preferably, 6-membered) or the like is preferable,

where benzene is particularly preferable.

"The substituent" that may be possessed by "a 5- to 7-membered cyclic ring" of "a 5- to 7-membered cyclic ring that may be substituted", which is indicated by A, is exemplified by a group similar to "the substituent" that may be possessed by "a 5- to 6-membered cyclic ring" of "a 5- to 6-membered cyclic ring that may be substituted", which is indicated by R^1 . Also, such a substituent for A may be substituted at any positions of 1 to 4 (preferably, 1 to 2) of the same or different rings, and the substituent may be possessed at any substitutable position, whether it is any of the positions that are indicated by E_1 and E_2 or any of other positions.

In the above-mentioned formula (I), "a 5- to 7-membered cyclic ring" of "a 5- to 7-membered cyclic ring that may be substituted", which is indicated by B, is exemplified by a 5- to 7-membered cyclic ring that may have substituents at optional, substitutable positions, which is represented by formula



or the like.

In the above-mentioned formula (I), the bivalent group that is indicated by Y indicates a bivalent group, with which ring B forms a 5- to 7-membered cyclic ring that may be substituted, and is exemplified by a bivalent group such as, for example,

(1) $-(CH_2)_{a1}-O-(CH_2)_{a2}-$ (each of $a1$ and $a2$ indicates 0, 1 or 2 in the same or different manner. Hereupon, the sum of $a1$ and $a2$ is 2 or less), $-O-(CH=CH)-$, $-(CH=CH)-O-$,

(2) $-(CH_2)_{b1}-S(O)_m-(CH_2)_{b2}-$ (m indicates an integer of 0 to 2, and each of $b1$ and $b2$ indicates 0, 1 or 2 in the same or different manner. Hereupon, the sum of $b1$ and $b2$ is 2 or less), $-S(O)_m-(CH=CH)-$, $-(CH=CH)-S(O)_m-$,

(3) $-(CH_2)_{d1}-$ ($d1$ indicates 0, 1 or 2), $-CH_2-(CH=CH)-$, $-(CH=CH)-CH_2-$, $-CH=CH-$, $-CH=$,

(4) $-(CH_2)_{e1}-NH-(CH_2)_{e2}-$ (each of $e1$ and $e2$ indicates 0, 1 or 2 in the same or different manner. Hereupon, the sum of $e1$ and $e2$ is 2 or less), $-NH-(CH=CH)-$, $-(CH=CH)-NH-$, $-(CH_2)_{e6}-(N=CH)-(CH_2)_{e7}-$, $-(CH_2)_{e7}-(CH=N)-(CH_2)_{e6}-$ (either of $e6$ and $e7$

indicates 0, and the other indicates 0 or 1), $-(CH_2)_{e8}-(N=N)-(CH_2)_{e9}-$ (either of $e8$ and $e9$ indicates 0, and the other indicates 0 or 1) or the like. Specifically, the bivalent group is exemplified by, for example, a bivalent group such as $-O-$, $-O-CH_2-$, $-O-CH_2-CH_2-$, $-O-(CH=CH)-$, $-S(O)_m-$ (m indicates an integer of 0 to 2), $-S(O)_m-CH_2-$ (m

indicates an integer of 0 to 2), $-S(O)_m-CH_2-$ (m

indicates an integer of 0 to 2), $-S(O)_m-CH_2-CH_2-$ (m indicates an integer of 0 to 2), $-S(O)_m-(CH=CH)-$, (m indicates an integer of 0 to 2), $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH=$, $-CH=CH-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-NH-$, $-N=CH-$, $-CH=N-$, $-N=N-$ (respectively, the bonding indicated starts from ring A) or the like.

In addition, said bivalent group may have a substituent, and said substituent is exemplified by a group similar to "the substituent" that may be possessed by "a 5- to 6-membered cyclic ring" of "a 5- to 6-membered cyclic ring that may be substituted", which is indicated by R^1 , oxo and the like, where a lower (C_{1-3}) alkyl (for example, methyl, ethyl, propyl or the like), phenyl, oxo, the hydroxyl group or the like is particularly preferable. Furthermore, said bivalent group may be $-O-C(O)-$ (the bonding indicated starts from ring A) or the like. The substituent for such a bivalent group may be substituted at any same or different positions of 1 to 4 (preferably, 1 to 2). The substituent position may be any position that is substitutable to said bivalent group.

As for the bivalent group that is indicated by Y, a group such as $-Y'-(CH_2)_{m'}-$ (Y' indicates $-S(O)_m-$ (m indicates an integer of 0 to 2), $-O-$, $-NH-$ or $-CH_2-$, and m' indicates an integer of 0 to 2), $-CH=$, $-CH=CH-$, $-N=CH-$, $-(CH_2)_{m'}-Y'-$ (Y' indicates $-S(O)_m-$ (m indicates an integer

of 0 to 2), -O-, -NH- or -CH₂-, and m' indicates an integer of 0 to 2), -CH=N- or the like, with starting the bonding indicated from ring A, is preferable, where a group such as -Y'-(CH₂)_{m'}- (Y' indicates -S(O)_m- (m indicates an integer of 0 to 2), -O-, -NH- or -CH₂-, and m' indicates an integer of 0 to 2), -CH=, -CH=CH-, -N=CH- or the like, with starting the bonding indicated from ring A, is more preferable, and a group (ring B indicates a 7-membered ring) such as -Y'-(CH₂)₂- (Y' indicates -S(O)_m- (m indicates an integer of 0 to 2), -O-, -NH- or -CH₂-), with starting the bonding indicated from ring A, is most preferable.

"The substituent" that may be possessed by "a 5- to 7-membered cyclic ring" of "a 5- to 7-membered cyclic ring that may be substituted", which is indicated by B, is exemplified by a group similar to "the substituent" that may be possessed by "a 5- to 6-membered cyclic ring" of "a 5- to 6-membered cyclic ring that may be substituted", which is indicated by R¹. Also, such a substituent for B may be substituted at any positions of 1 to 4 (preferably, 1 to 2) of the same or different rings, but it is preferable that the position of E₃ is unsubstituted.

In the above-mentioned formula (I), it is preferable that each of E₃ and E₄ is the carbon atom that may be substituted (preferably, the carbon atom that is not substituted), and b indicates a double bond.

In the above-mentioned formula (I), "a bivalent cyclic ring group" indicated by Z^1 is exemplified by a group that is formed by removing two hydrogen atoms from a group similar to "a 5- to 6-membered cyclic ring" of "a 5- to 6-membered cyclic ring that may be substituted", or the like, where a bivalent cyclic ring group, which is formed by removing two hydrogen atoms from benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine or tetrahydropyran, is more preferable, and a bivalent cyclic ring group, which is formed by removing two hydrogen atoms from benzene, cyclohexane or piperidine (preferably, benzene) is most preferably used.

"A bivalent cyclic ring group" indicated by Z^1 may have a substituent similar to "a substituent" that is possessed by "a 5- to 6-membered cyclic ring" of "a 5- to 6-membered cyclic ring that may be substituted", but it is preferable not to have a substituent other than X^2 and Z^2 , and also it is preferable that the substitution position for Z^2 is para to X^2 in the case where Z^1 is a 6-membered, bivalent cyclic ring group (preferably, phenylene).

In the above-mentioned formula (I), "a bivalent group, in which the number of atoms constituting the straight-chain portion is 1 to 4", which is indicated by Z^2 , is exemplified by a bivalent group that has a hydrocarbon

chain having the carbon number of 1 to 4, which may be substituted (for example, a C_{1-4} alkylene, a C_{2-4} alkenylene or the like, preferably a C_{1-3} alkylene, more preferably methylene), or the like.

5 A bivalent group, which is indicated by Z^2 , may be any group having a bivalent chain, in which the number of atoms constituting the straight-chain portion is 1 to 4, and is exemplified by, for example, an alkylene chain represented by $-(CH_2)_{k1}-$ ($k1$ is an integer of 1 to 4), an
10 alkenylene chain represented by $-(CH_2)_{k2}-(CH=CH)-(CH_2)_{k3}-$ (each of $k2$ and $k3$ indicates an integer of 1 to 4 in the same or different manner. Hereupon, the sum of $k2$ and $k3$ is 2 or less) or the like.

 A bivalent group, which is indicated by X^1 , X^2
15 and Z^2 , may have a substituent at an optional position (preferably, on the carbon atom), where such a substituent may be any one that is capable of being bonded to a bivalent chain constituting the straight-chain portion, is exemplified by, for example, a lower (C_{1-6}) alkyl (for
20 example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl or the like), a lower (C_{3-7}) cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like), formyl, a lower (C_{2-7}) alkanoyl
25 (for example, acetyl, propionyl, butyryl or the like), a

phosphono group that may be esterified, the carboxyl group that may be esterified, the hydroxyl group, oxo or the like, where preferably a lower alkyl having the carbon number of 1 to 6 (preferably a C₁₋₃ alkyl), the hydroxyl group, oxo or the like is exemplified.

Said phosphono group that may be esterified is exemplified by a group represented by $-P(O)(OR^7)(OR^8)$ [wherein each of R⁷ and R⁸ indicates hydrogen, an alkyl group having the carbon number of 1 to 6 or a cycloalkyl group having the carbon number of 3 to 7, and may be bonded together to form a 5- to 7-membered cyclic ring].

In the above-mentioned formula, an alkyl group having the carbon number of 1 to 6, which is represented by R⁷ and R⁸, is exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl or the like, and a cycloalkyl having the carbon number of 3 to 7 is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like), where a lower alkyl having the carbon number of 1 to 6 is exemplified preferably, and a lower alkyl having the carbon number of 1 to 3 is exemplified more preferably. R⁷ and R⁸ may be the same or different, but it is preferable to be the same. Also, in the case where R⁷ and R⁸ are bonded together to form a 5- to 7-membered cyclic ring, R⁷ and R⁸ are bonded together to

form a straight-chained C_{2-4} alkylene side chain represented by $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$. Said side chain may have substituents, and such a substituent is exemplified by, for example, the hydroxyl group, a halogen or the like.

5 The carboxyl group, which is esterified for the carboxyl group that may be esterified, is exemplified by a group, wherein the carboxyl group is bonded with an alkyl group having the carbon number of 1 to 6 or a cycloalkyl having the carbon number of 3 to 7, such as methoxycarbonyl,
10 ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl or the like.

 A bivalent group, which is indicated by Z^2 , is
15 exemplified by a C_{1-3} alkylene that may be substituted, where a C_{1-3} alkylene that may be substituted with a C_{1-3} alkyl, the hydroxyl group or oxo is more preferable.

 Furthermore, as for a bivalent group, which is indicated by Z^2 , a group represented by $-Z'-(CH_2)_n-$ or $-(CH_2)_n-Z'-$ (Z' indicates $-CH(OH)-$, $-C(O)-$ or $-CH_2-$, n indicates an integer of 0 to 2 and each methylene group may have 1 to 2 groups of the same or different substituent),
20 with starting from the benzene ring, is preferable, a group represented by $-Z'-(CH_2)_n-$ (Z' indicates $-CH(OH)-$, $-C(O)-$ or $-CH_2-$, n indicates an integer of 0 to 2 (preferably, n
25 or $-CH_2-$, n indicates an integer of 0 to 2 (preferably, n

indicates 0) and each methylene group may have 1 to 2 groups of the same or different substituents), with starting from the benzene ring, is more preferable and methylene is most preferable.

5 In the above-mentioned formula (I), "an amino group" of "an amino group that may be substituted, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide" indicated by R^2 , is exemplified by an amino group that may have 1 to 2 substituents, an amino
10 group that has 4 substituents, where the nitrogen atom may be converted into a quaternary ammonium, or the like. In the case where the substituents on the nitrogen atom are 2 or more, these substituents may be the same or different, and in the case where the substituents on the nitrogen atom
15 are 3, the amino group may be of any type of $-N^+R_3$, $-N^+R_2R'$, $-N^+RR'R''$ (each of R, R' and R'' indicates hydrogen or a substituent in a different manner). In addition, a counter anion for the amino group, in which the nitrogen atom is converted into a quaternary ammonium, is exemplified by, in
20 addition to an anion of a halogen atom (for example, Cl^- , Br^- , I^- or the like) or the like, an anion derived from an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, an anion derived from an organic acid such as formic acid,
25 acetic acid, trifluoroacetic acid, fumaric acid, oxalic

acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like and an anion derived from an acidic amino acid such as aspartic acid, glutamic acid and the like, where Cl^- , Br^- , I^- or the like is more preferable.

Examples of substituents for said amino group include substituents such as,

- (1) an alkyl that may be substituted (for example, a C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl or the like, preferably a lower (C_{1-6}) alkyl or the like is exemplified);
- (2) a cycloalkyl that may be substituted and may contain heteroatoms (for example, a C_{3-7} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like is exemplified);
- (2-1) said cycloalkyl contains one heteroatom selected from the sulfur atom, the oxygen atom and the nitrogen atom, and may form oxirane, thiolan, aziridine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydropyran, tetrahydrothiopyran, tetrahydrothiopyran 1-oxide, piperidine or the like (preferably, a 6-membered ring such as tetrahydropyran, tetrahydrothiopyran, piperidine or the like), where the binding position with the amino group is

preferably position 3 or position 4 (preferably, position 4);

(2-2) also, said cycloalkyl may condensed with the benzene ring to form an indane (for example, indan-2-yl, indan-2-yl or the like), tetrahydronaphthalene, (for example, tetrahydronaphthalen-5-yl, tetrahydronaphthalen-6-yl or the like) or the like (preferably, indane);

(2-3) furthermore, said cycloalkyl may be crosslinked via a straight-chained, atom chain having the carbon number of 1 to 2 to form a crosslinked, cyclic hydrocarbon residue such as bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl or the like (preferably, a cycloalkyl having a crosslink via a straight-chained, atom chain having the carbon number of 1 to 2, or the like, more preferably bicyclo[2.2.1]heptyl or the like);

(3) an alkenyl that may be substituted (for example, an alkenyl that has the carbon number of 2 to 10 such as allyl, crotyl, 2-pentenyl, 3-hexenyl or the like, preferably a lower (C_{2-6}) alkenyl, or the like is exemplified);

(4) a cycloalkenyl that may be substituted (for example, an cycloalkenyl that has the carbon number of 3 to 7 such as 2-cyclopentenyl, 2-cyclohexenyl 2-cyclopentenylmethyl, 2-cyclohexenylmethyl or the like, or the like is exemplified);

(5) an aralkyl that may be substituted (for example, a phenyl-C₁₋₄ alkyl (for example, benzyl, phenethyl or the like) or the like is exemplified);

(6) formyl or an acyl that may be substituted (for example, an alkanoyl that has the carbon number of 2 to 4 (for example, acetyl, propionyl, butyryl, isobutyryl or the like), an alkylsulfonyl that has the carbon number of 1 to 4 (for example, methanesulfonyl, ethanesulfonyl or the like), an alkoxycarbonyl that has the carbon number of 1 to 4 (methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl or the like), an aralkyloxycarbonyl that has the carbon number of 7 to 10 (for example, benzyloxycarbonyl or the like) or the like is exemplified);

(7) an aryl that may be substituted (for example, phenyl, naphthyl or the like is exemplified); and

(8) a heterocyclic ring group that may be substituted (a group that is formed by removing one hydrogen atom from a 5- to 6-membered, aromatic heterocyclic ring, which contains 1 to 4 heteroatoms of 1 to 2 kinds selected from the nitrogen atom, the sulfur atom and the oxygen atom, such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole or the like, a group that is formed by removing one hydrogen atom from a 5- to 6-membered, non-aromatic heterocyclic ring,

which contains 1 to 4 heteroatoms of 1 to 2 kinds selected from the nitrogen atom, the sulfur atom and the oxygen atom, such as tetrahydrofuran, tetrahydrothiophene, dithiolan, oxathiolan, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran, tetrahydropyran or the like, or the like; preferably, a group, which is formed by removing one hydrogen atom from a 5- to 6-membered, non-aromatic heterocyclic ring, or the like; and more preferably, a group, which is formed by removing one hydrogen atom from a 5- to 6-membered, non-aromatic heterocyclic ring, which has one heteroatom, such as tetrahydrofuran, piperidine, tetrahydropyran, tetrahydrothiopyran or the like) and the like. In addition, the substituents of said amino group may be bonded each other to form a 5- to 7-membered, cyclic amino such as piperidine, piperazine, morpholine, thiomorpholine or the like.

Examples of the substituents that may be possessed by (1) an alkyl that may be substituted, (2) a cycloalkyl that may be substituted, (3) an alkenyl that may be substituted, (4) a cycloalkenyl that may be substituted, (5) an aralkyl that may be substituted, (6) an acyl that may be substituted, (7) an aryl that may be substituted and

(8) a heterocyclic ring group that may be substituted, which are described above, include a halogen (for example, fluorine, chlorine, bromine, iodine or the like), a lower (C₁₋₄) alkyl that may be halogenated, a C₁₋₄ alkoxyl that may be halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like), a C₁₋₄ alkylenedioxy (for example, -O-CH₂-O-, -O-CH₂-CH₂-O- or the like), formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like), a phenyl-lower (C₁₋₄) alkyl, a C₃₋₇ cycloalkyl, cyano, nitro, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-C₁₋₄ alkylcarbamoyl or the like), a lower (C₁₋₄) alkoxycarbonyl, a lower (C₇₋₁₀) aralkyloxycarbonyl, the oxo group (preferably, a halogen, a lower (C₁₋₄) alkyl that may be halogenated, a C₁₋₄ alkoxyl that may be halogenated, a phenyl-lower (C₁₋₄) alkyl, a C₃₋₇ cycloalkyl, cyano, the

hydroxyl group or the like) and the like, where the number of the substituents is preferably 1 to 3.

In the above-mentioned formula (I), "an amino group that may be substituted, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide" indicated by R^2 , is preferably an amino group that may have 1 to 3 substituents selected from,

(1) a straight-chained or branched, lower (C_{1-6}) alkyl that may have 1 to 3 groups of a halogen, cyano, the hydroxyl group or a C_{3-7} cycloalkyl;

(2) a C_{5-8} cycloalkyl that may have 1 to 3 groups of a halogen, a lower (C_{1-4}) alkyl that may be halogenated or a phenyl-lower (C_{1-4}) alkyl, may contain one heteroatom selected from the sulfur atom, the oxygen atom and the nitrogen atom, may be condensed with the benzene ring and may be crosslinked via a straight-chained, atom chain having the carbon number of 1 to 2, (for example, cyclopentyl, cyclohexyl, cycloheptyl cyclooctyl, tetrahydropyranyl, tetrahydrothiapyranyl, piperidinyl, indanyl, tetrahydronaphthalenyl, bicyclo[2.2.1]heptyl or the like);

(3) a phenyl-lower (C_{1-4}) alkyl that may have 1 to 3 groups of a halogen, a lower (C_{1-4}) alkyl that may be halogenated or a C_{1-4} alkoxyl that may be halogenated;

(4) a phenyl that may have 1 to 3 groups of a halogen, a

lower (C_{1-4}) alkyl that may be halogenated or a C_{1-4} alkoxyl that may be halogenated; and

(5) a 5- to 6-membered, aromatic heterocyclic ring that may have 1 to 3 groups of a halogen, a lower (C_{1-4}) alkyl that may be halogenated, a C_{1-4} alkoxyl that may be halogenated, a (C_{1-4}) alkoxy-(C_{1-4}) alkoxyl that may be halogenated, a phenyl-lower (C_{1-4}) alkyl, cyano or the hydroxyl (for example, a group that is formed by removing one hydrogen atom from furan, thiophene, pyrrole, pyridine or the like).

10 In the above-mentioned formula (I), "a nitrogen-containing, heterocyclic ring" of "a nitrogen-containing, heterocyclic ring group that may be substituted and may contain the sulfur atom or the oxygen atom as a ring-constituting atom, where the nitrogen atom may be converted
15 into a quaternary ammonium or the N-oxide" is exemplified by a 5- to 6-membered, aromatic heterocyclic ring, which may contain, in addition to one nitrogen atom, 1 to 3 heteroatoms of 1 to 2 kinds selected from the nitrogen atom, the sulfur atom and the oxygen atom, such as pyrrole,
20 imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole or the like, a 5- to 8-membered, non-aromatic heterocyclic ring, which may contain, in addition to one nitrogen atom, 1 to 3 heteroatoms of 1 to 2 kinds
25 selected from the nitrogen atom, the sulfur atom and the

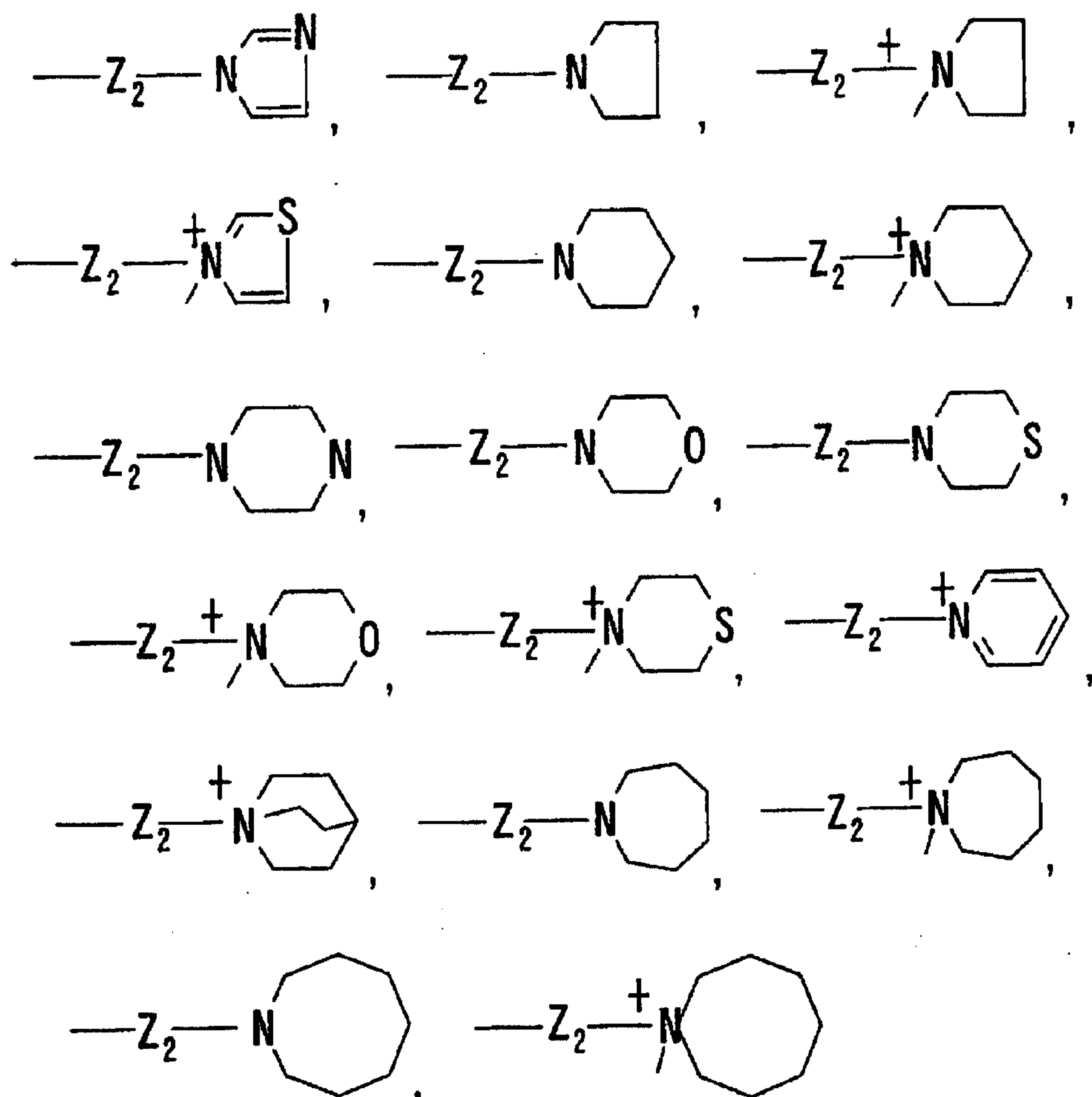
oxygen atom, such as pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, azacycloheptane, azacyclooctane (azokane) or the like, or the like, where each of these nitrogen-containing, heterocyclic rings may be crosslinked via a straight-chained, atom chain having the carbon number of 1 to 2 and may form a crosslinked, nitrogen-containing, heterocyclic ring such as azabicyclo[2.2.1]heptane, azabicyclo[2.2.2]octane (quinuclidine) or the like (preferably, piperidine, which may have a crosslink via a straight-chained, atom chain having the carbon number of 1 to 2, or the like).

Among the specific examples of the above-mentioned, nitrogen-containing, heterocyclic ring, pyridine, imidazole, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine and azabicyclo[2.2.2]octane (preferably, 6-membered, cyclic rings) are preferable.

The nitrogen atom of said "nitrogen-containing, heterocyclic ring" may be converted into a quaternary ammonium, or may be oxidized. In the case where the nitrogen atom of said "nitrogen-containing, heterocyclic ring" is converted into a quaternary ammonium, a counter anion for "the nitrogen-containing, heterocyclic ring group, in which the nitrogen atom is converted into a quaternary

ammonium", is exemplified by, in addition to an anion of a halogen atom (for example, Cl^- , Br^- , I^- or the like) or the like, an anion derived from an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, an anion derived from an organic acid such as formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like and an anion derived from an acidic amino acid such as aspartic acid, glutamic acid and the like, where Cl^- , Br^- , I^- or the like is more preferable.

Said "nitrogen-containing, heterocyclic ring" may be bonded with a bivalent group, which is indicated by Z^2 , via either of the carbon atom or the nitrogen atom and may be bonded on the carbon atom constituting the cyclic ring, as in the case of 2-pyridyl, 3-pyridyl, 2-piperidyl or the like, whereas a bonding as in the case of



or the like is preferable.

Examples of substituents of said "nitrogen-containing, heterocyclic ring" include a halogen (for
 5 example, fluorine, chlorine, bromine, iodine or the like),
 a lower (C_{1-4}) alkyl that may be substituted, a lower (C_{1-4})
 alkoxyl that may be substituted, a phenyl that may be
 substituted, a mono- or diphenyl-lower (C_{1-4}) alkyl that may
 10 be substituted, a C_{3-7} cycloalkyl that may be substituted,

cyano, nitro, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-C₁₋₄ alkylcarbamoyl or the like), a lower (C₁₋₄) alkoxycarbonyl, formyl, a (C₂₋₄) alkanoyl, a (C₁₋₄) alkylsulfonyl, a heterocyclic ring group that may be substituted (a group that is formed by removing one hydrogen atom from a 5- to 6-membered, aromatic heterocyclic ring, which contains 1 to 4 heteroatoms of 1 to 2 kinds selected from the nitrogen atom, the sulfur atom and the oxygen atom, such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole or the like, a group that is formed by removing one hydrogen atom from a 5- to 6-membered, non-aromatic heterocyclic ring, which contains 1 to 4 heteroatoms of 1 to 2 kinds selected from the nitrogen atom, the sulfur atom and the oxygen atom, such as tetrahydrofuran, tetrahydrothiophene, dithiolan, oxathiolan,

pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran, tetrahydropyran, tetrahydrothiopyran
5 or the like, or the like, where the number of the substituents is preferably 1 to 3. Also, the nitrogen in said "nitrogen-containing, heterocyclic ring" may be oxidized.

Examples of the substituents, which may be
10 possessed by "a lower (C_{1-4}) alkyl that may be substituted", "a lower (C_{1-4}) alkoxy that may be substituted", "a phenyl that may be substituted", "a mono- or diphenyl-lower (C_{1-4}) alkyl that may be substituted", "a C_{3-7} cycloalkyl that may be substituted" and "a heterocyclic ring group that may be
15 substituted", as the substituents that may be possessed by said "nitrogen-containing, heterocyclic ring", include, for example, a halogen (for example, fluorine, chlorine, bromine, iodine or the like), a lower (C_{1-4}) alkyl that may be halogenated, a lower (C_{3-10}) cycloalkyl, a lower (C_{3-10})
20 cycloalkenyl, a C_{1-4} alkoxy that may be halogenated (for example, methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy or the like), formyl, a C_{2-4} alkanoyl (for example, acetyl, propionyl or the like), a C_{1-4} alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like), a C_{1-3}
25 alkylenedioxy (for example, methylenedioxy, ethylenedioxy

or the like), cyano, nitro, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-C₁₋₄ alkylcarbamoyl or the like), a lower (C₁₋₄) alkoxycarbonyl and the like, where the number of the substituents is preferably 1 to 3.

In the above-mentioned formula (I), the substituent, which may be possessed by "a nitrogen-containing, heterocyclic ring" of "a nitrogen-containing, heterocyclic ring group that may be substituted and may contain the sulfur atom or the oxygen atom as a ring-constituting atom, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide" is exemplified preferably by (1) a halogen, (2) cyano, (3) the hydroxyl group, (4) the carboxyl group, (5) a lower (C₁₋₄) alkoxycarbonyl, (6) a lower (C₁₋₄) alkyl that may be substituted with a halogen, the hydroxyl group or a lower (C₁₋₄) alkoxy, (7) a lower (C₁₋₄) alkoxy that may be

substituted with a halogen, the hydroxyl group or a lower
(C₁₋₄) alkoxyl, (8) a phenyl that may be substituted with a
halogen, a lower (C₁₋₄) alkyl, the hydroxyl group, a lower
(C₁₋₄) alkoxyl or a C₁₋₃ alkylenedioxy, (9) a mono- or
5 diphenyl-lower (C₁₋₄) alkyl that may be substituted with a
halogen, a lower (C₁₋₄) alkyl, the hydroxyl group, a lower
(C₁₋₄) alkoxyl or a C₁₋₃ alkylenedioxy, (10) a group that is
formed by removing one hydrogen atom from a 5- to 6-
membered, aromatic heterocyclic ring, such as furan,
10 thiophene, pyrrole, pyridine or the like, or the like.

In the above-mentioned formula (I), "a group that
is bonded via the sulfur atom", which is indicated by R²,
is exemplified by a group represented by -S(O)_m-R^s (wherein
m indicates an integer of 0 to 2 and R^s indicates a
15 substituent). In the above-mentioned formula, examples of
the substituent indicated by R^s include, for example,

(1) an alkyl that may be substituted (for example, a C₁₋₁₀
alkyl such as methyl, ethyl, propyl, isopropyl, butyl,
isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl,
20 neopentyl, hexyl, heptyl, octyl, nonyl, decyl or the like,
preferably a lower (C₁₋₆) alkyl, or the like is
exemplified);

(2) a cycloalkyl that may be substituted and may contain
heteroatoms (for example, a C₃₋₇ cycloalkyl such as
25 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

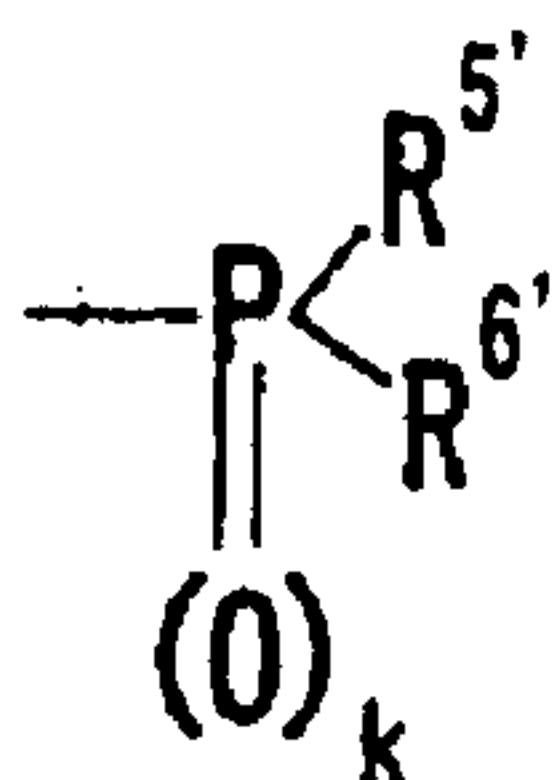
cycloheptyl or the like is exemplified);

(3) an aralkyl that may be substituted (for example, a phenyl-C₁₋₄ alkyl (for example, benzyl, phenethyl or the like) or the like is exemplified); and

5 (4) an aryl that may be substituted (for example, phenyl, naphthyl or the like is exemplified), where examples of the substituents that may be possessed by (1) an alkyl that may be substituted, (2) a cycloalkyl that may be substituted, (3) an aralkyl that may be substituted and (4) an aryl that
10 may be substituted, which are described above, include a halogen (for example, fluorine, chlorine, bromine, iodine or the like), nitro, cyano, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be
15 substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or
20 amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-C₁₋₄ alkylcarbamoyl or the like), a C₁₋₄ alkyl that may be halogenated (for example, trifluoromethyl, methyl, ethyl or the like), a C₁₋₄ alkoxyl that may be halogenated (for
25 example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy,

trifluoroethoxy or the like), formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like) or the like, where the number of the substituents is preferably 1 to 3.

In the above-mentioned formula (I), "the hydrocarbon atom" for the hydrocarbon atom that may be substituted, which is indicated by R^{5'} and R^{6'}, in "a group represented by formula



(wherein k indicates 0 or 1, the phosphorus atom may form a phosphonium salt when k is 0, and each of R^{5'} and R^{6'} indicates the hydrocarbon atom that may be substituted, the hydroxyl group that may be substituted or an amino group that may be substituted (preferably, the hydrocarbon atom that may be substituted or an amino group that may be substituted; more preferably the hydrocarbon atom that may be substituted) and R^{5'} and R^{6'} may bind each other to form a cyclic ring group together with the adjacent phosphorus atom)", which is indicated by R², is exemplified by,

(1) an alkyl that may be substituted (for example, a C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl,

isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl or the like, preferably a lower (C_{1-6}) alkyl, or the like is exemplified);

5 (2) a cycloalkyl that may be substituted (for example, a C_{3-7} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like);

(3) an alkenyl that may be substituted (for example, an alkenyl that has the carbon number of 2 to 10 such as allyl, 10 crotyl, 2-pentenyl, 3-hexenyl or the like, preferably a lower (C_{2-6}) alkenyl, or the like is exemplified);

(4) a cycloalkenyl that may be substituted (for example, an cycloalkenyl that has the carbon number of 3 to 7 such as 2-cyclopentenyl, 2-cyclohexenyl 2-cyclopentenylmethyl, 2- 15 cyclohexenylmethyl or the like, or the like is exemplified);

(5) an alkynyl that may be substituted (for example, an alkynyl that has the carbon number of 2 to 10 such as ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-pentynyl, 3- 20 hexynyl or the like, preferably a lower (C_{2-6}) alkynyl, or the like is exemplified);

(6) an aralkyl that may be substituted (for example, a phenyl- C_{1-4} alkyl (for example, benzyl, phenethyl or the like) or the like is exemplified); and

25 (7) an aryl that may be substituted (for example, phenyl,

naphthyl or the like is exemplified), where examples of the substituents that may be possessed by (1) an alkyl that may be substituted, (2) a cycloalkyl that may be substituted, (3) an alkenyl that may be substituted, (4) a cycloalkenyl
5 that may be substituted, (5) an alkynyl that may be substituted, (6) an aralkyl that may be substituted and (7) an aryl that may be substituted, which are described above, include a halogen (for example, fluorine, chlorine, bromine, iodine or the like), nitro, cyano, the hydroxyl group, the
10 thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine,
15 morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-C₁₋₄ alkylcarbamoyl or the like), a C₁₋₄ alkyl that may be
20 halogenated (for example, trifluoromethyl, methyl, ethyl or the like), a C₁₋₆ alkoxyl that may be halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like, formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄
25 alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl

or the like) or the like, where the number of the substituents is preferably 1 to 3.

The hydroxyl group that may be substituted, which is indicated by $R^{5'}$ and $R^{6'}$, is exemplified by the hydroxyl group that may be possessed by, for example, (1) an alkyl that may be substituted (for example, a C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl or the like, preferably a lower (C_{1-6}) alkyl, or the like is exemplified);

(2) a cycloalkyl that may be substituted (for example, a C_{3-7} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like);

(3) an alkenyl that may be substituted (for example, an alkenyl that has the carbon number of 2 to 10 such as allyl, crotyl, 2-pentenyl, 3-hexenyl or the like, preferably a lower (C_{2-6}) alkenyl, or the like is exemplified);

(4) a cycloalkenyl that may be substituted (for example, an cycloalkenyl that has the carbon number of 3 to 7 such as 2-cyclopentenyl, 2-cyclohexenyl 2-cyclopentenylmethyl, 2-cyclohexenylmethyl or the like, or the like is exemplified);

(5) an aralkyl that may be substituted (for example, a phenyl- C_{1-4} alkyl (for example, benzyl, phenethyl or the like) or the like is exemplified);

(6) formyl or an acyl that may be substituted (for example, an alkanoyl that has the carbon number of 2 to 4 (for example, acetyl, propionyl, butyryl, isobutyryl or the like), an alkylsulfonyl that has the carbon number of 1 to 4 (for example, methanesulfonyl, ethanesulfonyl or the like) or the like is exemplified); and
(7) an aryl that may be substituted (for example, phenyl, naphthyl or the like is exemplified).

Examples of the substituents that may be possessed by (1) an alkyl that may be substituted, (2) a cycloalkyl that may be substituted, (3) an alkenyl that may be substituted, (4) a cycloalkenyl that may be substituted, (5) an aralkyl that may be substituted, (6) an acyl that may be substituted and (7) an aryl that may be substituted, which are described above, include a halogen (for example, fluorine, chlorine, bromine, iodine or the like), nitro, cyano, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl,

a di-C₁₋₄ alkylcarbamoyl or the like), a C₁₋₄ alkyl that may be halogenated (for example, trifluoromethyl, methyl, ethyl or the like), a C₁₋₆ alkoxy that may be halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like, formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like) and the like, where the number of the substituents is preferably 1 to 3.

Also, in the above-mentioned formula, R^{5'} and R^{6'} may bind each other to form a cyclic ring group together with the adjacent phosphorus atom (preferably, a 5- to 7-membered cyclic ring). Such a cyclic ring may have substituents and examples of said substituents include a halogen (for example, fluorine, chlorine, bromine, iodine or the like), nitro, cyano, the hydroxyl group, the thiol group that may be substituted (for example, thiol, a C₁₋₄ alkylthio or the like), an amino group that may be substituted (for example, amino, a mono-C₁₋₄ alkylamino, a di-C₁₋₄ alkylamino, a 5- to 6-membered cyclic ring amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole or the like, or the like), the carboxyl group that may be esterified or amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl, carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-C₁₋₄

alkylcarbamoyl or the like), a C₁₋₄ alkyl that may be halogenated (for example, trifluoromethyl, methyl, ethyl or the like), a C₁₋₆ alkoxyl that may be halogenated (for example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy or the like, formyl, a C₂₋₄ alkanoyl (for example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like) and the like, where the number of the substituents is preferably 1 to 3.

10 In the above-mentioned formula (I), a counter anion in the case where the phosphorus atom forms a phosphonium salt is exemplified by, in addition to an anion of a halogen atom (for example, Cl⁻, Br⁻, I⁻ or the like) or the like, an anion derived from an inorganic acid such as
15 hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, an anion derived from an organic acid such as formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid,
20 methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like and an anion derived from an acidic amino acid such as aspartic acid, glutamic acid and the like, where Cl⁻, Br⁻, I⁻ or the like is more preferable.

25 An amino group that may be substituted, which is

indicated by R^{5'} and R^{6'}, is exemplified by an amino group that may have 1 to 2 groups such as,

(1) an alkyl that may be substituted (for example, a C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl or the like, preferably a lower (C₁₋₆) alkyl, or the like is exemplified);

(2) a cycloalkyl that may be substituted (for example, a C₃₋₇ cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like);

(3) an alkenyl that may be substituted (for example, an alkenyl that has the carbon number of 2 to 10 such as allyl, crotyl, 2-pentenyl, 3-hexenyl or the like, preferably a lower (C₂₋₆) alkenyl, or the like is exemplified);

(4) a cycloalkenyl that may be substituted (for example, an cycloalkenyl that has the carbon number of 3 to 7 such as 2-cyclopentenyl, 2-cyclohexenyl 2-cyclopentenylmethyl, 2-cyclohexenylmethyl or the like, or the like is exemplified);

(5) formyl or an acyl that may be substituted (for example, an alkanoyl that has the carbon number of 2 to 4 (for example, acetyl, propionyl, butyryl, isobutyryl or the like), an alkylsulfonyl that has the carbon number of 1 to 4 (for example, methanesulfonyl, ethanesulfonyl or the

like) or the like is exemplified); and

(6) an aryl that may be substituted (for example, phenyl, naphthyl or the like is exemplified).

Examples of the substituents that may be
5 possessed by (1) an alkyl that may be substituted, (2) a
cycloalkyl that may be substituted, (3) an alkenyl that may
be substituted, (4) a cycloalkenyl that may be substituted,
(5) an acyl that may be substituted and (6) an aryl that
may be substituted, which are described above, include a
10 halogen (for example, fluorine, chlorine, bromine, iodine
or the like), nitro, cyano, the hydroxyl group, the thiol
group that may be substituted (for example, thiol, a C₁₋₄
alkylthio or the like), an amino group that may be
substituted (for example, amino, a mono-C₁₋₄ alkylamino, a
15 di-C₁₋₄ alkylamino, a 5- to 6-membered cyclic ring amino
such as tetrahydropyrrole, piperazine, piperidine,
morpholine, thiomorpholine, pyrrole, imidazole or the like,
or the like), the carboxyl group that may be esterified or
amidated (for example, carboxyl, a C₁₋₄ alkoxycarbonyl,
20 carbamoyl, a mono-C₁₋₄ alkylcarbamoyl, a di-C₁₋₄
alkylcarbamoyl or the like), a C₁₋₄ alkyl that may be
halogenated (for example, trifluoromethyl, methyl, ethyl or
the like), a C₁₋₆ alkoxyl that may be halogenated (for
example, methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy,
25 trifluoroethoxy or the like, formyl, a C₂₋₄ alkanoyl (for

example, acetyl, propionyl or the like), a C₁₋₄ alkylsulfonyl (for example, methanesulfonyl, ethanesulfonyl or the like) and the like, where the number of the substituents is preferably 1 to 3.

5 The substituents for "an amidino group that may be substituted" and "a guanidino group that may be substituted" are exemplified by substituents similar to those for "an amino group that may be substituted, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide" that is indicated by R².
10

 It is preferable that R² is (1) an amino group that may be substituted, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide, (2) a nitrogen-containing, heterocyclic ring group that may be substituted and may contain the sulfur atom or the oxygen atom as a ring-constituting atom, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide, (3) an amidino group that may be substituted or (4) a guanidino group that may be substituted and it is more preferable that R² is an amino group that may be substituted, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide, or the like. Also, R² may be an amidino group that may be substituted or a guanidino group that may be substituted.
20

25 It is more preferable that R² is -NRR'' or -

N⁺RR'R'' (wherein each of R, R' and R'' indicates an aliphatic hydrocarbon group (an aliphatic-chain hydrocarbon group and an aliphatic, cyclic hydrocarbon group) that may be substituted or an alicyclic (non-aromatic), heterocyclic
5 ring group that may be substituted).

In the above-mentioned formula, "an aliphatic hydrocarbon group that may be substituted" and "an alicyclic, heterocyclic ring group that may be substituted", which are indicated by R, R' and R'', are exemplified by
10 substituents similar to "an aliphatic hydrocarbon group that may be substituted (for example, an alkyl, a cycloalkyl, an alkenyl, a cycloalkenyl or the like, each of which may be substituted)" and "an alicyclic, heterocyclic
15 ring group that may be substituted (for example, a 5- to 6-membered, non-aromatic, heterocyclic ring that may be substituted or the like)", which are exemplified by as the substituents that may be possessed by "an amino group that may be substituted" indicated by R².

Especially, as for R and R', an aliphatic
20 hydrocarbon group that may be substituted (for example, an alkyl, an alkenyl or the like, each of which may be substituted) is preferable, a C₁₋₆ alkyl group that may be substituted is more preferable and the methyl that may be substituted is particularly preferable.

25 It is preferable that R'' is an aliphatic

hydrocarbon group that may be substituted (preferably, a
C₃₋₈ cycloalkyl group that may be substituted; more
preferably, a cyclohexyl that may be substituted) or an
alicyclic, heterocyclic ring group that may be substituted
5 (preferably, a saturated alicyclic, heterocyclic ring group
that may be substituted (preferably, a 6-membered cyclic
ring group); more preferably, tetrahydropyranyl that may be
substituted, tetrahydrothiopyranyl that may be substituted
or piperidyl that may be substituted; and particularly
10 preferably, tetrahydropyranyl that may be substituted).

The following compounds are preferable as the
compounds represented by formula (I).

N-[4-[N-Methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-
7-[2-(4-propoxyphenyl)ethoxy]-1,1-dioxo-2,3-dihydro-1-
15 benzothiepine-4-carboxamide;
N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-
7-[(3-propoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-
benzothiepine-4-carboxamide;
N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-
20 7-[(2-propoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-
benzothiepine-4-carboxamide;
N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-
7-[(4-chlorobenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-
benzothiepine-4-carboxamide;
25 N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-

7-[(4-ethoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide;

N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[[4-(propoxymethyl)benzyl]oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide;

N-[1-(tetrahydropyran-4-yl)piperidin-4-yl]-7-(4-phenyl)-2,3-dihydro-1-benzooxepine-4-carboxamide;

N-[4-[(2-imidazolin-2-yl)methyl]phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzooxepine-4-carboxamide;

10 N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(4-propoxyphenyl)methoxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide;

15 N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(4-propoxyethoxyphenyl)methoxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide;

N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[3-(4-propoxyphenyl)propoxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide; and the like.

As for a salt of any of the compounds represented by formula (I) of the present invention, a pharmaceutically permissible salt is preferable and is exemplified by a salt with an inorganic base, a salt with an organic base, a salt with an inorganic acid, a salt with an organic acid, a salt with a basic or acidic amino acid and the like. Preferable examples of a salt with an inorganic base

include an alkali metal salt such as the sodium salt, the potassium salt and the like; an alkaline earth metal salt such as the calcium salt, the magnesium salt and the like; as well as the aluminum salt, the ammonium salt and the like. Preferable examples of a salt with an organic base include salts with any of trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like. Preferable examples of a salt with an inorganic acid include salts with any of hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of a salt with an organic acid include salts with any of formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of a salt with a basic amino acid include salts with any of arginine, lysine, ornithine and the like, and preferable examples of a salt with an acidic amino acid include salts with any of aspartic acid, glutamic acid and the like. The compounds represented by formula (I) of the present invention may be in the form of hydrates or may be in the form of non-hydrates. Also, in the case where any of the compounds represented by formula

(I) of the present invention exists in configurational isomers, diastereomers, conformers or the like, they can be separated into each isomer according to a well-known, separation/purification means. Also, in the case where any
5 of the compounds represented by formula (I) of the present invention is in the form of racemates, they may be separated according to a conventional optical resolution means into the (S) form and the (R) form, where each of the optically active compounds and the racemates is encompassed
10 in the present invention.

The prodrug of any of the compounds represented by formula (I) to be employed in the present invention or a salt thereof [hereinafter, it may be designated as compound (I).] refers to a compound that is converted into compound
15 (I) by a reaction with an enzyme, gastric acid or the like under a physiological condition in the living body, namely, a compound that is converted into compound (I) by oxidation, reduction, hydrolysis or the like, each of which is carried out enzymatically, and a compound that is converted into
20 compound (I) by hydrolysis with gastric acid or the like. Examples of the prodrug of compound (I) include a compound, wherein the amino group in compound (I) is acylated, alkylated or phosphorylated (for example, a compound, wherein the amino group in compound (I) is converted into
25 eicosanoylamino, alanylamino, pentylaminocarbonylamino, (5-

methyl-2-oxo-1,3-dioxolan-4-yl)methoxycarbonylamino,
tetrahydrofuranylamino, pyrrolidylmethylamino,
pivaloyloxymethylamino or tert-butylamino, or the like); a
compound, wherein the hydroxyl group in compound (I) is
5 acylated, alkylated, phosphorylated or converted into the
borate (for example, a compound, wherein the hydroxyl group
in compound (I) is converted into acetyloxy, palmitoyloxy,
propanoyloxy, pivaloyloxy, succinyloxy, fumaryloxy,
alanyloxy, or dimethylaminomethylcarbonyloxy, or the like);
10 a compound, wherein the carboxyl group in compound (I) is
esterified or amidated (for example, a compound, wherein
the carboxyl group in compound (I) is subjected to ethyl
esterification, phenyl esterification, carboxyoxymethyl
esterification, dimethylaminomethyl esterification,
15 pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl
esterification, phthalidyl esterification, (5-methyl-2-oxo-
1,3-dioxolan-4-yl)methyl esterification,
cyclohexyloxycarbonyl esterification, or conversion into
the methyl amide, or the like); and the like. These
20 compounds can be produced from compound (I) according to a
well-known method.

Moreover, the prodrug of compound (I) may be a
compound that is converted into compound (I) under a
physiological condition as described in "Development of
25 Drugs", Volume 7, Molecular Design, Hirokawa Shoten, 1990;

pages 163-198.

Also, compound (I) may be labeled with an isotope (for example, ^3H , ^{14}C , ^{35}S , ^{125}I or the like) or the like.

Any of the compounds represented by formula (I) of the present invention or a salt thereof (hereinafter, in the case where it abbreviated as compound (I), a salt thereof as well as any of the compounds represented by formula (I) and a salt thereof shall be included) can be alone, or by compounding with a pharmaceutically
5
10 permissible carrier, orally or parenterally administered as a solid formulation such as a tablet, a capsule, a granule, a powder or the like; or a liquid formulation such as a syrup, an injection or the like.

The parenterally administered form is exemplified
15 by an injection, a drip, a suppository, a pessary and the like, where a pessary is particularly useful for the prophylaxis of the HIV infectious diseases.

As for the pharmaceutically permissible carrier, any of a variety of organic or inorganic carrier substances, which have been conventionally employed as formulation materials, is used and compounded as a bulking agent, a
20 lubricant, a binding agent and a disintegrator in a solid formulation; a vehicle, a solubilizing agent, a suspending agent, an isotonicity agent, a buffering agent and an
25 analgesic in a liquid formulation. Also, as needed,

formulation excipients such as a preservative, an antioxidant, a stabilizer, a coloring agent, a sweetening agent and the like can be used. Preferable examples of the bulking agent include, for example, lactose, sucrose, D-mannitol, starch, crystalline cellulose, light anhydrous silicic acid and the like. Preferable examples of the lubricant include, for example, magnesium stearate, potassium stearate, talc, colloidal silica and the like. Preferable examples of the binding agent include, for example, crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone and the like. Preferable examples of the disintegrator include, for example, starch, carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, sodium carboxymethyl starch and the like. Preferable examples of the vehicle include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil and the like. Preferable examples of the solubilizing agent include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisamionemethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like. Preferable examples of the suspending agent include, for example, a surface active agent such as stearyltriethanolamine, sodium lauryl sulfate,

laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glycerin monostearate and the like; a hydrophilic, high molecular substance such as polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and the like, and the like. Preferable examples of the isotonicity agent include, for example, sodium chloride, glycerin, D-mannitol, and the like. Preferable examples of the buffering agent include, for example, a buffer solution of a phosphate, an acetate, a carbonate or a citrate and the like. Preferable examples of the analgesic include, for example, benzyl alcohol and the like. Preferable examples of the preservative include, for example, paraoxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like. Preferable examples of the antioxidant include, for example, sulfites, ascorbic acid and the like.

Any of the compounds represented by formula (I) of the present invention or a salt thereof may be employed in combination with another prophylactic/therapeutic agent of HIV infectious diseases (particularly a prophylactic/therapeutic agent of AIDS). In this case, these drugs can be formulated by compounding, separately or at the same time, with a pharmacologically permissible

carrier, a bulking agent, a binding agent, a diluent and the like, and the resulting preparation can be orally or parenterally administered as the pharmaceutical composition for the prophylaxis and/or therapeutics. In the case where
5 the drugs are formulated separately, the separately formulated preparations can be administered by admixing by the use of a diluent at the time of usage, whereas each of the separately formulated preparations may be administered to the same subject at the same time or separately with a
10 time difference. A kit product for administering the separately formulated preparations by admixing by the use of a diluent at the time of usage (for example, a kit for injection comprising ampoules, each containing a particular drug, and a diluent for dissolving 2 or more kinds of drugs
15 by admixing at the time of usage, or the like), a kit product for administering each of the separately formulated preparations to the same subject at the same time or separately with a time difference (for example, a kit for tablets, which encloses the tablets, each containing a
20 particular drug, in a same bag or separate bags, as needed, fitted with a time field where the times for administration of the drugs are described, and allows to administer 2 or more kinds of drugs at the same time or separately with a time difference, or the like) and the like are encompassed
25 in the pharmaceutical compositions of the present invention.

Specific examples of other prophylactic/therapeutic agents of HIV infectious diseases, which are to be employed in combination with the compounds represented by formula (I) of the present invention or salts thereof, include nucleic acid reverse transcriptase inhibitors such as zidovudine, didanosine, zalcitabine, lamivudine, stavudine, abacavir, adefovir, adefovir dipivoxil, fozivudine tidoxil and the like; non-nucleic acid reverse transcriptase inhibitors such as nevirapine, delavirdine, efavirenz, loviride, immunocal, olitipraz and the like (contain drugs, which have an antioxidant action, such as immunocal, olitipraz and the like); protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, palinavir, lasinavir and the like; and the like.

As for the nucleic acid reverse transcriptase inhibitors, zidovudine, didanosine, zalcitabine, lamivudine, stavudine and the like are preferable, as for non-nucleic acid reverse transcriptase inhibitors, nevirapine, delavirdine and the like are preferable and as for the protease inhibitors, saquinavir, ritonavir, indinavir, nelfinavir and the like are preferable.

Processes for the production of the compounds represented by formula (I) or salts thereof are shown in the following.

The compounds represented by formula (I) or salts thereof can be produced according to the well-known processes. For instance, they can be produced according to the following processes. Also, the compounds represented
5 by formula (I) or salts thereof can be produced according to the process described in Japanese Patent Kokai Publication No. 1996-73476 or a modified process thereof.

Compounds, which are to be used in each of the following production processes, may form salts similar to
10 compounds (I), as far as the reactions are not disturbed.

Also, in the case where a compound to be used as the raw material has an amino group, the carboxyl group and the hydroxyl group as substituents in each of the following reactions, such protective groups that are employed in
15 general in the peptide chemistry may be introduced to these groups, where the objective compounds can be obtained by removal of the protecting groups after the reactions, as needed.

As for the protective group for an amino group,
20 there is employed, for example, a C_{1-6} alkylcarbonyl (for example, acetyl, propionyl or the like), formyl, a phenylcarbonyl, a C_{1-6} alkyloxycarbonyl (for example, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl or the like), a phenyloxycarbonyl (for example, benzoxycarbonyl or
25 the like), a C_{7-10} aralkyloxycarbonyl (for example,

benzyloxycarbonyl or the like), trityl, phthaloyl or the like, each of which may have substituents. As for these substituents, there is employed a halogen atom (for example, fluorine, chlorine, bromine, iodine or the like), a C₁₋₆ alkylcarbonyl (for example, acetyl, propionyl, butyryl or the like), the nitro group or the like, where the number of the substituents is about 1 to 3.

As for the protective group for the carboxyl group, there is employed, for example, a C₁₋₆ alkyl (for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or the like), phenyl, trityl, silyl or the like, each of which may have substituents. As for these substituents, there is employed a halogen atom (for example, fluorine, chlorine, bromine, iodine or the like), a C₁₋₆ alkylcarbonyl (for example, acetyl, propionyl, butyryl or the like), formyl, the nitro group or the like, where the number of the substituents is about 1 to 3.

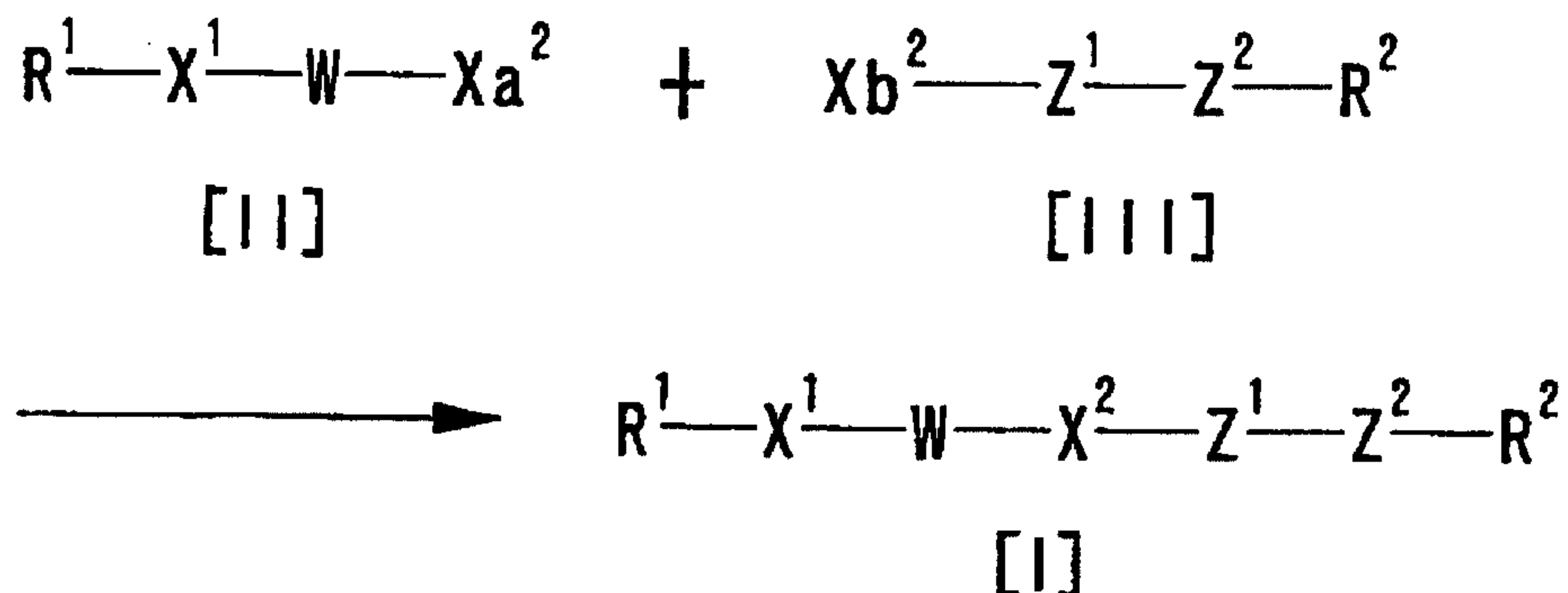
As for the protective group for the hydroxyl group, there is employed, for example, a C₁₋₆ alkyl (for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or the like), phenyl, a C₇₋₁₀ aralkyl (for example, benzyl or the like), a C₁₋₆ alkylcarbonyl (for example, acetyl, propionyl or the like), formyl, a phenylcarbonyl, a C₇₋₁₀ aralkyloxycarbonyl (for example, benzyloxycarbonyl or the like), pyranyl, furanyl, silyl or the like, each of

which may have substituents. As for these substituents, there is employed a halogen atom (for example, fluorine, chlorine, bromine, iodine or the like), a C₁₋₆ alkyl, phenyl, a C₇₋₁₀ aralkyl, the nitro group or the like, where the
5 number of the substituents is about 1 to 4.

Also, as for the methods for introduction and removal of the protective groups, the well-known methods or modified methods thereof [for example, methods described in PROTECTIVE GROUPS IN ORGANIC SYNTHESIS (by J. F. W. McOmie
10 et al., Plenum Press Company) are employed, where methods to treat with, for example, an acid, a base, a ultraviolet light, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate or the like are employed as the methods
15 for removal.

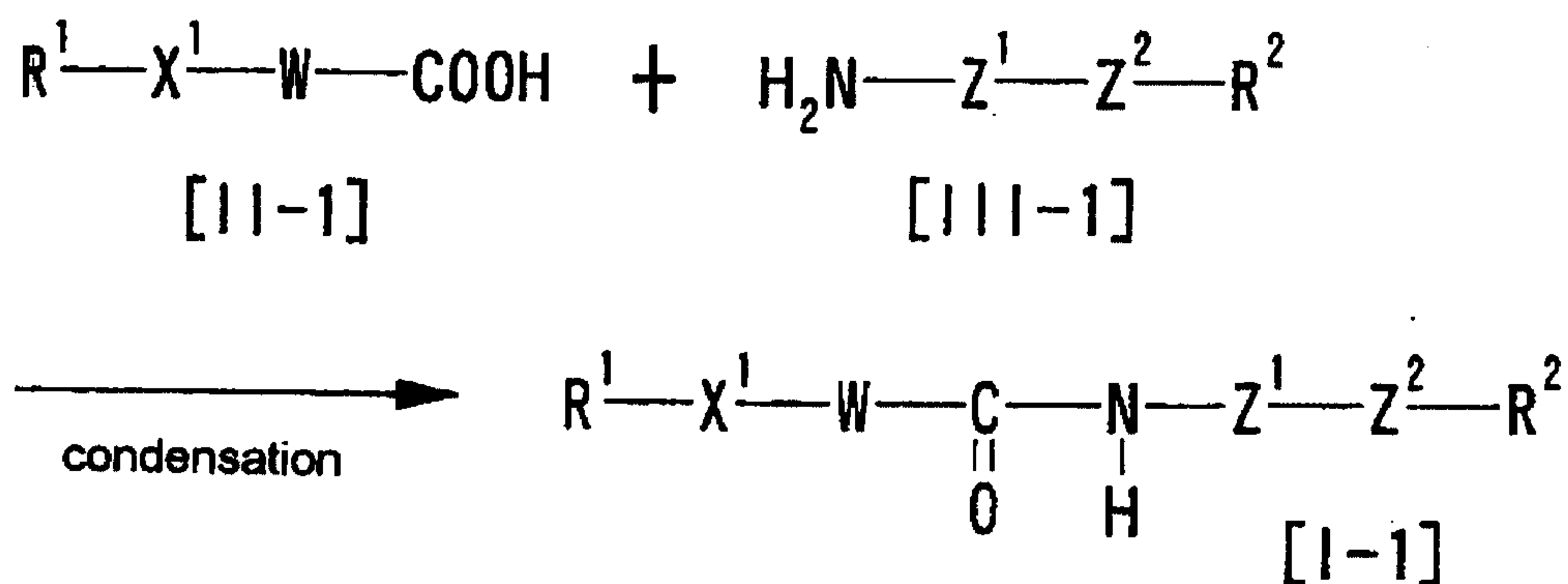
[Method A]

Compound (I) or a salt thereof can be produced, according to the reaction shown below, by reacting compound [II] or a salt thereof with compound [III] or a salt
20 thereof.



[wherein a group, which reacts with the substituent Xb^2 in compound [III] or a salt thereof to form X^2 , is indicated by Xa^2 (for example, the carboxyl group or the like) and a group, which reacts with the substituent Xa^2 in compound [II] or a salt thereof to form X^2 , is indicated by Xb^2 (for example, the amino group or the like) and other symbols have the same meanings as mentioned hereinabove.]

10 In the following is shown the production process in the case where Xa^2 is the carboxyl group, Xb^2 is the amino group and X^2 is -CO-NH- .



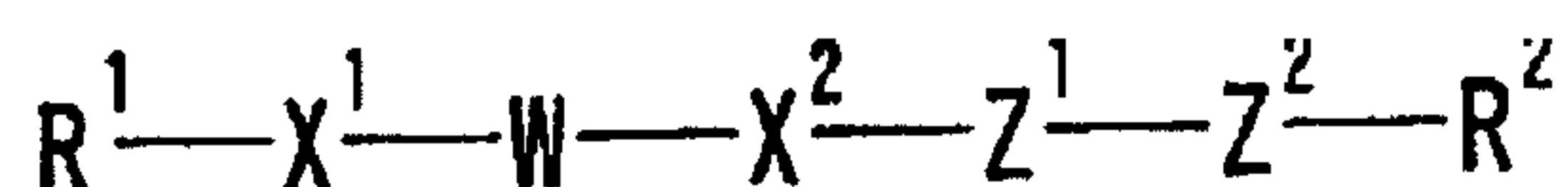
[each symbol of the formula has the same meaning as mentioned hereinabove]

In the present method, compound [I-1] is produced
5 be reacting a carboxylic acid derivative [II-1] with an amine derivative [III-1].

The condensation reaction of [II-1] and [III-1] is carried out according to a conventional means for peptide synthesis. Said means for peptide synthesis may be
10 followed by an optional known method, a method described in, for example, M. Bodansky and M. A. Ondetti, Peptide Synthesis, Interscience, New York, 1996; F. M. Finn and K. Hofmann, The Proteins, Volume 2, H. Nenrath and R. L. Hillor, Ed., Academic Press Inc., New York, 1976; Nobuo
15 Izumiya et al. "Bases and Experiments for Peptide Synthesis", Maruzen Kabushiki Kaisha, 1985, or the like, as exemplified by the azide method, the chloride method, the acid anhydride method, the mixed acid anhydride method, the DCC method, the active ester method, the method by the use
20 of Woodward reagent K, the carbonyl diimidazole method, the oxidation-reduction method, the DCC/HONB method or the like, as well as the WSC method, the method by the use of diethyl cyanophosphonate or the like. The present condensation reaction can be carried out in a solvent. The solvent is
25 exemplified by, for example, N,N-dimethylformamide,

dimethyl sulfoxide, pyridine, chloroform, dichloromethane, tetrahydrofuran, dioxane, acetonitrile or an adequate mixture of these solvents. The reaction temperature is usually about -20°C to about 50°C, preferably about -10°C to about 30°C. The reaction time is usually about 2 hour to about 40 hours. The thus-obtained compound (I-1) can be subjected to isolation and purification according to the known separation and purification means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, trans-solubilization, chromatography and the like.

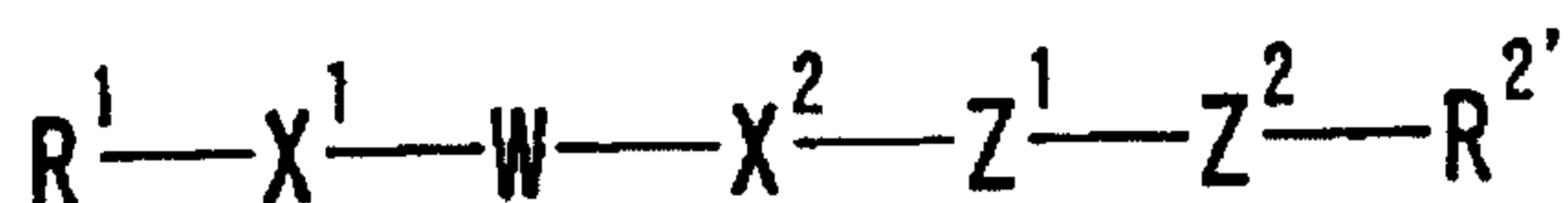
[Method B]



[I-2]

(1) ammonium formation
(2) tert-amination

(3) reductive amination or
(4) oxidation



[I']

[1] In the case where $R^{2''}$ represented in compound [I-2] is, for example, a tertiary amine residue, quaternary compound [I'] can be produced by reacting compound [I-2] with a halogenated alkyl or a halogenated aralkyl. Herein, the halogen atom is exemplified by chlorine, bromine, iodine or

the like, and a halogenated alkyl (for example, a halogenated, lower (C_{1-6}) alkyl or the like) or a halogenated aralkyl (for example, a halogenated, lower (C_{1-4}) alkylphenyl or the like) is used usually in an amount of about 1 to 5 moles per one mole of compound [I-2]. The present reaction can be carried out in an inactive solvent, as exemplified by, for example, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethyl acetamide or a mixed solvent thereof. The reaction temperature is a temperature range of about 10°C to about 160°C, preferably about 20°C to about 120°C. The reaction time is usually about one hour to about 100 hours, preferably, about 2 hours to about 40 hours. In addition, the present reaction is carried out preferably under an atmosphere of an inert gas (for example, nitrogen, argon or the like).

[2] In the case where $R^{2''}$ represented in compound [I-2] is, for example, a secondary amine residue, tertiary compound [I'] can be produced by reacting compound [I-2] with a halogenated alkyl or a halogenated aralkyl. Herein, the halogen atom is exemplified by chlorine, bromine, iodine or the like, and a halogenated alkyl or a halogenated aralkyl is used usually in an amount of about 1 to 2 moles per one mole of compound [I-2]. This reaction can be allowed to proceed smoothly, as needed, by addition of an about

equimolar amount to 3 molar amount of a base such as triethylamine, diisopropylethylamine, pyridine, lithium hydride, sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, sodium hydrogen
5 carbonate or the like, and further by addition of sodium iodide, potassium iodide or the like.

The present tertiary amination reaction can be carried out in an inactive solvent, as exemplified by, for example, methanol, ethanol, propanol, isopropanol, n-
10 butanol, tetrahydrofuran, diethyl ether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine or the like, or a mixed solvent thereof. The reaction temperature is a temperature
15 range of about 0°C to about 180°C for about one hour to about 40 hours. In addition, the present reaction is carried out preferably under an atmosphere of an inert gas (for example, nitrogen, argon or the like).

[3] In the case where R^{2''} represented in compound [I-2] is,
20 for example, a secondary amine residue, tertiary compound [I'] can be produced by reacting compound [I-2] with an aldehyde compound in the presence of a reductive amination reagent such as sodium triacetoxyborohydride, sodium cyanoborohydride, sodium borohydride or the like. It is
25 preferable that the reaction conditions of the present

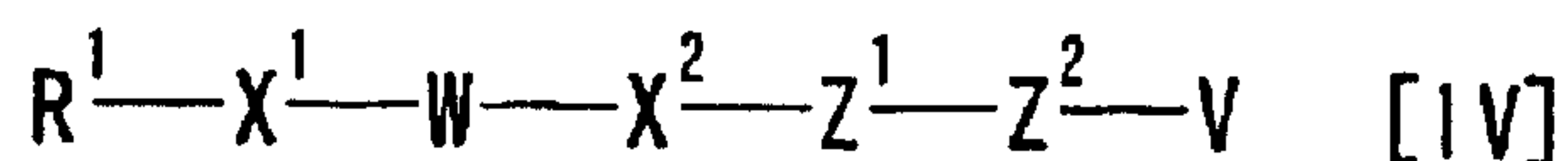
reductive amination reaction are altered depending on the reagent to be used, where, for instance, in the case where sodium triacetoxyborohydride is used, the reaction can be carried out in an inactive solvent, as exemplified by, for example, dichloromethane, chloroform, 1,2-dichloroethane, tetrahydrofuran (THF), diethyl ether, dioxane, acetonitrile, dimethylformamide (DMF) or the like, or a mixed solvent thereof. The present reagent is used in an amount of about 1 to 2 molar equivalents per one mole of compound [I-2].

The reaction is carried out usually at a temperature range of about 0°C to about 80°C for about one hour to about 40 hours. In addition, the present reaction is carried out preferably under an atmosphere of an inert gas (for example, nitrogen, argon or the like).

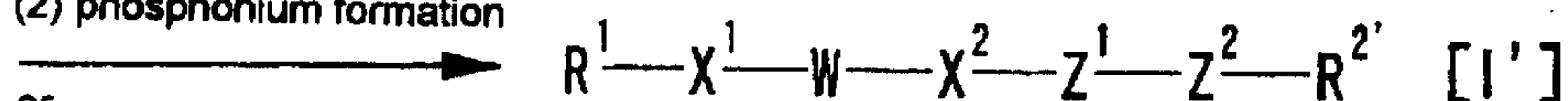
[4] In the case where $R^{2''}$ represented in compound [I-2] is, for example, a sulfide residue or a tertiary amine residue, compound [I'] having the sulfinyl group, the sulfonyl group or the amine oxide group can be produced by reacting compound [I-2] with an oxidizing agent such as m-chloroperbenzoic acid, perbenzoic acid, paranitroperbenzoic acid, magnesium monoperoxyphthalate, peracetic acid, hydrogen peroxide, sodium periodate, potassium periodate or the like. It is preferable that the reaction conditions of this oxidation reaction are altered depending on the oxidizing reagent to be used, where, for instance, in the

case where m-chloroperbenzoic acid is used, the reaction can be carried out in an inactive solvent, as exemplified by, for example, dichloromethane, chloroform, 1,2-dichloroethane, tetrahydrofuran, acetone, ethyl acetate or the like, or a mixed solvent thereof. The oxidizing reagent is used in an amount of about 1 to 3 molar equivalents per one mole of compound [I-2]. The reaction is carried out usually at a temperature range of about -20°C to about 80°C, (preferably, about -25°C to about 25°C for about one hour to about 40 hours.

[Method C]



(1) ammonium formation
(2) phosphonium formation
or
(3) replacement reaction



V in compound [IV] indicates a halogen atom (for example, chlorine, bromine, iodine or the like) or a sulfonyloxy group (the methanesulfonyloxy group, the trifluoromethanesulfonyloxy group, the benzenesulfonyloxy group or the toluenesulfonyloxy group) and other symbols indicate the same meanings as indicated hereinabove.

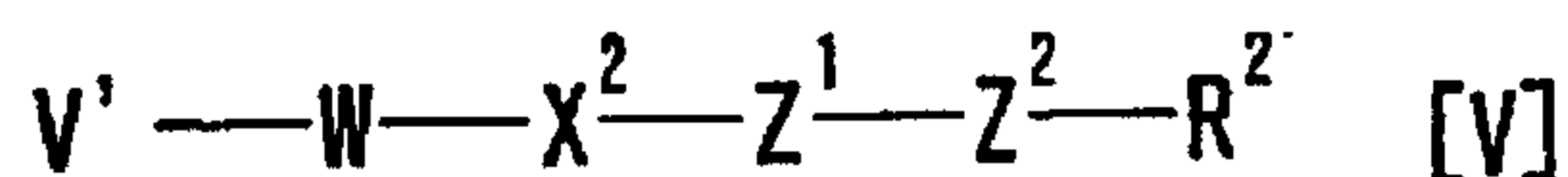
[1] Quaternary compound [I'] can be produced by reacting

compound [IV] with a tertiary amine. The present reaction can be carried out in an inactive solvent, as exemplified by, for example, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF),
5 dimethyl acetamide or the like, or a mixed solvent thereof. The tertiary amine is used in an amount of about 1 to 3 moles per one mole of compound [IV]. The present reaction is carried out at a temperature range of about 10°C to about 120°C for about one hour to about 40 hours. In
10 addition, the present reaction is carried out preferably under an atmosphere of an inert gas (for example, nitrogen, argon or the like).

[2] Quaternary compound [I'] can be produced by reacting compound [IV] with a tertiary phosphine. The present
15 reaction can be carried out in an inactive solvent, as exemplified by, for example, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, dimethylformamide (DMF) or the like, or a mixed solvent thereof. The tertiary phosphine is used in
20 an amount of about 1 to 2 moles per one mole of compound [IV]. The present reaction is carried out at a temperature range of about 20°C to about 150°C for about one hour to about 50 hours. In addition, the present reaction is carried out preferably under an atmosphere of an inert gas
25 (for example, nitrogen, argon or the like).

[3] Compound [I'] having a secondary or tertiary amino group or a thio group can be produced by reacting compound [IV] with a primary or secondary amine compound or a thiol compound. The primary or secondary amine compound or the thiol compound is used usually in an amount of about 1 to 3 moles per one mole of compound [IV]. This reaction can be allowed to proceed smoothly, as needed, by addition of an about equimolar amount to 3 molar amount of a base such as triethylamine, diisopropylethylamine, pyridine, lithium hydride, sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate or the like, and further by addition of sodium iodide, potassium iodide or the like. The present substitution reaction can be carried out in an inactive solvent, as exemplified by, for example, methanol, ethanol, propanol, isopropanol, n-butanol, tetrahydrofuran, diethyl ether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine or the like, or a mixed solvent thereof. The reaction is carried out at a temperature range of about -10°C to about 180°C for about one hour to about 40 hours. In addition, the present reaction is carried out preferably under an atmosphere of an inert gas (for example, nitrogen, argon or the like).

[Method D]



(1) condensation reaction
with Pd catalyst
(Suzuki reaction, etc.)



(2) etherification reaction
(Mitsunobu reaction, etc.)

or

(3) vinylation reaction
(Wittig reaction, etc.)

5 [1] Compound [V] [wherein V' indicates a halogen atom (for
example, bromine, iodine or the like) or a sulfonyloxy
group (the trifluoromethanesulfonyloxy group or the like)
and other symbols indicate the same meanings as indicated
hereinabove] is subjected to, for example, the Suzuki
10 reaction [a cross condensation reaction of an arylboric
acid and, for example, an aryl halide or an
aryloxytrifluoromethanesulfonate by the use of a palladium
catalyst; A. Suzuki, et al., Synth. Commun. 1981, 11, 513]
to be able to produce compound [I''], wherein X¹ indicates
15 a bond and R^{1'} indicates a 5- to 6-membered, cyclic ring
aromatic group. Compound [I''] can be obtained by the use
of an arylboric acid in an about equimolar amount to 1.5
molar amount per one mole of compound [V].

Also, compound [V] is subjected to, for example,
20 a cross condensation reaction with an arylacetylene

compound in the presence of a palladium catalyst [dichlorobis(triphenylphosphine)palladium or the like] [K. S. Y. Lau, et al., J. Org. Chem. 1981, 46, 2280; J. W. Tilley, S. Zawoisky, et al., J. Org. Chem. 1988, 53, 386] to be able to produce compound [I''] having an acetylenic bond, wherein X¹ indicates -C≡C-. Compound [I''] can be obtained by the use of an arylacetylene compound, usually, in an about equimolar amount to 2 molar amount per one mole of compound [V].

[2] Compound [V] [wherein V' indicates the hydroxyl group and other symbols indicate the same meanings as indicated hereinabove] is subjected to, for example, the Mitsunobu reaction [the etherification reaction by the use of a condensing agent such as, for example, triphenylphosphine and diethyl azodicarboxylate; O. Mitsunobu, et al., Synthesis, 1981, 1] to be able to produce compound [I''] having an ether bond. Compound [I''] can be obtained by the use of the corresponding alcohol compound or phenol compound in an about equimolar amount to 3 molar amount per one mole of compound [V].

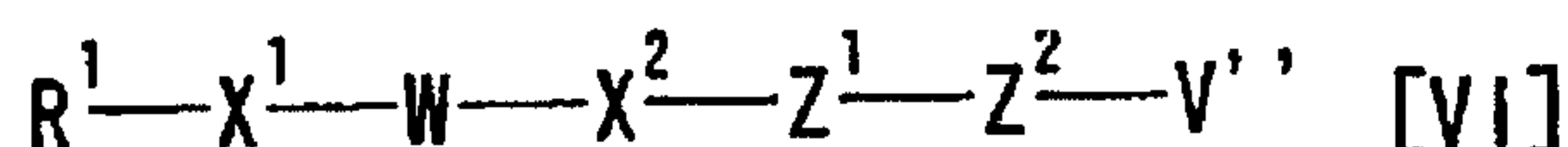
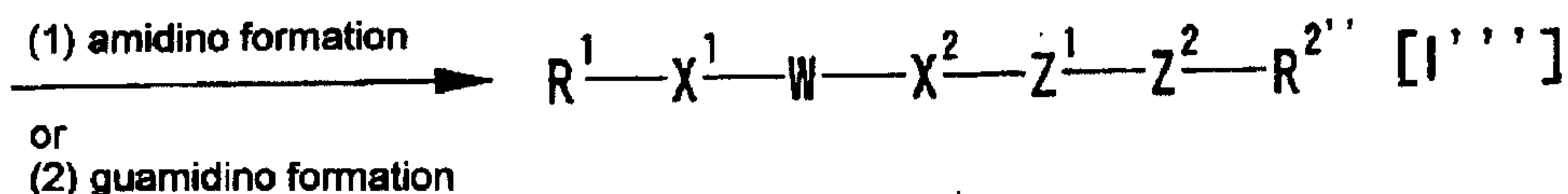
In addition, compound [I''] having an ether bond can be produced also by the etherification reaction of compound [V] with a reactive compound such as a halo (chloro, iodo or the like) compound, a tosylate compound, a mesylate compound or the like. Said reactive compound is

used usually in an about equimolar amount to 3 molar amount per one mole of compound [V]. This reaction can be allowed to proceed smoothly, as needed, by addition of an about equimolar amount to 3 molar amount of a base such as triethylamine, diisopropylethylamine, pyridine, lithium hydride, sodium hydride, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate or the like, and further by addition of sodium iodide, potassium iodide or the like. The present substitution reaction can be carried out in an inactive solvent, as exemplified by, for example, tetrahydrofuran, diethyl ether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine or the like, or a mixed solvent thereof. The reaction is carried out at a temperature range of about -10°C to about 180°C for about one hour to about 40 hours. In addition, the present reaction is carried out preferably under an atmosphere of an inert gas (for example, nitrogen, argon or the like).

[3] Compound [V] [wherein V' indicates the carbonyl group or a phosphonium salt, each of which may be substituted, or a phosphorous acid ester residue and other symbols indicate the same meanings as indicated hereinabove] is subjected to,

for example, the Wittig reaction [A. Maercker, Org. React. 14, 270 (1965)] or the Wittig-Horner-Emmons reaction [J. Boutagy, R. Thomas, Chem. Rev., 74, 87 (1974)] to be able to produce compound [I''] having a vinyl bond. The corresponding carbonyl compound or phosphonium salt, or the phosphorous acid ester residue is used usually, in an about equimolar amount to 1.5 molar amount per one mole of compound [V].

[Method E]



[1] First, compound [VI] [wherein V'' indicates the cyano group and other symbols indicate the same meanings as indicated hereinabove] is reacted with a lower alcohol such as methanol, ethanol, propanol or the like in the presence of an acid such as hydrochloric acid or the like to obtain an imidate compound. The present reaction is carried out usually by the use of an excess amount of the above-mentioned alcohol at a temperature range of about -10°C to about 50°C for about one hour to about 40 hours. Also, the present reaction can be carried out in an inactive solvent,

as exemplified by, for example, diethyl ether, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane or the like, or a mixed solvent thereof.

Next, the thus-obtained imidate compound is
5 subjected to the substitution reaction with a primary or secondary amine compound to be able to produce an amidine compound [I''']. The primary or secondary amine compound is used usually in an amount of about 1 to 5 moles per one mole of the imidate compound. This reaction can be allowed
10 to proceed smoothly, as needed, by addition of an about equimolar amount to 3 molar amount of a desalting agent such as triethylamine, pyridine, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate or the like. The
15 present substitution reaction can be carried out in an inactive solvent, as exemplified by, for example, methanol, ethanol, propanol, isopropanol, n-butanol, tetrahydrofuran, diethyl ether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-
20 dichloroethane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine or the like, or a mixed solvent thereof. The reaction is carried out at a temperature range of about 0°C to about 150°C for about one hour to about 50 hours. In addition, the present reaction is carried out preferably
25 under an atmosphere of an inert gas (for example, nitrogen,

argon or the like).

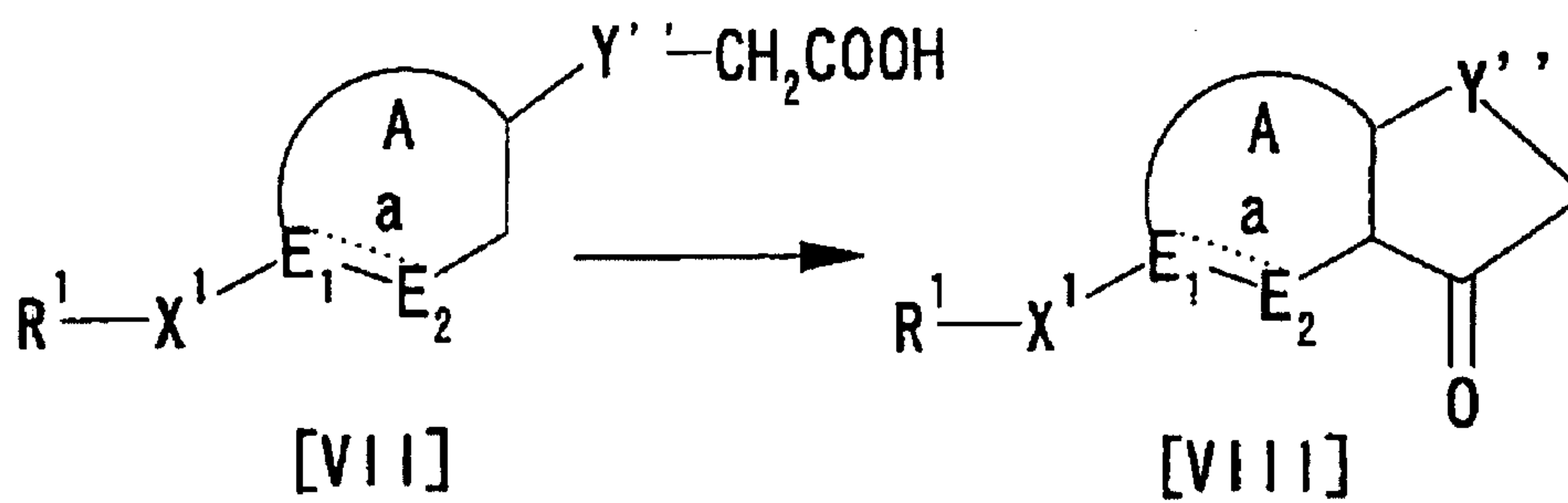
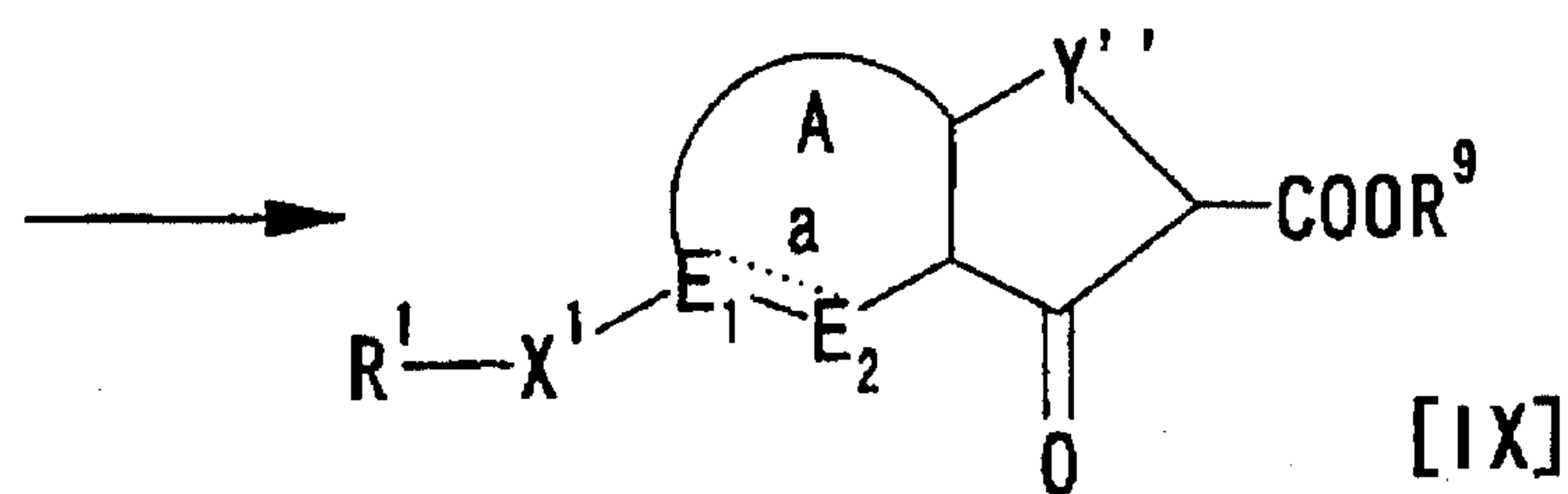
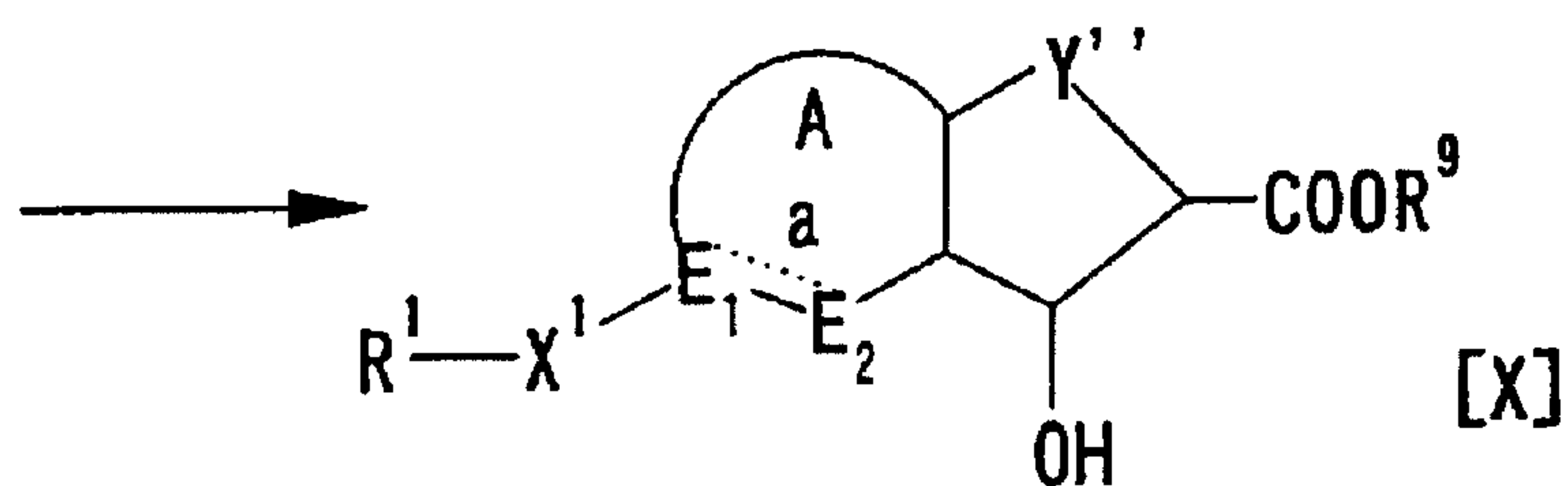
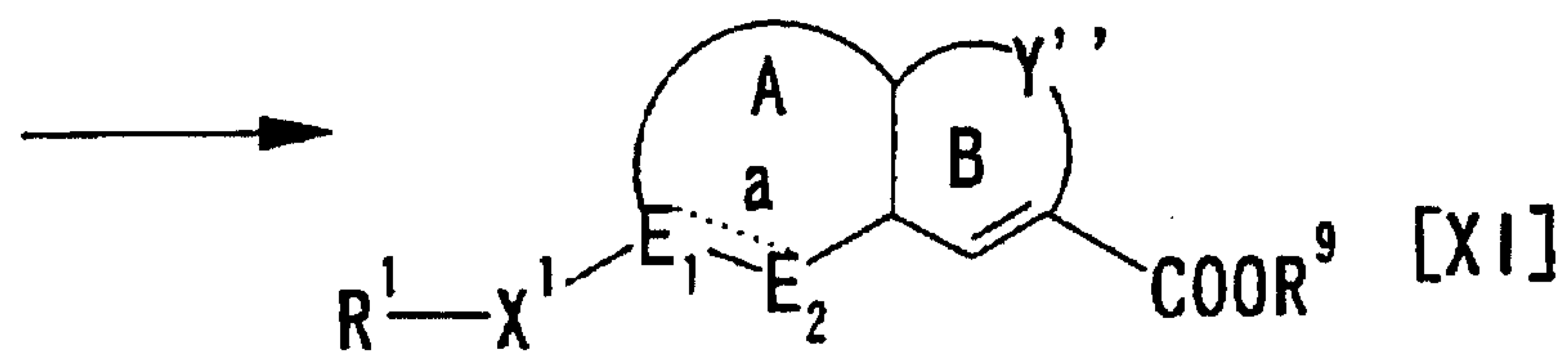
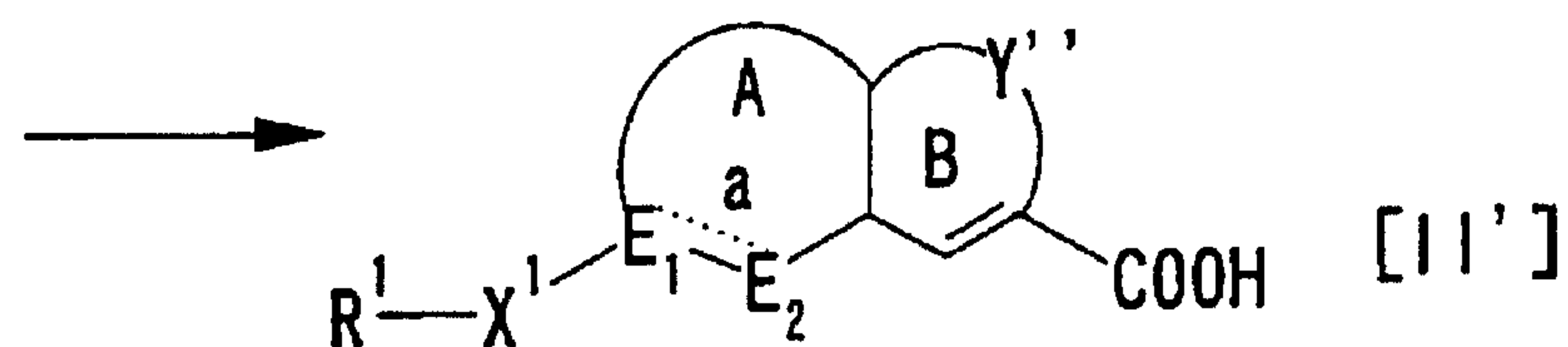
[2] Compound [VI] [wherein V'' indicates the amino group and other symbols indicate the same meanings as indicated hereinabove] is subjected to the substitution reaction with
5 an S-alkyl (for example, methyl, ethyl or the like)-isothiourea compound to be able to produce a guanidine compound [I''']. The S-alkyl-isothiourea compound is used usually in an equimolar amount to about 2 molar amount per one mole of compound [VI]. This reaction can be allowed to
10 proceed smoothly, as needed, by addition of an about equimolar amount to 3 molar amount of a desalting agent such as triethylamine, pyridine, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate or the like. The
15 present substitution reaction can be carried out in an inactive solvent, as exemplified by, for example, methanol, ethanol, propanol, isopropanol, n-butanol, tetrahydrofuran, diethyl ether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-
20 dichloroethane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine or the like, or a mixed solvent thereof. The reaction is carried out at a temperature range of about 0°C to about 150°C for about one hour to about 50 hours. In addition, the present reaction is carried out preferably
25 under an atmosphere of an inert gas (for example, nitrogen,

argon or the like).

The thus-obtained compound (I) can be subjected to isolation and purification according to the known separation and purification means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, trans-solubilization, chromatography and the like.

Compound [II-1] to be used as the starting material can be produced according to a known process (for instance, the process described in Japanese Patent Kokai Publication No. 1996-73476 or the like) or a modified process thereof, where, for instance, the material can be produced according to the process shown in reaction scheme I as well as the process indicated in Reference Examples described hereinafter or a modified process thereof.

Reaction Scheme I



[wherein R⁹ indicates a C₁₋₄ alkyl group, Y'' indicates a bivalent group without an unsaturated bond, through which

ring B forms a 5- to 7-membered cyclic ring, and other symbols indicate the same meanings as indicated hereinabove.]

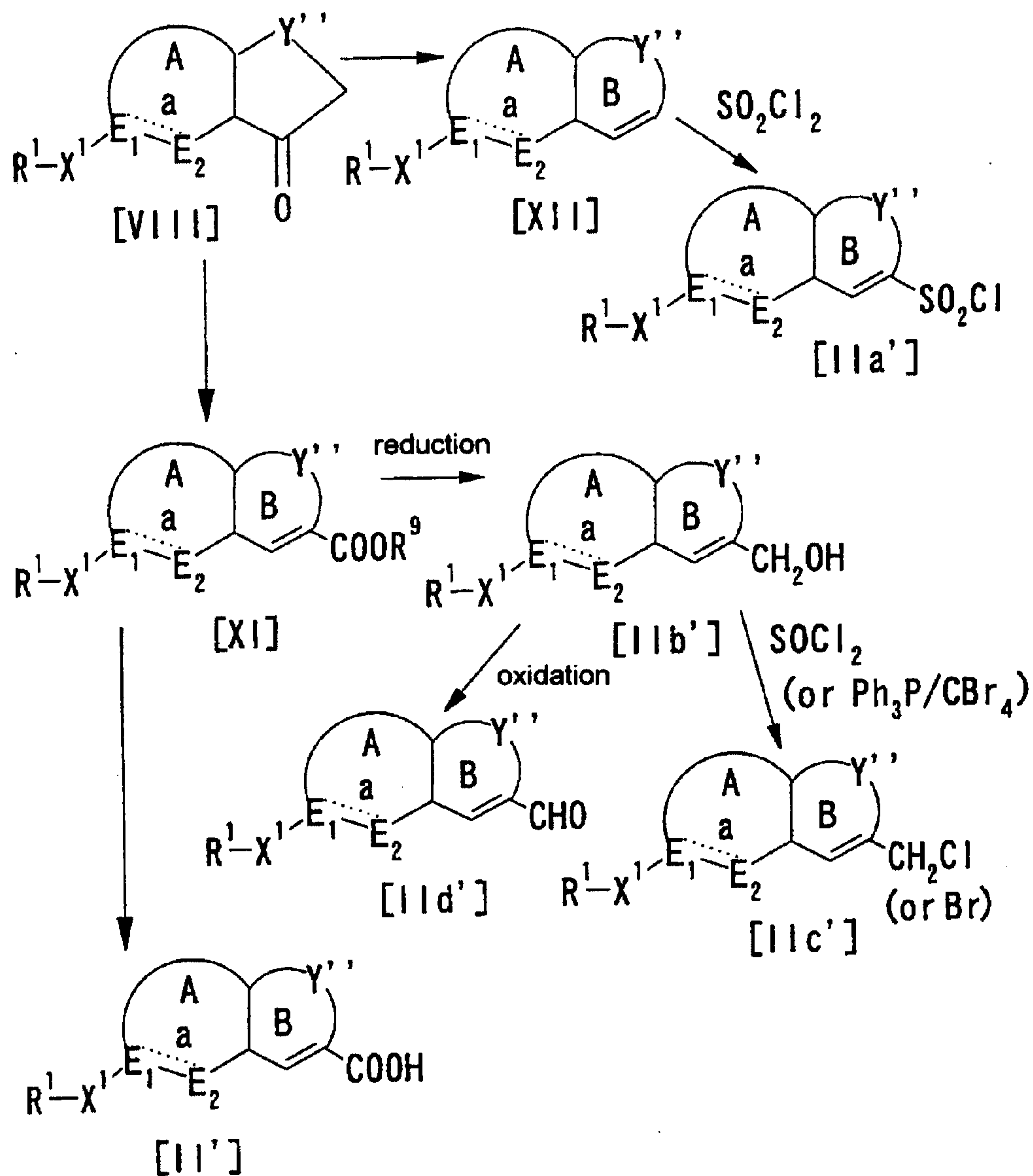
In the present process, first, a compound represented by formula [VII] is heated with polyphosphoric acid, or compound [VII] is treated with thionyl chloride, oxalyl chloride, phosphorus pentachloride or the like to be converted into the corresponding acid chloride, which is then subjected to cyclization by the conventional Friedel-Crafts reaction to produce compound [III]. Next, compound [III] is reacted with a carbonic acid ester in the presence of a base to produce a keto ester [IX]. Compound [IX] is converted into compound [X] by catalytic hydrogenation or the reduction reaction with sodium borohydride or the like. Compound [X] is subjected to the dehydration reaction according to a conventional method to produce an unsaturated carboxylic acid ester [XI], which is then subjected to the ester-hydrolysis reaction to produce an unsaturated carboxylic acid [II'].

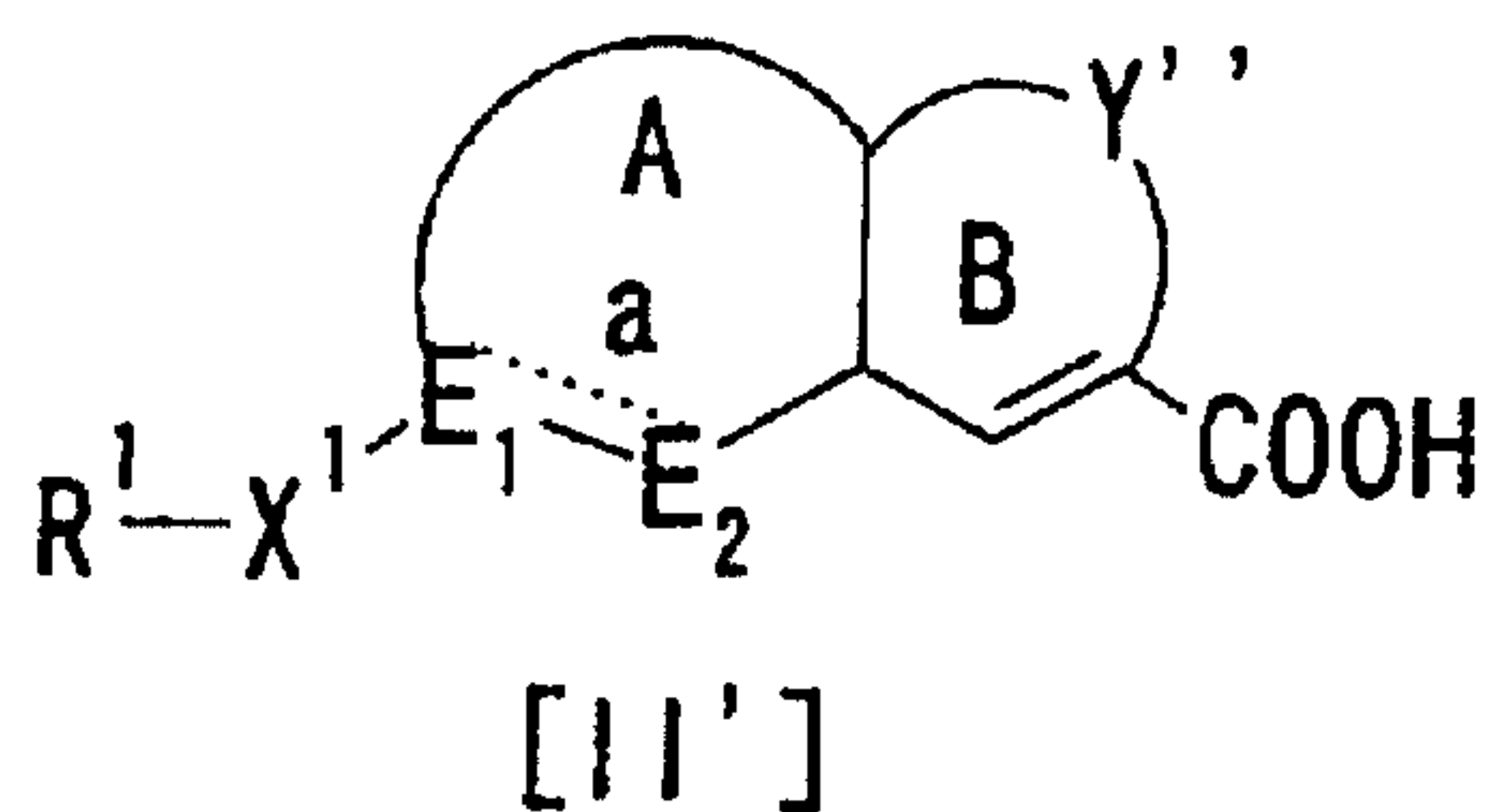
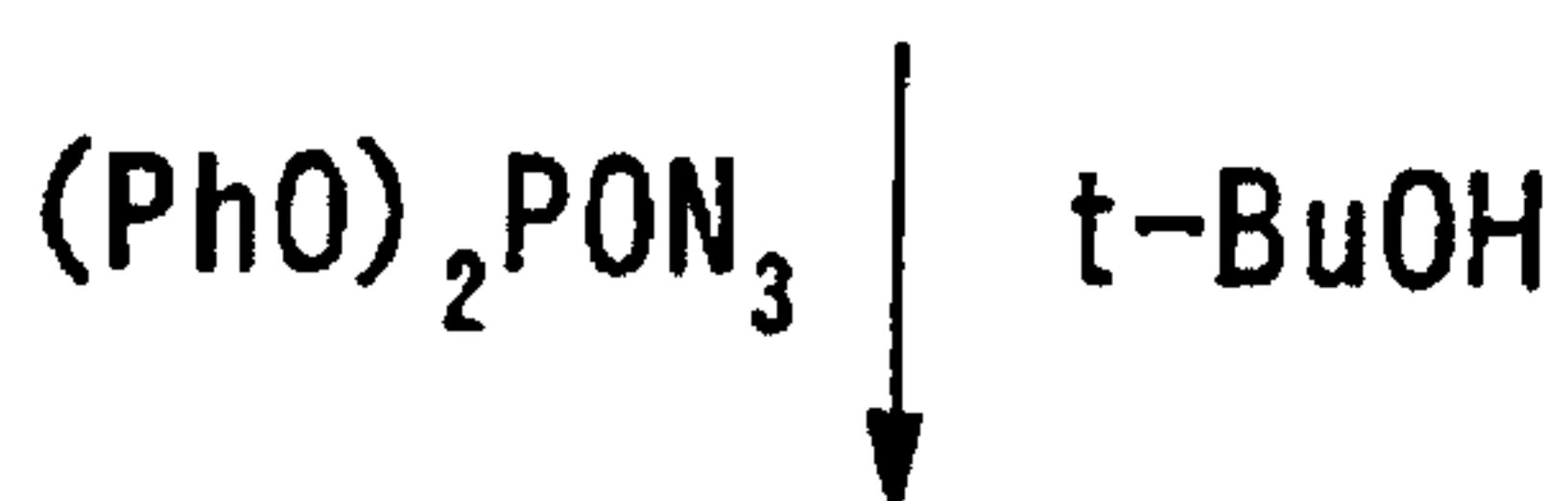
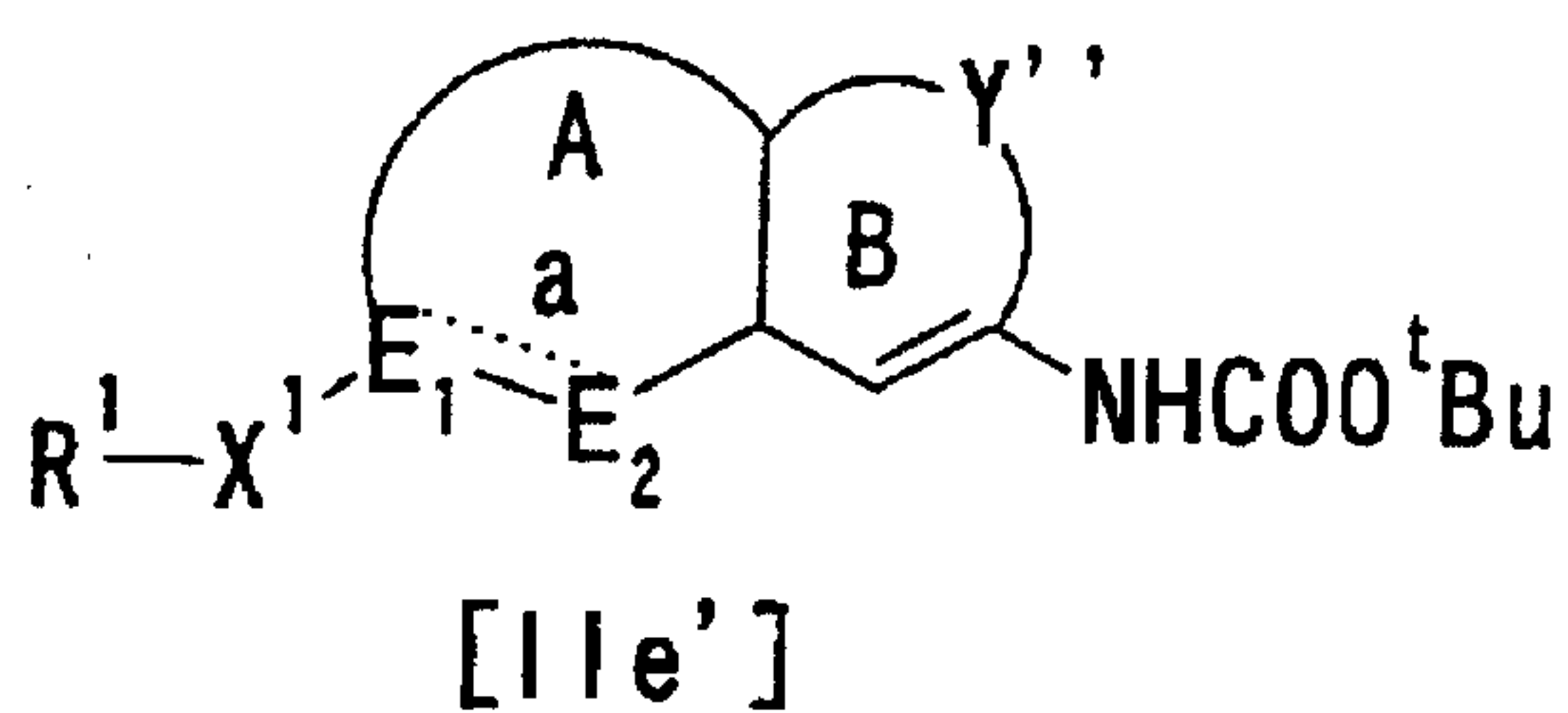
Of compound [II] to be used as the starting material, a compound wherein Xa^2 is not the carboxylic acid (for example, compound [II] wherein Xa^2 is the chlorosulfonyl group, the hydroxymethyl group, a halo (chloro or bromo) methyl group, the formyl group, the acetamido group or the like) can be produced according to

the process shown in reaction scheme II as well as the process indicated in Reference Examples described hereinafter or a modified process thereof.

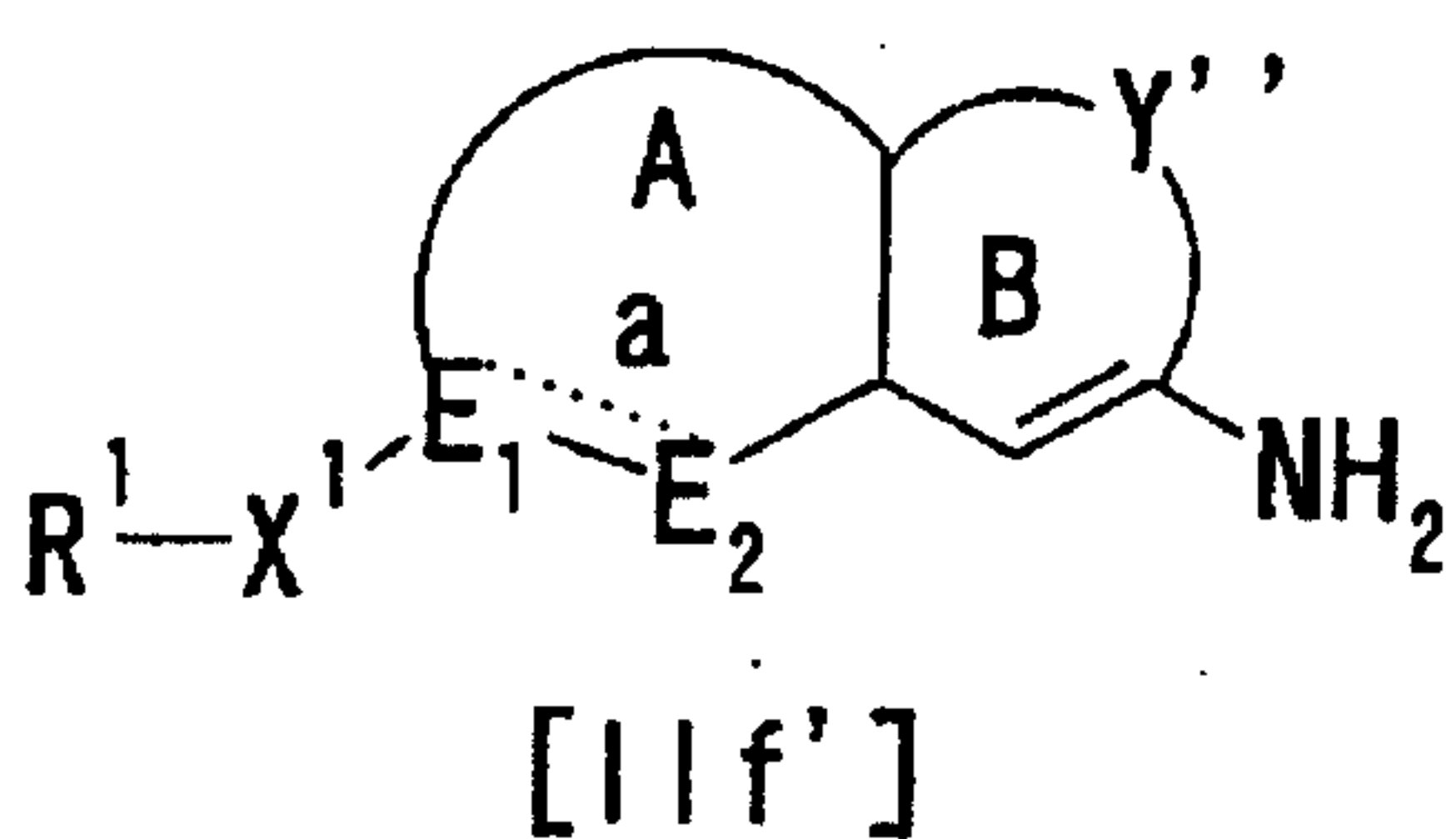
Reaction Scheme II

5





acid hydrolysis



5 [each of the symbols in the formula indicates the same meaning as indicated hereinabove.]

The sulfonyl chloride compound [II'a] can be produced by subjecting a compound represented by formula

[VIII] to the reduction according to a conventional method (the reduction with sodium borohydride or by catalytic hydrogenation or the like) followed by the dehydration reaction to produce compound [XII], which is subjected to the reaction with sulfuryl chloride.

The hydroxymethyl compound [II'b] can be produced by subjecting an ester compound represented by formula [XI] to the reduction according to a conventional method (the reduction with sodium borohydride, lithium aluminum hydride, diisobutylaluminum hydride (DIBAL) or the like). The thus-obtained hydroxymethyl compound [II'b] is subjected to the chlorination reaction with thionyl chloride or the like, or to the bromination reaction with triphenylphosphine-carbon tetrabromide or the like to be able to produce the halomethyl compound [II'c].

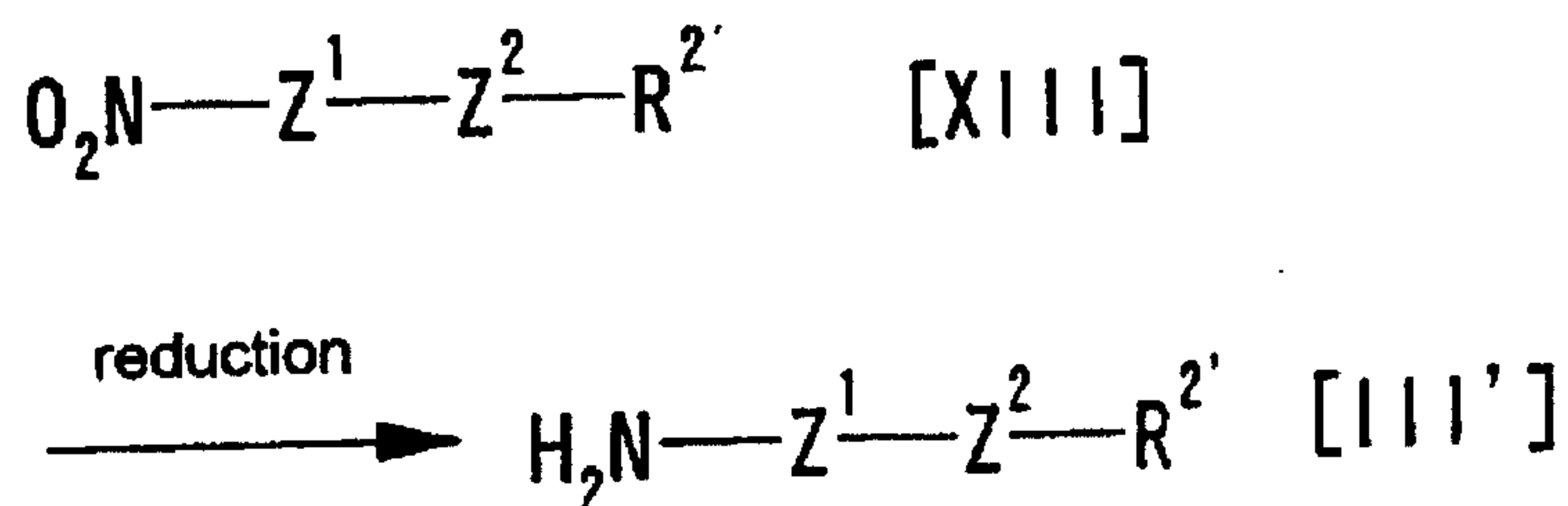
Also, the formyl compound [II'd] can be produced by subjecting a hydroxymethyl compound to the oxidation reaction with activated manganese dioxide or the like.

Furthermore, the amine compound [II'f] can be produced by subjecting a carboxylic acid compound represented by formula [II'] to the rearrangement reaction according to a conventional method with, for example, diphenylphosphoric acid amide (DPPA)-t-butanol to produce a urethane compound [II'e], which is then subjected to the acid-hydrolysis reaction.

The thus-obtained compound [II'a], [II'b], [II'c],
 [II'd], [II'e] or [II'f] and a compound represented by
 formula [III] are subjected to a variety of the above-
 mentioned reactions such as the amidation reaction, the
 5 tertiary amination reaction, the reductive amination
 reaction, the vinylation reaction, the etherification
 reaction, the alkylation (aralkylation) reaction and the
 like to be able to be converted into the compounds
 represented by formula (I) wherein X^2 is not the
 10 carbonylamido group.

In addition, compound [III-1] also can be
 produced according to a known process (for instance, the
 process described in Japanese Patent Kokai Publication No.
 1996-73476 or the like) or a modified process thereof,
 15 where, for instance, the material can be produced according
 to the process shown in reaction scheme III as well as the
 process indicated in Reference Examples described
 hereinafter or a modified process thereof.

20 Reaction Scheme III



[each of the symbols in the formula indicates the same meaning as indicated hereinabove.]

The reduction reaction of compound [III] can be
5 carried out according to the well-known methods. For
instance, the reduction with a metal, the reduction with a
metal hydride, the reduction with a metal hydride complex,
the reduction with diborane and a substituted diborane,
catalytic hydrogenation or the like. In other words, this
10 reaction is carried out by treating compound [XIII] with a
reducing agent. The reducing agent is exemplified by a
metal and a metallic salt such as a metal such as reduced
iron, zinc powder or the like, an alkaline metal
borohydride (for example, sodium borohydride, lithium
15 borohydride or the like), a metal hydride complex such as
lithium aluminum hydride or the like, a metal hydride such
as sodium hydride or the like, an organotin compound (such
as triphenyltin hydride or the like), a nickel compound, a
zinc compound or the like, a catalytic hydrogenation agent
20 by the use of a transition-metal catalyst such as platinum,
rhodium or the like and hydrogen, diborane and the like,
where a catalytic hydrogenation agent by the use of a
transition-metal catalyst such as platinum, rhodium or the
like and hydrogen as well as the reduction with a metal
25 such as reduced iron or the like are advantageously carried

out. The reaction is carried out in an organic solvent that is inert to the reaction. As for said solvent to be used, there is selected appropriately, depending on the kind of the reducing agent, from, for example, benzene, 5 toluene, xylene, chloroform, carbon tetrachloride, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, diethyl ether, tetrahydrofuran, dioxane, methanol, ethanol, propanol, isopropanol, 2-methoxyethanol, N,N-dimethylformamide, acetic acid or a mixed solvent 10 thereof. The reaction temperature is about -20°C to about 150°C, particularly preferably, about -0°C to about 100°C, and the reaction hour is about one hour to about 24 hours.

The thus-obtained compound (III') can be subjected to isolation and purification according to the 15 known separation and purification means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, trans-solubilization, chromatography and the like.

Because any of the compounds represented by 20 formula (I) of the present invention or a salt thereof possesses a potent CCR5 antagonistic action, it is employed for the prophylaxis and the therapeutics of a variety of HIV infectious diseases in the human, for example, AIDS. Any of the compounds represented by formula (I) of the 25 present invention or a salt thereof is of a low toxicity

and can be employed safely.

Any of the compounds represented by formula (I) of the present invention or a salt thereof can be employed as a CCR5 antagonistic agent, for instance, as a prophylactic and therapeutic agent of AIDS and a depressant against the pathologic progress of AIDS.

The daily dosage of any of the compounds represented by formula (I) or a salt thereof is different depending on the condition and the weight of the patient as well as the administration method, where, in the case of the oral administration, the dosage as the active ingredient [any of the compounds represented by formula (I) or a salt thereof] per an adult (a body weight of 50 kg) is about 5 mg to 1000 mg, preferably about 10 mg to 600 mg, further preferably about 10 mg to 300 mg, particularly preferably about 15 to 150 mg, where the daily dosage is administered once or with being divided in 2 to 3 times.

Also, in the case where any of the compounds represented by formula (I) or a salt thereof is employed in combination with a reverse transcriptase inhibitor and/or a protease inhibitor, the dosage of the reverse transcriptase inhibitor or the protease inhibitor is appropriately selected, for example, in a range of more than about 1/200 to 1/2 fold and less than 2 to 3 fold on the basis of the ordinary dosage. Furthermore, in the case where 2 or more

kinds of drugs are employed in combination, when a drug affects the metabolism of other drugs, the dosage of each of the drugs is appropriately modulated, but the dosage of each of the drugs in the case of the administration as a
5 single formulation is employed in general.

The ordinary dosages of the representative reverse transcriptase inhibitors and protease inhibitors are indicated, for instances, in the following.

Zidovudine: 100 mg
10 Didanosine: 125 to 200 mg
Zalcitabine: 0.75 mg
Lamivudine: 150 mg
Stavudine: 30 to 40 mg
Saquinavir: 600 mg
15 Ritonavir: 600 mg
Indinavir: 800 mg
Nelfinavir: 750 mg

In addition, in the following are shown the specific embodiments for the case where any of the
20 compounds represented by formula (I) or a salt thereof is employed in combination with the reverse transcriptase inhibitor and/or the protease inhibitor.

[1] About 10 to 300 mg of any of the compounds represented by formula (I) or a salt thereof per an adult (a body
25 weight of 50 kg) is administered to the same subject in a

pattern of combination with about 50 to 200 mg of zidovudine. Each of the drugs may be administered respectively at the same time, or may be administered at a time difference within 12 hours.

5 [2] About 10 to 300 mg of any of the compounds represented by formula (I) or a salt thereof per an adult (a body weight of 50 kg) is administered to the same subject in a pattern of combination with about 300 to 1200 mg of saquinavir. Each of the drugs may be administered
10 respectively at the same time, or may be administered at a time difference within 12 hours.

Best Mode for Carrying out the Invention

The present invention is embodied in more detail
15 by the following Experimental Examples, Formulation Examples, Reference Examples and Examples, but this embodiment is merely illustrative, and is not intended to restrict the present invention.

The genetic engineering procedures described
20 below were based on the methods described in the textbook (Maniatis, et al., Molecular Cloning, Cold Spring Harbor Laboratory, 1989) or the methods described in the protocols attached to the reagents.

25 Examples

Experimental Examples

(1) Cloning of human CCR5 chemokine receptor

CCR5 gene was cloned from human splenic cDNA by PCR method. With the use of 0.5 ng of splenic cDNA (Toyobo Co., Ltd., QUICK-Clone cDNA) as the template, the primer set, which were prepared by referring to the base sequence of the CCR5 gene reported by Samson et al. (Biochemistry 35 (11), 3362-3367 (1996)),

Sequence Number 1 described in experimental example (1) of WO99/32100 [sequence length: 34; sequence type: nucleic acid; chain number: single chain; topology: linear; sequence species: other nucleic acid, synthetic DNA] and Sequence Number 2 described in experimental example (1) of WO99/32100 [sequence length: 34; sequence type: nucleic acid; chain number: single chain; topology: linear; sequence species: other nucleic acid, synthetic DNA]

were added in amounts of 25 pmol each, and the PCR reaction was carried out in a DNA Thermal Cycler 480 (Perkin-Elmer Corp.) by the use of TaKaRa EX Taq (Takara Shuzo Co., Ltd.) (reaction conditions: 30 cycles of treatments at 95°C for one minute, at 60°C for one minute and at 75°C for 5 minutes). The PCR product was electrophoresed on an agarose gel, a DNA fragment of about 1.0 kb was recovered and then CCR5 gene was cloned by the use of Original TA Cloning Kit (Funakoshi Co., Ltd.).

(2) Preparation of expression plasmid of human CCR5

After the above-obtained plasmid was digested with restriction enzymes XbaI (Takara Shuzo Co., Ltd.) and BamHI (Takara Shuzo Co., Ltd.), the product was electrophoresed on an agarose gel to recover a DNA fragment of about 1.0 kb. This DNA fragment and a plasmid pcDNA3.1 (Funakoshi) expressible in animal cells, which is digested with XbaI and BamHI, were mixed and ligated by the use of DNA Ligation Kit Ver. 2 (Takara Shuzo Co., Ltd.), and competent cells of Escherichia coli JM109 (Takara Shuzo Co., Ltd.) were transformed with the ligation product to obtain plasmid pCKR5.

(3) Introduction of expression plasmid of human CCR5 into CHO-K1 cells and expression thereof

After CHO-K1 cells, which were grown in a 750-ml, tissue culture flask (Beckton, Dickinson and Company) using Ham F12 medium (Nihon Pharmaceutical Co., Ltd.) containing 10% fetal calf serum (Life Technologies Oriental, Inc.), were removed from the flask with 0.5/L trypsin-0.2 g/L EDTA (Life Technologies Oriental, Inc.), the cells were washed with PBS (Life Technologies Oriental, Inc.), were centrifuged (1000 rpm, 5 minutes) and were suspended in PBS. Next, DNA was introduced into the cells by the use of Gene Pulser (Bio-Rad Laboratories Inc.) under the following

conditions. In other words, 8×10^6 cells and 10 μg human CCR5 expression plasmid pCKR5 were added into a cuvette with a 0.4-cm gap, and the cells were electroporated at 0.25 kV under a capacitance of 960 μF . Subsequently, the
5 cells were transferred to Ham F12 medium containing 10% fetal calf serum, and were cultivated for 24 hours. The cells were then removed from the flask again for centrifugation, were then suspended in Ham F12 medium containing 10% fetal serum albumin containing geneticin
10 (Life Technologies Oriental, Inc.) at a final concentration of 500 $\mu\text{g}/\text{ml}$, were diluted to 10^4 cells/ml and were seeded into 96-well plates (Beckton, Dickinson and Company) to obtain geneticin-resistant strains.

Next, after the thus-obtained geneticin-resistant
15 strains were cultivated in a 96-well plate (Beckton, Dickinson and Company), cells expressing CCR5 were selected from the resistant strains. In other words, the binding reaction was carried out at room temperature for 40 minutes in an assay buffer (Ham F12 medium containing 0.5% BSA and
20 20 mM HEPES (Wako Pure Chemical Industries, Ltd.)) that is supplemented with 200 pM [^{125}I]-RANTES (Amersham plc) as a ligand, and the cells were washed with ice-cold PBS, were then stirred after adding 50 $\mu\text{l}/\text{well}$ of 1M NaOH and were counted for radioactivity in a γ -counter to select CHO/CCR5
25 strains, the cells to which the ligand was specifically

bound.

(4) Evaluation of compounds based on CCR5-
antagonistic activity

CHO/CCR5 strains were seeded into 96-well
5 microplates at a density of 5×10^4 cells/well, and were
cultivated for 24 hours. After the culture fluid was
removed by suction, the assay buffer containing a test
compound (1 μ M) was added to each well, and a ligand [^{125} I]-
RANTES (Amersham Corporation) was added to a final
10 concentration of 100 pM, after which the reaction was
carried out at room temperature for 30 minutes. Next,
after the assay buffer was removed by suction, the cells
were washed twice with ice-cold PBS. Subsequently, 200 μ l
of MicroScint-20 (Packard Industry Company, Inc.) was added
15 to each well, which was counted for radioactivity in a Top
Count (Packard Industry Company, Inc.).

Percentages of CCR5-binding inhibition by test
compounds were determined according to the method described
above. The results are shown in Table 1.

20 Table 1

Compound No.	Inhibition of binding (%)
19	86
20	94
21	98
56	74
94	76
100	89
108	86
121	82

Preparations of a CCR5 antagonist (for example, prophylactic and therapeutic drugs of HIV infection, prophylactic and therapeutic drugs of AIDS or the like), which contains as the active ingredient any of the compounds represented by formula (1) of the present invention or salts thereof, may be manufactured, for example, according to the following formulations:

Formulation Examples

10 1. Capsule preparation

(1) Compound obtained in Example 21	40 mg
(2) Lactose	70 mg
(3) Microcrystalline cellulose	9 mg
(4) Magnesium stearate	1 mg

15 1 capsule 120 mg

(1), (2), (3) and a half of (4) are mixed and are then granulated. Thereto is added the remaining (4), and the entire components are encapsulated.

2. Tablets

(1) Compound obtained in Example 21	40 mg
(2) Lactose	58 mg
(3) Corn starch	18 mg
(4) Microcrystalline cellulose	3.5 mg
(5) Magnesium stearate	0.5 mg

25 1 tablet 120 mg

(1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed and are then granulated. To the granules are added the remaining (4) and (5), and the resulting mixture is pressure-molded into tablets.

5 Reference Example 1

A solution of 4-methoxythiophenol (9.66 g), ethyl 4-bromobutyrate (13.5 g) and potassium carbonate (18.8 g) in DMF (200 ml) was stirred at room temperature for 4 hours. The reaction mixture was mixed with water and was extracted
10 with ethyl acetate. The organic layer was washed with water and an aqueous saturated solution of sodium chloride, and was dried with magnesium sulfate. After concentration under reduced pressure, into a solution of the residue in ethanol (200 ml) was added at room temperature a 1 N
15 aqueous solution of sodium hydroxide (85 ml), and the resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was evaporated under reduced pressure to remove the ethanol and was then extracted with diethyl ether. The organic layer was washed with an
20 aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the precipitated crystals were collected by filtration. The crystals were washed with hexane to obtain 4-[(4-methoxyphenyl)thio]butyric acid (13.09 g) as
25 colorless crystals.

^1H -NMR (200 MHz, CDCl_3) δ 1.81-1.96 (2H, m), 2.51 (2H, t, $J = 7.3$ Hz), 2.87 (2H, t, $J = 7.1$ Hz), 3.80 (3H, s), 6.85 (2H, d, $J = 8.8$ Hz), 7.35 (2H, d, $J = 8.8$ Hz).

Reference Example 2

5 A mixture of 4-[(4-methoxyphenyl)thio]butyric acid (10.0 g) and polyphosphoric acid (145 g) was stirred at 80-90°C for 25 minutes. The reaction mixture was mixed with ice and was extracted with ethyl acetate. The organic layer was washed with water, an aqueous saturated solution of sodium bicarbonate and an aqueous saturated solution of sodium chloride, and was dried with magnesium sulfate. After concentration under reduced pressure, the residue was subjected to separation and purification using column chromatography (ethyl acetate/hexane 1 : 7) to obtain 7-methoxy-3,4-dihydro-1-benzothiepin-5(2H)-one (3.87 g) as a yellow oily substance.

15 ^1H -NMR (200 MHz, CDCl_3) δ 2.17-2.31 (2H, m), 2.94 (2H, t, $J = 6.8$ Hz), 3.07 (2H, t, $J = 6.6$ Hz), 3.83 (3H, s), 6.94 (1H, dd, $J = 8.6, 3.0$ Hz), 7.383 (1H, d, $J = 8.6$ Hz), 8.384 (1H, d, $J = 3.0$ Hz).

Reference Example 3

25 A suspension of 7-methoxy-3,4-dihydro-1-benzothiepin-5(2H)-one (3.87 g) and sodium methoxide (5.0 g) in dimethyl carbonate (50 ml) was heated at reflux for 4 hours. The reaction mixture was mixed with 1 N

hydrochloric acid (100 ml) and was then extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. The resulting organic layer was concentrated under reduced pressure to obtain a yellow oily substance (4.96 g). Into a mixture of the thus-obtained oily substance, sodium borohydride (0.7 g) and THF (50 ml) was added dropwise at -40°C methanol (5 ml), and the resulting mixture was stirred at -10°C to -20°C for one hour. The reaction mixture was mixed with water and was then extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. The resulting organic layer was concentrated under reduced pressure to obtain a yellow oily substance (4.80 g). Into a solution of the thus-obtained oily substance and triethylamine (7.5 ml) in THF (50 ml) was added at 0°C methanesulfonyl chloride (2.09 ml), and the resulting mixture was stirred at 0°C for 0.5 hour and at room temperature for one hour. To this reaction mixture was added 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) (4.0 ml), and the resulting mixture was stirred for 2.5 hours. The reaction mixture was mixed with water and was then extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and

was dried with magnesium sulfate. After concentration under reduced pressure, the residue was subjected to separation and purification using column chromatography (ethyl acetate/hexane 1 : 5) to obtain methyl 7-methoxy-2,3-dihydro-1-benzothiepine-4-carboxylate (3.00 g) as a yellow oily substance.

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 2.86-2.92 (2H, m), 3.18-3.24 (2H, m), 3.81 (3H, s), 3.84 (3H, s), 6.78 (1H, dd, $J = 8.4, 3.0$ Hz), 6.90 (1H, d, $J = 3.0$ Hz), 7.41 (1H, d, $J = 8.4$ Hz), 7.77 (1H, s).

Reference Example 4

Into a solution of methyl 7-methoxy-2,3-dihydro-1-benzothiepine-4-carboxylate (3.00 g) in THF (30 ml) was added at 0°C 70% 3-chloroperbenzoic acid (6.5 g), and the resulting mixture was stirred at 0°C for 0.5 hour and at room temperature for one hour. The reaction mixture was mixed with an aqueous solution of sodium thiosulfate, was stirred for a few minutes and was then extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium bicarbonate (3 times) and an aqueous saturated solution of sodium chloride, and was dried with magnesium sulfate. After concentration under reduced pressure, the precipitated crystals were collected by filtration. The crystals were washed with diisopropyl ether to obtain methyl 7-methoxy-1,1-dioxo-2,3-dihydro-1-

benzothiepine-4-carboxylate (3.15 g) as colorless crystals.

M. p. 144-145°C

¹H-NMR (200 MHz, CDCl₃) δ 3.04-3.10 (2H, m), 3.59-3.65 (2H, m), 3.86 (3H, s), 3.90 (3H, s), 6.96-7.02 (2H, m),
5 7.79 (1H, s), 8.10 (1H, d, J = 10.0 Hz).

Elemental Analysis. Calcd. for C₁₃H₁₄O₅S: C, 55.31; H, 5.00. Found: C, 55.18; H, 5.01.

Reference Example 5

A mixture of methyl 7-methoxy-1,1-dioxo-2,3-
10 dihydro-1-benzothiepine-4-carboxylate (300 mg), 48% hydrobromic acid (3 ml) and acetic acid (3 ml) was heated at reflux for 4 hours. After concentration under reduced pressure, 48% hydrobromic acid (3 ml) and acetic acid (3 ml) were further added to the reaction mixture, which was
15 heated at reflux for 8 hours. After concentration under reduced pressure, the precipitated crystals were collected by filtration. The crystals were washed with diisopropyl ether to obtain 7-hydroxy-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (224 mg) as light yellow
20 crystals.

M. p. 260-265°C

¹H-NMR (200 MHz, DMSO-d₆) δ 2.84-2.90 (2H, m), 3.61-3.68 (2H, m), 6.92-7.02 (2H, m), 7.62 (1H, s), 7.85 (1H, d, J = 8.4 Hz).

25 Elemental Analysis. Calcd. for C₁₁H₁₀O₅S·0.1 H₂O: C,

51.59; H, 4.02. Found: C, 51.38; H, 3.87.

Reference Example 6

To a solution of 7-hydroxy-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (856 mg) in methanol (10 ml) was added sulfuric acid (0.1 ml), and the resulting mixture was heated at reflux for 23 hours. After concentration under reduced pressure, the reaction mixture was mixed with water and was then extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the precipitated crystals were collected by filtration. The crystals were washed with diisopropyl ether to obtain methyl 7-hydroxy-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (848 mg) as light yellow crystals.

M. p. 176-178°C

¹H-NMR (200 MHz, CDCl₃) δ 3.04-3.10 (2H, m), 3.59-3.66 (2H, m), 3.86 (3H, s), 6.01 (1H, br s), 6.90-6.94 (2H, m), 7.74 (1H, s), 8.05 (1H, d, J = 9.4 Hz).

Elemental Analysis. Calcd. for C₁₂H₁₂O₅S: C, 53.72; H, 4.51. Found: C, 53.67; H, 4.58.

Reference Example 7

A mixture of methyl 7-hydroxy-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (300 mg), 4-

chlorobenzyl chloride (210 mg), potassium carbonate (214 mg) and DMF (10 ml) was stirred at room temperature for 13 hours and at 50°C for 3 hours. The reaction mixture was mixed with water and was then extracted with ethyl acetate.

5 The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the residue was subjected to separation and purification using column chromatography (ethyl acetate/hexane 1 : 1) to
10 obtain methyl 7-[(4-chlorobenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (272 mg) as colorless crystals.

M. p. 130-133°C

¹H-NMR (200 MHz, CDCl₃) δ 3.07 (2H, t, J = 6.2 Hz),
15 3.58-3.65 (2H, m), 3.86 (3H, s), 5.12 (2H, s), 7.00-7.05 (2H, m), 7.32-7.42 (4H, m), 7.77 (1H, s), 8.10 (1H, d, J = 8.4 Hz).

Elemental Analysis. Calcd. for C₁₉H₁₇O₅SCl: C, 58.09; H, 4.36. Found: C, 58.11; H, 4.61.

20 Reference Example 8

Into a solution of methyl 7-[(4-chlorobenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (200 mg) in THF/methanol (3/1.5 ml) was added at room temperature an aqueous solution (0.7 ml) of
25 potassium carbonate (140 mg), and the resulting mixture was

stirred at 65-70°C for 23 hours. After cooling to room temperature, 1 N hydrochloric acid was added to the reaction mixture until the pH was adjusted to 5, and the precipitated crystals were collected by filtration. The
5 crystals were washed with water, 2-propanol and diisopropyl ether to obtain 7-[(4-chlorobenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (149 mg) as light yellow crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ 2.91 (2H, t, J = 6.6
10 Hz), 3.68 (2H, t, J = 6.6 Hz), 5.26 (2H, s), 7.22 (1H, dd, J = 8.8, 2.6 Hz), 7.37-7.54 (5H, m), 7.72 (1H, s), 7.95 (1H, d, J = 8.8 Hz).

Reference Example 9

To a solution of methyl 7-hydroxy-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (300 mg), 4-
15 ethoxybenzyl alcohol (0.36 g) and triphenylphosphine (0.62 g) in THF (10 ml) was added at 0°C diisopropyl azodicarboxylate (0.47 ml), and the resulting mixture was stirred at room temperature for 3.5 days. After
20 concentration under reduced pressure, the residue was subjected to separation and purification using column chromatography (ethyl acetate/hexane 1 : 1) to obtain methyl 7-[(4-ethoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (279 mg) as colorless crystals.

25 ¹H-NMR (200 MHz, CDCl₃) δ 1.43 (3H, t, J = 7.0 Hz),

3.03-3.10 (2H, m), 3.58-3.65 (2H, m), 3.85 (3H, s), 4.05 (2H, q, J = 7.0 Hz), 5.07 (2H, s), 6.92 (2H, d, J = 8.8 Hz) 7.01-7.06 (2H, m), 7.33 (2H, d, J = 8.8 Hz), 7.77 (1H, s), 8.08 (1H, d, J = 9.2 Hz).

5 Reference Example 10

 Into a suspension of methyl 7-[(4-ethoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (200 mg) in THF/methanol (6/3 ml) was added at room temperature an aqueous solution (0.7 ml) of potassium
10 carbonate (137 mg), and the resulting mixture was stirred at 70°C for 16.5 hours. After cooling to room temperature, 1 N hydrochloric acid was added to the reaction mixture, which was extracted with ethyl acetate. The organic layer
15 sodium chloride, and was dried with magnesium sulfate. After concentration under reduced pressure, the precipitated crystals were collected by filtration. The crystals were washed with diisopropyl ether to obtain methyl
20 7-[(4-ethoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (147 mg) as colorless crystals.

M. p. 180-184°C

¹H-NMR (200 MHz, DMSO-d₆) δ 1.33 (3H, t, J = 7.0 Hz), 2.86-2.93 (2H, m), 3.65-3.71 (2H, m), 4.03 (2H, q, J =
25 7.0 Hz), 5.15 (2H, s), 6.95 (2H, d, J = 8.8 Hz), 7.21 (1H,

dd, $J = 8.6, 2.4$ Hz), 7.37-7.41 (3H, m), 7.72 (1H, m), 7.94 (1H, d, $J = 8.6$ Hz).

Elemental Analysis. Calcd. for $C_{20}H_{20}O_6S$: C, 61.84; H, 5.19. Found: C, 61.85; H, 5.35.

5 Reference Example 11

A mixture of methyl 7-hydroxy-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (200 mg), 4-fluorobenzyl chloride (0.090 ml), potassium carbonate (134 mg) and DMF (5 ml) was stirred at 55°C for 7 hours. The reaction mixture was mixed with water and was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the residue was subjected to separation and purification using column chromatography (ethyl acetate/hexane 1 : 1) to obtain methyl 7-[(4-fluorobenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (162 mg) as colorless crystals.

M. p. 141-143°C

20 ^1H -NMR (200 MHz, $CDCl_3$) δ 3.03-3.10 (2H, m), 3.58-3.65 (2H, m), 3.85 (3H, s), 5.11 (2H, s), 7.01-7.14 (4H, m), 7.37-7.44 (2H, m), 7.77 (1H, m), 8.10 (1H, d, $J = 9.2$ Hz).

Elemental Analysis. Calcd. for $C_{19}H_{17}O_5SF$: C, 60.63; H, 4.55. Found: C, 60.52; H, 4.66.

25 Reference Example 12

Into a suspension of methyl 7-[(4-fluorobenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (327.4 mg) in THF/methanol (4/2 ml) was added at room temperature an aqueous solution (1.0 ml) of
5 potassium carbonate (240 mg), and the resulting mixture was stirred at 60°C for 20 hours. After cooling to room temperature, 1 N hydrochloric acid (5 ml) was added to the reaction mixture, which was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated
10 solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the precipitated crystals were collected by filtration. The crystals were washed with diisopropyl ether to obtain 7-[(4-fluorobenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (241 mg) as light yellow
15 crystals.

M. p. 270-273°C

¹H-NMR (200 MHz, DMSO-d₆) δ 2.87-2.94 (2H, m), 3.65-3.72 (2H, m), 5.23 (2H, s), 7.20-7.29 (3H, m), 7.43
20 (1H, d, J = 2.2 Hz), 7.50-7.57 (2H, m), 7.72 (1H, s), 7.95 (1H, d, J = 8.8 Hz).

Elemental Analysis. Calcd. for C₁₈H₁₅O₅SF: C, 59.66; H, 4.17. Found: C, 59.43; H, 4.41.

Reference Example 13

25 Into a solution of methyl 7-hydroxy-1,1-dioxo-

2,3-dihydro-1-benzothiepine-4-carboxylate (500 mg), 3-pyridinemethanol (405 mg) and triphenylphosphine (0.98 g) in THF (10 ml) was added at 0°C diethyl azodicarboxylate (a 40% solution in toluene) (1.62 g), and the resulting mixture was stirred at room temperature for 20 hours. After concentration under reduced pressure, the residue was subjected to separation and purification using column chromatography (ethyl acetate) to obtain methyl 7-(3-pyridylmethoxy)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (694 mg) as colorless crystals.

Into a suspension of methyl 7-(3-pyridylmethoxy)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (650 mg) in THF/methanol (6/3 ml) was added at room temperature an aqueous solution (1.4 ml) of potassium carbonate (415 mg), and the resulting mixture was stirred at 60°C for 19 hours. Into this reaction mixture was added further an aqueous solution (0.7 ml) of potassium carbonate (207 mg), and the resulting mixture was stirred further at 60°C for 3 days. After cooling to room temperature, 1 N hydrochloric acid was added to the reaction mixture until the pH was adjusted to 7-8, and the precipitated crystals were collected by filtration. The crystals were washed with diisopropyl ether to obtain methyl 7-(3-pyridylmethoxy)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (493 mg) as colorless crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ 2.87-2.94 (2H, m),
3.66-3.72 (2H, m), 5.31 (2H, s), 7.25 (1H, dd, J = 8.8, 2.6
Hz), 7.43-7.49 (2H, m), 7.73 (1H, s), 7.89-7.93 (1H, m),
7.96 (1H, d, J = 8.8 Hz), 8.58 (1H, dd, J = 4.8, 1.4 Hz),
5 8.70 (1H, d, J = 1.4 Hz).

Reference Example 14

Into a solution of methyl 4-hydroxymethylbenzoate
in DMF (100 ml) was added at 0°C 60% sodium hydride (1.3 g),
and the resulting mixture was stirred at room temperature
10 for 4 days. The reaction mixture was mixed with water and
was extracted with ethyl acetate. The organic layer was
washed with water and an aqueous saturated solution of
sodium chloride, and was dried with magnesium sulfate.
After concentration under reduced pressure, the residue was
15 subjected to separation and purification using column
chromatography (ethyl acetate/hexane 1 : 9) to obtain
methyl 4-propoxymethylbenzoate (2.09 g) as a colorless oily
substance.

¹H-NMR (200 MHz, CDCl₃) δ 0.95 (3H, t, J = 7.3 Hz),
20 1.57-1.74 (2H, m), 3.46 (2H, t, J = 6.6 Hz), 3.92 (3H, s),
4.56 (2H, s), 7.41 (2H, d, J = 8.7 Hz), 8.02 (2H, d, J =
8.7 Hz).

Reference Example 15

Into a suspension of lithium aluminum hydride
25 (0.40 g) in diethyl ether (25 ml) was added dropwise at 0°C

a solution of methyl 4-(propoxymethyl)benzoate (2.09 g) in diethyl ether (25 ml) over a period of one hour. After stirring at room temperature for 2 hours, water (0.4 ml), a 15% aqueous solution of sodium hydroxide (0.4 ml) and water (0.4 ml) were added to the reaction mixture at 0°C, and the resulting mixture was stirred at room temperature for 2 hours. After addition of magnesium sulfate, the solid was removed by filtration. The filtrate was evaporated under reduced pressure to remove the solvent to obtain 4-(propoxymethyl)benzyl alcohol (1.81 g) as a colorless oily substance.

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 0.94 (3H, t, $J = 7.3$ Hz), 1.57-1.69 (3H, m), 3.43 (2H, t, $J = 6.6$ Hz), 4.51 (2H, s), 4.69 (2H, d, $J = 5.8$ Hz), 7.35 (4H, s).

Reference Example 16

Into a solution of methyl 7-hydroxy-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (400 mg), 4-(propoxymethyl)benzyl alcohol (502 mg) and triphenylphosphine (782 mg) in THF (10 ml) was added at 0°C diethyl azodicarboxylate (a 40% solution in toluene) (1.30 g), and the resulting mixture was stirred at room temperature for 68 hours. After concentration under reduced pressure, the residue was subjected to separation and purification using column chromatography (ethyl acetate/hexane 1 : 1) to obtain methyl 7-[[4-

(propoxymethyl)benzyl]oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (1.15 g) as colorless crystals.

Into a solution of methyl 7-[[4-(propoxymethyl)benzyl]oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (1.15 g) in THF/methanol (10/5 ml) was added at room temperature an aqueous solution (2.1 ml) of potassium carbonate (622 mg), and the resulting mixture was stirred at 60°C for 2 days. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate. To the aqueous layer was added 1 N hydrochloric acid until the pH was adjusted to 2-3, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the precipitated crystals were collected by filtration. The crystals were washed with diisopropyl ether to obtain 7-[[4-(propoxymethyl)benzyl]oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (425 mg) as colorless crystals.

M. p. 210-213°C

¹H-NMR (200 MHz, DMSO-d₆) δ 0.88 (3H, t, J = 7.4 Hz), 1.46-1.64 (2H, m), 2.87-2.93 (2H, m), 3.38 (2H, t, J = 6.6 Hz), 3.65-3.71 (2H, m), 4.46 (2H, s), 5.24 (2H, s), 7.22 (1H, dd, J = 8.8, 2.6 Hz), 7.33-7.47 (5H, m), 7.72 (1H,

s), 7.94 (1H, d, J = 8.8 Hz).

Elemental Analysis. Calcd. for $C_{22}H_{24}O_6S$: C, 63.44; H, 5.81. Found: C, 63.29; H, 5.76.

Example 1 (Production of compound 1)

5 Into a suspension of 7-[(4-chlorobenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (110 mg) in THF (5 ml) were added at room temperature thionyl chloride (0.042 ml) and one drop of DMF, and the resulting mixture was stirred for one hour. After concentration
10 under reduced pressure to remove the solvent, the residue dissolved in THF (5 ml) was added dropwise to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (70 mg) and triethylamine (0.2 ml) in THF (5 ml) at room temperature. After being stirred at room temperature for
15 2.5 hours, the reaction mixture was mixed with water and was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the residue was
20 subjected to purification using column chromatography (ethanol/ethyl acetate 1 : 3) and to recrystallization (ethanol) to obtain 7-[[4-(chlorobenzyl)oxy]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-3,4-dihydro-1-benzothiepine-4-carboxamide (compound
25 1) (104 mg) as colorless crystals.

M. p. 237-239°C

¹H-NMR (200 MHz, CDCl₃) δ 1.67-1.82 (4H, m), 2.21 (3H, s), 2.55-2.72 (1H, m), 3.09 (2H, t, J = 6.8 Hz), 3.30-3.44 (2H, m), 3.58 (2H, s), 3.69 (2H, t, J = 6.8 Hz), 3.98-4.09 (2H, m), 5.12 (2H, s), 6.98-7.09 (2H, m), 7.21 (1H, s), 7.32 (2H, d, J = 8.4 Hz), 7.37-7.42 (4H, m), 7.54 (2H, d, J = 8.4 Hz), 7.91 (1H, s), 8.10 (1H, d, J = 8.8 Hz).

Elemental Analysis. Calcd. for C₃₁H₃₃N₂O₅SCl: C, 64.07; H, 5.72, N, 4.82. Found: C, 64.03; H, 5.81, N, 5.00.

10 Example 2 (Production of compound 2)

Into a solution of 7-[(4-ethoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (110 mg) in THF (5 ml) were added at room temperature thionyl chloride (0.041 ml) and one drop of DMF, and the resulting mixture was stirred for one hour. After concentration under reduced pressure to remove the solvent, the residue dissolved in THF (5 ml) was added dropwise to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (69 mg) and triethylamine (0.2 ml) in THF (5 ml) at room temperature. After being stirred at room temperature for 1.5 hours, the reaction mixture was mixed with water and was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the residue was

subjected to purification using column chromatography (ethanol/ethyl acetate 1 : 3) and to recrystallization (ethanol) to obtain 7-[[4-(ethoxybenzyl)oxy]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-3,4-dihydro-1-benzothiepine-4-carboxamide (compound 2) (109 mg) as colorless crystals.

M. p. 211-213°C

¹H-NMR (200 MHz, CDCl₃) δ 1.43 (3H, t, J = 7.2 Hz), 1.68-1.82 (4H, m), 2.21 (3H, s), 2.54-2.74 (1H, m), 3.05-3.12 (2H, m), 3.29-3.44 (2H, m), 3.58 (2H, s), 3.66-3.72 (2H, m), 3.98-4.10 (4H, m), 5.07 (2H, s), 6.92 (2H, d, J = 8.8 Hz), 6.98 (1H, d, J = 2.6 Hz), 7.04 (1H, dd, J = 8.4, 2.6 Hz), 7.20 (1H, s), 7.30-7.35 (4H, m), 7.54 (2H, d, J = 8.8 Hz), 7.91 (1H, s), 8.09 (1H, d, J = 8.4 Hz).

Elemental Analysis. Calcd. for C₃₃H₃₈N₂O₆S: C, 67.10; H, 6.48, N, 4.74. Found: C, 66.94; H, 6.50, N, 4.89.

Example 3 (Production of compound 3)

Into a suspension of 7-[(4-fluorobenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (170 mg) in THF (5 ml) were added at room temperature thionyl chloride (0.068 ml) and one drop of DMF, and the resulting mixture was stirred for one hour. After concentration under reduced pressure to remove the solvent, the residue dissolved in THF (10 ml) was added dropwise to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline

(114 mg) and triethylamine (0.2 ml) in THF (5 ml) at 0°C. After being stirred at room temperature for 20 hours, the reaction mixture was mixed with water and was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the residue was subjected to purification using column chromatography (ethanol/ethyl acetate 1 : 3) and to recrystallization (ethanol) to obtain 7-(4-fluorobenzyloxy)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-3,4-dihydro-1-benzothiepine-4-carboxamide (compound 3) (206 mg) as colorless crystals.

M. p. 232-234°C

¹H-NMR (200 MHz, CDCl₃) δ 1.67-1.83 (4H, m), 2.20 (3H, s), 2.55-2.72 (1H, m), 3.06-3.13 (2H, m), 3.31-3.44 (2H, m), 3.57 (2H, s), 3.65-3.72 (2H, m), 3.99-4.10 (2H, m), 5.11 (2H, s), 6.98-7.15 (4H, m), 7.21 (1H, s), 7.32 (2H, d, J = 8.4 Hz), 7.37-7.44 (2H, m), 7.53 (2H, d, J = 8.4 Hz), 7.80 (1H, s), 8.10 (1H, d, J = 8.8 Hz).

Elemental Analysis. Calcd. for C₃₁H₃₃N₂O₅SF: C, 65.94; H, 5.89, N, 4.96. Found: C, 65.59; H, 5.67, N, 4.97.

Example 4 (Production of compound 4)

Into a solution of 7-(3-pyridylmethoxy)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (200

mg) in DMF (5 ml) was added at room temperature thionyl chloride (0.084 ml), and the resulting mixture was stirred for one hour. After concentration under reduced pressure to remove the solvent, the residue dissolved in DMF (5 ml) was added dropwise to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (141 mg) and triethylamine (0.4 ml) in THF (5 ml) at room temperature. After being stirred at room temperature for 18 hours, the reaction mixture was mixed with water and was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the residue was subjected to purification using column chromatography (ethyl acetate) and to recrystallization (ethanol) to obtain N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(3-pyridylmethoxy)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (compound 4) (77 mg) as colorless crystals.

M. p. 225-229°C

¹H-NMR (200 MHz, CDCl₃) δ 1.67-1.80 (4H, m), 2.21 (3H, s), 2.55-2.74 (1H, m), 3.07-3.14 (2H, m), 3.30-3.44 (2H, m), 3.57 (2H, s), 3.67-3.73 (2H, m), 3.99-4.09 (2H, m), 5.17 (2H, s), 7.01-7.08 (2H, m), 7.22 (1H, s), 7.30-7.40 (3H, m), 7.53 (2H, d, J = 8.4 Hz), 7.73-7.81 (1H, m), 7.83-7.89 (1H, m), 8.12 (1H, d, J = 8.6 Hz), 8.62-8.72 (2H, m).

Elemental Analysis. Calcd. for $C_{30}H_{33}N_3O_5S \cdot 0.2 H_2O$:
C, 65.36; H, 6.11, N, 7.62. Found: C, 65.13; H, 6.07, N,
7.50.

Example 5 (Production of compound 5)

5 Into a solution of 7-[[(4-
(propoxymethyl)benzyl)oxy]-1,1-dioxo-2,3-dihydro-1-
benzothiepine-4-carboxylic acid (200 mg) in THF (5 ml) were
added at room temperature thionyl chloride (0.070 ml) and
one drop of DMF, and the resulting mixture was stirred for
10 one hour. After concentration under reduced pressure to
remove the solvent, the residue dissolved in THF (10 ml)
was added dropwise to a solution of 4-[N-methyl-N-
(tetrahydropyran-4-yl)aminomethyl]aniline (116 mg) and
triethylamine (0.27 ml) in THF (5 ml) at 0°C. After being
15 stirred at room temperature for 2 days, the reaction
mixture was mixed with water and was extracted with ethyl
acetate. The organic layer was washed with an aqueous
saturated solution of sodium chloride and was dried with
magnesium sulfate. After concentration under reduced
20 pressure, the residue was subjected to purification using
column chromatography (ethanol/ethyl acetate 1 : 3) and to
recrystallization (ethanol) to obtain N-[4-[N-methyl-N-
(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[[(4-
(propoxymethyl)benzyl)oxy]-1,1-dioxo-2,3-dihydro-1-
25 benzothiepine-4-carboxamide (compound 5) (199 mg) as

colorless crystals.

M. p. 201-203°C

^1H -NMR (200 MHz, CDCl_3) δ 0.95 (3H, t, $J = 7.5$ Hz),
1.58-1.84 (6H, m), 2.20 (3H, s), 2.56-2.73 (1H, m), 3.05-
5 3.12 (2H, m), 3.31-3.44 (2H, m), 3.46 (2H, t, $J = 6.6$ Hz),
3.57 (2H, s), 3.65-3.72 (2H, m), 3.99-4.10 (2H, m), 4.52
(2H, s), 5.15 (2H, s), 6.98-7.07 (2H, m), 7.20 (1H, s),
7.32 (2H, d, $J = 8.6$ Hz), 7.39 (4H, m), 7.53 (2H, d, $J =$
8.6 Hz), 7.85 (1H, s), 8.09 (1H, d, $J = 8.8$ Hz).

10 Elemental Analysis. Calcd. for $\text{C}_{35}\text{H}_{42}\text{N}_2\text{O}_6\text{S}$: C,
67.94; H, 6.84, N, 4.53. Found: C, 67.86; H, 6.69, N, 4.57.

Reference Example 17

A mixture of ethynylbenzene (511 mg, 5.00 mmol),
methyl 7-bromo-2,3-dihydro-1-benzooxepine-4-carboxylate
15 (708 mg, 2.50 mmol),
dichlorobis(triphenylphosphine)palladium (176 mg, 0.25
mmol), copper iodide (48 mg, 0.25 mmol) and triethylamine
(15 ml) was stirred at 80°C for 17 hours. The reaction
mixture was concentrated under reduced pressure and was
20 mixed with ethyl acetate (70 ml), and the resulting mixture
was washed successively with 1 N hydrochloric acid (5 ml $\times$
3) and an aqueous saturated solution of sodium chloride (5
ml). The organic layer was dried with anhydrous magnesium
sulfate and was then concentrated under reduced pressure,
25 and the residue was subjected to column chromatography

(silica gel: 35 g, ethyl acetate/hexane = 1/19). The objective fractions were concentrated under reduced pressure and were mixed with diisopropyl ether, and an insoluble material was collected by filtration. The insoluble material was washed with diisopropyl ether and was then dried under reduced pressure to obtain methyl 7-phenylethynyl-2,3-dihydro-1-benzoxepine-4-carboxylate (525 mg, 1.73 mmol, 69%).

IR (KBr): 1709, 1501 cm^{-1} .

^1H -NMR (CDCl_3) δ : 2.9-3.05 (2H, m), 3.83 (3H, s), 4.2-4.35 (2H, m), 6.96 (1H, d, $J = 8.6$ Hz), 7.3-7.6 (8H, m).

Reference Example 18

To methyl 7-phenylethynyl-2,3-dihydro-1-benzoxepine-4-carboxylate (463 mg, 1.52 mmol) were added methanol (10 ml), THF (10 ml) and a 1 N aqueous solution of sodium hydroxide (4.56 ml), and the resulting mixture was stirred at room temperature for 24 hours. After addition of 1 N hydrochloric acid (4.56 ml), the reaction mixture was concentrated under reduced pressure and was mixed with water, and an insoluble material was collected by filtration. The insoluble material was successively washed with water and diisopropyl ether, and was then dried under reduced pressure to obtain 7-phenylethynyl-2,3-dihydro-1-benzoxepine-4-carboxylic acid (417 mg, 1.44 mmol, 94%).

¹H-NMR (DMSO-d₆) δ: 2.8-2.95 (2H, m), 4.2-4.35 (2H, m), 7.02 (1H, d, J = 8.6 Hz), 7.35-7.6 (7H, m), 7.72 (1H, d, J = 2.2 Hz).

Example 6 (Production of compound 6)

5 To 7-phenylethynyl-2,3-dihydro-1-benzooxepine-4-carboxylic acid (140 mg, 0.48 mmol) dissolved in DMF (7 ml) were added at 0°C 1-hydroxybenzotriazole (72 mg, 0.53 mmol), 4-[N-methyl-N-(tetrahydropyranyl)aminomethyl]aniline (117 mg, 0.53 mmol), 1-ethyl-3-(3-
10 dimethylaminopropyl)carbodiimide hydrochloride (139 mg, 0.73 mmol), triethylamine (0.202 ml, 1.45 mmol) and 4-dimethylaminopyridine (3 mg), and the resulting mixture was stirred at room temperature for 14 hours. The reaction mixture was concentrated under reduced pressure and was
15 mixed with ethyl acetate (60 ml), and the resulting mixture was washed successively with water (5 ml x 3), an aqueous saturated solution of sodium bicarbonate (5 ml x 3) and an aqueous saturated solution of sodium chloride (5 ml). The organic layer was dried with anhydrous magnesium sulfate
20 and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate). The objective fractions were concentrated under reduced pressure and were mixed with diisopropyl ether, and an insoluble material was collected
25 by filtration. The insoluble material was washed with

diisopropyl ether and was then dried under reduced pressure to obtain N-[4-[N-methyl-N-(4-tetrahydropyranyl)aminomethyl]phenyl]-7-phenylethynyl-2,3-dihydro-1-benzooxepine-4-carboxamide (compound 6) (202 mg, 0.41 mmol, 85%).

IR (KBr): 1653, 1595, 1514, 1501 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.5-1.85 (4H, m), 2.22 (3H, s), 2.5-2.8 (1H, m), 3.0-3.15 (2H, m), 3.3-3.45 (2H, m), 3.58 (2H, s), 3.95-4.15 (2H, m), 4.3-4.45 (2H, m), 6.99 (1H, d, $J = 8.4$ Hz), 7.15 (1H, s), 7.25-7.6 (11H, m).

Reference Example 19

To 3-hydroxy-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene (1.76 g, 10.0 mmol) dissolved in DMF (10 ml) were added potassium carbonate (2.76 g, 20.2 mmol) and benzyl bromide (1.308 ml, 11.0 mmol), and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, and the residue was mixed with water (20 ml) and extracted with ethyl acetate (20 ml $\times$ 3). The combined organic layers were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 35 g, ethyl acetate/hexane = 1/9). The objective fractions were concentrated under reduced pressure to obtain 3-benzyloxy-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene (2.79 g).

IR (KBr): 1674 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3) δ : 1.7-1.95 (4H, m), 2.65-2.8 (2H, m), 2.8-2.95 (2H, m), 5.08 (2H, s), 7.04 (1H, dd, $J = 2.6$, 8.4 Hz), 7.13 (1H, d, $J = 8.4$ Hz), 7.25-7.5 (6H, m).

5 Reference Example 20

To 3-benzyloxy-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene (2.72 g) dissolved in dimethyl carbonate (30 ml) was added sodium methoxide (2.70 g, 50.0 mmol), and the resulting mixture was stirred at reflux with heating
10 (110°C) for 6 hours. The reaction mixture was mixed with 1 N hydrochloric acid (60 ml) under ice cooling and was concentrated under reduced pressure to remove the organic solvent, and the aqueous layer was then extracted with ethyl acetate (30 ml $\times$ 3). The combined organic layers
15 were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 40 g, ethyl acetate/hexane = 1/30). The objective fractions were concentrated under reduced pressure to obtain methyl 3-
20 benzyloxy-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene-6-carboxylate (2.88 g, 8.88 mmol).

Reference Example 21

To methyl 3-benzyloxy-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene-6-carboxylate (2.81 g, 8.66 mmol)
25 dissolved in a mixed solvent of dichloromethane (40 ml) and

methanol (10 ml) was added at -40°C (inner temperature) sodium borohydride (500 mg, 13.2 mmol), and the resulting mixture was stirred at -15°C to -10°C for 2 hours. The reaction mixture was cooled to -40°C, was mixed with water (20 ml) and extracted with dichloromethane (40 ml, 10 ml x 2). The combined organic layers were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure. To the residue dissolved in THF (30 ml) were added at 0°C triethylamine (6.04 ml, 43.3 mmol) and methanesulfonyl chloride (1.10 ml, 13.0 mmol), and the resulting mixture was stirred at room temperature for 20 hours. In order to complete the reaction, DBU (3.89 ml, 26.0 mmol) was added, and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, was mixed with water and was extracted with ethyl acetate (30 ml x 3). The combined organic layers were washed with 1 N hydrochloric acid (5 ml x 3), were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 60 g, ethyl acetate/hexane = 1/30 → 1/9). The objective fractions were concentrated under reduced pressure to obtain methyl 2-benzyloxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (2.32 g, 7.52 mmol, 87%).

IR (KBr): 1709 cm⁻¹.

¹H-NMR (CDCl₃) δ: 1.95-2.1 (2H, m), 2.55-2.65 (2H, m), 2.7-2.8 (2H, m), 3.81 (3H, s), 5.06 (2H, s), 6.84 (1H, dd, J = 2.6, 8.4 Hz), 6.94 (1H, d, J = 2.6 Hz), 7.06 (1H, d, J = 8.4 Hz), 7.5-7.7 (5H, m), 7.64 (1H, s).

5 Reference Example 22

To methyl 2-benzyloxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (2.28 g, 7.39 mmol) suspended in methanol (25 ml) was added a 1N aqueous solution of sodium hydroxide (23 ml), and the resulting
10 mixture was stirred at room temperature for 13 hours. In order to complete the reaction, tetrahydrofuran (25 ml) was added, and the resulting mixture was stirred at 60°C for 2 hours. The reaction mixture was mixed with 1 N hydrochloric acid (23 ml) at room temperature, was
15 concentrated under reduced pressure and was mixed with water, and an insoluble material was collected by filtration. The insoluble material was washed with water and was dried under reduced pressure to obtain 2-benzyloxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (2.09 g,
20 7.10 mmol, 96%).

¹H-NMR (CDCl₃) δ: 1.95-2.15 (2H, m), 2.55-2.7 (2H, m), 2.7-2.85 (2H, m), 5.07 (2H, s), 6.87 (1H, dd, J = 2.7, 8.3 Hz), 6.96 (1H, d, J = 2.7 Hz), 7.08 (1H, d, J = 8.3 Hz), 7.25-7.5 (5H, m), 7.77 (1H, s).

25 Example 7 (Production of compound 7)

To a mixture of 2-benzyloxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (200 mg, 0.68 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (165 mg, 0.75 mmol), 1-hydroxybenzotriazole (101 mg, 0.75 mmol) and DMF (10 ml) were added at 0°C 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (235 mg, 1.23 mmol) and triethylamine (0.284 ml, 2.04 mmol), and the resulting mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure, ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed successively with water (5 ml x 3), an aqueous saturated solution of sodium bicarbonate (5 ml x 3) and an aqueous saturated solution of sodium chloride (5 ml). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate). The objective fractions were concentrated under reduced pressure and were mixed with diisopropyl ether, and an insoluble material was collected by filtration. The insoluble material was washed with diisopropyl ether and was then dried under reduced pressure to obtain 2-benzyloxy-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (compound 7) (276 mg, 0.56 mmol, 82%).

IR (KBr): 1651, 1601, 1514 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.6-1.85 (4H, m), 2.0-2.25 (2H, m), 2.21 (3H, s), 2.5-2.85 (5H, m), 3.3-3.45 (2H, m), 3.57 (2H, s), 3.95-4.1 (2H, m), 5.07 (2H, s), 6.85 (1H, dd, $J = 2.7, 8.2$ Hz), 6.92 (1H, d, $J = 2.7$ Hz), 7.09 (1H, d, $J = 8.2$ Hz), 7.25-7.5 (5H, m), 7.31 (2H, d, $J = 8.6$ Hz), 7.55 (2H, d, $J = 8.6$ Hz), 7.58 (1H, s).

Reference Example 23

To 3-hydroxy-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene (1.76 g, 10.0 mmol) dissolved in DMF (10 ml) were added potassium carbonate (2.76 g, 20.0 mmol) and 4-methylbenzyl bromide (2.04 g, 11.0 mmol), and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, and the residue was mixed with water (20 ml) and extracted with ethyl acetate (20 ml $\times$ 3). The combined organic layers were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 40 g, ethyl acetate/hexane = 1/30). The objective fractions were concentrated under reduced pressure to obtain 3-(4-methylbenzyloxy)-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene (2.74 g, 9.77 mmol, 98%).

IR (KBr): 1674 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.7-1.95 (4H, m), 2.36 (3H, s),

2.7-2.8 (2H, m), 2.8-2.95 (2H, m), 5.04 (2H, s), 7.03 (1H, dd, $J = 2.8, 8.5$ Hz), 7.12 (1H, d, $J = 8.5$ Hz), 7.19 (2H, d, $J = 7.9$ Hz), 7.32 (2H, d, $J = 7.9$ Hz), 7.36 (1H, d, $J = 2.8$ Hz).

5 Reference Example 24

To 3-(4-methylbenzyloxy)-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene (2.67 g, 9.52 mmol) dissolved in dimethyl carbonate (40 ml) was added sodium methoxide (2.57 g, 47.6 mmol), and the resulting mixture was stirred at reflux with heating (110°C) for 6 hours. The reaction mixture was mixed with 1 N hydrochloric acid (60 ml) under ice cooling and was concentrated under reduced pressure to remove the organic solvent, and then the aqueous layer was extracted with ethyl acetate (30 ml × 3). The combined organic layers were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 40 g, ethyl acetate/hexane = 1/30). The objective fractions were concentrated under reduced pressure to obtain methyl 3-(4-methylbenzyloxy)-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene-6-carboxylate (2.84 g, 8.39 mmol, 88%).

 Reference Example 25

To methyl 3-(4-methylbenzyloxy)-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene-6-carboxylate (2.77 g, 8.19

mmol) dissolved in a mixed solvent of dichloromethane (40 ml) and methanol (10 ml) was added at -40°C (inner temperature) sodium borohydride (465 mg, 12.3 mmol), and the resulting mixture was stirred at -20°C to -10°C for 2 hours. The reaction mixture was cooled to -40°C, was mixed with water (20 ml) and extracted with dichloromethane (40 ml, 10 ml x 2). The combined organic layers were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure. To the residue dissolved in THF (30 ml) were added at 0°C triethylamine (5.70 ml, 40.9 mmol) and methanesulfonyl chloride (0.95 ml, 12.3 mmol), and the resulting mixture was stirred at room temperature for 12 hours. In order to complete the reaction, DBU (3.67 ml, 24.5 mmol) and dichloromethane (30 ml) were added, and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, was mixed with water (30 ml) and was extracted with ethyl acetate (30 ml x 3). The combined organic layers were washed with 1 N hydrochloric acid (5 ml x 3), were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 60 g, ethyl acetate/hexane = 1/30 → 1/9). The objective fractions were concentrated under reduced pressure to obtain methyl 2-(4-methylbenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-

carboxylate (2.40 g, 7.44 mmol, 91%).

IR (KBr): 1709 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.95-2.1 (2H, m), 2.36 (3H, s),
2.55-2.65 (2H, m), 2.7-2.8 (2H, m), 3.81 (3H, s), 5.01 (2H,
5 s), 6.83 (1H, dd, $J = 3.0, 8.4$ Hz), 6.92 (1H, d, $J = 3.0$
Hz), 7.05 (1H, d, $J = 8.4$ Hz), 7.19 (2H, d, $J = 8.0$ Hz),
7.32 (2H, d, $J = 8.0$ Hz), 7.64 (1H, s).

Reference Example 26

To methyl 2-(4-methylbenzyloxy)-6,7-dihydro-5H-
10 benzocycloheptene-8-carboxylate (2.34 g, 7.26 mmol)
dissolved in a mixed solvent of methanol (25 ml) and THF
(25 ml) was added a 1N aqueous solution of sodium hydroxide
(23 ml), and the resulting mixture was stirred at room
temperature for 18 hours. The reaction mixture was mixed
15 with 1 N hydrochloric acid (23 ml) at room temperature, was
concentrated under reduced pressure and was mixed with
water, and an insoluble material was collected by
filtration. The insoluble material was washed successively
with water and hexane, and was dried under reduced pressure
20 to obtain 2-(4-methylbenzyloxy)-6,7-dihydro-5H-
benzocycloheptene-8-carboxylic acid (2.11 g, 6.84 mmol,
94%).

IR (KBr): 1663 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.95-2.1 (2H, m), 2.36 (3H, s),
25 2.55-2.7 (2H, m), 2.7-2.85 (2H, m), 5.02 (2H, s), 6.86 (1H,

dd, $J = 2.7, 8.1$ Hz), 6.95 (1H, d, $J = 2.7$ Hz), 7.07 (1H, d, $J = 8.1$ Hz), 7.19 (2H, d, $J = 8.1$ Hz), 7.32 (2H, d, $J = 8.1$ Hz), 7.77 (1H, s).

Example 8 (Production of compound 8)

5 To a mixture of 2-(4-methylbenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (200 mg, 0.65 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (157 mg, 0.71 mmol), 1-hydroxybenzotriazole (96 mg, 0.71 mmol) and DMF (10 ml)
10 were added at 0°C 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (186 mg, 0.97 mmol) and triethylamine (0.271 ml, 1.94 mmol), and the resulting mixture was stirred at room temperature for 4 days. The reaction mixture was concentrated under reduced pressure,
15 ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed successively with water (5 ml $\times$ 3), an aqueous saturated solution of sodium bicarbonate (5 ml $\times$ 3) and an aqueous saturated solution of sodium chloride (5 ml). The organic layer was dried with
20 anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate). The objective fractions were concentrated under reduced pressure and were mixed with diisopropyl ether, and an
25 insoluble material was collected by filtration. The

insoluble material was washed with diisopropyl ether and was then dried under reduced pressure to obtain 2-(4-methylbenzyloxy)-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (compound 8) (273 mg, 0.53 mmol, 82%).

IR (KBr): 1651, 1601, 1518 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.6-1.85 (4H, m), 2.0-2.2 (2H, m), 2.21 (3H, s), 2.36 (3H, s), 2.5-2.85 (5H, m), 3.3-3.45 (2H, m), 3.57 (2H, s), 3.95-4.1 (2H, m), 5.02 (2H, s), 6.84 (1H, dd, $J = 2.5, 8.1$ Hz), 6.91 (1H, d, $J = 2.5$ Hz), 7.08 (1H, d, $J = 8.1$ Hz), 7.19 (2H, d, $J = 8.3$ Hz), 7.31 (2H, d, $J = 8.6$ Hz), 7.32 (2H, d, $J = 8.3$ Hz), 7.55 (2H, d, $J = 8.6$ Hz), 7.60 (1H, s).

Reference Example 27

To 3-hydroxy-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene (1.76 g, 10.0 mmol) dissolved in DMF (20 ml) were added potassium carbonate (2.76 g, 20.0 mmol) and 4-phenylbenzyl bromide (2.72 g, 11.0 mmol), and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, ethyl acetate (30 ml) and THF (30 ml) were added to the residue and the resulting mixture was washed with water (10 ml, 5 ml $\times$ 3) and an aqueous saturated solution of sodium chloride (5 ml). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated

under reduced pressure, and the residue was mixed with diisopropyl ether, and an insoluble material was collected by filtration. The insoluble material was washed with diisopropyl ether and was then dried under reduced pressure
5 to obtain 3-(4-phenylbenzyloxy)-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene (3.00 g, 8.76 mmol, 88%).

IR (KBr): 1674 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.7-1.95 (4H, m), 2.7-2.8 (2H, m), 2.8-2.95 (2H, m), 5.13 (2H, s), 7.06 (1H, dd, $J = 2.6$,
10 8.4 Hz), 7.14 (1H, d, $J = 8.4$ Hz), 7.3-7.65 (10H, m).

Reference Example 28

To 3-(4-phenylbenzyloxy)-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene (2.90 g, 8.47 mmol) dissolved in dimethyl carbonate (80 ml) was added sodium
15 methoxide (2.29 g, 42.4 mmol), and the resulting mixture was stirred at reflux with heating (110°C) for 6 hours. The reaction mixture was mixed with 1 N hydrochloric acid (60 ml) under ice cooling and was concentrated under reduced pressure to remove the organic solvent, and then
20 the aqueous layer was extracted with a mixed solvent of ethyl acetate and THF ((30 ml/15 ml) $\times$ 3). The combined organic layers were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel:
25 50 g, ethyl acetate/hexane = 1/30). The objective

fractions were concentrated under reduced pressure, diisopropyl ether was added to the residue and an insoluble material was collected by filtration. The insoluble material was washed with diisopropyl ether and was then
5 dried under reduced pressure to obtain methyl 3-(4-phenylbenzyloxy)-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene-6-carboxylate (2.47 g, 6.17 mmol, 73%).

Reference Example 29

To methyl 3-(4-phenylbenzyloxy)-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene-6-carboxylate (2.31 g, 5.77
10 mmol) dissolved in a mixed solvent of dichloromethane (50 ml) and methanol (15 ml) was added at -40°C (inner temperature) sodium borohydride (327 mg, 8.64 mmol), and the resulting mixture was stirred at -20°C to -10°C for 2
15 hours. The reaction mixture was cooled to -40°C, was mixed with water (20 ml) and extracted with dichloromethane (50 ml, 10 ml x 2). The combined organic layers were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure. To the residue dissolved in
20 dichloromethane (40 ml) were added at 0°C triethylamine (4.02 ml, 28.8 mmol) and methanesulfonyl chloride (0.67 ml, 8.7 mmol), and the resulting mixture was stirred at room temperature for 16 hours. In order to complete the reaction, DBU (2.59 ml, 17.3 mmol) was added, and the
25 resulting mixture was stirred at room temperature for 12

hours. The reaction mixture was concentrated under reduced pressure, was mixed with water (30 ml) and was extracted with ethyl acetate (40 ml, 15 ml $\times$ 2). The combined organic layers were washed with 1 N hydrochloric acid (5 ml $\times$ 3), were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 60 g, toluene). The objective fractions were concentrated under reduced pressure and the residue was mixed with ethyl acetate and diisopropyl ether, and an insoluble material was collected by filtration. The insoluble material was washed with diisopropyl ether and was then dried under reduced pressure to obtain methyl 2-(4-phenylbenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (1.31 g, 3.41 mmol, 59%).

IR (KBr): 1707 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.95-2.15 (2H, m), 2.55-2.7 (2H, m), 2.7-2.8 (2H, m), 3.82 (3H, s), 5.10 (2H, s), 6.87 (1H, dd, $J = 2.7, 8.3$ Hz), 6.96 (1H, d, $J = 2.7$ Hz), 7.08 (1H, d, $J = 8.3$ Hz), 7.3-7.7 (10H, m).

Reference Example 30

To methyl 2-(4-phenylbenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (1.22 g, 3.17 mmol) dissolved in a mixed solvent of methanol (20 ml) and THF (35 ml) was added a 1N aqueous solution of sodium hydroxide

(10 ml), and the resulting mixture was stirred at room temperature for 18 hours and at 60°C for 2 hours. The reaction mixture was mixed with 1 N hydrochloric acid (12 ml) at room temperature, was concentrated under reduced pressure and was mixed with water, and an insoluble material was collected by filtration. The insoluble material was washed successively with water and hexane, and was dried under reduced pressure to obtain 2-(4-phenylbenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (1.38 g).

¹H-NMR (DMSO-d₆) δ: 1.8-2.0 (2H, m), 2.4-2.55 (2H, m), 2.65-2.8 (2H, m), 5.16 (2H, s), 6.91 (1H, dd, J = 2.6, 8.4 Hz), 7.08 (1H, d, J = 2.6 Hz), 7.12 (1H, d, J = 8.4 Hz), 7.3-7.75 (10H, m).

Example 9 (Production of compound 9)

To a mixture of 2-(4-phenylbenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (200 mg, 0.54 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (131 mg, 0.59 mmol), 1-hydroxybenzotriazole (80 mg, 0.59 mmol) and DMF (10 ml) were added at 0°C 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (207 mg, 1.08 mmol) and triethylamine (0.226 ml, 1.62 mmol), and the resulting mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure,

ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed successively with water (5 ml × 3), an aqueous saturated solution of sodium bicarbonate (5 ml × 3) and an aqueous saturated solution of sodium chloride (5 ml). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate). The objective fractions were concentrated under reduced pressure and were mixed with diisopropyl ether, and an insoluble material was collected by filtration. The insoluble material was washed with diisopropyl ether and was then dried under reduced pressure to obtain 2-(4-phenylbenzyloxy)-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (compound 9) (243 mg, 0.42 mmol, 79%).

IR (KBr): 1651, 1601, 1516 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.55-1.85 (4H, m), 2.0-2.25 (2H, m), 2.21 (3H, s), 2.5-2.85 (5H, m), 3.25-3.45 (2H, m), 3.58 (2H, s), 3.95-4.15 (2H, m), 5.11 (2H, s), 6.87 (1H, dd, $J = 2.9, 8.0$ Hz), 6.94 (1H, d, $J = 2.9$ Hz), 7.10 (1H, d, $J = 8.0$ Hz), 7.2-7.7 (14H, m).

Reference Example 31

To methyl 2-hydroxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (327 mg, 1.50 mmol)

dissolved in DMF (6 ml) were added potassium carbonate (415 mg, 3.00 mmol) and 4-fluorobenzyl bromide (0.206 ml, 1.65 mmol), and the resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed with water (5 ml x 3) and an aqueous saturated solution of sodium chloride (5 ml). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate/hexane = 1/25). The objective fractions were concentrated under reduced pressure to obtain methyl 2-(4-fluorobenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (485 mg, 1.49 mmol, 99%).

IR (KBr): 1707 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.95-2.15 (2H, m), 2.55-2.8 (4H, m), 3.82 (3H, s), 5.02 (2H, s), 6.83 (1H, dd, $J = 2.7, 8.2$ Hz), 6.92 (1H, d, $J = 2.7$ Hz), 7.0-7.15 (2H, m), 7.07 (1H, d, $J = 8.2$ Hz), 7.35-7.45 (2H, m), 7.64 (1H, s).

Reference Example 32

To 2-(4-fluorobenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (462 mg, 1.42 mmol) dissolved in a mixed solvent of methanol (5 ml) and THF (5 ml) was added a 1N aqueous solution of sodium hydroxide

(4.3 ml), and the resulting mixture was stirred at 50°C for 2 hours. The reaction mixture was mixed with 1 N hydrochloric acid (4.3 ml) at 0°C, was concentrated under reduced pressure and was mixed with water, and an insoluble material was collected by filtration. The insoluble material was washed with water and was dried under reduced pressure to obtain 2-(4-fluorobenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (458 mg).

Example 10 (Production of compound 10)

To a mixture of 2-(4-fluorobenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (170 mg, 0.54 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (144 mg, 0.65 mmol), 1-hydroxybenzotriazole (88 mg, 0.65 mmol) and DMF (6 ml) were added at 0°C 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (209 mg, 1.09 mmol) and triethylamine (0.228 ml, 1.64 mmol), and the resulting mixture was stirred at room temperature for 2 days. The reaction mixture was concentrated under reduced pressure, ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate (10 ml, 5 ml x 2). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel:

15 g, ethyl acetate). The objective fractions were concentrated under reduced pressure, diisopropyl ether was added to the residue and an insoluble material was collected by filtration. The insoluble material was washed
5 with diisopropyl ether and was then dried under reduced pressure to obtain 2-(4-fluorobenzyloxy)-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (compound 10) (228 mg, 0.44 mmol, 81%).

10 IR (KBr): 1651, 1603, 1514 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.5-1.85 (4H, m), 2.0-2.25 (2H, m), 2.21 (3H, s), 2.55-2.85 (5H, m), 3.3-3.45 (2H, m), 3.58 (2H, s), 3.95-4.15 (2H, m), 5.02 (2H, s), 6.83 (1H, dd, J = 2.7, 8.3 Hz), 6.90 (1H, d, J = 2.7 Hz), 7.0-7.15 (2H, m),
15 7.09 (1H, d, J = 8.3 Hz), 7.29 (1H, s), 7.31 (2H, d, J = 8.5 Hz), 7.35-7.45 (2H, m), 7.55 (2H, d, J = 8.5 Hz), 7.59 (1H, s).

Reference Example 33

To methyl 2-hydroxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (327 mg, 1.50 mmol)
20 dissolved in DMF (6 ml) were added potassium carbonate (415 mg, 3.00 mmol) and 2,4-difluorobenzyl bromide (0.212 ml, 1.65 mmol), and the resulting mixture was stirred at room temperature for 17 hours. The reaction mixture was
25 concentrated under reduced pressure, ethyl acetate (40 ml)

was added to the residue and the resulting mixture was washed with water (5 ml $\times$ 2) and an aqueous saturated solution of sodium chloride (5 ml). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate/hexane = 1/25). The objective fractions were concentrated under reduced pressure to obtain methyl 2-(2,4-difluorobenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (500 mg, 1.45 mmol, 97%).

IR (KBr): 1709 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.95-2.1 (2H, m), 2.55-2.8 (4H, m), 3.82 (3H, s), 5.07 (2H, s), 6.75-7.0 (4H, m), 7.07 (1H, d, $J = 8.0$ Hz), 7.4-7.55 (1H, m), 7.64 (1H, s).

Reference Example 34

To 2-(2,4-difluorobenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (477 mg, 1.39 mmol) dissolved in a mixed solvent of methanol (5 ml) and THF (5 ml) was added a 1N aqueous solution of sodium hydroxide (4.2 ml), and the resulting mixture was stirred at 50°C for 2 hours. The reaction mixture was mixed with 1 N hydrochloric acid (4.2 ml) at 0°C, was concentrated under reduced pressure and was mixed with water, and an insoluble material was collected by filtration. The insoluble material was washed with water and was dried under reduced

pressure to obtain 2-(2,4-difluorobenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (436 mg, 1.32 mmol, 95%).

Example 11 (Production of compound 11)

5 To a mixture of 2-(2,4-difluorobenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (170 mg, 0.51 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (136 mg, 0.62 mmol), 1-hydroxybenzotriazole (83 mg, 0.61 mmol) and DMF (6 ml) were
10 added at 0°C 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (197 mg, 1.03 mmol) and triethylamine (0.215 ml, 1.54 mmol), and the resulting mixture was stirred at room temperature for 2 days. The reaction mixture was concentrated under reduced pressure,
15 ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate (10 ml, 5 ml x 2). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the
20 residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate). The objective fractions were concentrated under reduced pressure, diisopropyl ether was added to the residue and an insoluble material was collected by filtration. The insoluble material was washed
25 with diisopropyl ether and was then dried under reduced

pressure to obtain 2-(2,4-difluorobenzyloxy)-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (compound 11) (228 mg, 0.43 mmol, 83%).

5 IR (KBr): 1651, 1601, 1510 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.5-1.85 (4H, m), 2.0-2.25 (2H, m), 2.21 (3H, s), 2.55-2.85 (5H, m), 3.25-3.45 (2H, m), 3.57 (2H, s), 3.95-4.1 (2H, m), 5.07 (2H, s), 6.75-7.0 (4H, m), 7.09 (1H, d, $J = 8.0$ Hz), 7.29 (1H, s), 7.31 (2H, d, $J = 8.6$ Hz), 7.4-7.65 (1H, m), 7.55 (2H, d, $J = 8.6$ Hz), 7.59 (1H, s).

10

Reference Example 35

To methyl 2-hydroxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (327 mg, 1.50 mmol) dissolved in DMF (6 ml) were added potassium carbonate (415 mg, 3.00 mmol) and 2,6-difluorobenzyl chloride (268 mg, 1.65 mmol), and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed with water (5 ml $\times$ 2) and an aqueous saturated solution of sodium chloride (5 ml). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl

15

20

25

acetate/hexane = 1/25). The objective fractions were concentrated under reduced pressure to obtain methyl 2-(2,6-difluorobenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (507 mg, 1.47 mmol, 98%).

5 IR (KBr): 1709 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.95-2.15 (2H, m), 2.55-2.8 (4H, m), 3.82 (3H, s), 5.11 (2H, s), 6.85-7.0 (2H, m), 6.87 (1H, dd, $J = 2.8, 8.2$ Hz), 7.08 (1H, d, $J = 8.2$ Hz), 7.25-7.45 (1H, m), 7.66 (1H, s).

10 Reference Example 36

To 2-(2,6-difluorobenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (486 mg, 1.41 mmol) dissolved in a mixed solvent of methanol (7 ml) and THF (7 ml) was added a 1N aqueous solution of sodium hydroxide (4.4 ml), and the resulting mixture was stirred at 50°C for 6 hours. The reaction mixture was mixed with 1 N hydrochloric acid (4.4 ml) at 0°C, was concentrated under reduced pressure and was mixed with water, and an insoluble material was collected by filtration. The insoluble material was washed with water and was dried under reduced pressure to obtain 2-(2,6-difluorobenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (450 mg, 1.36 mmol, 97%).

Example 12 (Production of compound 12)

25 To a mixture of 2-(2,6-difluorobenzyloxy)-6,7-

dihydro-5H-benzocycloheptene-8-carboxylic acid (170 mg, 0.51 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (136 mg, 0.62 mmol), 1-hydroxybenzotriazole (83 mg, 0.61 mmol) and DMF (8 ml) were
5 added at 0°C 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (197 mg, 1.03 mmol) and triethylamine (0.215 ml, 1.54 mmol), and the resulting mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure,
10 ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate (10 ml, 5 ml x 2). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the
15 residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate). The objective fractions were concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (10 ml). Thereto was added at
20 0°C 4 N hydrogen chloride (a solution in ethyl acetate, 0.5 ml), and an insoluble material was collected by filtration. The insoluble material was washed with ethyl acetate and was then dried under reduced pressure to obtain 2-(2,6-difluorobenzyloxy)-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-
25 carboxamide hydrochloride (compound 12) (255 mg, 0.45 mmol,

87%).

IR (KBr): 1651, 1597, 1522 cm^{-1} .

^1H -NMR (DMSO- d_6) δ : 1.55-2.2 (6H, m), 2.45-2.65 (2H, m), 2.59 (3H, s), 2.65-2.85 (2H, m), 3.2-3.6 (3H, m), 3.9-4.1 (2H, m), 4.12 (1H, d, $J = 12.4$ Hz), 4.44 (1H, d, $J = 12.4$ Hz), 5.11 (2H, s), 6.93 (1H, dd, $J = 2.4, 8.1$ Hz), 7.07 (1H, d, $J = 2.4$ Hz), 7.1-7.3 (3H, m), 7.25 (1H, s), 7.45-7.65 (1H, m), 7.53 (2H, d, $J = 8.4$ Hz), 7.82 (2H, d, $J = 8.4$ Hz).

Reference Example 37

To methyl 2-hydroxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (327 mg, 1.50 mmol) dissolved in DMF (6 ml) were added potassium carbonate (415 mg, 3.00 mmol) and 3,5-bis(trifluoromethyl)benzyl bromide (302 mg, 1.65 mmol), and the resulting mixture was stirred at room temperature for 17 hours. The reaction mixture was concentrated under reduced pressure, ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed with water (5 ml $\times$ 2) and an aqueous saturated solution of sodium chloride (5 ml). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate/hexane = 1/25). The objective fractions were concentrated under reduced pressure, hexane was added to

the residue and an insoluble material was collected by filtration. The insoluble material was washed with hexane and was then dried under reduced pressure to obtain methyl 2-[3,5-bis(trifluoromethyl)benzyloxy]-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (524 mg, 1.22 mmol, 81%).

IR (KBr): 1709 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.95-2.15 (2H, m), 2.55-2.7 (2H, m), 2.7-2.85 (2H, m), 3.82 (3H, s), 5.16 (2H, s), 6.85 (1H, dd, $J = 2.7, 8.2$ Hz), 6.95 (1H, d, $J = 2.7$ Hz), 7.11 (1H, d, $J = 8.2$ Hz), 7.66 (1H, s), 7.86 (1H, s), 7.91 (2H, s).

Reference Example 38

To methyl 2-[3,5-bis(trifluoromethyl)benzyloxy]-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (494 mg, 1.15 mmol) dissolved in a mixed solvent of methanol (7 ml) and THF (7 ml) was added a 1N aqueous solution of sodium hydroxide (3.5 ml), and the resulting mixture was stirred at 50°C for 4 hours. The reaction mixture was mixed with 1 N hydrochloric acid (3.5 ml) at 0°C, was concentrated under reduced pressure and was mixed with water, and an insoluble material was collected by filtration. The insoluble material was washed with water and was dried under reduced pressure to obtain 2-[3,5-bis(trifluoromethyl)benzyloxy]-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (475 mg, 1.10 mmol, 96%).

Example 13 (Production of compound 13)

To a mixture of 2-[3,5-bis(trifluoromethyl)benzyloxy]-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (170 mg, 0.40 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline dihydrochloride (127 mg, 0.43 mmol), 1-hydroxybenzotriazole (64 mg, 0.47 mmol) and DMF (8 ml) were added at 0°C 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (151 mg, 0.79 mmol) and triethylamine (0.275 ml, 1.97 mmol), and the resulting mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure, ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate (10 ml, 5 ml x 2). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate). The objective fractions were concentrated under reduced pressure, diisopropyl ether was added to the residue and an insoluble material was collected by filtration. The insoluble material was washed with diisopropyl ether and was then dried under reduced pressure to obtain 2-[3,5-bis(trifluoromethyl)benzyloxy]-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (compound 13) (189 mg, 0.30

mmol, 76%).

IR (KBr): 1653, 1601, 1514 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.6-1.85 (4H, m), 2.0-2.25 (2H, m), 2.21 (3H, s), 2.55-2.85 (5H, m), 3.25-3.45 (2H, m),
5 3.58 (2H, s), 3.95-4.1 (2H, m), 5.16 (2H, s), 6.85 (1H, dd, $J = 2.7, 8.2$ Hz), 6.94 (1H, d, $J = 2.7$ Hz), 7.13 (1H, d, $J = 8.2$ Hz), 7.31 (1H, s), 7.32 (2H, d, $J = 8.6$ Hz), 7.55 (2H, d, $J = 8.6$ Hz), 7.60 (1H, s), 7.86 (1H, s), 7.91 (2H, s).

Reference Example 39

10 To triphenylphosphine (590 mg, 2.25 mmol), 4-ethoxybenzyl alcohol (342 mg, 2.25 mmol) and methyl 2-hydroxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (327 mg, 1.50 mmol) dissolved in THF (6 ml) was added at 0°C a
15 solution of diisopropyl azodicarboxylate (0.439 ml, 2.23 mmol) in THF (2 ml), and the resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography (silica gel: 50 g, ethyl acetate/hexane = 1/25 $\rightarrow$ 1/19). The objective fractions
20 were concentrated under reduced pressure, diisopropyl ether was added to the residue and an insoluble material was collected by filtration. The insoluble material was washed with diisopropyl ether and was then dried under reduced pressure to obtain methyl 2-(4-ethoxybenzyloxy)-6,7-
25 dihydro-5H-benzocycloheptene-8-carboxylate (308 mg, 0.87

mmol, 58%).

IR (KBr): 1709 cm^{-1} .

^1H -NMR (CDCl_3): δ 1.42 (3H, t, $J = 7.0$ Hz), 1.95-2.1 (2H, m), 2.55-2.8 (4H, m), 3.81 (3H, s), 4.05 (2H, q, $J = 7.0$ Hz), 4.97 (2H, s), 6.84 (1H, dd, $J = 2.7, 8.3$ Hz), 6.91 (2H, d, $J = 8.7$ Hz), 6.92 (1H, d, $J = 2.7$ Hz), 7.34 (2H, d, $J = 8.7$ Hz), 7.65 (1H, s).

Reference Example 40

To methyl 2-(4-ethoxybenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (296 mg, 0.84 mmol) dissolved in a mixed solvent of methanol (4 ml) and THF (4 ml) was added a 1N aqueous solution of sodium hydroxide (2.5 ml), and the resulting mixture was stirred at 50°C for 4 hours. The reaction mixture was mixed with 1 N hydrochloric acid (2.5 ml) at 0°C, was concentrated under reduced pressure and was mixed with water, and an insoluble material was collected by filtration. The insoluble material was washed with water, and was dried under reduced pressure to obtain 2-(4-ethoxybenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (283 mg, 0.84 mmol).

Example 14 (Production of compound 14)

To a mixture of 2-(4-ethoxybenzyloxy)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (170 mg, 0.50 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (133 mg, 0.60 mmol), 1-

hydroxybenzotriazole (81 mg, 0.60 mmol) and DMF (8 ml) were added at 0°C 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (193 mg, 1.01 mmol) and triethylamine (0.21 ml, 1.51 mmol), and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate (10 ml, 5 ml $\times$ 2). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate). The objective fractions were concentrated under reduced pressure, diisopropyl ether was added to the residue and an insoluble material was collected by filtration. The insoluble material was washed with diisopropyl ether and was then dried under reduced pressure to obtain 2-(4-ethoxybenzyloxy)-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (compound 14) (234 mg, 0.43 mmol, 86%).

IR (KBr): 1651, 1601, 1514 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.42 (3H, t, $J = 7.0$ Hz), 1.55-1.85 (4H, m), 2.0-2.25 (2H, m), 2.21 (3H, s), 2.55-2.85 (5H, m), 3.3-3.45 (2H, m), 3.57 (2H, s), 3.95-4.15 (2H, m), 4.04

(2H, q, $J = 7.0$ Hz), 4.98 (2H, s), 6.84 (1H, dd, $J = 2.8$, 8.4 Hz), 6.90 (1H, d, $J = 2.8$ Hz), 6.91 (2H, d, $J = 8.8$ Hz), 7.08 (1H, d, $J = 8.4$ Hz), 7.28 (1H, s), 7.31 (2H, d, $J = 8.4$ Hz), 7.34 (2H, d, $J = 8.8$ Hz), 7.55 (2H, d, $J = 8.4$ Hz),
5 7.61 (1H, s).

Reference Example 41

To 3-methoxy-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene (20.32 mg, 107 μ mol) dissolved in dimethyl carbonate (500 ml) was added sodium methoxide
10 (28.85 g, 534 mmol), and the resulting mixture was stirred at reflux with heating (110°C) for 6 hours. The reaction mixture was mixed with 2 N hydrochloric acid (320 ml) under ice cooling and was concentrated under reduced pressure to remove the organic solvent, and then the aqueous layer was
15 extracted with ethyl acetate (200 ml, 150 ml $\times$ 3). The combined organic layers were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 150 g, ethyl acetate/hexane = 1/19). The
20 objective fractions were concentrated under reduced pressure to obtain methyl 3-methoxy-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene-6-carboxylate (24.20 g, 97.5 μ mol, 91%).

Reference Example 42

25 To methyl 3-methoxy-5-oxo-6,7,8,9-tetrahydro-5H-

benzocycloheptene-6-carboxylate (1079 mg, 4.35 mmol) dissolved in a mixed solvent of dichloromethane (10 ml) and methanol (2.5 ml) was added at -40°C (inner temperature) sodium borohydride (300 mg, 7.93 mmol), and the resulting mixture was stirred at -15°C to -10°C for 1.5 hours. The reaction mixture was cooled to -40°C, was mixed with water (10 ml) and extracted with dichloromethane (× 3). The combined organic layers were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure. To the residue dissolved in dichloromethane (15 ml) were added at 0°C triethylamine (3.03 ml, 21.7 mmol) and methanesulfonyl chloride (0.505 ml, 6.52 mmol), and the resulting mixture was stirred at room temperature for 18 hours. In order to complete the reaction, DBU (1.95 ml, 13.0 mmol) was added, and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, was mixed with water and was extracted with ethyl acetate (× 3). The combined organic layers were washed with 1 N hydrochloric acid (× 3) and an aqueous saturated solution of sodium chloride, were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel, ethyl acetate/hexane = 1/9). The objective fractions were concentrated under reduced pressure to obtain methyl 2-

methoxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (730 mg, 3.14 mmol, 72%).

IR (KBr): 1709 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.95-2.1 (2H, m), 2.55-2.8 (4H, m), 3.80 (3H, s), 3.82 (3H, s), 6.77 (1H, dd, $J = 2.7, 8.3$ Hz), 6.85 (1H, d, $J = 2.7$ Hz), 7.06 (1H, d, $J = 8.3$ Hz), 7.66 (1H, s).

Reference Example 43

To methyl 2-methoxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (5.07 g, 21.8 mmol) dissolved in dichloromethane (100 ml) was added dropwise at -60°C to -70°C (inner temperature) boron tribromide (a 1 M solution in dichloromethane, 87 ml), and the resulting mixture was stirred for 5 hours while raising the temperature from -70°C to room temperature. The reaction mixture was mixed with diethyl ether and water (100 ml) in the order, and was extracted with dichloromethane (100 ml, 50 ml $\times$ 2). The combined organic layers were dried with anhydrous magnesium sulfate, and were then concentrated under reduced pressure. To the residue dissolved in methanol (150 ml) was added sulfuric acid (0.5 ml), and the resulting mixture was stirred under reflux with heating (100°C) for 24 hours. The reaction mixture was concentrated under reduced pressure, was mixed with ethyl acetate (150 ml) and was washed with an aqueous saturated

solution of sodium chloride (30 ml $\times$ 3). After drying with anhydrous magnesium sulfate, the organic layer was concentrated under reduced pressure, diisopropyl ether was added to the residue and an insoluble material was collected by filtration. The insoluble material was washed with diisopropyl ether and was then dried under reduced pressure to obtain methyl 2-hydroxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (4.31 g, 19.7 mmol, 90%).

IR (KBr): 1686 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.95-2.15 (2H, m), 2.55-2.8 (4H, m), 3.82 (3H, s), 6.71 (1H, dd, $J = 2.5, 8.1$ Hz), 6.81 (1H, d, $J = 2.5$ Hz), 7.02 (1H, d, $J = 8.1$ Hz), 7.63 (1H, s).

Reference Example 44

To methyl 2-hydroxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (400 mg, 1.83 mmol) dissolved in DMF (8 ml) were added potassium carbonate (507 mg, 3.67 mmol) and cyclohexylmethyl bromide (0.511 ml, 3.66 mmol), and the resulting mixture was stirred at room temperature for 23 hours and at 100°C for 6 hours. The reaction mixture was concentrated under reduced pressure, water was added to the residue and the resulting mixture was extracted with ethyl acetate ($\times$ 3). The combined organic layers were dried with anhydrous magnesium sulfate and were then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel:

15 g, ethyl acetate/hexane = 1/19). The objective fractions were concentrated under reduced pressure, hexane was added to the residue and an insoluble material was collected by filtration. The insoluble material was washed
5 with hexane and was then dried under reduced pressure to obtain methyl 2-cyclohexylmethoxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (452 mg, 1.44 mmol, 78%).

IR (KBr): 1709 cm^{-1} .

^1H -NMR (CDCl_3) δ : 0.9-2.1 (13H, m), 2.55-2.8 (4H, m), 3.74 (2H, d, $J = 6.2$ Hz), 3.81 (3H, s), 6.76 (1H, dd, $J = 2.5, 8.1$ Hz), 6.84 (1H, d, $J = 2.5$ Hz), 7.04 (1H, d, $J = 8.1$ Hz), 7.65 (1H, s).

Reference Example 45

To methyl 2-cyclohexylmethoxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (425 mg, 1.35 mmol)
15 dissolved in a mixed solvent of methanol (5 ml) and THF (5 ml) was added a 1N aqueous solution of sodium hydroxide (4 ml), and the resulting mixture was stirred at 50°C for 6 hours. The reaction mixture was mixed with 1 N
20 hydrochloric acid (4 ml) at 0°C, was concentrated under reduced pressure and was mixed with water, and an insoluble material was collected by filtration. The insoluble material was washed with water and was dried under reduced pressure to obtain 2-cyclohexylmethoxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (389 mg, 1.29 mmol,
25

96%).

Example 15 (Production of compound 15)

To a mixture of 2-cyclohexylmethyloxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (170 mg, 0.57 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (150 mg, 0.68 mmol), 1-hydroxybenzotriazole (84 mg, 0.62 mmol) and DMF (6 ml) were added at 0°C 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (217 mg, 1.13 mmol) and triethylamine (0.237 ml, 1.70 mmol), and the resulting mixture was stirred at room temperature for 4 days. The reaction mixture was concentrated under reduced pressure, ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate (10 ml, 5 ml x 2). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate). The objective fractions were concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (10 ml). Thereto was added at 0°C 4 N hydrogen chloride (a solution in ethyl acetate, 0.285 ml), and an insoluble material was collected by filtration. The insoluble material was washed with ethyl acetate and was then dried under reduced pressure to obtain

2-cyclohexylmethyloxy-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-carboxamide hydrochloride (compound 15) (258 mg, 0.48 mmol, 85%).

5 IR (KBr): 1651, 1601, 1522 cm^{-1} .

^1H -NMR (DMSO-d_6) δ : 0.9-1.4 (5H, m), 1.5-2.2 (12H, m), 2.4-2.65 (2H, m), 2.59 (3H, s), 2.65-2.8 (2H, m), 3.2-3.6 (3H, m), 3.77 (2H, d, $J = 5.8$ Hz), 3.9-4.1 (2H, m), 4.12 (1H, d, $J = 12.4$ Hz), 4.43 (1H, d, $J = 12.4$ Hz), 6.80
10 (1H, dd, $J = 2.5, 8.6$ Hz), 6.94 (1H, d, $J = 2.5$ Hz), 7.12 (1H, d, $J = 8.6$ Hz), 7.25 (1H, s), 7.54 (2H, d, $J = 8.6$ Hz), 7.81 (2H, d, $J = 8.6$ Hz), 10.14 (1H, s).

Reference Example 46

To triphenylphosphine (1.18 g, 4.50 mmol),
15 cyclohexanol (0.468 ml, 4.50 mmol) and methyl 2-hydroxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (327 mg, 1.50 mmol) dissolved in THF (6 ml) was added at 0°C a solution of diisopropyl azodicarboxylate (0.886 ml, 4.50 mmol) in THF (4 ml), and the resulting mixture was stirred
20 at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography (silica gel: 45 g, ethyl acetate/hexane = 1/25). The objective fractions were concentrated under reduced pressure to obtain methyl 2-cyclohexyloxy-6,7-dihydro-5H-benzocycloheptene-8-
25

carboxylate (434 mg, 1.44 mmol, 96%).

IR (KBr): 1709 cm^{-1} .

^1H -NMR (CDCl_3): δ 1.15-2.1 (12H, m), 2.55-2.65 (2H, m), 2.65-2.8 (2H, m), 3.81 (3H, s), 4.1-4.3 (1H, m), 6.77
5 (1H, dd, $J = 2.7, 8.1$ Hz), 6.85 (1H, d, $J = 2.7$ Hz), 7.03
(1H, d, $J = 8.1$ Hz), 7.64 (1H, s).

Reference Example 47

To methyl 2-cyclohexyloxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (412 mg, 1.37 mmol)
10 dissolved in a mixed solvent of methanol (5 ml) and THF (5 ml) was added a 1N aqueous solution of sodium hydroxide (4.0 ml), and the resulting mixture was stirred at 50°C for 6 hours. The reaction mixture was mixed with 1 N hydrochloric acid (4.0 ml) at 0°C, was concentrated under
15 reduced pressure and was mixed with water, and an insoluble material was collected by filtration. The insoluble material was washed with water and was dried under reduced pressure to obtain 2-cyclohexyloxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (388 mg, 1.35 mmol,
20 99%).

Example 16 (Production of compound 16)

To a mixture of 2-cyclohexyloxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (170 mg, 0.59 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (157
25 mg, 0.71 mmol), 1-hydroxybenzotriazole (96 mg, 0.71 mmol)

and DMF (8 ml) were added at 0°C 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (228 mg, 1.19 mmol) and triethylamine (0.248 ml, 1.78 mmol), and the resulting mixture was stirred at room temperature
5 for 24 hours. The reaction mixture was concentrated under reduced pressure, ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate (10 ml, 5 ml × 2). The organic layer was dried with anhydrous
10 magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate). The objective fractions were concentrated under reduced pressure, diisopropyl ether was added to the residue and an
15 insoluble material was collected by filtration. The insoluble material was washed with diisopropyl ether and was then dried under reduced pressure to obtain 2-cyclohexyloxy-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-
20 carboxamide (compound 16) (248 mg, 0.51 mmol, 85%).

IR (KBr): 1651, 1601, 1514 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.15-2.25 (16H, m), 2.21 (3H, s),
2.5-2.85 (5H, m), 3.25-3.45 (2H, m), 3.57 (2H, s), 3.95-4.1
(2H, m), 4.1-4.3 (1H, m), 6.77 (1H, dd, $J = 2.7, 8.2$ Hz),
25 6.85 (1H, d, $J = 2.7$ Hz), 7.06 (1H, d, $J = 8.2$ Hz), 7.29

(1H, s), 7.31 (2H, d, J = 8.4 Hz), 7.55 (2H, d, J = 8.4 Hz), 7.60 (1H, s).

Reference Example 48

To triphenylphosphine (2361 mg, 9.00 mmol), 1-
5 tert-butoxycarbonyl-4-hydroxypiperidine (1812 mg, 9.00
mmol) and methyl 2-hydroxy-6,7-dihydro-5H-
benzocycloheptene-8-carboxylate (655 mg, 3.00 mmol)
dissolved in THF (15 ml) was added at 0°C a solution of
diisopropyl azodicarboxylate (1.772 ml, 9.00 mmol) in THF
10 (2 ml), and the resulting mixture was stirred at room
temperature for 24 hours. The reaction mixture was
concentrated under reduced pressure and the residue was
subjected to column chromatography (silica gel: 70 g, ethyl
acetate/hexane = 1/9 → 1/7). The objective fractions were
15 concentrated under reduced pressure to obtain methyl 2-[(1-
tert-butoxycarbonylpiperidin-4-yl)oxy]-6,7-dihydro-5H-
benzocycloheptene-8-carboxylate (1270 mg).

IR (KBr): 1698 cm^{-1} .

^1H -NMR (CDCl_3): δ 1.47 (9H, s), 1.6-2.1 (6H, m),
20 2.55-2.7 (2H, m), 2.7-2.8 (2H, m), 3.2-3.45 (2H, m), 3.6-
3.8 (2H, m), 3.82 (3H, s), 4.35-4.55 (1H, m), 6.78 (1H, dd,
J = 2.7, 8.3 Hz), 6.87 (1H, d, J = 2.7 Hz), 7.05 (1H, d, J
= 8.3 Hz), 7.63 (1H, s).

Reference Example 49

25 To methyl 2-[(1-tert-butoxycarbonylpiperidin-4-

yl)oxy]-6,7-dihydro-5H-benzocycloheptene-8-carboxylate
(1245 mg, 3.10 mmol) dissolved in a mixed solvent of
methanol (10 ml) and THF (10 ml) was added a 1N aqueous
solution of sodium hydroxide (9.3 ml), and the resulting
5 mixture was stirred at room temperature for 23 hours. The
reaction mixture was mixed with 1 N hydrochloric acid (9.3
ml) at 0°C, was concentrated under reduced pressure and was
mixed with water, and an insoluble material was collected
by filtration. The insoluble material was washed with
10 water, and was dried under reduced pressure to obtain 2-
[(1-tert-butoxycarbonylpiperidin-4-yl)oxy]-6,7-dihydro-5H-
benzocycloheptene-8-carboxylic acid (1150 mg, 2.97 mmol,
96%).

Example 17 (Production of compound 17)

15 To a mixture of 2-[(1-tert-
butoxycarbonylpiperidin-4-yl)oxy]-6,7-dihydro-5H-
benzocycloheptene-8-carboxylic acid (1088 mg, 2.81 mmol),
4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline
hydrochloride (742 mg, 3.37 mmol), 1-hydroxybenzotriazole
20 (455 mg, 3.37 mmol) and DMF (30 ml) were added at 0°C 1-[3-
(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
(1077 mg, 5.62 mmol) and triethylamine (1.174 ml, 8.42
mmol), and the resulting mixture was stirred at room
temperature for 3 days. The reaction mixture was
25 concentrated under reduced pressure, ethyl acetate (160 ml)

was added to the residue and the resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate (40 ml, 20 ml $\times$ 2). The organic layer was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 70 g, ethyl acetate). The objective fractions were concentrated under reduced pressure to obtain 2-[(1-tert-butoxycarbonylpiperidin-4-yl)oxy]-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (compound 17) (1446 mg, 2.45 mmol, 87%).

IR (KBr): 1694, 1667, 1599, 1514 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.47 (9H, s), 1.5-2.0 (8H, m), 2.0-2.25 (2H, m), 2.21 (3H, s), 2.5-2.85 (5H, m), 3.2-3.45 (4H, m), 3.57 (2H, s), 3.6-3.8 (2H, m), 3.95-4.1 (2H, m), 4.35-4.5 (1H, m), 6.78 (1H, dd, $J = 2.6, 8.2$ Hz), 6.85 (1H, d, $J = 2.6$ Hz), 7.07 (1H, d, $J = 8.2$ Hz), 7.29 (1H, s), 7.31 (2H, d, $J = 8.4$ Hz), 7.55 (2H, d, $J = 8.4$ Hz), 7.61 (1H, s).

Reference Example 50

To triphenylphosphine (1.18 g, 4.50 mmol), tetrahydropyran-4-ol (0.429 g, 4.50 mmol) and methyl 2-hydroxy-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (327 mg, 1.50 mmol) dissolved in THF (10 ml) was added at 0°C a

solution of diisopropyl azodicarboxylate (0.886 ml, 4.50 mmol) in THF (2 ml), and the resulting mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography (silica gel: 45 g, ethyl acetate/hexane = 1/25). The objective fractions were concentrated under reduced pressure to obtain methyl 2-[(tetrahydropyran-4-yl)oxy]-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (427 mg, 1.41 mmol, 94%).

10 IR (KBr): 1709 cm^{-1} .

^1H -NMR (CDCl_3): δ 1.65-1.9 (2H, m), 1.9-2.1 (4H, m), 2.55-2.7 (2H, m), 2.7-2.8 (2H, m), 3.5-3.65 (2H, m), 3.82 (3H, s), 3.9-4.05 (2H, m), 4.35-4.55 (1H, m), 6.79 (1H, dd, $J = 2.4, 8.3$ Hz), 6.87 (1H, d, $J = 2.4$ Hz), 7.05 (1H, d, $J = 8.3$ Hz), 7.63 (1H, s).

Reference Example 51

To methyl 2-[(tetrahydropyran-4-yl)oxy]-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (406 mg, 1.34 mmol) dissolved in a mixed solvent of methanol (7 ml) and THF (7 ml) was added a 1N aqueous solution of sodium hydroxide (4.0 ml), and the resulting mixture was stirred at 60°C for 5 hours. The reaction mixture was mixed with 1 N hydrochloric acid (4.0 ml) at 0°C, was concentrated under reduced pressure and was mixed with water, and an insoluble material was collected by filtration. The insoluble

material was washed with water and was dried under reduced pressure to obtain 2-[(tetrahydropyran-4-yl)oxy]-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (307 mg, 1.28 mmol, 96%).

5 Example 18 (Production of compound 18)

To a mixture of 2-[(tetrahydropyran-4-yl)oxy]-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (170 mg, 0.59 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline dihydrochloride (190 mg, 0.65 mmol),
10 1-hydroxybenzotriazole (96 mg, 0.71 mmol) and DMF (8 ml) were added at 0°C 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (226 mg, 1.18 mmol) and triethylamine (0.411 ml, 2.95 mmol), and the resulting mixture was stirred at room temperature for 3 days. The
15 reaction mixture was concentrated under reduced pressure, ethyl acetate (40 ml) was added to the residue and the resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate (10 ml, 5 ml x 2). The organic layer was dried with anhydrous magnesium sulfate
20 and was then concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel: 15 g, ethyl acetate). The objective fractions were concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (10 ml). Thereto was added at
25 0°C 4 N hydrogen chloride (a solution in ethyl acetate, 0.6

ml), and an insoluble material was collected by filtration. The insoluble material was washed with ethyl acetate and was then dried under reduced pressure to obtain 2-
5 [(tetrahydropyran-4-yl)oxy]-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-carboxamide hydrochloride (compound 18) (264 mg, 0.50 mmol, 85%).

IR (KBr): 1649, 1597, 1522 cm^{-1} .

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.45-2.2 (10H, m), 2.45-2.65
10 (2H, m), 2.59 (3H, s), 2.65-2.8 (2H, m), 3.2-3.55 (5H, m), 3.75-4.1 (4H, m), 4.12 (1H, d, $J = 13.1$ Hz), 4.44 (1H, d, $J = 13.1$ Hz), 4.45-4.65 (1H, m), 6.86 (1H, dd, $J = 2.4, 8.1$ Hz), 7.02 (1H, d, $J = 2.4$ Hz), 7.13 (1H, d, $J = 8.1$ Hz), 7.25 (1H, s), 7.55 (2H, d, $J = 8.4$ Hz), 7.82 (2H, d, $J =$
15 8.4 Hz).

Reference Example 52

Into a solution of methyl 7-hydroxy-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (400 mg), 4-propoxyphenethyl alcohol (537 mg) and triphenylphosphine
20 (782 mg) in THF (10 ml) was added at 0°C diethyl azodicarboxylate (a 40% solution in toluene) (1.36 ml), and the resulting mixture was stirred at room temperature for 24 hours. After concentration under reduced pressure, the residue was subjected to separation and purification using
25 column chromatography (ethyl acetate/hexane 1 : 1) to

obtain methyl 7-[[4-(propoxyphenethyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (1.2 g).

Into a solution of methyl 7-[[4-(propoxyphenethyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (1.2 g) in THF/methanol (10/5 ml) was added at room temperature an aqueous solution (2.1 ml) of potassium carbonate (622 mg), and the resulting mixture was stirred at 60°C for 24 hours. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate. To the aqueous layer was added 1 N hydrochloric acid (10 ml), and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the precipitated crystals were collected by filtration. The crystals were washed with diisopropyl ether to obtain 7-[[4-(propoxyphenethyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (330 mg) as colorless crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ 0.97 (3H, t, J = 7.5 Hz), 1.62-1.80 (2H, m), 2.86-2.92 (2H, m), 2.99 (2H, t, J = 7.0 Hz), 3.63-3.70 (2H, m), 3.89 (2H, t, J = 6.6 Hz), 4.28 (2H, t, J = 7.0 Hz), 6.86 (2H, d, J = 8.8 Hz), 7.13 (1H, dd, J = 8.8, 2.6 Hz), 7.23 (2H, d, J = 8.8 Hz), 7.33 (1H, d, J = 2.6 Hz), 7.72 (1H, s), 7.91 (1H, d, J = 8.8 Hz).

Reference Example 53

Into a solution of methyl 7-hydroxy-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (400 mg), 3-propoxybenzyl alcohol (495 mg) and triphenylphosphine (782 mg) in THF (10 ml) was added at 0°C diethyl azodicarboxylate (a 40% solution in toluene) (1.36 ml), and the resulting mixture was stirred at room temperature for 24 hours. After concentration under reduced pressure, the residue was subjected to separation and purification using column chromatography (ethyl acetate/hexane 1 : 2) to obtain methyl 7-(3-propoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (650 mg).

Into a solution of methyl 7-(3-propoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (650 mg) in THF/methanol (5/2.5 ml) was added at room temperature an aqueous solution (2.1 ml) of potassium carbonate (622 mg), and the resulting mixture was stirred at 60°C for 24 hours. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate. To the aqueous layer was added 1 N hydrochloric acid (10 ml), and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the precipitated crystals were collected by

filtration. The crystals were washed with diisopropyl ether to obtain 7-(3-propoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (379 mg) as colorless crystals.

5 M. p. 205-206°C

¹H-NMR (200 MHz, DMSO-d₆) δ 0.97 (3H, t, J = 7.3 Hz), 1.63-1.82 (2H, m), 2.87-2.93 (2H, m), 3.65-3.71 (2H, m), 3.93 (2H, t, J = 6.4 Hz), 5.22 (2H, s), 6.88-6.93 (1H, m), 6.99-7.03 (2H, m), 7.22 (1H, dd, J = 8.7, 2.5 Hz), 7.30
10 (1H, t, J = 8.8 Hz), 7.43 (1H, d, J = 2.5 Hz), 7.72 (1H, s), 7.94 (1H, d, J = 8.7 Hz).

Elemental Analysis. Calcd. for C₂₁H₂₂O₆S: C, 62.67; H, 5.51. Found: C, 62.35; H, 5.45.

Reference Example 54

15 Into a solution of methyl 7-hydroxy-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (400 mg), 2-propoxybenzyl alcohol (537 mg) and triphenylphosphine (782 mg) in THF (10 ml) was added at 0°C diethyl azodicarboxylate (a 40% solution in toluene) (1.36 ml), and
20 the resulting mixture was stirred at room temperature for 24 hours. After concentration under reduced pressure, the residue was subjected to separation and purification using column chromatography (ethyl acetate/hexane 1 : 2) to obtain methyl 7-(2-propoxybenzyl)oxy]-1,1-dioxo-2,3-
25 dihydro-1-benzothiepine-4-carboxylate (0.67 g).

Into a solution of methyl 7-(2-propoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.67 g) in THF/methanol (10/5 ml) was added at room temperature an aqueous solution (2.1 ml) of potassium carbonate (622 mg), and the resulting mixture was stirred at 60°C for 24 hours. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate. To the aqueous layer was added 1 N hydrochloric acid (15 ml), and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the precipitated crystals were collected by filtration. The crystals were washed with diisopropyl ether to obtain 7-(2-propoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (270 mg) as light yellow crystals.

M. p. 157-160°C

¹H-NMR (200 MHz, DMSO-d₆) δ 0.96 (3H, t, J = 7.4 Hz), 1.64-1.82 (2H, m), 2.91 (2H, t, J = 6.4 Hz), 3.68 (2H, t, J = 6.4 Hz), 4.00 (2H, t, J = 6.4 Hz), 5.20 (2H, s), 6.96 (1H, t, J = 7.2 Hz), 7.05 (1H, d, J = 8.4 Hz), 7.20 (1H, dd, J = 8.8, 2.4 Hz), 7.28-7.44 (3H, m), 7.72 (1H, s), 7.94 (1H, d, J = 8.8 Hz).

Elemental Analysis. Calcd. for C₂₁H₂₂O₆S: C, 62.67; H, 5.51. Found: C, 62.40; H, 5.38.

Example 19 (Production of compound 19)

Into a solution of 7-[(4-(propoxyphenethyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (180 mg) in THF (5 ml) were added at room temperature thionyl chloride (0.063 ml) and DMF (one drop), and the resulting mixture was stirred for one hour. After concentration under reduced pressure to remove the solvent, the residue dissolved in THF (10 ml) was added dropwise to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (105 mg) and triethylamine (0.18 ml) in THF (2 ml) at room temperature. After being stirred at room temperature for 5 hours, the reaction mixture was mixed with water and was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the residue was subjected to purification using column chromatography (ethanol/ethyl acetate 1 : 2) and to recrystallization (ethanol) to obtain N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(4-(propoxyphenethyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (compound 19) (153 mg) as colorless crystals.

M. p. 157-158°C

¹H-NMR (200 MHz, CDCl₃) δ 1.03 (3H, t, J = 7.3 Hz), 1.62-1.86 (6H, m), 2.21 (3H, s), 2.54-2.71 (1H, m), 2.99-

3.13 (4H, m), 3.29-3.45 (2H, m), 3.57 (2H, s), 3.63-3.70
(2H, m), 3.90 (2H, t, J = 6.6 Hz), 3.97-4.09 (2H, m), 4.19
(2H, t, J = 7.0 Hz), 6.84-6.95 (4H, m), 7.18 (2H, d, J =
8.4 Hz), 7.19 (1H, s), 7.32 (2H, d, J = 8.4 Hz), 7.53 (2H,
5 d, J = 8.4 Hz), 7.79 (1H, s), 8.06 (1H, d, J = 8.8 Hz).

Elemental Analysis. Calcd. for $C_{35}H_{42}N_2O_6S$: C,
67.94; H, 6.84, N, 4.35. Found: C, 68.13; H, 6.83, N, 4.49.

Example 20 (Production of compound 20)

Into a solution of 7-[(3-(propoxybenzyl)oxy)-1,1-
10 dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (180
mg) in THF (5 ml) were added at room temperature thionyl
chloride (0.065 ml) and DMF (one drop), and the resulting
mixture was stirred for one hour. After concentration
under reduced pressure to remove the solvent, the residue
15 dissolved in THF (10 ml) was added dropwise to a solution
of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline
(108 mg) and triethylamine (0.19 ml) in THF (2 ml) at room
temperature. After being stirred at room temperature for
67 hours, the reaction mixture was mixed with water and was
20 extracted with ethyl acetate. The organic layer was washed
with an aqueous saturated solution of sodium chloride and
was dried with magnesium sulfate. After concentration
under reduced pressure, the residue was subjected to
purification using column chromatography (ethanol/ethyl
25 acetate 1 : 3) and to recrystallization (ethanol) to obtain

N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(3-(propoxybenzyl)oxy)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (compound 20) (204 mg) as colorless crystals.

5 M. p. 197-199°C

¹H-NMR (200 MHz, CDCl₃) δ 1.04 (3H, t, J = 7.3 Hz), 1.64-1.87 (6H, m), 2.20 (3H, s), 2.54-2.72 (1H, m), 3.06-3.13 (2H, m), 3.29-3.45 (2H, m), 3.57 (2H, s), 3.65-3.72 (2H, m), 3.93 (2H, t, J = 6.4 Hz), 3.98-4.09 (2H, m), 5.12
10 (2H, s), 6.85-7.07 (4H, m), 7.20 (1H, s), 7.30-7.34 (4H, m), 7.53 (2H, d, J = 8.4 Hz), 7.76 (1H, s), 8.09 (1H, d, J = 8.8 Hz).

Elemental Analysis. Calcd. for C₃₄H₄₀N₂O₆S: C, 67.53; H, 6.67, N, 4.63. Found: C, 67.49; H, 6.63, N, 4.46.

15 Example 21 (Production of compound 21)

Into a solution of 7-[(2-propoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (180 mg) in THF (5 ml) were added at room temperature thionyl chloride (0.065 ml) and DMF (one drop), and the resulting
20 mixture was stirred for one hour. After concentration under reduced pressure to remove the solvent, the residue dissolved in THF (10 ml) was added dropwise into a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (108 mg) and triethylamine (0.18 ml) in THF (2 ml) at room
25 temperature. After being stirred at room temperature for 2

days, the reaction mixture was mixed with water and was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration
5 under reduced pressure, the residue was subjected to purification using column chromatography (silica gel: ethanol/ethyl acetate 1 : 3) and to recrystallization (ethanol) to obtain N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(2-propoxybenzyl)oxy]-1,1-dioxo-
10 2,3-dihydro-1-benzothiepine-4-carboxamide (compound 21) (139 mg) as colorless crystals.

M. p. 190-192°C

¹H-NMR (200 MHz, CDCl₃) δ 1.03 (3H, t, J = 7.3 Hz), 1.63-1.87 (6H, m), 2.20 (3H, s), 2.55-2.73 (1H, m), 3.09
15 (2H, t, J = 6.6 Hz), 3.31-3.43 (2H, m), 3.57 (2H, s), 3.68 (2H, t, J = 6.6 Hz), 4.00 (2H, t, J = 6.4 Hz), 3.98-4.10 (2H, m), 5.21 (2H, s), 6.90-7.02 (3H, m), 7.07 (1H, dd, J = 8.8, 2.6 Hz), 7.21 (1H, s), 7.28-7.41 (4H, m), 7.53 (2H, d, J = 8.4 Hz), 7.77 (1H, s), 8.08 (1H, d, J = 8.4 Hz).

20 Elemental Analysis. Calcd. for C₃₄H₄₀N₂O₆S: C, 67.53; H, 6.67; N, 4.63. Found: C, 67.69; H, 6.65; N, 4.53.

Reference Example 55

A mixed solution of 2-hydroxy-5-bromobenzyl alcohol (3.00 g) and 2-bromo-4'-methylacetophenone (3.50 g)
25 and potassium carbonate (2.45 g) in acetone (50 ml) was

stirred at 80°C for 4 hours. After cooling to room temperature, a solid material was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was subjected to separation and purification using column chromatography (ethyl acetate/hexane 2 : 3 → 1 : 1) to obtain 2-[4-bromo-2-(hydroxymethyl)phenoxy]-1-(4-methylphenyl)-1-ethanone (3.60 g) as colorless crystals.

M. p. 125-127°C

¹H-NMR (200 MHz, CDCl₃) δ 2.44 (3H, s), 3.43 (1H, t, J = 6.8 Hz), 4.73 (2H, d, J = 6.8 Hz), 5.36 (2H, s), 6.72 (1H, d, J = 8.8 Hz), 7.24-7.36 (3H, m), 7.45 (1H, d, J = 2.6 Hz), 7.86 (2H, d, J = 8.4 Hz)

IR (KBr) 3412, 1686, 1606, 1483, 1412, 1234, 1018, 810 cm⁻¹.

Elemental Analysis. Calcd. for C₁₆H₁₅O₃Br: C, 57.33; H, 4.51; Br, 23.84. Found: C, 57.33; H, 4.41; Br, 23.86.

Reference Example 56

Into a solution of 2-[4-bromo-2-(hydroxymethyl)phenoxy]-1-(4-methylphenyl)-1-ethanone (3.00 g) in acetonitrile (20 ml) was added at room temperature triphenylphosphine hydrobromide (3.17 g), and the resulting mixture was refluxed with heating for 2 days under a nitrogen atmosphere. After cooling to room temperature, the reaction mixture was mixed with diethyl ether, and the

resulting crystals were collected by filtration to obtain [5-bromo-2-[2-(4-methylphenyl)-2-oxoethoxy]benzyl](triphenyl)phosphonium bromide (5.94 g) as colorless crystals.

5 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 2.44 (3H, s), 4.82 (2H, s), 5.29 (2H, d, $J = 14.0$ Hz), 6.75 (1H, d, $J = 8.8$ Hz), 7.25-7.39 (4H, m), 7.52-7.81 (15H, m), 7.88 (2H, d, $J = 8.2$ Hz).

10 IR (KBr) 1691, 1489, 1437, 1234, 1120, 816, 748, 717, 689, 505 cm^{-1} .

Reference Example 57

Into a suspension of [5-bromo-2-[2-(4-methylphenyl)-2-oxoethoxy]benzyl](triphenyl)phosphonium bromide (5.53 g) in ethanol (20 ml) was added at room temperature a 20% solution of sodium ethoxide in ethanol (2.85 g), and the resulting mixture was stirred for 24 hours. After addition of water (15 ml) to the reaction mixture, a solid material was collected by filtration and was washed with water. The solid material were purified by 20 recrystallization (ethanol) to obtain 6-bromo-3-(4-methylphenyl)-2H-1-benzopyran (2.16 g) as colorless crystals.

M. p. 143°C (dec.)

25 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 2.38 (3H, s), 5.15 (2H, d, $J = 1.4$ Hz), 6.69-6.74 (2H, m), 7.16-7.28 (4H, m), 7.33

(2H, d, $J = 8.4$ Hz).

IR (KBr) 1479, 1217, 898, 813 cm^{-1} .

Elemental Analysis. Calcd. for $\text{C}_{16}\text{H}_{13}\text{OBr}$: C, 63.81; H, 4.35; Br, 26.53. Found: C, 63.67; H, 4.37; Br, 26.50.

Reference Example 58

Into a solution of 6-bromo-3-(4-methylphenyl)-2H-1-benzopyran (0.5 g) in THF (15 ml) was added at -78°C 1.6 M butyl lithium (a hexane solution) (1.14 ml) under a nitrogen atmosphere. The resulting mixture was stirred at -78°C for one hour, was then mixed with dry ice and was stirred for additional one hour. After addition of 1 N hydrochloric acid (10 ml), the resulting mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the resulting crystals were collected by filtration, and the crystals were washed with diethyl ether and hexane to obtain 3-(4-methylphenyl)-2H-1-benzopyran-6-carboxylic acid (218 mg) as colorless crystals.

M. p. 255°C (dec.)

^1H -NMR (200 MHz, CDCl_3) δ 2.33 (3H, s), 5.27 (2H, d, $J = 1.0$ Hz), 6.89 (1H, d, $J = 8.2$ Hz), 7.10 (1H, s), 7.24 (2H, d, $J = 8.3$ Hz), 7.48 (2H, d, $J = 8.3$ Hz), 7.71 (1H, dd, $J = 8.2, 2.2$ Hz), 7.77 (1H, d, $J = 2.2$ Hz).

IR (KBr) 2976, 1676, 1302, 1223, 806 cm^{-1} .

Elemental Analysis. Calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_3$: C, 76.68; H, 5.30. Found: C, 76.47; H, 5.37.

Example 22 (Production of compound 22)

5 Into a solution of 3-(4-methylphenyl)-2H-1-benzopyran-6-carboxylic acid (130 mg) in THF (10 ml) were added at room temperature oxalyl chloride (0.07 ml) and one drop of DMF, and the resulting mixture was stirred for one hour. After concentration under reduced pressure to remove
10 the solvent, to the residue dissolved in THF (20 ml) were added at 0°C 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (118 mg) and triethylamine (0.15 ml), and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water
15 with vigorous stirring to stop the reaction, and the resulting mixture was extracted with chloroform. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the residue was
20 purified by recrystallization (ethanol) to obtain 3-(4-methylphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2H-1-benzopyran-6-carboxamide (compound 22) (162 mg) as light yellow crystals.

M. p. 230-235°C

25 ^1H -NMR (200 MHz, CDCl_3) δ 1.52-1.84 (4H, m), 2.21

(3H, s), 2.39 (3H, s), 2.56-2.74 (1H, m), 3.30-3.45 (2H, m),
3.58 (2H, s), 3.99-4.10 (2H, m), 5.26 (2H, d, $J = 1.6$ Hz),
6.82 (1H, s), 6.90 (1H, d, $J = 9.2$ Hz), 7.22 (2H, d, $J =$
8.0 Hz), 7.30-7.37 (4H, m), 7.56-7.66 (4H, m), 7.72 (1H, br
5 s).

IR (KBr) 3305, 2947, 2843, 1647, 1599, 1518, 1491,
1406, 1315, 1238, 1140, 810 cm^{-1} .

Elemental Analysis. Calcd. for $\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_3 \cdot 0.2 \text{ H}_2\text{O}$:
C, 76.31; H, 6.92; N, 5.93. Found: C, 76.31; H, 7.02; N,
10 5.88.

Reference Example 59

Into a solution of sodium ethoxide (a 20%
solution in ethanol, 22.2 g) in toluene (100 ml) was added
at 0°C over a period of more than 10 minutes a solution of
15 4-bromobenzaldehyde (10 g) and ethyl azidoacetate (7.0 g)
in toluene (50 ml). After being stirred at room
temperature for 2 hours, the reaction mixture was mixed
with water and was extracted with ethyl acetate. The
organic layer was washed with an aqueous saturated solution
20 of sodium chloride and was dried with magnesium sulfate.
After concentration under reduced pressure, the residue was
subjected to separation and purification using column
chromatography (ethyl acetate/hexane 1 : 19) to obtain
ethyl (Z)-2-azido-3-(4-bromophenyl)acrylate (6.24 g) as a
25 yellow oily substance.

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 1.40 (3H, t, $J = 7.2$ Hz), 4.38 (2H, q, $J = 7.2$ Hz), 6.83 (1H, s), 7.51 (2H, d, $J = 8.6$ Hz), 7.69 (2H, d, $J = 8.6$ Hz).

IR (neat): 2121, 1713, 1398, 1379, 1315, 1281,
5 1250, 1076, 1011, 824 cm^{-1} .

Reference Example 60

A solution of ethyl (Z)-2-azido-3-(4-bromophenyl)acrylate (6.24 g) in xylene (200 ml) was heated at reflux for 4 hours. After cooling to room temperature,
10 the reaction mixture was concentrated under reduced pressure, and the precipitated crystals were collected by filtration. The crystals were washed with xylene and hexane to obtain ethyl 6-bromo-1H-indole-2-carboxylate (3.21 g) as colorless crystals.

15 M. p. 187-188°C

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 1.43 (3H, t, $J = 7.2$ Hz), 4.41 (2H, q, $J = 7.2$ Hz), 7.18-7.28 (2H, m), 7.53-7.59 (2H, m), 8.78-8.97 (1H, m).

IR (KBr) 3321, 1695, 1522, 1315, 1240, 1201, 1020,
20 822, 763, 733 cm^{-1} .

Elemental Analysis. Calcd. for $\text{C}_{11}\text{H}_{10}\text{NO}_2\text{Br}$: C, 49.28; H, 3.76; N, 5.22. Found: C, 49.45; H, 3.63; N, 5.06.

Reference Example 61

A mixture of ethyl 6-bromo-1H-indole-2-carboxylate (2.5 g) and 4-methylphenylboric acid (1.39 g),
25

potassium carbonate (2.58 g) and toluene/ethanol/water (90/9/9 ml) was stirred at room temperature for one hour. Into the reaction mixture was added tetrakis(triphenylphosphine)palladium (0.32 g), and the resulting mixture was heated at reflux for 18 hours. After cooling to room temperature, the mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the residue was subjected to purification using column chromatography (ethyl acetate/hexane 1 : 5 → 1 : 2 → 1 : 1) and to recrystallization (ethyl acetate/hexane) to obtain ethyl 6-(4-methylphenyl)-1H-indole-2-carboxylate (1.92 g) as colorless crystals.

M. p. 163-165°C

¹H-NMR (200 MHz, CDCl₃) δ 1.43 (3H, t, J = 7.2 Hz), 2.41 (3H, s), 4.42 (2H, q, J = 7.2 Hz), 7.23-7.27 (2H, m), 7.29 (1H, s), 7.41 (1H, dd, J = 8.4, 1.6 Hz), 7.51-7.61 (3H, m), 7.73 (1H, d, J = 8.4 Hz), 8.86-8.98 (1H, m).

IR (KBr) 3290, 1689, 1520, 1333, 1282, 1217, 820, 795 cm⁻¹.

Elemental Analysis. Calcd. for C₁₈H₁₇NO₂: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.48; H, 6.21; N, 4.89.

Reference Example 62

Into a mixed solution of ethyl 6-(4-

5 methylphenyl)-1H-indole-2-carboxylate (0.6 g) in
ethanol/THF (10/10 ml) was added at room temperature a 2 N
aqueous solution of sodium hydroxide (5 ml), and the
resulting mixture was stirred for 64 hours. After addition
of 1 N hydrochloric acid (15 ml), the reaction mixture was
concentrated under reduced pressure. Water was added to
the residue, and the resulting mixture was extracted with
ethyl acetate. The organic layer was washed with an
aqueous saturated solution of sodium chloride and was dried
10 with magnesium sulfate. After concentration of the organic
layer under reduced pressure, the precipitated crystals
were collected by filtration. The crystals were washed
with hexane to obtain 6-(4-methylphenyl)-1H-indole-2-
carboxylic acid (509 mg) as colorless crystals.

15 M. p. 260°C (dec.)

¹H-NMR (200 MHz, DMSO-d₆) δ 2.35 (3H, s), 7.10 (1H,
s), 7.28 (2H, d, J = 8.0 Hz), 7.35 (1H, dd, J = 8.4, 1.8
Hz), 7.56 (2H, d, J = 8.0 Hz), 7.61 (1H, d, J = 1.8 Hz),
7.71 (1H, d, J = 8.4 Hz), 11.81 (1H, s).

20 IR (KBr) 3410, 1666, 1525, 1439, 1273, 1215, 800
cm⁻¹.

Elemental Analysis. Calcd. for C₁₆H₁₃NO₂: C, 76.48;
H, 5.21; N, 5.57. Found: C, 76.66; H, 5.05; N, 5.34.

Example 23 (Production of compound 23)

25 Into a solution of 6-(4-methylphenyl)-1H-indole-

2-carboxylic acid (200 mg) in THF (10 ml) were added at room temperature oxalyl chloride (0.35 ml) and one drop of DMF, and the resulting mixture was stirred for one hour. After concentration under reduced pressure to remove the solvent, to the residue dissolved in THF (20 ml) were added at 0°C 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (193 mg) and triethylamine (0.22 ml) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into water with vigorous stirring to stop the reaction, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration of the organic layer under reduced pressure, the precipitated crystals were purified by recrystallization (ethanol) to obtain 6-(4-methylphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1H-indole-2-carboxamide (compound 23) (97 mg) as colorless crystals.

M. p. 246-250°C

¹H-NMR (200 MHz, DMSO-d₆) δ 1.45-1.79 (4H, m), 2.12 (3H, s), 2.36 (3H, s), 2.46-2.69 (1H, m), 3.19-3.38 (2H, m), 3.54 (2H, s), 3.84-3.96 (2H, m), 7.24-7.46 (6H, m), 7.57 (2H, d, J = 8.0 Hz), 7.66 (1H, s), 7.69-7.80 (3H, m), 10.20 (1H, s), 11.78 (1H, s).

IR (KBr) 3298, 1655, 1601, 1537, 1333, 812 cm^{-1} .

Elemental Analysis. Calcd. for $\text{C}_{29}\text{H}_{31}\text{N}_3\text{O}_2 \cdot 0.2 \text{ H}_2\text{O}$:
C, 76.19; H, 6.92; N, 9.19. Found: C, 76.01; H, 6.81; N,
9.12.

5 Reference Example 63

Into a solution of ethyl 6-(4-methylphenyl)-1H-indole-2-carboxylate (0.9 g) in DMF (10 ml) was added at 0°C sodium hydride (60%, 0.14 g), and the resulting mixture was stirred for 15 minutes. Into the reaction mixture was
10 added methyl iodide (0.22 ml), and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was mixed with water and was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with
15 magnesium sulfate. After concentration of the organic layer under reduced pressure, the residue was subjected to separation and purification using column chromatography (ethyl acetate/hexane 1 : 4) and further to recrystallization (ethyl acetate/hexane) to obtain ethyl 1-methyl-6-(4-methylphenyl)-1H-indole-2-carboxylate (0.80 g)
20 as colorless crystals.

M. p. 98-99°C

^1H -NMR (200 MHz, CDCl_3) δ 1.42 (3H, t, $J = 7.0$ Hz),
2.41 (3H, s), 4.12 (3H, s), 4.38 (2H, q, $J = 7.0$ Hz),
25 7.26-7.32 (3H, m), 7.40 (1H, dd, $J = 8.4, 1.4$ Hz), 7.54-

7.60 (3H, m), 7.71 (1H, d, $J = 8.4$ Hz).

IR (KBr) 1705, 1504, 1400, 1223, 1153, 1084, 822, 798 cm^{-1} .

Elemental Analysis. Calcd. for $\text{C}_{19}\text{H}_{19}\text{NO}_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.99; H, 6.50; N, 4.60.

Reference Example 64

Into a mixed solution of ethyl 1-methyl-6-(4-methylphenyl)-1H-indole-2-carboxylate (0.7 g) in ethanol/THF (20/10 ml) was added at room temperature a 2 N aqueous solution of sodium hydroxide (1.5 ml), and the resulting mixture was stirred for 24 hours. After addition of 1 N hydrochloric acid (5 ml), the reaction mixture was concentrated under reduced pressure. Water was added to the residue, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with magnesium sulfate. After concentration under reduced pressure, the precipitated crystals were collected by filtration. The crystals were washed with hexane to obtain 1-methyl-6-(4-methylphenyl)-1H-indole-2-carboxylic acid (600 mg) as colorless crystals.

M. p. 259°C (dec.)

^1H -NMR (200 MHz, DMSO-d_6) δ 2.36 (3H, s), 4.09 (3H, s), 7.23 (1H, s), 7.29 (2H, d, $J = 7.6$ Hz), 7.42 (1H, dd, $J = 8.4, 1.4$ Hz), 7.66-7.74 (3H, m), 7.80 (1H, s).

IR (KBr) 2916, 1680, 1512, 1470, 1433, 1257, 1228, 920, 820, 798 cm^{-1} .

Elemental Analysis. Calcd. for $\text{C}_{17}\text{H}_{15}\text{NO}_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.87; H, 5.76; N, 5.22.

5 Example 24 (Production of compound 24)

 Into a solution of 1-methyl-6-(4-methylphenyl)-1H-indole-2-carboxylic acid (200 mg) in THF (10 ml) were added at room temperature oxalyl chloride (0.20 ml) and one drop of DMF, and the resulting mixture was stirred for one
10 hour. After concentration under reduced pressure to remove the solvent, to the residue dissolved in THF (30 ml) were added
 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (183 mg) and triethylamine (0.21 ml) at 0°C, and the resulting mixture was stirred at room
15 temperature for 18 hours. After pouring into water with vigorous stirring to stop the reaction, the reaction mixture was concentrated under reduced pressure, and the precipitate was collected by filtration. The precipitate was washed with ethanol and ethyl acetate to obtain a crude
20 product. The crude product was purified by recrystallization (ethanol) to obtain 1-methyl-6-(4-methylphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1H-indole-2-carboxamide (compound
24) (298 mg) as colorless crystals.

25 M. p. 225-226°C

¹H-NMR (200 MHz, CDCl₃) δ 1.62-1.83 (4H, m), 2.22 (3H, s), 2.42 (3H, s), 2.56-2.75 (1H, m), 3.29-3.45 (2H, m), 3.59 (2H, s), 3.98-4.11 (2H, m), 4.14 (3H, s), 7.02 (1H, s), 7.26-7.36 (4H, m), 7.43 (1H, dd, J = 8.0, 1.4 Hz), 7.57-7.61 (5H, m), 7.71 (1H, d, J = 8.8 Hz), 7.91 (1H, s).

IR (KBr) 3298, 1647, 1516, 1462, 1389, 1300, 1250, 1142, 810 cm⁻¹.

Elemental Analysis. Calcd. for C₃₀H₃₃N₃O₂: C, 77.06; H, 7.11; N, 8.99. Found: C, 76.98; H, 7.02; N, 8.99.

Reference Example 65

Into a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzooxepine-4-carboxylic acid (280 mg) in methanol (20 ml)/ethyl acetate (10 ml) was added 10% palladium on charcoal (50% water content, 70 mg). Hydrogen gas was introduced, and the resulting mixture was stirred at room temperature for 17 hours and at 50°C for 3 hours, and was then filtered to remove the catalyst. The filtrate was concentrated, and the residue was recrystallized from ethyl acetate/hexane to obtain 7-(4-methylphenyl)-2,3,4,5-tetrahydro-1-benzooxepine-4-carboxylic acid (187 mg) as colorless crystals.

M. p. 182-184°C

¹H-NMR (200 MHz, CDCl₃) δ: 2.2-2.3 (2H, m), 2.38 (3H, s), 2.7-2.85 (1H, m), 3.05-3.3 (2H, m), 3.8-3.9 (1H, m), 4.3-4.4 (1H, m), 7.04 (1H, d, J = 8.6), 7.22 (2H, d, J

= 8.2), 7.3-7.4 (2H, m), 7.44 (2H, d, J = 8.4).

IR (KBr) 1692, 1491, 1310, 1250, 1227, 1051, 964, 814 cm^{-1} .

Elemental Analysis. Calcd. for $\text{C}_{18}\text{H}_{18}\text{O}_3$: C, 76.57;
5 H, 6.43. Found: C, 76.48; H, 6.30.

Example 25 (Production of compound 25)

Into a solution of 7-(4-methylphenyl)-2,3,4,5-tetrahydro-1-benzoxepine-4-carboxylic acid (141 mg) and 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (110
10 mg) in DMF (4 ml) were added under ice cooling diethyl cyanophosphonate (0.08 ml) and triethylamine (0.08 ml). After being stirred at 0°C for 30 minutes and at room temperature for 8 hours, an aqueous solution of sodium bicarbonate was added into the reaction mixture under ice
15 cooling. The resulting mixture was extracted with ethyl acetate, and the extract was washed with an aqueous saturated solution of sodium chloride. The extract was dried with anhydrous magnesium sulfate and was then concentrated under reduced pressure. The residue was
20 subjected to purification using silica gel column chromatography (ethyl acetate/hexane = 4/1) and further to recrystallization from ethyl acetate/hexane to obtain N-[4-[(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)phenyl]-7-(4-methylphenyl)-2,3,4,5-tetrahydro-1-benzoxepine-4-
25 carboxamide (compound 25) (43 mg) as colorless crystals.

M. p. 172-174°C

¹H-NMR (200 MHz, CDCl₃) δ: 1.4-2.0 (4H, m), 2.15-2.45 (2H, m), 2.38 (6H, s), 2.65-2.85 (1H, m), 2.9-3.1 (2H, m), 3.2-3.4 (3H, m), 3.7-3.9 (3H, m), 3.9-4.1 (2H, m), 4.4-4.55 (1H, m), 7.05 (2H, d, J = 8.8), 7.22 (2H, d, J = 8.2), 7.3-7.5 (5H, m), 7.6-7.75 (2H, m).

IR (KBr) 1665, 1609, 1541, 1491, 1418, 1252, 1061, 818 cm⁻¹.

Reference Example 66

10 1,4-Dibromobenzene (25 g) was dissolved in concentrated sulfuric acid (30 ml). Thereto was added dropwise under ice cooling a mixed solution of concentrated sulfuric acid (30 ml)/nitric acid (8.9 ml). After 14 hours at room temperature, the reaction mixture was poured into
15 ice water, was mixed with potassium carbonate and was extracted with ethyl acetate. The extract was washed successively with an aqueous solution of potassium bicarbonate and an aqueous saturated solution of sodium chloride, was dried (anhydrous magnesium sulfate) and was
20 then concentrated. The residue was subjected to purification using silica gel column chromatography (hexane) to obtain 1,4-dibromo-2-nitrobenzene (13.3 g) as light yellow crystals.

¹H-NMR (200 MHz, CDCl₃) δ: 7.56 (dd, 1H, J = 2.2, 8.6), 7.62 (d, 1H, J = 8.6), 7.99 (d, 1H, J = 2.2).

IR (KBr) 1537, 1458, 1352, 1034 cm^{-1} .

Reference Example 67

Into a solution of 1,4-dibromo-2-nitrobenzene (5.4 g) in THF (300 ml) was added phenyllithium (11.7 ml) under cooling at -100°C in a liquid nitrogen/diethyl ether bath. After stirring for 30 minutes, DMF (5.9 ml) was added dropwise, and the resulting mixture was stirred for one hour in a dry ice/ acetone bath. Thereto was added 1 N sulfuric acid (40 ml), and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous solution of sodium chloride, was dried (anhydrous magnesium sulfate) and was then concentrated. The residue was subjected to purification using silica gel column chromatography (ethyl acetate/hexane = 1/8) to obtain 4-dibromo-2-nitrobenzaldehyde (3.53 g) as a brown solid.

^1H -NMR (200 MHz, CDCl_3) δ : 7.85 (d, 1H, $J = 8.2$), 7.94 (dd, 1H, $J = 1.8, 8.2$), 8.27 (d, 1H, $J = 1.8$), 10.39 (s, 1H).

IR (KBr) 1699, 1595, 1559, 1534, 1346, 1190, 878, 820 cm^{-1} .

Reference Example 68

To 4-dibromo-2-nitrobenzaldehyde (1.89 g) were added 4-methylphenylboric acid (1.23 g), a 2 M aqueous solution of potassium carbonate (10 ml), ethanol (10 ml)

and toluene (30 ml), and, after stirring at room temperature under an argon atmosphere for 30 minutes, tetrakis(triphenylphosphine)palladium (380 mg) was added thereto, and the resulting mixture was refluxed overnight.

5 The reaction mixture was extracted with ethyl acetate, and the extract was washed successively with water and an aqueous solution of sodium chloride, was dried (anhydrous magnesium sulfate) and was then concentrated. The residue was subjected to purification using silica gel column
10 chromatography (ethyl acetate/hexane = 1/9) to obtain 4-(4-methylphenyl)-2-nitrobenzaldehyde (1.17 g) as a light brown powder.

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 2.44 (s, 3H), 7.33 (d, 2H, $J = 8.4$), 7.57 (d, 2H, $J = 8.4$), 7.96 (dd, 1H, $J = 1.6$, 8.2), 8.04 (d, 1H, $J = 8.2$), 8.29 (d, 1H, $J = 1.6$), 10.44
15 (s, 1H).

IR (KBr) 1696, 1609, 1534, 1520, 1350, 1188, 814 cm^{-1} .

Reference Example 69

20 Into a solution of 4-(4-methylphenyl)-2-nitrobenzaldehyde (590 mg) in THF (50 ml) was added a solution of sodium hydrosulfite (2.66 g)/water (25 ml). After being stirred at room temperature for 10 minutes, the reaction mixture was extracted with ethyl acetate, and the
25 extract was washed with an aqueous solution of sodium

chloride. The extract was dried (anhydrous magnesium sulfate) and was then concentrated to obtain 2-amino-4-(4-methylphenyl)benzaldehyde (0.26 g) as a light brown powder.

¹H-NMR (200 MHz, CDCl₃) δ: 2.41 (s, 3H), 5.8-6.4
5 (br, 2H), 6.84 (d, 1H, J = 1.6), 6.98 (dd, 1H, J = 1.6, 8.2), 7.26 (d, 2H, J = 8.2), 7.45-7.6 (m, 3H), 9.89 (s, 1H).

IR (KBr) 1671, 1620, 1591, 1539, 1393, 1208, 1192, 795 cm⁻¹.

Reference Example 70

10 Into a solution of 2-amino-4-(4-methylphenyl)benzaldehyde (0.23 g) and pyruvic acid (192 mg) in methanol (20 ml) was added a solution of sodium hydroxide (349 mg)/methanol (20 ml), and the resulting mixture was stirred at 50-60°C for 9 hours and was then
15 concentrated. The concentrate was extracted with water, and the aqueous layer was washed twice with diethyl ether and was then mixed with 1 N hydrochloric acid to adjust the pH to 1-2. The resulting mixture was extracted with ethyl acetate, and the extract was washed with an aqueous
20 solution of sodium chloride. The extract was dried (anhydrous magnesium sulfate) and was then concentrated. The residue was subjected to purification using silica gel column chromatography (ethyl acetate/methanol = 4/1) to obtain 4-(4-methylphenyl)quinoline-2-carboxylic acid (117
25 mg) as an orange powder.

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 2.40 (s, 3H), 7.37 (d, 2H, $J = 8.2$), 7.80 (d, 2H, $J = 8.2$), 8.0-8.2 (m, 3H), 8.39 (s, 1H), 8.59 (d, 1H, $J = 8.0$).

IR (KBr) 1620, 1555, 1454, 1404, 1173, 816 cm^{-1} .

5 Example 26 (Production of compound 26)

Into a solution of 4-(4-methylphenyl)quinoline-2-carboxylic acid (100 mg) in THF (5 ml) were added under ice cooling DMF (one drop) and oxalyl chloride (0.04 ml), and the resulting mixture was stirred at 0°C for 30 minutes.

10 On the other hand, into a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (92 mg) in THF (5 ml) were added under ice cooling triethylamine (0.33 ml) and then the above-prepared, acid chloride solution, and the resulting mixture was stirred at room temperature for

15 one hour. The reaction mixture was mixed with water under ice cooling and was extracted with ethyl acetate. The extract was washed with an aqueous solution of sodium chloride, was dried (anhydrous magnesium sulfate) and was concentrated under reduced pressure. The residue was

20 subjected to purification using silica gel column chromatography (ethyl acetate/methanol = 9/1) and further to recrystallization from ethyl acetate/diethyl ether to obtain

25 N-[4-[(N-methyl-N-(tetrahydropyran-4-yl))aminomethyl]phenyl]-7-(4-methylphenyl)quinoline-2-carboxamide (compound 26) (27 mg) as colorless crystals.

M. p. 148-150°C

¹H-NMR (200 MHz, CD₃OD) δ: 1.6-1.9 (m, 4H), 2.25 (s, 3H), 2.43 (s, 3H), 2.6-2.8 (m, 1H), 3.3-3.5 (m, 2H), 3.66 (s, 2H), 3.9-4.1 (m, 2H), 7.35 (d, 2H, J = 7.8), 7.39 (d, 2H, J = 7.8), 7.74 (d, 2H, J = 7.8), 7.85 (d, 2H, J = 7.8), 7.95-8.05 (m, 1H), 8.08 (d, 1H, J = 8.8), 8.26 (d, 1H, J = 8.2), 8.45-8.5 (m, 1H), 8.51 (d, 1H, J = 8.2).

IR (KBr) 1678, 1522, 1497, 1410, 812 cm⁻¹.

Elemental Analysis. Calcd. for C₃₀H₃₁N₃O₂·0.2 H₂O: C, 76.80; H, 6.75; N, 8.96. Found: C, 76.84; H, 6.59; N, 8.86.

Example 27 (Production of compound 27)

Into a solution of 3-(4-methylphenyl)-2H-1-benzopyran-6-carboxylic acid (150 mg) in THF (10 ml) were added at room temperature oxalyl chloride (0.07 ml) and subsequently one drop of DMF, and the resulting mixture was stirred for one hour. After evaporation of the solvent under reduced pressure, to the residue dissolved in THF (20 ml) were added at 0°C 1-(4-aminobenzyl)phosphorinan-1-oxide (138 mg) and triethylamine (0.16 ml), and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was poured into water with vigorous stirring to stop the reaction and was extracted with chloroform. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with

magnesium sulfate. After concentration under reduced pressure, the residue was purified by recrystallization (ethanol) to obtain 3-(4-methylphenyl)-N-(4-pentamethylenephosphorylmethylphenyl)-2H-1-benzopyran-6-carboxamide (compound 27) (204 mg) as light yellow crystals.

M. p. 235°C (dec.)

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 1.40-2.16 (10H, m), 2.39 (3H, s), 3.15 (2H, d, $J = 13.6$ Hz), 5.25 (2H, d, $J = 1.4$ Hz), 6.82 (1H, s), 6.89 (1H, d, $J = 9.2$ Hz), 7.18-7.29 (4H, m), 7.35 (2H, d, $J = 8.4$ Hz), 7.62-7.70 (4H, m), 8.21-8.32 (1H, m).

IR (KBr) 3226, 1645, 1603, 1541, 1514, 1491, 1410, 1329, 1201, 1165, 1134, 837 cm^{-1} .

Elemental Analysis. Calcd. for $\text{C}_{29}\text{H}_{30}\text{NO}_3\text{P} \cdot 0.3 \text{ H}_2\text{O}$: C, 73.03; H, 6.47; N, 2.94. Found: C, 73.07; H, 6.57; N, 2.87.

Example 28 (Production of compound 28)

Into a solution of 3-(4-methylphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2H-1-benzopyran-6-carboxamide (80 mg) in DMF (30 ml) was added at room temperature methyl iodide (0.04 ml), and the resulting mixture was stirred for 3 days. After evaporation of the solvent under reduced pressure, ethyl acetate was added to the residue, and the precipitated crystals were collected by filtration to obtain N,N-

dimethyl-N-[4-[[3-(4-methylphenyl)-2H-1-benzopyran-6-carbonyl]amino]benzyl]-4-tetrahydropyranylammonium iodide (compound 28) (87 mg) as light yellow crystals.

M. p. 215-218°C (dec.)

5 ¹H-NMR (200 MHz, DMSO-d₆) δ 1.75-2.00 (2H, m),
2.10-2.23 (2H, m), 2.34 (3H, s), 2.89 (6H, s), 3.26-3.43
(2H, m), 3.49-3.68 (1H, m), 4.01-4.12 (2H, m), 4.47 (2H, s),
5.29 (2H, d, J = 1.0 Hz), 6.96 (1H, d, J = 8.0 Hz), 7.10
(1H, s), 7.26 (2H, d, J = 8.0 Hz), 7.48-7.57 (4H, m), 7.75-
10 7.80 (2H, m), 7.92 (2H, d, J = 8.8 Hz), 10.34 (1H, s).

IR (KBr) 3273, 1647, 1597, 1524, 1493, 1323, 810
cm⁻¹.

Elemental Analysis. Calcd. for C₃₁H₃₅N₂O₃I·1.2 H₂O:
C, 58.90; H, 5.96; N, 4.43. Found: C, 58.85; H, 5.66; N,
15 4.48.

Reference Example 71

Into acetic acid (42 ml) were added dropwise
under ice cooling sulfuric acid (28 ml), subsequently N-(2-
(4-bromophenyl)ethyl)trifluoroacetamide (7.8 g) and
20 paraformamide (1.27 g) and the resulting mixture was
stirred overnight under a nitrogen atmosphere. The
reaction mixture was poured into ice water and was
extracted with ethyl acetate. The organic layer was washed
with an aqueous solution of sodium hydrogen carbonate,
25 water and an aqueous saturated solution of sodium chloride,

and was then dried with anhydrous magnesium sulfate. The resulting organic layer was evaporated under reduced pressure to remove the solvent to obtain 7-bromo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (8.1 g) as a colorless oil.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 2.87-2.94 (2H, m), 3.81-3.91 (2H, m), 4.72 (0.7H, s), 4.77 (1.3H, s), 7.02-7.09 (1H, m), 7.27-7.37 (2H, m).

IR (neat) ν : 2907, 1696 cm^{-1} .

Reference Example 72

To 7-bromo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (8.1 g), 4-methylphenylboric acid (3.9 g), a 2 M aqueous solution of potassium carbonate (40 ml) and ethanol (40 ml) was added toluene (100 ml), and the resulting mixture was stirred at room temperature under an argon atmosphere for 30 minutes. Thereto was added tetrakis(triphenylphosphine)palladium (1.26 g), and the resulting mixture was refluxed under an argon atmosphere for 4.5 hours. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and an aqueous saturated solution of sodium chloride, and was then dried with anhydrous magnesium sulfate. After evaporation of the solvent under reduced pressure, methanol (200 ml) and a 2 M aqueous solution of potassium carbonate (50 ml) were added to the residue, and the resulting

mixture was stirred overnight at room temperature. After concentration, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and was then back-extracted with 1 N hydrochloric acid. The aqueous layer was made alkaline with a 1 N aqueous solution of sodium hydroxide, was then saturated with sodium chloride and was extracted with ethyl acetate. The organic layer was washed with an aqueous saturated solution of sodium chloride and was dried with anhydrous magnesium sulfate. The resulting organic layer was evaporated under reduced pressure to remove the solvent to obtain 7-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (4.2 g) as colorless crystals.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 2.39 (3H, s), 2.83 (1.5H, t, $J = 6.0$ Hz), 2.91-2.93 (1H, m), 3.17 (1.5H, t, $J = 6.0$ Hz), 3.33 (0.5H, s), 3.82 (0.5H, s), 4.08 (1.5H, s), 7.13-7.25 (4H, m), 7.36 (1H, dd, $J = 1.8, 7.8$), 7.44-7.49 (2H, m).

IR (KBr) ν : 2919, 1427 cm^{-1} .

Elemental Analysis. Calcd. for $\text{C}_{16}\text{H}_{17}\text{N} \cdot 0.1 \text{ H}_2\text{O}$: C, 85.37; H, 7.70; N, 6.22. Found: C, 85.34; H, 7.57; N, 6.10.

Reference Example 73

A solution of 4-(chloromethyl)phenylisocyanate (0.38 g) in tetrahydrofuran was added dropwise under ice cooling into a solution of 7-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (0.5 g) in tetrahydrofuran. The

resulting mixture was stirred for one hour and was then evaporated to remove the solvent to obtain 4-(7-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinolin-2-ylcarbonylamino)benzyl chloride (0.82 g) as colorless
5 crystals.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 2.40 (3H, s), 2.98 (2H, t, J = 5.8 Hz), 3.77 (2H, t, J = 6.1 Hz), 4.57 (2H, s), 4.73 (2H, s), 6.48 (1H, br), 7.23-7.30 (4H, m), 7.34-7.49 (7H, m).

IR (KBr) ν : 3303, 3023, 1645 cm^{-1} .

10 Elemental Analysis. Calcd. for $\text{C}_{24}\text{H}_{23}\text{ClN}_2\text{O} \cdot 0.2 \text{ H}_2\text{O}$: C, 73.07; H, 5.98; N, 7.10. Found: C, 73.04; H, 5.86; N, 7.10.

Reference Example 74

Oxalyl chloride (0.4 ml) was added under ice
15 cooling into a suspension of 4-bromomethylphenylacetic acid (0.52 g) in dichloromethane (4 ml). Dimethylformamide (a catalytic amount) was then added thereto, and the resulting mixture was stirred at room temperature for 2 hours. After the reaction mixture was evaporated to remove the solvent,
20 a solution of the residue in tetrahydrofuran was added dropwise under ice cooling into a solution of 7-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (0.5 g) and diisopropylethylamine (0.5 ml) in tetrahydrofuran. After being stirred at room temperature for 30 minutes, the
25 resulting mixture was mixed with ethyl acetate, and the

precipitate was removed by filtration. The filtrate was washed with water and an aqueous saturated solution of sodium chloride and was then dried with anhydrous magnesium sulfate. The resulting organic layer was evaporated under reduced pressure to remove the solvent to obtain 2-(4-bromomethylphenylacetyl)-7-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (0.7 g) as a light yellow oil.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 2.39 (3H, s), 2.75 (1.1H, t, $J = 5.9$ Hz), 2.89 (0.9H, t, $J = 6.0$ Hz), 3.69 (1.1H, t, $J = 5.9$ Hz), 3.82 (2H, s), 3.88 (0.9H, t, $J = 6.0$ Hz), 4.44-4.57 (2H, m), 4.66 (0.9H, s), 4.82 (1.1H, s), 7.13-7.47 (11H, m).

IR (neat) ν : 3023, 2922, 1642 cm^{-1} .

Example 29 (Production of compound 29)

A solution of 4-(7-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinolin-2-ylcarbonylamino)benzyl chloride (0.2 g) and 1-methyl piperidine (0.19 ml) in dimethylformamide (5 ml) was stirred overnight at room temperature under a nitrogen atmosphere. The reaction mixture was evaporated to remove the solvent and was mixed with ethyl acetate, and the precipitate was collected by filtration. The precipitate was recrystallized from ethanol to obtain 1-methyl-1-(4-((7-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonylamino)benzyl)piperidinium chloride (compound 29)

(0.23 g) as colorless crystals.

M. p. 179-180°C (dec.)

¹H-NMR (δ ppm, DMSO-d₆) 1.45-1.65 (2H, m), 1.75-1.95 (4H, m), 2.34 (3H, s), 2.86-2.92 (5H, m), 3.24-3.32
5 (4H, m), 3.76 (2H, t, J = 5.9 Hz), 4.48 (2H, s), 4.73 (2H, s), 7.25-7.29 (3H, m), 7.38-7.49 (4H, m), 7.55 (2H, d, J = 8.2 Hz), 7.65 (2H, d, J = 8.6 Hz), 8.91 (1H, br).

IR (KBr) ν: 3364, 3285, 2948, 1663 cm⁻¹.

Elemental Analysis. Calcd. for C₃₀H₃₆ClN₃O·H₂O: C, 70.92; H, 7.54; N, 8.27. Found: C, 70.97; H, 7.80; N, 8.03.
10

Example 30 (Production of compound 30)

A solution of 4-(7-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinolin-2-ylcarbonylamino)benzyl chloride (0.2 g) and 1-ethylpiperidine (0.21 ml) in
15 dimethylformamide (5 ml) was stirred overnight at room temperature under a nitrogen atmosphere. The reaction mixture was evaporated to remove the solvent and was mixed with ethyl acetate, and the precipitate was collected by filtration to obtain 1-ethyl-1-(4-((7-(4-methylphenyl)-
20 1,2,3,4-tetrahydroisoquinolin-2-yl)carbonylamino)benzyl)piperidinium chloride (compound 30) (0.24 g) as a light red, amorphous substance.

¹H-NMR (δ ppm, DMSO-d₆) 1.33 (3H, t, J = 7.2 Hz), 1.40-1.65 (2H, m), 1.75-1.95 (4H, m), 2.35 (3H, s), 2.89
25 (2H, t, J = 5.6 Hz), 3.10-3.33 (6H, m), 3.76 (2H, t, J =

5.6 Hz), 4.45 (2H, s), 4.73 (2H, s), 7.24-7.29 (3H, m), 7.35-7.48 (4H, m), 7.55 (2H, d, J = 8.2 Hz), 7.65 (2H, d, J = 8.4 Hz), 8.91 (1H, br).

IR (KBr) ν : 3236, 2948, 1651 cm^{-1} .

5 Elemental Analysis. Calcd. for $\text{C}_{31}\text{H}_{38}\text{ClN}_3\text{O} \cdot 0.8 \text{ H}_2\text{O}$: C, 71.81; H, 7.70; N, 8.10. Found: C, 71.87; H, 7.79; N, 7.91.

Example 31 (Production of compound 31)

A solution of 2-(4-bromomethylphenylacetyl)-7-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (0.2 g) and 1-methylpiperidine (0.17 ml) in dimethylformamide (5 ml) was stirred overnight at room temperature under a nitrogen atmosphere. The reaction mixture was evaporated to remove the solvent and was mixed with ethyl acetate, and the precipitate was collected by filtration. The precipitate was dissolved in ethanol, and the solvent was evaporated to obtain 1-methyl-1-(4-((7-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonylmethyl)benzyl)piperidinium bromide (compound 31) (0.24 g) as a colorless amorphous substance.

^1H -NMR (δ ppm, DMSO-d_6) 1.40-1.70 (2H, m), 1.78-1.91 (4H, m), 2.34 (3H, s), 2.77-2.88 (2H, m), 2.93 (3H, s), 3.21-3.27 (4H, m), 3.69-3.82 (2H, m), 3.90 (2H, s), 4.53 (2H, d, J = 8.0 Hz), 4.76 (2H, d, J = 20.8 Hz), 7.20-7.30 (3H, m), 7.39-7.56 (8H, m).

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

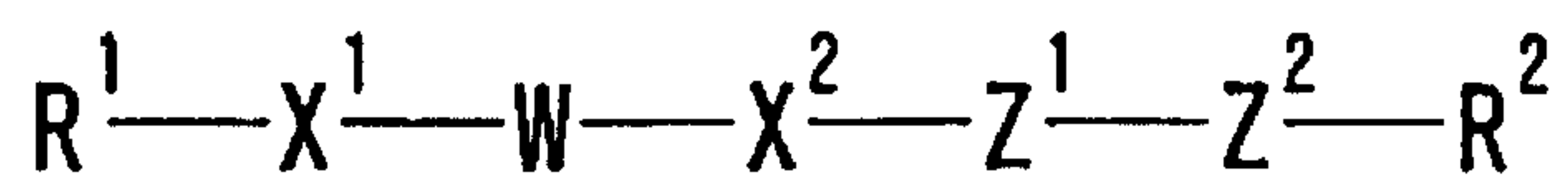
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

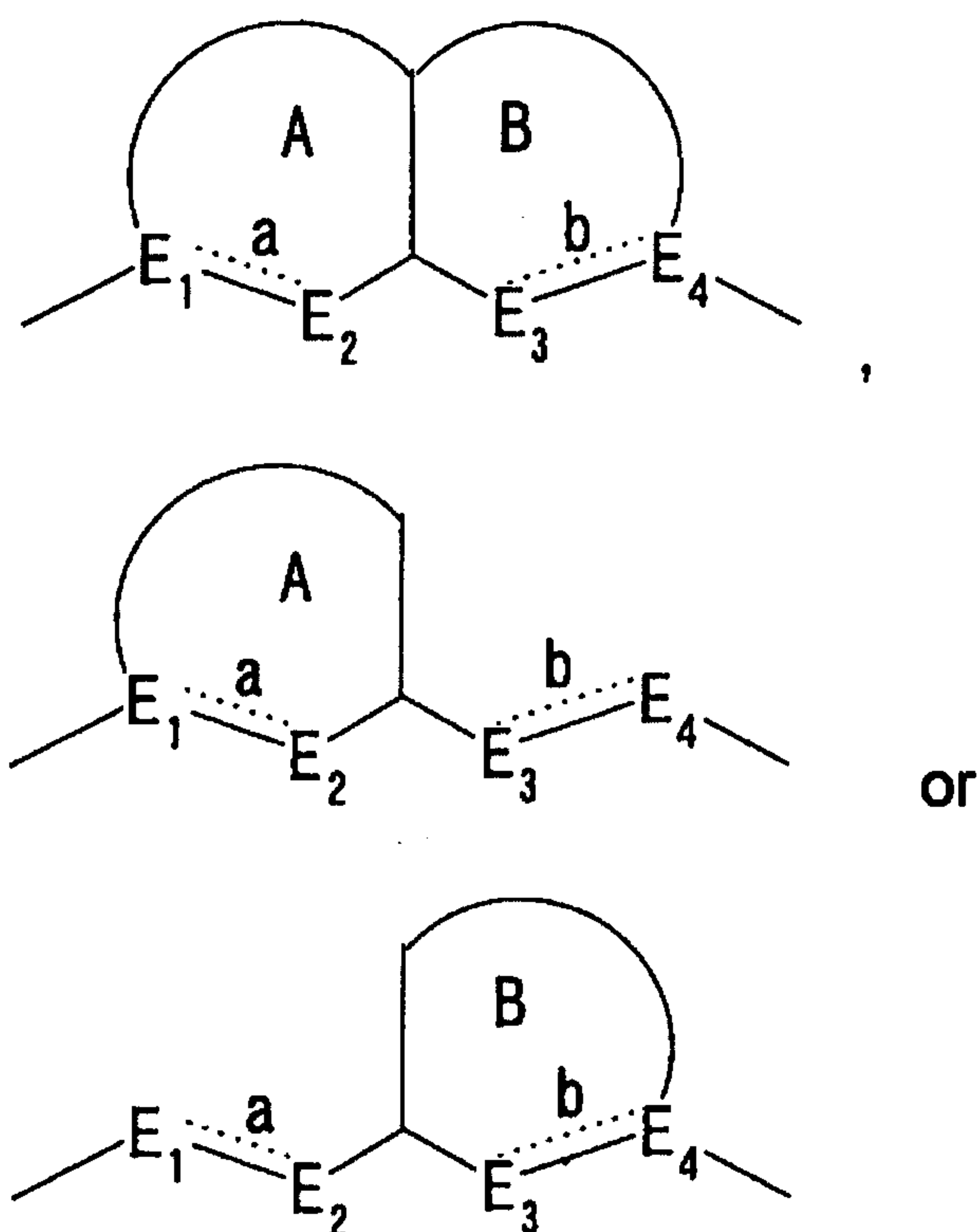
Claims

1. A compound represented by formula



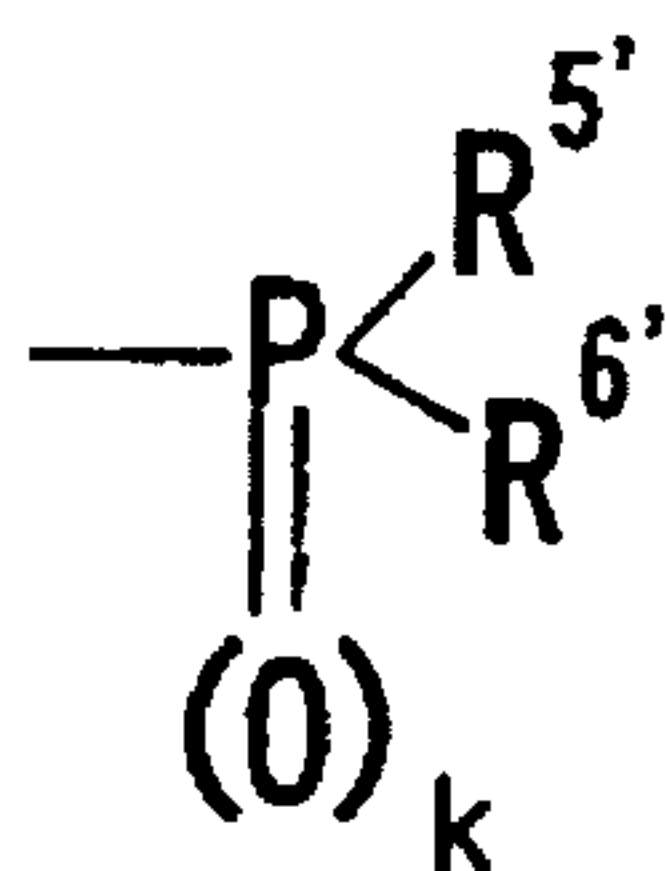
- 5 wherein R^1 indicates a 5- to 6-membered cyclic ring group that may be substituted, X^1 indicates a bond or a bivalent group, in which the number of atoms constituting the straight-chain portion is 1 to 4, W indicates a bivalent group that is represented by formula

10

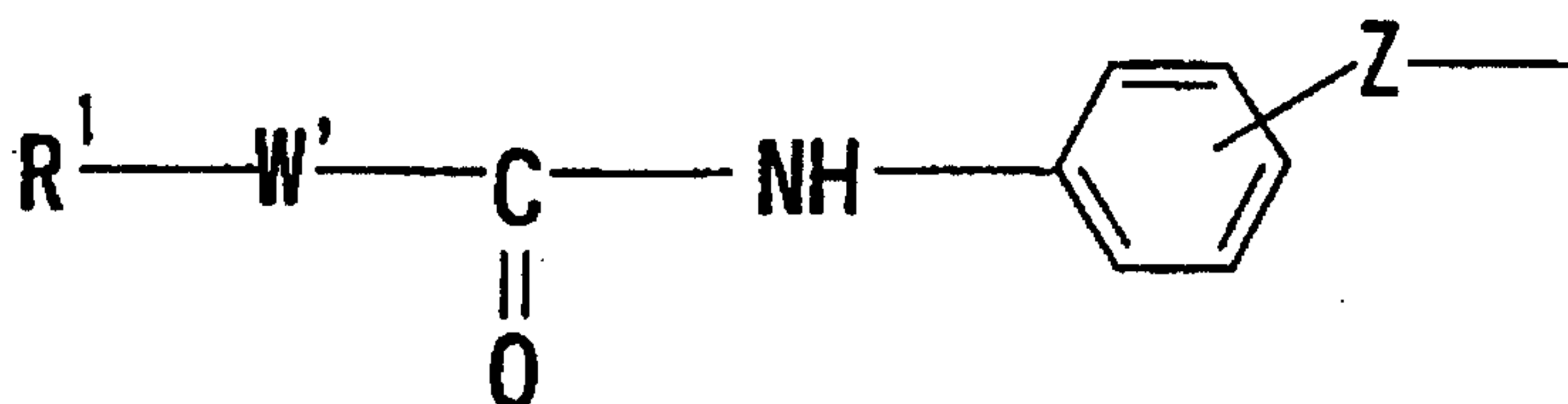


(wherein each of ring A and ring B indicates a 5- to 7-

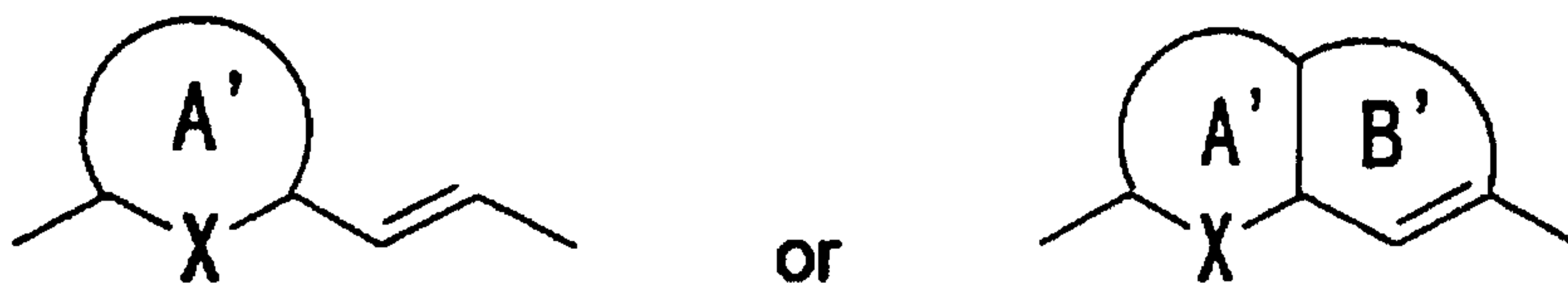
membered cyclic ring group that may be substituted, each of
 E_1 and E_4 indicates the carbon atom that may be substituted
 or the nitrogen atom that may be substituted, each of E_2
 and E_3 indicates the carbon atom that may be substituted or
 5 the nitrogen atom that may be substituted, the sulfur atom
 that may be oxidized or the oxygen atom and each of a and b
 indicates to be a single bond or a double bond), X^2
 indicates a bivalent group, in which the number of atoms
 constituting the straight-chain portion is 1 to 4, Z^1
 10 indicates a bond or a bivalent cyclic ring group, Z^2
 indicates a bond or a bivalent cyclic ring group, in which
 the number of atoms constituting the straight-chain portion
 is 1 to 4, and R^2 indicates (1) an amino group that may be
 substituted, where the nitrogen atom may be converted into
 15 a quaternary ammonium or the N-oxide, (2) a nitrogen-
 containing, heterocyclic ring group that may be substituted
 and may contain the sulfur atom or the oxygen atom as a
 ring-constituting atom, where the nitrogen atom may be
 converted into a quaternary ammonium or the N-oxide, (3) a
 20 group that is bonded via the sulfur atom, (4) a group
 represented by formula



(wherein k indicates 0 or 1, the phosphorus atom may form a phosphonium salt when k is 0, and each of R^{5'} and R^{6'} indicates the hydrocarbon atom that may be substituted, the hydroxyl group that may be substituted or an amino group that may be substituted, and R^{5'} and R^{6'} may bind each other to form a cyclic ring group together with the adjacent phosphorus atom), (5) an amidino group that may be substituted or (6) a guanidino group that may be substituted; provided that, when a group represented by formula R¹-X¹-W-X²-Z¹-Z²- indicates a group represented by formula

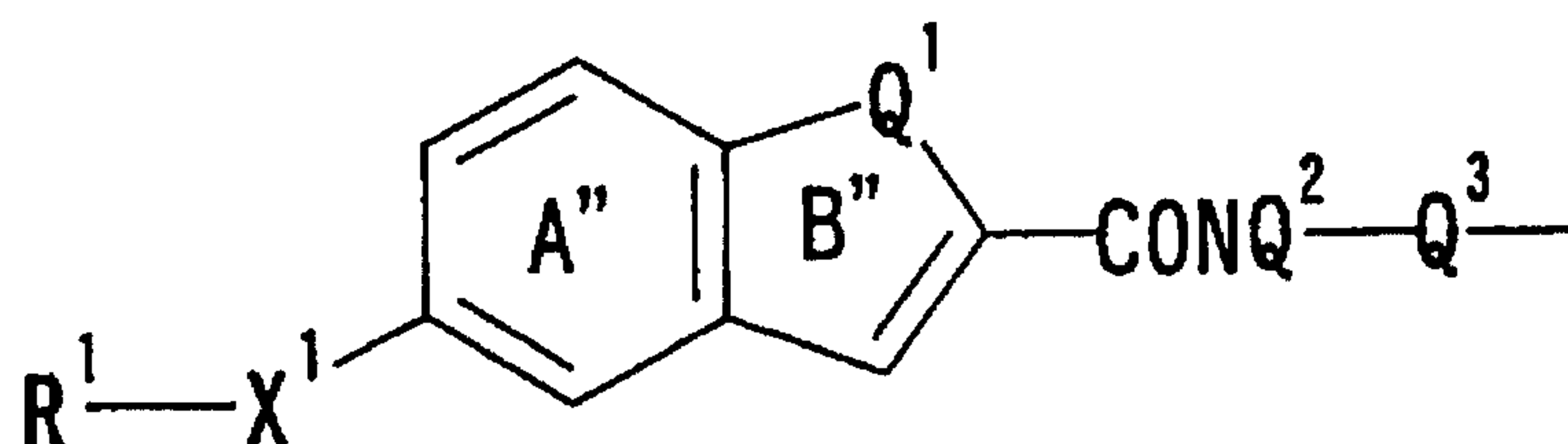


(wherein R¹ indicates the same meaning as described above, W' indicates a bivalent group represented by formula

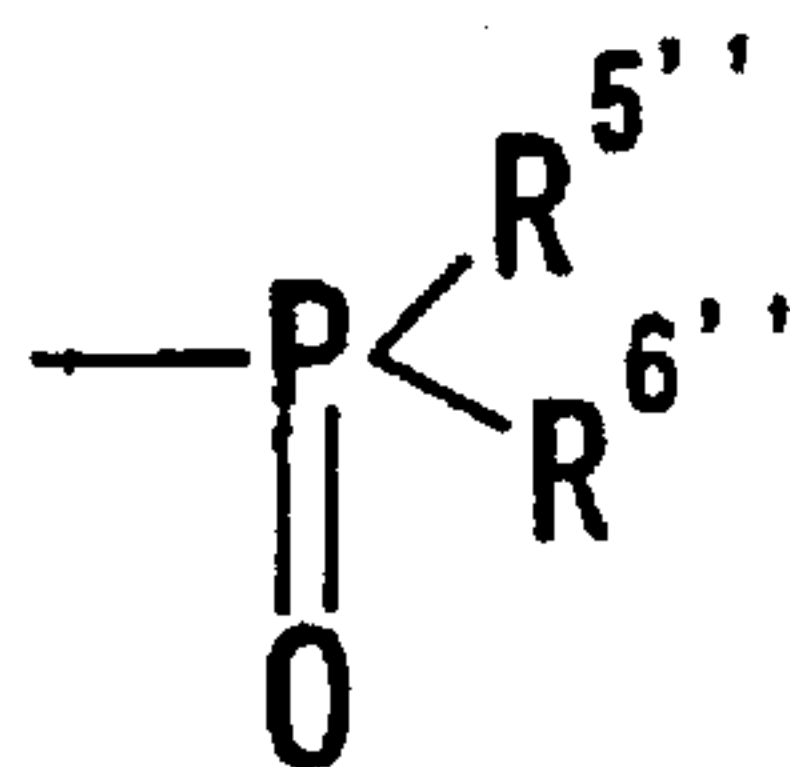


(wherein ring A' indicates a 5- to 6-membered aromatic ring that may be substituted, X indicates the carbon atom that may be substituted, the nitrogen atom that may be substituted, the sulfur atom or the oxygen atom and ring B' indicates a 5- to 7-membered ring that may be substituted)

and Z indicates a bivalent group, in which the number of atoms constituting the straight-chain portion is 1 to 4, R² indicates an amidino group that may be substituted or a guanidino group that may be substituted; when a group
 5 represented by formula R¹-X¹-W-X²-Z¹-Z²- indicates a group represented by formula



(wherein R¹ and X¹ indicate the same meanings as described above, ring A'' indicates a benzene ring that may be substituted, Q¹ indicates a bivalent group, in which ring
 10 B'' forms a 5- to 7-membered ring, Q² indicates the hydrogen atom, a hydrocarbon group that may be substituted, a heterocyclic ring group that may be substituted and Q³ indicates a bond or a bivalent group), R² does not indicate
 15 a group represented by formula



(wherein each of R^{5''} and R^{6''} indicates the hydroxyl group that may be substituted, and R^{5''} and R^{6''} may bind each other to form a cyclic ring group together with the
 20 adjacent phosphorus atom); or salts thereof.

2. A prodrug of the compound or salt thereof as claimed in Claim 1.

3. The compound as claimed in Claim 1, wherein R^1 is a group that is formed by removing one hydrogen atom from benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine or tetrahydrofuran, each of which may be substituted.

4. The compound as claimed in Claim 1, wherein R^1 is a phenyl that may be substituted.

5. The compound as claimed in Claim 1, wherein X^1 is a bond, $-(CH_2)_{a'}-$ (wherein a' indicates an integer of 1 to 4), $-(CH_2)_{b'}-X^3-$ (wherein b' indicates an integer of 0 to 3 and X^3 indicates an imino group that may be substituted, the carbonyl group, the oxygen atom or the sulfur atom that may be oxidized), $-CH=CH-$, $-C\equiv C-$, $-CO-NH-$ or $-SO_2-NH-$.

6. The compound as claimed in Claim 1, wherein X^1 is a bond.

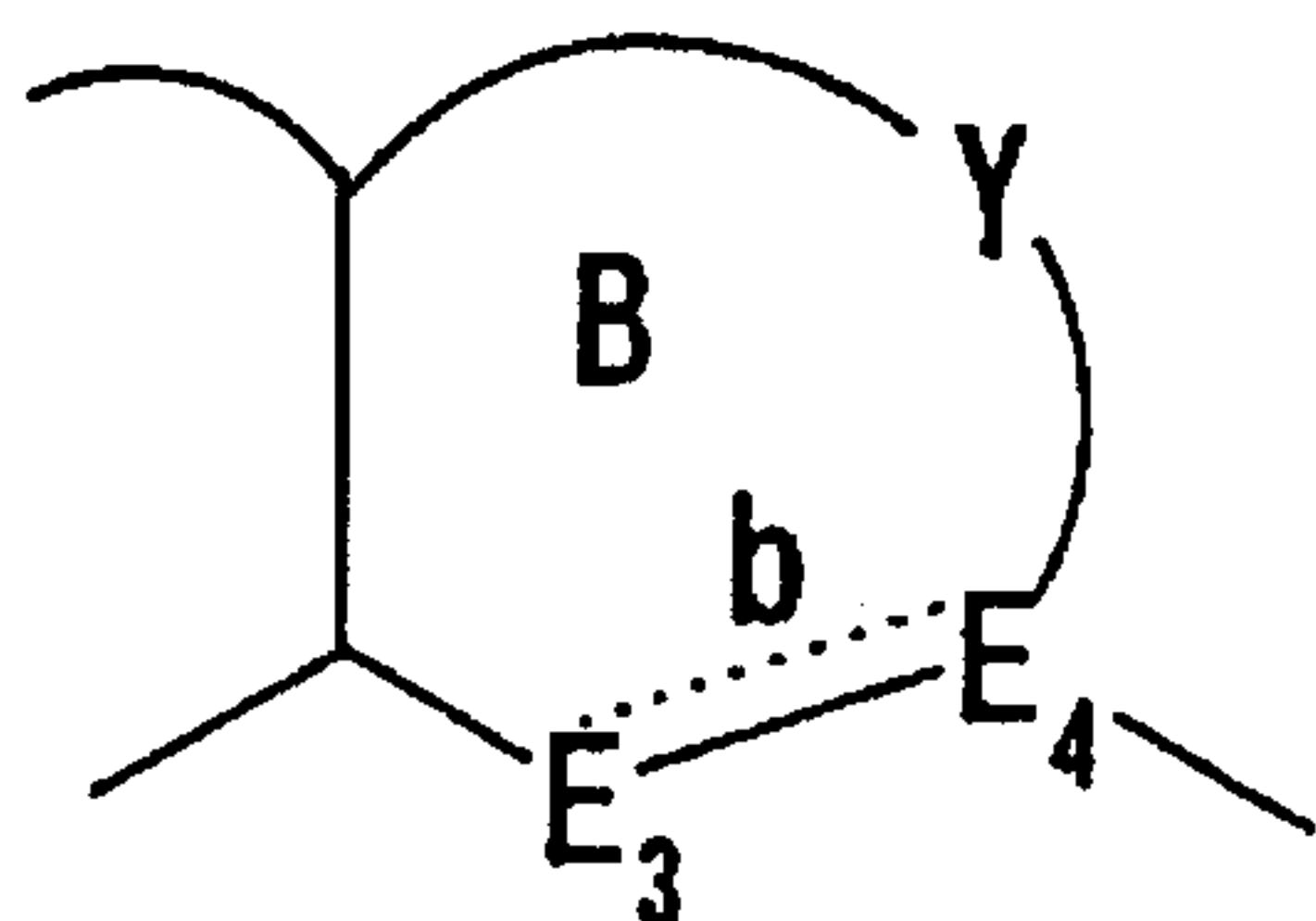
7. The compound as claimed in Claim 1, wherein X^1 is $-(CH_2)_{b'}-X^3-$ (wherein b' indicates an integer of 0 to 3, and X^3 indicates an imino group that may be substituted, the carbonyl group, the oxygen atom or the sulfur atom that may be oxidized).

8. The compound as claimed in Claim 1, wherein

ring A is furan, thiophene, pyrrole, pyridine, pyran or benzene, each of which may be substituted.

9. The compound as claimed in Claim 1, wherein ring A is a benzene that may be substituted.

5 10. The compound as claimed in Claim 1, wherein ring B is a 5- to 7-membered ring that may be substituted at a substitutable optional position, which is represented by formula



10

wherein E₃ indicates the carbon atom that may be substituted or the nitrogen atom that may be substituted, E₄ indicates the carbon atom that may be substituted or the
 15 nitrogen atom, b indicates a single bond or a double bond and Y indicates -Y'-(CH₂)_m- (Y' indicates -S(O)_m- (m indicates an integer of 0 to 2), -O-, -NH- or -CH₂-, and m' indicates an integer of 0 to 2), -CH=, -CH=CH- or -N=CH-).

11. The compound as claimed in Claim 10, wherein
 20 Y indicates -Y'-(CH₂)₂- (Y' indicates -S(O)_m- (m indicates an integer of 0 to 2), -O-, -NH- or -CH₂-).

12. The compound as claimed in Claim 1, wherein

E_3 indicates the carbon atom that may be substituted, E_4 indicates the carbon atom that may be substituted and b indicates a double bond.

13. The compound as claimed in Claim 1, wherein
5 X^2 is $-(CH_2)_{a'}-$ (a' indicates an integer of 1 to 4), $-(CH_2)_{b'}-X^3-$ (b' indicates an integer of 0 to 3, and X^3 indicates an imino group that may be substituted, the carbonyl group, the oxygen atom or the sulfur atom that may be oxidized), $-CH=CH-$, $-C\equiv C-$, $-CO-NH-$ or $-SO_2-NH-$.

10 14. The compound as claimed in Claim 1, wherein X^2 is $-CO-NH-$.

15 15. The compound as claimed in Claim 1, wherein Z^1 is (1) a bond or (2) a bivalent cyclic ring group that is formed by removing two hydrogen atoms from benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine or tetrahydropyran, each of which may be substituted.

20 16. The compound as claimed in Claim 1, wherein Z^1 is (1) a bond or (2) a bivalent cyclic ring group that is formed by removing two hydrogen atoms from benzene, cyclohexane or piperidine, each of which may be substituted.

17. The compound as claimed in Claim 1, wherein Z^1 is a phenylene that may be substituted.

25 18. The compound as claimed in Claim 1, wherein

Z^2 is a bond or a C_{1-3} alkylene that may be substituted.

19. The compound as claimed in Claim 1, wherein Z^2 is a bivalent group that has a skeleton represented by $-Z'-(CH_2)_n-$ (Z' indicates $-CH(OH)-$, $-C(O)-$ or $-CH_2-$, and n indicates an integer of 0 to 2) and may have a substituent at an optional methylene group.

20. The compound as claimed in Claim 1, wherein Z^2 is a bond or a methylene.

21. The compound as claimed in Claim 1, wherein Z^1 is a 6-membered, bicyclic ring group, and Z^2 is substituted at the para position of X^2 .

22. The compound as claimed in Claim 1, wherein R^2 is (1) an amino group that may be substituted, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide, (2) a nitrogen-containing, heterocyclic ring group that may be substituted and may contain the sulfur atom or the oxygen atom as a ring-constituting atom, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide, (3) an amidino group that may be substituted or (4) a guanidino group that may be substituted.

23. The compound as claimed in Claim 1, wherein R^2 is an amino group that may be substituted.

24. The compound as claimed in Claim 1, wherein R^2 is an amidino group that may be substituted or a

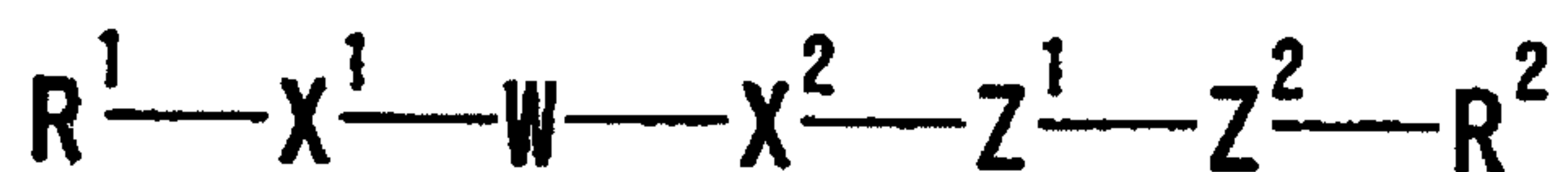
guanidino group that may be substituted.

25. N-[4-[N-Methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[2-(4-propoxyphenyl)ethoxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(3-propoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(2-propoxybenzyl)oxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(4-propoxyphenyl)methoxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(4-propoxyethoxyphenyl)methoxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[3-(4-propoxyphenyl)propoxy]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, or salts thereof.

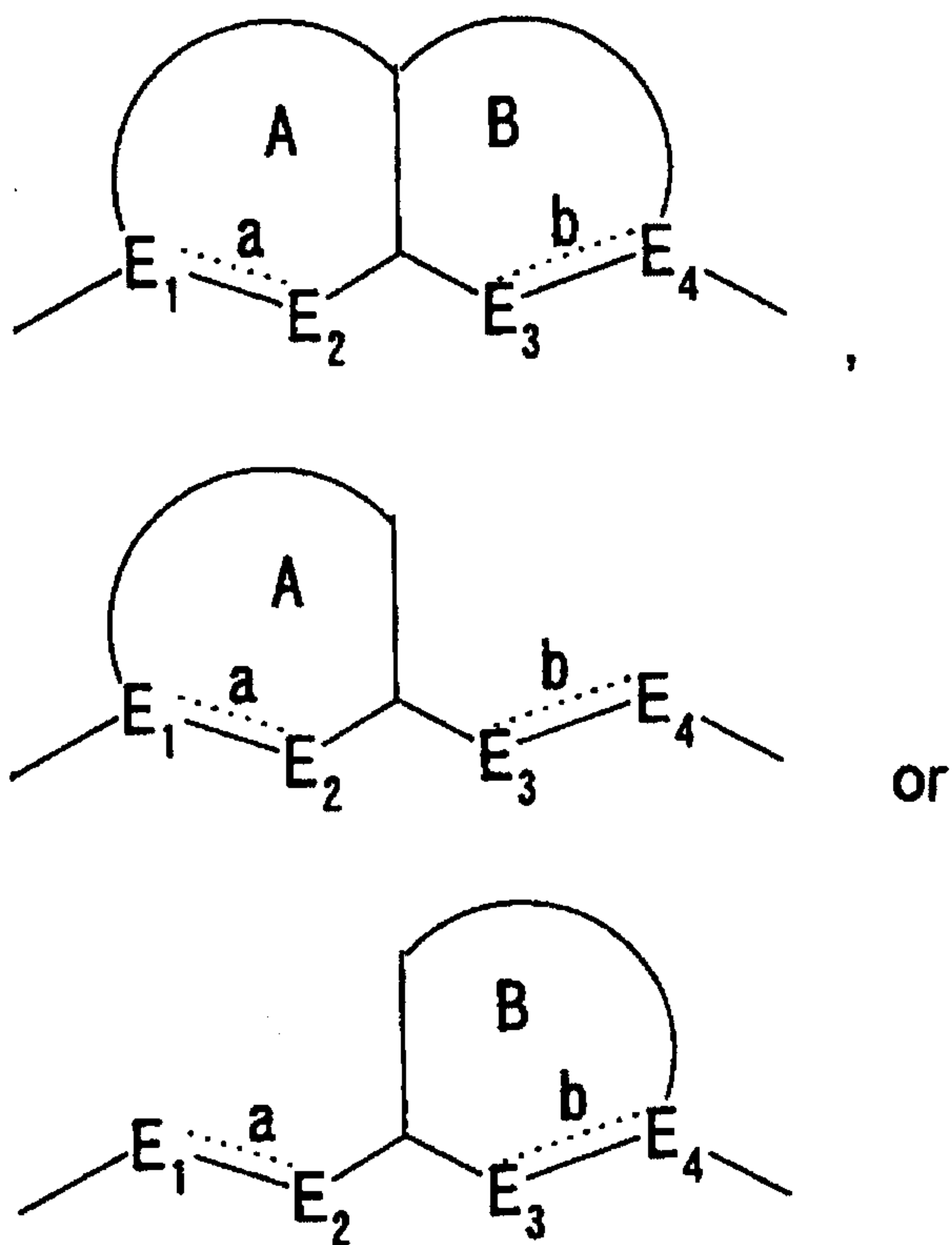
26. Prodrug of the compound or salt thereof as claimed in Claim 25.

27. A pharmaceutical composition comprising the compound or salt thereof as claimed in Claim 1.

28. A pharmaceutical composition for CCR antagonism comprising a compound represented by formula

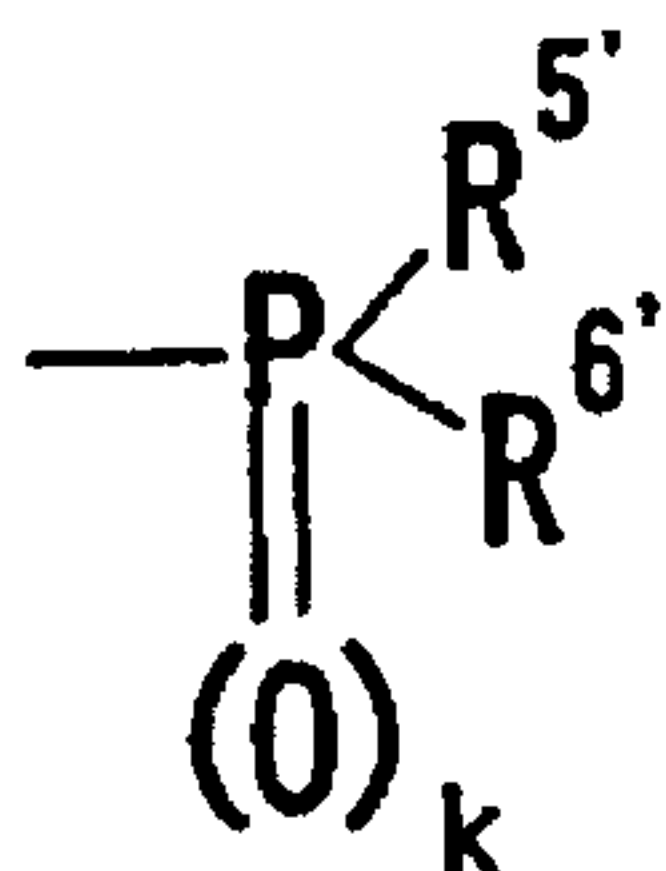


wherein R^1 indicates a 5- to 6-membered cyclic ring group that may be substituted, X^1 indicates a bond or a bivalent group, in which the number of atoms constituting the straight-chain portion is 1 to 4, W indicates a bivalent group that is represented by formula



(wherein each of ring A and ring B indicates a 5- to 7-membered cyclic ring group that may be substituted, each of E_1 and E_4 indicates the carbon atom that may be substituted

or the nitrogen atom that may be substituted, each of E₂
 and E₃ indicates the carbon atom that may be substituted or
 the nitrogen atom that may be substituted, the sulfur atom
 that may be oxidized or the oxygen atom and each of a and b
 5 indicates to be a single bond or a double bond), X²
 indicates a bivalent group, in which the number of atoms
 constituting the straight-chain portion is 1 to 4, Z¹
 indicates a bond or a bivalent cyclic ring group, Z²
 indicates a bond or a bivalent cyclic ring group, in which
 10 the number of atoms constituting the straight-chain portion
 is 1 to 4, and R² indicates (1) an amino group that may be
 substituted, where the nitrogen atom may be converted into
 a quaternary ammonium or the N-oxide, (2) a nitrogen-
 containing, heterocyclic ring group that may be substituted
 15 and may contain the sulfur atom or the oxygen atom as a
 ring-constituting atom, where the nitrogen atom may be
 converted into a quaternary ammonium or the N-oxide, (3) a
 group that bonded via the sulfur atom, (4) a group
 represented by formula

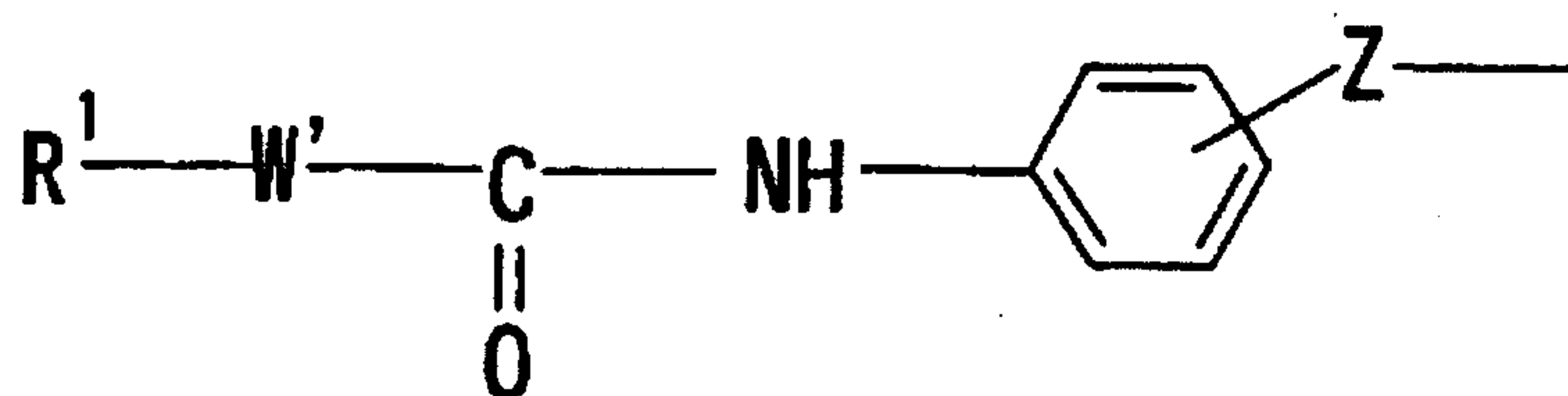


20

(wherein k indicates 0 or 1, the phosphorus atom may form a
 phosphonium salt when k is 0, and each of R^{5'} and R^{6'}

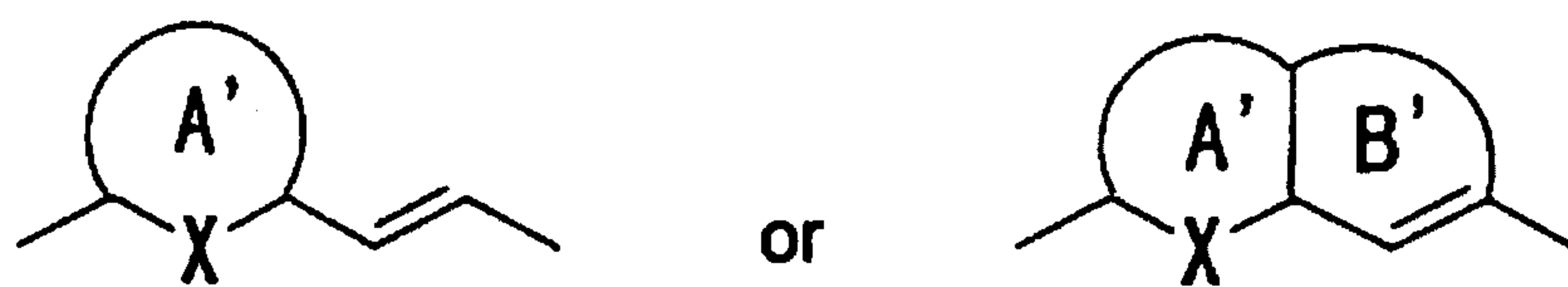
indicates the hydrocarbon atom that may be substituted, the hydroxyl group that may be substituted or an amino group that may be substituted and $R^{5'}$ and $R^{6'}$ may bind each other to form a cyclic ring group together with the adjacent
 5 phosphorus atom), (5) an amidino group that may be substituted or (6) a guanidino group that may be substituted; provided that, when a group represented by formula $R^1-X^1-W-X^2-Z^1-Z^2-$ indicates a group represented by formula

10



(wherein R^1 indicates the same meaning as described above, W' indicates a bivalent group represented by formula

15



(wherein ring A' indicates a 5- to 6-membered aromatic ring that may be substituted, X indicates the carbon atom that
 20 may be substituted, the nitrogen atom that may be substituted, the sulfur atom or the oxygen atom and ring B'

indicates a 5- to 7-membered ring that may be substituted)
and Z indicates a bivalent group, in which the number of
atoms constituting the straight-chain portion is 1 to 4),
R² indicates an amidino group that may be substituted or a
5 guanidino group that may be substituted; or a salt thereof.

29. The composition as claimed in Claim 28 which
is a prophylactic/therapeutic agent of HIV infectious
diseases.

30. The composition as claimed in Claim 28 which
10 is a prophylactic/therapeutic agent of AIDS.

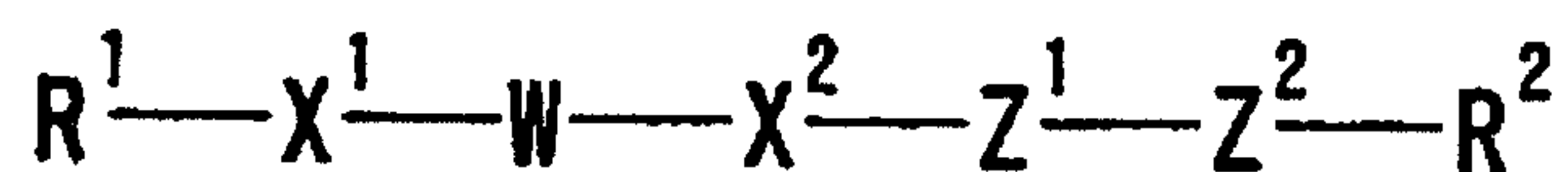
31. The composition as claimed in Claim 28 which
is a depressant against the pathologic progress of AIDS.

32. The composition as claimed in Claim 29 which
is in combination with a protease inhibitor and/or a
15 reverse transcriptase inhibitor.

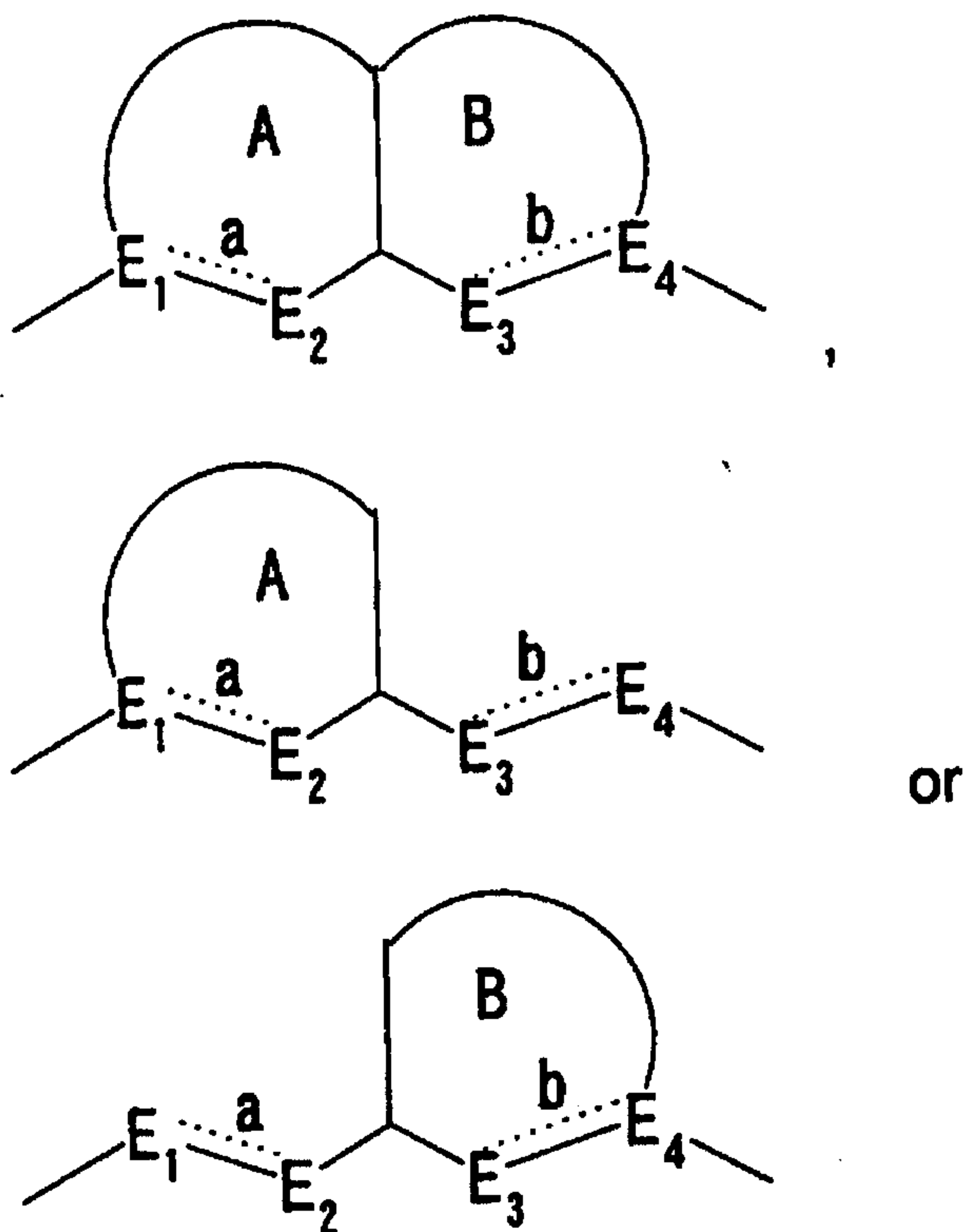
33. The composition as claimed in Claim 32,
wherein the reverse transcriptase inhibitor is zidovudine,
didanosine, zalcitabine, lamivudine, stavudine, nevirapine,
delavirdine, efavirenz or abacavir.

20 34. The composition as claimed in Claim 32,
wherein the protease inhibitor is saquinavir, ritonavir,
indinavir, amprenavir or nelfinavir.

35. Use of a compound represented by
formula

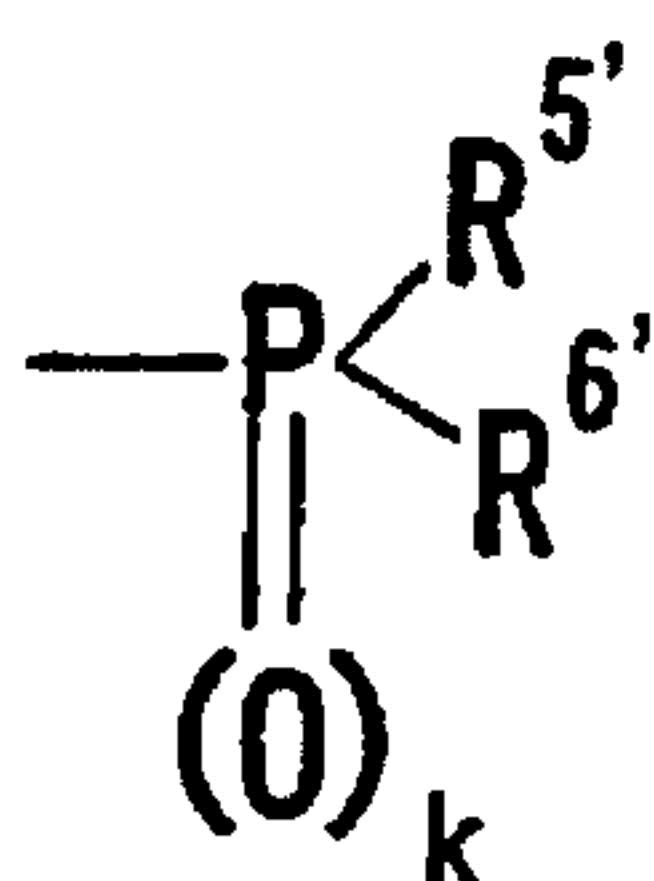


wherein R^1 indicates a 5- to 6-membered cyclic ring group that may be substituted, X^1 indicates a bond or a bivalent group, in which the number of atoms constituting the straight-chain portion is 1 to 4, W indicates a bivalent group that is represented by formula



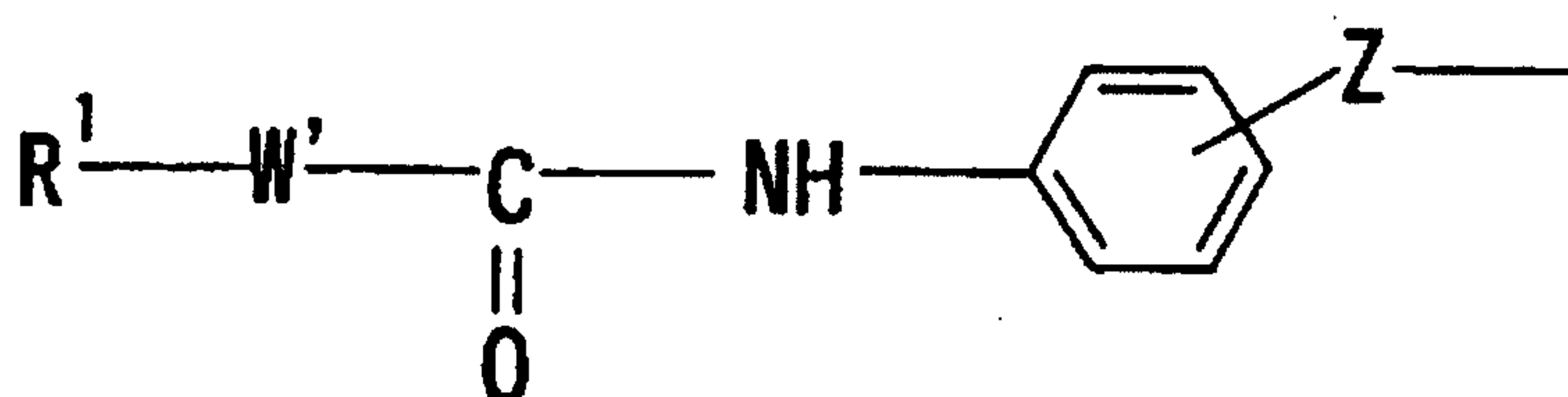
(wherein each of ring A and ring B indicates a 5- to 7-membered cyclic ring group that may be substituted, each of E_1 and E_4 indicates the carbon atom that may be substituted or the nitrogen atom that may be substituted, each of E_2

and E₃ indicates the carbon atom that may be substituted or the nitrogen atom that may be substituted, the sulfur atom that may be oxidized or the oxygen atom and each of a and b indicates to be a single bond or a double bond), X² indicates a bivalent group, in which the number of atoms constituting the straight-chain portion is 1 to 4, Z¹ indicates a bond or a bivalent cyclic ring group, Z² indicates a bond or a bivalent cyclic ring group, in which the number of atoms constituting the straight-chain portion is 1 to 4, and R² indicates (1) an amino group that may be substituted, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide, (2) a nitrogen-containing, heterocyclic ring group that may be substituted and may contain the sulfur atom or the oxygen atom as a ring-constituting atom, where the nitrogen atom may be converted into a quaternary ammonium or the N-oxide, (3) a group that bonded via the sulfur atom, (4) a group represented by formula

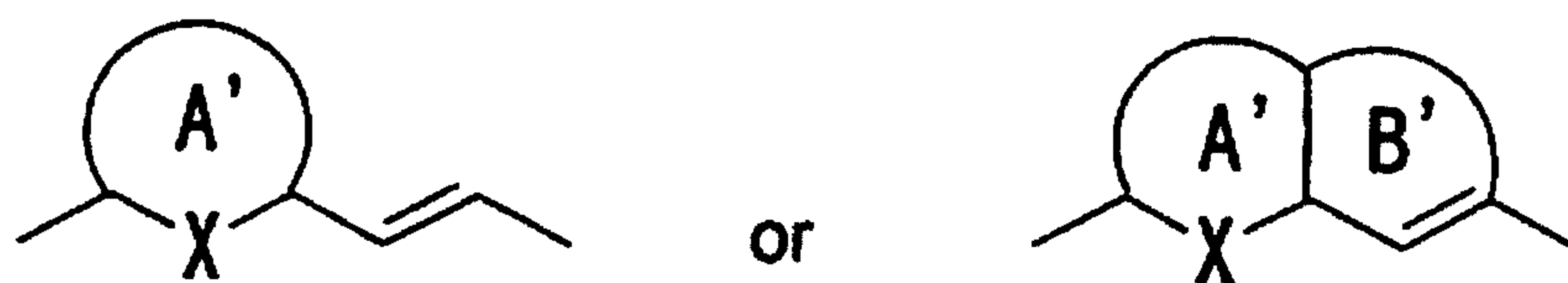


(wherein k indicates 0 or 1, the phosphorus atom may form a phosphonium salt when k is 0, and each of R^{5'} and R^{6'} indicates the hydrocarbon atom that may be substituted, the

hydroxyl group that may be substituted or an amino group that may be substituted and $R^{5'}$ and $R^{6'}$ may bind each other to form a cyclic ring group together with the adjacent phosphorus atom), (5) an amidino group that may be substituted or (6) a guanidino group that may be substituted; provided that, when a group represented by formula $R^1-X^1-W-X^2-Z^1-Z^2-$ indicates a group represented by formula



(wherein R^1 indicates the same meaning as described above, W' indicates a bivalent group represented by formula



(wherein ring A' indicates a 5- to 6-membered aromatic ring that may be substituted, X indicates the carbon atom that may be substituted, the nitrogen atom that may be substituted, the sulfur atom or the oxygen atom and ring B' indicates a 5- to 7-membered ring that may be substituted) and Z indicates a bivalent group, in which the number of atoms constituting the straight-chain portion is 1 to 4),

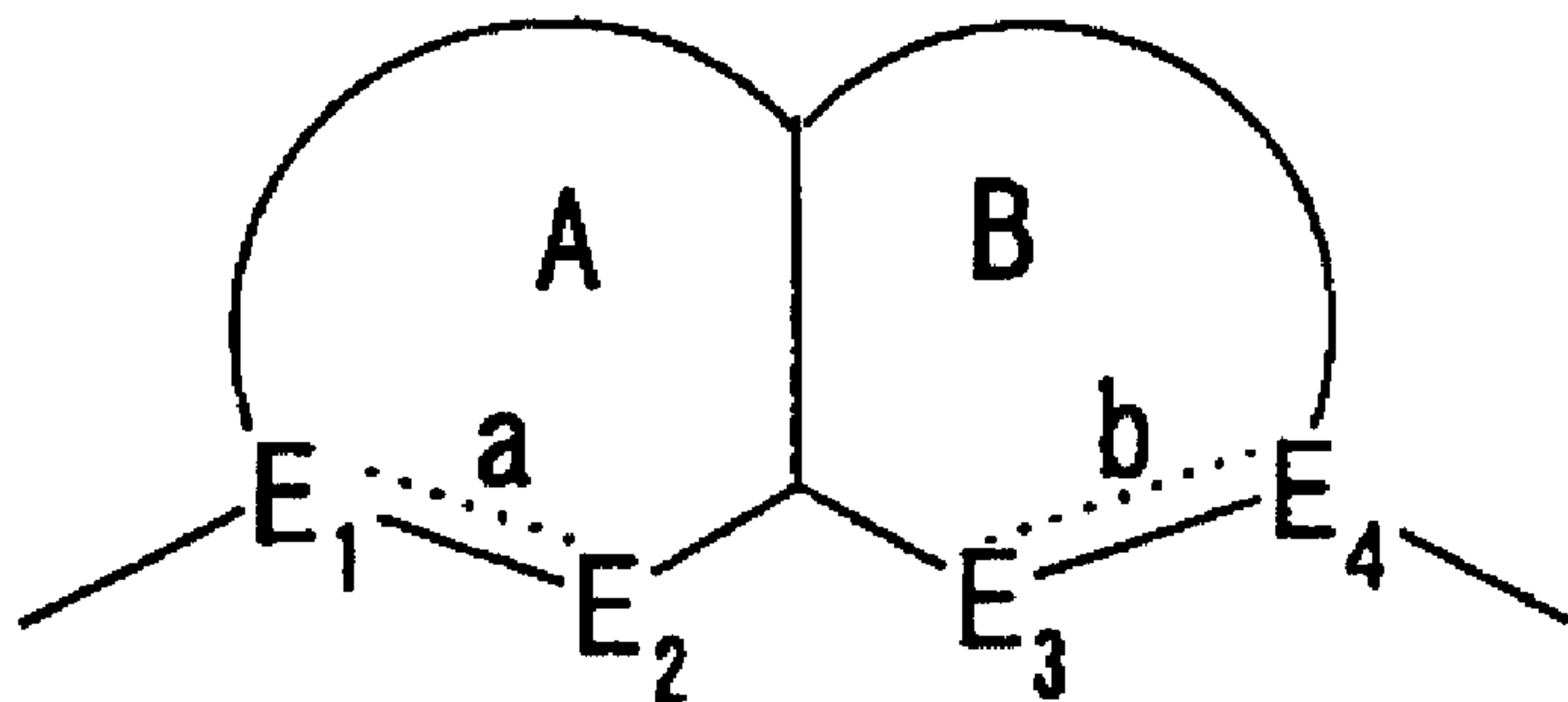
R² indicates an amidino group that may be substituted or a guanidino group that may be substituted; or a salt thereof, together with a protease inhibitor and/or a reverse transcriptase inhibitor, for preventing and/or treating HIV
5 infectious diseases.

36. A method for antagonizing CCR comprising administering an effective amount of the compound or a salt thereof as claimed in Claim 28 to the mammals.

37. Use of the compound or salt thereof as
10 claimed in Claim 28 for manufacturing a medicine for CCR antagonism.

Fetherstonhaugh & Co.
Ottawa, Canada
Patent Agents

$$R^1 - X^1 - W - X^2 - Z^1 - Z^2 - R^2 \quad (I)$$



(II)