INSTRUCTIONS

(a) If Convention application insert "Convention"

AMENDED

AUSTRALIAN PATENT OFFICE

(a) CONVENTION

AUSTRALIA 633539

Patents Act

(b) Delete one

APPLICATION FOR A (b) STANDARD/~~PETTY~~ PATENT

(c) Insert FULL name(s) of applicant(s)

~~I~~/We (c) TOYAMA CHEMICAL CO., LTD.

(d) Insert FULL address(es) of applicant(s)

of (d) 2-5, 3-chome, Nishishinjuku, Shinjuku-ku, Tokyo, Japan

(e) Delete one

hereby apply for the grant of a (e) Standard/~~Petty~~ Patent for an invention entitled

(f) Insert TITLE of invention

(f) 1,2-ETHANEDIOL DERIVATIVE AND SALT THEREOF, PROCESS FOR PRODUCING THE SAME, AND CEREBRAL FUNCTION-IMPROVING AGENT COMPRISING THE SAME

(g) Insert "complete" or "provisional" or "petty patent"

which is described in the accompanying (g) complete specification.

(Note: The following applies only to Convention applications)

Details of basic application(s)

(h) Insert number, country and filing date for the/or each basic application

	Application No.	Country	Filing Date
(h)	01-032714	Japan	14 February 1989
	01-068953	Japan	20 March 1989
	01-106107	Japan	26 April 1989
	02-24501	Japan	5 February 1990
	02-24502	Japan	5 February 1990
	02-24503	Japan	5 February 1990

Address for Service: PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia 3000

(i) Insert date of signing

Dated (i) 26 March 1990

(j) Signature of applicant(s) (For body corporate see headnote*)

(k) Corporate seal if any

(k)

(j) PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
TOYAMA CHEMICAL CO., LTD.

Note: No legalization or other witness required

PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia

P17/2/83

AUSTRALIA

Patents Act

DECLARATION FOR A PATENT APPLICATION

▼ INSTRUCTIONS

(a) Insert "Convention" if applicable

(b) Insert FULL name(s) of applicant(s)

In support of the (a) convention application made by (b)

TOYAMA CHEMICAL CO., LTD.,

(c) Insert "of addition" if applicable

(d) Insert TITLE of invention

(hereinafter called "applicant(s)" for a patent (c) for an invention entitled (d) "1,2-ETHANEDIOL DERIVATIVE AND SALT THEREOF, PROCESS FOR PRODUCING THE SAME, AND CEREBRAL FUNCTION-IMPROVING AGENT COMPRISING THE SAME"

(e) Insert FULL name(s) AND address(es) of declarant(s) (See headnote*)

I/~~We~~ (e) Katsuhiko NAKANO, c/o TOYAMA CHEMICAL CO., LTD., of 2-5, 3-chome, Nishishinjuku, Shinjuku-ku, Tokyo, Japan,

do solemnly and sincerely declare as follows:

1. ~~I am/We are the applicant(s).~~

(or, in the case of an application by a body corporate)

1. I am/~~We are~~ authorized to make this declaration on behalf of the applicant(s).
2. ~~I am/We are the actual inventor(s) of the invention.~~

(or, where the applicant(s) is/are not the actual inventor(s))

(f) Insert FULL name(s) AND address(es) of actual inventor(s)

2. (f)

Please see reverse side.

(g) Recite how applicant(s) derive(s) title from actual inventor(s) (See headnote**)

~~is~~/are the actual inventor(s) of the invention and the facts upon which the applicant(s) is/~~are~~ entitled to make the application are as follows:

(g)

The applicant is the assignee of the invention from the inventors.

(Note: Paragraphs 3 and 4 apply only to Convention applications)

(h) Insert country, filing date, and basic applicant(s) for the/or EACH basic application

3. The basic application(s) for patent or similar protection on which the application is based ~~is~~/are identified by **country, filing date, and basic applicant(s)** as follows:

(h)
in Japan on February 14, 1989 by TOYAMA CHEMICAL CO., LTD.
in Japan on March 20, 1989 by TOYAMA CHEMICAL CO., LTD.
in Japan on April 26, 1989 by TOYAMA CHEMICAL CO., LTD.
in Japan on February 5, 1990 by TOYAMA CHEMICAL CO., LTD.
in Japan on February 5, 1990 by TOYAMA CHEMICAL CO., LTD.
in Japan on February 5, 1990 by TOYAMA CHEMICAL CO., LTD.

4. The basic application(s) referred to in paragraph 3 hereof ~~was~~/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

(k) Insert PLACE of signing

(l) Insert DATE of signing

(m) Signature(s) of declarant(s)

Note: No legalization or other witness required

Declared at (k) Tokyo, Japan

Dated (l) March 22, 1990

(m) TOYAMA CHEMICAL CO., LTD.

Katsuhiko Nakano

President, Katsuhiko NAKANO

To: The Commissioner of Patents

P18/7/78

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia

Satoshi ONO, of 2-5, Nakajima-3-chome, Toyama-shi, Japan.

Tetsuo YAMAFUJI, of 1-3, Yoshitani, Fuchumachi, Nei-gun, Toyama-ken, Japan.

Hisaaki CHAKI, of 455-1, Oharaya, Oyamamachi, Kaminiikawa-gun, Toyama-ken, Japan.

Mutsuko MAEKAWA, of 65-5, Shimokumano, Toyama-shi, Japan.

Yozo TODO, of 2091-12, Ishisaka, Toyama-shi, Japan.

Hirokazu NARITA, of 6-40, Okudahonmachi, Toyama-shi, Japan.

AU9049392

(12) PATENT ABRIDGMENT (11) Document No. AU-B-49392/90
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 633539

(54) Title
1,2 ETHANEDIOL DERIVATIVE AND SALT THEREOF, PROCESS FOR PRODUCING THE SAME, AND CEREBRAL FUNCTION-IMPROVING AGENT COMPRISING THE SAME

International Patent Classification(s)

(51)[5]	C07C 217/10	A61K 031/13	A61K 031/14	A61K 031/34
	A61K 031/38	A61K 031/40	A61K 031/44	A61K 031/54
	C07C 201/10	C07C 205/34	C07C 213/00	C07C 227/16
	C07C 229/10	C07C 269/00	C07C 271/42	C07C 311/24
	C07C 311/29	C07C 319/20	C07C 323/19	C07D 207/08
	C07D 207/14	C07D 207/27	C07D 207/28	C07D 207/48
	C07D 209/08	C07D 209/34	C07D 211/22	C07D 211/42
	C07D 211/46	C07D 211/70	C07D 211/82	C07D 213/30
	C07D 213/64	C07D 213/74	C07D 213/81	C07D 215/06
	C07D 215/14	C07D 215/22	C07D 217/04	C07D 233/60
	C07D 233/64	C07D 235/06	C07D 239/42	C07D 241/04
	C07D 241/06	C07D 265/30	C07D 277/24	C07D 277/64
	C07D 279/12	C07D 307/42	C07D 307/79	C07D 319/18
	C07D 333/16	C07D 333/44	C07D 333/54	C07D 333/56
	C07D 405/12	C07D 409/12	C07D 413/12	C07D 453/02
	A61K 031/135	A61K 031/335	A61K 031/415	A61K 031/425
	A61K 031/445	A61K 031/495	A61K 031/535	C07D 295/088

(21) Application No. : 49392/90 (22) Application Date : 13.02.90

(30) Priority Data

(31) Number	(32) Date	(33) Country
1-032714	14.02.89	JP JAPAN
1-068958	20.03.89	JP JAPAN
1-106187	26.04.89	JP JAPAN
2-24501	05.02.90	JP JAPAN
2-24502	05.02.90	JP JAPAN
2-24503	05.02.90	JP JAPAN

(43) Publication Date : 23.08.90

(44) Publication Date of Accepted Application : 04.02.93

(71) Applicant(s)
TOYAMA CHEMICAL CO., LTD.

(72) Inventor(s)
SATOSHI ONO; TETSUO YAMAFUJI; HISAAKI CHAKI; MUTSUKO MAEKAWA; YOZO TODO; HIROKAZU NARITA

(74) Attorney or Agent
PHILLIPS ORMONDE & FITZPATRICK , 367 Collins Street, MELBOURNE VIC 3000

(56) Prior Art Documents
AU 17098/88 C07D 401/14
AU 10983/88 C07D 207/08

(57)

This invention relates to a 1,2-ethanediol derivative and a salt thereof, a process for producing the same, and a cerebral function-improving agent comprising the same. The cerebral function-improving agent of this invention is useful for treating cerebrovascular dementia, senile dementia, Alzheimer's dementia, sequelae of ischemic encephalopathy and

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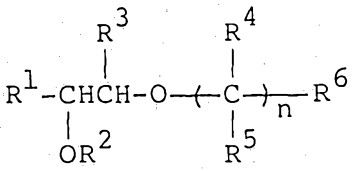
cerebral apoplexy.

Claim

1. A 1,2-ethanediol derivative represented by the following general formula or a salt thereof:

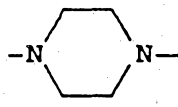


wherein R^1 represents a substituted or unsubstituted phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl or heterocyclic group; R^2 represents a hydrogen atom, a lower alkyl group or a hydroxyl-protecting group; R^3 represents a hydrogen atom or a lower alkyl group; nR^4's and nR^5's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups; R^6 represents an ammonio group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrrolyl, pyrrolidinyl, piperidyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, tetrahydropyridyl, pyrimidinyl, morpholinyl, thiomorpholinyl, quinolyl, quinolizinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinuclidinyl, thiazolyl, tetrazolyl, thiadiazolyl, pyrrolinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, purinyl and indazolyl groups; and n represents 0 or an integer of 1 to 6, wherein the substituent on R^1 is selected from the group consisting of halogen atoms, substituted or unsubstituted amino,

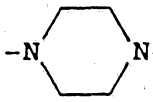
.../3

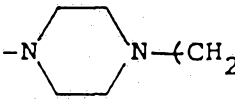
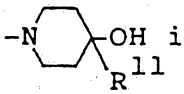
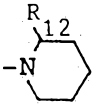
lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino and heterocyclic groups, ~~protected amino groups,~~ protected or unprotected hydroxyl groups, nitro group, oxo group and lower alkylenedioxy groups; the substituted lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino or heterocyclic group as the substituent of R^1 and the substituted nitrogen-containing heterocyclic group as R^6 have each at least one substituent selected from the group consisting of halogen atoms, protected or unprotected hydroxyl groups, protected or unprotected amino groups, protected or unprotected carboxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by a protected or unprotected hydroxyl group, unsubstituted or halogen-substituted aryl groups, unsubstituted or halogen-substituted aroyl groups, unsubstituted lower alkoxy groups, lower alkoxy groups substituted by a lower alkoxy group, lower acyl groups, ar-lower alkyl groups, ar-lower alkenyl groups, heterocyclic groups, heterocyclic-CO- groups, oxo group, lower alkylsulfonyl groups and arylsulfonyl groups; and the substituted amino group as the substituent of R^1 and the substituted amino group as R^6 have each at least one substituent selected from the group consisting of protected or unprotected hydroxyl groups, unsubstituted lower alkyl groups, lower alkyl group substituted by a protected or

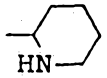
unprotected carboxyl or hydroxyl group, cycloalkyl groups, aryl groups, lower acyl groups, ar-lower alkyl groups, heterocyclic groups, unsubstituted or oxo-substituted heterocyclic-CO- groups, adamantyl group, lower alkylsulfonyl groups and aryl-sulfonyl groups, provided that there are excluded the compounds in which R^1 is a phenyl group which may optionally be substituted by the halogen atom or the lower alkyl, lower alkylenedioxy, lower alkoxy or protected or unprotected hydroxyl group and R^6 is $-NR^7R^8$ in which R^7 represents an ar-lower alkyl or heterocyclic group and R^8 represents a hydrogen atom or a lower alkyl group, or R^7 and R^8 form, when taken with the N atom,


in which R^9 represents an aryl or

heterocyclic group and i represents 0 or an integer of 1 to 3,


in which R^9 has the same meaning as defined above,


in which R^8 and i have the same meanings as defined above, 
in which R^{11} represents an aryl group, 
in which R^{12} represents a carboxyl group or a lower alkoxycarbonyl group or 
in which R^{12} has the same meaning as defined above,

and the compounds in which R^1 represents an unsubstituted or lower alkyl-substituted phenyl group and R^6 represents a di-lower alkylamino group,  ,  or  and the compound in which R^1 represents an unsubstituted phenyl group and R^6 represents  ;

all the above heterocyclic groups being selected from the

...5

group consisting of the nitrogen-containing heterocyclic groups mentioned in the definition of R^6 and furyl, thienyl, benzothienyl, pyranyl, isobenzofuranyl, oxazolyl, benzofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinoxalyl, dihydroquinoxalyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzopyrrolyl, 2,3-dihydro-4H-1-thianaphthyl, 2,3-dihydrobenzofuranyl, benzo[b]dioxanyl, imidazo[2,3-a]pyridyl, benzo[b]piperazinyl, chromenyl, isothiazolyl, isoxazolyl, oxadiazolyl, pyridazinyl, isoindolyl and isoquinolyl groups.

AUSTRALIA

Patents Act

633539

COMPLETE SPECIFICATION
(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

Applicant(s):

Toyama Chemical Co., Ltd.
2-5, 3-chome,, Nishishinjuku, Shinjuku-ku, Tokyo, JAPAN

Address for Service is:

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne 3000 AUSTRALIA

Complete Specification for the invention entitled:

1,2-ETHANEDIOL DERIVATIVE AND SALT THEREOF, PROCESS FOR PRODUCING THE SAME, AND CEREBRAL FUNCTION-IM PROVING AGENT COMPRISING THE SAME

Our Ref : 163565
POF Code: 1096/46850

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

6006

This invention relates to a 1,2-ethanediol derivative and a salt thereof, a process for producing the same, and a cerebral function-improving agent comprising the same. The cerebral function-improving agent of this invention is useful for treating cerebrovascular dementia, senile dementia, Alzheimer's dementia, sequelae of ischemic encephalopathy and cerebral apoplexy.

As 1,2-ethanediol derivatives, there are known, for example, those described in U.S. Patent No. 2,928,845; J. Pharm. Sci., vol. 50, pp. 769-771 (1961); Farmaco. Ed. Sci., vol. 19, pp. 1056-1065 (1964); etc.

These compounds are in use as a local anesthetic. However, nothing is known as to their use as a cerebral function-improving agent, an antiamnesic agent or a nootropic agent.

WO No. 88/8424 describes that 1,2-ethanediol derivatives can be used for the remedy of Alzheimer's disease and other degenerative neurological disorders. However, no specific description or example of these derivatives is given in the application.

Drugs such as cerebral metabolic enhancers, cerebrovasodilators and the like are currently in use for the remedy of various dementias, particularly dementia of Alzheimer's type and cerebrovascular

dementia.

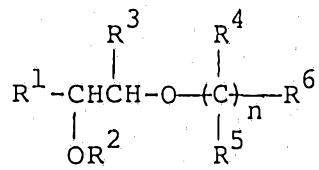
However, no cerebral function-improving agent has been found as yet which is useful for treating cerebrovascular dementia, senile dementia, Alzheimer's dementia, sequelae of ischemic encephalopathy and cerebral apoplexy.

An object of this invention is to provide a novel 1,2-ethanediol derivative and a salt thereof.

Another object of this invention is to provide a process for producing a novel 1,2-ethanediol derivative and a salt thereof.

Still another object of this invention is to provide a novel cerebral function-improving agent which is useful for treating cerebrovascular dementia, senile dementia, Alzheimer's dementia, sequelae of ischemic encephalopathy and cerebral apoplexy and yet has little side effect.

The present inventors have made study in order to solve the above-mentioned problems. As a result, it has been found that a 1,2-ethanediol derivative represented by the following general formula [I] or a salt thereof has an excellent antiamnesic activity and an excellent antihypoxic activity and is very useful as a cerebral function-improving agent:

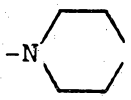


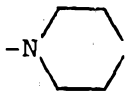
[I]

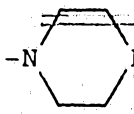
wherein R^1 represents a substituted or unsubstituted phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl or heterocyclic group; R^2 represents a hydrogen atom, a lower alkyl group or a hydroxyl-protecting group; R^3 represents a hydrogen atom or a lower alkyl group; nR^4's and nR^5's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups; R^6 represents an ammonio group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrrolyl, pyrrolidinyl, piperidyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, tetrahydropyridyl, pyrimidinyl, morpholinyl, thiomorpholinyl, quinolyl, quinolizinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinuclidinyl, thiazolyl, tetrazolyl, thiadiazolyl, pyrrolinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, purinyl and indazolyl groups; and n represents 0 or an integer of 1 to 6; wherein the substituent on R^1 is selected from the group consisting of halogen atoms, substituted or unsubstituted amino, lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkyl-sulfonylamino, arylsulfonylamino and heterocyclic groups, ~~and protected amino groups,~~ protected or unprotected hydroxyl groups, nitro group, oxo group and lower

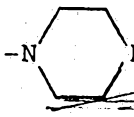
alkylenedioxy groups; the substituted lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino or heterocyclic group as the substituent of R^1 and the substituted nitrogen-containing heterocyclic group as R^6 have each at least one substituent selected from the group consisting of halogen atoms, protected or unprotected hydroxyl groups, protected or unprotected amino groups, protected or unprotected carboxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by a protected or unprotected hydroxyl group, unsubstituted or halogen-substituted aryl groups, unsubstituted or halogen-substituted aroyl groups, unsubstituted lower alkoxy groups, lower alkoxy groups substituted by a lower alkoxy group, lower acyl groups, ar-lower alkyl groups, ar-lower alkenyl groups, heterocyclic groups, heterocyclic-CO- groups, oxo group, lower alkylsulfonyl groups and arylsulfonyl groups; and the substituted amino group as the substituent of R^1 and the substituted amino group as R^6 have each at least one substituent selected from the group consisting of protected or unprotected hydroxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by a protected or unprotected carboxyl or hydroxyl group, cycloalkyl groups, aryl groups, lower acyl groups, ar-lower alkyl groups, heterocyclic groups, unsubstituted

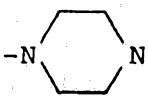
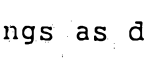
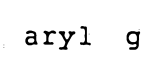
or oxo-substituted heterocyclic-CO- groups, adamantyl group, lower alkylsulfonyl groups and arylsulfonyl groups, provided that there are excluded the compounds in which R^1 is a phenyl group which may optionally be substituted by the halogen atom or the lower alkyl, lower alkylenedioxy, lower alkoxy or protected or unprotected hydroxyl group and R^6 is $-NR^7R^8$ in which R^7 represents an ar-lower alkyl or heterocyclic group and R^8 represents a hydrogen atom or a lower alkyl group, or R^7 and R^8 form, when taken with the N atom,

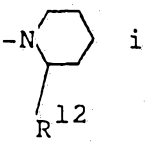

in which R^9 represents an aryl or heterocyclic group and i represents 0 or an integer of 1 to 3,

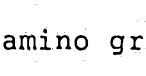

in which R^9 has the same meaning as defined above,

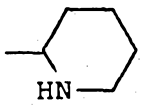

in which R^{10} represents a heterocyclic group,


in which R^{10} has the same meaning as defined above,


in which R^8 and i have the same meanings as defined above,  in which R^{11} represents an aryl group,  in which R^{12} represents a carboxyl group or a lower alkoxycarbonyl group or


in which R^{12} has the same meaning as defined above

and the compounds in which R^1 represents an unsubstituted or lower alkyl-substituted phenyl group and R^6 represents a di-lower alkylamino group,  , or and the

compound in which R^1 represents an unsubstituted phenyl group and R^6 represents  ;

all the above heterocyclic groups being selected from the group consisting of the nitrogen-containing heterocyclic

groups mentioned in the definition of R^6 and furyl, thienyl, benzothienyl, pyranyl, isobenzofuranyl, oxazolyl, benzofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinoxalyl, dihydroquinoxalyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzopyrrolyl, 2,3-dihydro-4H-1-thianaphthyl, 2,3-dihydrobenzofuranyl, benzo[b]dioxanyl, imidazo-[2,3-a]pyridyl, benzo[b]piperazinyl, chromenyl, isothiazolyl, isoxazolyl, oxadiazolyl, pyridazinyl, isoindolyl and isoquinolyl groups.

Incidentally, the cerebral function-improving agent mentioned herein refers to a cerebral function-improving agent having not only effects possessed by conventional cerebral function-improving agents, for example, sequelae of ischemic encephalopathy and cerebral apoplexy but also therapeutic or prophylactic effects for amnesia and dementias (e.g. cerebrovascular dementia, senile dementia and Alzheimer's dementia).

In the present specification, the following terms have the following definitions unless otherwise specified.

The term "halogen atom" means, for example, a fluorine atom, a chlorine atom, a bromine atom and an iodine atom; the term "lower alkyl group" means C_{1-6} alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, hexyl and the like; the term "lower alkoxy group" means C_{1-6} alkyl-O- groups; the term "lower alkylthio group" means C_{1-6} alkyl-S- groups; the term "lower alkenyl group" means C_{2-6}alkenyl

groups such as vinyl, propenyl, butenyl, pentenyl, hexenyl and the like; the term "lower alkenyloxy group" means C_{2-6}alkenyl-O- groups; the term "cycloalkyl group" means C_{3-6}cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like; the term "aryl group" means phenyl, naphthyl, indanyl and indenyl groups; the term "aryloxy group" means aryl-O- groups; the term "ar-lower alkyl group" means ar-C_{1-4} alkyl groups such as benzyl, diphenylmethyl, trityl, phenethyl and the like; the term "ar-lower alkoxy group" means ar-C_{1-4}alkyl-O- groups; the term "ar-lower alkylthio group" means aryl-C_{1-4}alkyl-S- groups; the term "lower alkylenedioxy group" means C_{1-4}alkylenedioxy groups such as methylenedioxy, ethylenedioxy and the like; the term "lower acyl group" means C_{1-6}acyl groups such as formyl, acetyl, butyryl and the like; the term "aroyl group" means aryl-CC- groups; the term "lower alkylsulfonyl group" means C_{1-6}alkyl-SO_2- groups; the term "arylsulfonyl group" means aryl-SO_2- groups; ther term "ar-lower alkylsulfonyl group" means aryl-C_{1-6}alkyl-SO_2- groups; the term "lower alkylsulfonyloxy group" means C_{1-6}alkyl-SO_2-O- groups; the term "aryl-sulfonyloxy group" means aryl-SO_2-O- groups; the term "lower alkylsulfonylamino group" means C_{1-6}alkyl-SO_2-NH- groups; the term "arylsulfonylamino group" means aryl-SO_2NH- groups; the term "di-lower alkylamino group" means di-C_{1-6}alkyl-NH- groups and the term "ammonio group" means tri-lower alkylammonio groups such as

trimethylammonio, triethylammonio; the term "lower alkoxycarbonyl group" means C_{1-6}alkyl-O-CO- groups and the like.

The protective groups for hydroxyl group, carboxyl group and amino group include those conventional protective groups for hydroxyl group, carboxyl group and amino group which are described in Protective Groups in Organic Synthesis ~~by~~ (Theodra W. Green, 1981, John Wiley & Sons, Inc). In particular, the protective group for hydroxyl group specifically includes, for example, lower alkyl, lower acyl, tetrahydropyranyl and ar-lower alkyl groups such as substituted or unsubstituted benzyl. ~~or tetrahydropyranyl.~~

The salt of the 1,2-ethanediol derivative represented by the general formula [I] can be any pharmaceutically acceptable salt. It includes, for example, salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and the like; salts with carboxylic acids such as formic acid, acetic acid, oxalic acid, fumaric acid, maleic acid, malic acid, tartaric acid, aspartic acid and the like; salts with sulfonic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalene-sulfonic acid and the like; and salts with alkali metals such as sodium, potassium and the like.

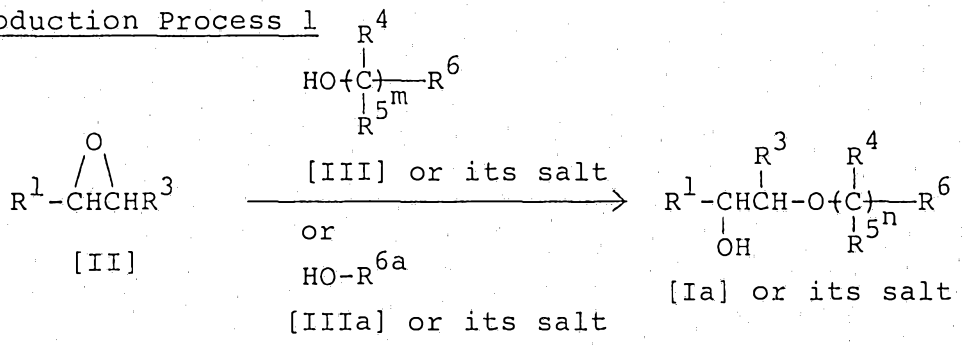
When the 1,2-ethanediol derivative of the general formula [I] or its salt has isomers (e.g. optical isomers, geometrical isomers, tautomers), all of these isomers are included in this invention. Also, the

hydrate, solvate and all crystal forms of the compound of this invention are included in this invention.

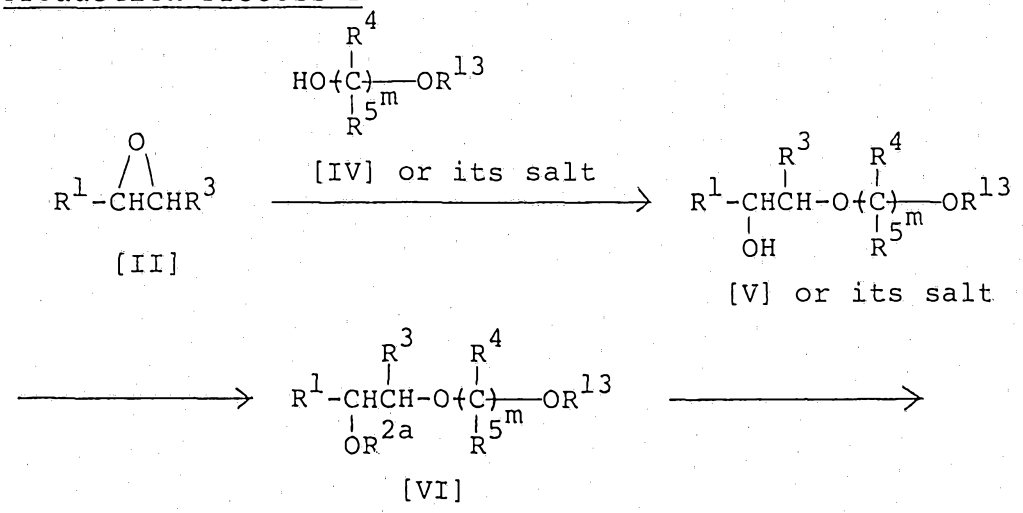
Next, there is described a process for producing a 1,2-ethanediol derivative of the general formula [I] or a salt thereof.

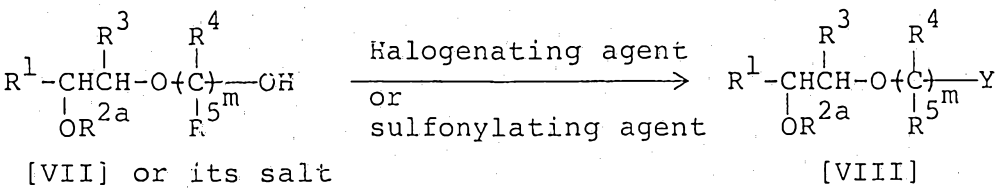
The 1,2-ethanediol derivative of the general formula [I] or its salt can be produced by per se known processes or their appropriate combinations, for example, the following production processes.

Production Process 1



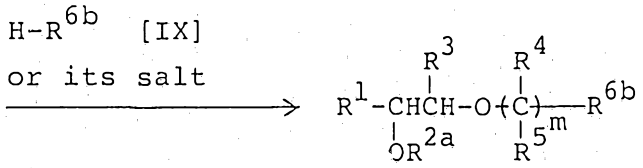
Production Process 2





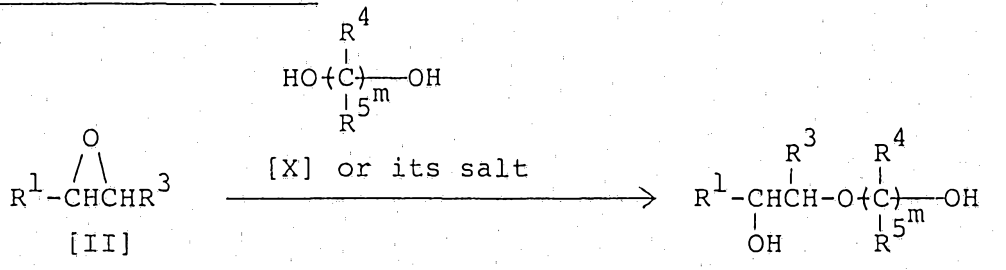
[VII] or its salt

[VIII]



[Ib] or its salt

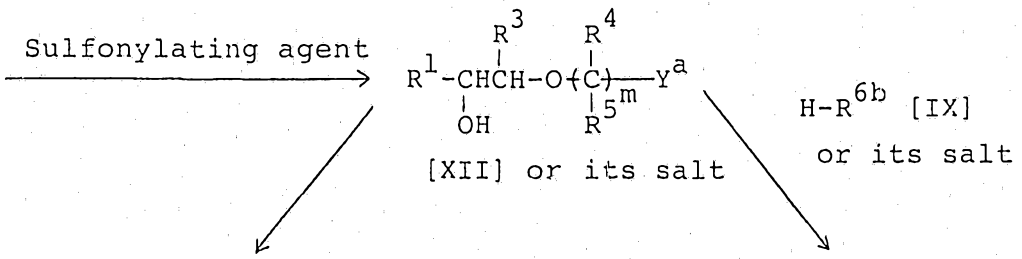
Production Process 3



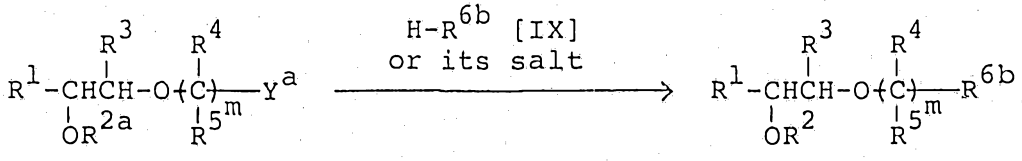
[II]

[X] or its salt

[XI] or its salt



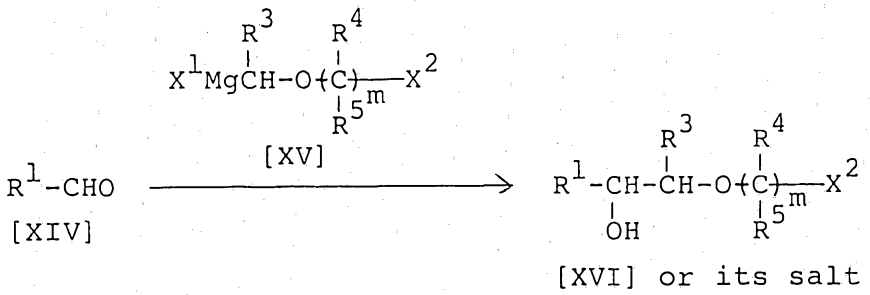
[XII] or its salt



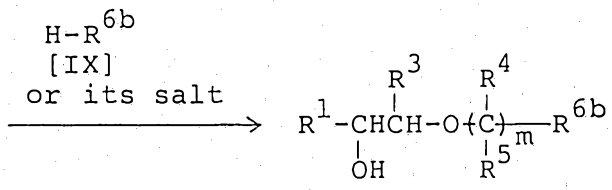
[XIII]

[Ic] or its salt

Production Process 4



[XIV] [XV] [XVI] or its salt



[Id] or its salt

In the above reaction schemes, R^1, R^{2a}, R^3, R^4, R^5, R^6 and n have the same meanings as defined above; R^{2a} represents the same hydroxyl-protecting group as in the definition of R^2; R^{6a} represents the same substituted or unsubstituted nitrogen-containing heterocyclic group as in the definition of R^6, provided that the heterocyclic group has a free valence on a carbon atom forming the heterocyclic ring; R^{6b} represents the same substituted or unsubstituted nitrogen-containing heterocyclic group as in the definition of R^6, provided that the nitrogen-containing heterocyclic group has a free valence on a nitrogen atom forming the heterocyclic ring, or a substituted or unsubstituted amino group; R^{13} represents the same hydroxyl-protecting group as in the definition of R^2; X^1 and X^2, which may be the same or different, represent halogen atoms, Y represents a

removable group such as a halogen atom, a lower alkylsulfonyloxy group, an arylsulfonyloxy group or the like; Y^a represents an arylsulfonyloxy group; and m represents an integer of 1-6.

As the salts of the compounds of the general formulas [III], [IIIa], [IV], [V], [VII], [IX], [X], [XI], [XII], [XVI], [Ia], [Ib], [Ic] and [Id], there can be mentioned the same salts as the salts of the compound of the general formula [I].

Next, each of the above production processes is described.

Production Process 1

A compound of the general formula [II] is reacted with a compound of the general formula [III] or its salt or a compound of the general formula [IIIa] or its salt in the presence or absence of a base to obtain a compound of the general formula [Ia] or its salt.

The solvent to be used in this reaction can be any solvent unless it adversely affects the reaction. There can be mentioned, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; sulfoxides such as dimethylsulfoxide and the like; amides such as N,N-dimethylformamide and the like; and ethers such as tetrahydrofuran, dioxane and the like. These solvents can be used alone or in admixture of two or more. It is also possible to use the compound of the general formula [III] or [IIIa] as the solvent.

As the base to be used optionally, there can be mentioned, for example, ~~soldium~~ sodium hydride, metallic sodium and potassium tert-butoxide.

In the reaction, the compound of the general formula [III] or its salt, or the compound of the general formula [IIIa] or its salt is used in an amount of 1-100 moles, preferably 1-10 moles, per mole of the compound of the general formula [II].

The base as an optional component is used in an amount of 0.01-1.2 moles per mole of the compound of the general formula [II].

This reaction can be effected usually at 20-150°C, preferably 70-90°C, for 1 minutes to 24 hours, preferably 5 minutes to 5 hours.

Production Process 2

(1) A compound of the general formula [II] is reacted with a compound of the general formula [IV] or its salt in the presence or absence of a base to obtain a compound of the general formula [V] or its salt.

This reaction can be effected in the same manner as described in Production Process 1.

The obtained compound of the general formula [V] or its salt may be used in the subsequent reaction without being isolated.

(2) The compound of the general formula [V] or its salt is subjected to conventional reaction for protection of hydroxyl group to obtain a compound of the general formula [VI].

The obtained compound of the general formula [VI] may be used in the subsequent reaction without being isolated.

Then, the compound of the general formula [VI] is subjected to reaction for selective removal of the hydroxyl-protecting group to obtain a compound of the general formula [VII] or its salt.

The obtained compound of the general formula [VII] or its salt may be used in the subsequent reaction without being isolated.

These reactions can be effected according to per se known methods, for example, the method described in Protective Groups in Organic Synthesis [Theodra W. Green (1981), John Wiley & Sons, Inc.] or a method similar thereto.

The combination of the hydroxyl-protecting groups (R^{13} and R^{2a}) to be used in these reactions can be selected appropriately.

(3) The compound of the general formula [VII] or its salt is reacted with a halogenating agent or a sulfonylating agent in a solvent in the presence or absence of a base to obtain a compound of the general formula [VIII].

The solvent to be used in the reaction can be any solvent unless it adversely affects the reaction. There can be mentioned, for example, halogenated hydrocarbons such as methylene chloride, chloroform and the like; ethers such as tetrahydrofuran, dioxane and the like; nitriles such as acetonitrile and the like;

and amides such as N,N-dimethylformamide and the like. These solvents can be used alone or in admixture of two or more.

As the base to be used optionally, there can be mentioned, for example, organic and inorganic bases such as triethylamine, diisopropylethylamine, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), pyridine, potassium tert-butoxide, sodium carbonate, potassium carbonate, sodium hydride and the like.

As the halogenating agent, there can be mentioned, for example, phosphorus oxychloride, phosphorus oxybromide, phosphorus trichloride, phosphorus pentachloride, thionyl chloride and the like.

As the sulfonylating agent, there can be mentioned, for example, methanesulfonyl chloride, p-toluenesulfonyl chloride and the like.

Each of the halogenating agent, the sulfonylating agent and the base as an optional component is used in an amount of at least 1 mole, preferably 1-2 moles, per mole of the compound of the general formula [VII] or its salt.

This reaction can be effected usually at -10° to 100°C, preferably 0° to 40°C, for 10 minutes to 30 hours.

The obtained compound of the general formula [VIII] may be used as it is, in the subsequent reaction without being isolated.

(4) The compound of the general formula [VIII] is

reacted with a compound of the general formula [IX] or its salt in the presence or absence of a catalyst in the presence or absence of a base to obtain a compound of the general formula [Ib] or its salt.

The solvent to be used in this reaction can be any solvent unless it adversely affects the reaction. There can be mentioned, for example, the same solvents as mentioned in (3) of Production Process 2.

As the catalyst to be used optionally, there can be mentioned, for example, potassium iodide, sodium iodide and the like.

The catalyst is used in an amount of 0.1-1 mole per mole of the compound of the general formula [VIII].

As the base to be used optionally, there can be mentioned, for example, the same bases as mentioned in (3) of Production Process 2.

Each of the compound of the general formula [IX] or its salt and the base as an optional component is used in an amount of at least 1 mole, preferably 1-20 moles, per mole of the compound of the general formula [VIII].

This reaction can be effected usually at 10-150°C, preferably 20-100°C for 10 minutes to 20 hours.

Production Process 3

(1) A compound of the general formula [II] is reacted with a compound of the general formula [X] or its salt in the presence or absence of a base to obtain

a compound of the general formula [XI] or its salt.

This reaction can be effected in accordance with the same method as mentioned in Production Process 1.

(2) The compound of the general formula [XI] or its salt is reacted with a sulfonylating agent in a solvent in the presence or absence of a base to obtain a compound of the general formula [XII] or its salt.

The solvent to be used in this reaction can be any solvent unless it adversely affects the reaction. There can be mentioned, for example, the same solvents as mentioned in (3) of Production Process 2.

As the base to be used optionally, there can be mentioned, for example, the same bases as mentioned in (3) of Production Process 2.

As the sulfonylating agent, there can be mentioned, for example, p-toluenesulfonyl chloride and the like.

Each of the sulfonylating agent and the base as an optional component is used in an amount of at least 0.95 mole, preferably 1-2 moles, per mole of the compound of the general formula [XI] or its salt.

This reaction can be effected usually at -10° to 100°C, preferably 0° to 40°C, for 10 minutes to 30 hours.

The obtained compound of the general formula [XII] or its salt may be used in the subsequent reaction without being isolated.

(3) The compound of the general formula [XII] or

its salt is subjected to conventional reaction for protection of hydroxyl group to obtain a compound of the general formula [XIII].

The reaction can be effected in accordance with per se known methods, for example, the method described in Protective Groups in Organic Synthesis [Theodra W. Green (1981), John Wiley & Sons, Inc.] or a method similar thereto.

The obtained compound of the general formula [XIII] may be used in the subsequent reaction without being isolated.

(4) The compound of the general formula [XII] or its salt or the compound of general formula [XIII] is reacted with a compound of the general formula [IX] or its salt in the presence or absence of a base to obtain a compound of the general formula [Ic] or its salt.

This reaction can be effected in the same method as described in (4) of Production Process 2.

Production Process 4

(1) A compound of the general formula [XIV] is reacted with a compound of the general formula [XV] to obtain a compound of the general formula [XVI] or its salt.

The solvent to be used in this reaction can be any solvent unless it adversely affects the reaction. There can be mentioned, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; and aromatic hydrocarbons such as benzene, toluene

and the like. These solvents can be used alone or in admixture of two or more.

In this reaction, the compound of the general formula [XV] is used in an amount of 0.8-100 moles, preferably 0.8-10 moles, per mole of the compound of the general formula [XIV].

This reaction can be effected usually at -78° to 100°C, preferably -78° to 50°C for 5 minutes to 24 hours.

The obtained compound of the general formula [XVI] or its salt may be used in the subsequent reaction without being isolated.

Incidentally, the compound of the general formula [XV] to be used in this reaction can be produced according to a per se known method, for example, the method described in Bull. Soc. Chim. Fr., 1967 (5), pp. 1533-40.

(2) The compound of the general formula [XVI] or its salt is reacted with a compound of the general formula [IX] or its salt in the presence or absence of a base to obtain a compound of the general formula [Id] or its salt.

The solvent to be used in this reaction can be any solvent unless it adversely affects the reaction. There can be mentioned, for example, halogenated hydrocarbons such as methylene chloride, chloroform and the like; ethers such as tetrahydrofuran, dioxane and the like; alcohols such as ethanol, propanol, butanol and

the like; nitriles such as acetonitrile and the like; and amides such as N,N-dimethylformamide and the like. These solvents can be used alone or in admixture of two or more.

As the base to be used optionally, there can be mentioned, for example, the same bases as mentioned in (3) of Production Process 2.

Each of the compound of the general formula [IX] or its salt and the base as an optional component is used in an amount of at least 1 mole, preferably 1-20 moles, per mole of the compound of the general formula [XVI] or its salt.

This reaction can be effected usually at 10-150°C, preferably 20-100°C, for 10 minutes to 20 hours.

In the above production processes, the reactants or base can also be used as solvent depending on the nature of the reactants or base.

In the above production processes, when the compounds of the general formulas [II], [III], [IIIa], [IV], [V], [VI], [VII], [VIII], [IX], [X], [XI], [XII], [XIII], [XIV], [XV] and [XVI], have isomers (e.g. optical isomers, geometrical isomers, tautomers), the compounds can be used in any isomer form. Further, the compounds can be used in a hydrate form, a solvate form or any crystal form.

When the compounds of the general formulas [II], [III], [IIIa], [IV], [V], [VI], [VII], [VIII],

[IX], [XII], [XIII], [XIV], [XV], [XVI], [I], [Ia], [Ib], [Ic] and [Id] have a hydroxyl group, an amino group or a carboxyl group, it is possible to previously protect these groups with a conventional protective group and to remove, after the reaction, the protective group, if necessary, according to a per se known method.

The compound thus obtained may be subjected to conventional isolation and purification procedures such as column chromatography, crystallization, distillation, extraction and the like.

The 1,2-ethanediol derivative of the general formula [I] or its salt can be converted into other 1,2-ethanediol derivative of the general formula [I] or its salt by subjecting the former compound to appropriate combination of per se known reactions such as oxidation reaction, reduction reaction, addition reaction, acylation reaction, alkylation reaction, sulfonylation reaction, deacylation reaction, substitution reaction, dehydration reaction, hydrolysis reaction and the like.

The compound of the general formula [II] which is the starting material for producing the compound of this invention can be produced by per se known processes, for example, the process described in JACS, vol. 87, p. 1353 (1965) and the process described in Shin Jikken Kagaku Koza, vol. 14, p. 579 (1977), Maruzen.

The compound of this invention, when used as a

drug, may be appropriately mixed with excipients such as filler, carrier, diluent and the like and can be formed into tablets, capsules, powders, granules, fine granules, pills, suspensions, emulsions, liquids, syrups, injections, etc. according to conventional methods. These drugs can be administered orally or parenterally. The dosage route, dose and number of administrations can be appropriately varied depending upon the age, weight and symptom of patient, but in the case of oral administration, generally 0.01-500 mg of the present compound can be administered daily to an adult patient in one to several portions.

Next, the pharmacological activities of representative compounds of this invention are described.

The numbers of the test compounds used in the following pharmacological tests refer to the numbers of the compounds shown in Production Examples appearing hereinafter.

1. Effect of test compound on hypoxia

A test compound dissolved in physiological saline (100 mg/kg) was orally administered to a ddY female mouse (5-6 weeks old, each group consisting of 10 mice). After 1 (or 30 minutes*) hour from the administration, each mouse was placed in a 300-ml glass chamber, and a gas mixture consisting of 4% of oxygen and 96% of nitrogen was passed through the chamber at a rate of 5 liters/min. A time from the start of gas passing to the death of each mouse was measured.

To a control mice group was orally administered only physiological saline.

The antihypoxic activity of the test compound was calculated from the following formula:

$$\frac{\text{Mean survival time of mice of administration group}}{\text{Mean survival time of mice of control group}} \times 100\ (\%)$$

The results are shown in Table 1.

Table 1

Compound No.	Antihypoxic activity (%)	Compound No.	Antihypoxic activity (%)
1	155	48	160
2	119	49	151
3	245*	54	137
9	113	55	207
14	184*	56	182
15	194*	58	133
16	116	61	184*
19	168*	62	127
23	241*	67	247*
27	201*	71	147
33	224*	83	177*
34	221	84	175*
36	139	86	130*
37	148	87	179
42	194	89	156*
46	150*	92	169
47	165*	95	164

- To be cont'd -

Table 1 (Cont'd)

Compound No.	Antihypoxic activity (%)	Compound No.	Antihypoxic activity (%)
96	176*	204	176*
97	138*	207	136*
98	164*	208	242*
100	171*	209	148*
102	140*	211	177*
104	160*	213	149
119	175*	215	197
120	162*	218	157*
121	149*	219	222*
122	142*	220	183*
123	140*	221	183*
125	172*	222	152*
126	172*	223	149*
129	158*	224	155
131	167*	225	157*
132	133*	228	144
134	201*	229	123
137	163*	230	177
139	162*	231	246
151	182	232	150
152	180	236	177
153	185	237	149
167	165	238	123
180	176*	239	150
181	132	243	159
187	153*	246	128
188	144*	247	124
195	176*	250	145*
197	164*	251	186*
203	177*	252	190*

- To be cont'd -

Table 1 (Cont'd)

Compound No.	Antihypoxic Activity (%)	Compound No.	Antihypoxic Activity (%)
256	154	342	157*
259	155*	343	160*
260	124	344	268*
261	126	345	185*
271	150*	347	162*
272	185*	348	251*
279	198	349	209*
282	160*	350	147*
283	183	353	132*
289	157*	357	189*
302	182*	358	211*
303	168	365	155*
309	198*	368	135*
312	221*	369	143*
313	154*	375	156*
320	212*	377	221*
325	217*	383	293*
327	160*	385	161*
330	242*	386	169*
332	230*	387	228*
334	246*	388	213*
336	224*	390	248*
337	309*	394	241*
338	144*	396	316*
339	131*	398	171*
340	163*	405	137*

Note: * Mice were placed in the chamber after 30 minutes from the administration instead of after 1 hr from the administration.

2. Effect of test compound on amnesia

(1) Electroconvulsive shock (ECS)-induced amnesia

A test compound dissolved in physiological saline was intraperitoneally administered to a ddY male mouse (5-6 weeks old, each group consisting of 10 mice). The acquisition trial in passive avoidance task was carried out after 1 hour from the administration. Each mouse was placed in the bright compartment of a two-compartment step-through type passive avoidance apparatus consisting of a bright compartment and a dark compartment (MPA-100M manufactured by Muromachi Kikai). When the mouse entered the dark compartment, the guilotine door of the dark compartment was closed; after 0.5 second, an inescapable footshock (1.6 mA, 3 seconds) was delivered. Immediately thereafter, ECS (25 mA, 0.5 second) was applied through the both eyes of the mouse. After 24 hours, in the retention trial, the mouse was again placed in the bright compartment and the response latency for mouse to enter the dark compartment was measured. If the mouse avoided longer than 300 seconds, a ceiling score of 300 seconds was assigned.

A control mice group to which only physiological saline had been administered intraperitoneally, and response latency was also measured in the same manner.

Antiamnesic activity was taken as a median of the response latencies of the 10 mice and expressed by the following symbols:

- : 0-60 seconds

\+ : 61-100 seconds

++ : 101-150 seconds

+++ : 151-300 seconds

The results are shown in Table 2.

Table 2

Compound No.	Dosage (mg/Kg)	Antiamnesic activity
2	3	+
3	3	+++
8	3	+
15	3	+++
19	3	+
23	10	+
29	3	+
44	10	++
48	3	++
52	3	+
53	3	+++
58	10	++
61	3	++
67	3	++
70	3	++
76	3	++
78	3	++
115	3	++
159	3	+
160	3	++
170	3	++
176	3	++
189	3	+++

- To be cont'd -

Table 2 (Cont'd)

228	10	+
229	3	+
235	10	++
237	3	++
239	10	+
243	3	++
252	3	+++
261	3	+
266	3	++
315	3	++
316	3	+
319	10	++

(2) Effect of test compound on cycloheximide-induced amnesia

It was reported by Yamazaki et al. [Drugs, Mind and Action, vol. 3, pp. 127-136 (1983)] that cycloheximide interfers with the retrieval process of memory of mouse. Hence, the following test was carried out.

A test was carried out in accordance with the method described in Drugs, Mind and Action, vol. 3, pp. 127-136 (1983) and Folia Pharmacologica Japonica, vol. 89, pp. 243-252 (1987).

As the test apparatus, there was used a step-down type passive avoidance training box. It was a black acrylic resin box of 22 cm x 22 cm x 21 cm (height) whose floor portion consisted of a stainless steel grid and which had, at one corner of the floor grid, a platform of 7 cm x 7 cm x 2 cm (height).

Cycloheximide was dissolved in physiological saline, and injected subcutaneously at 120 mg/kg to a ddY male mouse (5-6 weeks old, each group consisting of 10 mice). In an acquisition trial, after 15 minutes from the administration, each mouse was placed on the platform in the above test apparatus. As soon as the mouse stepped down the platform, a 2 mA current was delivered for 2 seconds, immediately after which the mouse was returned to its home cage. A retention test was performed 24 hours after the acquisition. To each mouse which had been treated with cycloheximide was orally administered a test compound dissolved in physiological saline; after 30 minutes from the administration, the mouse was again placed on the platform and the response latency for mouse to step down was measured. If the mouse avoided longer than 300 seconds, a ceiling score of 300 seconds was assigned.

A control mice group to which only physiological saline had been administered orally, ~~was also subjected to the measurement of~~ and was also measured response latency in the same manner.

Antiamnesic activity was taken as a median of the response latencies of the 10 mice and expressed by the following symbols:

- : 0-60 seconds
+ : 61-100 seconds
+- : 101-150 seconds
+++ : 151-300 seconds

The results are shown in Table 3.

Table 3

Compound No.	Dosage (mg/Kg)	Antiamnesic activity
1	3	++
7	10	+
9	10	+
14	3	+++
15	3	+++
16	10	+
25	3	+
28	10	+
42	3	+
48	3	++
49	3	++
54	3	++
56	3	+
60	3	+++
65	3	++
82	3	++
83	3	+
84	10	++
100	3	++
110	10	++
112	3	+++
113	3	++
115	3	+++
147	3	+++
151	3	+++
153	3	++
165	10	+
178	3	+++

- To be cont'd -

Table 3 (Cont'd)

181	10	++
194	3	+
196	3	+++
219	3	+
220	10	++
221	10	+
228	3	++
229	10	++
230	3	+
232	10	++
233	3	+
234	3	+
235	3	+++
238	3	+
240	3	+
241	3	++
242	3	++
244	3	++
245	10	++
246	3	++
248	3	++
251	3	+++
252	30	+++
257	3	+
260	3	+
261	3	+++
262	3	+
263	10	+
266	30	+
280	10	+
312	10	+
317	3	++
320	3	++

- To be cont'd -

Table 3 (Cont'd)

324	10	++
325	10	++
333	3	+
334	3	+
338	3	++
339	10	+
340	3	+
341	3	+
343	10	++
346	3	+
350	3	++
351	3	+
352	3	++
353	3	+
358	10	++
360	10	+
365	3	+
367	3	+++
368	3	+
Control	-	-

3. Inhibitory activity for acetylcholinesterase

A test was conducted in accordance with the method of Ellman et al. [Biochem. Pharmacol., vol. 7, pp. 88-95, 1961].

That is, acetylthiocholine (as a substrate) was added to a phosphate buffer solution containing 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB), a test compound and a mouse cerebral homogenate (as an acetylcholinesterase source). The resulting mixture was incubated, and the amount of the resulting

5-thio-2-nitrobenzoic acid was photometrically measured at 412 nm.

The inhibitory activity for acetylcholinesterase of the test compound was expressed by the inhibition (%) when the final concentration of the test compound was 10 µg/ml.

The results are shown in Table 4.

Table 4

Compound No.	Inhibition (%)	Compound No.	Inhibition (%)
6	13	78	90
30	22	83	93
34	26	86	50
37	45	89	44
38	36	90	52
40	26	97	38
47	38	103	36
48	51	113	45
54	83	165	24
55	22	182	38
58	45	190	76
60	71	222	83
61	89	223	74
62	78	224	36
65	62	225	43
67	90	228	30
70	91	230	25
71	87	233	59
72	92	237	44
73	89	239	22

- To be cont'd -

Table 4 (Cont'd)

Compound No.	Inhibition (%)	Compound No.	Inhibition (%)
241	31	341	61
246	30	342	67
247	26	350	42
260	43	352	26
302	38	372	30
319	30	377	23
322	20	386	47
329	45	405	59
336	21		

4. Acute toxicity

A test compound dissolved in physiological saline was intravenously administered to a group of 3 ddY male mice (5-6 weeks old) to examine the acute toxicity of the test compound.

As a result, test compound Nos. 1, 2, 3, 6, 8, 9, 15, 16, 25, 30, 33, 34, 38, 40, 42, 44, 46, 52, 53, 54, 65, 67, 70, 71, 112, 119, 120, 126, 132, 147, 151, 159, 160, 170, 176, 178, 182, 190, 194, 209, 219, 220, 221, 229, 235, 236, 240, 251, 256, 279, 283, 309, 312, 313, 315, 316, 319, 325, 327, 337, 360, 368, 369, 375, 377, 385, 390 and 396 gave no death case at 50 mg/kg.

It is easily appreciated from the above test results that the compound of this invention is excellent in antihypoxic activity, antiamnesic activity and inhibitory activity for acetylcholinesterase and

has low toxicity.

From the above result, it is also easily appreciated that the cerebral function-improving agent of this invention is useful for treating cerebrovascular dementia, senile dementia, Alzheimer's dementia, sequelae of ischemic encephalopathy and cerebral apoplexy.

Next, the process for producing the compound of this invention is specifically described by way of Production Examples.

In the Production Examples, the mixing ratio of eluant is by volume in all cases and, as the carrier in column chromatography, there was used a silica gel (Kieselgel 60, Art. 7734) manufactured by Merck Co.

The abbreviations used in the Production Examples have the following meanings.

Me: methyl, Et: ethyl, i-Pr: isopropyl, t-Bu: tert-butyl, Ac: acetyl, Ph: phenyl, DPM: diphenylmethyl, Bz: benzyl, Tr: trityl, IPA: isopropyl alcohol, IPE: diisopropyl ether, PTS: p-toluenesulfonic acid.

In the following sentences and tables, the substances in [ ] refer to solvents used in recrystallization.

Production example 1

(1) A mixture of 10.8 g of (L)-~~benzoylcystine~~ dibenzoylcystine, 1.6 g of lithium borohydride, 2.4 g of tert-butanol and

180 ml of tetrahydrofuran was refluxed for 1 hour and then cooled to -60°C. Thereto was added 6.1 g of 4-benzyloxyphenacyl bromide. The mixture was stirred for 30 minutes at the same temperature and further for 3 hours at -40° to -30°C. The reaction mixture was added to a mixture of 100 ml of water and 200 ml of diethyl ether. The organic layer was separated, washed with water, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: toluene) to obtain 2.8 g of (S)-1-(4-benzyloxyphenyl)-2-bromoethanol.

(2) 2.8 g of (S)-1-(4-benzyloxyphenyl)-2-bromoethanol was dissolved in a mixed solvent of 20 ml of methanol and 10 ml of tetrahydrofuran. To the solution was added a solution of 0.8 g of potassium hydroxide dissolved in 4 ml of water, with ice cooling. The mixture was stirred for 5 minutes at the same temperature and further for 10 minutes at room temperature. The reaction mixture was added to a mixture of 50 ml of diethyl ether and 50 ml of ice water. The organic layer was separated. The aqueous layer was extracted with 25 ml of diethyl ether. The extract was combined with the previously separated organic layer. The combined organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium

sulfate. The solvent was removed by distillation under reduced pressure to obtain 1.4 g of (S)-2-(4-benzyloxyphenyl)oxirane.

Melting point: 56-61°C

Optical rotation: $[\alpha]_D^{25}$ = +5.2° (C=2, $CHCl_3$)

The following compounds were obtained in the same manner.

o(S)-2-(3-Methylphenyl)oxirane

$[\alpha]_D^{25}$ = +15.7° (C=2, $CHCl_3$)

o(S)-2-(4-Phenoxyphenyl)oxirane

$[\alpha]_D^{25}$ = +12.5° (C=4, $CHCl_3$)

Production Example 2

(1) A solution of 23 g of (+)-diisopinocamphenylchloroborane dissolved in 30 ml of tetrahydrofuran was cooled to -25°C. Thereto was added 12 g of 4-benzyloxyphenacyl bromide. The resulting mixture was stirred for 4 hours at -20° to -15°C. The reaction mixture was added to a mixture of 150 ml of diethyl ether and 100 ml of ice water. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: hexane:toluene = 1:2) to obtain 6.8 g of (R)-1-(4-benzyloxyphenyl)-2-bromoethanol.

(2) 6.0 g of (R)-1-(4-benzyloxyphenyl)-2-bromoethanol was dissolved in a mixed solvent of 50 ml of methanol and 25 ml of tetrahydrofuran. Thereto was added a solution of 1.5 g of potassium hydroxide dissolved in 5 ml of water, with ice cooling. The resulting mixture was stirred for 5 minutes at the same temperature and further for 10 minutes at room temperature. The reaction mixture was added to a mixture of 100 ml of diethyl ether and 100 ml of ice water. The organic layer was separated. The aqueous layer was extracted with 50 ml of diethyl ether. The extract was combined with the previously separated organic layer. The combined organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 3.7 g of (R)-2-(4-benzyloxyphenyl)oxirane.

Melting point: 58-67°C

Optical rotation: $[\alpha]_D^{26} = -14.4°$ (C=2, $CHCl_3$)

The following compounds were obtained in the same manner.

o(R)-2-(3-Methylphenyl)oxirane

$[\alpha]_D^{27} = -18.6°$ (C=2, $CHCl_3$)

o(R)-2-(4-Phenoxyphenyl)oxirane

$[\alpha]_D^{25} = -11.3°$ (C=2, $CHCl_3$)

Production Example 3

3.4 g of potassium tert-butoxide was added to 31 ml of 2-(N,N-dimethylamino)ethanol. The resulting mixture was heated to 80°C. Thereto was dropwise added 7.7 g of 2-(3-fluorophenyl)oxirane over 40 minutes. The mixture was stirred for 3 hours at the same temperature. The reaction mixture was added to a mixture of 200 ml of ice water and 200 ml of ethyl acetate. The organic layer was separated. To the organic layer was added 50 ml of water. The mixture was adjusted to pH 1 with 6 N hydrochloric acid. The aqueous layer was separated and mixed with 100 ml of chloroform. The resulting mixture was adjusted to pH 11 with a 2 N aqueous sodium hydroxide solution. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 5/1). The resulting oily product was dissolved in 25 ml of acetone. Hydrogen chloride gas was blown into the solution. The resulting crystals were collected by filtration, washed with acetone and dried to obtain 3.1 g of 2-[2-(N,N-dimethylamino)ethoxy]-1-(3-fluorophenyl)ethanol hydrochloride (compound No. 1).

Melting point: 164-165°C [EtOH]

The compounds shown in Table 5 were obtained in the same manner.

In Table 5, R^1, R^2, R^3, R^{4a}, R^{4b}, R^6, na and nb each show a substituent or integer used in the following formula.

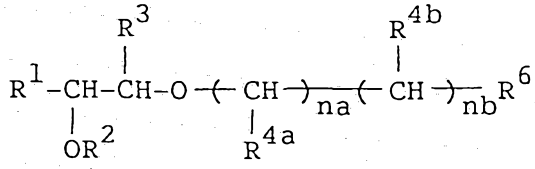


Table 5

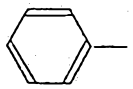
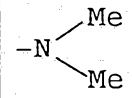
Compound No.	R^1	R^2	R^3	R^{4a}	R^{4b}	R^6	na	nb	Addition salt	Melting point (°C)
2		H	H	H	H		1	1	HCl	184-185 [EtOH]
3*a	" (R-form)	"	"	"	"	"	"	"	"	174.5-175 [Me_2CO-EtOH]

Table 5 (cont'd)

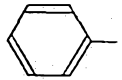
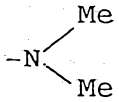
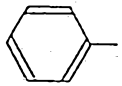
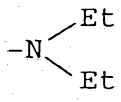
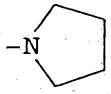
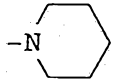
4*b	 (S-form)	H	H	H	H		1	1	HCl	174.5-175 [Me_2CO-EtOH]
5		"	"	"	"		"	"	-	Oily
6	"	"	"	"	"		"	"	HCl	173-174 [EtOH-Et_2O]
7	"	"	"	"	"		"	"	"	163.5-164.5 [EtOH-Et_2O]

Table 5 (cont'd)

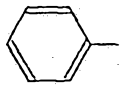
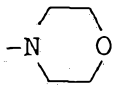
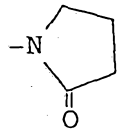
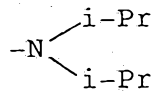
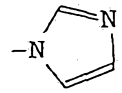
8		H	H	H	H		1	1	HCl	153-154.5 [EtOH-Et_2O]
9	"	"	"	"	"		"	"	-	Oily
10	"	"	"	"	"		"	"	"	"
11	"	"	"	"	"		"	"	"	"

Table 5 (cont'd)

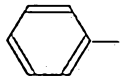
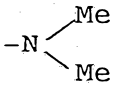
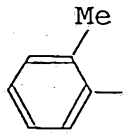
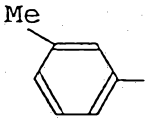
12		H	H	H	H		2	1	-	Oily
13	"	"	"	"	"	"	3	3	HCl	Amorphous
14		"	"	"	"	"	1	1	"	198-199 [EtOH]
15		"	"	"	"	"	"	"	"	165-166 [IPA]

Table 5 (cont'd)

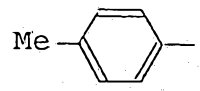
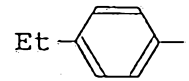
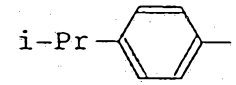
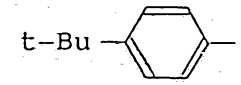
16		H	H	H	H		1	1	HCl	181.5-183 [EtOH]
17		"	"	"	"	"	"	"	"	201.5-203 [IPA]
18		"	"	"	"	"	"	"	"	194.5-196.5 [EtOH]
19		"	"	"	"	"	"	"	"	251-252 [EtOH]

Table 5 (cont'd)

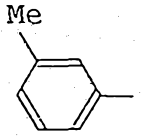
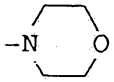
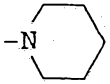
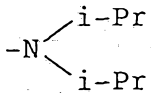
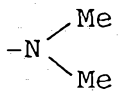
20		H	H	H	H		1	1	HCl	141-143 [EtOH-Et_2O]
21	"	"	"	"	"		"	"	"	136.5-137.5 [EtOH-Et_2O]
22	"	"	"	"	"		"	"	-	Oily
23	"	"	"	"	"		2	2	"	"

Table 5 (cont'd)

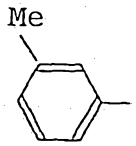
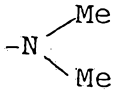
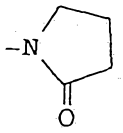
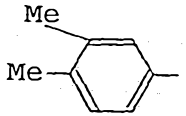
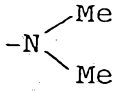
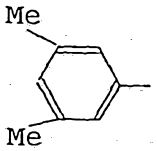
24		H	H	H	H		1	2	-	Oily
25	"	"	"	"	"		"	1	"	".
26		"	"	"	"		"	"	HCl	184-185 [EtOH]
27		"	"	"	"	"	"	"	"	158-159 [IPA]

Table 5 (cont'd)

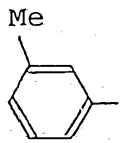
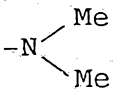
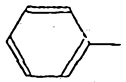
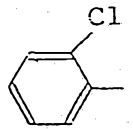
28		H	H	Me	H		1	1	-	Oily
29	"	"	"	H	Me	"	"	"	"	"
30		"	Me	"	H	"	"	"	HCl	190-191 [MeOH-Et_2O]
31		"	H	"	"	"	"	"	"	203-204 [EtOH]

Table 5 (cont'd)

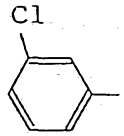
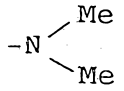
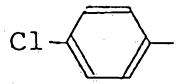
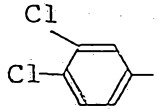
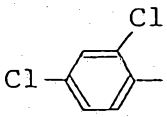
32		H	H	H	H		1	1	HCl	170-171 [Me_2CO]
33		"	"	"	"	"	"	"	"	188.5-190 [MeOH-Et_2O]
34		"	"	"	"	"	"	"	"	156.5-157.5 [EtOH-Et_2O]
35		"	"	"	"	"	"	"	"	184-184.5 [EtOH]

Table 5 (cont'd)

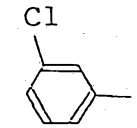
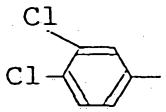
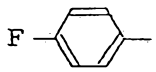
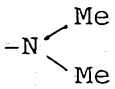
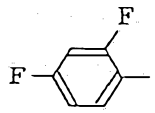
36		H	H	H	H		1	1	HCl	131-132 [EtOH-Et_2O]
37		"	"	"	"	"	"	"	"	178.5-179.5 [EtOH-Et_2O]
38		"	"	"	"		"	"	"	171-172 [EtOH]
39		"	"	"	"	"	"	"	"	182-182.5 [EtOH]

Table 5 (cont'd)

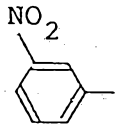
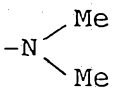
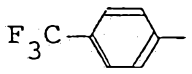
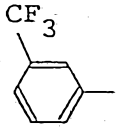
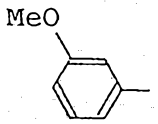
40		H	H	H	H		1	1	HCl	228-229.5 [EtOH-Et_2O]
41		"	"	"	"	"	"	"	"	193.5-194.5 [EtOH]
42		"	"	"	"	"	"	"	"	168.5-169.5 [EtOH-Et_2O]
43		"	"	"	"	"	"	"	"	146-147 [EtOH]

Table 5 (cont'd)

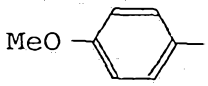
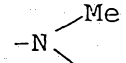
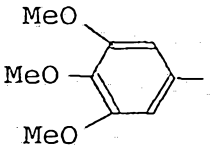
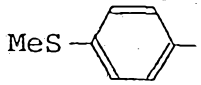
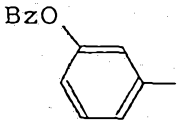
44		H	H	H	H		1	1	HCl	171-173 [EtOH]
45		"	"	"	"	"	"	"	PTS	140-141 [EtOH]
46		"	"	"	"	"		"	HCl	179.5-181.5 [EtOH-Et_2O]
47		"	"	"	"	"	"	"	"	169-171 [EtOH]

Table 5 (cont'd)

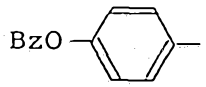
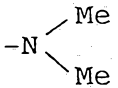
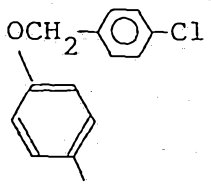
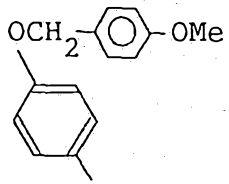
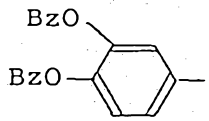
48		H	H	H	H		1	1	HCl	186-186.5 [EtOH]
49		"	"	"	"	"	"	"	"	188-188.5 [EtOH]
50		"	"	"	"	"	"	"	"	199-199.5 [MeOH-EtOH]
51		"	"	"	"	"	"	"	-	Oily

Table 5 (cont'd)

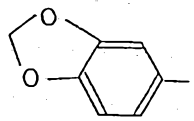
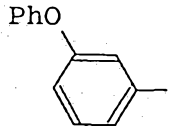
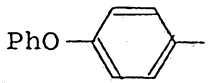
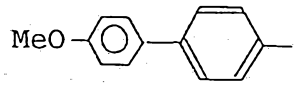
52		H	H	H	H	-N(Me)(Me)	1	1	HCl	149.5-151 [Me_2CO]
53		"	"	"	"	"	"	"	"	140-141 [EtOH-Et_2O]
54		"	"	"	"	"	"	"	"	174.5-176.5 [MeCN]
55		"	"	"	"	"	"	"	"	229-231 [MeCN]

Table 5 (cont'd)

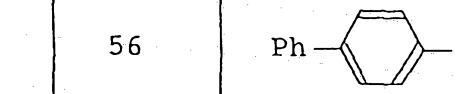
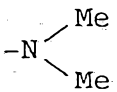
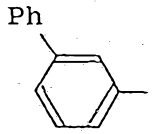
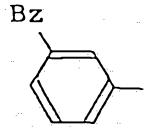
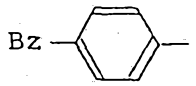
56		H	H	H	H		1	1	HCl	217.5-218.5 [EtOH]
57		"	"	"	"	"	"	"	"	138-140 [EtOH-Et_2O]
58		"	"	"	"	"	"	"	"	153-154 [EtOH]
59		"	"	"	"	"	"	"	"	179-181 [EtOH]

Table 5 (cont'd)

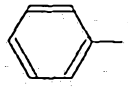
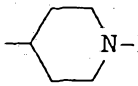
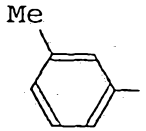
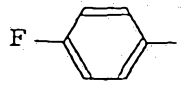
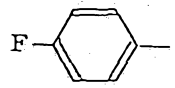
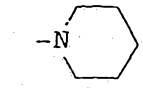
60		H	H	H	H		1	1	-	Oily
61		"	"	"	"	"	"	"	"	"
62		"	"	"	"	"	"	"	"	50-52
63		"	"	"	"		"	"	HCl	160-161 [EtOH-Et_2O]

Table 5 (cont'd)

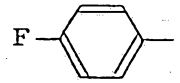
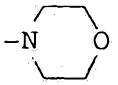
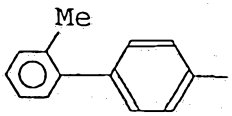
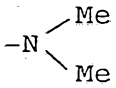
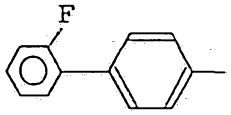
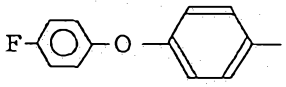
64		H	H	H	H		1	1	HCl	151-152.5 [EtOH-Et_2O]
65		"	"	"	"		"	"	"	223-225 [EtOH-IPA]
66		"	"	"	"	"	"	"	"	215-216 [MeOH-EtOH]
67		"	"	"	"	"	"	"	"	180.5-181.5 [MeCN]

Table 5 (cont'd)

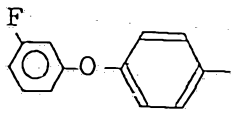
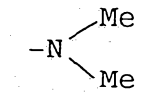
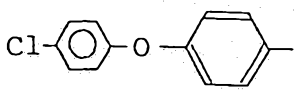
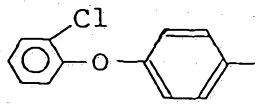
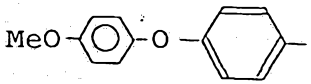
68		H	H	H	H		1	1	HCl	168.5-169.5 [IPA]
69		"	"	"	"	"	"	"	"	177.5-178.5 [MeCN]
70		"	"	"	"	"	"	"	"	194.5-195 [MeCN]
71		"	"	"	"	"	"	"	"	162-162.5 [IPA]

Table 5 (cont'd)

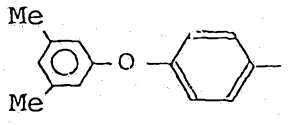
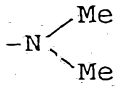
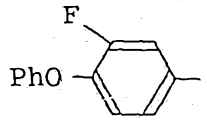
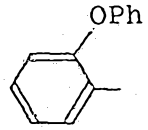
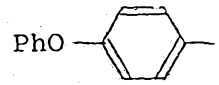
72		H	H	H	H		1	1	HCl	171-172 [IPA]
73		"	"	"	"	"	"	"	"	162-162.5 [IPA]
74		"	"	"	"	"	"	"	"	147.5-148.5 [Me_2CO-Et_2O]
75		"	"	"	"	"	2	"	-	Oily

Table 5 (cont'd)

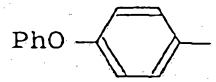
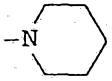
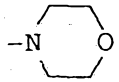
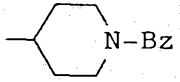
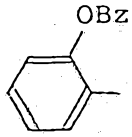
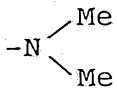
76		H	H	H	H		1	1	HCl	160-160.5 [IPA]
77	"	"	"	"	"		"	"	"	192.5-193 [MeCN]
78	"	"	"	"	"		"	"	-	Oily
79		"	"	"	"		"	"	HCl	124-125 [MeCN]

Table 5 (cont'd)

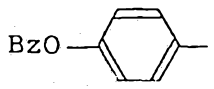
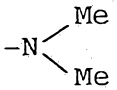
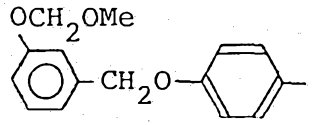
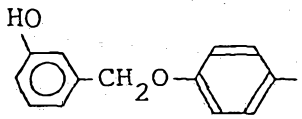
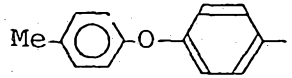
80		H	H	H	H		2	1	-	121.5-123 [AcOEt-Et_2O]
81		"	"	"	"	"	1	"	"	Oily
82*c		"	"	"	"	"	"	"	HCl	179-181 [EtOH]
83		"	"	"	"	"	"	"	"	189.5-190 [IPA]

Table 5 (cont'd)

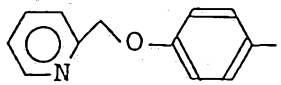
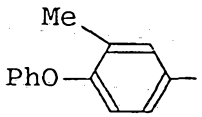
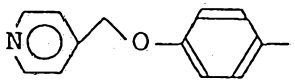
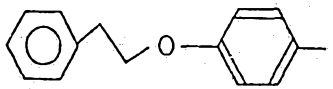
84		H	H	H	H		1	1	2HCl	157-158 [EtOH]
85		"	"	"	"	"	"	"	HCl	161-162.5 [IPA]
86		"	"	"	"	"	"	"	2HCl	157.5-159.5 [EtOH]
87		"	"	"	"	"	"	"	HCl	172-173 [IPA]

Table 5 (cont'd)

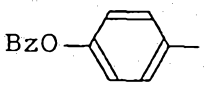
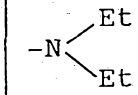
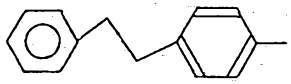
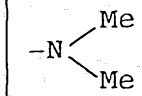
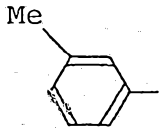
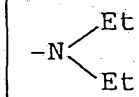
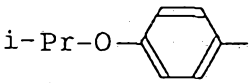
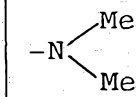
88		H	H	H	H		1	1	-	Oily
89		"	"	"	"		"	"	HCl	222.5-223.5 [EtOH]
90		"	"	"	"		"	"	-	Oily
91		"	"	"	"		"	"	HCl	204.5-205 [EtOH-Me_2CO]

Table 5 (cont'd)

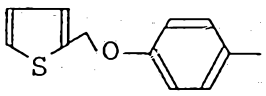
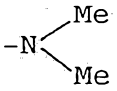
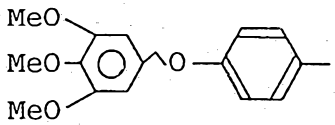
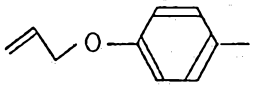
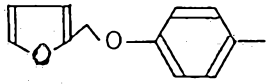
92		H	H	H	H		1	1	HCl	168.5-169 [EtOH-AcOEt]
93		"	"	"	"	"	"	"	"	193-194 [EtOH-AcOEt]
94		"	"	"	"	"	"	"	"	154.5-156 [MeCN]
95		"	"	"	"	"	"	"	"	168.5-169.5 [EtOH-AcOEt]

Table 5 (cont'd)

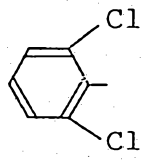
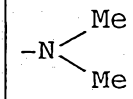
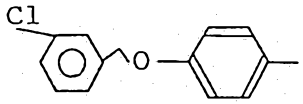
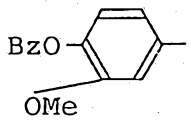
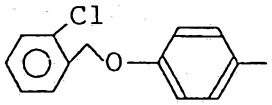
96		H	H	H	H		1	1	HCl	197-198 [IPA-AcOEt]
97		"	"	"	"	"	"	"	"	176-178 [EtOH]
98		"	"	"	"	"	"	"	"	140.5-142 [IPA]
99		"	"	"	"	"	"	"	"	181.5-182.5 [EtOH]

Table 5 (cont'd)

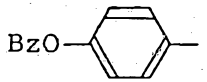
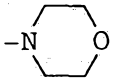
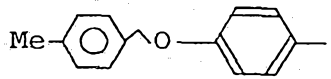
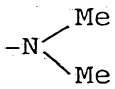
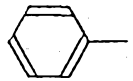
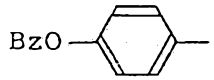
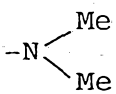
100		H	H	H	H		1	1	HCl	170-170.5 [EtOH-Me_2CO]
101		"	"	"	"		"	"	"	199-199.5 [EtOH]
102*d		"	"	"	"	$-NH_2$	"	"	1/2 Fumaric acid	181-182.5
103*e	 (R-form)	"	"	"	"		"	"	HCl	194-194.5 [EtOH-Me_2CO]

Table 5 (cont'd)

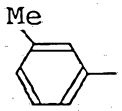
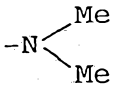
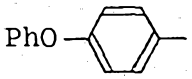
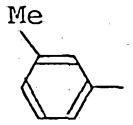
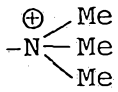
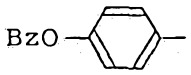
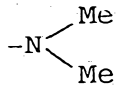
104*f	 (R-form)	H	H	H	H		1	1	HCl	164-165 [EtOH-Me_2CO]
105*g	 (R-form)	"	"	"	"	"	"	"	"	193-194 [MeCN]
106*h		"	"	"	"		"	"	1/2 1,5-Naphthalenedisulfonic acid	Amorphous
107*i	 (S-form)	"	"	"	"		"	"	HCl	195-196 [EtOH-Me_2CO]

Table 5 (cont'd)

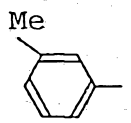
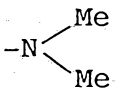
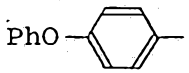
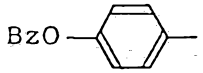
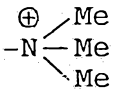
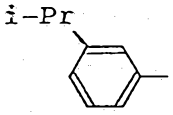
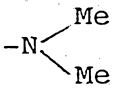
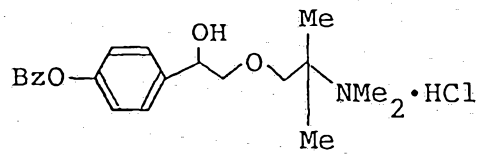
108*j	 (S-form)	H	H	H	H		1	1	HCl	163-164.5 [EtOH-Me_2CO]
109*k	 (S-form)	"	"	"	"	"	"	"	"	187.5-188.5 [MeCN]
110*h		"	"	"	"		"	"	1/2 1,5-Naphthalenedisulfonic acid	168-170 (decomp.)
111		"	"	"	"		"	"	-	Oily

Table 5 (cont'd)

112		171-173 [EtOH-Et_2O]

Note: *a: Optical rotation: -43.3° (27°C, C=3, EtOH)

*b: Optical rotation: +43.3° (24°C, C=3, EtOH)

*c: Obtained by treating compound No. 81 with p-toluenesulfonic acid.

*d: A tricyl group was used as an amino-protecting group.

*e: Optical rotation: -38.9° (28°C, C=1.5, MeOH)

*f: Optical rotation: -45.8° (25°C, C=1.5, MeOH)

*g: Optical rotation: -38.5° (25°C, C=1.5, EtOH)

*h: Obtained by reacting 1 mole of a dimethylamino form with 0.5 mole of dimethyl 1,5-naphthalenedisulfonate.

*i: Optical rotation: +37.3° (23°C, C=1.5, MeOH)

*j: Optical rotation: +40.2° (23°C, C=1.5, MeOH)

*k: Optical rotation: +28.4° (23°C, C=1.5, EtOH)

Production Example 4

A mixture of 5.00 g of 1-benzyl-4-hydroxypiperidine, 1.97 g of potassium tert-butoxide and 4 ml of dimethyl sulfoxide was heated to 80°C. Thereto was dropwise added 2.10 g of styrene oxide over 40 minutes. The resulting mixture was stirred for 3 hours at the same temperature. The reaction mixture was added to a mixture of 100 ml of ice water and 80 ml of ethyl acetate. The mixture was adjusted to pH 11.5 with 6 N hydrochloric acid. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 10/1). The resulting oily product was dissolved in 8 ml of ethanol. To the solution were added 1 ml of a 6 N dry hydrogen chloride-ethanol solution and 20 ml of diethyl ether. The mixture was stirred for 30 minutes at room temperature. The resulting crystals were collected by filtration, washed with a mixture of 2 ml of ethanol and 2 ml of diethyl ether, and dried to obtain 930 mg of 2-(1-benzylpiperidin-4-yloxy)-1-phenylethanol hydrochloride (compound No. 113).

Melting point: 193-195°C

The compounds shown in Table 6 were obtained in the same manner.

In Table 6, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following formula:

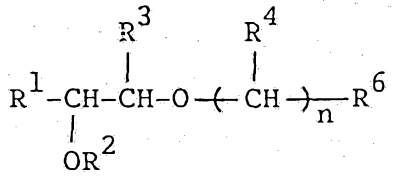


Table 6

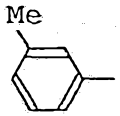
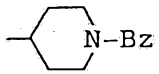
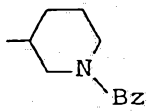
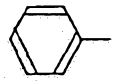
Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
114		H	H	-		0	HCl	180-181.5 [IPA]
115	"	"	"	"		"	"	202-204
116		"	"	"		"	-	119-120

Table 6 (cont'd)

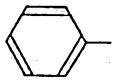
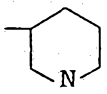
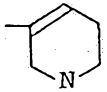
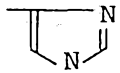
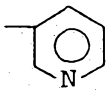
117		H	H	H		1	HCl	153-155 [Me_2CO-EtOH]
118	"	"	"	"		"	"	Oily
119	"	"	"	"		"	-	92-95
120	"	"	"	"		"	HCl	Oily

Table 6 (cont'd)

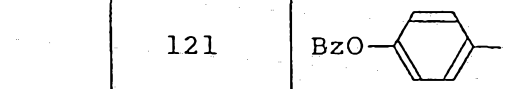
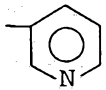
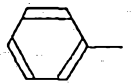
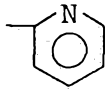
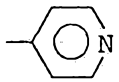
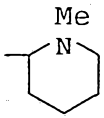
121		H	H	H		1	-	78-81 [AcOEt-IPE]
122		"	"	"		"	HCl	129.5-131.5 [AcOEt-IPE]
123	"	"	"	"		"	"	157.5-159.5
124	"	"	"	"		"	"	137-138.5 [Me_2CO]

Table 6 (cont'd)

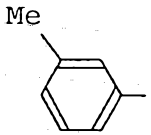
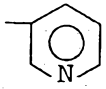
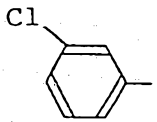
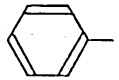
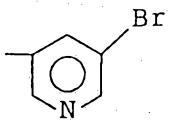
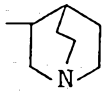
125		H	H	H		1	HCl	Oily
126		"	"	"	"	"	"	"
127		"	"	"		"	"	"
128	"	"	"	"		"	-	"

Table 6 (cont'd)

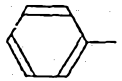
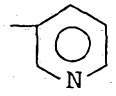
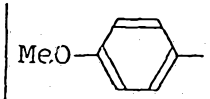
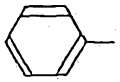
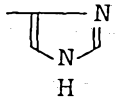
129*1	 (S-form)	H	H	H		1	-	61-61.5 [EtOH-IPE]
130*2	" (R-form)	"	"	"	"	"	"	61-61.5 [EtOH-IPE]
131		"	"	"	"	"	"	71.5-72 [EtOH-IPE]
132*3		"	"	"		"	"	118-119.5

Table 6 (cont'd)

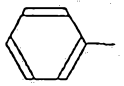
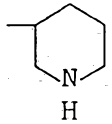
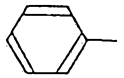
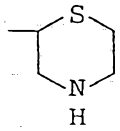
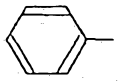
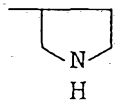
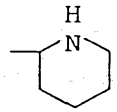
133*3		H	H	H		1	HCl	147.5-149 [IPA-AcOEt]
134*3	 (1R-form)	"	"	"		"	"	Oily
135*3		"	"	"		"	"	104.5-106.5 [IPA-AcOEt]
136*3	"	"	"	"		"	"	220-221 [EtOH-AcOEt]

Table 6 (cont'd)

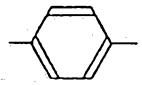
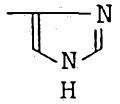
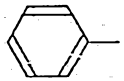
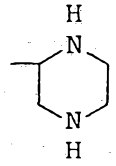
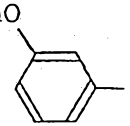
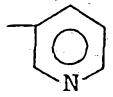
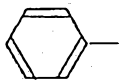
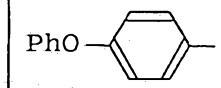
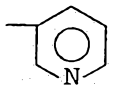
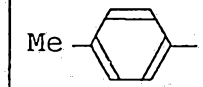
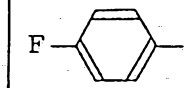
137*3	BzO 	H	H	H		1	-	154-156 [IPA-AcOEt]
138*4		"	"	"		"	2HCl	241-242 (decomp.)
139	PhO 	"	"	"		"	-	53.5-54.5 [Et_2O]
140		"	"	"	"	3	"	Oily

Table 6 (cont'd)

141		H	H	H		1	-	84.5-85.5 [EtOH-IPE]
142		"	"	"	"	"	"	65.5-66.5 [EtOH-IPE]
143		"	"	"	"	"	"	68-69 [EtOH-IPE]

Note: *1: Optical rotation: +23.3° (25°C, C=1, MeOH)

*2: Optical rotation: -22.5° (25°C, C=1, MeOH)

*3: The reaction was effected using a trityl group as an amino-protecting group.

*4: The reaction was effected using a formyl group as an amino-protecting group.

Production Example 5

(1) A mixture of 4.30 g of 4-benzyl-2-hydroxymethylmorpholine, 930 mg of potassium tert-butoxide and 4 ml of dimethyl sulfoxide was heated to 80°C. Thereto was dropwise added 2.50 g of styrene oxide over 20 minutes. The resulting mixture was stirred for 2 hours at the same temperature. The reaction mixture was added to a mixture of 30 ml of diethyl ether and 30 ml of ice water. The organic layer was separated and mixed with 10 ml of water. The mixture was adjusted to pH 2.0 with 6 N hydrochloric acid. The aqueous layer was separated and mixed with 30 ml of diethyl ether. The mixture was adjusted to pH 11 with a 2 N aqueous sodium hydroxide solution. The organic layer was separated, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography (eluant: toluene/ethyl acetate = 1/1) to obtain 2.00 g of oily 1-phenyl-2-[(4-benzylmorpholin-2-yl)methoxy]ethanol (compound No. 144).

The compounds shown in Table 7 were obtained in the same manner.

In Table 7, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following formula:

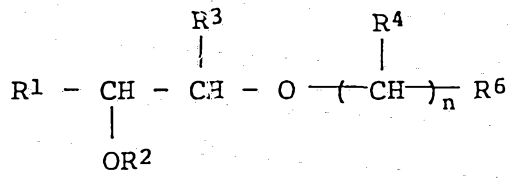
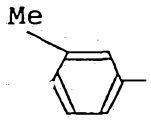
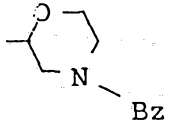
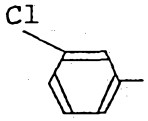
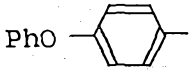
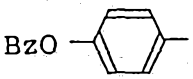
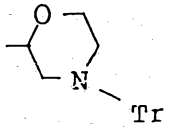
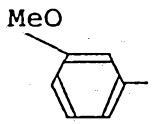
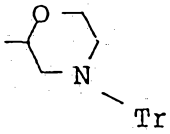


Table 7

Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
145		H	H	H		1	-	Oily
146		"	"	"	"	"	"	"
147		"	"	"	"	"	"	"
148		"	"	"		"	"	"

- Cont'd -

Table 7 (Cont'd)

149		H	H	H		1	-	Oily
150		"	"	"	"	"	"	"

(2) A mixture of 1.00 g of 1-phenyl-2-[(4-benzylmorpholin-2-yl)methoxy]ethanol, 500 mg of 5% palladium-carbon and 10 ml of methanol was subjected to hydrogenation for 4 hours at room temperature under atmospheric pressure. After the completion of the reaction, palladium-carbon was removed by filtration. The solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography (eluant: chloroform/methanol = 10/1) to obtain 450 mg of an oily product. The oily product was dissolved in 2.5 ml of isopropanol. The solution was mixed with 220 mg of fumaric acid. The mixture was stirred for 1 hour at room temperature. The resulting crystals were collected by filtration, washed with 2 ml of isopropanol and dried to obtain 460 mg of 1/2 fumarate of 1-phenyl-2-[(morpholin-2-yl)methoxy]ethanol (compound No. 151).

Melting point: 146.5-147°C [EtOH]

The compounds shown in Table 8 were obtained in the same manner.

In Table 8, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following formula:

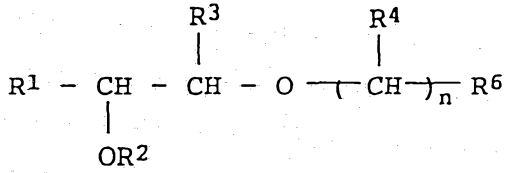
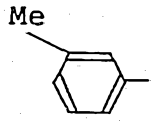
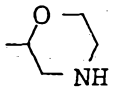
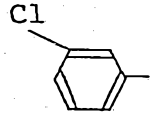


Table 8

Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
152		H	H	H		1	1/2 Fumaric acid	155-156 [EtOH]
153		"	"	"	"	"	HCl	Amorphous
154		"	"	"	"	"	1/2 Fumaric acid	142-142.5 [EtOH-Me_2CO]

(3) 7 g of 1-(3-methoxyphenyl)-2-[(4-trityl-morpholin-2-yl)methoxy]ethanol was dissolved in 35 ml of acetone. To the solution was added 2.6 ml of a 5.9 N dry hydrogen chloride-ethanol solution with ice cooling. The mixture was stirred for 2 hours at room temperature. After the completion of the reaction, the solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 50 ml of water and 30 ml of ethyl acetate. The aqueous layer was separated and washed with ethyl acetate. Thereto was added 50 ml of chloroform. The resulting mixture was adjusted to pH 11 with a 1 N aqueous sodium hydroxide solution. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/methanol = 5/1) to obtain 1 g of an oily product. The oily product was dissolved in 3 ml of isopropanol. Thereto was added 430 mg of fumaric acid. The mixture was stirred for 1 hour at room temperature. The resulting crystals were collected by filtration and dried to obtain 800 mg of 1/2 fumarate of 1-(3-methoxyphenyl)-2-[(morpholin-2-yl)methoxy]ethanol (compound No. 155).

Melting point: 122-123.5°C [EtOH]

The compounds shown in Table 9 were obtained in the same manner.

In Table 9, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following formula:

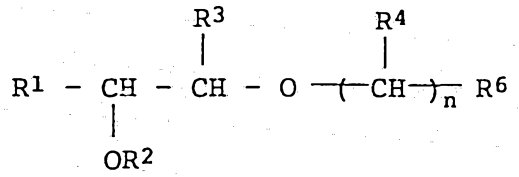
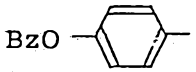
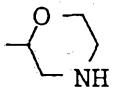
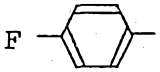


Table 9

Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
156		H	H	H		1	1/2 Fumaric acid	147-148.5 [EtOH]
157		"	"	"	"	"	"	126-127 [IPA]

Production Example 6

(1) 5.1 g of potassium tert-butoxide was added to 105 ml of ethylene glycol mono-tert-butyl ether. The mixture was heated to 80°C. Thereto was dropwise added 35.0 g of 2-(3-chlorophenyl)oxirane over 1 hour. The mixture was stirred for 2 hours at the same temperature. The reaction mixture was added to a mixture of 100 ml of ice water and 100 ml of ethyl acetate. The organic layer was separated, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was subjected to further distillation under reduced pressure to obtain 37.7 g of colorless oily 1-(3-chlorophenyl)-2-(2-tert-butoxyethoxy)ethanol having a boiling point of 140-146°C/0.9 mmHg.

(2) 37.0 g of 1-(3-chlorophenyl)-2-(2-tert-butoxyethoxy)ethanol was dissolved in 70 ml of methylene chloride. To the solution were added 12.9 g of pyridine and 16.6 g of acetic anhydride. The resulting mixture was stirred for 24 hours at room temperature. The reaction mixture was added to a mixture of 150 ml of ice water and 100 ml of methylene chloride. The resulting mixture was adjusted to pH 2 with 6 N hydrochloric acid. The organic layer was separated, washed with a saturatred aqueous sodium hydrogencarbonate solution and water in this order, and dried over anhydrous magnesium sulfate. The solvent was

removed by distillation under reduced pressure to obtain 40.0 g of oily 1-acetoxy-1-(3-chlorophenyl)-2-(2-tert-butoxyethoxy)ethane.

(3) 40.0 g of 1-acetoxy-1-(3-chlorophenyl)-2-(2-tert-butoxyethoxy)ethane was dissolved in 40 ml of methylene chloride. To the solution was added 80 ml of trifluoroacetic acid with ice cooling. The mixture was stirred for 12 hours at room temperature. After the completion of the reaction, the solvent was removed by distillation under reduced pressure. The residue was mixed with 100 ml of toluene. The solvent was further removed by distillation under reduced pressure. The residue thus obtained was dissolved in a mixture of 90 ml of ethanol and 10 ml of water. To the solution was added 10.7 g of sodium hydrogencarbonate at room temperature. The mixture was adjusted to pH 6-7 with a saturated aqueous sodium hydrogencarbonate solution, and then concentrated to about a half volume under reduced pressure. To the concentrate was added 100 ml of ethyl acetate. The organic layer was separated. The aqueous layer was extracted with 50 ml of ethyl acetate. The extract was combined with the previously separated organic layer. The combined organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography (eluant: toluene/ethyl acetate = 3/1) to obtain 19.4 g of oily

1-acetoxy-1-(3-chlorophenyl)-2-(2-hydroxyethoxy)-ethane.

(4) To a mixture of 19.0 g of 1-acetoxy-1-(3-chlorophenyl)-2-(2-hydroxyethoxy)ethane and 95.0 ml of methylene chloride containing 9.1 ml of methanesulfonyl chloride was dropwise added 16.4 ml of triethylamine with ice cooling over 1 hour. The resulting mixture was stirred for 10 minutes at the same temperature and further for 1 hour at room temperature. The reaction mixture was added to a mixture of 50.0 ml of methylene chloride and 50.0 ml of ice water. The resulting mixture was adjusted to pH 2.0 with 6 N hydrochloric acid. The organic layer was separated, washed with water and dried ~~with~~ over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 24.5 g of oily 1-acetoxy-1-(3-chlorophenyl)-2-(2-methanesulfonyloxyethoxy)ethane.

(5) 1.40 g of 1-acetoxy-1-(3-chlorophenyl)-2-(2-methanesulfonyloxyethoxy)ethane was dissolved in 7 ml of N,N-dimethylformamide. To the solution were added 0.69 ml of N-methylpiperazine and 1.03 g of potassium carbonate. The mixture was stirred for 3 hours at 80°C. The reaction mixture was cooled and added to a mixture of 30 ml of ice water and 30 ml of diethyl ether. The organic layer was separated. The aqueous layer was extracted with 20 ml of diethyl ether. The extract was combined with the previously separated organic layer. The combined organic layer was washed

with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was mixed with 7 ml of methanol and 45 mg of sodium methoxide. The mixture was allowed to stand overnight at room temperature. The solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 20 ml of ethyl acetate and 10 ml of water. The organic layer was separated. The aqueous layer was extracted with 20 ml of ethyl acetate. The extract was combined with the previously separated organic layer. The combined organic layer was washed with a saturated aqueous sodium chloride solution and then purified by column chromatography (eluant: chloroform/methanol = 10/1). To the resulting oily product were added 10 ml of ethanol and 1.2 ml of a 6 N dry hydrogen chloride-ethanol solution in this order. To the resulting mixture was added 10 ml of diethyl ether. The mixture was stirred for 30 minutes. The resulting crystals were collected by filtration, washed with a mixture of 2 ml of ethanol and 2 ml of diethyl ether, and dried to obtain 770 mg of 1-(3-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)ethoxy]ethanol dihydrochloride (compound No. 158).

Melting point: 211-213°C [MeOH-EtOH]

The compounds shown in Table 10 were obtained in the same manner.

In Table 10, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following formula:

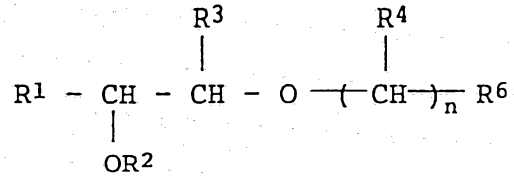
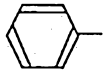
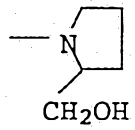
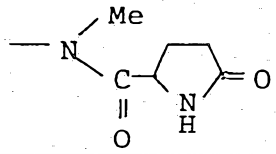
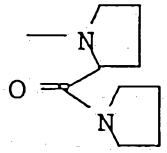
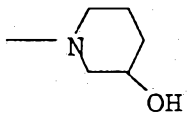
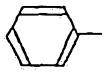
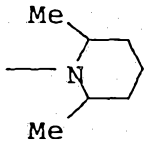
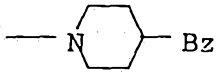
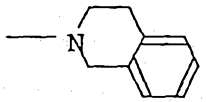
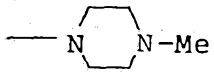
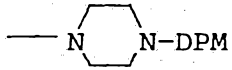


Table 10

Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
159		H	H	H		2	-	Oily
160	"	"	"	"		"	"	134.5-136.5 [IPA]
161	"	"	"	"		"	"	Oily
162	"	"	"	"		"	HCl	138-140 [IPA]

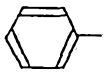
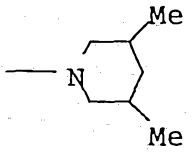
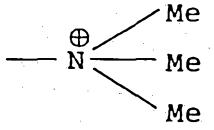
- Cont'd -

Table 10 (Cont'd)

163		H	H	H		2	-	Oily
164	"	"	"	"		"	HCl	164.5 - 166.5
165	"	"	"	"		"	"	169-171 [EtOH]
166	"	"	"	"		"	2HCl	169-171 [CH_2Cl_2-EtOH]
167	"	"	"	"		"	-	104.5 - 105.5 [EtOH]

- Cont'd -

Table 10 (Cont'd)

168		H	H	H		2	-	Oily
169*a	"	"	"	"		"	1/2 1,5-Naphthalenedisulfonic acid	208-210 [MeOH-Et_2O]

Note: *a: 1 mole of a dimethylamino form was reacted with 0.5 mole of dimethyl 1,5-naphthalenedisulfonate, to obtain the desired product.

Production Example 7

A mixture of 2.0 g of 1-(4-benzyloxyphenyl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol hydrochloride, 500 mg of 10% palladium-carbon and 10 ml of methanol was subjected to hydrogenation for 2 hours at room temperature under atmospheric pressure. After the completion of the reaction, palladium-carbon was removed by filtration. The solvent was removed by distillation under reduced pressure to obtain 1.4 g of 1-(4-hydroxyphenyl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol hydrochloride (Compound No. 170).

Melting point: 169.5-170.5°C [EtOH]

The compounds shown in Table 11 were obtained in the same manner.

In Table 11, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following formula:

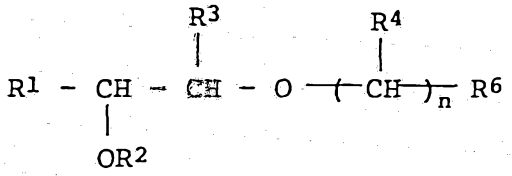
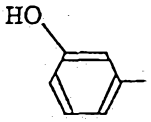
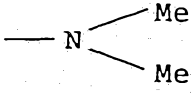
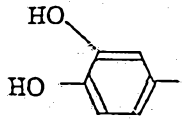
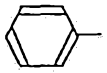
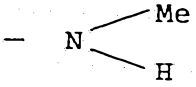
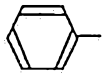
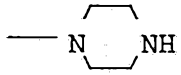
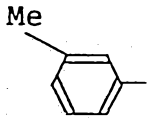
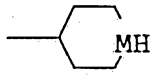
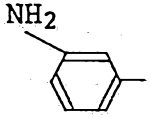
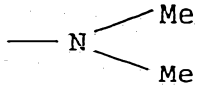


Table 11

Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
171		H	H	H		2	HCl	150-152 [EtOH]
172	"	Ac	"	"	"	"	"	Amorphous
173		H	"	"	"	"	-	Oily
174		"	"	"		"	HCl	145-147

- Cont'd -

Table 11 (Cont'd)

175		H	H	H		2	2HCl	204.5 - 206.5 [MeOH]
176		"	"	"		"	-	Oily
177		"	"	"		"	HCl	151-153

Production Example 8

0.65 ml of pyridine and 0.99 ml of acetic anhydride were added to 1 g of 1-(3-methylphenyl)-2-[2-(morpholin-4-yl)ethoxy]ethanol. The mixture was stirred for 3 hours at room temperature. The reaction mixture was subjected to distillation under reduced pressure to remove the solvent. To the residue were added 20 ml of ethyl acetate and 10 ml of water. The mixture was adjusted to pH 10 with potassium carbonate. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography (eluant: chloroform/ethanol = 30/1) to obtain 1 g of oily 1-acetoxy-1-(3-methylphenyl)-2-[2-(morpholin-4-yl)ethoxy]ethane (compound No. 178).

The compounds shown in Table 12 were obtained in the same manner.

In Table 12, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following formula:

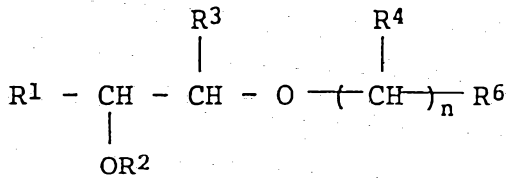
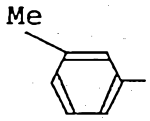
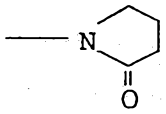
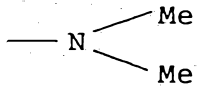
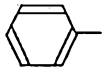
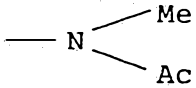
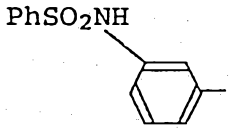
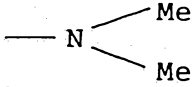
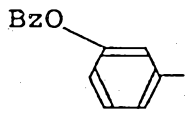
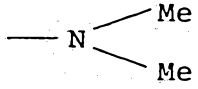
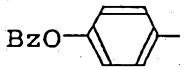
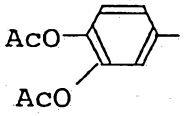
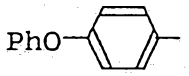
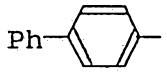


Table 12

Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
179		Ac	H	H		2	-	Oily
180	"	"	"	"		"	"	"
181*d		H	"	"		"	"	"
182*e		"	"	"		"	HCl	174.5 - 176.5 [EtOH]

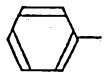
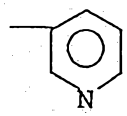
- Cont'd -

Table 12 (Cont'd)

183		Ac	H	H		2	HCl	169.5 - 170.5 [EtOH]
184		"	"	"	"	"	"	131.5 - 132.5 [Me_2CO]
185		"	"	"	"	"	"	Oily
186		"	"	"	"	"	-	Oily
187		"	"	"	"	"	"	144.5 - 146.5 [EtOH-Et_2O]

- Cont'd -

Table 12 (Cont'd)

188		Ac	H	H		1	HCl	Oily

Note: *d: The indicated compound was obtained by reacting compound No. 174 with acetic anhydride.

*e: The indicated compound was obtained by reacting compound No. 177 with benzenesulfonyl chloride in pyridine.

Production Example 9

50 ml of a 1:1 mixture of chloroform and water was added to 3.30 g of 1-acetoxy-1-(3-hydroxyphenyl)-2-[2-(N,N-dimethylamino)ethoxy]ethane hydrochloride. To the mixture was added 750 mg of sodium carbonate with ice cooling. The organic layer was separated and dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was mixed with 20 ml of benzene. The mixture was heated to 60°C. To the resulting solution was dropwise added a solution of 870 mg of ethyl isocyanate dissolved in 5 ml of benzene in 10 minutes. The mixture was stirred for 40 minutes at the same temperature. After the completion of the reaction, the solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 10/1) to obtain an oily product. The oily product was dissolved in 10 ml of ethanol. Hydrogen chloride gas was blown into the solution. The solvent was removed by distillation under reduced pressure to obtain 1.90 g of 1-acetoxy-1-[3-(N-ethylcarbamoyloxy)phenyl]-2-[2-(N,N-dimethylamino)-ethoxy]ethane hydrochloride (compound No. 189).

Melting point: 111.5-113.5°C [Me_2CO]

In the same manner, there was obtained oily 1-acetoxy-1-[3-(3-chlorophenylcarbamoyloxy)phenyl]-2-[2-

(N,N-dimethylamino)ethoxy]ethane hydrochloride (compound No. 190).

Production Example 10

(1) 9.5 g of potassium tert-butoxide was added to 92 ml of ethylene glycol. The mixture was heated to 80°C. Thereto was dropwise added, in 3 hours, a solution of 34.7 g of 2-(4-benzyloxyphenyl)oxirane dissolved in 220 ml of dimethyl sulfoxide. The resulting mixture was stirred for 30 minutes at the same temperature. The reaction mixture was cooled, and added to a mixture of 1 liter of ice water and 600 ml of ethyl acetate. The resulting mixture was adjusted to pH 7 with 6 N hydrochloric acid. The organic layer was separated. The aqueous layer was extracted with 200 ml of ethyl acetate. The extract was combined with the previously separated organic layer. The combined organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 10/1) to obtain 25 g of 1-(4-benzyloxyphenyl)-2-(2-hydroxyethoxy)ethanol.

Melting point: 116.5-117°C [MeCN]

(2) 22.7 g of 1-(4-benzyloxyphenyl)-2-(2-hydroxyethoxy)ethanol was dissolved in 140 ml of pyridine. The solution was cooled to -20°C. To the solution was added 19 g of p-toluenesulfonyl chloride. The resulting mixture was heated to 0°C and stirred for 15 hours at the same temperature. The rection mixture was added to a mixture of 300 ml of ice water and 200 ml of diethyl ether. The resulting mixture was adjusted to pH 2 with 6 N hydrochloric acid. The organic layer was separated. The aqueous layer was extracted with 100 ml of diethyl ether. The extract was combined with the previously separated organic layer. The combined organic layer was washed with 1 N hydrochloric acid, water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography (eluant: toluene/ethyl acetate = 3/1) to obtain 20.5 g of oily 1-(4-benzyloxyphenyl)-2-[2-(p-toluenesulfonyloxy)ethoxy]ethanol.

(3) To a mixture of 20 g of 1-(4-benzyloxyphenyl)-2-[2-(p-toluenesulfonyloxy)ethoxy]ethanol and 40 ml of methylene chloride containing 8.2 g of 3,4-dihydro-2H-pyrane was added 2.3 g of pyridinium p-toluenesulfonate at room temperature. The resulting mixture was refluxed for 30 minutes. The reaction mixture was cooled ~~to room temperature~~ and added to a mixture of 100 ml of ice water and 100 ml of methylene chloride. The organic

layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 18.6 g of light yellow oily 1-(4-benzyloxyphenyl)-1-(2-tetrahydropyranyloxy)-2-[2-(p-toluenesulfonyloxy)ethoxy]ethane.

(4) A mixture of 2 g of 1-(4-benzyloxyphenyl)-1-(2-tetrahydropyranyloxy)-2-[2-(p-toluenesulfonyloxy)-ethoxy]ethane, 5.9 ml of a 40% aqueous methylamine solution and 20 ml of ethanol was refluxed for 2 hours. The reaction mixture was cooled and added to a mixture of 50 ml of ice water and 50 ml of diethyl ether. The organic layer was separated. The aqueuos layer was extracted twice each with 20 ml of diethyl ether. The extracts were combined with the previously separated organic layer. The combined organic layer was mixed with 10 ml of water. The mixture was adjusted to pH 1.0 with 6 N hydrochloric acid. The aqueous layer was separated and stirred for 30 minutes at room temperature. Thereto was added 30 ml of chloroform. The resulting mixture was adjusted to pH 12 with a 5% aqueous sodium hydroxide solution. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was mixed with 10 ml of acetone. Hydrogen chloride gas was blown into the mixture with ice cooling. The resulting crystals were collected by filtration, washed with

acetone, and dried to obtain 620 mg of 1-(4-benzyloxyphenyl)-2-(2-methylaminoethoxy)ethanol hydrochloride (compound No. 191).

Melting point: 173-173.5°C [EtOH]

The compounds shown in Table 13 were obtained in the same manner.

In Table 13, R^1, R^2, R^3, R^{4a}, R^{4b}, R^6, na and nb each show a substituent or integer used in the following formula:

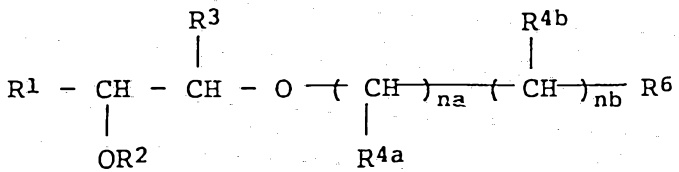
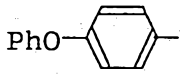
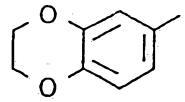
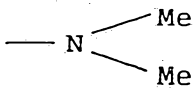
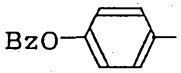
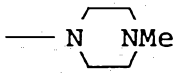
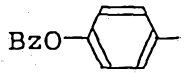
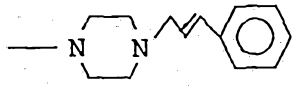
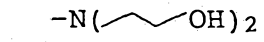
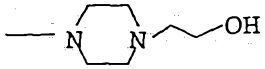
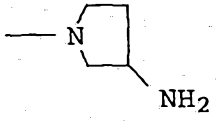


Table 13

Compound No.	R^1	R^2	R^3	R^{4a}	R^{4b}	R^6	na	nb	Addition salt	Melting point (°C)
192		H	H	H	H	-NMe H	1	1	HCl	158-158.5 [IPA]
193	"	"	"	"	"	-N-i-Pr H	"	"	"	170-170.5 [EtOH]
194		"	"	"	"		"	"	"	180-181 [EtOH-AcOEt]
195		"	"	"	"		"	"	2HCl	178-180.5 [MeCN-Et_2O]

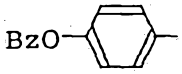
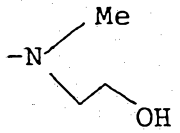
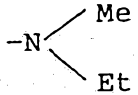
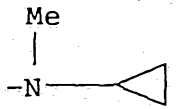
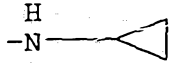
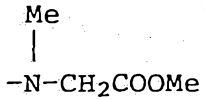
- Cont'd -

Table 13 (Cont'd)

196		H	H	H	H	-N-i-Pr H	1	1	HCl	174.5-175 [IPA]
197	"	"	"	"	"		"	"	2HCl	212.5-213 [MeOH]
198	"	"	"	"	"		"	"	-	Oily
199	"	"	"	"	"		"	"	2HCl	158.5 - 160.5 [EtOH]
200	"	"	"	"	"		"	"	-	55-58

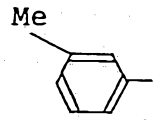
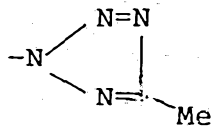
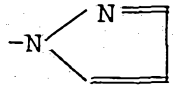
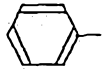
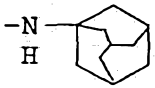
- Cont'd -

Table 13 (Cont'd)

201		H	H	H	H		1	1	-	36-38
202	"	"	"	"	"		"	"	"	Oily
203	"	"	"	"	"		"	"	HCl	139-141 [IPA-AcOEt]
204	"	"	"	"	"		"	"	"	163-164 [EtOH-MeCN]
205	"	"	"	"	"		"	"	-	Oily

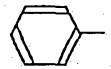
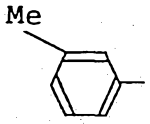
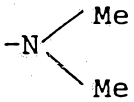
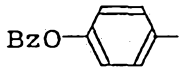
- Cont'd -

Table 13 (Cont'd)

206		H	H	H	H		1	1	-	Oily
207	"	"	"	"	"		"	"	"	"
208	"	"	"	"	"		"	"	HCl	148.5 - 149.5 [IPA-AcOEt]
209		"	"	"	"	"	"	"	"	173.5 - 175.5 [EtOH-Me_2CO]
210	"	"	"	"	"		"	"	PTS	198-200 [EtOH-AcOEt]

- Cont'd -

Table 13 (Cont'd)

211		H	H	H	H	-N-t-Bu H	1	1	HCl	161-162.5 [IPA-AcOEt]
212*1		Me	"	"	"		"	"	"	Oily
213*1		"	"	"	"	"	"	"	-	"

Note: *1: Methoxylation was effected using diazomethane-boron trifluoride in place of using 3,4-dihydro-2H-pyran, to obtain the desired product.

Production Example 11

A mixture of 500 mg of 2-[(imidazol-4-yl)methoxy]-1-phenylethanol, 1.1 ml of pyridine, 1.1 ml of triethylamine and 1.1 ml of acetic anhydride was stirred for 1 hour at 100°C. The reaction mixture was cooled to room temperature. The solvent was removed by distillation under reduced pressure. To the residue were added 1.1 ml of methyl iodide and 5 ml of acetonitrile. The mixture was allowed to stand at room temperature for 24 hours. The solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 4 ml of ethanol and 6.8 ml of a 5% aqueous sodium hydroxide solution. The resulting mixture was stirred at room temperature for 6 hour. The solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 30 ml of chloroform and 20 ml of water. The organic layer was separatd, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The resulting oily product was purified by column chromatography (eluant: chloroform/ethanol = 10/1). Diisopropyl ether was added to the resulting white crystals, and the resulting mixture was filtered to obtainn 450 mg of 2-[(1-methylimidazol-5-yl)methoxy]-1-phenylethanol (compound No. 214).

Melting point: 102-105°C

The following compound was obtained in the same manner.

1-(4-Benzyloxyphenyl)-2-[(1-methylimidazol-5-yl)-methoxy]ethanol (compound No. 215)

Melting point: 148.5-150.5°C [IPA-AcOEt]

Production Example 12

1.23 g of N,N'-dicyclohexylcarbodiimide was added, with ice cooling, to a solution of 1.08 g of 2-(2-aminoethoxy)-1-phenylethanol, 730 mg of nicotinic acid, 810 mg of 1-hydroxybenzotriazole and 0.83 ml of triethylamine dissolved in 5 ml of tetrahydrofuran. The resulting mixture was stirred at the same temperature for 5 minutes and further at room temperature for 1 hour. To the reaction mixture was added 11 ml of ethyl acetate. The insolubles were removed by filtration. To the filtrate was added 5 ml of water and the mixture was adjusted to pH 2 with 6 N hydrochloric acid. The aqueous layer was separated. The organic layer was extracted with 5 ml of water. The extract was combined with the previously separated aqueous layer. The combined aqueous layer was mixed with 20 ml of chloroform and adjusted to pH 10 with potassium carbonate. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by

column chromatography (eluant: chloroform/ethanol = 15/1) to obtain 400 mg of oily 2-(2-nicotinoylamino-ethoxy)-1-phenylethanol (compound No. 216).

IR (neat) cm^{-1}: $\nu_{C=O}$ 1635

Production Example 13

(1) 5 g of (S)-4-benzyl-2-acetoxymethylmorpholine was dissolved in 10 ml of ethanol. To the solution was added a solution of 1 g of sodium hydroxide dissolved in 5 ml of water with ice cooling. The mixture was stirred at room temperature for 10 minutes. The reaction mixture was added to 50 ml of ice water and extracted with 50 ml of chloroform. The organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 30/1) to obtain 3.6 g of oily (S)-4-benzyl-2-hydroxymethylmorpholine.

(2) 3.5 g of (S)-4-benzyl-2-hydroxymethyl-morpholine was dissolved in 5 ml of ethanol. To the solution was added 5 ml of a 5.9 N dry hydrogen chloride-ethanol solution with ice cooling. The resulting mixture was stirred for 10 minutes at the same temperature. Thereto was added a mixture of 500 mg of 5% palladium-carbon and 10 ml of methanol. The resulting mixture was subjected to hydrogenation for 3

hours at 40°C. After the completion of the reaction, palladium-carbon was removed by filtration. The solvent was removed by distillation under reduced pressure to obtain a yellow oily product. To the oily product were added 20 ml of dry methylene chloride and 4.7 ml of triethylamine. The resulting mixture was stirred at room temperature for 30 minutes. Thereto was dropwise added a solution of 4.7 g of trityl chloride dissolved in 10 ml of methylene chloride in 20 minutes, with ice cooling. The mixture was stirred at room temperature for 3 hours and added to 50 ml of ice water. The organic layer was separated and 20 ml of water was added thereto. The resulting mixture was adjusted to pH 12 with a 1 N aqueous sodium hydroxide solution. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain a yellow oily product. The oily product was mixed with 10 ml of diisopropyl ether. The resulting crystals were collected by filtration to obtain 2.7 g of (S)-4-trityl-2-hydroxymethylmorpholine.

Melting point: 142.0-142.5°C [AcOEt-IPE]

Optical rotation: $[\alpha]_D^{27} = -10.9°$ (C=1, $CHCl_3$)

The (2R)-form having the following properties was obtained in the same manner.

Melting point: 142.0-142.5°C [AcOEt-IPE]

Optical rotation: $[\alpha]_D^{27}$ = +10.9° (C=1, $CHCl_3$)

(3) The same procedure as in (1) of Production Example 5 was repeated, except that the styrene oxide and the 4-benzyl-2-hydroxymethylmorpholine were replaced by (S)-2-phenyloxirane and (S)-4-trityl-2-hydroxymethylmorpholine, respectively, to obtain oily (1S,2'S)-1-phenyl-2-[(4-tritylmorpholin-2-yl)methoxy]ethanol (compound No. 217).

(4) In 20 ml of acetone was dissolved (1S,2'S)-1-phenyl-2-[(4-tritylmorpholin-2-yl)methoxy]ethanol. To the solution was added, with ice cooling, 7 ml of a 5.9 N dry hydrogen chloride-ethanol solution. The resulting mixture was stirred for 30 minutes at room temperature to effect a reaction. After the completion of the reaction, the solvent was removed by distillation under reduced pressure. The residue thus obtained was added to a mixture of 30 ml of ice water and 30 ml of ethyl acetate. The aqueous layer was separated and washed with 30 ml of ethyl acetate, after which 50 ml of chloroform was added thereto. The resulting mixture was adjusted to pH 11 with a 2 N aqueous sodium hydroxide solution. The organic layer was separated, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 1.9 g of a yellow oily product. The oily product was dissolved in 10 ml of ethanol. To the solution was

added 720 mg of oxalic acid. The resulting mixture was heated to obtain a solution. The solution was allowed to stand overnight at room temperature. The resulting crystals were collected by filtration and dried to obtain 1.8 g of (1S,2'S)-1-phenyl-2-[(morpholin-2-yl)methoxy]ethanol oxalate (compound No. 218).

Melting point: 130-132°C [EtOH]

Optical rotation: $[\alpha]_D^{24}$ = +19.9° (C=1, $CHCl_3$)

The following compounds were obtained in the same manner.

(1R,2'S)-1-phenyl-2-[(morpholin-2-yl)methoxy]ethanol maleate (compound No. 219)

Melting point: 136-136.5°C [EtOH]

Optical rotation: $[\alpha]_D^{25}$ = -21.7° (C=1, CH_3OH)

(1S,2'R)-1-phenyl-2-[(morpholin-2-yl)methoxy]ethanol maleate (compound No. 220)

Melting point: 136-136.5°C [EtOH]

Optical rotation: $[\alpha]_D^{25}$ = +22.2° (C=1, CH_3OH)

(1R,2'R)-1-phenyl-2-[(morpholin-2-yl)methoxy]ethanol oxalate (compound No. 221)

Melting point: 131-132.5°C [EtOH]

Optical rotation: $[\alpha]_D^{25}$ = -20.4° (C=1, CH_3OH)

Production Example 14

(1) 1.19 g of 4-benzylthiobenzaldehyde was dissolved in 20 ml of tetrahydrofuran. The solution was cooled to -10°C. Thereto was dropwise added 10 ml of a tetrahydrofuran solution containing 2 M of 2-chloroethoxymethylmagnesium chloride in 10 minutes. The resulting mixture was stirred for 1 hour with ice cooling. The reaction mixture was added to a mixture of 50 ml of ice water, 50 ml of ethyl acetate and 1 g of ammonium chloride. The resulting mixture was adjusted to pH 2 with 6 N hydrochloric acid. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography [eluant: toluene/ethyl acetate = 20/1] to obtain 1.34 g of 1-(4-benzylthiophenyl)-2-(2-chloroethoxy)ethanol.

Melting point: 49.5-50.5°C [hexane-IPE]

(2) A mixture of 600 mg of 1-(4-benzylthiophenyl)-2-(2-chloroethoxy)ethanol, 4 ml of a 50% aqueous dimethylamine solution, 310 mg of potassium iodide and 5 ml of ethanol was refluxed for 4 hours. To the reaction mixture was further added 4 ml of a 50% aqueous dimethylamine solution. The resulting mixture was refluxed for 4 hours. The reaction mixture was cooled to room temperature. The solvent was removed by

distillation under reduced pressure. To the residue thus obtained were added 30 ml of ethyl acetate and 30 ml of water. The resulting mixture was adjusted to pH 10.5 with potassium carbonate. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was dissolved in 15 ml of acetone. To the solution was added 0.4 ml of a 5 N dry hydrogen chloride-ethanol solution. The resulting crystals were collected by filtration to obtain 590 mg of 1-(4-benzylthiophenyl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol hydrochloride (compound No. 222).

Melting point: 173.5-174.5°C [EtOH]

The compounds shown in Table 14 were obtained in the same manner.

In Table 14, R^1, R^2, R^3, R^{4a}, R^{4b}, R^6, na and nb each show a substitutent or integer used in the following formula:

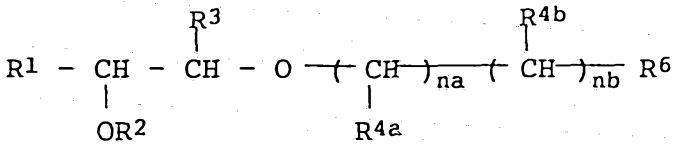
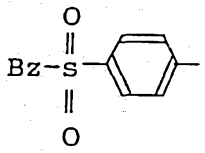
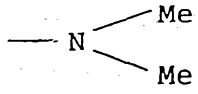
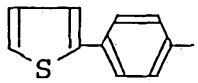
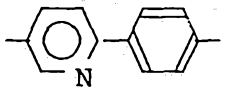
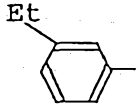
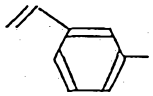


Table 14

Compound No.	R^1	R^2	R^3	R^{4a}	R^{4b}	R^6	na	nb	Addition salt	Melting point (°C)
223		H	H	H	H		1	1	HCl	194-195 [EtOH]
224		"	"	"	"	"	"	"	"	207-208 [EtOH-AcOEt]
225		"	"	"	"	"	"	"	Maleic acid	168-170 (decomp.)
226		"	"	"	"	"	"	"	HCl	159.5 - 160.5 [EtOH-AcOEt]
227		"	"	"	"	"	"	"	"	141-142 [EtOH-AcOEt]

Production Example 15

A mixture of 13.2 g of potassium tert-butoxide and 47.2 ml of 2-(N,N-dimethylamino)ethanol was heated to 80°C. Thereto was dropwise added 40.0 g of 2-(1-naphthyl)oxirane in 3.5 hours. The resulting mixture was stirred for 1.5 hours at 80-85°C. The reaction mixture was cooled and added to a mixture of 100 ml of ethyl acetate and 100 ml of ice water. The resulting mixture was adjusted to pH 11.5 with 6 N hydrochloric acid. The organic layer was separated. The aqueous layer was extracted with 50 ml of ethyl acetate. The extract was combined with the previously separated organic layer. The combined organic layer was washed with water and a saturated aqueous sodium chloride solution, in this order and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was subjected to distillation to obtain a fraction having a boiling point of 152-163°C/0.6-0.8 mmHg. The oily product obtained was dissolved in 200 ml of acetone. Into the solution was blown hydrogen chloride gas with ice cooling. The resulting crystals were collected by filtraiton, washed with acetone, and dried to obtain 22.7 g of 2-[2-(N,N-dimethylamino)ethoxy]-1-(1-naphthyl)ethanol hydrochloride (compound No. 228).

Melting point: 196-197°C [EtOH]

The compounds shown in Table 15 were obtained in the same manner.

In Table 15, R^1, R^2, R^3, R^{4a}, R^{4b}, R^6, na and nb each show a substituent or integer used in the following formula:

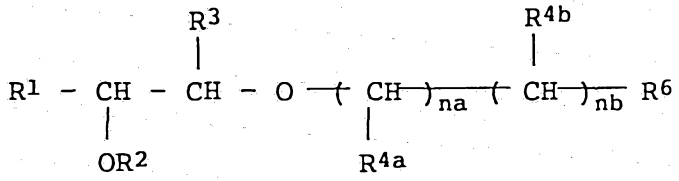
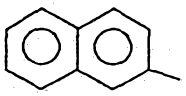
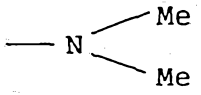
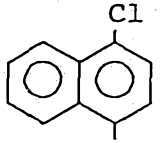
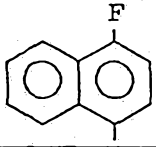
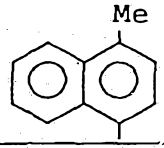
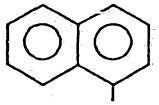
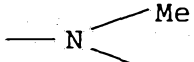
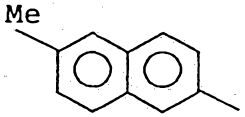
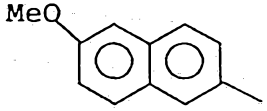
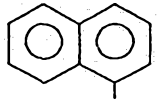
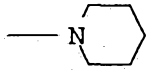


Table 15

Compound No.	R^1	R^2	R^3	R^{4a}	R^{4b}	R^6	na	nb	Addition salt	Melting point (°C)
229		H	H	H	H		1	1	HCl	193-194 [EtOH]
230		"	"	"	"	"	"	"	"	149-150 [Me_2CO-EtOH]
231		"	"	"	"	"	"	"	"	178-179 [Me_2CO-EtOH]
232		"	"	"	"	"	"	"	"	184-185 [Me_2CO-EtOH]

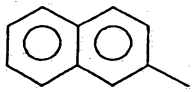
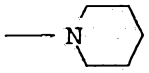
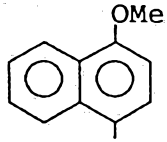
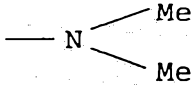
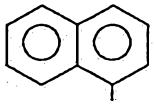
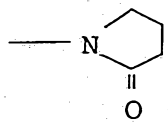
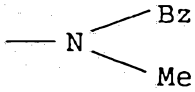
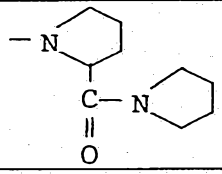
- Cont'd -

Table 15 (Cont'd)

233*		H	H	H	H		2	1	-	Oily
234*	"	"	"	"	"	"	"	2	"	"
235		"	"	"	"	"	1	1	HCl	213-214 [IPA]
236		"	"	"	"	"	"	"	"	205-205.5 [MeOH-EtOH]
237		"	"	"	"		"	"	"	174-174.5 [EtOH-Et_2O]

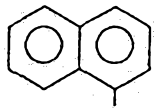
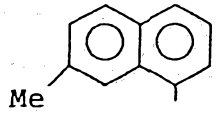
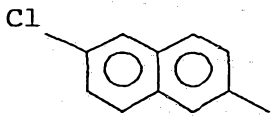
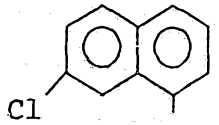
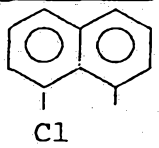
- Cont'd -

Table 15 (Cont'd)

238		H	H	H	H		1	1	HCl	156.5-158 [EtOH-Et_2O]
239		"	"	"	"		"	"	"	157-158 [IPA]
240*		"	"	"	"		1	1	-	Oily
241*	"	"	"	"	"		"	"	"	"
242*	"	"	"	"	"		"	"	"	"

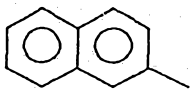
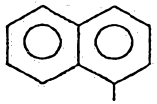
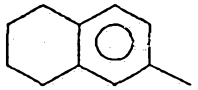
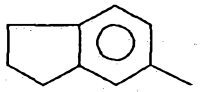
- Cont'd -

Table 15 (Cont'd)

243		H	H	H	H	—N(Et)(Et)	1	1	HCl	155.5-157 [IPA]
244		"	"	"	"	—N(Me)(Me)	"	"	"	151.5 - 153.5 [IPA]
245		"	"	"	"	"	"	"	"	193.5 - 196.5 [EtOH]
246		"	"	"	"	"	"	"	"	166.5-168 [IPA]
247		"	"	"	"	"	"	"	"	161-163 [EtOH]

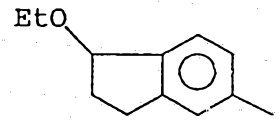
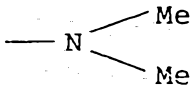
- Cont'd -

Table 15 (Cont'd)

248		H	H	H	H	—N(Et)(Et)	1	1	HCl	100.5 - 101.5 [IPA-AcOEt]
249		"	Me	"	"	—N(Me)(Me)	"	"	"	186.5-188 [EtOH-Me_2CO]
250	"	"	H	Me	"	"	"	"	Fumaric acid	197-198.5 [EtOH-AcOEt]
251		"	"	H	"	"	"	"	HCl	199.5-201 [IPA-AcOEt]
252		"	"	"	"	"	"	"	"	198-199.5 [IPA]

- Cont'd -

Table 15 (Cont'd)

253		H	H	H	H		1	1	HCl	157-159 [IPA]

Note: *: These compounds were not subjected to a step of converting into a hydrochloride.

Production Example 16

(1) A mixture of 6.0 g of 2-hydroxymethyl-4-trityl-morpholine, 1.0 g of potassium tert-butoxide and ml of dimethyl sulfoxide was heated to 80°C. Thereto was dropwise added, at 80-85°C in 2 hours, a solution of 2.8 g of 2-(2-naphthyl)oxirane dissolved in 6 ml of dimethyl sulfoxide. The resulting mixture was stirred at the same temperature for 3 hours. The reaction mixture was cooled and added to a mixture of 60 ml of ice water and 60 ml of ethyl acetate. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 9.0 g of oily 1-(2-naphthyl)-2-[(4-tritylmorpholin-2-yl)-methoxy]ethanol (compound No. 254).

In the same manner, there was obtained oily 1-(1-naphthyl)-2-[(4-tritylmorpholin-2-yl)methoxy]-ethanol (compound No. 255).

(2) In 50 ml of acetone was dissolved 9.0 g of 1-(2-naphthyl)-2-[(4-tritylmorpholin-2-yl)methoxy]-ethanol. To the solution was added 3.5 ml of a 5.9 N dry hydrogen chloride-ethanol solution with ice cooling. The mixture was stirred for 2 hours at room temperature to effect reaction. After the completion of the reaction, the solvent was removed by distillation under

reduced pressure. To the residue thus obtained were added 50 ml of water and 30 ml of ethyl acetate. The aqueous layer was separated and washed with 30 ml of ethyl acetate. Thereto was added 50 ml of ethyl acetate. The resulting mixture was adjusted to pH 10.5 with potassium carbonate. The organic layer was separated, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/methanol = 5/1) to obtain 1.2 g of an oily product. The oily product was dissolved in 5 ml of isopropanol. To the solution was added 0.5 g of fumaric acid. The mixture was heated to obtain a solution. The solution was allowed to stand at room temperature overnight. The resulting crystals were collected by filtration to obtain 0.9 g of 1-(2-naphthyl)-2-[(morpholin-2-yl)methoxy]ethanol 1/2 fumarate (compound No. 256).

Melting point: 141-144°C [EtOH]

In the same manner, there was obtained amorphous 1-(1-naphthyl)-2-[(mropholin-2-yl)methoxy]ethanol hydrochloride (compound No. 257).

Production Example 17

(1) A mixture of 4.5 g of potassium tert-butoxide and 45 ml of ethylene glycol was heated to 80°C. Thereto

was dropwise added 13.7 g of 2-(1-naphthyl)oxirane in 1 hour. The resulting mixture was stirred for 1 hour at the same temperature. The reaction mixture was cooled and added to a mixture of 50 ml of ethyl acetate and 50 ml of ice water. The organic layer was separated. The aqueous layer was extracted twice each with 20 ml of ethyl acetate. The extracts were combined with the previously separated organic layer. The combined organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: toluene/ethyl acetate = 1/3) to obtain 8.3 g of 2-(2-hydroxyethoxy)-1-(1-naphthyl)-ethanol.

Melting point: 91-92°C [IPE]

In the same manner, there was obtained 2-(2-hydroxyethoxy)-1-(2-naphthyl)ethanol.

Melting point: 105-106°C [AcOEt]

(2) 8.3 g of 2-(2-hydroxyethoxy)-1-(1-naphthyl)-ethanol was dissolved in 50 ml of pyridine. The solution was cooled to -25°C. Thereto was added 6.8 g of p-toluenesulfonyl chloride. The resulting mixture was allowed to stand at 0-5°C for 24 hours and further at room temperature for 4 hours. The reaction mixture

was added to a mixture of 103 ml of 6 N hydrochloric acid, 50 ml of ice water and 100 ml of diethyl ether. The resulting mixture was adjusted to pH 2.0 with 6 N hydrochloric acid. The organic layer was separated. The aqueous layer was extracted with 20 ml of diethyl ether. The extract was combined with the previously separated organic layer. The combined organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: toluene/ethyl acetate = 10/1) to obtain 6.3 g of colorless, oily 1-(1-naphthyl)-2-[2-(p-toluenesulfonyloxy)ethoxy]ethanol.

In the same manner, there was obtained colorless, oily 1-(2-naphthyl)-2-[2-(p-toluenesulfonyloxy)ethoxy]-ethanol.

(3) 0.82 g of pyridinium p-toluenesulfonate was added to a solution of 6.3 g of 1-(1-naphthyl)-2-[2-(p-toluenesulfonyloxy)ethoxy]ethanol and 2.97 ml of 3,4-dihydro-2H-pyran dissolved in 63 ml of methylene chloride at room temperature. The resulting mixture was stirred at the same temperature for 20 minutes and further at 35-40°C for 10 minutes. The reaction mixture was cooled, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by

distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: toluene/ethyl acetate = 10/1) to obtain 7.53 g of colorless, oily 1-(1-naphthyl)-1-(tetrahydropyran-2-yloxy)-2-[2-(p-toluenesulfonyloxy)ethoxy]ethane.

In the same manner, there was obtained colorless, oily 1-(2-naphthyl)-1-(tetrahydropyran-2-yloxy)-2-[2-(p-toluenesulfonyloxy)ethoxy]ethane.

(4) A mixture of 7.5 g of 1-(1-naphthyl)-1-(tetrahydropyran-2-yloxy)-2-[2-(p-toluenesulfonyloxy)-ethoxy]ethane, 2.65 ml of N-methylpiperazine, 3.96 g of potassium carbonate and 38 ml of N,N-dimethylformamide was stirred for 2 hours at 90-100°C. The reaction mixture was cooled ~~to room~~ temperature and added to a mixture of 100 ml of diethyl ether and 100 ml of ice water. The organic layer was separated. The aqueous layer was extracted twice each with 25 ml of diethyl ether. The extracts were combined with the previously separated organic layer. The combined organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 10/1) to obtain 3.36 g of colorless, oily 2-[2-(4-methylpiperazin-1-yl)ethoxy]-

1-(1-naphthyl)-1-(tetrahydropyran-2-yloxy)ethane (compound No. 258).

(5) In 30 ml of acetone was dissolved 3.3 g of 2-[2-(4-methylpiperazin-1-yl)ethoxy]-1-(1-naphthyl)-1-(tetrahydropyran-2-yloxy)ethane. To the solution were added 3.46 g of p-toluenesulfonic acid monohydrate and 7 ml of water at room temperature. The resulting mixture was stirred at the same temperature for 30 minutes and further at 40°C for 1 hour. The reaction mixture was added to a mixture of 60 ml of chloroform and 60 ml of ice water. The mixture was adjusted to pH 11 with a 10% aqueous sodium hydroxide solution. The organic layer was separated. The aqueous layer was extracted with 20 ml of chloroform. The extract was combined with the previously separated organic layer. The combined organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was dissolved in 40 ml of acetone. Hydrogen chloride gas was blown into the solution with ice cooling. The resulting solution was stirred at room temperature for 30 minutes. Thereto was added 40 ml of diethyl ether. The resulting mixture was stirred at the same temperature for 30 minutes. The resulting crystals were collected by filtration, washed with acetone, and dried to obtain 2.35 g of 2-[2-(4-methylpiperazin-1-yl)ethoxy]-1-(1-naphthyl)ethanol

dihydrochloride (compound No. 259).

Melting point: 230.5-231.5°C [MeOH]

Production Example 18

The same procedure as in (4) and (5) of Production Example 17 was repeated, except that the N-methylpiperazine was replaced by N-(p-fluorobenzoyl)-piperidine, to obtain 2-{2-[4-(p-fluorobenzoyl)piperidin-1-yl]ethoxy}-1-(1-naphthyl)ethanol hydrochloride (compound No. 260).

Melting point: 204.5-205.5°C [MeOH]

Production Example 19

In 20 ml of ethanol was dissolved 2 g of 1-(1-naphthyl)-1-(tetrahydropyran-2-yloxy)-2-[2-(p-toluene-sulfonyloxy)ethoxy]ethane. To the solution was added 6.60 g of a 40% aqueous methylamine solution at room temperature. The mixture was refluxed for 1 hour. The reaction mixture was cooled and added to a mixture of 20 ml of ice water and 50 ml of diethyl ether. The organic layer was separated. The aqueous layer was extracted with 20 ml of diethyl ether. The extract was combined with the previously separated organic layer. To the combined organic layer was added 15 ml of water and the resulting mixture was adjusted to pH 1.5 with 6 N hydrochloric acid. The aqueous layer was separated. The organic layer was extracted twice each with 10 ml of water. The extracts were combined with the previously

separated aqueous layer. The combined aqueous layer was mixed with 25 ml of chloroform and adjusted to pH 11 with a 10% aqueous sodium hydroxide solution. The organic layer was separated. The aqueous layer was extracted twice each with 10 ml of chloroform. The extracts were combined with the previously separated organic layer. The combined organic layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 1.27 g of an oily product. The oily product was dissolved in 10 ml of acetone. Into the solution was blown hydrogen chloride gas with ice cooling. Thereto was added 10 ml of diethyl ether. The resulting crystals were collected by filtration to obtain 0.72 g of 2-[2-(N-methylamino)ethoxy]-1-(1-naphthyl)ethanol hydrochloride (compound No. 261).

Melting point: 137.5-139°C [IPA]

The compounds shown in Table 16 were obtained in the same manner.

In Table 16, R^1, R^2, R^3, R^{4a}, R^{4b}, R^6, na and nb each show a substituent or integer used in the following formula:

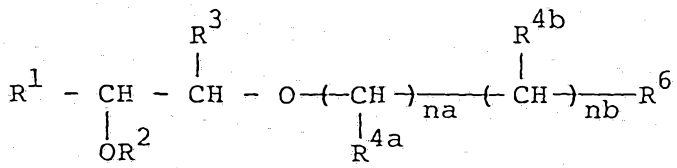
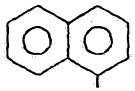
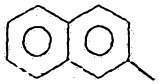


Table 16

Compound No.	R^1	R^2	R^3	R^{4a}	R^{4b}	R^6	na	nb	Addition salt	Melting point (°C)
262		H	H	H	H		1	1	HCl	180-181 [EtOH]
263	"	"	"	"	"		"	"	-	159.5-162
264	"	"	"	"	"		"	"	1/2 Maleic acid	184-185 [IPA-AcOEt]
265		"	"	"	"		"	"	HCl	170-171 [EtOH]
266	"	"	"	"	"		"	"	"	180.5-181.5 [IPA-EtOH]

Production Example 20

A mixture of 3.5 g of potassium tert-butoxide, 9.4 g of N-tritylethanolamine and 50 ml of dimethyl sulfoxide was heated to 85°C. Thereto was added 5.3 g of 2-(1-naphthyl)oxirane. The resulting mixture was stirred at the same temperature for 5 minutes. The reaction mixture was cooled and added to a mixture of 100 ml of ethyl acetate and 150 ml of ice water. The organic layer was separated. The aqueous layer was extracted with 50 ml of ethyl acetate. The extract was combined with the previously separated organic layer. The combined organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 80 ml of a 50% aqueous formic acid solution and 40 ml of tetrahydrofuran. The resulting mixture was stirred at 50-60°C for 1 hour. The reaction mixture was cooled. The solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 60 ml of ethyl acetate and 60 ml of water. The resulting mixture was adjusted to pH 2 with 6 N hydrochloric acid. The aqueous layer was separated. The organic layer was extracted twice each with 15 ml of water. The extracts were combined with the previously separated aqueous layer. To the combined aqueous layer was added 100 ml of chloroform and the resulting mixture

was adjusted to pH 10.5 with potassium carbonate. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. To the residue thus obtained was added 10 ml of diisopropyl ether. The resulting crystals were collected by filtration and dried to obtain 1.8 g of 2-(2-aminoethoxy)-1-(1-naphthyl)ethanol (compound No. 267).

Melting point: 89.5-92°C [$CHCl_3$-Et_2O]

Production Example 21

7 ml of water and 7 ml of dioxane were added to 0.7 g of 2-(2-aminoethoxy)-1-(1-naphthyl)-ethanol to obtain a solution. To the solution was added 0.32 g of potassium carbonate. The resulting mixture was heated to 50°C. Thereto was added 0.35 g of 2-chloropyrimidine. The resulting mixture was refluxed for 3 hours. Thereto were added 0.32 g of potassium carbonate and 0.35 g of 2-chloropyrimidine. The resulting mixture was further refluxed for 2.5 hours. The reaction mixture was cooled and added to a mixture of 20 ml of ethyl acetate and 20 ml of ice water. The organic layer was separated. The aqueous layer was extracted with 10 ml of ethyl acetate. The extract was combined with the previously separated organic layer. To the combined organic layer was added 15 ml of water and the resulting mixture was adjusted to pH 1.5 with 6 N hydrochloric acid. The aqueous layer was

separated. The organic layer was extracted with 10 ml of water. The extract was combined with the previously separated aqueous layer. To the combined aqueous layer was added 50 ml of methylene chloride and the resulting mixture was adjusted to pH 10.5 with potassium carbonate. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 20/1) to obtain an oily product. To the oily product were added 4 ml of ethanol and 0.21 g of maleic acid. The resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture was added 2 ml of diethyl ether. The resulting mixture was stirred at the same temperature for 1 hour. The resulting crystals were collected by filtration and dried to obtain 0.53 g of 1-(1-naphthyl)-2-{2-[(pyrimidin-2-yl)amino]ethoxy}-ethanol maleate (compound No. 268).

Melting point: 101.5-103°C [EtOH-AcOEt]

Production Example 22

0.62 g of N,N'-dicyclohexylcarbodiimide was added to a mixture of 0.7 g of 2-(2-aminoethoxy)-1-(1-naphthyl)ethanol, 0.37 g of nicotinic acid, 0.41 g of 1-hydroxybenzotriazole, 0.42 ml of triethylamine and 4 ml of tetrahydrofuran with ice cooling. The resulting mixture was stirred at the same temperature

for 5 minutes and further at room temperature for 1 hour. To the reaction mixture was added 6 ml of ethyl acetate. The insolubles were removed by filtration. To the filtrate were added 15 ml of ethyl acetate and 20 ml of water. The resulting mixture was adjusted to pH 2 with 6 N hydrochloric acid. The aqueous layer was separated. The organic layer was extracted twice each with 10 ml of water. The extracts were combined with the previsously separated aqueous layer. To the combined aqueous layer was added 30 ml of chloroform and the resulting mixture was adjusted to pH 10.5 with potassium carbonate. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 10/1) to obtain an oily product. The oily product was dissolved in 7 ml of acetone. To the solution was added 0.43 ml of a 5 N dry hydrogen chloride-ethanol solution. The resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture was added 3 ml of diethyl ether. The resulting mixture was stirred at the same temperature for 1 hour. The resulting crystals were collected by filtration and dried to obtain 0.67 g of 1-(1-naphthyl)-2-[2-(nicotinoylamino)ethoxy]ethanol hydrochloride (compound no. 269).

Melting point: 162.5-163.5°C [EtOH-AcOEt]

Production Example 23

The same procedure as in (1) of Production Example 16 was repeated, except that the 2-(2-naphthyl)-oxirane and the 2-hydroxymethyl-4-tritylmorpholine were replaced by 2-(1-naphthyl)oxirane and 1,4-diformyl-2-piperazinyl methanol, respectively, to obtain oily 2-[(1,4-diformylpiperazin-2-yl)methoxy]-1-(1-naphthyl)-ethanol (compound No. 270).

The compounds shown in Table 17 were obtained in the same manner.

In Table 17, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following general formula:

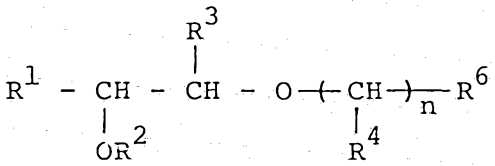
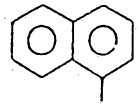
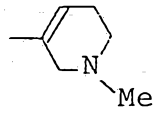
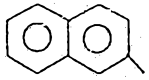
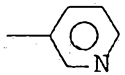
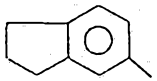


Table 17

Compound No.	R^1	R^2	R^3	R^4	R^6	n	Melting point (°C)
271		H	H	H		1	98-100 [AcOEt]
272		"	"	"		"	83-85 [AcOEt-IPE]
273		"	"	"	"	"	72-73.5 [AcOEt-IPE]

Production Example 24

In 1.5 ml of methanol was dissolved 250 mg of 2-[(1,4-diformylpiperazin-2-yl)methoxy]-1-(1-naphthyl)-ethanol. To the solution was added 1.5 ml of a 5 N dry hydrogen chloride-ethanol solution. The mixture was allowed to stand at room temperature overnight. The resulting crystals were collected by filtration, washed with ethanol, and dried to obtain 180 mg of 1-(1-naphthyl)-2-[(piperazin-2-yl)methoxy]ethanol dihydrochloride (compound No. 274).

Melting point: 199-201°C (decomp.)

Production Example 25

The compound obtained in the same manner as in (1) of Production Example 16 was reacted with hydrogen chloride gas in the same manner as in the production of the hydrochloride of Production Example 22, to obtain the compounds shown in Table 18.

In Table 18, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following general formula:

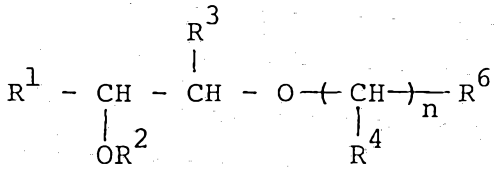
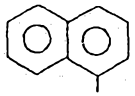
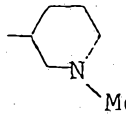
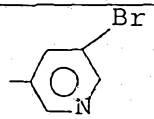
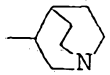
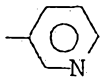


Table 18

Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
275		H	H	H		1	HCl	162-164 [EtOH-Et_2O]
276	"	"	"	"		"	"	143-146
277	"	"	"	-		0	"	151.5-154 [EtOH-Et_2O]
278	"	"	"	H		1	"	154-156 [EtOH-IPA]

Production Example 26

The compounds shown in Table 19 were obtained in the same manner as in (1) and (2) of Production Example 16.

In Table 19, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following general formula:

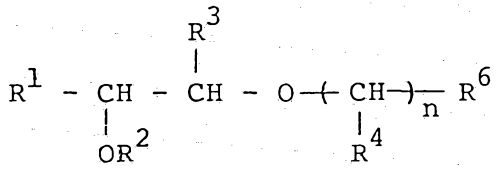
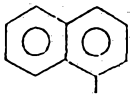
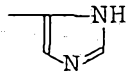
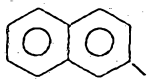
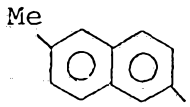


Table 19

Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
279		H	H	H		1	-	Oily
280	"	"	"	"	"	"	1/2 Fumaric acid	167.5-170 [EtOH]
281		"	"	"	"	"	-	122-123 [Me_2CO-AcOEt]
282		"	"	"	"	"	-	138-139 [Me_2CO-AcOEt]

Production Example 27

2-(Imidazol-5-yl)methoxy-1-(1-naphthyl)-ethanol was reacted with methyl iodide to obtain oily 2-(1-methylimidazol-5-yl)methoxy-1-(1-naphthyl)ethanol (compound No. 283).

Production Example 28

(1) 6.0 g of 6-benzyloxy-2-naphthaldehyde was dissolved in 60 ml of tetrahydrofuran. The solution was cooled to -30°C. Thereto was dropwise added, in 10 minutes, 30 ml of a tetrahydrofuran solution containing 1.6 M of 2-chloroethoxymethylmagnesium chloride. The resulting mixture was stirred for 1 hour with ice cooling. The reaction mixture was added to a mixture of 100 ml of ice water, 100 ml of ethyl acetate and 3.6 g of ammonium chloride. The mixture was adjsuted to pH 2 with 6 N hydrochloric acid. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium chloride. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: toluene/ethyl acetate = 20/1) to obtain a solid. To the solid was added 10 ml of diisopropyl ether. The resulting mixture was stirred at room temperature for 1 hour. The resulting crystals were collected by filtration and dried to obtain 4.7 g of 1-(6-benzyloxy-2-naphthyl)-2-(2-chloroethoxy)ethanol.

Melting point: 86-87.5°C [IPE]

(2) A mixture of 4.5 g of 1-(6-benzyloxy-2-naphthyl)-2-(2-chloroethoxy)ethanol, 1 g of potassium iodide, 10 ml of a 50% aqueous dimethylamine solution and 20 ml of ethanol was refluxed for 3 hours. To the reaction mixture was added 10 ml of a 50% aqueous dimethylamine solution. The resulting mixture was further refluxed for 6 hours. The reaction mixture was cooled and concentrated to about a half volume under reduced pressure. To the concentrate were added 100 ml of ethyl acetate and 100 ml of water. The mixture was adjusted to pH 10.5 with potassium carbonate. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. To the residue thus obtained was added 30 ml of diethyl ether. The resulting crystals were collected by filtration and dried to obtain 3.9 g of 1-(6-benzyloxy-2-naphthyl)-2-[2-(N,N-dimethylamino)ethoxy]-ethanol (compound No. 284).

Melting point: 100-100.5°C [EtOH-H_2O]

1-(6-Benzyloxy-2-naphthyl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol was treated in the same manner as in Production Example 22, to obtain 1-(6-benzyloxy-2-naphthyl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol

hydrochloride (compound No. 285).

Melting point: 220-220.5°C [EtOH]

Production Example 29

In 12 ml of pyridine was suspended 3.0 g of 1-(6-benzyloxy-2-naphthyl)-2-[2-(N,N-dimethylamino)-ethoxy]ethanol. To the suspension was added 1.6 ml of acetic anhydride. The resulting mixture was stirred at room temperature for 24 hours. After the completion of the reaction, the solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 60 ml of ethyl acetate and 60 ml of water. The mixture was adjusted to pH 10.5 with potassium carbonate. The organic layer was separated. The aqueous layer was extracted with 30 ml of ethyl acetate. The extract was combined with the previously separated organic layer. The combined organic-layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was dissolved in 30 ml of acetone. To the solution was added 1.5 ml of a 5 N dry hydrogen chloride-ethanol solution. The resulting mixture was stirred at room temperature for 1 hour. The resulting cyrstals were collected by filtration and dried to obtain 2.6 g of 1-acetoxy-1-(6-benzyloxy-2-naphthyl)-2-[2-(N,N-dimethylamino)ethoxy]ethane hydrochloride (compound

No. 286).

Melting point: 157-158°C [MeCN]

Production Example 30

A mixture of 2.0 g of 1-acetoxy-1-(6-benzyloxy-2-naphthyl)-2-[2-(N,N-dimethylamino)ethoxy]-ethane hydrochloride, 0.5 g of 5% palladium-carbon and 40 ml of ethanol was subjected to hydrogenation at room temperature under atmospheric pressure. After the completion of the reaction, the palladium-carbon was removed by filtration. The solvent was removed by distillation under reduced pressure. Acetone was added to the residue thus obtained. The resulting crystals were collected by filtration and dried to obtain 0.76 g of 1-acetoxy-1-(6-hydroxy-2-naphthyl)-2-[2-(N,N-dimethylamino)ethoxy]ethane hydrochloride (compound No. 287).

Melting point: 150.5-151.5°C [EtOH]

Production Example 31

A mixture of 360 mg of 1-acetoxy-1-(6-hydroxy-2-naphthyl)-2-[2-(N,N-dimethylamino)ethxoy]ethane hydrochloride, 10 ml of water and 15 ml of chloroform was adjusted to pH 9 with a saturated aqueous sodium hydrogencarbonate solution. The organic layer was separated. The aqueous layer was extracted twice each with 10 ml of chloroform. The extracts were combined with the previously separated organic layer. The combined

organic layer was washed with saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was dissolved in 6 ml of benzene. To the solution was added 0.12 ml of ethyl isocyanate. The resulting mixture was stirred for 4 hours at 80°C. The reaction mixture was cooled. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 20/1) to obtain an oily product. The oily product was treated in the same manner as in Production Example 22 to obtain, as an amorphous, 150 mg of 1-acetoxy-1-[6-(N-ethylcarbamoyl)oxy-2-naphthyl]-2-[2-(N,N-dimethylamino)ethoxy]ethane hydrochloride (compound No. 288).

Production Example 32

2-[2-(N,N-dimethylamino)ethoxy]-1-(8-nitro-1-naphthyl)ethanol was obtained in the same manner as in (1) and (2) of Production Example 27. This compound was reacted with oxalic acid in the same manner as in (2) of Production Example 16 to obtain 2-[2-(N,N-dimethylamino)ethoxy]-1-(8-nitro-1-naphthyl)ethanol oxalate (compound No. 289).

Melting point: 150-158.5°C

Production Example 33

A mixture of 150 mg of 2-[2-(N,N-dimethylamino)ethoxy]-1-(8-nitro-1-naphthyl)ethanol oxalate, 150 mg of 5% palladium-carbon and 3 ml of methanol was subjected to hydrogenation at room temperature for 30 minutes under atmospheric pressure. After the completion of the reaction, the palladium-carbon was removed by filtration. The filtrate was subjected to distillation under reduced pressure to remove the solvent. The residue thus obtained was added to a mixture of 30 ml of ice water and 30 ml of chloroform. The mixture was adjusted to pH 11 with a 2 N aqueous sodium hydroxide solution. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was dissolved in 1 ml of ethanol. Thereto was added 0.2 ml of a 5.9 N dry hydrogen chloride-ethanol solution. The resulting crystals were collected by filtration and dried to obtain 110 mg of 1-(8-amino-1-naphthyl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol dihydrochloride (compound No. 290).

Melting point: 195-198°C (decomp.) [AcOEt-EtOH]

Production Example 34

Triethylamine was added to 1-(8-amino-1-naphthyl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol

hydrochloride. The resulting mixture was reacted with methanesulfonyl chloride to obtain oily 2-[2-(N,N-dimethylamino)ethoxy]-1-(8-methylsulfonylamino-1-naphthyl)ethanol hydrochloride (compound No. 291).

Production Example 35

The same procedure as in (1) and (2) of Production Example 28 was repeated, except that the 6-benzyloxy-2-naphthaldehyde was replaced by 4-(N,N-dimethylamino)-1-naphthaldehyde, to obtain oily 1-[4-(N,N-dimethylamino)-1-naphthyl]-2-[2-(N,N-dimethylamino)ethoxy]ethanol dihydrochloride (compound No. 292).

Production Example 36

13 ml of ethanol was added to 1.3 g of 1-[4-(N,N-dimethylamino)-1-naphthyl]-2-[2-(N,N-dimethylamino)-ethoxy]ethanol dihydrochloride. The resulting mixture was refluxed for 1 hour. The reaction mixture was cooled. The solvent was removed by distillation under reduced pressure. To the residue thus obtained was added a mixture of 20 ml of ethyl acetate and 20 ml of water. The resulting mixture was adjusted to pH 10 with potassium carbonate. The organic layer was separated, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 1.3 g of oily 1-ethoxy-1-[4-(N,N-dimethylamino)-1-naphthyl]-2-[2-(N,N-dimethyl-

amino)ethoxy]ethane (compound No. 293).

Production Example 37

(1) 9.6 g of 5-bromo-1-hydroxyindane was dissolved in 100 ml of dry methylene chloride. To the solution were added, at room temperature, 570 mg of pyridinium p-toluenesulfonate and 4.5 ml of 3,4-dihydro-2H-pyran. The resulting mxiture was stirred at the same temperature for 3 hours. The reaction mixture was added to ice water. The organic layer was separated, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: toluene/ethyl acetate = 15/1) to obtain 13.1 g of oily 5-bromo-1-(tetrahydropyran-2-yloxy)indane.

(2) 8.1 g of 5-bromo-1-(tetrahydropyran-2-yloxy)-indane was dissolved in 100 ml of anhdyrous tetrahydrofuran under a nitrogen atmosphere. To the solution was dropwise added 20 ml of a 1.5 N n-butyllithium-hexane solution at -65°C in 10 minutes. The resulting mixture was stirred at the same temperature for 5 minutes. Thereto was added 2.3 ml of anhydrous N,N-dimethylformamide. The reaction mixture was heated to room temperature and added to a mixture of 100 ml of ice water, 100 ml of diethyl ether and 2 g of ammonium

chloride. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: toluene/ethyl acetate = 15/1) to obtain 6.5 g of 5-formyl-1-(tetrahydropyran-2-yloxy)indane.

(3) The same procedure as in (1) and (2) of Production Example 28 was repeated, except that the 6-benzyloxy-2-naphthaldehyde was replaced by 5-formyl-1-(tetrahydropyran-2-yloxy)indane, to obtain oily 2-[2-(N,N-dimethylamino)ethoxy]-1-[1-(tetrahydropyran-2-yloxy)indan-5-yl]ethanol (compound No. 294).

(4) A mixture of 2.5 g of 2-[2-(N,N-dimethylamino)ethoxy]-1-[1-(tetrahydropyran-2-yloxy)indan-5-yl]-ethanol, 8 ml of acetic anhydride and 0.64 ml of pyridine was stirred at room temperature for 1 hour. The reaction mixture was added to a mixture of 50 ml of ice water and 50 ml of diethyl ether. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/methanol = 10/1) to obtain 1.9 g of oily 1-acetoxy-2-[2-(N,N-dimethylamino)ethoxy]-1-[1-(tetrahydropyran-2-yloxy)-

indan-5-yl]ethane (compound No. 295).

(5) 1.8 g of 1-acetoxy-2-[2-(N,N-dimethylamino)-ethoxy]-1-[1-(tetrahydropyran-2-yloxy)indan-5-yl]ethane was added to 30 ml of a 4:2:1 mixed solution of acetic acid, tetrahydrofuran and water. The resulting mixture was stirred at 70°C for 2 hours. The reaction mixture was cooled and added to a mixture of 100 ml of water and 100 ml of diethyl ether. The resulting mixture was adjusted to pH 8.5 with potassium carbonate. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 10/1) to obtain 1.0 g of oily 1-acetoxy-1-[(1-hydroxy)indan-5-yl]-2-[2-(N,N-dimethylamino)ethoxy]ethane (compound No. 296).

(6) In 5 ml of pyridine was dissolved 1.0 g of 1-acetoxy-1-[(1-hydroxy)indan-5-yl]-2-[2-(N,N-dimethylamino)-ethoxy]ethane. To the solution was added 0.3 ml of methanesulfonyl chloride at room temeprature. The resulting mixture was stirred at the same temperature overnight. The reaction mixture was added to a mixture of 50 ml of ice water and 50 ml of diethyl ether. The resulting mixture was adjusted to pH 8.5 with potassium carbonate. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent

was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/methanol = 10/1) to obtain 80 mg of oily 1-acetoxy-1-(1H-inden-6-yl)-2-[2-(N,N-dimethylamino)ethoxy]ethane (compound No. 297).

(7) In 0.5 ml of methanol was dissolved 80 mg of 1-acetoxy-1-(1H-inden-6-yl)-2-[2-(N,N-dimethylamino)-ethoxy]ethane. To the solution was added 80 mg of a 28% sodium methoxide-methanol solution with ice cooling. The resulting mixture was stirred at room temperature for 20 minutes. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/methanol = 20/1) to obtain a yellow oily product. The oily product was dissolved in 0.1 ml of ethanol. To the solution was added 0.1 ml of a 5.9 N dry hydrogen chloride-ethanol solution at room temperature. The resulting crystals were collected by filtration to obtain 20 mg of 1-(1H-inden-6-yl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol hydrochloride (compound No. 298).

Melting point: 168-171°C (decomp.) [AcOEt-EtOH]

~~Production Example 38~~

In the same manner as in the production of hydrochloride in (5) of Production Example 37 and Production Example 22, 1-[(1-hydroxy)indan-5-yl]-2-~~[2-(N,N-dimethylamino)ethoxy]ethanol hydrochloride~~

Note: In the above name of the compound No. 297 and 298 obtained, respectively, the term "inden-6-yl" was used because it is not clear yet to which carbon of the indene the carbon of the ethoxy group bonds.

Production Example 38

In the same manner as in the production of hydrochloride in (5) of Production Example 37 and Production Example 22, 1-[(1-hydroxy)indan-5-yl]-2-[2-(N,N-dimethylamino)-ethoxy]ethanol hydrochloride

(compound No. 299) was obtained.

Melting point: 150-152°C [IPA]

Production Example 39

2-[2-(N,N-dimethylamino)ethoxy]-1-(1-naphthyl)ethanol hydrochloride was reacted with acetic anhydride in pyridine in the presence of triethylamine to obtain oily 1-acetoxy-2-[2-(N,N-dimethylamino)ethoxy]-1-(1-naphthyl)ethane (compound No. 300).

Production Example 40

The compound obtained from 2-[2-(6-methylnaphthyl)]oxirane in the same manner as in (1) of Production Example 16 was reacted with hydrogen chloride gas in the same manner as in the production of hydrochloride in Production Example 22, to obtain oily 2-[2-(N-methyl-2,3-dihydropyridin-6H-5-yl)methoxy]-1-[2-(6-methylnaphthyl)]ethanol (compound No. 301).

Production Example 41

The compounds shown in Table 20 were obtained in the same manner as in (1) and (2) of Production Example 28.

In Table 20, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following formula:

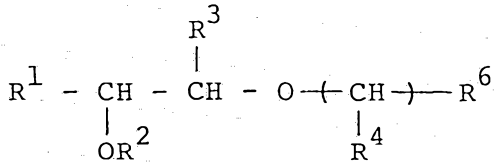


Table 20

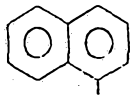
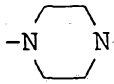
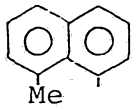
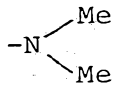
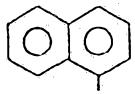
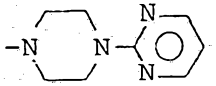
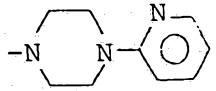
Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
302		H	H	H		2	2HCl	237-238 (decomp.) [EtOH-H_2O]
303		"	"	"		"	HCl	191-191.5 [IPA]
304		"	"	"		"	2HCl	175-176.5 (decomp.) [EtOH]
305	"	"	"	"		"	"	122-124 [EtOH]

Table 20 (Cont'd)

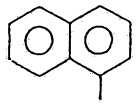
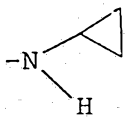
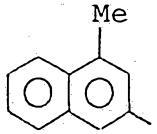
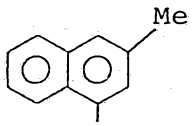
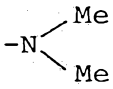
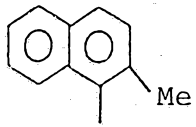
306		H	H	H	-N(Me)H	3	-	119-120 [AcOEt]
307	"	"	"	"	-N(i-Pr)H	"	HCl	139-140.5 [EtOH-AcOEt]
308	"	"	"	"		"	"	111.5-112 [EtOH-AcOEt]
309		"	"	"	-N(Me)Me	2	"	186-187 [EtOH-AcOEt]

Table 20 (Cont'd)

310		H	H	H		2	HCl	160-161.5 [EtOH-AcOEt]
311		"	"	"	"	"	"	149-150 [EtOH-Me_2CO]

Production Example 42

1.7 g of potassium tert-butoxide was added to 31 ml of 2-(N,N-dimethylamino)ethanol. The resulting mixture was heated to 80°C. To the solution was dropwise added, at 80-85°C in 1.5 hours, a solution of 5.2 g of 2-(benzo[b]thiophen-5-yl)oxirane dissolved in 8 ml of dimethyl sulfoxide. The resulting mixture was stirred at the same temperature for 1 hour. The reaction mixture was cooled and added to a mixture of 60 ml of ethyl acetate and 60 ml of ice water. The organic layer was separated. The aqueous layer was extracted with 30 ml of ethyl acetate. The extract was combined with the previously separated organic layer. To the combined organic layer was added 50 ml of ice water and the resulting mixture was adjusted to pH 1.5 with 6 N hydrochloric acid. The aqueous layer was separated and 50 ml of chloroform was added thereto. The resulting mixture was adjusted to pH 10.5 with potassium carbonate. The organic layer was separated, washed with water and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The resulting oily product was dissolved in 50 ml of acetone. To the solution was added 4.3 ml of a 5 N dry hdyrogen chloride-ethanol solution. The resulting mixture was stirred at room temperature for 1 hour and 20 ml of diethyl ether was then added thereto. The resulting mixture was further stirred for 1 hour. The resulting crystals were collected

by filtration and dried to obtain 3.3 g of 1-(benzo[b]-thiophen-5-yl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol hydrochloride (compound No. 312).

Melting point: 191.5-192.5°C [EtOH-Me_2CO]

The compounds shown in Table 21 were obtained in the same manner.

In Table 21, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following formula:

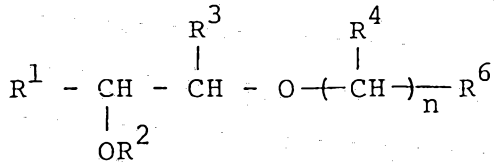


Table 21

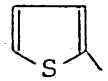
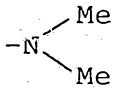
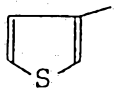
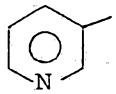
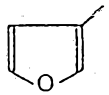
Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
313		H	H	H		2	HCl	139-141
314		"	"	"	"	"	"	165.5-166 [EtOH-Et_2O]
315		"	"	"	"	"	2HCl	143-146 [EtOH]
316		"	"	"	"	"	HCl	128.5-130 [EtOH]

Table 21 (Cont'd)

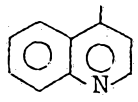
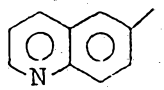
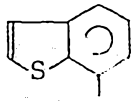
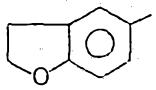
317		H	H	H	-N(Me)Me	2	2HCl	185-185.5 [EtOH-IPA]
318		"	"	"	"	"	HCl	128-130
319		"	"	"	"	"	Fumaric acid	136-136.5 [IPA]
320		"	"	"	"	"	HCl	166.5-167.5 [IPA-AcOEt]
321		"	"	"	"	"	"	168.5-169.5 [IPA]

Table 21 (Cont'd)

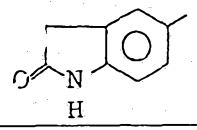
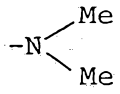
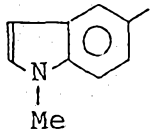
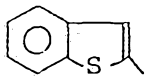
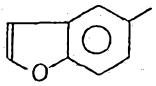
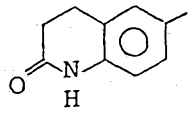
322		H	H	H		2	HCl	169-170
323		"	"	"	"	"	-	Oily
324		"	"	"	"	"	"	188.5-189 [EtOH-AcOEt]
325		"	"	"	"	"	"	168-169.5 [IPA-AcOEt]
326		"	"	"	"	"	"	169-172 [EtOH]

Table 21 (Cont'd)

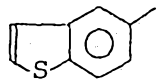
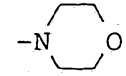
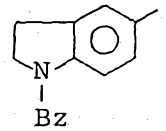
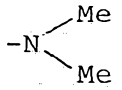
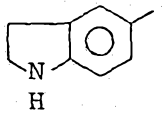
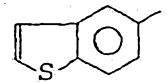
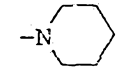
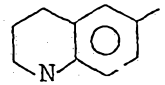
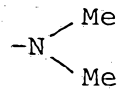
327		H	H	H		2	HCl	166.5-167.5 [EtOH-Me_2CO]
328		"	"	"		"	-	Oily
329*		"	"	"	"	"	2HCl	"
330		"	"	"		"	HCl	167.5-169
331		"	"	"		"	2HCl	Oily

Table 21 (Cont'd)

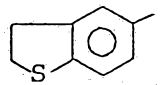
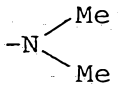
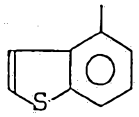
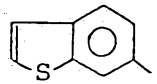
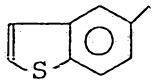
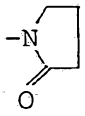
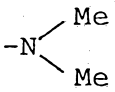
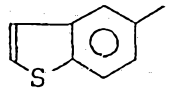
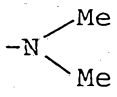
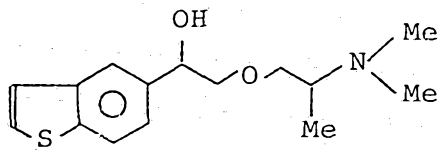
332		H	H	H		2	HCl	207.5-210 [EtOH]
333		"	"	"	"	"	"	190.5-192 [EtOH-IPA]
334		"	"	"	"	"	"	171-172 [IPA-AcOEt]
335		"	"	"		"	-	Oily
336	"	"	"	"		3	-	81.5-85

Table 21 (Cont'd)

337		H	H	H		4	HCl	105-107 [EtOH-AcOEt]
338							Fumaric acid	123-124.5 [EtOH-AcOEt]

Note. *: This compound can be obtained by subjecting compound No. 328 to conventional hydrogenation reaction.

Production Example 43

A mixture of 1.6 g of 3-pyridinemethanol, 1.7 g of potassium tert-butoxide and 23 ml of dimethyl sulfoxide was heated to 80°C. Thereto was added 2.4 g of 2-(benzo[b]furan-5-yl)oxirane. The resulting mixture was stirred at 85-90°C for 15 minutes. The reaction mixture was added to a mixture of 50 ml of ice water and 50 ml of ethyl acetate. The resulting mixture was adjusted to pH 1 with 6 N hydrochloric acid. The aqueous layer was separated and 30 ml of ethyl acetate was added thereto. The resulting mixture was adjusted to pH 9.5 with potassium carbonate. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 50/1) to obtain 0.56 g of 1-(benzo[b]furan-5-yl)-2-(pyridin-3-ylmethoxy)-ethanol (compound No. 339).

Melting point: 85-86°C [IPE-EtOH]

The compounds shown in Table 22 were obtained in the same manner.

In Table 22, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following formula:

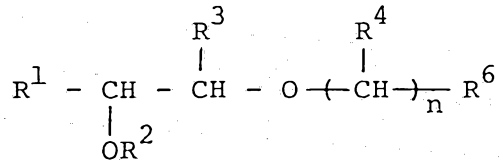


Table 22

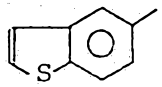
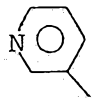
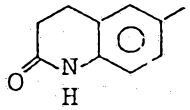
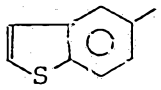
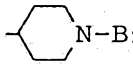
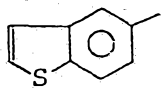
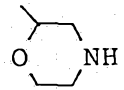
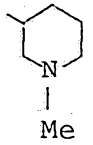
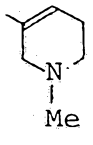
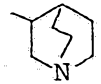
Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
340		H	H	H		1	-	106.5-107.5 [AcOEt-IPE]
341		"	"	"	"	"	HCl	Oily
342		"	"	"		2	-	"

Table 22 (Cont'd)

343		H	H	H		1	-	121.5-125 [AcOEt]
344	"	"	"	"		"	"	127-129.5 [EtOH-IPE]
345	"	"	"	"		"	"	95.5-98 [AcOEt]
346	"	"	"	-		0	HCl	181-185 [EtOH-AcOEt]

Production Example 44

(1) A mixture of 5.7 g of potassium tert-butoxide and 57 ml of ethylene glycol was heated to 80°C. Thereto was added, in 1.5 hours, a solution of 18 g of 2-(benzo[b]thiophen-5-yl)oxirane dissolved in 30 ml of dimethyl sulfoxide. The resulting mixture was stirred at the same temperature for 30 minutes. The reaction mixture was added to a mixture of 120 ml of ice water and 80 ml of ethyl acetate. The organic layer was separated. The aqueous layer was extracted twice each with 30 ml of ethyl acetate. The extracts were combined with the previously separated organic layer. The combined organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography (eluant: chloroform/ethanol = 20/1) to obtain 9.1 g of 1-(benzo[b]thiophen-5-yl)-2-(2-hydroxyethoxy)-ethanol.

Melting point: 119-120.5°C [EtOH-AcOEt]

(2) In 54 ml of pyridine was dissolved 9.0 g of 1-(benzo[b]thiophen-5-yl)-2-(2-hydroxyethoxy)ethanol. To the solution was added, at -25°C, 7.2 g of p-toluenesulfonyl chloride. The mixture was allowed to stand at 0-5°C for 24 hours and further at room temperature for 4 hours. The reaction mixture was added to

a mixture of 103 ml of 6 N hydrochloric acid, 50 ml of ice water and 100 ml of diethyl ether. The resulting mixture was adjusted to pH 2.0 with 6 N hydrochloric acid. The organic layer was separated. The aqueous layer was extracted with 30 ml of diethyl ether. The extract was combined with the previously separated organic layer. The combined organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography (eluant: toluene/ethyl acetate = 10/1) to obtain 7.7 g of colorless oily 1-(benzo[b]thiophen-5-yl)-2-[2-(p-toluenesulfonyloxy)ethoxy]ethanol.

(3) 0.97 g of pyridinium p-toluenesulfonate was added, at room temperature, to a solution of 7.6 g of 1-(benzo[b]thiophen-5-yl)-2-[2-(p-toluenesulfonyloxy)-ethoxy]ethanol and 3.5 ml of 3,4-dihydro-2H-pyran dissolved in 40 ml of methylene chloride. The mixture was stirred at the same temperature for 20 minutes and further at 40-45°C for 30 minutes. The reaction mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 8.7 g of colorless, oily 1-(benzo[b]-thiophen-5-yl)-1-(2-tetrahydropyranyloxy)-2-[2-(p-toluenesulfonyloxy)ethoxy]ethane.

(4) In 15 ml of ethanol was dissolved 1.5 g of 1-(benzo[b]thiophen-5-yl)-1-(2-tetrahydropyranyloxy)-2-[2-(p-toluenesulfonyloxy)ethoxy]ethane. To the solution was added 4.9 ml of a 40% aqueous methylamine solution. The resulting mixture was refluxed for 1 hour. The reaction mixture was added to a mixture of 20 ml of ice water and 20 ml of diethyl ether. The organic layer was separated. The aqueous layer was extracted with 20 ml of diethyl ether. The extract was combined with the previously separated organic layer. To the combined organic layer was added 20 ml of water. The resulting mixture was adjusted to pH 1.5 with 6 N hydrochloric acid and stirred at room temperature for 20 minutes. The aqueous layer was separated. The organic layer was extracted with 10 ml of water. The extract was combined with the previously separated aqueous layer. To the combined aqueous layer was added 30 ml of methylene chloride. The resulting mixture was adjusted to pH 11 with a 10% aqueous sodium hydroxide solution. The organic layer was separated. The aqueous layer was extracted with 15 ml of methylene chloride. The extract was combined with the previously separated organic layer and the combined organic layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was dissolved in 7 ml of acetone. To the solution was added 0.5 ml of a 5 N dry hydrogen chloride-ethanol

solution. The resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture was added 7 ml of diethyl ether. ~~The resulting crystals were added 7 ml of diethyl ether.~~ The resulting crystals were collected by filtration to obtain 0.5 g of 1-(benzo[b]thiophen-5-yl)-2-(N-methylaminoethoxy)ethanol hydrochloride (compound No. 347).

Melting point: 201.5-202.5°C [EtOH-Me_2CO]

The compounds shown in Table 23 were obtained in the same manner.

In Table 23, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following formula:

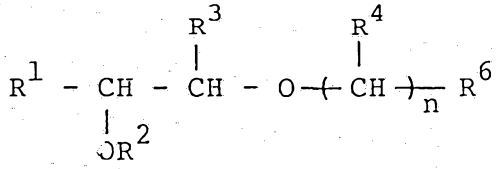


Table 23

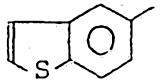
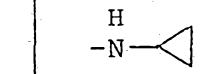
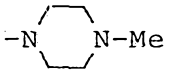
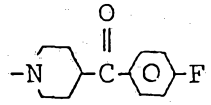
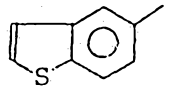
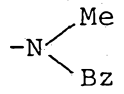
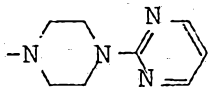
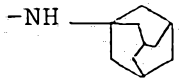
Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
348		H	H	H		2	HCl	196.5-197.5 [EtOH-Me_2CO]
349	"	"	"	"		"	2HCl	232-234 [MeOH-Me_2CO]
350	"	"	"	"		"	HCl	219.5-220 [EtOH-AcOEt]

Table 23 (Cont'd)

351		H	H	H		2	Oxalic acid	138-149 [EtOH-AcOEt]
352	"	"	"	"		"	HCl	170.5-171.5 [EtOH-AcOEt]
353	"	"	"	"		"	"	222.5-223 [EtOH-AcOEt]

Production Example 45

(1) The same procedure as in Production Example 43 was repeated, except that the 2-(benzo[b]furan-5-yl)-oxirane and the 3-pyridinemethanol were replaced by 2-(benzo[b]thiophen-5-yl)oxirane and 1,4-diformyl-2-piperazinemethanol, respectively, to obtain oily 1-(benzo[b]thiophen-5-yl)-2-[(1,4-diformylpiperazin-2-yl)methoxy]ethanol (compound No. 354).

(2) In 1.5 ml of methanol was dissolved 270 mg of 1-(benzo[b]thiophen-5-yl)-2-[(1,4-diformylpiperazin-2-yl)methoxy]ethanol. To the solution was added 1.5 ml of a 5 N dry hydrogen chloride-ethanol solution. The resulting mixture was allowed to stand at room temperature overnight. The resulting crystals were collected by filtration, washed with ethanol, and dried to obtain 150 mg of 1-(benzo[b]thiophen-5-yl)-2-[(piperazin-2-yl)methoxy]ethanol dihydrochloride (compound No. 355).

Melting point: 216-218°C (decomp.)

Production Example 46

(1) A mixture of 10 g of 2-(N-tritylamino)ethanol, 3.7 g of potassium tert-butoxide and 30 ml of dimethyl sulfoxide was heated to 85°C. Thereto was added a solution of 5.8 g of 2-(benzo[b]thiophen-5-yl)oxirane dissolved in 10 ml of dimethyl sulfoxide. The resulting mixture was stirred at the same temperature for 5 minutes. The reaction mixture was added to a

mixture of 150 ml of ice water and 100 ml of ethyl acetate. The organic layer was separated. The aqueous layer was extracted with 30 ml of ethyl acetate. The extract was combined with the previously separated organic layer. The combined organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 70 ml of a 50% aqueous formic acid solution and 30 ml of tetrahydrofuran. The resulting mixture was stirred at 50-60°C for 1 hours. The solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 50 ml of ethyl acetate and 30 ml of water. The resulting mixture was adjusted to pH 2 with 6 N hydrochloric acid. The aqueous layer was separated. The organic layer was extracted twice each with 10 ml of water. The extracts were combined with the previously separated aqueous layer. To the combined aqueous layer was added 50 ml of methylene chloride and the resulting mixture was adjusted to pH 10.5 with potassium carbonate. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 1.2 g of 1-(benzo[b]thiophen-5-yl)-2-(2-aminoethoxy)ethanol (compound No. 356).

Melting point: 87-90.5°C [EtOH-IPE]

(2) 1.1 g of 1-(benzo[b]thiophen-5-yl)-2-(2-aminoethoxy)ethanol was dissolved in 10 ml of ethanol. To the solution was added 290 mg of fumaric acid. The resulting mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added 7 ml of diethyl ether. The resulting mixture was stirred at the same temperature for 1 hour. The resulting crystals were collected by filtration and dried to obtain 1.2 g of 1-(benzo[b]thiophen-5-yl)-2-(2-aminoethoxy)ethanol 1/2 fumarate (compound No. 357).

Melting point: 204.5-205.5°C [MeOH-EtOH]

Production Example 47

The same procedure as in Production Example 46 was repeated, except that the 2-(N-tritylamino)-ethanol was replaced by (1-tritylimidazol-4-yl)methanol, to obtain 1-(benzo[b]thiophen-5-yl)-2-[(imidazolyl)-methoxy]ethanol (compound No. 358) having a melting point of 128-129°C [AcOEt].

In the above name of the compound obtained, the term "(imidazolyl)methoxy" was used because it is not clear yet to which carbon of the 4- and 5-position carbons of the imidazolyl group the carbon of the methoxy group bonds.

Production Example 48

0.46 g of 1-(benzo[b]thiophen-5-yl)-2-(2-aminoethoxy)ethanol was dissolved in a mixture of 5 ml

of water and 5 ml of dioxane. Thereto was added 0.21 g of sodium carbonate. The resulting mixture was heated to 50°C. Thereto was added 0.22 g of 2-chloropyrimidine. The resulting mixture was refluxed for 3 hours. The reaction mixture was added to a mixture of 30 ml of ice water and 30 ml of ethyl acetate. The organic layer was separated. The aqueous layer was extracted with 10 ml of ethyl acetate. The extract was combined with the previously separated organic layer. To the combined organic layer was added 20 ml of water and the resulting mixture was adjusted to pH 1.5 with 6 N hydrochloric acid. The aqueous layer was separated. The organic layer was extracted with 10 ml of water. The extract was combined with the previously separated aqueous layer. To the combined aqueous layer was added 50 ml of methylene chloride and the resulting mixture was adjusted to pH 10.5 with potassium carbonate. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 20/1) to obtain an oily product. To the oily product were added 2 ml of ethanol and 70 mg of maleic acid. The resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture was added 2 ml of diethyl ether. The resulting crystals were collected by filtration and dried to obtain 0.28 g of 1-(benzo[b]-

thiophen-5-yl)-2-{[2-(pyrimidin-2-yl)amino]ethoxy}-ethanol 1/2 maleate (compound No. 359).

Melting point: 113.5-114.5 C [IPA-AcOEt]

Production Example 49

0.39 g of N,N'-dicyclohexylcarbodiimide was added, with ice cooling, to a mixture of 0.45 g of 1-(benzo[b]thiophen-5-yl)-2-(2-aminoethoxy)ethanol, 0.23 g of nicotinic acid, 0.26 g of 1-hydroxybenzotriazole, 0.26 ml of triethylamine and 3 ml of tetrahydrofuran. The resulting mixture was stirred at the same temperature for 5 minutes and further at room temperature for 2 hours. To the reaction mixture were added 20 ml of water and 20 ml of ethyl acetate. The insolubles were removed by filtration. The filtrate was adjusted to pH 1.5 with 6 N hydrochloric acid. The aqueous layer was separated. The organic layer was extracted twice each with 5 ml of water. The extracts were combined with the previously separated aqueous layer. To the combined aqueous layer was added 30 ml of chloroform and the resulting mixture was adjusted to pH 10.5 with potassium carbonate. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 10/1). The resulting oily product was dissolved in 3 ml of ethanol. To the solution

was added 0.24 ml of a 5 N dry hydrogen chloride-ethanol solution. The resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture was added 1.5 ml of diethyl ether. The resulting mixture was stirred at the same temperature for 1 hour. The resulting crystals were collected by filtration and dried to obtain 0.31 g of 1-(benzo[b]thiophen-5-yl)-2-[2-(nicotinoylamino)ethoxy]ethanol hydrochloride (compound No. 360).

Melting point: 152-153°C [EtOH-AcOEt]

Production Example 50

(1) 1.6 g of 4-methyl-2-formylthiazole was dissolved in 30 ml of tetrahydrofuran. The solution was cooled to -30°C. Thereto was dropwise added, in 10 minutes, 10 ml of a tetrahydrofuran solution containing 1.6 M of 2-chloroethoxymethylmagnesium chloride. The mixture was stirred for 1 hour with ice cooling. The reaction mixture was added to a mixture of 50 ml of ice water, 50 ml of ethyl acetate and 2 g of ammonium chloride. The resulting mixture was adjusted to pH 7 with 6 N hydrochloric acid and stirred at the same temperature for 5 minutes. The reaction mixture was adjusted to pH 6 with a saturated aqueous sodium hydrogencarbonate solution. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent

was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: toluene/ethyl acetate = 4/1) to obtain 1.3 g of oily 1-(4-methyl-2-thiazolyl)-2-(2-chloroethoxy)ethanol.

(2) A mixture of 1.2 g of 1-(4-methyl-2-thiazolyl)-2-(2-chloroethoxy)ethanol, 3 ml of a 50% aqueous dimethylamine solution, 0.45 g of potassium iodide and 20 ml of ethanol was refluxed for 3 hours. To the reaction mixture was added 3 ml of a 50% aqueous dimethylamine solution. The resulting mixture was refluxed for 3 hours. The solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 30 ml of ethyl acetate and 30 ml of water. The resulting mixture was adjusted to pH 1.5 with 6 N hydrochloric acid. The aqueous layer was separated and washed with 10 ml of ethyl acetate. Thereto was added 30 ml of ethyl acetate. The resulting mixture was adjusted to pH 10.5 with potassium carbonate. The organic layer was separated, washed with 10 ml of water and 10 ml of a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was dissolved in 6 ml of ethanol. To the solution were added 0.6 ml of a 5 N dry hydrogen chloride-ethanol solution and 6 ml of diethyl ether. The mixture was stirred at room temperature for 1 hour. The resulting crystals were

collected by filtration, washed with 2 ml of a 1:1 mixture of diethyl ether and ethanol, and dried to obtain 390 mg of 1-(4-methyl-2-thiazolyl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol hydrochloride (compound No. 361).

Melting point: 159-160°C [IPA-AcOEt]

The compounds shown in Table 24 were obtained in the same manner.

In Table 24, R^1, R^2, R^3, R^4, R^6 and n each show a substituent or integer used in the following formula:

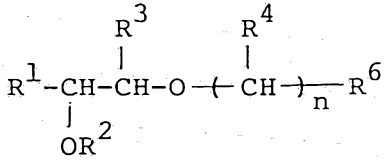


Table 24

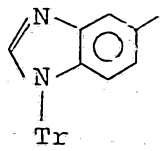
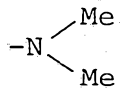
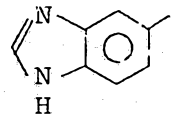
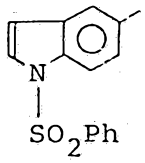
Compound No.	R^1	R^2	R^3	R^4	R^6	n	Addition salt	Melting point (°C)
362		H	H	H		2	-	Oily
363 *1		"	"	"	"	"	2HCl	185-186.5 [EtOH-AcOEt]
364		"	"	"	"	"	-	Oily

Table 24 (Cont'd)

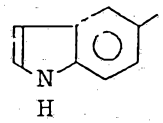
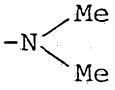
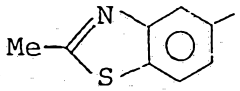
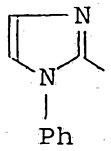
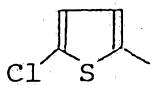
365 *2		H	H	H		2	-	Oily
366		"	"	"	"	"	HCl	175-176 [EtOH-AcOEt]
367		"	"	"	"	"	2HCl	Oily
368		"	"	"	"	"	HCl	182.5-183 [EtOH-AcOEt]

Table 24 (Cont'd)

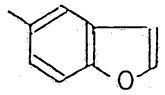
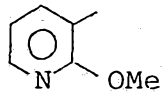
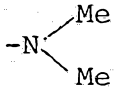
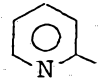
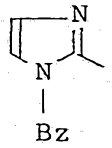
369		H	H	H	$-NH_2$	2	1/2 Fumaric acid	170-173
370		"	"	"		"	2HCl	116-117 [EtOH-Me_2CO]
371		"	"	"	"	"	"	179-179.5 [EtOH-AcOEt]
372		"	"	"	"	"	"	155-156 [EtOH-AcOEt]

Table 24 (Cont'd)

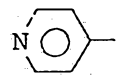
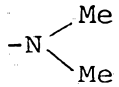
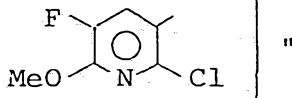
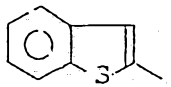
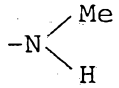
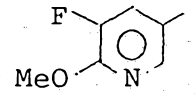
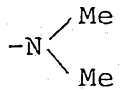
373		H	H	H		2	2HCl	184-186 [EtOH-AcOEt]
374		"	"	"	"	"	HCl	196-197 [MeOH]
375		"	"	"		"	"	193-193.5 [EtOH-AcOEt]
376 *3		"	"	"		"	"	162-163 [IPA]

Table 24 (Cont'd)

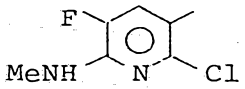
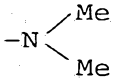
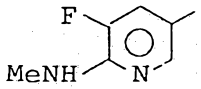
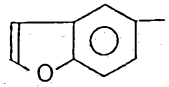
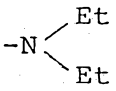
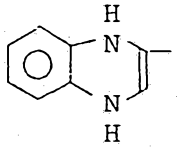
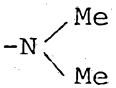
377		H	H	H		2	HCl	153.5-154 [IPA]
378		"	"	"	"	"	2HCl	176-179
379		"	"	"		"	-	Oily
380		"	"	"		"	"	"

Table 24 (Cont'd)

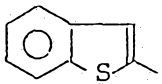
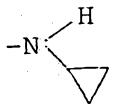
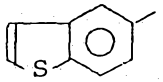
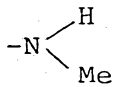
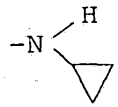
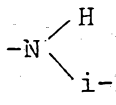
381		H	H	H		2	HCl	194.5-195 [EtOH-AcOEt]
382		"	"	"		3	-	109-111 [AoOEt]
383	"	"	"	"		"	HCl	133.5-134.5 [EtOH-AcOEt]
384	"	"	"	"		"	"	136.5-139.5 [EtOH-AcOEt]

Table 24 (Cont'd)

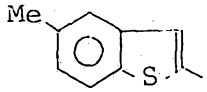
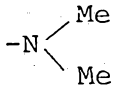
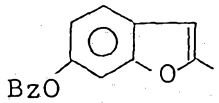
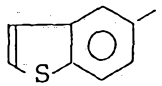
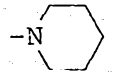
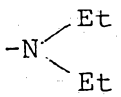
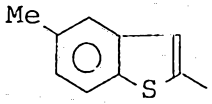
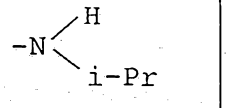
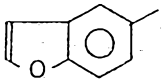
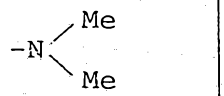
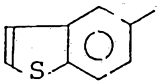
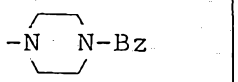
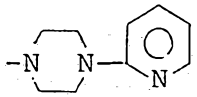
385		H	H	H		2	HCl	193-193.5 [EtOH-AcOEt]
386		"	"	"	"	"	"	171.5-172 [EtOH-AcOEt]
387		"	"	"		3	"	137.5-139.5 [EtOH-AcOEt]
388	"	"	"	"		2	"	138.5-139 [EtOH-AcOEt]

Table 24 (Cont'd)

389		H	H	H		2	HCl	184-184.5 [EtOH-AcOEt]
390		"	"	"		3	-	68.5-69.5 [Hexane]
391		"	"	"		2	2HCl	250-252.5 (decomp.) [MeOH-H_2O]
392	"	"	"	"		"	"	155-157 [EtOH]

Table

Table 24 (Cont'd)

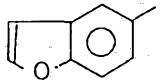
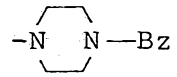
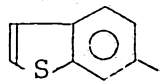
393		H	H	H	-N(H)Me	3	-	65-67.5 [IPA-IPE]
394	"	"	"	"		2	2HCl	234-234.5 [MeOH-AcOEt]
395	"	"	"	"	-N(H)Me	"	HCl	178-180.5 [IPA-AcOEt]
396		"	"	"	-N(Me)Me	3	-	52-53 [IPE]

Table 24 (Cont'd)

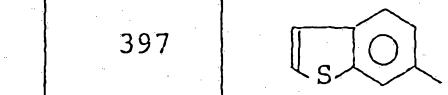
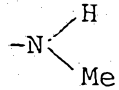
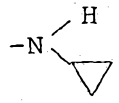
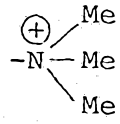
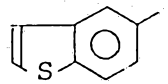
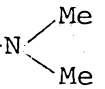
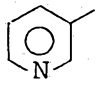
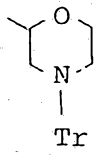
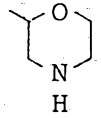
397		H	H	H		3	-	81.5-83 [IPA-IPE]
398	"	"	"	"	"	2	HCl	196-198 [EtOH-AcOEt]
399	"	"	"	"		"	"	190-192.5 [EtOH-AcOEt]
400		"	"	"		"	1/2 1,5-naphthalene-disulfonic acid	Amorphous

Table 24 (Cont'd)

401		Ac	H	H		2	HCl	Oily
402		H	"	"		1	—	"
403	"	"	"	"		"	1/2 Maleic acid	110-117

Note: *1: This compound can be obtained by subjecting compound No. 362 to hydrolysis reaction using hydrochloric acid.

*2: This compound can be obtained by subjecting compound No. 364 to hydrolysis reaction using sodium hydroxide.

*3: This compound can be obtained by subjecting compound No. 374 to conventional hydrogenation reaction.

Production Example 51

(1) A mixture of 9.2 g of 1-(2-thienyl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol and 18 ml of acetic anhydride was refluxed for 10 minutes. The reaction mixture was dropwise added to a mixture of 7.8 ml of concentrated nitric acid and 27 ml of acetic anhydride at 0°C in 30 minutes. The resulting mixture was stirred at the same temperature for 2 hours. The reaction mixture was added to a saturated aqueous sodium hydrogencarbonate solution with the pH of the resulting mixture having been adjusted to 7 with a 40% aqueous sodium hydroxide solution. The resulting mixture was adjusted to pH 10 with a 40% aqueous sodium hydroxide solution and 300 ml of chloroform was added thereto. The organic layer was separated and 300 ml of water was added thereto. The resulting mixture was adjusted to pH 2 with 6 N hydrochloric acid. The aqueous layer was separated and 300 ml of chloroform was added thereto. The resulting mixture was adjusted to pH 10 with a 40% aqueous sodium hydroxide solution. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 10.4 g of oily 1-(5-nitro-2-thienyl)-1-acetoxy-2-[2-(N,N-dimethylamino)ethoxy]ethane (compound No. 404).

(2) In 10 ml of methanol was dissolved 320 mg of 1-(5-nitro-2-thienyl)-1-acetoxy-2-[2-(N,N-dimethylamino)-

ethoxy]ethane. To the solution was added 1.27 ml of a 1 N aqueous sodium hydroxide solution. The resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture were added 40 ml of chloroform and 40 ml of water. The organic layer was separated and 30 ml of water was added thereto. The resulting mixture was adjusted to pH 2 with 6 N hydrochloric acid. The aqueous layer was separated and 30 ml of chloroform was added thereto. The resulting mixture was adjusted to pH 11 with a 10% aqueous sodium hydroxide solution. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 3 ml of methanol and 1 ml of a 5 N dry hydrogen chloride-ethanol solution. The solvent was removed by distillation under reduced pressure. To the residue thus obtained was added 5 ml of ethanol. The resulting crystals were collected by filtration and dried to obtain 170 mg of 1-(5-nitro-2-thienyl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol (compound No. 405).

Melting point: 189-191.5°C (decomp.)

Production Example 52

(1) In 10 ml of pyridine was dissolved 3.4 g of 2-[2-(N,N-dimethylamino)ethoxy]-1-(6-benzyloxybenso[b]-furan-2-yl)ethanol. To the solution was added 1.8 ml of acetic anhydride. The resulting mixture was stirred

at room temperature for 17.5 hours. The solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 40 ml of ethyl acetate and 40 ml of water. The resulting mixture was adjusted to pH 7 with sodium hydrogencarbonate. The organic layer was separated. The aqueous layer was extracted with 20 ml of ethyl acetate. The extract was combined with the previously separated organic layer. The combined organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 1/1) to obtain 3.25 g of oily 1-acetoxy-1-(6-benzyloxybenzo[b]furan-2-yl)-2-[2-(N,N-dimethylamino)-ethoxy]ethane (compound No. 406).

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

(2) A mixture of 3.2 g of 1-acetoxy-1-(6-benzyloxybenzo[b]furan-2-yl)-2-[2-(N,N-dimethylamino)-ethoxy]ethane, 0.6 g of 5% palladium-carbon, 0.67 ml of concentrated hydrochloric acid and 30 ml of methanol was subjected to hydrogenation at room temperature under atmospheric pressure for 1.5 hours. After the completion of the reaction, the palladium-carbon was removed by filtration. The solvent was removed by distillation under reduced pressure. To the residue thus obtained were added 20 ml of chloroform and 20 ml of water.

The resulting mixture was adjusted to pH 7 with sodium hydrogencarbonate. The organic layer was separated. The aqueous layer was extracted with 10 ml of chloroform. The extract was combined with the previously separated organic layer. The combined organic layer was washed with 5 ml of water, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/methanol = 7/1) to obtain 1.57 g of oily 1-acetoxy-1-(6-hydroxybenzo[b]furan-2-yl)-2-[2-(N,N-dimethylamino)ethoxy]ethane (compound No. 407).

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

(3) In 3.5 ml of benzene was dissolved 0.65 g of 1-acetoxy-1-(6-hydroxybenzo[b]furan-2-yl)-2-[2-(N,N-dimethylamino)ethoxy]ethane. To the solution was added 0.33 ml of ethyl isocyanate. The resulting mixture was stirred for 30 minutes at 80°C. The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluant: chloroform/ethanol = 6/1) to obtain an oily product. The oily product was treated with dry hydrogen chloride according to a conventional ~~an ordinary~~ method to obtain 0.58 g of oily 1-acetoxy-1-(6-N-ethylcarbamoyloxybenzo[b]furan-2-yl)-2-[2-(N,N-dimethylamino)ethoxy]ethane hydrochloride (compound No. 408).

IR (neat) cm^{-1}: $\nu_{C=O}$ 1730

Next, this invention is specifically described by way of Examples. However, this invention is in no way restricted to these Examples.

Example 1 (Tablets)

Tablets each containing 50 mg of 1-(4-benzyloxyphenyl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol hydrochloride (compound No. 48) were prepared using the following recipe according to the following method:

Per tablet:		
Compound No. 48	50 mg	①
Lactose	20 mg	①
Kollidon CL (BASF's product)	15 mg	①
Corn starch	30 mg	①
AVICEL PH 101 (Asahi Kasei's product)	50 mg	①
Polyvinylpyrrolidone K-90	5 mg	
Light silica	3 mg	②
Magnesium stearate	2 mg	②
Total	175 mg	

The components ① were kneaded with an aqueous solution containing 8% of Polyvinylpyrrolidone K-90. The kneaded product was dried at 40°C and mixed with the components ②. The resulting mixture was made into round tablets ~~tablets~~ each weighing 175 mg and having

a diameter of 8 mm.

Example 2 (Capsules)

Capsules each containing 50 mg of 2-[2-(N,N-dimethylamino)ethoxy]-1-[4-(4-phenyloxy)phenyl]ethanol hydrochloride (compound No. 54) were prepared using the following recipe according to the following method:

Per capsule:		
Compound No. 54	50 mg	①
Lactose	20 mg	
Corn starch	53 mg	
Kollidon CL (BASF's product)	2 mg	
Polyvinylpyrrolidone K-90	5 mg	
AVICEL PH 302 (Asahi Kasei's product)	18 mg	②
Magnesium stearate	2 mg	
Total	150 mg	

The components ① were kneaded with an aqueous solution containing 8% of Polyvinylpyrrolidone K-90. The kneaded product was dried at 40°C and mixed with the components ②. The resulting mixture was charged into No. 3 gelatin capsules in an amount of 150 mg per capsule to obtain capsules.

Example 3 (Liquid)

A liquid containing 25 mg of 2-[2-(N,N-dimethylamino)ethoxy]-1-(3-trifluoromethylphenyl)ethanol hydrochloride (compound No. 42) was prepared using the following recipe according to the following method:

Per ampule:	
Compound No. 42	25 mg
Methyl paraoxybenzoate	1 mg
Total	26 mg

The above components were dissolved in physiological saline and the total volume of the solution was made into 1 ml. The solution was filtered aseptically and charged into an ampule to obtain a liquid.

Example 4 (Injection)

An injection containing 25 mg of 2-[2-(N,N-dimethylamino)ethoxy]-1-(3-fluorophenyl)ethanol hydrochloride (compound No. 1) was prepared using the following recipe according to the following method:

Compound No. 1	25 mg
Manitol	75 mg
Total	100 mg

The above components were dissolved in 1.5 ml

of distilled water prepared for injection. The solution was filtered aseptically, charged into a 3-ml minivial, and freeze-dried to obtain an injection.

Example 5 (fine granules)

Fine granules each containing 50 mg of 2-(1-benzylpiperidin-4-yloxy)-1-phenylethanol hydrochloride (compound No. 112) were prepared using the following recipe according to the following method:

Compound No. 112	50 mg	①
α-Starch	200 mg	
Purified sucrose	250 mg	
Lactose	470 mg	
Polyvinylpyrrolidone K-90	30 mg	
Total	1000 mg	

The components ① were subjected to granulation under high speed stirring with an aqueous solution containing 8% of Polyvinylpyrrolidone K-90. The granules obtained were sieved through a 32-mesh screen and dried to obtain fine granules.

Example 6 (Tablets)

2-[2-(N,N-dimethylamino)ethoxy]-1-(3-methylphenyl)ethanol hydrochloride (compound No. 15), 2-[(1-methylimidazol-5-yl)methoxy]-1-(4-benzyloxyphenyl)-

ethanol (compound No. 215), 2-[2-(N,N-dimethylamino)-ethoxy]-1-(1-naphthyl)ethanol hydrochloride (compound No. 228), 2-[2-(N,N-dimethylamino)ethoxy]-1-(2-naphthyl)-ethanol hydrochloride (compound No. 229), 2-[2-(N,N-dimethylamino)ethoxy]-1-(benzo[b]thiophen-5-yl)ethanol hydrochloride (compound No. 312), 2-[(N-methyl-1H-1,2,5,6-tetrahydropyridin-3-yl)methyl]-1-(benzo[b]-thiophen-5-yl)ethanol (compound No. 345), 2-(2-amino-ethoxy)-1-(benzo[b]thiophen-5-yl)ethanol $\frac{1}{2}$ fumarate (compound No. 357), 2-[2-(N,N-diethylamino)ethoxy]-1-(benzo[b]thiophen-5-yl)ethanol hydrochloride (compound No. 388) and 2-[2-(4-benzylpiperazin-1-yl)ethyl]-1-(benzo[b]furan-5-yl)ethanol dihydrochloride (compound No. 394) were processed as in Example 1 to obtain tablets each containing 50 mg of one of the above compounds.

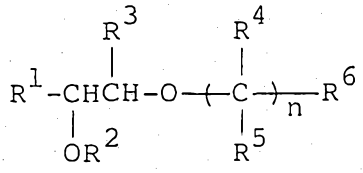
Example 7 (Capsules)

2-[2-(N,N-dimethylamino)ethoxy]-1-(3-methyl-phenyl)ethanol hydrochloride (compound No. 15), 2-[(1-methylimidazol-5-yl)methoxy]-1-(4-benzyloxyphenyl)-ethanol (compound No. 215), 2-[2-(N,N-dimethylamino)-ethoxy]-1-(1-naphthyl)ethanol hydrochloride (compound No. 228), 2-[2-(N,N-dimethylamino)ethoxy]-1-(2-naphthyl)ethanol hydrochloride (compound No. 229), 2-[2-(N,N-dimethylamino)ethoxy]-1-(benzo[b]thiophen-5-yl)ethanol hydrochloride (compound No. 312), 2-[(N-methyl-1H-1,2,5,6-tetrahydropyridin-3-yl)methyl]-

1 1-(benzo[b]thiophen-5-yl)ethanol (compound No. 345), 2-'2-aminoethoxy)-1-(benzo[b]thiophen-5-yl)ethanol 1/2 fumarate (compound No. 357), 2-[2-(N,N-diethylamino)-ethoxy]-1-(benzo[b]thiophen-5-yl)ethanol hydrochloride 5 (compound No. 388) and 2-[2-(4-benzylpiperazin-1-yl)ethyl]-1-(benzo[b]furan-5-yl)ethanol dihydrochloride (compound No. 394) were processed as in Example 2 to obtain capsules each containing 50 mg of one of the above compounds.

The claims defining the invention are as follows:

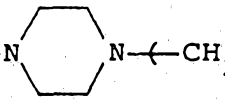
1. A 1,2-ethanediol derivative represented by the following general formula or a salt thereof:

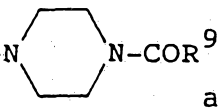


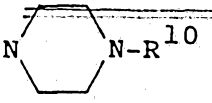
wherein R^1 represents a substituted or unsubstituted phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl or heterocyclic group; R^2 represents a hydrogen atom, a lower alkyl group or a hydroxyl-protecting group; R^3 represents a hydrogen atom or a lower alkyl group; nR^4's and nR^5's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups; R^6 represents an ammonio group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrrolyl, pyrrolidinyl, piperidyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, tetrahydropyridyl, pyrimidinyl, morpholinyl, thiomorpholinyl, quinolyl, quinolizinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinuclidinyl, thiazolyl, tetrazolyl, thiadiazolyl, pyrrolinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, purinyl and indazolyl groups; and n represents 0 or an integer of 1 to 6, wherein the substituent on R^1 is selected from the group consisting of halogen atoms, substituted or unsubstituted amino,

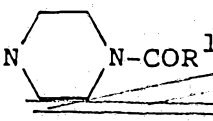
lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino and heterocyclic groups, ~~protected amino groups,~~ protected or unprotected hydroxyl groups, nitro group, oxo group and lower alkylenedioxy groups; the substituted lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino or heterocyclic group as the substituent of R^1 and the substituted nitrogen-containing heterocyclic group as R^6 have each at least one substituent selected from the group consisting of halogen atoms, protected or unprotected hydroxyl groups, protected or unprotected amino groups, protected or unprotected carboxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by a protected or unprotected hydroxyl group, unsubstituted or halogen-substituted aryl groups, unsubstituted or halogen-substituted aroyl groups, unsubstituted lower alkoxy groups, lower alkoxy groups substituted by a lower alkoxy group, lower acyl groups, ar-lower alkyl groups, ar-lower alkenyl groups, heterocyclic groups, heterocyclic-CO- groups, oxo group, lower alkylsulfonyl groups and arylsulfonyl groups; and the substituted amino group as the substituent of R^1 and the substituted amino group as R^6 have each

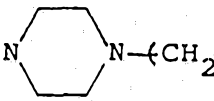
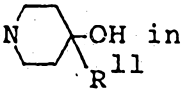
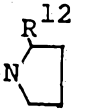
at least one substituent selected from the group consisting of protected or unprotected hydroxyl groups, unsubstituted lower alkyl groups, lower alkyl group substituted by a protected or unprotected carboxyl or hydroxyl group, cycloalkyl groups, aryl groups, lower acyl groups, ar-lower alkyl groups, heterocyclic groups, unsubstituted or oxo-substituted heterocyclic-CO- groups, adamantyl group, lower alkylsulfonyl groups and aryl-sulfonyl groups, provided that there are excluded the compounds in which R^1 is a phenyl group which may optionally be substituted by the halogen atom or the lower alkyl, lower alkylenedioxy, lower alkoxy or protected or unprotected hydroxyl group and R^6 is $-NR^7R^8$ in which R^7 represents an ar-lower alkyl or heterocyclic group and R^8 represents a hydrogen atom or a lower alkyl group, or R^7 and R^8 form, when taken with the N atom,

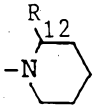

in which R^9 represents an aryl or heterocyclic group and i represents 0 or an integer of 1 to 3,

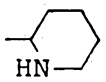

in which R^9 has the same meaning as defined above,


in which R^{10} represents a heterocyclic group,


in which R^{10} has the same meaning as defined above,


in which R^8 and i have the same meanings as defined above,  in which R^{11} represents an aryl group,  in which R^{12} represents a carboxyl group or a lower alkoxycarbonyl group or

 in which R^{12} has the same meaning as defined above,

and the compounds in which R^1 represents an unsubstituted or lower alkyl-substituted phenyl group and R^6 represents a di-lower alkylamino group,  ,  or  and the compound in which R^1 represents an unsubstituted phenyl group and R^6 represents  ;

all the above heterocyclic groups being selected from the group consisting of the nitrogen-containing heterocyclic groups mentioned in the definition of R^6 and furyl, thienyl, benzothienyl, pyranyl, isobenzofuranyl, oxazolyl, benzofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinoxalyl, dihydroquinoxalyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzopyrrolyl, 2,3-dihydro-4H-1-thianaphthyl, 2,3-dihydrobenzofuranyl, benzo[b]dioxanyl, imidazo[2,3-a]pyridyl, benzo[b]piperazinyl, chromenyl, isothiazolyl, isoxazolyl, oxadiazolyl, pyridazinyl, isoindolyl and isoquinolyl groups.

2. A 1,2-ethanediol derivative or a salt thereof according to claim 1, wherein R^1 represents a substituted or unsubstituted phenyl group; R^2 represents a hydrogen atom or a hydroxyl-protecting group; nR^4's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups; nR^5's represent hydrogen atoms; and R^6 represents an ammonio group or a substituted or unsubstituted amino (other than di-lower alkylamino) or nitrogen-containing heterocyclic group, the nitrogen-

containing heterocyclic group being selected from the group consisting of pyrrolyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, quinolyl, quinolidinyl, tetrahydroquinolinyl, ~~quinuclidinyl,~~ quinolizinyl, thiazolyl and thiadiazolyl groups.

3. A 1,2-ethanediol derivative or a salt thereof according to Claim 1, wherein R^1 represents a substituted or unsubstituted naphthyl group; R^2 represents a hydrogen atom or a hydroxyl-protecting group; nR^4's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups; nR^5's represent hydrogen atoms; and R^6 represents an ammonio group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, morpholinyl, quinolyl, quinolizinyl, tetrahydroquinolinyl, quinuclidinyl, thiazolyl and thiadiazolyl groups.

4. A 1,2-ethanediol derivative or a salt thereof according to Claim 1, wherein R^1 represents the substituted or unsubstituted heterocyclic group.

5. A 1,2-ethanediol derivative or a salt thereof according to Claim 1, wherein R^1 represents a naphthyl, indanyl or tetrahydronaphthyl group which may optionally be substituted by a halogen atom or a lower alkyl group; R^2 represents a hydrogen atom; R^3 represents a hydrogen atom; nR^4's and nR^5's represent hydrogen atoms; R^6

represents a morpholinyl group which has a free valence on a carbon atom forming the ring, a pyridyl group, an imidazolyl group, a phenyl-C_{1-4}alkyl group-substituted piperazinyl group or an amino group which may optionally be substituted by a lower alkyl ~~group~~ or ~~a~~ cycloalkyl group; and n represents an integer of 1 to 4.

6. A 1,2-ethanediol derivative or a salt thereof according to Claim 1, wherein R^1 represents a benzothienyl, benzofuranyl or 2,3-dihydrobenzothienyl group; R^2 represents a hydrogen atom; R^3 represents a hydrogen atom; nR^4's and nR^5's represent hydrogen atoms; R^6 represents a pyridyl group, a piperidinyl group which may optionally be substituted by a lower alkyl group, a 1,2,5,6-tetrahydropyridyl group which may optionally be substituted by a lower alkyl group, an imidazolyl group, a phenyl-C_{1-4}alkyl group-substituted piperazinyl group or an amino group which may optionally be substituted by a lower alkyl ~~group~~ or cycloalkyl group; and n represents an integer of 1 to 4.

7. 1-(4-Benzyloxyphenyl)-2-[2-(N,N-dimethylamino)-ethoxy]ethanol or a salt thereof.

8. 1-(4-Benzyloxyphenyl)-2-[(1-methyl-5-imidazolyl)-methoxy]ethanol or a salt thereof.

9. 2-(5-Imidazolylmethoxy)-1-(1-naphthyl)ethanol or salt thereof.

10. 2-(1-Methyl-5-imidazolylmethoxy)-1-(1-naphthyl)-ethanol or a salt thereof.

11. 1-(Benzo[b]thiophen-5-yl)-2-[2-(N,N-dimethyl-

amino)ethoxy]ethanol or a salt thereof.

12. 1-(Benzo[b]thiophen-5-yl)-2-[3-(N,N-dimethylamino)-propoxy]ethanol or a salt thereof.

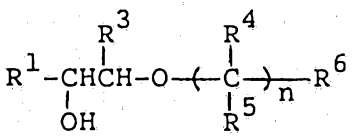
13. 1-(Benzo[b]thiophen-5-yl)-2-(5-imidazolyl-methoxy)-ethanol or a salt thereof.

14. 1-(Benzo[b]thiophen-5-yl)-2-[(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)methoxy]ethanol or a salt thereof.

15. 1-(Benzo[b]furan-5-yl)-2-[2-(N,N-dimethylamino)-ethoxy]ethanol or a salt thereof.

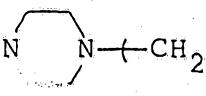
16. 1-(Benzo[b]thiophen-5-yl)-2-[2-(N,N-diethylamino)-ethoxy]ethanol or a salt thereof.

17. A process for producing a 1,2-ethanediol derivative represented by the following general formula or a salt thereof:

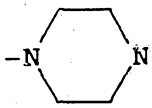


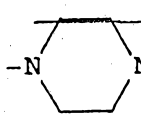
wherein R^1 represents a substituted or unsubstituted phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl or heterocyclic group; R^3 represents a hydrogen atom or a lower alkyl group; nR^4's and nR^5's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups; R^6 represents an ammonio group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrolyl,

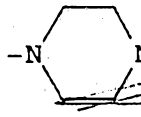
pyrrolidinyl, piperidyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, tetrahydropyridyl, pyrimidinyl, morpholinyl, thiomorpholinyl, quinolyl, quinolizinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinuclidinyl, thiazolyl, tetrazolyl, thiadiazolyl, pyrrolinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, purinyl and indazolyl groups; and n represents 0 or an integer of 1 to 6, wherein the substituent on R^1 is selected from the group consisting of halogen atoms, substituted or unsubstituted amino, lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino and heterocyclic groups, protected amino groups, protected or unprotected hydroxyl groups, nitro group, oxo group and lower alkylenedioxy groups; the substituted lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino or heterocyclic group as the substituent of R^1 and the substituted nitrogen-containing heterocyclic group as R^6 have each at least one substituent selected from the group consisting of halogen atoms, protected or unprotected hydroxyl groups, protected or unprotected amino groups, protected or unprotected carboxyl groups, unsubstituted

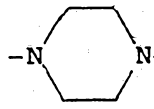
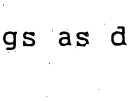
lower alkyl groups, lower alkyl groups substituted by a protected or unprotected hydroxyl group, unsubstituted or halogen-substituted aryl groups, unsubstituted or halogen-substituted aroyl groups, unsubstituted lower alkoxy groups, lower alkoxy groups substituted by a lower alkoxy group, lower acyl groups, ar-lower alkyl groups, ar-lower alkenyl groups, heterocyclic groups, heterocyclic-CO- groups, oxo group, lower alkylsulfonyl groups and arylsulfonyl groups; and the substituted amino group as the substituent of R^1 and the substituted amino group as R^6 have each at least one substituent selected from the group consisting of protected or unprotected hydroxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by a protected or unprotected carboxyl or hydroxyl group, cycloalkyl groups, aryl groups, lower acyl groups, ar-lower alkyl groups, heterocyclic groups, unsubstituted or oxo-substituted heterocyclic-CO- groups, adamantyl group, lower alkylsulfonyl groups and arylsulfonyl groups, provided that there are excluded the compounds in which R^1 is a phenyl group which may optionally be substituted by the halogen atom or the lower alkyl, lower alkylene-dioxy, lower alkoxy or protected or unprotected hydroxyl group and R^6 is $-NR^7R^8$ in which R^7 represents an ar-lower alkyl or heterocyclic group and R^8 represents a hydrogen atom or a lower alkyl group or R^7 and R^8 form, when taken with the N atom,  in which

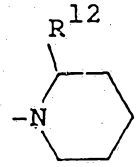
R^9 represents an aryl group and i represents 0 or an integer of 1 to 3,

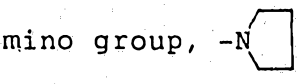
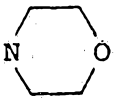
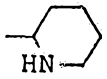
 in which R^9 has the same meaning as defined above,

 in which R^{10} represents a heterocyclic group,

 in which R^{10} has the same meaning as defined above,

 heterocyclic in which R^8 and i have the same meanings as defined above,  in which R^{11} represents an aryl group,  in which R^{12} represents a carboxyl group or a lower alkoxycarbonyl group or

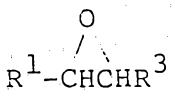
 in which R^{12} has the same meaning as defined above

and the compounds in which R^1 represents an unsubstituted or lower alkyl-substituted phenyl group and R^6 represents a di-lower alkylamino group,  or  and the compound in which R^1 represents an unsubstituted phenyl group and R^6 represents  ;

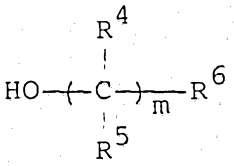
all the above heterocyclic groups being selected from the group consisting of the nitrogen-containing heterocyclic groups mentioned in the definition of R^6 and furyl, thienyl, benzothienyl, pyranyl, isobenzofuranyl, oxazolyl, benzofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinoxalyl, dihydroquinoxalyl,

2,3-dihydrobenzothienyl, 2,3-dihydro- benzopyrrolyl, 2,3-dihydro-4H-1-thianaphthyl, 2,3-dihydrobenzofuranyl,

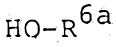
benzo[b]dioxanyl, imidazo[2,3-a]pyridyl, benzo[b]-piperazinyl, chromenyl, isothiazolyl, isoxazolyl, oxadiazolyl, pyridazinyl, isoindolyl and isoquinolyl groups, which comprises reacting a compound represented by the general formula:



wherein R^1 and R^3 have the same meanings as defined above, with a compound represented by the following general formula or a salt thereof:



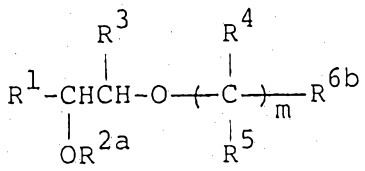
wherein mR^4's and mR^5's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups, R^6 has the same meaning as defined above and m represents an integer of 1 to 6, or a compound represented by the following general formula or a salt thereof:



wherein R^{6a} represents the same substituted or unsubstituted nitrogen-containing heterocyclic group as in the defintion of R^6, provided that the heterocyclic group

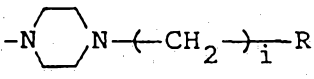
has a free valence on a carbon atom forming the heterocyclic ring.

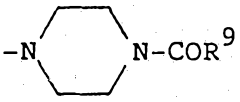
~~17.~~ 18. A process for producing a 1,2-ethanediol derivative represented by the following general formula or a salt thereof:

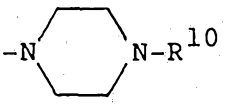


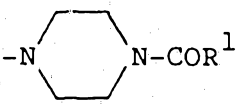
wherein R^1 represents a substituted or unsubstituted phenyl, naphtyl, indanyl, indenyl, tetrahydronaphthyl or heterocyclic group; R^{2a} represents a hydroxyl-protecting group; R^3 represents a hydrogen atom or a lower alkyl group; mR^4's and mR^5's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups; and R^{6b} represents a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group having a free valence on a carbon atom forming the heterocyclic ring and being selected from the group consisting of pyrrolyl, pyrrolidinyl, piperidyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, tetrahydropyridyl, pyrimidinyl, morpholinyl, thiomorpholinyl, quinolyl, quinolizinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinuclidinyl, thiazolyl, tetrazolyl, thiadiazolyl, pyrrolinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, purinyl and indazolyl groups;

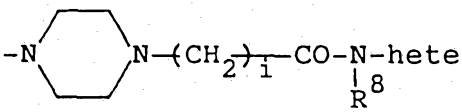
and m represents an integer of 1 to 6, wherein the substituent on R^1 is selected from the group consisting of halogen atoms, substituted or unsubstituted amino, lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino and heterocyclic groups, protected amino groups, protected or unprotected hydroxyl groups, nitro group, oxo group and lower alkylenedioxy groups; the substituted lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino or heterocyclic group as the substituent of R^1 and the substituted nitrogen-containing heterocyclic group as R^{6b} have each at least one substituent selected from the group consisting of halogen atoms, protected or unprotected hydroxyl groups, protected or unprotected amino groups, protected or unprotected carboxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by a protected or unprotected hydroxyl group, unsubstituted or halogen-substituted aryl groups, unsubstituted or halogen-substituted aroyl groups, unsubstituted lower alkoxy groups, lower alkoxy groups substituted by a lower alkoxy group, lower acyl groups, ar-lower alkyl groups, ar-lower alkenyl groups, heterocyclic groups, heterocyclic-CO-

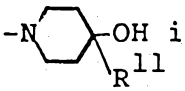
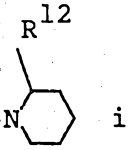
groups, oxo group, lower alkylsulfonyl groups and arylsulfonyl groups; and the substituted amino group as the substituent of R^1 and the substituted amino group as R^{6b} have each at least one substituent selected from the group consisting of protected or unprotected hydroxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by a protected or unprotected carboxyl or hydroxyl group, cycloalkyl groups, aryl groups, lower acyl groups, ar-lower alkyl groups, heterocyclic groups, unsubstitued or oxo-substituted heterocyclic-CO- groups, adamantyl group, lower alkylsulfonyl groups and aryl-sulfonyl groups, provided that there are excluded the compounds in which R^1 is a phenyl group which may optionally be substituted by the halogen atom or the lower alkyl, lower alkylenedioxy, lower alkoxy or protected or unprotected hydroxyl group and R^{6b} represents $-NR^7R^8$ in which R^7 represents an ar-lower alkyl group or a heterocyclic group and R^8 represents a hydrogen atom or a lower alkyl group or R^7 and R^8 form, when taken with the N atom,  in which R^9 represents an aryl or heterocyclic group and i represents 0 or an integer of 1 to 3,

 in which R^9 has the same meaning as defined above,

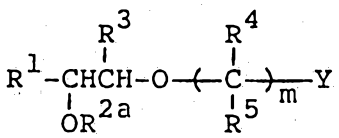
 in which R^{10} represents a heterocyclic group,

 in which R^{10} has the same meaning as defined above,

 in which R^8 and i have

the same meanings as defined above,  in which R^{11} represents an aryl group,  in which R^{12} represents a carboxyl group or a lower alkoxycarbonyl group or  in which R^{12} has the same meaning as defined above, and the compound in which R^1 represents an unsubstituted or lower alkyl-substituted phenyl group and R^6 represents a di-lower alkylamino group,  , or and the compound in which R^1 represents an unsubstituted phenyl group and R^6 represents  ;

all the above heterocyclic groups being selected from the group consisting of the nitrogen-containing heterocyclic groups mentioned in the definition of R^{6b} and furyl, thienyl, benzothienyl, pyranyl, isobenzofuranyl, oxazolyl, benzofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinoxalyl, dihydroquinoxalyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzopyrrolyl, 2,3-dihydro-4H-1-thianaphthyl, 2,3-dihydrobenzofuranyl, benzo[b]dioxanyl, imidazo[2,3-a]pyridyl, benzo[b]piperazinyl, chromenyl, isothiazolyl, isoxazolyl, oxadiazolyl, pyridazinyl, isoindolyl and isoquinolyl groups, which comprises reacting a compound represented by the general formula



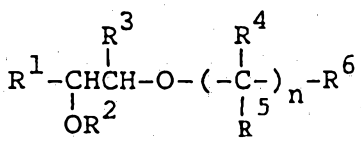
wherein R^1, R^{2a}, R^3, R^4, R^5 and m have the same meanings as defined above and Y represents a removable group, with a compound represented by the following general formula

or a salt thereof:

$$H\text{-}R^{6b}$$

wherein R^{6b} has the same meaning as defined above.

19. Use of a 1,2-ethanediol derivative represented by the following general formula or a salt thereof for preparing a drug for treating cerebrovascular dementia, senile dementia, Alzheimer's dementia, sequelae of ischemic encephalopathy or cerebral apoplexy in a patient by mixing said 1-2ethanediol derivative or a salt thereof with a pharmaceutically acceptable carrier:

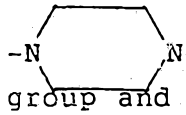


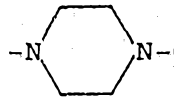
wherein R^1 represents a substituted or unsubstituted phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl or heterocyclic group; R^2 represents a hydrogen atom, a lower alkyl group or a hydroxyl-protecting group; R^3 represents a hydrogen atom or a lower alkyl group; nR^4's and nR^5's are the same as or different from one another

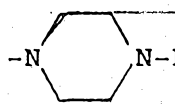
and represent hydrogen atoms or lower alkyl groups; R^6 represents an ammonio group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrrolyl, pyrrolidinyl, piperidyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, tetrahydropyridyl, pyrimidinyl, morpholinyl, thiomorpholinyl, quinolyl, quinolizinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinuclidinyl, thiazolyl, tetrazolyl, thiadiazolyl, pyrrolinyl, imidazolinyl, imidazolidinyl pyrazolinyl, pyrazolidinyl, purinyl and indazolyl groups; and n represents 0 or an integer of 1 to 6, wherein the substituent on R^1 is selected from the group consisting of halogen atoms, substituted or unsubstituted amino, lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino and heterocyclic groups, ~~protected amino groups~~, protected or unprotected hydroxyl groups, nitro group, oxo group and lower alkylenedioxy groups; the substituted lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino or heterocyclic group as the substituent of R^1 and the substituted nitrogen-containing heterocyclic group as R^6 have each

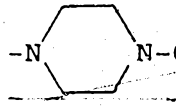
at least one substituent selected from the group consisting of halogen atoms, protected or unprotected hydroxyl groups, protected or unprotected amino groups, protected or unprotected carboxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by a protected or unprotected hydroxyl group, unsubstituted or halogen-substituted aryl groups, unsubstituted or halogen-substituted aroyl groups, unsubstituted lower alkoxy groups, lower alkoxy groups substituted by a lower alkoxy group, lower acyl groups, ar-lower alkyl groups, ar-lower alkenyl groups, heterocyclic groups, heterocyclic-CO- groups, oxo group, lower alkylsulfonyl groups and arylsulfonyl groups; the substituted amino group as the substituent of R^1 and the substituted amino group as R^6 have each at least one substituent selected from the group consisting of protected or unprotected hydroxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by a protected or unprotected carboxyl or hydroxyl group, cycloalkyl groups, aryl groups, lower acyl groups, ar-lower alkyl groups, heterocyclic groups, unsubstituted or oxo-substituted heterocyclic-CO- groups, adamantyl group, lower alkylsulfonyl groups and arylsulfonyl groups, provided that there are excluded the compounds in which R^1 is a phenyl group which may optionally be substituted by the halogen atom or the lower alkyl, lower alkylenedioxy, lower alkoxy or protected or unprotected hydroxyl group and R^6 is $-NR^7R^8$ in which R^7 represents an ar-lower alkyl or heterocyclic group

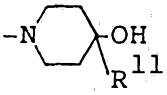
and R^8 represents a hydrogen atom or a lower alkyl group, R^7 and R^8 form, when taken with the N atom,

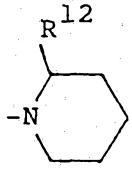
 in which R^9 represents an aryl group and i represents 0 or an integer of 1 to 3,

 in which R^9 has the same meaning as defined above,

 in which R^{10} represents a heterocyclic group,

 in which R^{10} has the same meaning as defined above,

 heterocyclic in which R^8 and i have the same meanings as defined above,  in which R^{11} represents an aryl group,  in which R^{12} represents a carboxyl group or a lower alkoxycarbonyl group or

 in which R^{12} has the same meaning as defined above;

all the above heterocyclic groups being selected from the group consisting of the nitrogen-containing heterocyclic groups mentioned in the definition of R^6 and furyl, thienyl, benzothienyl, pyranyl,

isobenzofuranyl, oxazolyl, benzofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinoxalyl, dihydroquinoxalyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzopyrrolyl, 2,3-dihydro-4H-1-thianaphthyl, 2,3-dihydrobenzofuranyl, benzo[b]dioxanyl, imidazo[2,3-a]pyridyl, benzo[b]piperazinyl, chromenyl, isothiazolyl, isoxazolyl, oxadiazolyl, pyridazinyl, isoindolyl and isoquinolyl groups.

~~19.~~ 20. Use of a 1,2-ethanediol derivative or a salt thereof according to Claim ~~18~~ 19, wherein R^1 represents a substituted or unsubstituted phenyl group; R^2 represents a hydrogen atom or a hydroxyl-ptotecting group; nR^4's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups; nR^5's represent hydrogen atoms; and R^6 represents an ammonio group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, morpholinyl, quinolyl, quinolizinyl, tetrahydroquinolinyl, quinuclidinyl, thiazolyl and thiadiazolyl groups.

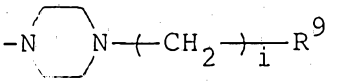
~~20.~~ 21. Use of a 1,2-ethanediol derivative or a salt thereof according to Claim ~~18~~ 19, wherein R^1 represents a substituted or unsubstituted naphthyl group; R^2 represents a hydrogen atom or a hydroxyl-protecting group; nR^4's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups; nR^5's

represent hydrogen atoms; and R^6 represents an ammonio group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, morpholinyl, quinolyl, quinolizinyl, tetrahydroquinolinyl, quinuclidinyl, thiazolyl and thiadiazolyl groups.

21. Use of a 1,2-ethanediol derivative or a salt thereof according to Claim 19, wherein R^1 represents the substituted or unsubstituted heterocyclic group.

23. Use of a 1,2-ethanediol derivative or a salt thereof according to Claim 19, wherein R^1 represents a substituted or unsubstituted phenyl, naphthyl, indanyl, tetrahydronaphthyl, furyl, thienyl, pyridyl, quinolyl, benzothienyl, 2,3-dihydrobenzofuranyl, indolyl, benzofuranyl, 2,3-dihydrobenzothienyl, 1,2,3,4-tetrahydroquinolinyl or imidazolyl group; R^6 represents an ammonio group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrrolinyl, piperidyl, piperazinyl, imidazolyl, pyridyl, morpholinyl, thiomorpholinyl, tetrahydropyridyl, quinuclidinyl and tetrazolyl, the substituent on R^1 is selected from the group consisting of halogen atoms; a lower alkyl groups; lower alkenyl groups; phenyl groups which may optionally be substituted by a halogen atom or a lower alkyl or lower alkoxy group; phenyl-C_{1-4}alkyl

groups; lower alkoxy groups which may optionally be substituted by a pyridyl, furyl or thienyl group; phenyl-C_{1-4}alkoxy groups which may optionally be substituted by a halogen atom or a lower alkyl, hydroxyl or lower alkoxy group; a phenoxy group; phenylaminocarbonyloxy groups which may optionally be substituted by a halogen atom; lower alkylaminocarbonyloxy groups; lower alkylthio groups; a phenylsulfonylamino group; amino groups which may optionally be substituted by a lower alkyl group; a hydroxyl group; a nitro group; an oxo group; phenyl-C_{1-4}alkylthio groups; phenyl-C_{1-4}alkylsulfonyl groups; a thienyl group; a pyridyl group; and lower alkylenedioxy groups; the substituent on R^6, when R^6 is a substituted amino group, is selected from the group consisting of lower alkyl groups which may optionally be substituted by a hydroxyl group; lower acyl ~~group~~; cycloalkyl groups; phenyl-C_{1-4}-alkyl groups; a pyrimidinyl group; a pyridincarbonyl group and an adamantyl group; and the substituent on R^6, when R^6 is a substituted nitrogen-containing heterocyclic group, is selected from the group consisting of halogen atoms; a hydroxyl group; lower alkyl groups which may optionally be substituted by a hydroxyl group; an amino group; lower acyl groups which may optionally be substituted by a pyrrolidinyl group; phenyl-C_{1-4}alkyl groups; phenyl-C_{2-4}alkenyl groups; aroyl groups which are substituted by a halogen atom; a pyridyl group and an oxo group; provided that there are excluded the compounds in which R^1 is a phenyl group which may

optionally be substituted by the halogen atom or the lower alkyl, lower alkoxy, lower alkylenedioxy or hydroxyl group and R^6 is $-NR^7R^8$ in which R^7 represents a phenyl-C_{1-4}alkyl or pyrimidinyl group and R^8 represents a hydrogen atom or a lower alkyl group, or R^7 and R^8 form, when taken with the N atom,  in which R^9 represents a phenyl group and i represents 0 or an integer of 1 to 3.

24. Use of a 1,2-ethanediol derivative or a salt thereof according to Claim 23, wherein R^1 represents a phenyl group which may optionally be substituted by a halogen atom; a phenyl-C_{1-4}alkoxy group; a phenyl group; a thienyl group; a phenoxy group which may optionally be substituted by a halogen atom or a lower alkoxy group; or a lower alkoxy group which may optionally be substituted by a thienyl group; R^2 represents a hydrogen atom; R^3 represents a hydrogen atom; nR^4's and nR^5's represent hydrogen atoms; R^6 represents a morpholinyl group which has a free valence on a carbon atom forming the ring, a pyridyl group, an imidazolyl group which may optionally be substituted by a lower alkyl group, or an amino group which may optionally be substituted by a lower alkyl or a cycloalkyl group.

25. Use of a 1,2-ethanediol derivative or a salt thereof according to Claim 23, wherein R^1 represents a naphthyl, indanyl or tetrahydronaphthyl group which may

optionally be substituted by a halogen atom or a lower alkyl group; R^2 represents a hydrogen atom; R^3 represents a hydrogen atom; nR^4's and nR^5's represent hydrogen atoms; R^6 represents a morpholinyl group which has a free valence on a carbon atom forming the ring, a pyridyl group, an imidazolyl group, a phenyl-C_{1-4}alkyl group-substituted piperazinyl group or an amino group which may optionally be substituted by a lower alkyl group or a cycloalkyl group; and n represents an integer of 1 to 4.

26. Use of a 1,2-ethanediol derivative or a salt thereof according to claim 23, wherein R^1 represents a benzothenyl, benzofuranyl or 2,3-dihydrobenzothienyl group; R^2 represents a hydrogen atom; R^3 represents a hydrogen atom; nR^4's and nR^5's represent hydrogen atoms; R^6 represents a pyridyl group; a piperidinyl group which may optionally be substituted by a lower alkyl group; a 1,2,5,6-tetrahydropyridyl group which may optionally be substituted by a lower alkyl group; an imidazolyl group; a phenyl-C_{1-4}alkyl group-substituted piperazinyl group or an amino group which may optionally be substituted by a lower alkyl group or a cycloalkyl group; and n represents an integer of 1 to 4.

27. Use of a 1,2-ethanediol derivative or a salt thereof according to claim 19, wherein the derivative or salt is 1-(4-benzyloxyphenyl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol or a salt thereof.

28. Use of a 1,2-ethanediol derivative or a salt thereof according to claim 19, wherein the derivative or salt is 1-(4-benzyloxyphenyl)-2-[(1-methyl-5-imidazolyl)methoxy]ethanol or a salt thereof.

29. Use of a 1,2-ethanediol derivative or a salt thereof according to claim 19 wherein the derivative or salt is 2-(5-imidazolylmethoxy)-1-(1-naphthyl)ethanol or a salt thereof.

30. Use of a 1,2-ethanediol derivative or a salt thereof according to claim 19, wherein the derivative or salt is 2-(1-methyl-5-imidazolylmethoxy)-1-(1-naphthyl)ethanol or a salt thereof.

31. Use of a 1,2-ethanediol derivative or a salt thereof according to claim 19, wherein the derivative or salt is 1-(benzo[b]thiophen-5-yl)-2-[2-(N,N-dimethylamino)ethoxy]-ethanol or a salt thereof.

32. Use of a 1,2-ethanediol derivative or a salt thereof according to claim 19, wherein the derivative or salts is 1-benzo[b]thiophen-5-yl)-2-[3-(N,N-dimethylamino)propoxy]-ethanol or a salt thereof.

33. Use of a 1,2-ethanediol derivative or a salt thereof according to claim 19, wherein the derivative or salt is 1-(benzo[b]thiophen-5-yl)-2-(5-imidazolylmethoxy)ethanol or a salt thereof.

34. Use of a 1,2-ethanediol derivative or a salt thereof according to claim 19, wherein the derivative or salt is 1-(benzo[b]thiophen-5-yl)-2-[(1-methyl-1,2,5,6-tetrahydro-pyridin-3-yl)methoxy]ethanol or a salt thereof.

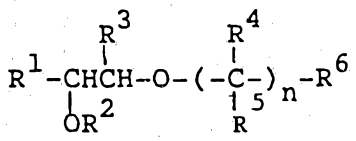
35. Use of a 1,2-ethanediol derivative or a salt thereof according to claim 19, wherein the derivative or salt is 1-(benzo[b]furan-5-yl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol or a salt thereof.

36. Use of a 1,2-ethanediol derivative or a salt thereof according to claim 19, wherein the derivative or salt is 2-[2-(N,N-dimethylamino)ethoxy]-1-(3-methylphenyl)ethanol or a salt thereof.

37. Use of a 1,2-ethanediol derivative or a salt according to claim 19, wherein the derivative or salt is 1-(benzo[b]thiophen-5-yl)-2-[2-(N,N-diethylamino)ethoxy]ethanol

or a salt thereof.

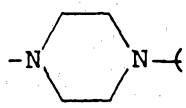
38. A pharmaceutical composition comprising a 1,2-ethanediol derivative represented by the following general formula or a salt thereof:

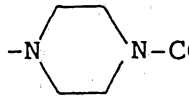


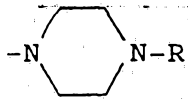
wherein R^1 represents a substituted or unsubstituted phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl or heterocyclic group; R^2 represents a hydrogen atom, a lower alkyl group or a hydroxyl-protecting group; R^3 represents a hydrogen atom or a lower alkyl group; nR^4's and nR^5's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups; and R^6 represents an ammonio group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrrolyl, pyrrolidinyl, piperidyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, tetrahydropyridyl, pyrimidinyl, morpholinyl,

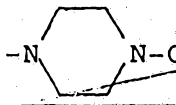
thiomorpholinyl, quinolyl, quinolizinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinuclidinyl, thiazolyl, tetrazolyl, thiadiazolyl, pyrrolinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, purinyl and indazolyl groups; and n represents 0 or an integer of 1 to 6, wherein the substituent on R^1 is selected from the group consisting of halogen atoms, substituted or unsubstituted amino, lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino and heterocyclic groups, ~~protected amino groups,~~ protected or unprotected hydroxyl groups, nitro group, oxo group and lower alkylenedioxy groups; the substituted lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino or heterocyclic group as the substituent of R^1 and the substituted nitrogen-containing heterocyclic group as R^6 have each at least one substituent selected from the group consisting of halogen atoms, protected or unprotected hydroxyl groups, protected or unprotected amino groups, protected or unprotected carboxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by a protected or unprotected hydroxyl group, unsubstituted or halogen-substituted aryl groups, unsubstituted or halogen-substituted aroyl groups,

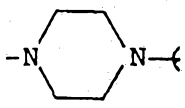
unsubstituted lower alkoxy groups, lower alkoxy groups substituted by a lower alkoxy group, lower acyl groups, ar-lower alkyl groups, ar-lower alkenyl groups, heterocyclic groups, heterocyclic-CO-groups, oxo group, lower alkylsulfonyl groups and arylsulfonyl groups; and the substituted amino group as the substituent of R^1 and the substituted amino group as R^6 have each at least one substituent selected from the group consisting of protected or unprotected hydroxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by a protected or unprotected carboxyl or hydroxyl group, cycloalkyl groups, aryl groups, lower acyl groups, ar-lower alkyl groups, heterocyclic groups, unsubstituted or oxo-substituted heterocyclic-CO- groups, adamantyl group, lower alkylsulfonyl groups and arylsulfonyl groups, provided that there are excluded the compounds in which R^1 is a phenyl group which may optionally be substituted by the halogen atom or the lower alkyl, lower alkylenedioxy, lower alkoxy or protected or unprotected hydroxyl group and R^6 represents $-NR^7R^8$ in which R^7 represents an ar-lower alkyl or heterocyclic group and R^8 represents a hydrogen atom or a lower alkyl group, or R^7 and R^8 form, when taken with the N atom,

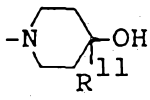
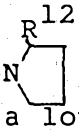
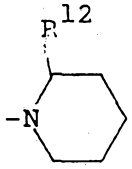
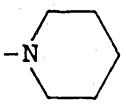
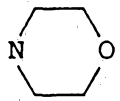
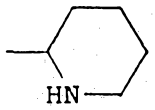

in which R^9 represents an aryl group and i represents 0 or an integer of 1 to 3,


in which R^9 has the same meaning as defined above,


in which R^{10} represents a heterocyclic group,

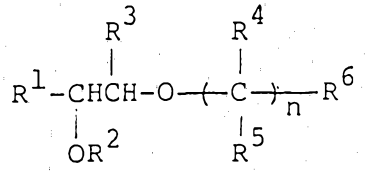

in which R^{10} has the same meaning as defined above,


heterocyclic group in which R^8 and i

have the same meanings as defined above,  in which R^{11} represents an aryl group,  in which R^{12} represents a carboxyl group or a lower alkoxycarbonyl group or  in which R^{12} has the same meaning as defined above and the compounds in which R^1 represents an unsubstituted or lower alkyl-substituted phenyl group and R^6 represents a di-lower alkylamino group,  ,  or  and the compound in which R^1 represents an unsubstituted phenyl group and R^6 represents  ;

all the above heterocyclic groups being selected from the group consisting of the nitrogen-containing heterocyclic groups mentioned in the definition of R^6 and furyl, thienyl, benzothienyl, pyranyl, isobenzofuranyl, oxazolyl, benzofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinoxalyl, dihydroquinoxalyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzopyrrolyl, 2,3-dihydro-4H-1-thianaphthyl, 2,3-dihydrobenzofuranyl, benzo[b]dioxanyl, imidazo[2,3-a]pyridyl, benzo[b]piperazinyl, chromenyl, isothiazolyl, isoxazolyl, oxadiazolyl, pyridazinyl, isoindolyl and isoquinolyl groups; in combination with a pharmaceutically acceptable inert excipient, diluent or carrier.

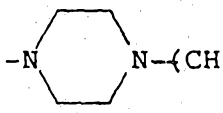
39. A method of treating cerebrovascular dementia, senile dementia, Alzheimer's dementia, sequelae of ischemic encephalopathy or cerebral apoplexy in a patient comprising administration to a patient in need a therapeutically effective amount of a 1,2-ethanediol derivative represented by the following general formula or a salt thereof:

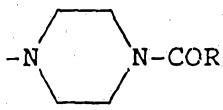


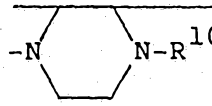
wherein R^1 represents a substituted or unsubstituted phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl or heterocyclic group; R^2 represents a hydrogen atom, a lower alkyl group or a hydroxyl-protecting group; R^3 represents a hydrogen atom or a lower alkyl group; nR^4's and nR^5's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups; R^6 represents an ammonio group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrrolyl, pyrrolidinyl, piperidyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, tetrahydropyridyl, pyrimidinyl, morpholinyl, thiomorpholinyl, quinolyl, quinolizinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinuclidinyl, thiazolyl, tetrazolyl, thiadiazolyl, pyrrolinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, purinyl and indazolyl groups; and n represents 0 or an integer of 1 to 6; wherein the substituent on R^1 is selected from the group consisting of halogen atoms, substituted or unsubstituted amino, lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio, lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl,

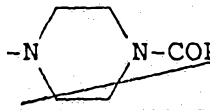
lower alkylsulfonylamino, arylsulfonylamino and heterocyclic groups, protected amino groups, protected or unprotected hydroxyl groups, nitro group, oxo group and lower alkylenedioxy groups; the substituted lower alkyl, aryl, ar-lower alkyl, lower alkoxy, ar-lower alkoxy, aryloxy, carbamoyloxy, lower alkylthio lower alkenyl, lower alkenyloxy, ar-lower alkylthio, ar-lower alkylsulfonyl, arylsulfonyl, lower alkylsulfonylamino, arylsulfonylamino or heterocyclic group as the substituent of R^1 and the substituted nitrogen-containing heterocyclic group as R^6 have each at least one substituent selected from the group consisting of halogen atoms, protected or unprotected hydroxyl groups, protected or unprotected amino groups, protected or unprotected carboxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by a protected or unprotected hydroxyl group, unsubstituted or halogen-substituted aryl groups, unsubstituted or halogen-substituted aroyl groups, unsubstituted lower alkoxy groups, lower alkoxy groups substituted by a lower alkoxy group, lower acyl groups, ar-lower alkyl groups, ar-lower alkenyl groups, heterocyclic groups, heterocyclic-CO- groups, oxo group, lower alkylsulfonyl groups and arylsulfonyl groups; and the substituted amino group as the substituent of R^1 and the substituted amino group as R^6 have each at least one substituent selected from the group consisting of protected or unprotected hydroxyl groups, unsubstituted lower alkyl groups, lower alkyl groups substituted by

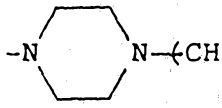
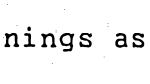
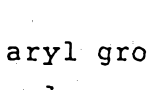
a protected or unprotected carboxyl or hydroxyl group, cycloalkyl groups, aryl groups, lower acyl groups, ar-lower alkyl groups, heterocyclic groups, unsubstituted or oxo-substituted heterocyclic-CO- groups, adamantyl group, lower alkylsulfonyl groups and arylsulfonyl groups, provided that there are excluded the compounds in which R^1 is a phenyl group which may optionally be substituted by the halogen atom or the lower alkyl, lower alkylenedioxy, lower alkoxy or protected or unprotected hydroxyl group and R^6 is $-NR^7R^8$ in which R^7 represents an ar-lower alkyl or heterocyclic group and R^8 represents a hydrogen atom or a lower alkyl group, or R^7 and R^8 form, when taken with the N atom,

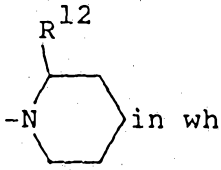

in which R^9 represents an aryl group and i represents 0 or an integer of 1 to 3,


in which R^9 has the same meaning as defined above,


in which R^{10} represents a heterocyclic group,


in which R^{10} has the same meaning as defined above,


in which R^8 and i have the same meanings as defined above,  in which R^{11} represents an aryl group,  in which R^{12} represents a carboxyl group or a lower alkoxycarbonyl group or


in which R^{12} has the same meaning as defined above;

all the above heterocyclic groups being selected from the

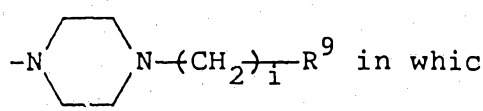
group consisting of the nitrogen-containing heterocyclic groups mentioned in the definition of R^6 and furyl, thienyl, benzothienyl, pyranyl, isobenzofuranyl, oxazolyl, benzofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinoxalyl, dihydroquinoxalyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzopyrrolyl, 2,3-dihydro-4H-1-thianaphthyl, 2,3-dihydrobenzofuranyl, benzo[b]dioxanyl, imidazo[2,3-a]pyridyl, benzo[b]piperazinyl, chromenyl, isothiazolyl, isoxazolyl, oxadiazolyl, pyridazinyl, isoindolyl and isoquinolyl groups.

40. A method according to claim 39, wherein R^1 represents a substituted or unsubstituted naphthyl group; R^2 represents a hydrogen atom or a hydroxyl-protecting group; nR^4's are the same as or different from one another and represent hydrogen atoms or lower alkyl groups; nR^5's represent hydrogen atoms; and R^6 represents an ammonic group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, morpholinyl, quinolyl, quinolidinyl, tetrahydroquinolyl, quinuclidinyl, thiazolyl and thiadiazolyl groups.

41. A method according to claim 39, wherein R^1 represents the substituted or unsubstituted heterocyclic group.

42. A method according to claim 39, wherein R^1 represents a substituted or unsubstituted phenyl, naphthyl, indanyl, tetrahydronaphthyl, furyl, thienyl, pyridyl, quinolyl, benzothienyl, 2,3-dihydrobenzofuranyl, indolyl, benzofuranyl, 2,3-dihydrobenzothienyl, 1,2,3,4-tetrahydroquinolinyl or imidazolyl group; R^6 represents an ammonio group or a substituted or unsubstituted amino or nitrogen-containing heterocyclic group, the nitrogen-containing heterocyclic group being selected from the group consisting of pyrrolinyl, piperidyl, piperazinyl, imidazolyl, pyridyl, morpholinyl, thiomorpholinyl, tetrahydropyridyl, quinuclidinyl and tetrazolyl, the substituent on R^1 is selected from the group consisting of halogen atoms; a lower alkyl groups, lower

alkenyl groups; phenyl groups which may optionally be substituted by a halogen atom or a lower alkyl or lower alkoxy group; phenyl-C_{1-4}alkyl groups; lower alkoxy groups which may optionally be substituted by a pyridyl, furyl or thienyl group; phenyl-C_{1-4}alkoxy groups which may optionally be substituted by a halogen atom or a lower alkyl, hydroxyl or lower alkoxy group; a phenoxy group; phenylaminocarbonyloxy groups which may optionally be substituted by a halogen atom; lower alkylaminocarbonyloxy groups; lower alkylthio groups; a phenylsulfonylamino group; amino groups which may optionally be substituted by a lower alkyl group; a hydroxyl group; a nitro group; an oxo group; phenyl-C_{1-4}alkylthio groups; phenyl-C_{1-4}alkylsulfonyl groups; a thienyl group; a pyridyl group; and lower alkylenedioxy groups; the substituent on R^6, when R^6 is a substituted amino group, is selected from the group consisting of lower alkyl groups which may optionally be substituted by a lower acyl group; cycloalkyl groups; phenyl-C_{1-4}alkyl groups; a pyrimidinyl group; a pyridincarbonyl group and an adamantyl group; and the substitutent on R^6, when R^6 is a substituted nitrogen-containing heterocyclic group, is selected from the group consisting of halogen atoms; a hydroxyl group; lower alkyl groups which may optionally be substituted by a hydroxyl group; an amino group; lower acyl groups which may optionally be substituted by a pyrrolidinyl group; phenyl-C_{1-4}alkyl groups; phenyl-C_{2-4}alkenyl groups; aroyl groups which are substituted by a halogen atom; a pyridyl group and an oxo group; provided that there are excluded the compounds in which R^1 is a phenyl group which may optionally be substituted by the halogen atom or the lower alkyl, lower alkoxy, lower alkylenedioxy or hydroxyl group and R^6 is $-NR^7R^8$ in which R^7 represents a phenyl-C_{1-4}alkyl or pyrimidinyl group and R^8 represents a hydrogen atom or a lower alkyl group, or R^7 and R^8 form, when taken with the N atom,



and i represents 0 or an integer of 1 to 3.

43. A method according to claim 42, wherein R^1 represents a phenyl group which may optionally be substituted by a halogen atom; a phenyl-C_{1-4}alkoxy group; a thienyl group; a phenoxy group which may optionally be substituted by a halogen atom or a lower alkoxy group or a lower alkoxy group which may optionally be substituted by a thienyl group; R^2 represents a hydrogen atom; R^3 represents a hydrogen atom; nR^4's and nR^5's represent hydrogen atoms; R^6 represents a morpholinyl group which has a free valence on a carbon atom forming the ring, a pyridyl group, an imidazolyl group which may optionally be substituted by a lower alkyl group, or an amino group which may optionally be substituted by a lower alkyl or a cycloalkyl group.

44. A method according to claim 42, wherein R^1 represents a naphthyl, idanyl or tetrahydronaphthyl group which may optionally be substituted by a halogen atom or a lower alkyl group; R^2 represents a hydrogen atom; R^3 represents a hydrogen atom; nR^4's and nR^5's represent hydrogen atoms; R^6 represents a morpholinyl group which has a free valence on a carbon atom forming the ring, a pyridyl group, an imidazolyl group, a phenyl-C_{1-4}alkyl group-substituted piperazinyl group or an amino group which may optionally be substituted by a lower alkyl group or a cycloalkyl group; and n represents an integer of 1 to 4.

45. A method according to claim 42, wherein R^1 represents a benzothienyl, benzofuranyl or 2,3-dihydrobenzothienyl group; R^2 represents a hydrogen atom; R^3 represents a hydrogen atom; nR^4's and nR^5's represent hydrogen atoms; R^6 represents a pyridyl group; a piperidinyl group which may optionally be substituted by a lower alkyl group; a 1,2,5,6-tetrahydropyridyl group which may optionally be substituted by a lower alkyl group; an imidazolyl group; a phenyl-C_{1-4}alkyl group-substituted piperazinyl group or an amino group which may optionally be substituted by a lower alkyl group or a cycloalkyl group; and n represents an integer of 1 to 4.

46. A method according to claim 39, wherein the derivative or salt is 1-(4-benzyloxyphenyl)-2-[2-(N,N-dimethyl-

amino)ethoxy]ethanol or a salt thereof.

47. A method according to claim 39, wherein the derivative or salt is 1-(4-benzyloxyphenyl)-2-[(1-methyl-5-imidazolyl)methoxy]ethanol or a salt thereof.

48. A method according to claim 39, wherein the derivative or salt is 2-(5-imidazolylmethoxy)-1-(1-naphthyl)-ethanol or a salt thereof.

49. A method according to claim 39, wherein the derivative or salt is 2-(1-methyl-5-imidazolylmethoxy)-1-(1-naphthyl)ethanol or a salt thereof.

50. A method according to claim 39, wherein the derivative or salt is 1-(benzo[b]thiophen-5-yl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol or a salt thereof.

51. A method according to claim 39, wherein the derivative or salts is 1-(benzo[b]thiophen-5-yl)-2-[3-(N,N-dimethylamino)propoxy]ethanol or a salt thereof.

52. A method according to claim 39, wherein the derivative or salt is 1-(benzo[b]thiophen-5-yl)-2-(imidazolyl-methoxy)ethanol or a salt thereof.

53. A method according to claim 39, wherein the derivative or salt is 1-(benzo[b]thiophen-5-yl)-2-[(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)methoxy]ethanol or a salt thereof.

54. A method according to claim 39, wherein the derivative or salt is 1-(benzo[b]furan-5-yl)-2-[2-(N,N-dimethylamino)ethoxy]ethanol or a salt thereof.

55. A method according to claim 39, wherein the derivative or salt is 2-[2-(N,N-dimethylamino)ethoxy]-1-(3-methylphenyl)ethanol or a salt thereof.

56. A method according to claim 39, wherein the derivative or salt is 1-(benzo[b]thiophen-5-yl)-2-[2-(N,N-diethylamino)ethoxy]ethanol or a salt thereof.

57. A pharmaceutical composition according to claim 38 in the form of tablets.

58. A pharmaceutical composition according to claim 38 in the form of capsules.

59. A pharmaceutical composition according to claim 38 in the form of a liquid.

60. A pharmaceutical composition according to claim 38 in the form of an injection.

61. A pharmaceutical composition according to claim 38 in the form of fine granules.

62. A 1,2-ethanediol derivative or salt thereof according to claim 1 substantially as hereinbefore described with reference to production examples 1-52.

63. A process according to claim 17 or 18 substantially as hereinbefore described with reference to production examples 1-52.

64. A pharmaceutical composition according to claim 38 substantially as hereinbefore described with reference to examples 1-7.

DATED: 22 June 1992

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