(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 200022511 B2
(10) Patent No. 756878

(54) Title
Oxygenic heterocyclic compounds

(51)[6] International Patent Classification(s)
C07D 317/64 C07D 321/00
A61K 031/335 C07D 405/04
A61K 031/36 C07D 407/04
C07D 319/16

(21) Application No: 200022511 (22) Application Date: 1999.09.03

(87) WIPO No: WO00/14085

(30) Priority Data

(31) Number	(32) Date	(33) Country
10/249685	1998.09.03	JP
11/82758	1999.03.26	JP

(43) Publication Date : 2000.03.27
(43) Publication Journal Date : 2000.05.18
(44) Accepted Journal Date : 2003.01.23

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世界知的所有権機関
国際事務局

PCT

特許協力条約に基づいて公開された国際出願

(51) 国際特許分類6
C07D 317/64, 319/16, 321/00, 405/04, 407/04, A61K 31/36, 31/335

A1

(11) 国際公開番号 WO00/14085

(43) 国際公開日 2000年3月16日(16.03.00)

(21) 国際出願番号 PCT/JP99/04788

(22) 国際出願日 1999年9月3日(03.09.99)

(30) 優先権データ
特願平10/249685 1998年9月3日(03.09.98) JP
特願平11/82758 1999年3月26日(26.03.99) JP

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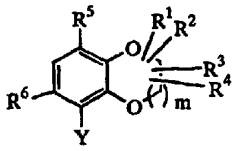
(81) 指定国 AU, BG, BR, CA, CN, CZ, HU, ID, IL, IN, JP, KR, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, VN, ZA, 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM)

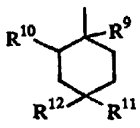
添付公開書類
国際調査報告書

(54)Title: OXYGENIC HETEROCYCLIC COMPOUNDS

(54)発明の名称 含酸素複素環化合物



(I)



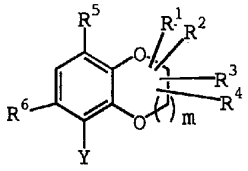
(II)

(57) Abstract

Oxygenic heterocyclic compounds represented by formula (I) or pharmacologically acceptable salts thereof: wherein m is an integer of 0 to 4; R^1, R^2, R^3, and R^4 are the same or different and each represents hydrogen, optionally substituted lower alkyl, etc.; R^5 represents optionally substituted lower alkoxy, etc.; R^6 represents hydrogen, etc.; and Y represents, e.g., formula (II) (wherein R^9 represents cyano, etc.; R^{10} represents hydrogen, etc.; R^{11} represents carboxy, etc.; and R^{12} represents hydrogen, etc.).

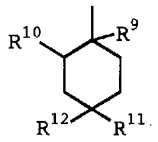
Abstract

The present invention relates to oxygen-containing heterocyclic compounds represented by the following formula (I):



(I)

wherein m represents an integer of 0 to 4; R^1, R^2, R^3 and R^4 independently represent a hydrogen atom, substituted or unsubstituted lower alkyl, etc.; R^5 represents substituted or unsubstituted lower alkoxy etc.; R^6 represents a hydrogen atom etc.; and Y represents the following formula (II):



(II)

wherein R^9 represents cyano etc., R^{10} represents a hydrogen atom etc., R^{11} represents carboxy etc., and R^{12} represents a hydrogen atom etc.; and the like; or

pharmaceutically acceptable salts thereof.

DESCRIPTION

OXYGEN-CONTAINING HETEROCYCLIC COMPOUNDS

Field of the Invention

The present invention relates to oxygen-containing heterocyclic compounds which have phosphodiesterase (PDE) IV inhibitory activity and which are useful as a therapeutic agent for inflammatory allergic diseases such as bronchial asthma, allergic rhinitis, atopic dermatitis and nephritis; autoimmune diseases such as chronic obstructive pulmonary lung disease, rheumatism, multiple sclerosis, Crohn's disease, psoriasis and systemic lupus erythematosus; diseases of the central nervous system such as depression, amnesia and dementia; organopathy associated with ischemic reflux caused by cardiac failure, shock and cerebrovascular disease, and the like; insulin-resistant diabetes; wounds; AIDS; osteoporosis; urinary stone; urinary incontinence and the like; and as a recuperative agent for fatigue, malaise and the like.

Background Art

Heretofore, it is known that the functions of numerous hormones and neurotransmitters are expressed by an increase in the concentration of adenosine 3',5'-cyclic monophosphate (cAMP) or guanosine 3',5'-cyclic monophosphate (cGMP), both of which are the secondary messengers in cells. The cellular concentrations of cAMP and cGMP are controlled by the generation and decomposition thereof, and their decomposition is carried out by phosphodiesterase (PDE). Therefore, when PDE is inhibited, the concentrations of these secondary cellular

messengers increase. Up to the present, 8 kinds of PDE isozymes have been found, and the isozyme-selective PDE inhibitors are expected to exhibit pharmaceutical effect based on their physiological significance and distribution in vivo [TiPS, 11, 150 (1990), ibid., 12, 19 (1991), and Biochemical & Biophysical Research Communications, 250, 751 (1998)].

It is known that the activation of inflammatory leukocytes can be suppressed by increasing the concentration of the cellular cAMP. The extraordinary activation of leukocytes causes secretion of inflammatory cytokines such as tumor necrosis factor (TNF), and expression of the cellular adhesion molecules such as intercellular adhesion molecules (ICAM), followed by cellular infiltration [J. Mol. Cell. Cardiol., 12 (Suppl. II), S61 (1989)].

It is known that the contraction of a respiratory smooth muscle can be suppressed by increasing the concentration of the cellular cAMP (T. J. Torphy in Directions for New Anti-Asthma Drugs, eds S. R. O'Donell and C. G. A. Persson, 1988, 37, Birkhauser-Verlag). The extraordinary contraction of a respiratory smooth muscle is a main symptom of bronchial asthma. Infiltration of inflammatory-leukocytes such as neutrophils is observed in lesions of organopathy associated with ischemic reflux such as myocardial ischemia. It has been found that the type IV PDE (PDE IV) mainly participates in the decomposition of cAMP in these inflammatory cells and tracheal smooth muscle cells. Therefore, the inhibitors selective for PDE IV are expected to have therapeutic and/or preventive effect on inflammatory diseases, respiratory obstructive diseases, and ischemic diseases.

The PDE IV inhibitors are expected to prevent the progress and spread of the inflammatory reaction transmitted by inflammatory cytokines such as TNFα and interleukin (IL)-8, because the PDE IV inhibitors suppress the secretion of these cytokines by increasing the concentration of cAMP. For example, TNFα is reported to be a factor of insulin-resistant diabetes because it declines the phosphorylating mechanism of insulin receptors in muscle and fat cells [J. Clin. Invest., 94, 1543 (1994)]. Similarly, it is suggested that the PDE IV inhibitors may be useful for autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and Crohn's disease because TNFα participates in the onset and progress of these diseases [Nature Medicine, 1, 211 (1995) and ibid., 1, 244 (1995)].

Further, participation of TNFα in the fatigued feeling after dialysis and that of patients suffering from cancer has been also reported [International Journal of Artificial Organs, 21, 83 (1998) and Oncology Nursing Forum, 19, 419 (1992)]. Accordingly, a PDE IV inhibitor can be expected to be effective for improvement in fatigue, malaise, and the like.

It has been reported that a drug which increases cAMP promotes the healing of wounds [The 68th Annual Meeting of Japan Pharmacological Society (in Nagoya), Presentation P3-116 (1995)].

PDE-IV inhibitors exhibit a therapeutic effect to carcinomatous osteopenia model, sciatic nerve excision model and ovariectomic model which are animal models for osteoporosis and their possibility as a therapeutic agent for osteoporosis is suggested [Jpn. J. Pharmacol., 79, 477 (1999)].

Relaxation of ureter has been known to promote the

excretion of calculus while a PDE IV inhibitor suppresses the vermicular movement of ureter, and therefore, there is a suggestion for the probability that it is effective for the therapy and/or prevention of urinary calculus [J. Urol., 160, 920 (1998)].

Japanese Published Unexamined Patent Application Nos. 95/242543 and 95/242655 disclose 1,4-benzodioxane derivatives as a therapeutic agent for hepatic diseases. WO 92/10494 discloses 1,4-benzodioxane derivatives having an antagonistic action to serotonin $(5HT)_3$ receptors.

In US 5166367, 1,4-benzodioxane derivatives having an anti-hallucination action are disclosed.

In Japanese Published Unexamined Patent Application No. 88/179868, 1,4-benzodioxane derivatives having a vasodilating action are disclosed.

AU 521225 discloses 1,4-benzodioxane derivatives as intermediates for the synthesis of cinnamoylpiperazine.

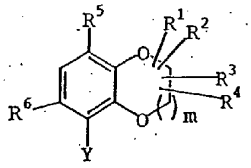
WO 98/22455 discloses 1,4-benzodioxane derivatives having PDE IV inhibitory activity.

Disclosure of the Invention

Novel and useful PDE IV inhibitors are expected to have a preventive or therapeutic effect to diseases of a broad range. An object of the present invention is to provide novel oxygen-containing heterocyclic compounds having a bronchodilating or an anti-inflammatory action due to the presence of a PDE IV-selective inhibiting action so that cAMP concentrations in cells are increased.

The present invention relates to oxygen-containing

heterocyclic compound represented by the following formula (I):



(I)

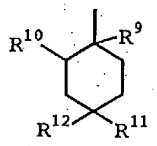
wherein m represents an integer of 0 to 4;
R^1, R^2, R^3 and R^4 independently represent a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, polycycloalkyl, substituted or unsubstituted lower alkoxycarbonyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted lower alkanoyloxy, cyano, hydroxy, substituted or unsubstituted lower alkoxy, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic hetecyclic group, substituted or unsubstituted aralkyl, or -$CONR^7R^8$ (wherein R^7 and R^8 independently represent a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group or substituted or unsubstituted aralkyl, or R^7 and R^8 are combined to represent a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom); two groups present on the same carbon atom among R^1, R^2, R^3 and R^4 are combined to represent a saturated

spiro carbon ring together with the said carbon atom; two groups present on the adjacent carbon atoms among R^1, R^2, R^3 and R^4 are combined to represent a saturated carbon ring together with the said adjacent two carbon atoms; two groups present on the adjacent carbon atoms among R^1, R^2, R^3 and R^4 are combined to represent a single bond (forming a double bond together with the already-existing bond);

R^5 represents hydroxy, or substituted or unsubstituted lower alkoxy;

R^6 represents a hydrogen atom or halogen;

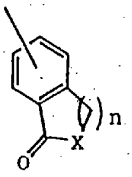
Y represents the following formula (II):



(II)

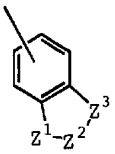
wherein R^9 represents cyano, ethynyl or carbamoyl, and R^{10} represents a hydrogen atom, or R^9 and R^{10} are combined to represent a single bond (forming a double bond together with the already-existing bond), R^{11} represents hydroxy, formyl, substituted or unsubstituted lower alkoxy, substituted or unsubstituted tetrazolyl, $-NR^{13}R^{14}$ (wherein R^{13} and R^{14} independently represent a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group or substituted or unsubstituted aralkyl, or R^{13} and R^{14} are combined to represent a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom), $-COOR^{15}$ (wherein R^{15} represents a hydrogen atom, or substituted or unsubstituted lower alkyl), $-CONR^{16}R^{17}$ (wherein R^{16} and R^{17} independently represent a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, or substituted or unsubstituted aralkyl, or R^{16} and R^{17} are combined to represent a substituted or

unsubstituted heterocyclic group together with the adjacent nitrogen atom), or $-CH_2COOR^{18}$ (wherein R^{18} represents a hydrogen atom or substituted or unsubstituted lower alkyl), R^{12} represents a hydrogen atom, or substituted or unsubstituted lower alkoxy, or R^{11} and R^{12} are combined together to represent $-OCH_2(CH_2)_pO-$ (wherein p represents an integer of 1 to 3), $-CR^{19}R^{20}O-$ (wherein R^{19} and R^{20} independently represent a hydrogen atom or cyano), $=CHOR^{21}$ (wherein R^{21} represents substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted aralkyl), $=CHCOOR^{22}$ (wherein R^{22} represents a hydrogen atom, or substituted or unsubstituted lower alkyl) or =O; the following formula (III):



(III)

wherein n represents an integer of 0 to 4, X represents CH_2, NR^{23} (wherein R^{23} represents a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, or substituted or unsubstituted aralkyl) or O; the following formula (IV):



(IV)

wherein Z^1-Z^2-Z^3 represents O-N=CH, S-N=CH, O-CH=CH, S-CH=CH, N=CH-S, N=CH-O, C(=O)-NH-NH, C(=O)-N=N, C(=O)-CH_2-C(=O), C(=O)-NR^a-C(=O) (wherein R^a represents a hydrogen atom, substituted or unsubstituted lower alkyl, or substituted or unsubstituted aralkyl) or CH_2-NR^b-C(=O) (wherein R^b represents a hydrogen atom, substituted or unsubstituted lower alkyl, or substituted or unsubstituted aryl); 2,1,3-benzothiadiazolyl; or 2,1,3-benzofurazanyl; or pharmaceutically acceptable salts thereof.

The present invention relates to oxygen-containing heterocyclic compounds wherein Y in the formula (I) is the formula (II) or pharmaceutically acceptable salts thereof. Among the above, oxygen-containing heterocyclic compounds wherein R^9 is cyano or pharmaceutically acceptable salts thereof are preferred.

In the present invention, oxygen-containing heterocyclic compounds wherein m is 0 or 1 in the formula (I) or pharmaceutically acceptable salts thereof, oxygen-containing heterocyclic compounds wherein all of R^1, R^2, R^3 and R^4 are hydrogen atoms or pharmaceutically acceptable salts thereof and oxygen-containing heterocyclic compounds wherein one group among R^1, R^2, R^3 and R^4 is substituted or unsubstituted lower alkyl while other three groups are hydrogen atoms or

pharmaceutically acceptable salts thereof are preferred examples as well.

Further, in the above-mentioned compounds group, oxygen-containing heterocyclic compounds wherein R^{11} represents carboxy or hydroxy, or R^{11} and R^{12} are combined together to represent =O or pharmaceutically acceptable salts thereof are preferred as well.

Furthermore, oxygen-containing heterocyclic compounds wherein Y in the formula (I) is the formula (III) or pharmaceutically acceptable salts thereof are preferred as well. Still further, among the above, oxygen-containing heterocyclic compounds wherein n is 1 or pharmaceutically acceptable salts thereof and oxygen-containing heterocyclic compounds wherein X is CH_2 or pharmaceutically acceptable salts thereof are preferred.

The present invention further relates to a pharmaceutical composition, which comprises at least one oxygen-containing heterocyclic compound represented by the formula (I) or pharmaceutically acceptable salts thereof.

The present invention furthermore relates to a phosphodiesterase (PDE) IV inhibitor, which comprises at least one oxygen-containing heterocyclic compound represented by the formula (I) or pharmaceutically acceptable salts thereof.

Hereinafter, the compounds represented by the formula (I) are referred to as a compound (I). The same applies to the compounds of other formula numbers.

In the definitions of the groups in the formula (I), the lower alkyl and the lower alkyl moiety of the lower alkoxy, the lower alkanoyl, the lower alkanoyloxy and the lower

alkoxycarbonyl include straight-chain or branched alkyl groups having 1 to 8 carbon atom(s) such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, hexyl, heptyl and octyl; the cycloalkyl includes cycloalkyl groups having 3 to 10 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl; and the polycycloalkyl includes polycycloalkyl groups having 5 to 12 carbon atoms such as bicyclo[3.2.1]octyl, bicyclo[4.3.2]undecyl, adamantyl and noradamantyl. The lower alkenyl includes straight-chain or branched alkenyl groups having 2 to 8 carbon atoms such as vinyl, 1-propenyl, allyl, methacryl, 1-butenyl, crotyl, pentenyl, isoprenyl, hexenyl, heptenyl and octenyl; and the cycloalkenyl includes cycloalkenyl groups having 4 to 10 carbon atoms such as cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl and cyclodecenyl. The aryl includes phenyl and naphthyl for example; and the aralkyl includes aralkyl groups having 7 to 15 carbon atoms such as benzyl, phenethyl, benzhydryl and naphthylmethyl. The aromatic heterocyclic group includes 5- or 6-membered monocyclic aromatic heterocyclic groups having 1 to 2 oxygen atom(s), 5- or 6-membered monocyclic aromatic heterocyclic groups having 1 to 2 sulfur atom(s), 5- or 6-membered monocyclic aromatic heterocyclic groups having 1 to 4 nitrogen atom(s), condensed bicyclic aromatic heterocyclic groups consisting of 5- and 6-membered rings and condensed bicyclic aromatic heterocyclic groups consisting of 6- and 6-membered rings, where oxygen, sulfur and nitrogen may be mixedly present therein. Specific examples thereof include furyl, thienyl, pyridyl, pyrazinyl,

pyrimidinyl, pyridazinyl, quinolyl, isoquinolyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthylidinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, indolyl, indazolyl, benzimidazolyl, benzotriazolyl and purinyl.

The heterocyclic group which is formed together with the adjacent nitrogen atom includes 5-, 6- or 7-membered monocyclic heterocyclic groups and condensed heterocyclic groups consisting of 6- and 6-membered rings, such as pyrrolidinyl, piperidino, piperazinyl, morpholino, thiomorpholino, homopiperidino, homopiperazinyl, tetrahydropyridyl, tetrahydroquinolyl and tetrahydroisoquinolyl.

The saturated spiro carbon ring which is formed by two groups present on the same carbon atom together with the said carbon atom and the saturated carbon ring which is formed by two groups present on the adjacent carbon atoms together with the said two carbon atoms include those having 3 to 10 carbon atoms such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane and cyclodecane. Halogen includes fluorine, chlorine, bromine and iodine atoms.

The substituents in the substituted lower alkyl, the substituted lower alkoxy, the substituted lower alkoxycarbonyl, the substituted lower alkanoyl, the substituted lower alkanoyloxy, the substituted lower alkenyl, the substituted cycloalkyl and the substituted cycloalkenyl are the same or different 1 to 3 substituent(s), such as lower alkyl, lower alkenyl, cyano, cycloalkyl, cycloalkenyl, hydroxy, lower alkoxy, carboxy and halogen where the lower alkyl, the lower alkenyl,

the cycloalkyl, the cycloalkenyl, the lower alkoxy and the halogen each have the same meanings as defined above.

The substituents in the substituted aryl, the substituted tetrazolyl, the substituted aromatic heterocyclic group, the substituted heterocyclic group which is formed together with the adjacent nitrogen atom and the substituted aralkyl are the same or different 1 to 3 substituent(s), such as substituted or unsubstituted lower alkyl, hydroxy, lower alkoxy, lower alkanoyl, lower alkoxycarbonyl, carboxy, carbamoyl, trifluoromethyl, amino, mono- or di-lower alkyl-substituted amino, cyano, nitro and halogen. The lower alkyl, the lower alkyl moiety of the lower alkoxy, the lower alkanoyl, the lower alkoxycarbonyl and the mono- or di-lower alkyl-substituted amino and the halogen each have the same meanings as defined above where the substituent(s) in the substituted lower alkyl has/have the same meaning(s) as defined above.

The pharmaceutically acceptable salts of the compound (I) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, and organic amine addition salts.

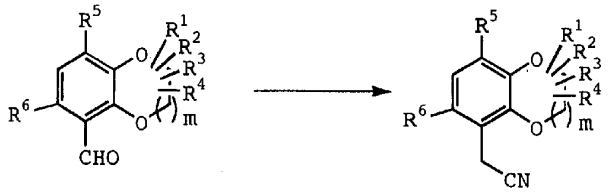
The pharmaceutically acceptable acid addition salts of the compound (I) include inorganic acid addition salts such as a hydrochloride, a sulfate, a nitrate, and a phosphate, and organic acid addition salts such as an acetate, a maleate, a fumarate, and a citrate; the pharmaceutically acceptable metal salts include alkali metal salts such as a sodium salt and a potassium salt, alkaline earth metal salts such as a magnesium salt and a calcium salt, an aluminium salt, and a zinc salt; the pharmaceutically acceptable ammonium salts include ammonium and tetramethylammonium; and the pharmaceutically acceptable

organic amine addition salts include an addition salt with morpholine or piperidine.

Processes for preparing the compound (I) are described below.

Producing method: The compound (I) can be obtained according to the following process.

Process 1



(V) (VI)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above.)

The starting compound (V) can be obtained by a known method [Khimiya Geterotsiklicheskikh Soedinenii, 12, 1614 (1982), etc.] or by a method similar thereto.

After the formyl group of the compound (V) is directly converted to the corresponding halogenated methyl derivative or after the formyl group of the compound (V) is reduced and the resulting hydroxymethyl derivative is converted to the corresponding halide or sulfonate derivative, it is reacted with a metal cyanide whereupon the compound (VI) can be obtained.

The compound (V) is reacted with one equivalent to a large excess of trialkylsilane halide or triarylsilane halide, or with one equivalent to a large excess of a halogenated salt and one equivalent to a large excess of trimethylsilyl chloride in an inert solvent at the temperature between -50°C and the boiling point of the used solvent for 5 minutes to 5 hours, followed

by treatment with one equivalent to a large excess of a reducing agent at the temperature between -50°C and the boiling point of the used solvent for 5 minutes to 48 hours, whereupon the corresponding halide can be obtained.

Alternatively, the compound (V) is treated with one equivalent to a large excess of a reducing agent in an inert solvent at the temperature between -50°C and the boiling point of the used solvent for 5 minutes to 48 hours whereby the corresponding hydroxylmethyl derivative is obtained. The resulting hydroxylmethyl derivative is reacted with one equivalent to a large excess of a halogenating agent in an inert solvent at the temperature between -30°C and the boiling point of the used solvent for 5 minutes to 120 hours to give the corresponding halide.

Alternatively, the resulting hydroxymethyl derivative is made to react with one equivalent to a large excess of an alkylsulfonyl chloride or an arylsulfonyl chloride in the presence of one equivalent to a large excess of a base in an inert solvent at the temperature between -30°C and the boiling point of the used solvent for 5 minutes to 120 hours whereby the corresponding sulfonate derivative is obtained.

The resulting halide or sulfonate derivative is made to react with one equivalent to a large excess of a metal cyanide in an insert solvent at the temperature between -30°C and the boiling point of the used solvent for 5 minutes to 120 hours whereupon the compound (VI) can be obtained.

Examples of the trialkylsilane halide or the triarylsilane halide are trimethylsilyl chloride, trimethylsilyl bromide, trimethylsilyl iodide, triethylsilyl

chloride, dimethylethylsilyl chloride and triphenylsilyl chloride.

Examples of the halogenated salt are lithium bromide, sodium bromide, potassium bromide, lithium chloride, sodium chloride, potassium chloride, lithium iodide, sodium iodide and potassium iodide.

Examples of the reducing agent are 1,1,3,3-tetramethyldisiloxane, triethylsilane, sodium borohydride, sodium cyanoborohydride, triacetoxyborohydride and lithium aluminum hydride.

Examples of the halogenating agent are hydrochloric acid, hydrogen bromide, hydrogen iodide, thionyl chloride, phosphorus oxychloride and phosphorus tribromide.

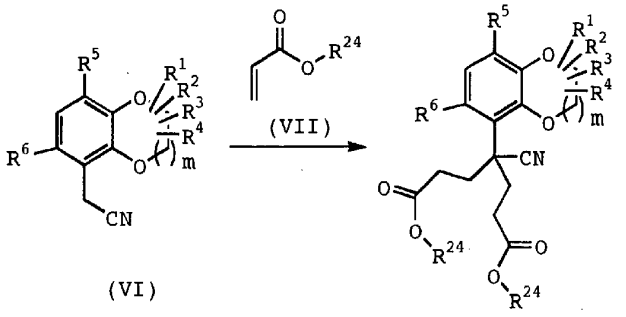
Examples of the base are triethylamine, diisopropyl-ethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene (hereinafter, abbreviated as DBU), potassium carbonate and sodium hydride.

Examples of the alkylsulfonyl chloride or arylsulfonyl chloride are methanesulfonyl chloride, p-toluenesulfonyl chloride and benzenesulfonyl chloride.

Examples of the metal cyanide are sodium cyanide, potassium cyanide and copper cyanide.

Examples of the inert solvent are tetrahydrofuran (hereinafter, abbreviated as THF), dioxane, 1,2-dimethoxyethane, diethyl ether, acetonitrile, dimethylformamide (hereinafter, abbreviated as DMF), dimethyl sulfoxide (hereinafter, abbreviated as DMSO), methanol, ethanol, propanol, dichloromethane, chloroform, benzene, toluene, pyridine and ethyl acetate.

Process 2



(VI) (VII) (VIII)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above and R^{24} stands for the lower alkyl having the same meaning as defined above.)

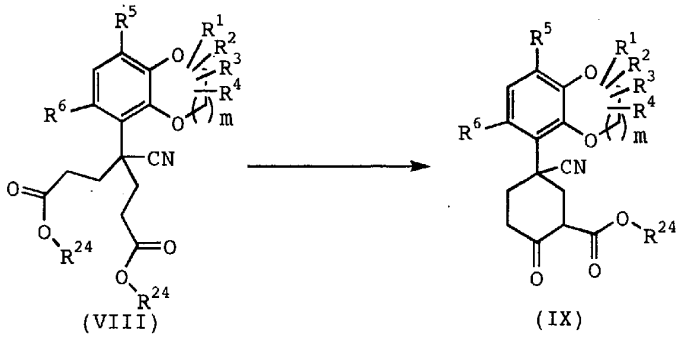
The compound (VIII) can be obtained by the following method.

The compound (VI) is made to react with the compound (VII) in an inert solvent in the presence of a catalytic amount to a large excess amount of a base at the temperature between 0°C and the boiling point of the used solvent for 5 minutes to 48 hours whereby the compound (VIII) can be obtained.

Examples of the base are benzyltrimethylammonium hydroxide (Triton B), sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, sodium methoxide, lithium diisopropylamide (hereinafter, abbreviated as LDA), pyridine, potassium *tert*-butoxide, DBU, triethylamine and diisopropylethylamine.

Examples of the inert solvent are THF, dioxane, diethyl ether, methanol, ethanol, 1-propanol, 2-propanol, n-butanol, *tert*-butyl alcohol, pyridine, acetonitrile, DMF, DMSO, 1,2-dimethoxyethane, diethylene glycol methyl ether, dichloromethane, chloroform, benzene and toluene.

Process 3



(VIII) (IX)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5, R^6 and R^{24} have the same meanings as defined above.)

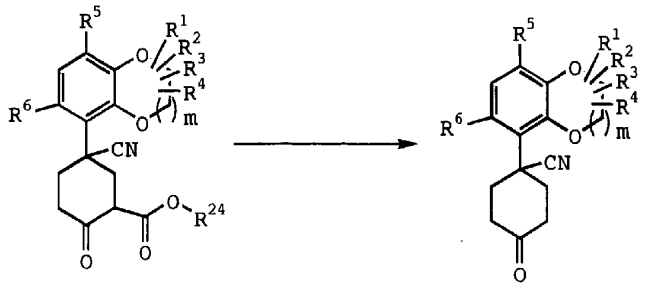
The compound (IX) can be obtained by the following method from the compound (VIII).

The compound (VIII) is made to react in an inert solvent in the presence of one equivalent to a large excess of a base at the temperature between 0°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (IX) can be obtained.

Examples of the base are sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, LDA, pyridine, potassium *tert*-butoxide, DBU, triethylamine and diisopropylethylamine.

Examples of the inert solvent are THF, dioxane, pyridine, diethyl ether, methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, *tert*-butyl alcohol, acetonitrile, DMF, DMSO, 1,2-dimethoxyethane, diethylene glycol methyl ether, dichloromethane, chloroform, benzene and toluene.

Process 4



(IX) (Ia)

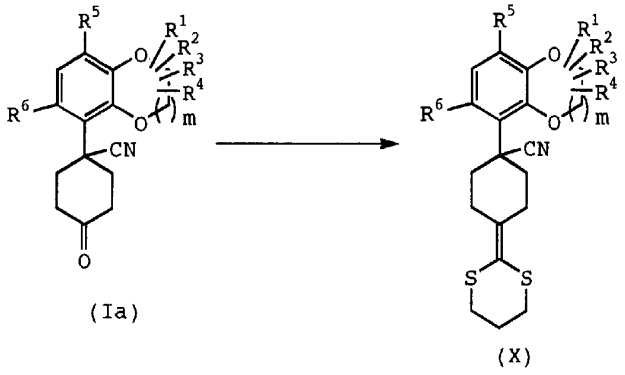
(In the formulae, m, R^1, R^2, R^3, R^4, R^5, R^6 and R^{24} have the same meanings as defined above.)

The compound (Ia) can be obtained according to the following reaction step.

The compound (IX) is treated in an inert solvent in the presence of one equivalent to a large excess of water at the temperature between 60°C and the boiling point of the used solvent for 5 minutes to 120 hours whereupon the compound (Ia) can be obtained. If necessary, a catalytic amount to an excess amount of a salt such as sodium chloride, lithium chloride, sodium iodide, lithium iodide or sodium cyanide may be added thereto.

Examples of the inert solvent are dioxane, toluene, DMF, DMSO, *tert*-butyl alcohol, acetonitrile, 1,2-dimethoxyethane, diethylene glycol methyl ether, ethylene glycol, triethylene glycol and water.

Process 5



(Ia) (X)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above.)

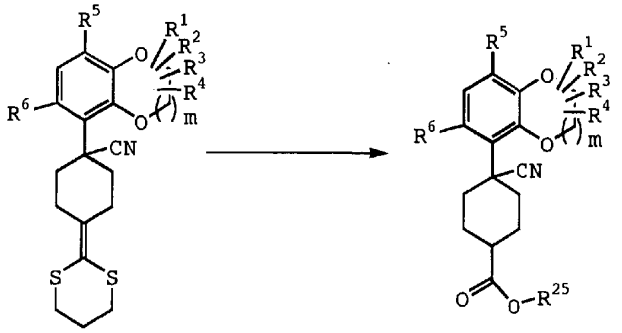
The compound (X) can be obtained according to the following reaction step.

2-Trimethylsilyl-1,3-dithiane is treated with a base in an inert solvent at the temperature between -100°C and 0°C, followed by reaction with the compound (Ia) at the temperature between -100°C and 30°C for 1 minute to 12 hours whereupon the compound (X) can be obtained.

Examples of the base are sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium methoxide, butyl lithium, LDA, lithium bistrimethylsilylamide, sodium bistrimethylsilylamide, potassium bistrimethylsilylamide, potassium *tert*-butoxide, DBU, triethylamine, diisopropylethylamine and ethyl magnesium bromide.

Examples of the inert solvent are THF, dioxane, diethyl ether, 1,2-dimethoxyethane and diisopropyl ether.

Process 6



(X) (Ib)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above and R^{25} represents the same lower alkyl as defined above.)

The compound (Ib) can be obtained according to the following reaction step.

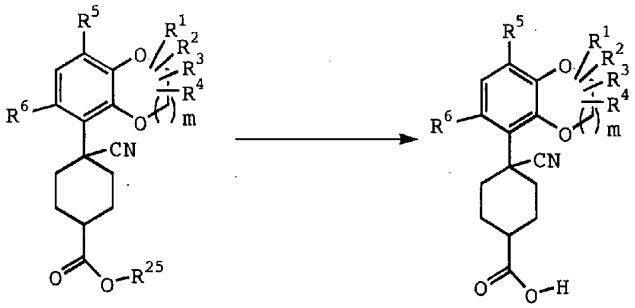
The compound (X) is treated in a solvent [with regard to the said solvent, a lower alcohol which will be mentioned later may be used solely or as a mixed solvent containing the lower alcohol (dioxane/lower alcohol, THF/lower alcohol, and the like); and the said lower alcohol also acts as a reagent for esterifying the carboxyl group which is obtained by the reaction] in the presence of one equivalent to an excess amount of a divalent mercury salt and an acid at the temperature between 0°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (Ib) can be obtained.

Examples of the divalent mercury salt are mercury chloride ($HgCl_2$) and mercury acetate [$Hg(OCOCH_3)_2$]. Examples of the acid are perchloric acid, sulfuric acid, hydrochloric acid, trifluoroacetic acid, p-toluenesulfonic acid, methanesulfonic acid and boron trifluoride.

Examples of the solvent are lower alcohols (methanol,

ethanol, 1-propanol, 2-propanol, 1-butanol, 2-methyl-1-propanol, 2-butanol, *tert*-butyl alcohol, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol, and the like), a mixed solvent of dioxane/a lower alcohol (wherein the lower alcohol has the same meaning as defined above) and a mixed solvent of THF/a lower alcohol (wherein the lower alcohol has the same meaning as defined above).

Process 7



(Ib) (Ic)

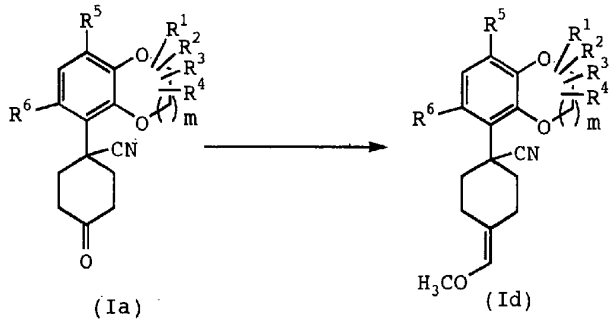
(In the formulae, m, R^1, R^2, R^3, R^4, R^5, R^6 and R^{25} have the same meanings as defined above.)

The compound (Ic) can be obtained according to the following reaction step.

The compound (Ib) is made to react with an aqueous solution of an alkali in an inert solvent at the temperature between 0°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (Ic) can be obtained.

Examples of the aqueous solution of an alkali are aqueous solutions of sodium hydroxide, potassium hydroxide and lithium hydroxide while examples of the inert solvent are ethanol, dioxane, methanol, THF, a mixed solvent of ethanol/THF, a mixed solvent of methanol/THF, and DMSO.

Process 8



(Ia) (Id)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above.)

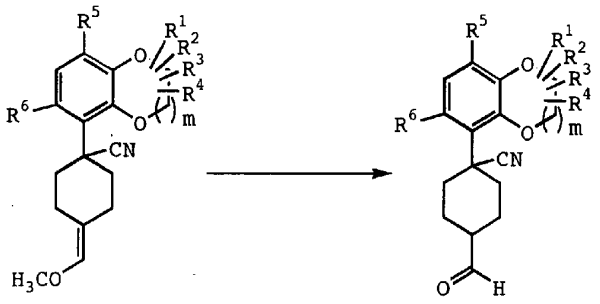
The compound (Id) can be obtained according to the following reaction step.

One equivalent to an excess amount of methoxymethyl-triphenylphosphonium chloride is treated with one equivalent to an excess amount of a base in an inert solvent at the temperature between -100°C and the boiling point of the used solvent, followed by reaction with the compound (Ia) at the temperature between -100°C and the boiling point of the used solvent for 5 minutes to 12 hours whereupon the compound (Id) can be obtained.

Examples of the base are sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium methoxide, butyl lithium, LDA, lithium bistrimethylsilylamide, sodium bistrimethylsilylamide, potassium bistrimethylsilylamide, potassium *tert*-butoxide, DBU, sodium amide and sodium ethoxide.

Examples of the inert solvent are THF, dioxane, diethyl ether, 1,2-dimethoxyethane, DMF and diisopropyl ether.

Process 9



(Id) (Ie)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above.)

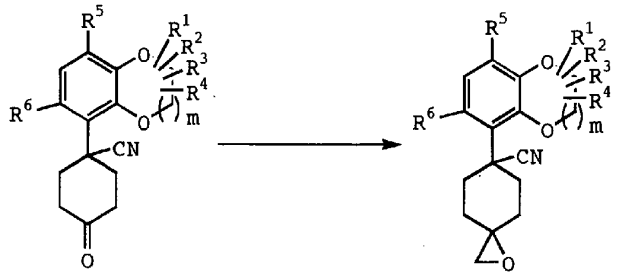
The compound (Ie) can be obtained according to the following reaction step.

The compound (Id) is made to react with a catalytic amount to an excess amount of an acid in the absence of a solvent or in an inert solvent at the temperature between 0°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (Ie) can be obtained.

Examples of the acid are hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid, methanesulfonic acid, 10-camphorsulfonic acid, boron trifluoride and aluminum chloride.

Examples of the inert solvent are THF, acetone, acetonitrile, methanol, ethanol, dioxane and a mixed solvent of such an inert solvent with water.

Process 10



(Ia) (If)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above.)

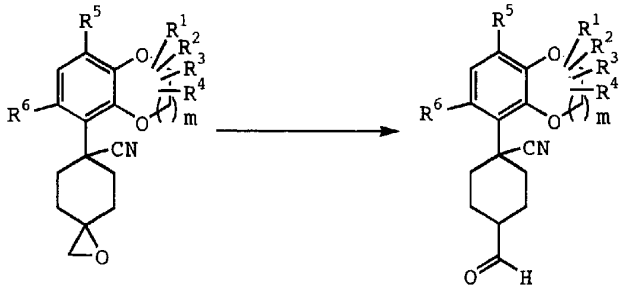
The compound (If) can be obtained according to the following reaction step.

The compound (Ia) is made to react with one equivalent to a large excess of trimethylsulfoxonium iodide or trimethylsulfonium iodide in the presence of one equivalent to a large excess of a base in an inert solvent at the temperature between -30°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (If) can be obtained.

Examples of the base are sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium methoxide, butyl lithium, LDA, lithium bistrimethylsilylamide, sodium bistrimethylsilylamide, potassium bistrimethylsilylamide, potassium *tert*-butoxide, DBU, sodium amide and sodium ethoxide.

Examples of the inert solvent are THF, dioxane, diethyl ether, 1,2-dimethoxyethane, DMF and diisopropyl ether.

Process 11



(If) (Ie)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above.)

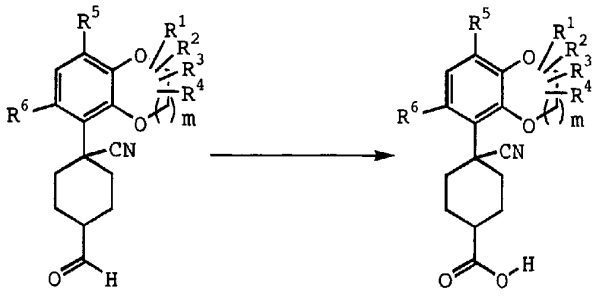
The compound (Ie) can be obtained according to the following reaction step.

The compound (If) is made to react with one equivalent to an excess amount of an acid in the absence of a solvent or in an inert solvent at the temperature between 0°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (Ie) can be obtained.

Examples of the acid are hydrochloric acid, sulfuric acid, hydrogen bromide, magnesium chloride, magnesium bromide, lithium bromide, trifluoroacetic acid, lithium perchlorate, p-toluenesulfonic acid, methanesulfonic acid, 10-camphorsulfonic acid, boron trifluoride, aluminum chloride and silica gel.

Examples of the inert solvent are THF, acetone, acetonitrile, methanol, ethanol and dioxane.

Process 12



(Ie) (Ic)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above.)

The compound (Ic) can be obtained according to the following reaction step.

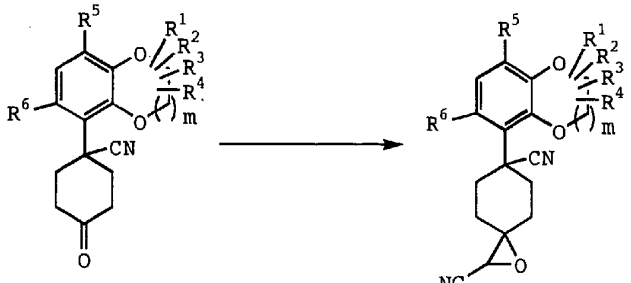
The compound (Ie) is made to react with one equivalent to an excess amount of an oxidizing agent in an inert solvent at the temperature between 0°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (Ic) can be obtained.

Examples of the oxidizing agent are chlorous acid, potassium permanganate and hydrogen peroxide.

When chlorous acid is used as an oxidizing agent, one equivalent to an excess amount of 2-methyl-2-butene, sulfamic acid, DMSO, an aqueous solution of hydrogen peroxide, or the like may be added if necessary, or further, one equivalent to an excess amount of sodium dihydrogen phophate may be added thereto.

Examples of the inert solvent are *tert*-butyl alcohol, acetic acid, DMSO, acetone and acetonitrile.

Process 13



(Ia) (Ig)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above.)

The compound (Ig) can be obtained according to the following reaction step.

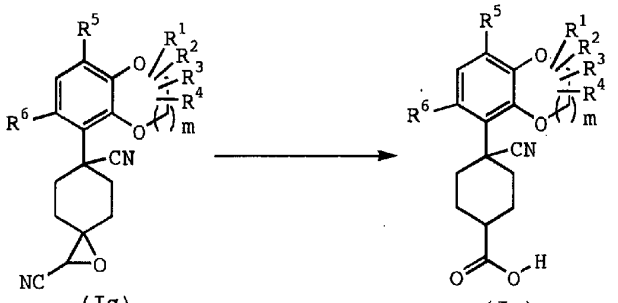
The compound (Ia) is made to react with one equivalent to a large excess of chloroacetonitrile in the presence of one equivalent to a large excess of a base in an inert solvent at the temperature between -10°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (Ig) can be obtained. If necessary, a catalytic amount to an excess amount of a salt such as benzyltriethylammonium chloride, benzyltriethylammonium bromide, benzyltrimethylammonium chloride, benzyltrimethylammonium bromide, tetrabutylammonium chloride, tetrabutylammonium bromide, tetraethylammonium chloride or triethylmethylammonium bromide may be added thereto.

Examples of the base are potassium carbonate, sodium carbonate, sodium hydride, potassium hydride, lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium methoxide, butyl lithium, potassium *tert*-butoxide, DBU and sodium ethoxide.

Examples of the inert solvent are methanol, ethanol,

1-propanol, 2-propanol, *tert*-butyl alcohol, ethyl acetate, toluene, THF, 1,2-dimethoxyethane, DMF, DMSO and diisopropyl ether.

Process 14



(Ig) (Ic)

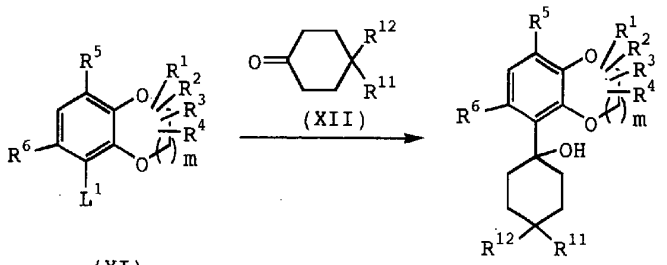
(In the formulae, m, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above.)

The compound (Ic) can be obtained according to the following reaction step.

The compound (Ig) is made to react with one equivalent to an excess amount of magnesium bromide or lithium bromide in the absence of a solvent or in an inert solvent in the presence of one equivalent to an excess amount of water at the temperature between 0°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (Ic) can be obtained.

Examples of the inert solvent are THF, DMF, acetone, acetonitrile, methanol, ethanol, dioxane and a mixed solvent of DMF/acetonitrile.

Process 15



(XI) (XII) (XIII)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5, R^6, R^{11} and R^{12} each have the same meanings as defined above and L^1 represents chlorine, bromine or iodine.)

The compound (XIII) can be obtained according to the following reaction step.

The starting compound (XI) can be obtained according to a known method (WO 98/22455) or a method similar thereto. A commercially available compound can be used as the compound (XII).

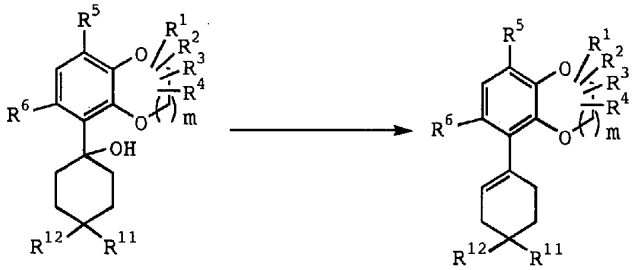
The compound (XI) is treated with one equivalent to an excess amount of a base in an inert solvent at the temperature between -100°C and room temperature for 5 minutes to 10 hours, followed by reaction with one equivalent to an excess amount of the compound (XII) at the temperature between -100°C and room temperature for 5 minutes to 30 hours whereupon the compound (XIII) can be obtained. If necessary, tetramethylethylenediamine, cerium chloride, or the like may be added thereto.

Examples of the base are lithium, magnesium, methyl lithium, methyl magnesium bromide, ethyl magnesium bromide and butyl lithium.

Examples of the inert solvent are THF, dioxane, diethyl

ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, benzene, toluene and hexane.

Process 16



(XIII) (Ih)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5, R^6, R^{11} and R^{12} have the same meanings as defined above.)

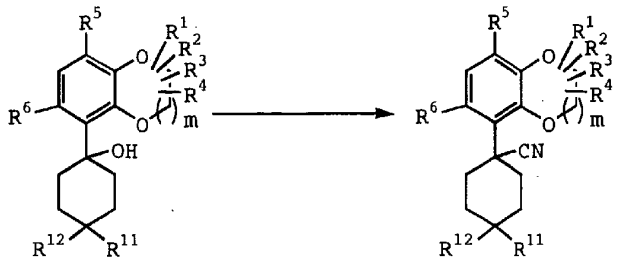
The compound (Ih) can be obtained according to the following reaction step.

The compound (XIII) is made to react with one equivalent to an excess amount of an acid in the absence of a solvent or in an inert solvent at the temperature between 0°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (Ih) can be obtained. If necessary, water may be added thereto.

Examples of the acid are hydrochloric acid, sulfuric acid, 10-camphorsulfonic acid, acetic acid, formic acid, trifluoroacetic acid, p-toluenesulfonic acid, methanesulfonic acid, boron trifluoride and aluminum chloride.

Examples of the inert solvent are THF, acetone, acetonitrile, toluene, xylene, methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, *tert*-butyl alcohol, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol and dioxane.

Process 17



(XIII) (Ii)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5, R^6, R^{11} and R^{12} have the same meanings as defined above.)

The compound (Ii) can be obtained according to the following reaction step.

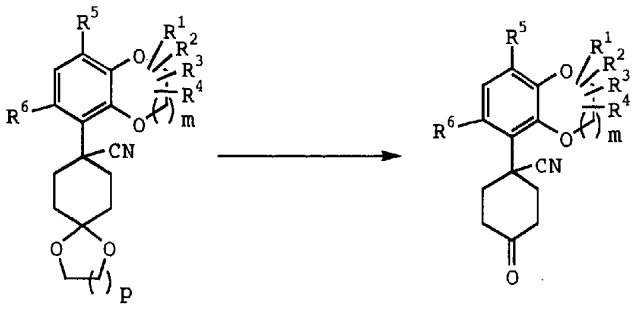
The compound (XIII) is made to react with one equivalent to an excess amount of a cyanide in the presence of one equivalent to an excess amount of an acid in an inert solvent at the temperature between -100°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (Ii) can be obtained.

Examples of the acid are hydrochloric acid, sulfuric acid, 10-camphorsulfonic acid, acetic acid, formic acid, trifluoroacetic acid, p-toluenesulfonic acid, methanesulfonic acid, titanium tetrachloride, boron trifluoride and aluminum chloride.

Examples of the cyanide are trimethylsilyl cyanide, sodium cyanide and potassium cyanide.

Examples of the inert solvent are THF, dioxane, diethyl ether, 1,2-dimethoxyethane, methanol, ethanol, acetonitrile, dichloromethane, 1,2-dichloroethane, chloroform and toluene.

Process 18



(Iia) (Ia)

(In the formulae, m, p, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above.)

The compound (Ia) can be obtained according to the following reaction step.

The starting compound (Iia) can be synthesized in such a manner that a compound (XIII) wherein R^{11} and R^{12} have a ketal structure is obtained using a compound (XII) wherein R^{11} and R^{12} have a ketal structure as a starting material in Process 15 and a method mentioned in Process 17 is applied using the compound (XIII) wherein R^{11} and R^{12} have a ketal structure as a starting material.

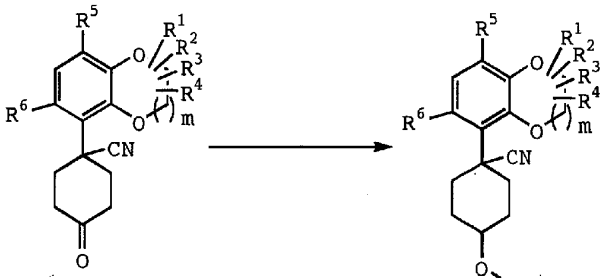
The compound (Iia) is made to react with one equivalent to an excess amount of an acid in the absence of a solvent or in an inert solvent at the temperature between 0°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (Ia) can be obtained.

Examples of the acid are hydrochloric acid, sulfuric acid, 10-camphorsulfonic acid, acetic acid, formic acid, trifluoroacetic acid, p-toluenesulfonic acid, methanesulfonic acid, boron trifluoride and aluminum chloride.

Examples of the inert solvent are THF, acetone,

acetonitrile, toluene, methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, *tert*-butyl alcohol, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol, dioxane and a mixed solvent of such an insert solvent with water.

Process 19



(Ia) (Ij)

(In the formulae, m, R^1, R^2, R^3, R^4, R^5 and R^6 have the same meanings as defined above.)

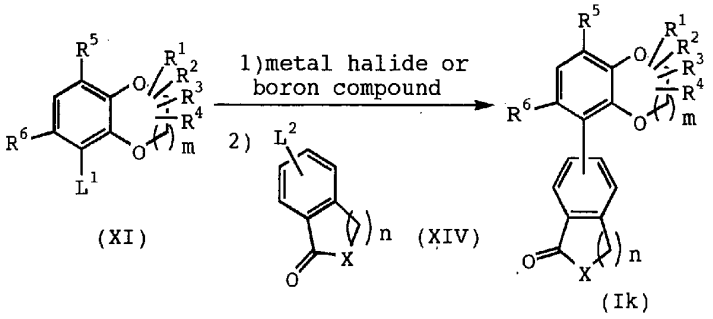
The compound (Ij) can be obtained according to the following reaction step.

The compound (Ia) is made to react with one equivalent to an excess amount of a reducing agent in an inert solvent at the temperature between -100°C and the boiling point of the used solvent for 5 minutes to 48 hours whereupon the compound (Ij) can be obtained.

Examples of the reducing agent are 1,1,3,3-tetramethyldisiloxane, triethylsilane, sodium borohydride, sodium cyanoborohydride, triacetoxy borohydrige and lithium aluminum hydride.

Examples of the inert solvent are methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, *tert*-butyl alcohol, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol and dioxane.

Process 20



(XI) (XIV) (Ik)

(In the formulae, m, n, R^1, R^2, R^3, R^4, R^5, R^6, L^1 and X each have the same meanings as defined above, and L^2 represents chlorine, bromine, iodine or a trifluoromethanesulfonate group.)

The compound (Ik) can be obtained according to the following reaction step.

With regard to the compound (XIV), the commercially available one may be used or it may be obtained according to a known method [Tetrahedron Lett., 30, 5499 (1992)].

After the compound (XI) is treated with a base in an inert solvent at the temperature between -100°C and room temperature for 5 minutes to 10 hours, the resulting compound is made to react with a metal halide or a boron compound at the temperature between -100°C and the boiling point of the used solvent for 5 minutes to 30 hours, followed by further reaction with the compound (XIV) in an inert solvent in the presence of a catalytic amount to an excess amount of a palladium complex at the temperature between room temperature and the boiling point of the used solvent for 5 minutes to 30 hours whereupon the compound (Ik) can be obtained. Incidentally, in the above reaction which is carried out in the presence of a catalytic amount to an excess amount of a palladium complex, a salt such as lithium chloride

or silver oxide may be added, if necessary.

Examples of the base are lithium, magnesium, methyl lithium, methyl magnesium bromide, ethyl magnesium bromide and butyl lithium.

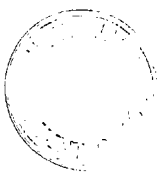
Examples of the metal halide are halogenated alkyl tin derivatives such as chlorotributyl tin and chlorotrimethyl tin and halogenated zinc derivatives such as zinc chloride, zinc bromide and zinc iodide while examples of the boron compound are trimethoxy boron, phenylboric acid and boric acid.

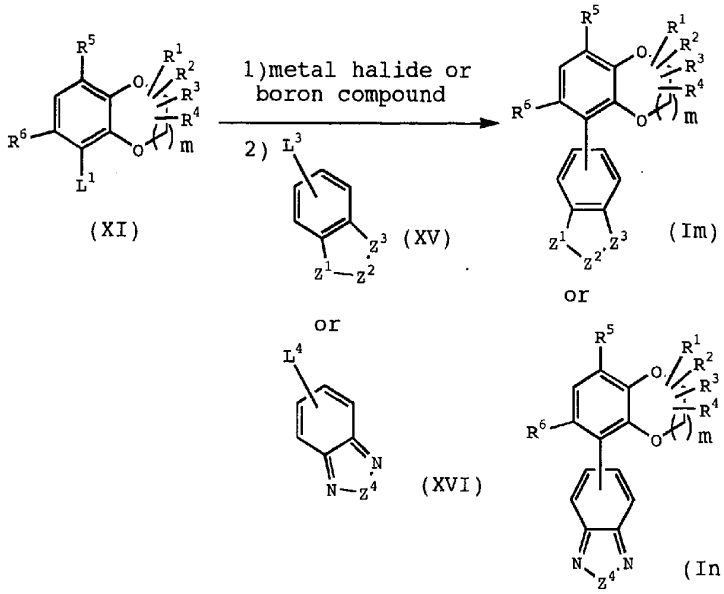
Examples of the palladium complex are tetrakis(triphenylphosphine) palladium, dichlorobis(triphenylphosphine) palladium, dichlorobis(acetonitrile) palladium, [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium and palladium acetate.

Examples of the inert solvent used in the reaction with a metal halide or a boron compound are THF, dioxane, diethyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, benzene, toluene and hexane.

Examples of the inert solvent used in the reaction in the presence of a palladium complex are THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, methanol, ethanol, 1-butanol, 2-propanol, dichloromethane, chloroform, acetonitrile, benzene, toluene, dimethylacetamide, DMF and DMSO.

Process 21





(In the formulae, m, R^1, R^2, R^3, R^4, R^5, R^6, L^1 and Z^1-Z^2-Z^3 each have the same meanings as defined above, Z^4 represents an oxygen atom or a sulfur atom, and L^3 and L^4 represent chlorine, bromine, iodine or a trifluoromethanesulfonate group.)

The compound (Im) and the compound (In) can be obtained according to the following reaction step.

With regard to the compound (XV) and the compound (XVI), the commercially available ones may be used or they may be obtained according to known methods [J. Chem. Soc., Perkin Trans. 1, 1954 (1973); J. Org. Chem., 60(7), 1936 (1995); Tetrahedron Lett., 30(42), 7719 (1994); Chem. Pharm. Bull., 40(10), 2597 (1992); J. Heterocyclic Chem., 7, 815 (1970); J. Chem. Soc. Chem. Comm., 1183 (1985); etc.]

The compound (XI) is treated with a base in an inert solvent at the temperature between -100°C and room temperature for 5 minutes to 10 hours, followed by reaction with a metal

halide or a boron compound at the temperature between -100°C and the boiling point of the used solvent for 5 minutes to 30 hours. The resulting compound is made to react with the compound (XV) in an inert solvent in the presence of a catalytic amount to an excess amount of a palladium complex or a nickel complex at the temperature between room temperature and the boiling point of the used solvent for 5 minutes to 30 hours whereby the compound (Im) can be obtained. Incidentally, when the compound (XVI) is used instead of the compound (XV) and the same reaction as in the case of the compound (XV) is carried out, the compound (In) is obtained.

In the above-mentioned reaction carried out in the presence of a catalytic amount to an excess amount of a palladium complex or a nickel complex, a salt such as lithium chloride or silver oxide may be added thereto, if necessary.

Examples of the base are lithium, magnesium, methyl lithium, methyl magnesium bromide, ethyl magnesium bromide and butyl lithium.

Examples of the metal halide are halogenated alkyl tin derivatives such as chlorotributyl tin and chlorotrimethyl tin and halogenated zinc derivatives such as zinc chloride, zinc bromide and zinc iodide while examples of the boron compound are trimethoxy boron, phenylboric acid and boric acid.

Examples of the palladium complex are tetrakis(triphenylphosphine) palladium, dichlorobis(triphenylphosphine) palladium, dichlorobis(acetonitrile) palladium, [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium and palladium acetate.

Examples of the nickel complex are [1,1'-bis(diphenylphosphino)ferrocene] dichloronickel and dichlorobis(triphenylphosphine) nickel.

Examples of the inert solvent used in the reaction with a metal halide or a boron compound are THF, dioxane, diethyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, benzene, toluene and hexane.

Examples of the inert solvent used in the reaction in the presence of a palladium complex or a nickel catalyst are THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, methanol, ethanol, 1-butanol, 2-propanol, dichloromethane, chloroform, acetonitrile, benzene, toluene, dimethylacetamide, DMF and DMSO.

The compound (Ima) which is the compound (Im) wherein Z^1-Z^2-Z^3 is C(=O)-NH-C(=O) can also be obtained in such a way that a reaction similar to that mentioned in Process 21 is carried out using the compound (XI) and a diethyl halogenated phthalate such as diethyl bromophthalate followed by hydrolysis and the product obtained thereby is made to react with urea.

The compound (I) wherein R^9 is carbamoyl can be obtained using the compound (I) wherein R^9 is cyano according to a known method ["Jikken Kagaku Koza (Handbook of Experimental Chemistry)", fourth edition, edited by the Chemical Society of Japan, 22, 151-154 (1992)] or a method similar thereto.

The compound (I) wherein R^9 is cyano is converted to the compound wherein the moiety corresponding to R^9 is an aldehyde according to a known method ["Jikken Kagaku Koza (Handbook of Experimental Chemistry)", fourth edition, edited by the

Chemical Society of Japan, 21, 89-94 (1992)] or a method similarly thereto, and then the compound (I) wherein R^9 is ethynyl can be obtained according to a known method ["Jikken Kagaku Koza (Handbook of Experimental Chemistry)", fourth edition, edited by the Chemical Society of Japan, 19, 306-307 (1992)] or a method similar thereto.

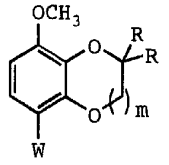
The intermediates and the desired compounds in each of the above-mentioned process can be isolated and purified by separation and purification methods conventionally used in synthetic organic chemistry such as filtration, extraction, washing, drying, concentration, recrystallization and various kinds of chromatography. The intermediates may be subjected to the subsequent reaction without particular purification.

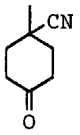
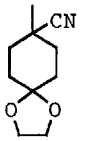
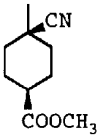
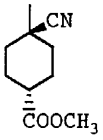
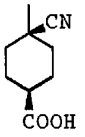
When it is desired to obtain a salt of the compound (I), the compound (I) is dissolved or suspended in a suitable solvent, then an acid or a base is added thereto, and the resulting salt may be isolated and purified.

Further, the compound (I) and pharmaceutically acceptable salts thereof can also exist in the form of adducts with water or various solvents, which are also within the scope of the present invention.

Specific examples of the compound (I) obtained according to the present invention are shown in Table 1.

Table 1(1)



Compd. No.	W	R	m
1		H	1
2		H	1
3		H	1
4		H	1
5		H	1

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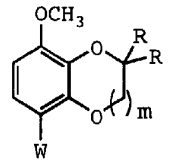
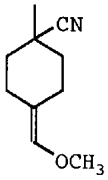
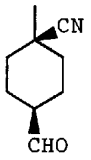
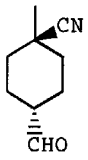
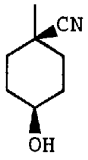
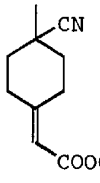


Compd. No.	W	R	m
6		H	1
7		H	1
8		H	1
9		H	1
10		H	1

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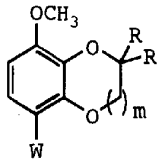
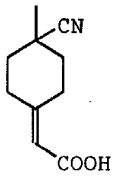
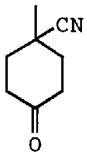
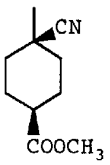
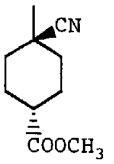
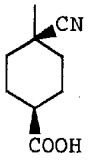


Compd. No.	W	R	m
11		H	1
12		CH_3	0
13		CH_3	0
14		CH_3	0
15		CH_3	0

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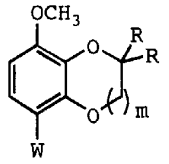


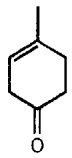
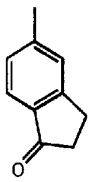
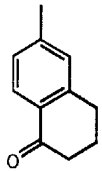
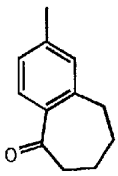
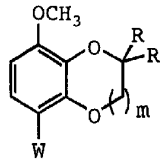
Compd. No.	W	R	m
16		H	1
17		H	1
18		H	1
19		H	1

Table 1(5)



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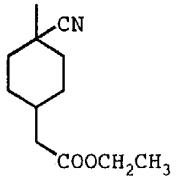
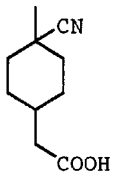
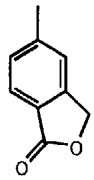
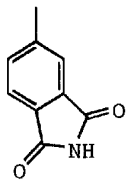
20		H	1
21		H	1
22		H	1
23		H	1

The pharmacological activities of the representative the compounds (I) are described in more detail by Test Examples.

Test Example 1: Inhibition Test on Recombinant Human PDE IV Enzyme

Human phosphodiesterase cDNA (HSPDE4A) was isolated from testicles. Its predicted amino acid sequence is identical with the sequence (HSPDE4A5) reported by Bolger, G. et al. (Mol. Cell. Biol., 6558 (1993)) except that 223 amino acids have been deleted from the N-terminal thereof. This recombinant protein was expressed by an *E. coli* expression plasmid and then purified. The PDE activity was measured in the following 2-step process according to the method of Kincaid, R. and Manganiello, V. [Method. Enzymol., 159, 457 (1988)]. The substrate used was [^{3}H]cAMP (final concentration: 1 μmol/liter), and the reaction was performed in a standard mixture containing N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (50 mmol/liter, pH 7.2), $MgCl_2$ (1 mmol/liter) and soybean trypsin inhibitor (0.1 mg/ml). The reaction was initiated by adding the enzyme thereto, and the mixture was incubated at 30 °C for 10 to 30 minutes. The reaction was quenched by hydrochloric acid, and the formed 5'-AMP was completely decomposed with 5'-nucleosidase. This sample was subjected to chromatography on DEAE-Sephadex A-25, and the eluted [^{3}H]adenosine was counted with a scintillation counter. The test compound was added after dissolved (concentration: 1.7 %) in DMSO.

In this study, Compound 5 showed enzyme inhibitory activity of over 87% at a drug concentration of 1 μmol/liter.

Although the compound (I) or pharmaceutically acceptable

salts thereof can also be administered as such, it is usually desirable to provide them in the form of various pharmaceutical preparations. Such pharmaceutical preparations may be used for animals and humans.

The pharmaceutical preparations according to the present invention may contain the compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient, alone or as a mixture with other therapeutically effective components. Further, such pharmaceutical preparations are obtained by any means which are well-known in the technical field of pharmaceutics after mixing the active ingredient with one or more pharmaceutically acceptable carriers.

Examples of the effective ingredient to be mixed therewith are a serotonin $(5HT)_3$ receptor antagonist, a serotonin $(5HT)_4$ receptor agonist, a serotonin $(5HT)_{1A}$ receptor agonist, a dopamine $(D)_2$ receptor antagonist, a histamine $(H)_1$ receptor antagonist, a muscarine receptor antagonist, a neurokinin $(NK)_1$ receptor antagonist and an endothelin $(ET)_A$ receptor antagonist.

It is desired to use the administration route which is the most effective in therapy such as oral administration and parenteral administration which includes intrabuccal, intratracheal, intrarectal, subcutaneous, intramuscular and intravenous administration.

The administration form includes sprays, capsules, tablets, granules, syrups, emulsions, suppositories, injections, ointments and tapes.

Liquid preparations such as emulsions and syrups which are suitable for oral administration can be obtained using water,

sugars such as sucrose, sorbitol and fructose, glycols such as polyethylene glycol and propylene glycol, oils such as sesame oil, olive oil and soybean oil, preservatives such as p-hydroxybenzoate and flavors such as strawberry flavor and peppermint. Capsules, tablets, powder and granules can be obtained using excipients such as lactose, glucose, sucrose and mannitol, disintegrators such as starch and sodium alginate, lubricants such as magnesium stearate and talc, binders such as polyvinyl alcohol, hydroxypropyl cellulose and gelatin, surfactants such as fatty acid esters, and plasticizers such as glycerin.

Preparations suitable for parenteral administration comprise a sterilized aqueous agent containing the active compound, which is preferably isotonic to the blood of a patient. For example, a solution for injection is prepared using a carrier such as a salt solution, a glucose solution or a mixture of a saline solution and a glucose solution. Preparations for intrarectal administration are prepared using a carrier such as cacao fat, hydrogenated fat and hydrogenated carboxylic acid, and provided as suppositories. Sprays are prepared using an active compound itself or an active compound with a carrier which can disperse the active compound as fine particles to facilitate absorption without stimulating oral or respiratory mucosa. Examples of such carriers are lactose and glycerin. Preparations such as aerosol and dry powder can be used depending on the properties of the active compound and carriers used.

These parenteral preparations may also contain one or more auxiliary components selected from diluents, flavors, preservatives, excipients, disintegrators, lubricants,

binders, surfactants, and plasticizers, all of which are mentioned in the above oral preparations.

The effective dose and administration schedule of the compound (I) or a pharmaceutically acceptable salt thereof may vary depending on the form of administration, the age and body weight of a patient, and the type or degree of the disease to be treated, but usually, in the case of oral administration, the compound (I) or a pharmaceutically acceptable salt thereof is administered in a dose of 0.01 mg to 1 g/adult/day, preferably 0.05 to 50 mg/adult/day, at one time or in several parts. In the case of parenteral administration such as intravenous administration, the compound (I) or a pharmaceutically acceptable salt thereof is administered in a dose of 0.001 to 100 mg/adult/day, preferably 0.01 to 10 mg/adult/day, at one time or in several parts. However, these doses vary depending on the various conditions described above.

Hereinafter, the mode of the present invention is described by Examples.

Best Mode for Carrying Out the Invention

Example 1. 4-Cyano-4-(8-methoxy-1,4-benzodioxan-5-yl) cyclohexanone (Compound 1)

(Step A) Synthesis of 2-(8-methoxy-1,4-benzodioxan-5-yl)acetonitrile (Compound 1a)

To a solution of 12 g (62 mmol) of 8-methoxy-1,4-benzodioxane-5-carbaldehyde in 140 ml of acetonitrile was added 12 g (110 mmol) of lithium bromide, and then 12 ml (95 mmol) of trimethylsilyl chloride was dropwise added thereto. After 15 minutes, the mixture was ice-cooled, and 19 ml (110 mmol)

of 1,1,3,3-tetramethyldisiloxane was dropwise added thereto, followed by stirring at room temperature for 2 hours. The mixture was diluted with methylene chloride, and then was filtered through Celite. The solvent was evaporated *in vacuo* from the filtrate to give a pale yellow oily substance. To a solution of the obtained crude 5-bromomethyl-8-methoxy-1,4-benzodioxane in 180 ml of DMF was added 9.2 g (190 mmol) of sodium cyanide, followed by stirring at room temperature for 60 hours. To the mixture was added water under ice-cooling, and a solid separated out therefrom was collected by filtration to give 6.8 g (53%) of Compound 1a as an ash-colored solid.

Melting Point: 121 - 125 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 3.60 (s, 2H), 3.88 (s, 3H), 4.33 (s, 4H), 6.50 (d, J = 8 Hz, 1H), 6.86 (d, J = 8 Hz, 1H).

MASS (m/z) 205 (M^+).

(Step B) Synthesis of dimethyl 4-cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)pimelate (Compound 1b)

To a solution of 6.2 g (30 mmol) of Compound 1a obtained in Step A in 94 ml of acetonitrile were added 1.4 ml (3.0 mmol) of a 40% methanolic solution of Triton B and 27 ml (300 mmol) of methyl acrylate, followed by heating under reflux for 5 hours. The mixture was allowed to stand for cooling, and then poured into water, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate, and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 2/1) to give 6.4 g (56%) of Compound 1b as a pale yellow oily substance.

^{1}H-NMR ($CDCl_3$, δ, ppm) 2.05-2.37 (m, 4H), 2.39-2.59 (m, 2H),

2.62-2.82 (m, 2H), 3.60 (s, 6H), 3.87 (s, 3H), 4.20-4.40 (m, 4H), 6.48 (d, J = 9 Hz, 1H), 7.01 (d, J = 9 Hz, 1H).

MASS (m/z) 377 (M^+).

(Step C) Synthesis of 4-cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)-2-methoxycarbonylcyclohexanone (Compound 1c)

To a solution of 6.4 g (17 mmol) of Compound 1b obtained in Step B in 96 ml of 1,2-dimethoxyethane was added 2.0 g (50 mmol) of 60% sodium hydride. After heating under reflux for 3 hours, the mixture was allowed to stand for cooling, poured into ice water, acidified with a 6 mol/liter aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 2/1) to give 5.0 g (86%) of Compound 1c as a white solid.

Melting Point: 129 - 132 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 2.21-2.50 (m, 3H), 2.61-2.89 (m, 2H), 3.11(d, J = 15 Hz, 1H), 3.79 (s, 3H), 3.89 (s, 3H), 4.37 (s, 4H), 6.49 (d, J = 9 Hz, 1H), 6.84 (d, J = 9 Hz, 1H), 12.2 (s, 1H).

MASS (m/z) 345 (M^+).

(Step D) Synthesis of Compound 1

A mixture of 5.0 g (15 mmol) of Compound 1c obtained in Step C, 50 ml of DMSO, 5 ml of water, and 5.0 g of sodium chloride was stirred at 150°C for 5 hours. The mixture was allowed to stand for cooling, and the water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate, and the solvent was

evaporated *in vacuo*. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 3/1) to give 3.6 g (86%) of Compound 1 as a white solid.

Melting Point: 157 - 161 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 2.21-2.41 (m, 2H), 2.45-2.72 (m, 4H), 2.81-3.00 (m, 2H), 3.89 (s, 3H), 4.37 (s, 4H), 6.51 (d, J = 9 Hz, 1H), 6.88 (d, J = 9 Hz, 1H).

MASS (m/z) 287 (M^+).

Example 2. 4-Cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexanone ethyleneketal (Compound 2)

(Step A) Synthesis of 4-hydroxy-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexanone ethyleneketal (Compound 2a)

In 65 ml of THF was dissolved 10 g (41 mmol) of 5-bromo-8-methoxy-1,4-benzodioxane, and 28 ml (45 mmol) of a 1.59 mol/liter solution of n-butyl lithium in hexane was dropwise added thereto at -78°C. After 15 minutes, a solution of 9.6 g (61 mmol) of 1,4-cyclohexadione monoethyleneketal in 50 ml of THF was dropwise added thereto. The mixture was stirred for 1 hour, followed by stirring at room temperature for 20 minutes. Water was added thereto, the mixture was extracted with ethyl acetate, and the extract was washed with brine and dried over sodium sulfate. The solvent was evaporated therefrom, and the residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 1/1) to give 9.0 g (68%) of Compound 2a as a white solid.

Melting Point: 94 - 96 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.58-1.72 (m, 2H), 1.88-2.28 (m, 6H), 3.57 (s, 1H), 3.86 (s, 3H), 3.90-4.07 (m, 4H), 4.35 (s, 4H), 6.46

(d, J = 9 Hz, 1H), 6.82 (d, J = 9 Hz, 1H).

MASS (m/z) 322 (M^+).

(Step B) Synthesis of Compound 2

In 4.9 ml of methylene chloride was dissolved 0.49 g (1.5 mmol) of Compound 2a obtained in Step A, 0.26 ml (1.9 mmol) of trimethylsilyl cyanide was added thereto at -78°C, then 0.20 ml (1.6 mmol) of a boron trifluoride-ethyl ether complex was dropwise added thereto, and the mixture was stirred for 10 minutes, followed by stirring at room temperature for 10 minutes. A saturated aqueous solution of sodium bicarbonate was added thereto and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 2/1) to give 0.30 g (61%) of Compound 2 as a colorless oily substance.

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.79-1.95 (m, 2H), 2.06-2.20 (m, 4H), 2.30-2.46 (m, 2H), 3.87 (s, 3H), 3.90-4.07 (m, 4H), 4.36 (s, 4H), 6.48 (d, J = 9 Hz, 1H), 6.82 (d, J = 9 Hz, 1H).

MASS (m/z) 331 (M^+).

Example 3. Compound 1

In 2.9 ml of acetone was dissolved 0.29 g (0.87 mmol) of Compound 2 obtained in Example 2, 1.2 ml (7.2 mmol) of a 6 mol/liter aqueous hydrochloric acid was added thereto, and the mixture was heated under reflux for 3 hours. The mixture was allowed to stand for cooling and poured into a saturated aqueous solution of sodium bicarbonate, the mixture was extracted with ethyl acetate, and the extract was washed with brine. The

mixture was dried over sodium sulfate, and the solvent was evaporated to give 0.23 g (92%) of Compound 1 as a white solid.

Example 4. Methyl *cis*-4-cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexanecarboxylate (Compound 3) and methyl *trans*-4-cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexanecarboxylate (Compound 4)

(Step A) Synthesis of 2-[4-cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexylidene]-1,3-dithiane (Compound 3a)

To a solution of 5.0 ml (26 mmol) of 2-trimethylsilyl-1,3-dithiane in 50 ml of THF was added dropwise 17 ml (26 mmol) of a 1.54 mol/liter solution of n-butyl lithium in hexane under ice-cooling. After 10 minutes, the mixture was cooled to -78°C, and a solution of 3.6 g (13 mmol) of Compound 1 obtained in Example 1 in 40 ml of THF was dropwise added thereto. After 10 minutes, to the mixture was added brine, followed by addition of water at room temperature. The mixture was extracted with ethyl acetate, the extract was dried over sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 4/1) to give 3.9 g (79%) of Compound 3a as a white solid.

Melting Point: 164 - 166 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.70-1.92 (m, 2H), 2.05-2.24 (m, 2H), 2.28-2.53 (m, 4H), 2.89 (t, J = 6 Hz, 4H), 3.18-3.38 (m, 2H), 3.87 (s, 3H), 4.36 (s, 4H), 6.47 (d, J = 9 Hz, 1H), 6.79 (d, J = 9 Hz, 1H).

MASS (m/z) 389 (M^+).

(Step B) Synthesis of Compound 3 and Compound 4

In 120 ml of methanol was suspended 3.9 g (10 mmol) of Compound 3a obtained in Step A, 1.7 ml (20 mmol) of 70% perchloric acid, and 4.3 g (16 mmol) of mercury chloride ($HgCl_2$) were added thereto, and the mixture was stirred for 4 hours. The mixture was diluted with methylene chloride and was filtered through Celite, the filtrate was poured into a saturated aqueous solution of sodium bicarbonate, and the mixture was extracted with methylene chloride. The organic layer was washed with brine and dried over sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 1/1) to give the crude Compound 3 as a white solid and also to give 0.18 g (5.5%) of Compound 4 as a colorless transparent oily substance. Compound 3 was further recrystallized from ethyl acetate to give 0.57 g (17%) of white crystals.

Compound 3

Melting Point: 123 - 124 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.75-2.22 (m, 6H), 2.27-2.51 (m, 3H), 3.71 (s, 3H), 3.88 (s, 3H), 4.36 (s, 4H), 6.48 (d, J = 9 Hz, 1H), 6.84 (d, J = 9 Hz, 1H).

MASS (m/z) 331 (M^+).

Compound 4

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.92-2.38 (m, 8H), 2.70-2.88 (m, 1H), 3.69 (s, 3H), 3.87 (s, 3H), 4.36 (s, 4H), 6.48 (d, J = 9 Hz, 1H), 6.81 (d, J = 9 Hz, 1H).

MASS (m/z) 331 (M^+).

Example 5. *cis*-4-Cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexanecarboxylic acid (Compound 5)

To a mixture of 0.55 g (1.7 mmol) of Compound 3 obtained in Example 4 and 3.3 ml of methanol was added 3.3 ml of THF to dissolve them. To the mixture was dropwise added 2.6 ml of a 1.3 mol/liter aqueous solution of potassium hydroxide, followed by stirring at room temperature for 1 hour. The mixture was poured into water, ethyl acetate was added thereto, and an aqueous layer was extracted. The aqueous layer was acidified with a 1 mol/liter aqueous hydrochloric acid, and the precipitated solid was collected by filtration and re-slurried with ethanol to give 0.45 g (86%) of Compound 5 as a white solid.

Melting Point: 228 - 230 °C

^{1}H-NMR (DMSO-d_6, δ, ppm) 1.59-1.90 (m, 4H), 1.94-2.10 (m, 2H), 2.20-2.45 (m, 3H), 3.75 (s, 3H), 4.27 (dd, J = 5, 12 Hz, 4H), 6.60 (d, J = 9 Hz, 1H), 6.79 (d, J = 9 Hz, 1H), 12.2 (br s, 1H).

MASS (m/z) 317 (M^+).

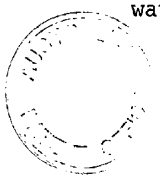
Elemental analysis: $C_{17}H_{19}NO_5$

Found (%) C : 64.09, H : 6.01, N : 4.51

Calcd. (%) C : 64.34, H : 6.03, N : 4.41

Example 6. 1-(8-Methoxy-1,4-benzodioxan-5-yl)-4-methoxymethylenecyclohexane carbonitrile (Compound 6)

In 320 ml of THF was suspended 34 g (99 mmol) of methoxymethyl triphenylphosphonium chloride, and 11 g (99 mmol) of potassium *tert*-butoxide was added thereto. The mixture was stirred at room temperature for 15 minutes, and a solution of 15 g (52 mmol) of Compound 1 obtained in Example 1 in 150 ml of THF was dropwise added thereto, followed by stirring at room temperature for 45 minutes. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate. The



organic layer was washed with brine and dried over sodium sulfate. The solvent was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 3/1) to give 14 g (82%) of Compound 6 as a white solid.

Melting Point: 112 - 113 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.67-1.82 (m, 2H), 2.08-2.60 (m, 5H), 2.82-2.98 (m, 1H), 3.57 (s, 3H), 3.87 (s, 3H), 4.36 (s, 4H), 5.84 (s, 1H), 6.47 (d, J = 9 Hz, 1H), 6.80 (d, J = 9 Hz, 1H).

MASS (m/z) 315 (M^+).

Example 7. *cis*-4-Cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexane carbaldehyde (Compound 7) and *trans*-4-cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexane carbaldehyde (Compound 8)

In 100 ml of acetone was dissolved 10 g (32 mmol) of Compound 6 obtained in Example 6, 210 ml of a 6 mol/liter aqueous hydrochloric acid was dropwise added thereto, and the mixture was stirred at room temperature for 2 hours, neutralized by adding a 5 mol/liter aqueous solution of sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate and then with brine. The mixture was dried over magnesium sulfate, the solvent was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 2/1) to give 7.7 g (80%) of Compound 7 and 1.7 g (18%) of Compound 8 each being as a colorless oily substance.

Compound 7

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.80-2.35 (m, 7H), 2.38-2.57 (m, 2H), 3.88 (s, 3H), 4.36 (s, 4H), 6.49 (d, J = 9 Hz, 1H), 6.85 (d, J = 9

Hz, 1H), 9.68 (s, 1H).

MASS (m/z) 301 (M^+).

Compound 8

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.75-1.96 (m, 2H), 2.06-2.37 (m, 6H), 2.56-2.65 (m, 1H), 3.87 (s, 3H), 4.33 (s, 4H), 6.46 (d, J = 9 Hz, 1H), 6.78 (d, J = 9 Hz, 1H), 9.73 (s, 1H).

MASS (m/z) 301 (M^+).

Example 8. *cis*-4-Cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexanecarboxylic acid (Compound 5)

In 155 ml of *tert*-butyl alcohol were dissolved 7.7 g (26 mmol) of Compound 7 obtained in Example 7, 3.1 g (26 mmol) of sodium dihydrogen phosphate and 12 ml (120 mmol) of 2-methyl-2-butene, 46 ml of a 80% aqueous solution of 3.2 g (28 mmol) of chlorous acid was dropwise added thereto under ice-cooling, and the mixture was stirred at room temperature for 1 hour. To the mixture was added 5.3 g (51 mmol) of sodium hydrogen sulfite, followed by stirring for 15 minutes, a 2 mol/ml aqueous solution of sodium hydroxide was added thereto, and the resulting mixture was washed with ethyl acetate. The mixture was adjusted to pH 3.5 with a 6 mol/liter aqueous hydrochloric acid, and the solid separated out therefrom was collected by filtration and recrystallized from ethanol to give 5.5 g (67%) of Compound 5 as white crystals.

Example 9. *cis*-4-Cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexanol (Compound 9)

In 8.4 ml of methanol was dissolved 0.42 g (1.5 mmol) of Compound 1 obtained in Example 1, and 0.11 g (3.0 mmol) of sodium

borohydride was added thereto under ice-cooling. The mixture was stirred at room temperature for 1 hour, 0.057 g (1.5 mmol) of sodium borohydride was added again under ice-cooling, followed by stirring at room temperature for 30 minutes, a 1 mol/liter aqueous hydrochloric acid was added thereto under ice-cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate, and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 1/2), followed by recrystallization from ethanol to give 0.20 g (48%) of Compound 9 as white crystals.

Melting Point: 137 - 138 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.75-1.99 (m, 4H), 2.01-2.22 (m, 2H), 2.30-2.54 (m, 2H), 3.56-3.79 (m, 1H), 3.87 (s, 3H), 4.38 (s, 4H), 6.48 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 1H).

MASS (m/z) 289 (M^+).

Elemental analysis: $C_{16}H_{19}NO_4 \cdot 0.1H_2O$

Found (%) C : 66.21, H : 6.94, N : 4.82

Calcd. (%) C : 66.01, H : 6.65, N : 4.81

Example 10. Ethyl 4-cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexanylideneacetate (Compound 10)

In 9.4 ml of THF was dissolved 0.72 ml (3.6 mmol) of triethyl phosphonoacetate, and 0.15 g (3.6 mmol) of 60% sodium hydride was added thereto under ice-cooling. The mixture was stirred at room temperature for 15 minutes, 0.94 g (3.3 mmol) of Compound 1 obtained in Example 1 was added thereto under ice-cooling, and the mixture was stirred at room temperature for 30 minutes. Then, water was added thereto under ice-cooling,

the mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. The solvent was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 2/1) to give 1.4 g (97%) of Compound 10 as a white solid.

Melting Point: 110 - 112 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.28 (t, J = 7 Hz, 3H), 1.85-2.10 (m, 2H), 2.31-2.60(m, 4H), 2.67-2.89 (m, 1H), 3.87 (s, 3H), 3.92-4.12 (m, 1H), 4.16 (q, J = 7 Hz, 2H), 4.36 (s, 4H), 5.71 (s, 1H), 6.48 (d, J = 9 Hz, 1H), 6.81 (d, J = 9 Hz, 1H).

MASS (m/z) 357 (M^+).

Example 11. 4-Cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexanylideneacetic acid (Compound 11)

In 3.1 ml of ethanol and 3.1 ml of THF was suspended 0.31 g (0.87 mmol) of Compound 10 obtained in Example 10, then 0.65 ml (1.3 mmol) of a 2 mol/liter aqueous solution of sodium hydroxide was added thereto, the mixture was stirred at 70°C for 1 hour, and then 0.65 ml (1.3 mmol) of a 2 mol/liter aqueous solution of sodium hydroxide was further thereto added thereto, followed by stirring at 70°C for 1 hour. A 1 mol/liter aqueous hydrochloric acid was dropwise added thereto under ice-cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate, the solvent was evaporated *in vacuo*, and the residue was triturated with ethanol to give 0.23 g (82%) of Compound 11 as a white solid.

Melting Point: 203 - 204 °C

^{1}H-NMR (DMSO-d_6, δ, ppm) 1.75-2.00 (m, 2H), 2.05-2.67 (m, 5H),

3.74 (s, 3H), 3.80-4.00 (m, 1H), 4.15-4.43 (m, 4H), 5.69 (s, 1H), 6.59 (d, J = 9 Hz, 1H), 6.81 (d, J = 9 Hz, 1H), 12.1 (br s, 1H).

MASS (m/z) 329 (M^+).

Elemental analysis: $C_{18}H_{19}NO_5 \cdot 0.1H_2O$

Found (%) C : 65.30, H : 6.09, N : 4.19

Calcd. (%) C : 65.29, H : 5.84, N : 4.23

Example 12. 4-Cyano-4-(2,2-dimethyl-7-methoxy-1,3-benzodioxol-4-yl)cyclohexanone (Compound 12)

(Step A) Synthesis of 2-(2,2-dimethyl-7-methoxy-1,3-benzodioxol-4-yl)acetonitrile (Compound 12a)

To a solution of 9.3 g (45 mmol) of 2,2-dimethyl-7-methoxy-1,3-benzodioxole-4-carbaldehyde obtained by the method mentioned in the Japanese Published Unexamined Patent Application No. 98/147585 and by a method similar thereto in 47 ml of acetonitrile was added 8.9 g (85 mmol) of lithium bromide, and then 8.5 ml (67 mmol) of trimethylsilyl chloride was dropwise added thereto. After 15 minutes, the mixture was ice-cooled, and 13 ml (76 mmol) of 1,1,3,3-tetramethyldisiloxane was dropwise added thereto, followed by stirring at room temperature for 2 hours. The resulting mixture was diluted with toluene and filtered through Celite. The solvent was evaporated *in vacuo* from the filtrate to give a pale yellow oily substance. To a solution of this crude 7-bromomethyl-2,2-dimethyl-4-methoxy-1,3-benzodioxole in 73 ml of DMF was added 5.0 g (102 mmol) of sodium cyanide, and the mixture was stirred at room temperature for 18 hours. Under ice-cooling, water was added thereto, and the mixture was extracted with ethyl acetate. The

organic layer was washed with brine and dried over sodium sulfate, and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 5/1) to give 9.1 g (92%) of Compound 12a as an ash-colored solid.

Melting Point: 58 - 59 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.71 (s, 6H), 3.60 (s, 2H), 3.88 (s, 3H), 6.50 (d, J = 9 Hz, 1H), 6.76 (d, J = 9 Hz, 1H).

MASS (m/z) 219 (M^+).

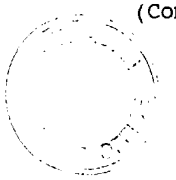
(Step B) Synthesis of dimethyl 4-cyano-4-(2,2-dimethyl-7-methoxy-1,3-benzodioxol-4-yl)pimelate (Compound 12b)

To a solution of 9.0 g (41 mmol) of Compound 12a obtained in Step A in 135 ml of acetonitrile were added 1.9 ml (4.1 mmol) of a 40% methanolic solution of Triton B and 37 ml (410 mmol) of methyl acrylate, and the mixture was stirred at room temperature for 30 minutes. Water and a 1 mol/liter aqueous hydrochloric acid were added thereto, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate, and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 5/2) to give 11 g (68%) of Compound 12b as a pale yellow oily substance.

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.69 (s, 6H), 2.05-2.31 (m, 4H), 2.40-2.64 (m, 4H), 3.60 (s, 6H), 3.89 (s, 3H), 6.49 (d, J = 9 Hz, 1H), 6.88 (d, J = 9 Hz, 1H).

MASS (m/z) 391 (M^+).

(Step C) Synthesis of 4-cyano-4-(2,2-dimethyl-7-methoxy-1,3-benzodioxol-4-yl)-2-methoxycarbonylcyclohexanone (Compound 12c)



To a solution of 11 g (27 mmol) of Compound 12b obtained in Step B in 161 ml of 1,2-dimethoxyethane was added 3.3 g (83 mmol) of 60% sodium hydride. After heating under reflux for 3 hours, the mixture was allowed to stand for cooling and poured into ice water, and the mixture was acidified with a 6 mol/liter aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 3/1) to give 8.4 g (86%) of Compound 12c as a white solid.

Melting Point: 146 - 147 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.71 (s, 3H), 1.73 (s, 3H), 2.12-2.27 (m, 1H), 2.32-2.55 (m, 2H), 2.67-3.00 (m, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 6.51 (d, J = 9 Hz, 1H), 6.92 (d, J = 9 Hz, 1H), 12.2 (s, 1H).

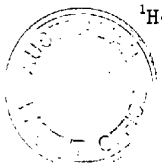
MASS (m/z) 359 (M^+).

(Step D) Synthesis of Compound 12

A mixture of 8.3 g (23 mmol) of Compound 12c obtained in the step C, 83 ml of DMSO, 8.3 ml of water and 8.3 g of sodium chloride was stirred at 150°C for 12 hours. The mixture was allowed to stand for cooling, water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 3/1) to give 5.6 g (81%) of Compound 12 as a white solid.

Melting Point: 153 - 154 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.72 (s, 6H), 2.35-2.61 (m, 6H), 2.77-2.97



(m, 2H), 3.90 (s, 3H), 6.53 (d, J = 9 Hz, 1H), 6.97 (d, J = 9 Hz, 1H).

MASS (m/z) 301 (M^+).

Example 13. Methyl *cis*-4-cyano-4-(2,2-dimethyl-7-methoxy-1,3-benzodioxol-4-yl)cyclohexanecarboxylate (Compound 13) and *trans*-4-cyano-4-(2,2-dimethyl-7-methoxy-1,3-benzodioxol-4-yl)cyclohexanecarboxylate (Compound 14)

(Step A) Synthesis of 2-[4-cyano-4-(2,2-dimethyl-7-methoxy-1,3-benzodioxol-4-yl)cyclohexylidene]-1,3-dithiane (Compound 13a)

To a solution of 0.56 ml (3.0 mmol) of 2-trimethylsilyl-1,3-dithiane in 5.6 ml of THF was dropwise added thereto 1.9 ml (3.0 mmol) of a solution of 1.54 mol/liter of butyl lithium in hexane under ice-cooling. After 15 minutes, the mixture was cooled to -78°C, and a solution of 0.42 g (1.4 mmol) of Compound 12 obtained in Example 12 in 0.6 ml of THF was dropwise added thereto. After 20 minutes, brine was added thereto and then water was added thereto at room temperature. The mixture was extracted with ethyl acetate, the extract was dried over sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 6/1) to give 0.53 g (93%) of Compound 13a as a white solid.

Melting Point: 194 - 197 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.72 (s, 6H), 1.86-2.53 (m, 8H), 2.90 (t, J = 6 Hz, 4H), 3.17-3.33 (m, 2H), 3.88 (s, 3H), 6.48 (d, J = 9 Hz, 1H), 6.86 (d, J = 9 Hz, 1H).

MASS (m/z) 403 (M^+).

(Step B) Synthesis of Compound 13 and Compound 14

To 105 ml of methanol was suspended 3.0 g (7.4 mmol) of Compound 13a obtained in Step A, then 1.3 ml (15 mmol) of 70% perchloric acid and 3.2 g (12 mmol) of mercury chloride ($HgCl_2$) were added thereto, and the mixture was stirred at 60°C for 1 hour. The mixture was diluted with methylene chloride and filtered through Celite, and the filtrate was poured into saturated aqueous sodium bicarbonate, followed by extraction with methylene chloride. The organic layer was washed with brine and dried over sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 3/1) to give 1.4 g (53%) of Compound 13 as a white solid and 0.31 g (12%) of Compound 14 as a colorless transparent oily substance.

Compound 13

Melting Point: 79 - 80 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.72 (s, 6H), 1.87-2.27 (m, 8H), 2.30-2.43 (m, 1H), 3.71 (s, 3H), 3.88 (s, 3H), 6.49 (d, J = 9 Hz, 1H), 6.92 (d, J = 9 Hz, 1H).

MASS (m/z) 345 (M^+).

Compound 14

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.71 (s, 6H), 1.90-2.26 (m, 8H), 2.72-2.80 (m, 1H), 3.70 (s, 3H), 3.88 (s, 3H), 6.48 (d, J = 9 Hz, 1H), 6.83 (d, J = 9 Hz, 1H).

MASS (m/z) 345 (M^+).

Example 14. *cis*-4-Cyano-4-(2,2-dimethyl-7-methoxy-1,3-benzodioxol-4-yl)cyclohexanecarboxylic acid (Compound 15)

To a mixture of 1.7 g (5.0 mmol) of Compound 13 obtained

in Example 13 and 10 ml of methanol was added 5.2 ml of THF to dissolve them. To the mixture was dropwise added thereto 7.7 ml (10 mmol) of a 1.3 mol/liter aqueous solution of potassium hydroxide, followed by stirring at room temperature for 2 hours. Water was added thereto, the mixture was washed with ethyl acetate, and the aqueous layer was acidified with a 1 mol/liter aqueous hydrochloric acid. The mixture was extracted with ethyl acetate, and the extract was washed with brine and dried over sodium sulfate. The solvent was evaporated, and the residue was recrystallized from ethanol to give 1.1 g (64%) of Compound 15 as white crystals.

Melting Point: 195 - 198 °C

^{1}H-NMR (DMSO-d_6, δ, ppm) 1.50-1.78 (m, 8H), 1.79-2.13 (m, 4H), 2.15-2.37 (m, 3H), 3.79 (s, 3H), 6.64 (d, J = 9 Hz, 1H), 6.81 (d, J = 9 Hz, 1H), 12.3 (br s, 1H).

MASS (m/z) 331 (M^+).

Elemental analysis: $C_{18}H_{21}NO_5$

Found (%) C : 65.33, H : 6.40, N : 4.27

Calcd. (%) C : 65.24, H : 6.39, N : 4.23

Example 15. 4-(8-Methoxy-1,4-benzodioxan-5-yl)-3-cyclohexenone (Compound 16)

To 1.2 g (3.6 mmol) of Compound 2a obtained in Step A of Example 2 and 1.2 mg (0.0063 mmol) of p-toluenesulfonic acid monohydrate were added 70 ml of water and 140 ml of toluene, followed by heating under reflux for 4 hours. The mixture was allowed to stand for cooling, the mixture was extracted with toluene, and the extract was washed with saturated aqueous sodium bicarbonate and then with brine. The mixture was dried

over sodium sulfate, the solvent was evaporated, and the residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 2/1) to give 0.88 g (94%) of Compound 16 as a pale yellow solid.

Melting Point: 56 - 59 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 2.59 (t, J = 7 Hz, 2H), 2.75-2.85 (m, 2H), 2.97-3.10 (m, 2H), 3.88 (s, 3H), 4.25-4.37 (m, 4H), 5.83 (t, J = 4 Hz, 1H), 6.48 (d, J = 8 Hz, 1H), 6.81 (d, J = 8 Hz, 1H). MASS (m/z) 260 (M^+).

Example 16. 5-(8-Methoxy-1,4-benzodioxan-5-yl)-1-indanone (Compound 17)

To a mixture of 0.30 g (1.8 mmol) of Compound A obtained in Reference Example 1 and 0.39 g (1.8 mmol) of commercially available 5-bromo-1-indanone was added 3.0 ml of DMF under a nitrogen atmosphere to dissolve them and 0.39 g (3.7 mmol) of sodium carbonate and 0.020 g (0.090 mmol) of palladium acetate were added thereto. The mixture was stirred at 100°C for 2 hours, followed by stirring at 110°C for 0.9 hour. Ethyl acetate was added to the reaction mixture, the solid was filtered off, and the resulting solution was partitioned. The organic layer was washed with brine and dried over sodium sulfate. After the solid was filtered off, the filtrate was concentrated *in vacuo*, and the concentrate was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 3/1) and recrystallized from acetone to give 0.15 g (28%) of Compound 17 as a white solid.

Melting Point: 168 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 2.70-2.74 (m, 2H), 3.18 (br t, 2H), 3.93 (s, 3H), 4.28-4.32 (m, 2H), 4.36-4.39 (m, 2H), 6.61 (d, J = 9

Hz, 1H), 6.90 (d, J = 9 Hz, 1H), 7.53 (dd, J = 2, 8 Hz, 1H), 7.61 (d, J = 2 Hz, 1H), 7.78 (d, J = 8 Hz, 1H).
MASS (m/z) 296 (M^+).

Example 17. 6-(8-Methoxy-1,4-benzodioxan-5-yl)-1-tetralone (Compound 18)

To a mixture of 0.37 g (1.7 mmol) of Compound A obtained in Reference Example 1 and 0.51 g (1.7 mmol) of 6-trifluoromethanesulfonyl-1-tetralone [Synthetic Communication, 23(21), 2965 (1993) etc.] was added 3.7 ml of DMF to dissolve them under a nitrogen atmosphere, and then 0.37 g (3.5 mmol) of sodium carbonate, and 0.020 g (0.090 mmol) of palladium acetate were added thereto. The mixture was stirred at 100°C for 1.5 hours, followed by stirring at 120°C for 2.3 hours. Ethyl acetate was added to the reaction mixture, the solid was filtered off, and the resulting solution was washed with water and with brine and dried over sodium sulfate. The solid was filtered off, the filtrate was concentrated *in vacuo*, and the concentrate was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 3/1) and recrystallized from acetone and then from ethanol to give 0.070 g (8.0%) of Compound 18 as a white solid.
Melting Point: 156 - 158 °C
^{1}H-NMR ($CDCl_3$, δ, ppm) 2.12-2.21(m, 2H), 2.67(t, J = 7 Hz, 2H), 3.01(t, J = 6 Hz, 2H), 3.93(s, 3H), 4.28-4.31 (m, 2H), 4.36-4.38 (m, 2H), 6.59 (d, J = 9 Hz, 1H), 6.88 (d, J = 9 Hz, 1H), 7.39 (d, J = 1 Hz, 1H), 7.46 (dd, J = 2, 8 Hz, 1H), 8.06 (d, J = 8 Hz, 1H).
MASS (m/z) 310 (M^+).

Example 18. 7-(8-Methoxy-1,4-benzodioxan-5-yl)-1-benzosuberone (Compound 19)

To a mixture of 0.37 g (1.6 mmol) of Compound A obtained in Reference Example 1 and 0.38 g (1.6 mmol) of 7-bromo-1-benzosuberone was added 3.3 ml of DMF under a nitrogen atmosphere to dissolve them and 0.33 g (3.1 mmol) of sodium carbonate and 0.020 g (0.080 mmol) of palladium acetate were added thereto. The mixture was stirred at 100°C for 6.5 hours, ethyl acetate was added to the reaction mixture, and the solid was filtered off. The resulting solution was washed with water and with brine and dried over sodium sulfate. The solid was filtered off, the filtrate was concentrated *in vacuo*, and the concentrate was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 3/1) and recrystallized from ethanol and then from acetone to give 0.16 g (32%) of Compound 19 as a white solid.

Melting Point: 124 - 126 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 1.83-1.94 (m, 4H), 2.74-2.78 (m, 2H), 2.96-3.01 (m, 2H), 3.93 (s, 3H), 4.28-4.31 (m, 2H), 4.36-4.39 (m, 2H), 6.59 (d, J = 9 Hz, 1H), 6.89 (d, J = 9 Hz, 1H), 7.36 (d, J = 2 Hz, 1H), 7.47 (dd, J = 2, 8 Hz, 1H), 7.79 (d, J = 8 Hz, 1H).

MASS (m/z) 324 (M^+).

Example 19. Ethyl 2-[4-cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexan-1-yl]acetate (Compound 20)

In 5.5 ml of ethanol and 8.0 ml of acetone was dissolved 0.55 g (1.5 mmol) of Compound 10 obtained in Example 10, 0.11

g of 10% palladium-carbon (containing 50% of water) was added thereto, and the mixture was subjected to a hydrogenation reaction at room temperature and ordinary pressure for 3 hours. After removal of the catalyst, the solvent was evaporated *in vacuo* from the filtrate to give 0.54 g (100%) of Compound 20 as a mixture of isomers in a pale yellow oily substance. NMR ($CDCl_3$, δ, ppm) 1.18-1.33 (m, 3H), 1.45-1.73 (m, 3H), 1.77-1.97(m, 4H), 2.25-2.42 (m, 4H), 3.87 and 3.88 (each s, total 3H), 4.04-4.27 (m, 2H), 4.35(s, 4H), 6.48 and 6.49 (each d, J = 9 Hz, total 1H), 6.84 and 6.88 (each d, J = 9 Hz, total 1H). MASS (m/z) 359 (M^+).

Example 20. 2-[4-Cyano-4-(8-methoxy-1,4-benzodioxan-5-yl)cyclohexan-1-yl]acetic acid (Compound 21)

In 4.1 ml of ethanol was dissolved 0.41 g (1.1 mmol) of Compound 20 obtained in Example 19, 1.1 ml of a 2 mol/liter aqueous solution of sodium hydroxide was added thereto, and the mixture was stirred at room temperature for 1 hour and then stirred at 60°C for 20 minutes. The mixture was allowed to stand for cooling, and water and ethyl acetate were added thereto, followed by separating into an organic layer and an aqueous layer. The aqueous layer was acidified with a 6 mol/liter aqueous hydrochloric acid and extracted with ethyl acetate, and the extract was washed with brine and dried over sodium sulfate. The solvent was evaporated *in vacuo*, toluene was added to the residue, and the solvent was evaporated *in vacuo*. To the residue was added diisopropyl ether, and the precipitated solid was collected by filtration and recrystallized from ethanol to give 0.13 g (36%) of Compound 21 as a mixture of isomers in white

crystals.

Melting Point: 149 - 150 °C

NMR (DMSO-d_6, δ, ppm) 1.25-1.57 (m, 2H), 1.63-1.95 (m, 5H), 2.08-2.35 (m, 4H), 3.74 (s, 3H), 4.15-4.42 (m, 4H), 6.59 (d, J = 9 Hz, 1H), 6.81 and 6.86 (each d, J = 9 Hz, total 1H), 12.1 (s, 1H).

MASS (m/z) 359 (M^+).

Example 21. 4-(8-Methoxy-1,4-benzodioxan-5-yl)-1(3*H*)-isobenzofuranone (Compound 22)

To 0.61 g of ethyl 4-(8-methoxy-1,4-benzodioxan-5-yl)-2-acetoxymethylbenzoate which was obtained by treating 0.40 g (1.9 mmol) of Compound A obtained in Reference Example 1 and 0.57 g (1.9 mmol) of Compound C obtained in Reference Example 3 in the same manner as in Example 17 were added 6.0 ml of ethanol and 1.2 ml of a 5 mol/liter solution of potassium hydroxide, the mixture was stirred at room temperature for 35 minutes, the solvent was evaporated *in vacuo*, and water was added to the residue. To the resulting solution was added a 6 mol/liter hydrochloric acid to adjust it to pH 2, and the precipitated solid was collected by filtration and dried *in vacuo* to give 0.46 g of a white solid.

To this solid was added 4.2 ml of acetic acid, followed by stirring at 90°C. A saturated aqueous solution of sodium bicarbonate was added to the reaction mixture so that acetic acid was neutralized, and ethyl acetate was added thereto for partition. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate and brine and dried over magnesium sulfate. The solid was filtered off, the filtrate

was concentrated *in vacuo*, and the concentrate was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 3/2) and recrystallized from ethanol to give 0.33 g (70%) of Compound 22 as a white solid.

Melting Point: 158 - 160 °C

NMR ($CDCl_3$, δ, ppm) 3.94 (s, 3H), 4.28-4.32 (m, 2H), 4.37-4.40 (m, 2H), 5.35 (s, 2H), 6.62 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 7.62 (s, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H).

MASS(m/z) 298(M^+).

Elemental analysis: $C_{17}H_{14}O_5$

Found (%) C: 68.55, H: 4.61

Calcd. (%) C: 68.45, H: 4.73

Example 22. 4-(8-Methoxy-1,4-benzodioxan-5-yl)phthalimide (Compound 23)

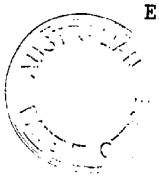
To 0.12 g (0.4 mmol) of Compound B obtained in Reference Example 2 were added 0.6 ml of ethylene glycol and 0.02 g (0.4 mmol) of urea in an argon stream, followed by stirring at 150°C for 5.3 hours. Ethanol was added to the reaction mixture at room temperature, and the solid separated out therefrom was collected by filtration and dried *in vacuo* to give 0.08 g (73%) of Compound 23 as a yellow solid.

Melting Point: 285 - 287 °C

NMR ($CDCl_3$, δ, ppm) 3.94 (s, 3H), 4.29-4.32 (m, 2H), 4.37-4.40 (m, 2H), 6.62 (d, J = 8.6 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 7.27 (br s, 1H), 7.84-7.88 (br t, 2H), 8.04 (s, 1H).

MASS(m/z) 311(M^+).

Elemental analysis: $C_{17}H_{13}NO_5$



Found (%) C: 65.49, H: 4.25, N: 4.22

Calcd. (%) C: 65.59, H: 4.21, N: 4.50

Reference Example 1. (8-Methoxy-1,4-benzodioxan-5-yl)boric acid (Compound A)

To 7.4 g (30 mmol) of 5-bromo-8-methoxy-1,4-benzodioxane was added 74 ml of THF to dissolve it, and after cooling the mixture to -78°C, 23 ml (35 mmol) of a 1.54 mol/liter solution of n-butyl lithium in hexane was added dropwise, followed by stirring at -78°C for 0.5 hour.

To this reaction mixture was added a solution of 4.8 ml (42 mmol) of trimethyl borate in 15 ml of THF at -78°C, and the mixture was stirred for 1.7 hours, followed by stirring for another 1.8 hours at room temperature. Hydrochloric acid was added thereto to adjust the mixture to pH 1, the mixture was extracted with ethyl acetate, and the extract was washed with water and brine and dried over magnesium sulfate. The solid was filtered off, and the solvent was evaporated *in vacuo* from the resulting solution, followed by recrystallization from toluene to give 4.35 g (68%) of Compound A as a milky white solid.

Melting Point: > 300 °C

^{1}H-NMR ($CDCl_3$, δ, ppm) 3.91 (s, 3H), 4.34-4.41 (m, 4H), 5.73 (s, 2H), 6.59 (d, J = 8 Hz, 1H), 7.37 (d, J = 8 Hz, 1H).

MASS (m/z) 210 (M^+).

Reference Example 2. 4-(8-Methoxy-1,4-benzodioxan-5-yl)phthalic acid (Compound B)

To 0.69 g (1.8 mmol) of diethyl 4-(8-methoxy-1,4-benzodioxan-5-yl)phthalate obtained by treating 0.70 g (3.3

mmol) of Compound A obtained in Reference Example 1 and 1.00 g (3.3 mmol) of known diethyl 4-bromophthalate by the same reaction as in Example 17 were added 7.0 ml of ethanol and 1.4 ml of a 6 mol/liter aqueous solution of potassium hydroxide, the mixture was stirred at room temperature for 2 hours, and ethanol was evaporated *in vacuo*. Water was added to the resulting solution, the mixture was adjusted to pH 2 with a 6 mol/liter hydrochloric acid, and the crystals separated out therefrom were collected by filtration and dried *in vacuo* to give 0.55 g (94%) of Compound B as a white solid.

Melting Point: 192 - 196 °C

NMR (DMSO-d_6, δ, ppm) 3.79 (s, 3H), 4.26 (s, 4H), 4.37-4.40 (m, 2H), 6.69 (d, J ≒ 8.6 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 7.63-7.72 (m, 3H), 13.07 (br s, 1H).

MASS(m/e) 312(M^+-18).

Reference Example 3. Ethyl 2-acetoxymethyl-4-bromobenzoate (Compound C)

(Step A) Ethyl 4-bromo-2-bromomethylbenzoate (Compound Ca)

To 10.0 g (41 mmol) of ethyl 4-bromo-2-methylbenzoate were added 300 ml of α,α,α-trifluorotoluene, 7.54 g (42 mmol) of N-bromosuccinimide and 2.0 g (12 mmol) of azobisisobutyronitrile, followed by stirring at 80°C for 5.5 hours. Water was added to the reaction mixture for partition, and the organic layer was washed with water and brine and dried over magnesium sulfate. The solid was filtered off, the filtrate was concentrated *in vacuo*, and the concentrate was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 20/1), followed by recrystallization

from hexane to give 4.07 g (31%) of Compound Ca as a white solid.

Melting Point: 56.0 - 57.0 °C

NMR ($CDCl_3$, δ, ppm) 1.42 (t, J = 7.1 Hz, 3H), 4.40 (q, J = 7.1Hz, 2H), 4.89 (s, 2H), 7.50 (dd, J = 2.0, 8.4 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H).

MASS(m/e) 300(M^+).

(Step B) Compound C

To 1.0 g (3.2 mmol) of Compound Ca were added 10 ml of acetic acid and 4.0 g (49 mmol) of sodium acetate, followed by stirring at 120°C for 0.5 hour. A saturated aqueous solution of sodium bicarbonate was added to the reaction mixture so that acetic acid was neutralized, and then ethyl acetate was added thereto for partition. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate and then with brine and dried over magnesium sulfate. The solid was filtered off, the filtrate was concentrated *in vacuo*, and the concentrate was purified by silica gel column chromatography (eluted with hexane/ethyl acetate = 25/1) to give 0.69 g (71%) of Compound C as a white solid.

Melting Point: 51.5 - 52.5 °C

NMR ($CDCl_3$, δ, ppm) 1.39 (t, J = 7.1 Hz, 3H), 2.17 (s, 3H), 4.36 (q, J = 7.1 Hz, 2H), 5.50 (s, 2H), 7.51 (dd, J = 2.0, 8.4 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H).

MASS(m/e) 300(M^+).

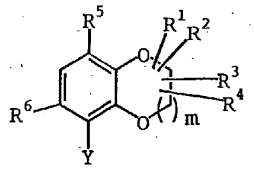
Industrial Applicability

According to the present invention, there can be provided oxygen-containing heterocyclic compounds which have phosphodiesterase (PDE) IV inhibitory activity and which are

useful as a therapeutic agent for inflammatory allergic diseases such as bronchial asthma, allergic rhinitis, atopic dermatitis and nephritis; autoimmune diseases such as chronic obstructive pulmonary lung disease, rheumatism, multiple sclerosis, Crohn's disease, psoriasis and systemic lupus erythematosus; diseases of the central nervous system such as depression, amnesia and dementia; organopathy associated with ischemic reflux caused by cardiac failure, shock and cerebrovascular disease, and the like; insulin-resistant diabetes; wounds; AIDS; osteoporosis; urinary stone; urinary incontinence and the like; or as a recuperative agent for fatigue, malaise and the like.

The claims defining the invention are as follows:

1. An oxygen-containing heterocyclic compound represented by the following formula (I):



(I)

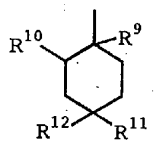
wherein m represents an integer of 0 to 4;
R^1, R^2, R^3 and R^4 independently represent a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, polycycloalkyl, substituted or unsubstituted lower alkoxycarbonyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted lower alkanoyloxy, cyano, hydroxy, substituted or unsubstituted lower alkoxy, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic hetecyclic group, substituted or unsubstituted aralkyl, or -$CONR^7R^8$ (wherein R^7 and R^8 independently represent a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group or substituted or unsubstituted aralkyl, or R^7 and R^8 are combined to represent a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom); two groups present on the same carbon atom among R^1, R^2, R^3 and R^4 are combined to represent a saturated

spiro carbon ring together with the said carbon atom; two groups present on the adjacent carbon atoms among R^1, R^2, R^3 and R^4 are combined to represent a saturated carbon ring together with the said adjacent two carbon atoms; two groups present on the adjacent carbon atoms among R^1, R^2, R^3 and R^4 are combined to represent a single bond (forming a double bond together with the already-existing bond);

R^5 represents hydroxy, or substituted or unsubstituted lower alkoxy;

R^6 represents a hydrogen atom or halogen;

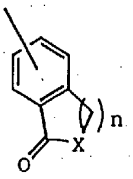
Y represents the following formula (II):



(II)

wherein R^9 represents cyano, ethynyl or carbamoyl, and R^{10} represents a hydrogen atom, or R^9 and R^{10} are combined to represent a single bond (forming a double bond together with the already-existing bond), R^{11} represents hydroxy, formyl, substituted or unsubstituted lower alkoxy, substituted or unsubstituted tetrazolyl, $-NR^{13}R^{14}$ (wherein R^{13} and R^{14} independently represent a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group or substituted or unsubstituted aralkyl, or R^{13} and R^{14} are combined to represent a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom), $-COOR^{15}$ (wherein R^{15} represents a hydrogen atom, or substituted or unsubstituted lower alkyl), $-CONR^{16}R^{17}$ (wherein R^{16} and R^{17} independently represent a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, or substituted or unsubstituted aralkyl, or R^{16} and R^{17} are combined to represent a substituted or

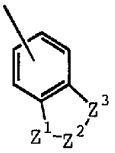
unsubstituted heterocyclic group together with the adjacent nitrogen atom), or $-CH_2COOR^{18}$ (wherein R^{18} represents a hydrogen atom or substituted or unsubstituted lower alkyl), R^{12} represents a hydrogen atom, or substituted or unsubstituted lower alkoxy, or R^{11} and R^{12} are combined together to represent $-OCH_2(CH_2)_pO-$ (wherein p represents an integer of 1 to 3), $-CR^{19}R^{20}O-$ (wherein R^{19} and R^{20} independently represent a hydrogen atom or cyano), $=CHOR^{21}$ (wherein R^{21} represents substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted aralkyl), $=CHCOOR^{22}$ (wherein R^{22} represents a hydrogen atom, or substituted or unsubstituted lower alkyl) or =O; the following formula (III):



(III)

wherein n represents an integer of 0 to 4, X represents CH_2, NR^{23} (wherein R^{23} represents a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, or substituted or unsubstituted aralkyl) or

or O; the following formula (IV):



(IV)

wherein Z^1-Z^2-Z^3 represents O-N=CH, S-N=CH, O-CH=CH, S-CH=CH, N=CH-S, N=CH-O, C(=O)-NH-NH, C(=O)-N=N, C(=O)-CH_2-C(=O), C(=O)-NR^a-C(=O) (wherein R^a represents a hydrogen atom, substituted or unsubstituted lower alkyl, or substituted or unsubstituted aralkyl) or CH_2-NR^b-C(=O) (wherein R^b represents a hydrogen atom, substituted or unsubstituted lower alkyl, or substituted or unsubstituted aryl); 2,1,3-benzothiadiazolyl; or 2,1,3-benzofurazanyl; or

a pharmaceutically acceptable salt thereof.

2. The oxygen-containing heterocyclic compound according to Claim 1, wherein Y is the formula (II) or a pharmaceutically acceptable salt thereof.

3. The oxygen-containing heterocyclic compound according to Claim 2, wherein R^9 is cyano; or a pharmaceutically acceptable salt thereof.

4. The oxygen-containing heterocyclic compound according to any one of Claims 1 to 3, wherein m is 0 or 1; or a pharmaceutically acceptable salt thereof.

5. The oxygen-containing heterocyclic compound according to any one of Claims 1 to 4, wherein all of R^1, R^2, R^3 and R^4 are hydrogen atoms, or one group among R^1, R^2, R^3 and R^4 is substituted or unsubstituted lower alkyl while other three groups are hydrogen atoms; or a pharmaceutically acceptable salt thereof.

6. The oxygen-containing heterocyclic compound according to any one of claims 1 to 5, wherein; R^{11} represents carboxy or hydroxy, or R^{11} and R^{12} are combined together to represent =O; or a pharmaceutically acceptable salt thereof.

7. The oxygen-containing heterocyclic compound according to claim 1, wherein Y is the formula (III); or a pharmaceutically acceptable salt thereof.

8. The oxygen-containing heterocyclic compound according to claim 7, wherein n is 1; or a pharmaceutically acceptable salt thereof.

9. The oxygen-containing heterocyclic compound according to claim 7 or claim 8, wherein X is CH_2; or a pharmaceutically acceptable salt thereof.

10. An oxygen-containing heterocyclic compound having phosphodiesterase (PDE) IV inhibitory activity, said compound substantially as hereinbefore described with reference to any one of the examples.

11. A phosphodiesterase (PDE) IV inhibitor, which comprises at least one oxygen-containing heterocyclic compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition, which comprises at least one oxygen-containing heterocyclic compound according to any one of claims 1 to 10, an inhibitor according to claim 11 or a pharmaceutically acceptable salt thereof.

13. A method for the treatment or prophylaxis of a condition which is amenable to inhibition of phosphodiesterase (PDE) IV, in a mammal requiring said treatment or prophylaxis, which method comprises administering to said mammal an effective amount of at least one compound according to any one of claims 1 to 10, an inhibitor according to claim 11 or a composition according to claim 12.

14. A compound according to any one of claims 1 to 10, an inhibitor according to claim 11 or a composition or formulation according to claim 12 when used in the treatment or prophylaxis of a condition which is amenable to inhibition of phosphodiesterase (PDE) IV.

15. A compound according to any one of claims 1 to 10, an inhibitor according to claim 11 or a composition or formulation according to claim 12 for use in the treatment or prophylaxis of a condition which is amenable to inhibition of phosphodiesterase (PDE) IV.

16. Use of a compound according to any one of claims 1 to 10 or an inhibitor according to claim 11 for the manufacture of a medicament for the treatment or prophylaxis of a condition which is amenable to inhibition of phosphodiesterase (PDE) IV.

17. The method, compound, inhibitor, composition, or use according to any one of claims 13 to 16, wherein the condition is selected from the group consisting of inflammatory allergic diseases such as bronchial asthma, allergic rhinitis, atopic dermatitis and nephritis; autoimmune diseases such as chronic obstructive pulmonary lung disease, rheumatism, multiple sclerosis, Crohn's disease, psoriasis and systemic lupus erythematosus; disease of the central nervous system such as depression, amnesia and dementia; organopathy associated with ischemic reflux caused by cardiac failure, shock and cerebrovascular disease, and the like; insulin-resistant diabetes; wounds; AIDS; osteoporosis; urinary stone; urinary incontinence and the like; and as a recuperative agent for fatigue, malaise and the like.

18. A process for preparing an oxygen-containing heterocyclic compound according to any one of claims 1 to 10, said process substantially as hereinbefore described with reference to any one of the examples.

Dated 31 October 2002

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