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(54) **DERIVES D'ETHANE-1,2-DIOL ET LEURS SELS; METHODE
DE PREPARATION ET AGENT A BASE DE CES PRODUITS
PERMETTANT D'AMELIORER LA FONCTION CEREBRALE**
(54) **1,2-ETHANEDIOL DERIVATIVE AND SALT THEREOF,
PROCESS FOR PRODUCING THE SAME, AND CEREBRAL
FUNCTION-IMPROVING AGENT COMPRISING THE SAME**

(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 cerebral apoplexy.



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ABSTRACT

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.

This is a divisional application of copending application 2,009,886, filed February 13, 1990.

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.

10 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 anti-amnesic agent or a nootropic agent.

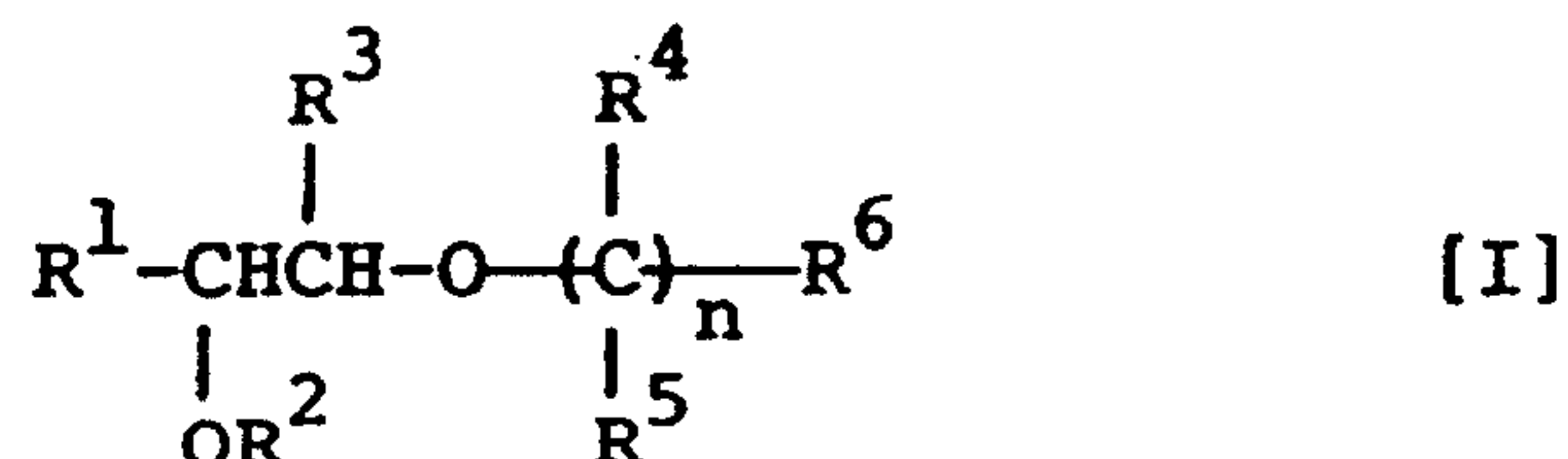
20 WO No. 88/8424 describes that 1,2-ethanediol derivatives can be used for the remedy of Alzheimer's disease and other degenerative neurological disorders. However, no specific description or example of these derivatives is given in the application.

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.

It has been found that a 1,2-ethanediol derivative represented by the following general formula [I] or a salt thereof has an excellent anti-amnesic activity and an excellent antihypoxic activity and is very useful as a cerebral function-improving agent:

10



wherein

R^1 represents an unsubstituted or C_{1-6} alkyl-substituted phenyl group;

R^2 represents a hydrogen atom, or a C_{1-6} alkyl, C_{1-6} acyl, benzyl, or tetrahydropyranyl group;

R^3 represents a hydrogen atom or a C_{1-6} alkyl group;

20 $n\text{R}^4$'s and $n\text{R}^5$'s, independently, represent hydrogen atoms or C_{1-6} alkyl groups, wherein n is zero or an integer of 1 to 6; and

R^6 represents an ammonio, di- C_{1-6} alkylamino, pyrrolidinyl, piperidyl or morpholinyl group, and a pharmaceutically-acceptable carrier.

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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).

10 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 C₁₋₆ 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 C₁₋₆ alkyl-O- groups; the term "lower alkylthio group" means C₁₋₆ alkyl-S- groups; the term "lower alkenyl group" means C₂₋₆ alkenyl

1 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,
 5 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,
 10 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
 15 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-CO- groups; the term "lower
 alkylsulfonyl group" means C_{1-6} alkyl-SO₂- groups; the
 term "arylsulfonyl group" means aryl-SO₂- groups;
 20 ther term "ar-lower alkylsulfonyl group" means aryl-
 C_{1-6} alkyl-SO₂- groups; the term "lower alkylsulfonyloxy
 group" means C_{1-6} alkyl-SO₂-O- groups; the term "aryl-
 sulfonyloxy group" means aryl-SO₂-O- groups; the term
 "lower alkylsulfonylamino group" means C_{1-6} alkyl-SO₂-NH-
 25 groups; the term "arylsulfonylamino group" means aryl-
 SO₂NH- 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

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

The protective groups for hydroxyl group,
5 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 Theodora W. Green, 1981, John Wiley
& Sons, Inc. In particular, the protective group for
10 hydroxyl group specifically includes, for example, lower
alkyl, lower acyl 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
15 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,
20 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.

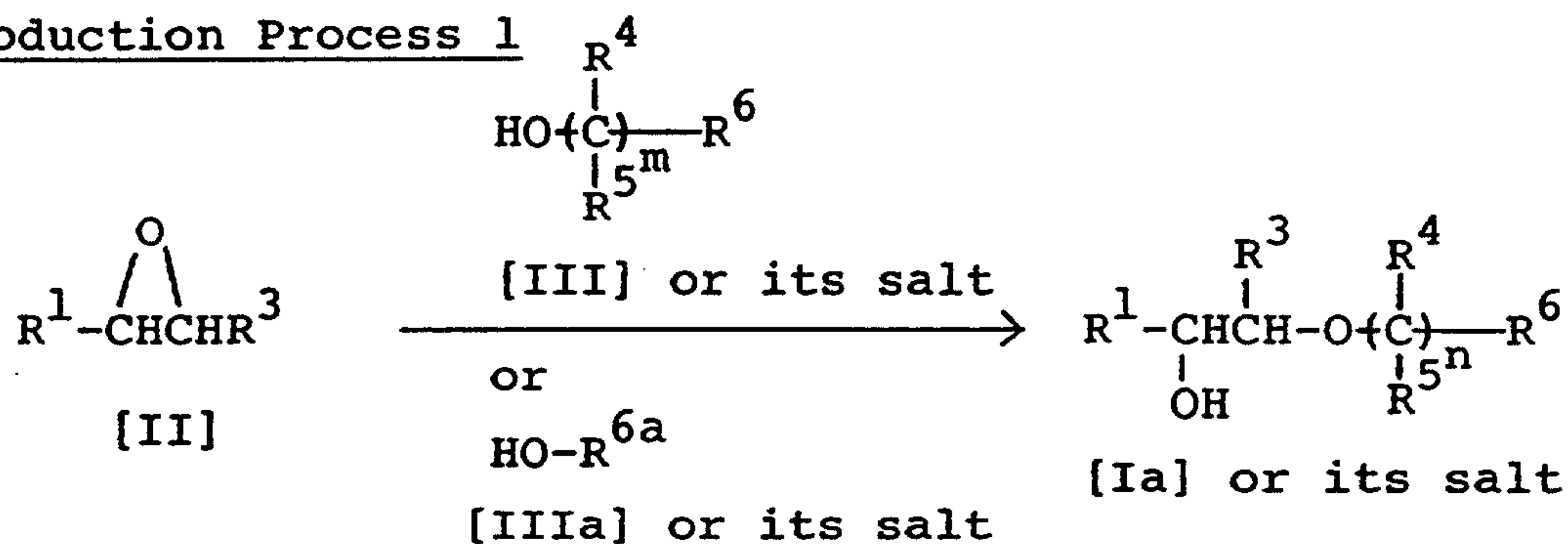
25 When the 1,2-ethanediol derivative of the
general formula [I] or its salt has isomers (e.g. optical
isomers, geometrical isomers, tautomers), all of these
isomers are included in this invention. Also, the

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

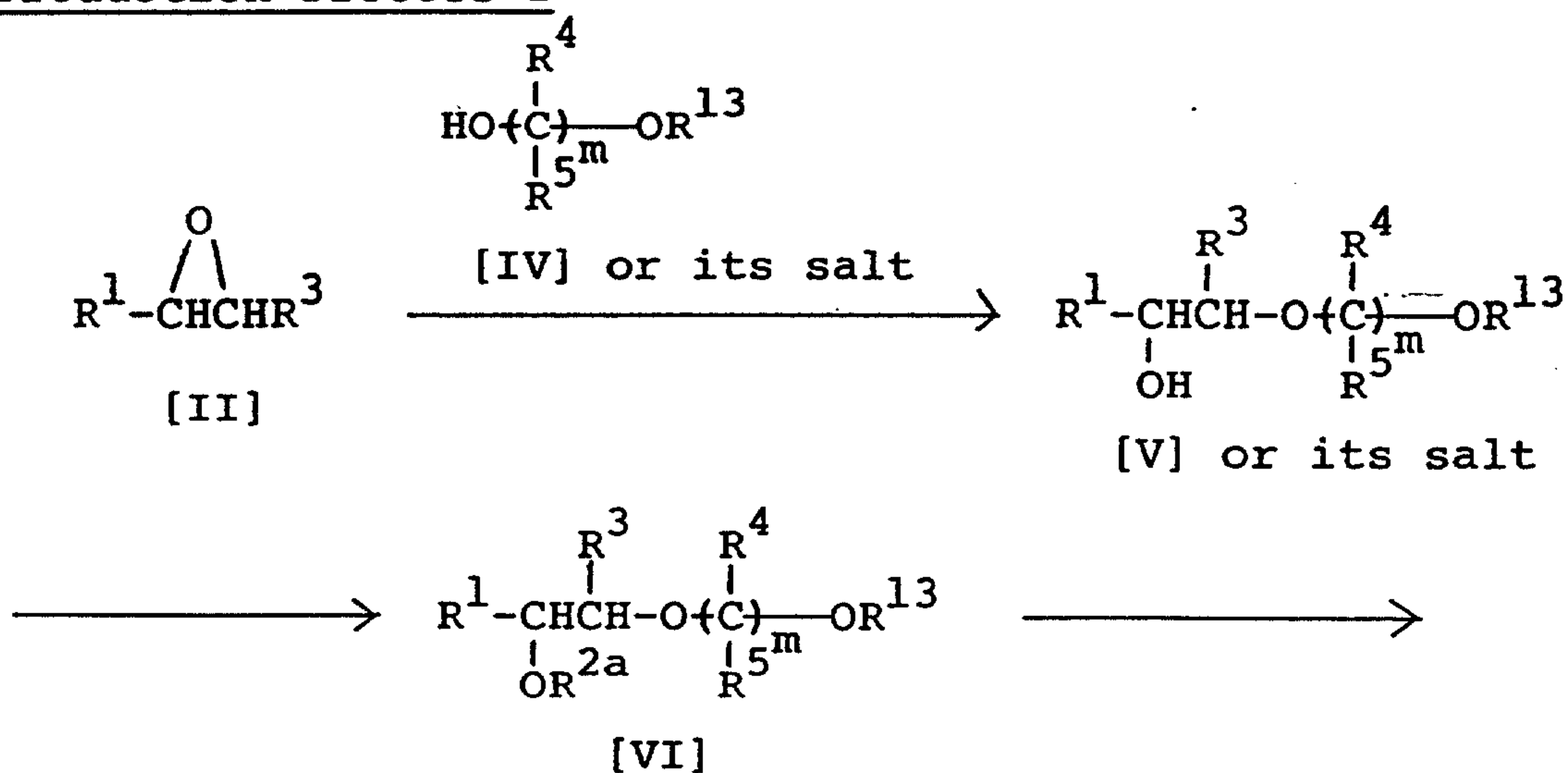
Next, there is described a process for producing a 1,2-ethanediol derivative of the general formula [I] or a salt thereof.

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.

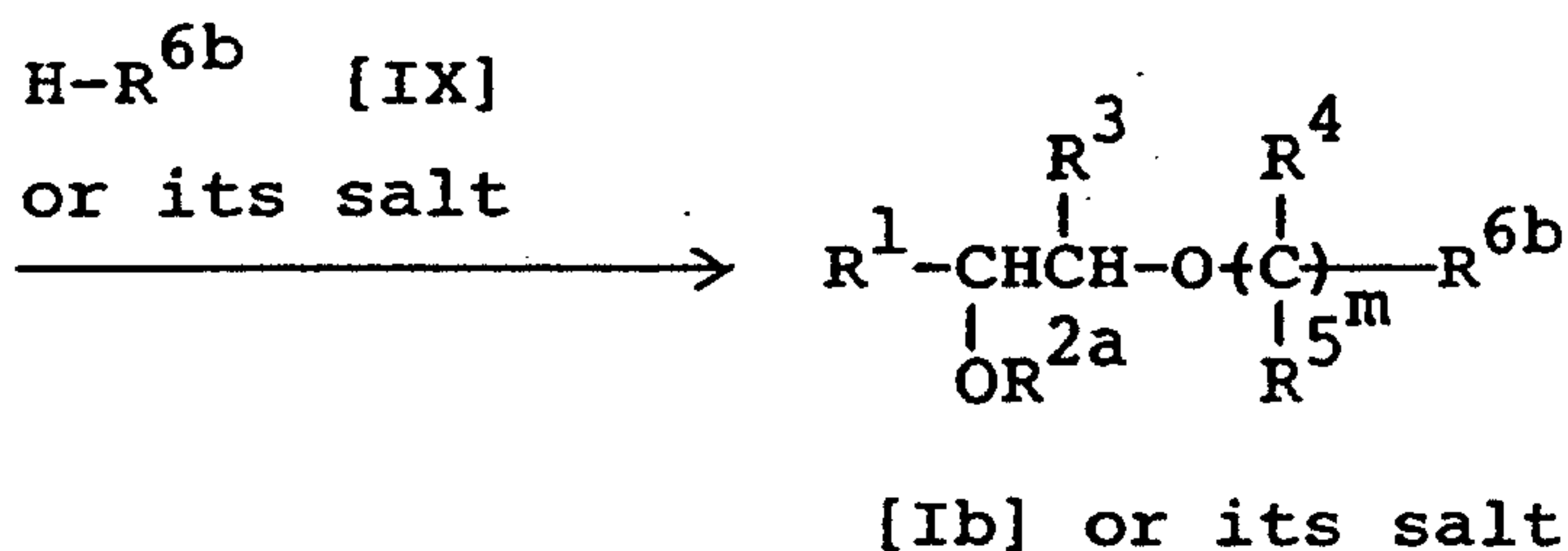
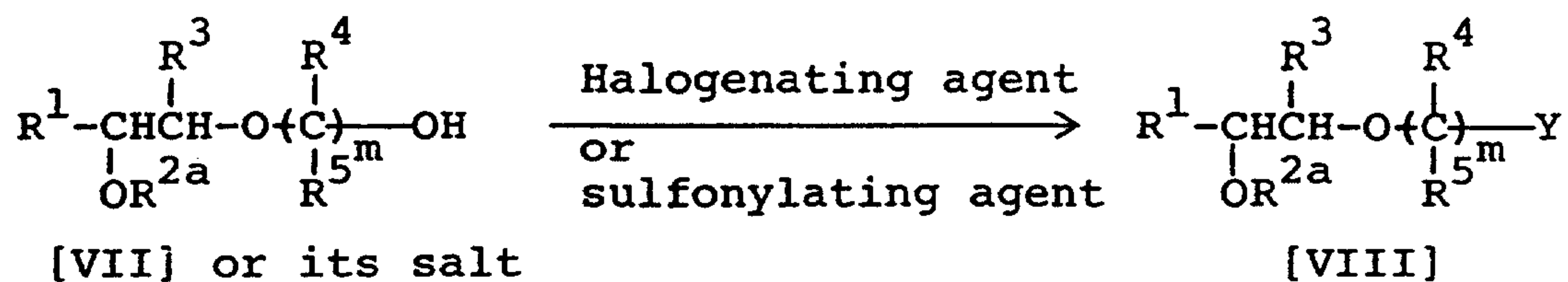
Production Process 1



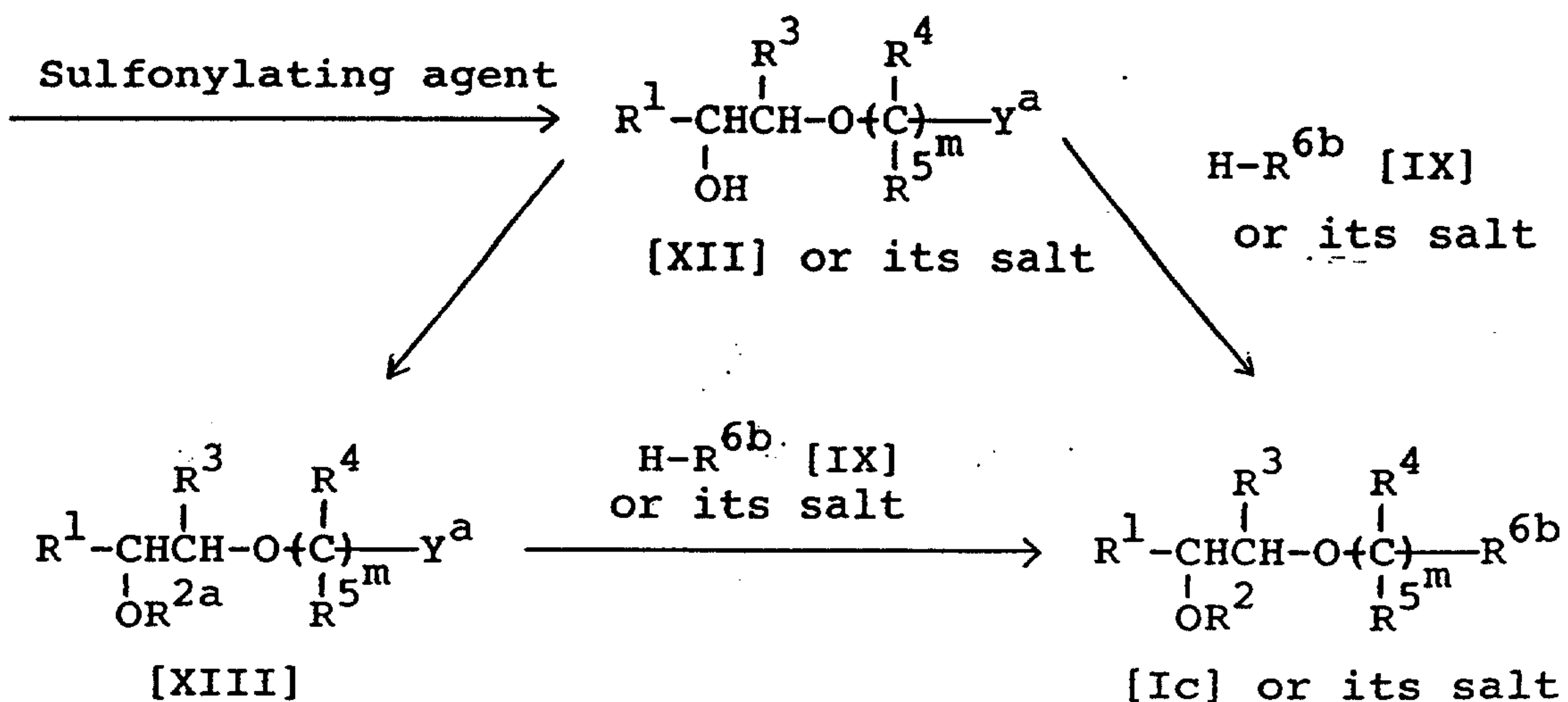
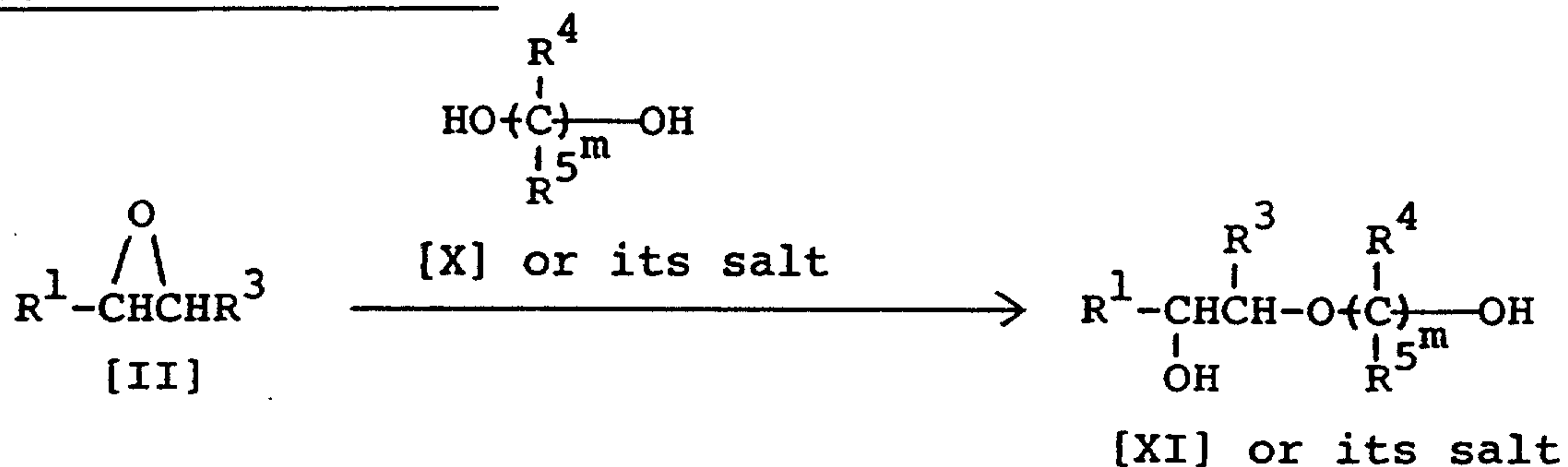
Production Process 2

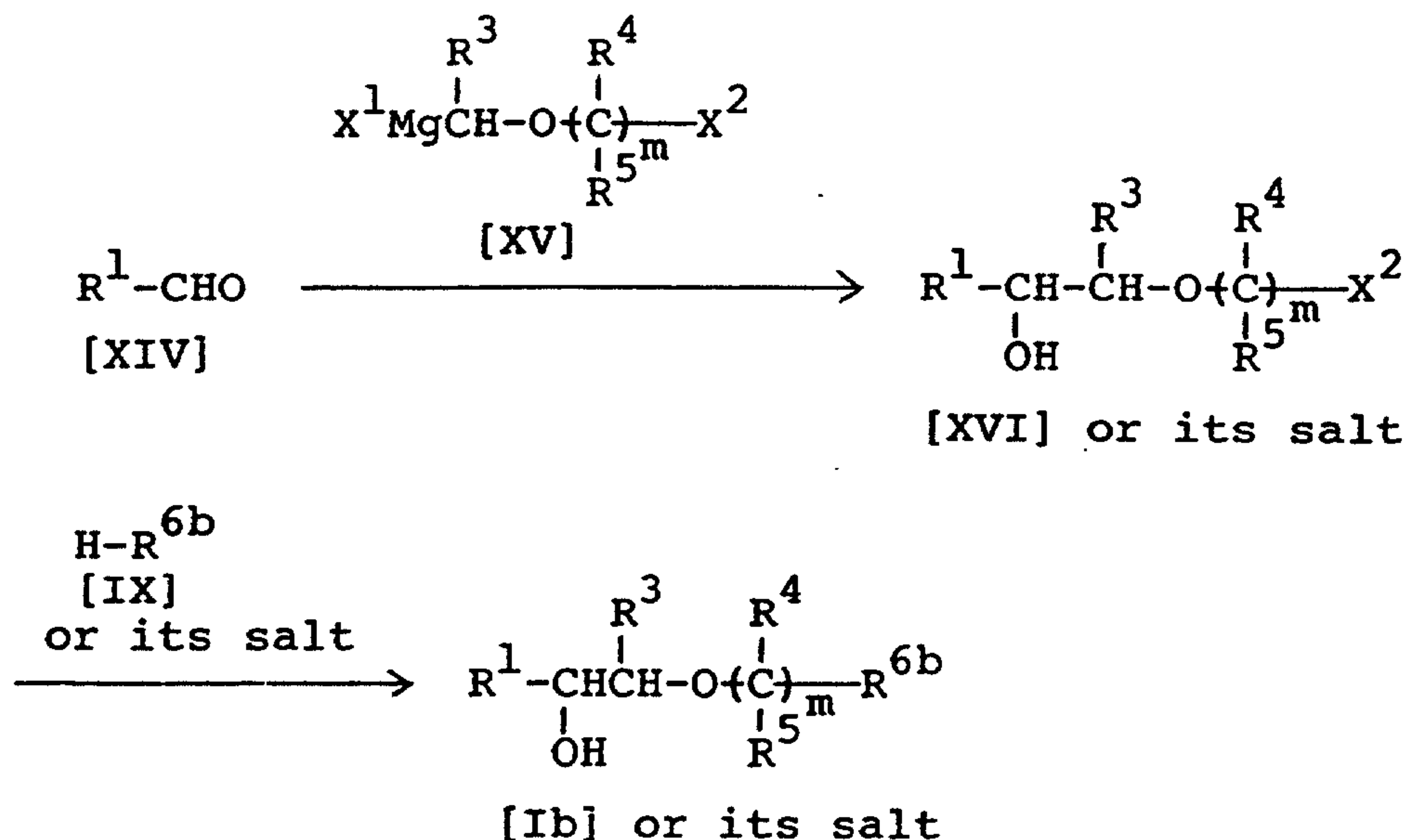


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Production Process 3



Production Process 4

- 1 In the above reaction schemes, R^1 , 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
- 5 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
- 10 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
- 15 definition of R^2 ; X^1 and X^2 , which may be the same or different, represent halogen atoms, Y represents a

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

5 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].

10 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.

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

 In the reaction, the compound of the general
5 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
10 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.

15 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.

20 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.

25 (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].

1 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]
5 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
10 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 [Theodora W.
Green (1981), John Wiley & Sons, Inc.] or a method
15 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
20 salt is reacted with a halogenating agent or a sulfonylat-
ing 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.
25 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;

1 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
5 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.

10 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
15 mentioned, for example, methanesulfonyl chloride,
p-toluenesulfonyl chloride and the like.

Each of the halogenating agent, the sulfonylat-
ing agent and the base as an optional component is used
in an amount of at least 1 mole, preferably 1-2 moles,
20 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.

25 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

1 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.

5 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
10 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].

15 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
20 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.

25 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

1 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
5 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.
10 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.

15 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
20 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.

25 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

1 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
5 with per se known methods, for example, the method
described in Protective Groups in Organic Synthesis
[Theodora W. Green (1981), John Wiley & Sons, Inc.] or a
method similar thereto.

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

(4) The compound of the general formula [XII] or
its salt or [XIII] is reacted with a compound of the
general formula [IX] or its salt in the presence or
15 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

20 (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
25 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

1 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.

10 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

1 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.

5 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
10 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
15 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
20 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
25 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],

1 [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
5 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,
10 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
15 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
20 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
25 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

1 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,
5 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,
10 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.

15 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

20 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
25 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.

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

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

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

- 5 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 -

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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.

1 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 guillotine 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.

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

* Trade mark

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- 1 - : 0-60 seconds
 + : 61-100 seconds
 ++ : 101-150 seconds
 +++ : 151-300 seconds

5 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	++

1 (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
5 interferes 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,
10 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
15 steel grid and which had, at one corner of the floor
 grid, a platform of 7 cm x 7 cm x 2 cm (height).

1 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
5 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
10 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
15 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
20 to the measurement of 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:

25 - : 0-60 seconds
 + : 61-100 seconds
 ++ : 101-150 seconds
 +++ : 151-300 seconds

1

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	-	-

1 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].

5 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
10 was incubated, and the amount of the resulting

- 1 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		

1 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
5 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,
10 221, 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
15 excellent in antihypoxic activity, antiamnesic activity
and inhibitory activity for acetylcholinesterase and

1 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
5 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
10 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.

15 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
20 alcohol, IPE: diisopropyl ether, PTS: p-toluenesulfonic acid.

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

25 Production example 1

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

1 180 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
5 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
10 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.
15 (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
20 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
25 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

1 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

5 Optical rotation: $[\alpha]_D^{25} = +5.2^\circ$ (C=2, CHCl₃)

The following compounds were obtained in the same manner.

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

$[\alpha]_D^{25} = +15.7^\circ$ (C=2, CHCl₃)

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

$[\alpha]_D^{25} = +12.5^\circ$ (C=4, CHCl₃)

Production Example 2

(1) A solution of 23 g of (+)-diisopinocampheyl-chloroborane 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.

1 (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
5 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
10 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,
15 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: $[\alpha]_D^{26} = -14.4^\circ$ (C=2, CHCl₃)

20 The following compounds were obtained in the
same manner.

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

$[\alpha]_D^{27} = -18.6^\circ$ (C=2, CHCl₃)

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

25 $[\alpha]_D^{25} = -11.3^\circ$ (C=2, CHCl₃)

1 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 5 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 10 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, 15 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 20 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).

25 Melting point: 164-165°C [EtOH]

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

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- 1 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.

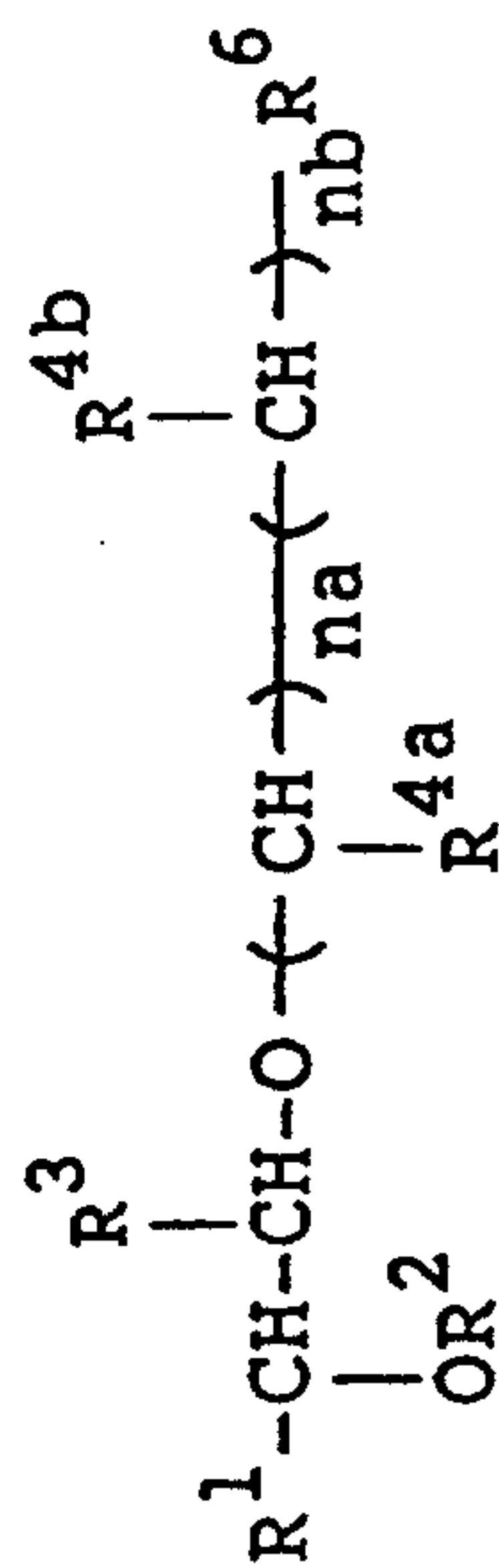


Table 5

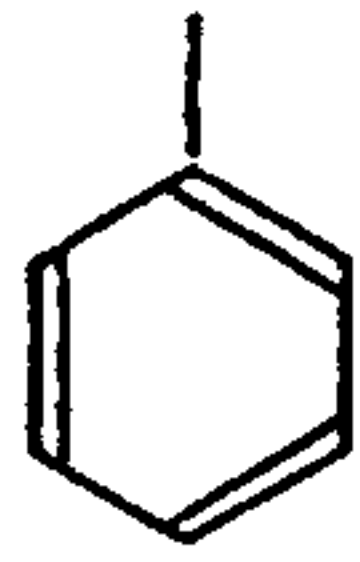
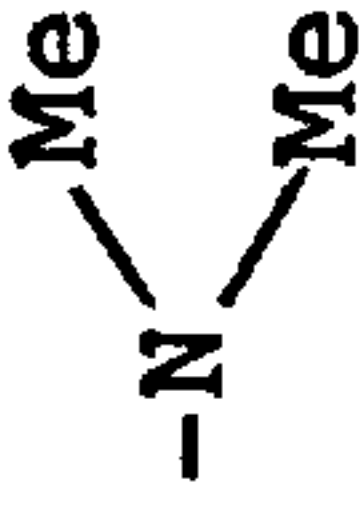
Compound No.	R ¹	R ²	R ³	R ^{4a}	R ^{4b}	R ⁶	na	nb	Addition salt	Melting point (°C)
2		H	H	H	H		1	1	HCl	184-185 [EtOH]
3 ^{*a}	" (R-form)	"	"	"	"	"	"	"	"	174.5-175 [Me ₂ CO-EtOH]

Table 5 (cont'd)

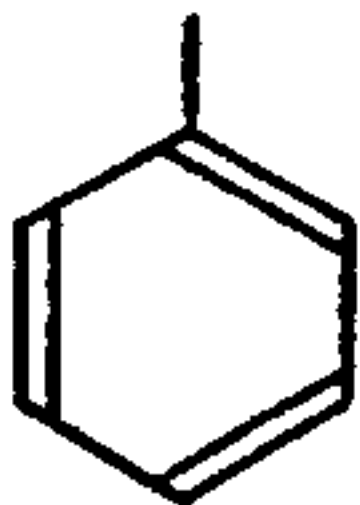
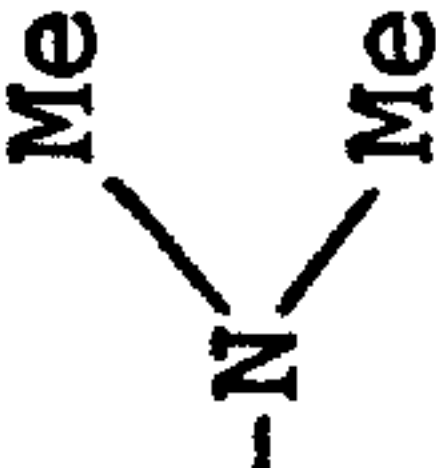
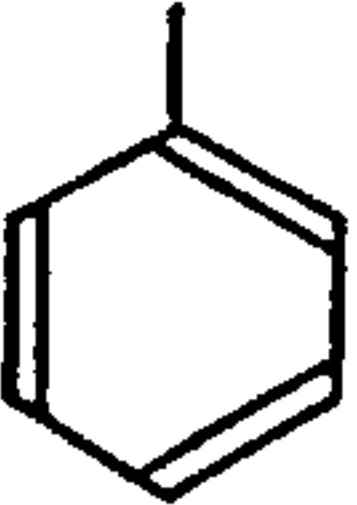
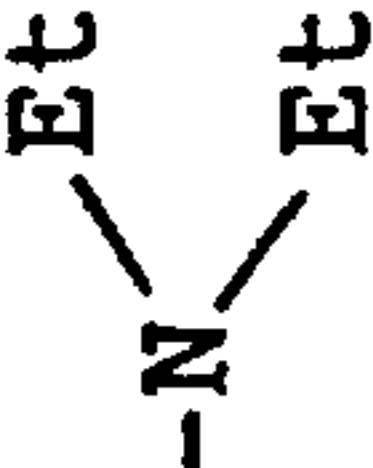
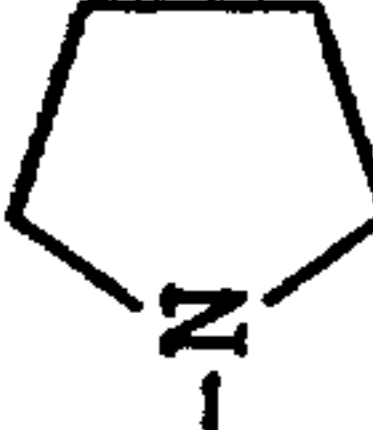
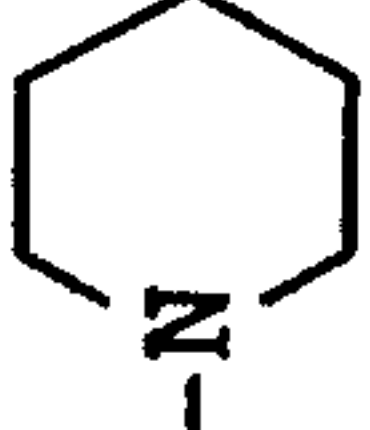
4 ^{*b}	 (S-form)	H	H	H	H	H	H		1	1	HCl	174.5-175 [Me ₂ CO- EtOH]
5		"	"	"	"	"	"		"	"	-	Oily
6	"	"	"	"	"	"	"		"	"	HCl	173-174 [EtOH- Et ₂ O]
7	"	"	"	"	"	"	"		"	"	"	163.5-164.5 [EtOH- Et ₂ O]

Table 5 (cont'd)

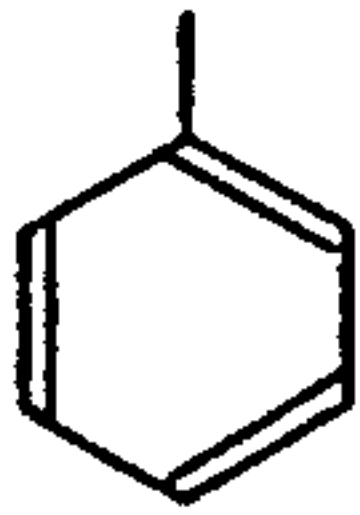
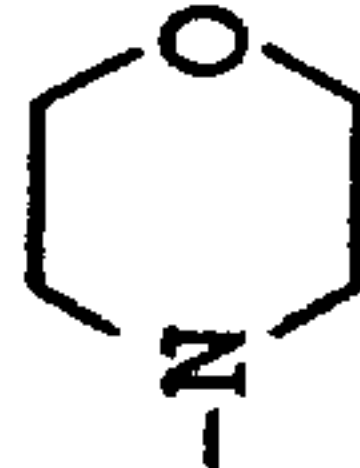
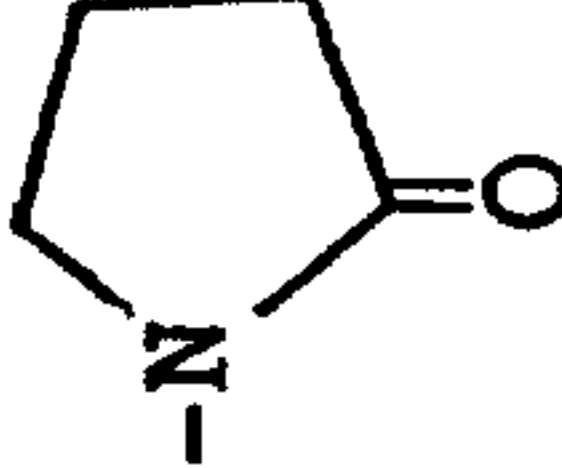
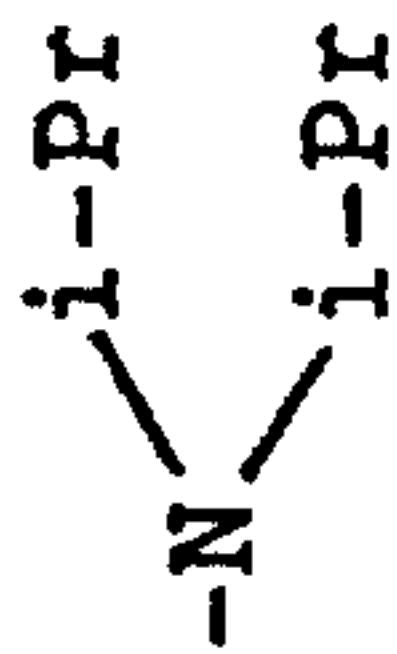
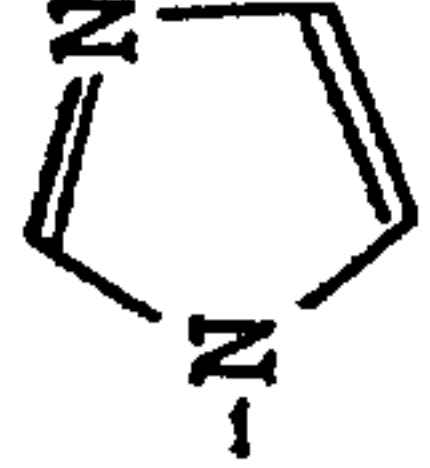
8		H	H	H	H		1	1	HCl	153-154.5 [EtOH- Et ₂ O]
9	"	"	"	"	"		"	"	-	Oily
10	"	"	"	"	"		"	"	"	"
11	"	"	"	"	"		"	"	"	"

Table 5 (cont'd)

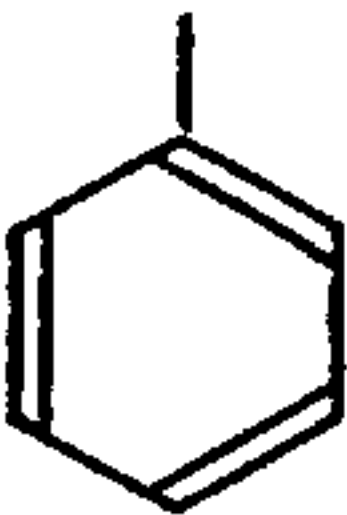
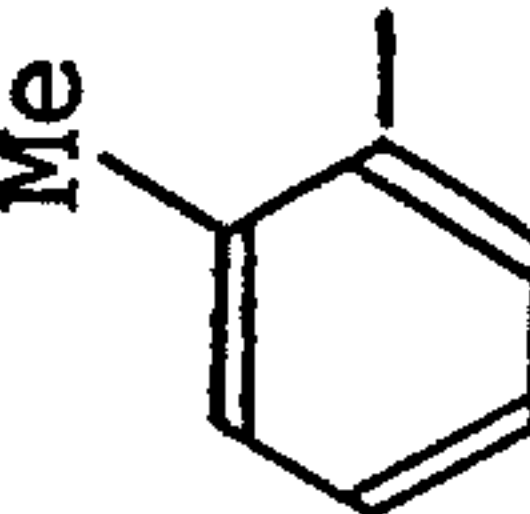
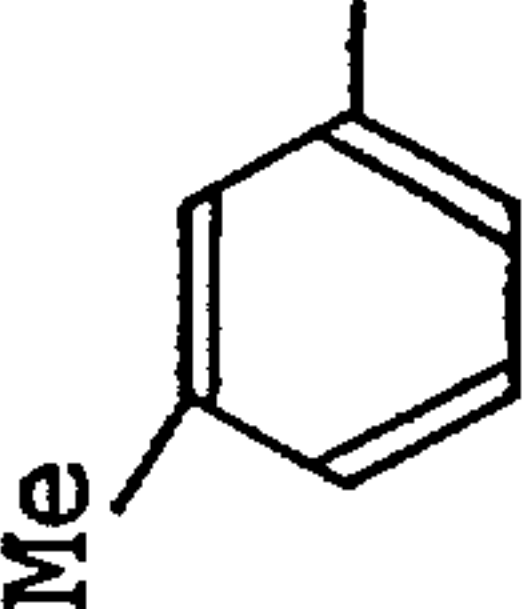
12		H	H	H	H	-N(Me)Me	2	1	-	Oily
13	"	"	"	"	"	"	3	3	HCl	Amorphous
14		"	"	"	"	"	1	1	"	198-199 [EtOH]
15		"	"	"	"	"	"	"	"	165-166 [IPA]

Table 5 (cont'd)

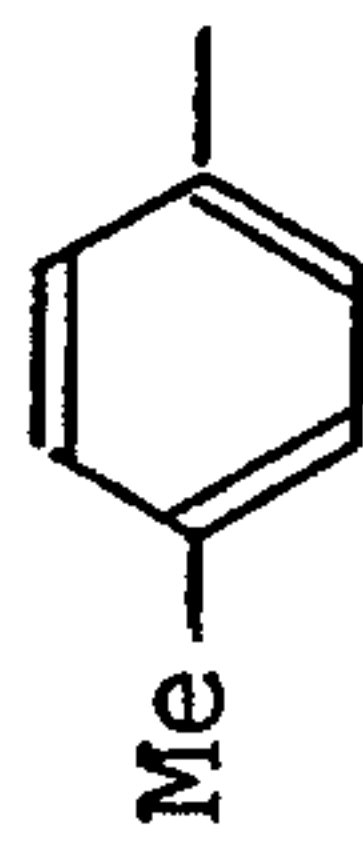
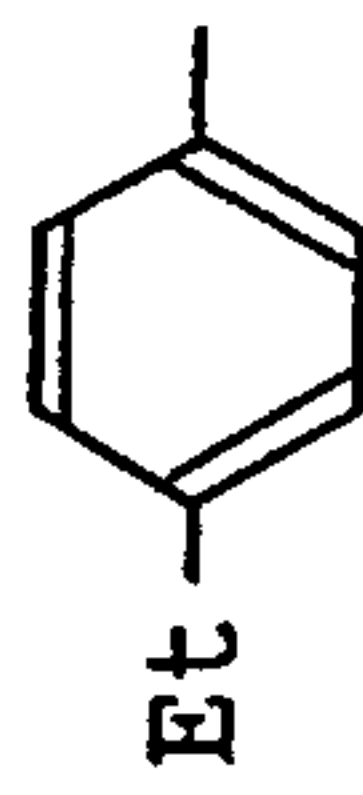
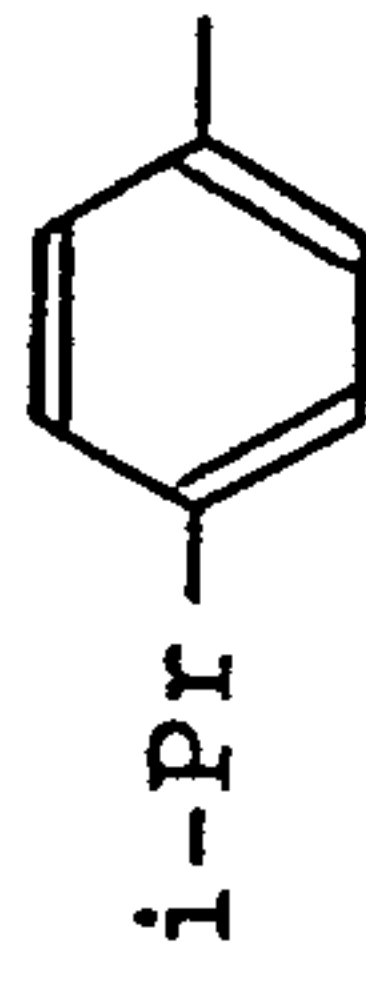
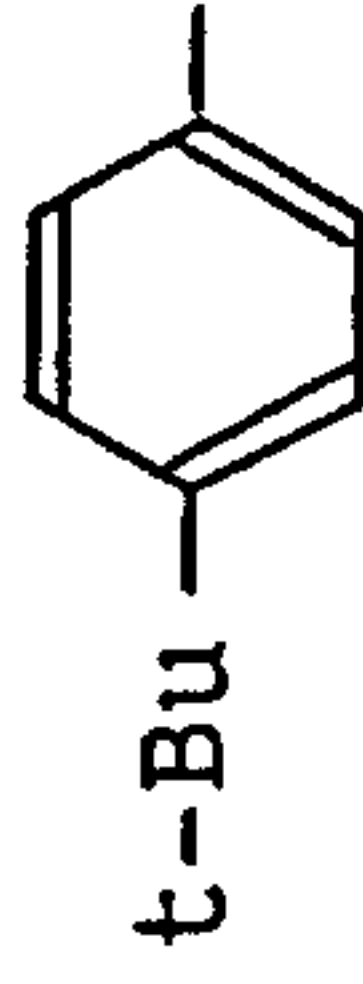
16		H	H	H	H	-N<Me Me	1	1	HCl	181.5-183 [EtOH]
17		"	"	"	"	"	"	"	"	201.5-203 [IPA]
18		"	"	"	"	"	"	"	"	194.5-196.5 [EtOH]
19		"	"	"	"	"	"	"	"	251-252 [EtOH]

Table 5 (cont'd)

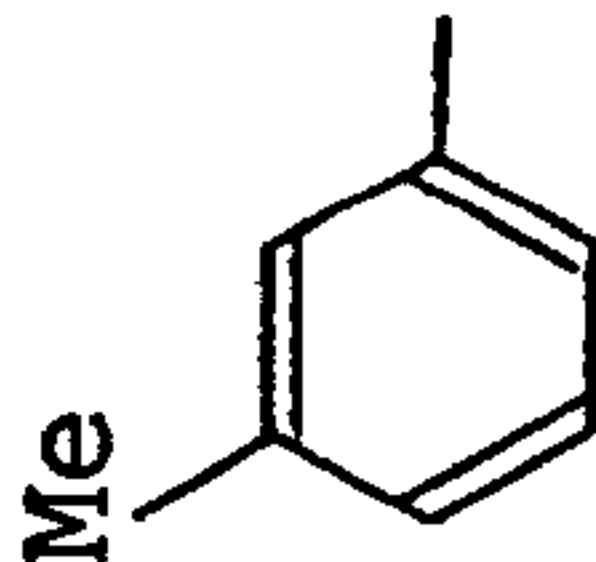
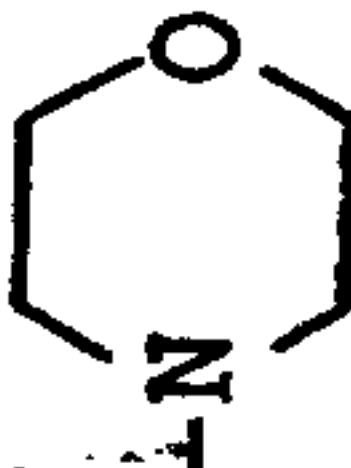
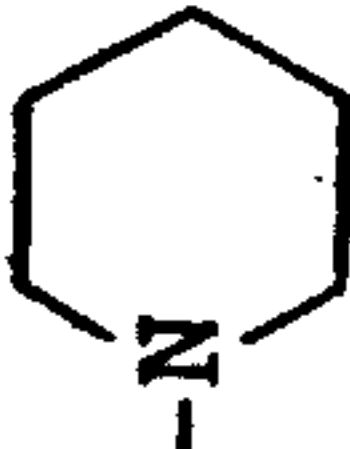
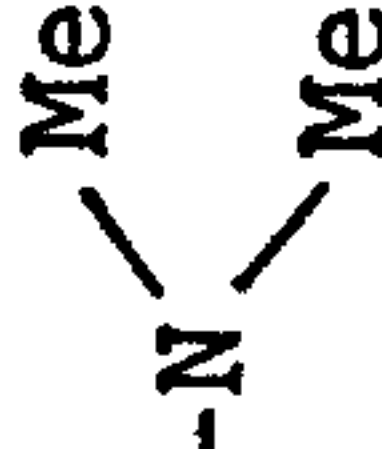
20		H	H	H	H		1	1	HCl	141-143 [EtOH- Et ₂ O]
21	"	"	"	"	"		"	"	"	136.5-137.5 [EtOH- Et ₂ O]
22	"	"	"	"	"		"	"	-	Oily
23	"	"	"	"	"		2	2	"	"

Table 5 (cont'd)

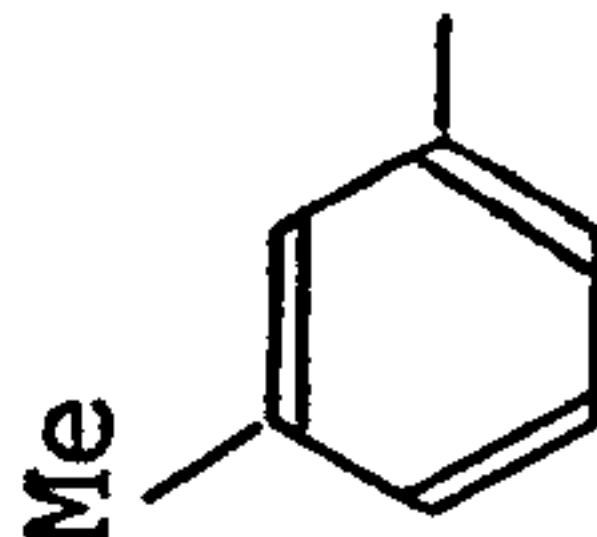
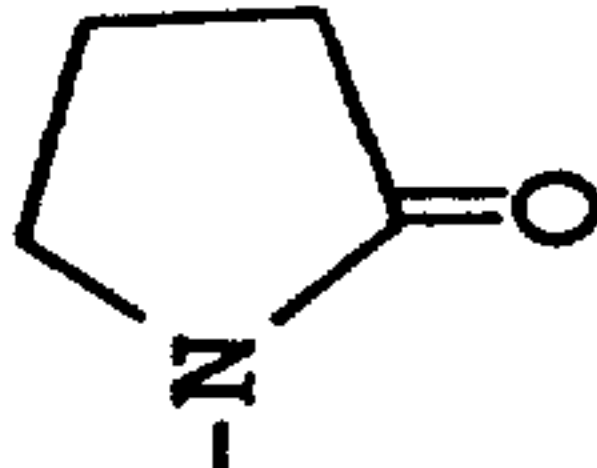
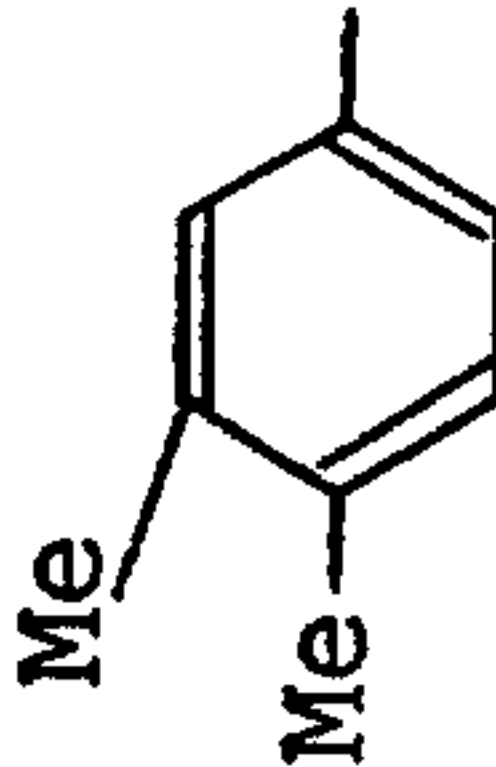
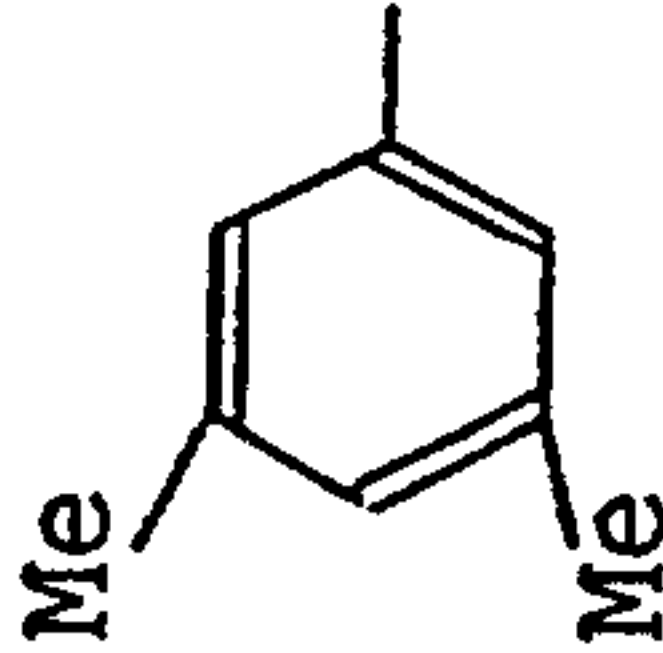
24		H	H	H	H	-N(Me)Me	1	2	-	Oily
25	"	"	"	"	"		"	1	"	"
26		"	"	"	"	-N(Me)Me	"	"	HCl	184-185 [EtOH]
27		"	"	"	"	"	"	"	"	158-159 [IPA]

Table 5 (cont'd)

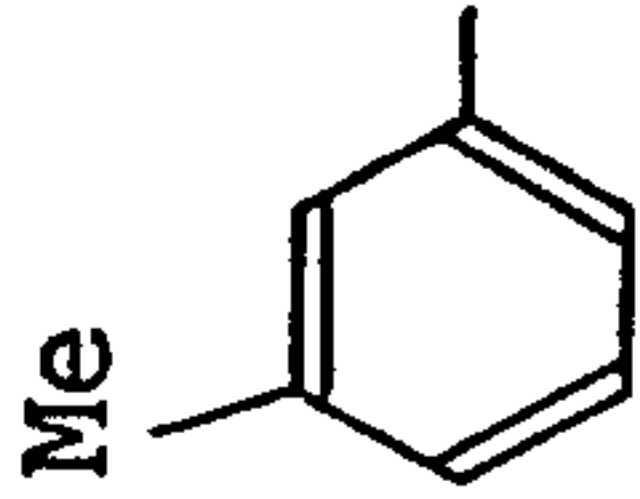
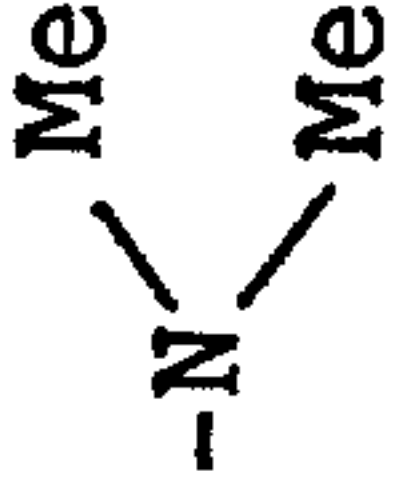
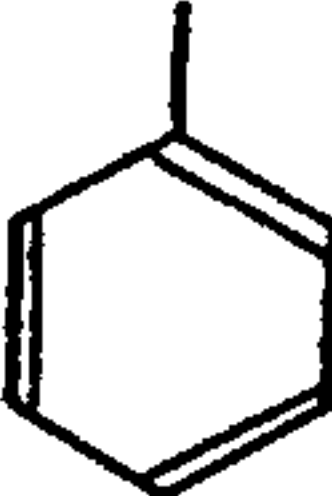
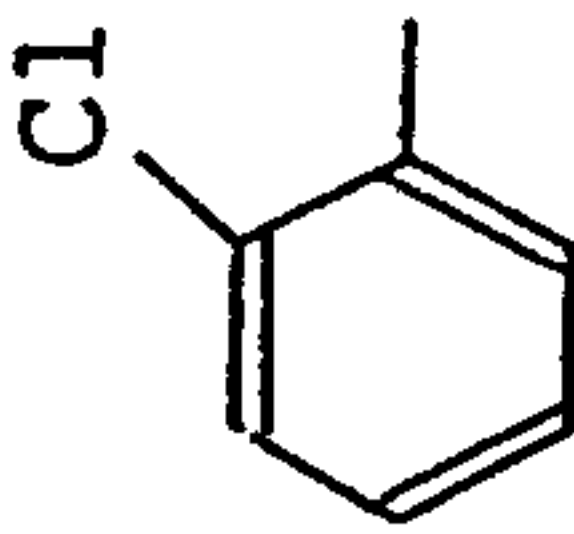
28		H	H	H	Me	H		l	l	-	Oily
29	"	"	"	"	H	Me	"	"	"	"	"
30		"	Me	"	"	H	"	"	"	HCl	190-191 [MeOH- Et ₂ O]
31		"	H	"	"	"	"	"	"	"	203-204 [EtOH]

Table 5 (cont'd)

[illegible]

Table 5 (cont'd)

36		H	H	H	H	H	H	H	-N	1	1	HCl	131-132 [EtOH- Et ₂ O]
37		"	"	"	"	"	"	"	"	"	"	"	178.5-179.5 [EtOH- Et ₂ O]
38		"	"	"	"	"	"	"	-N	"	"	"	171-172 [EtOH]
39		"	"	"	"	"	"	"	"	"	"	"	182-182.5 [EtOH]

Table 5 (cont'd)

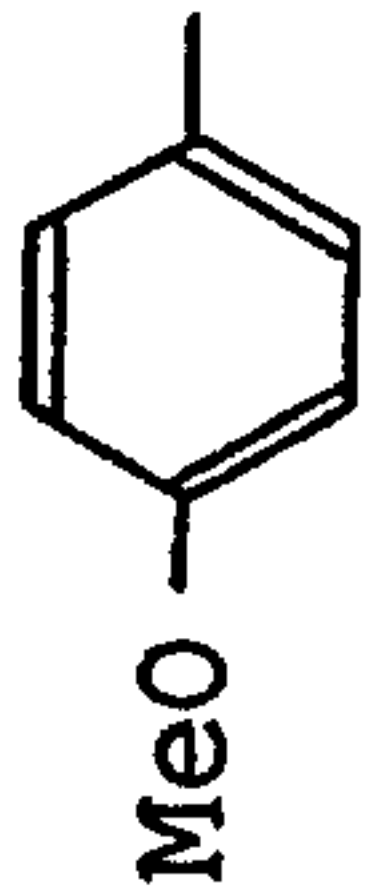
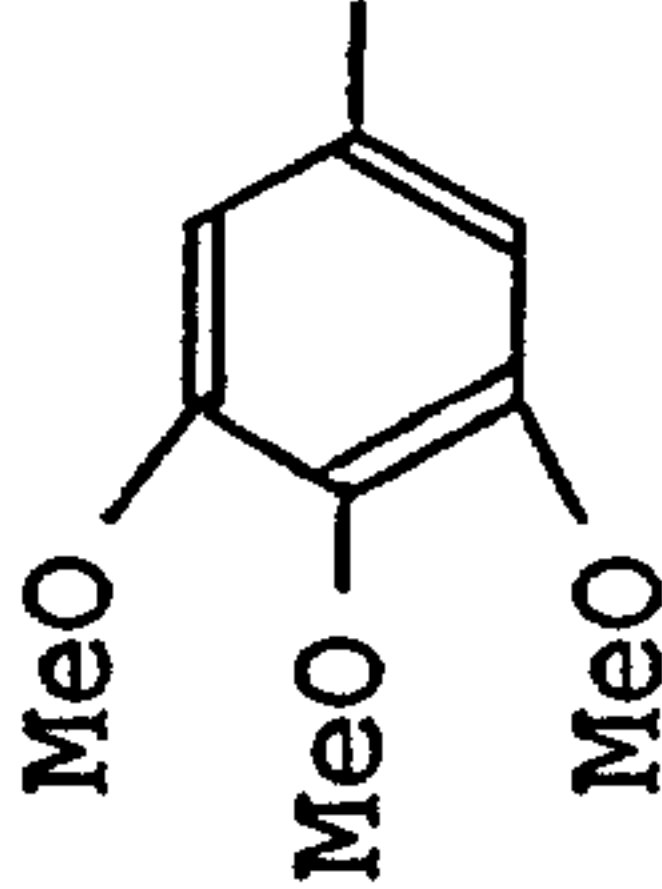
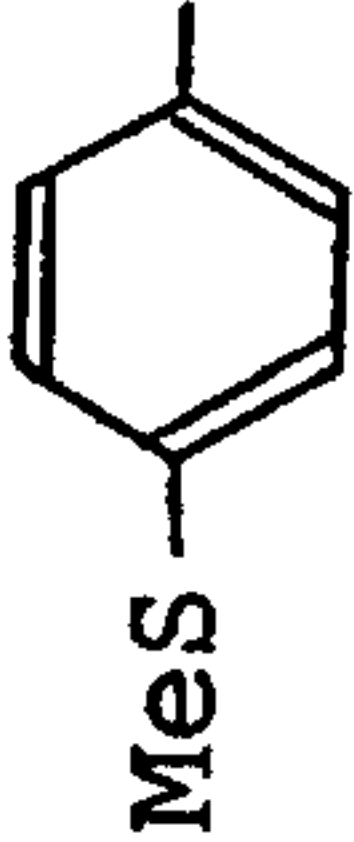
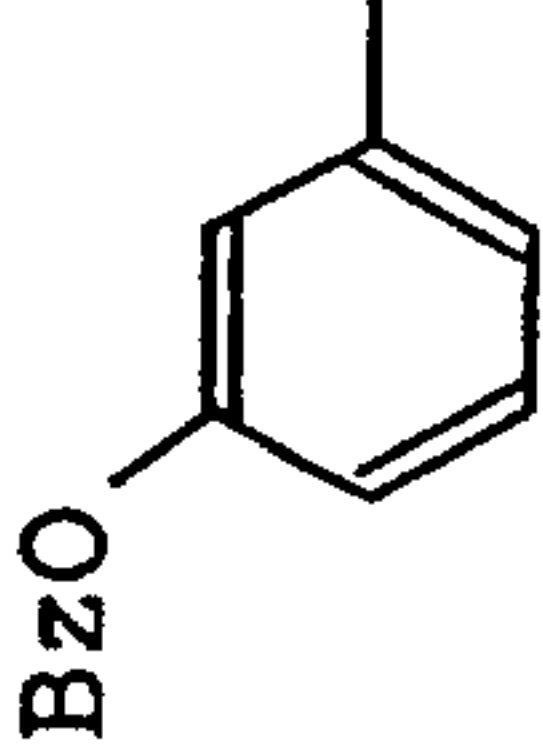
44		H	H	H	H	-N<Me<Me	1	1	HCl	171-173 [EtOH]
45		"	"	"	"	"	"	"	PTS	140-141 [EtOH]
46		"	"	"	"	"	"	"	HCl	179.5-181.5 [EtOH- Et ₂ O]
47		"	"	"	"	"	"	"	"	169-171 [EtOH]

Table 5 (cont'd)

	H	H	H	H	-N(Me) ₂	l	l	HCl	186-186.5 [EtOH]
48		BzO-	-						
49		OCH ₂ -	-					"	188-188.5 [EtOH]
50		OCH ₂ -	-					"	199-199.5 [MeOH-EtOH]
51		BzO-	-					-	Oily

Table 5 (cont'd)

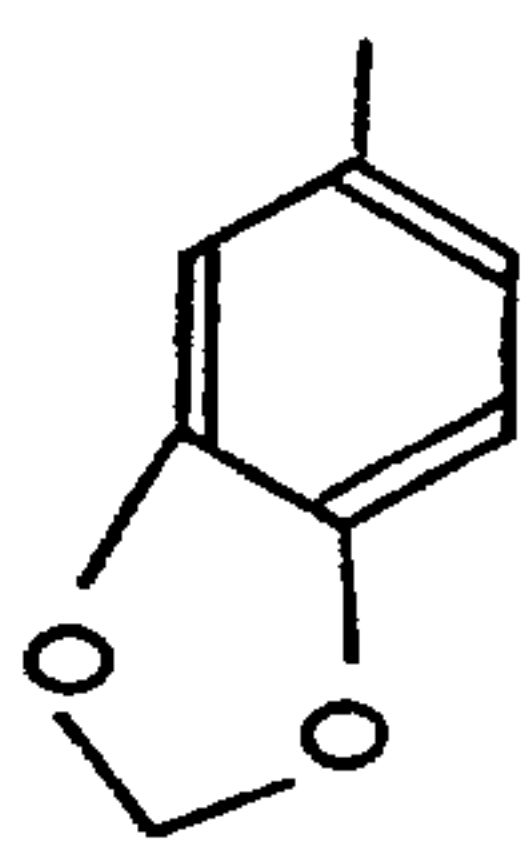
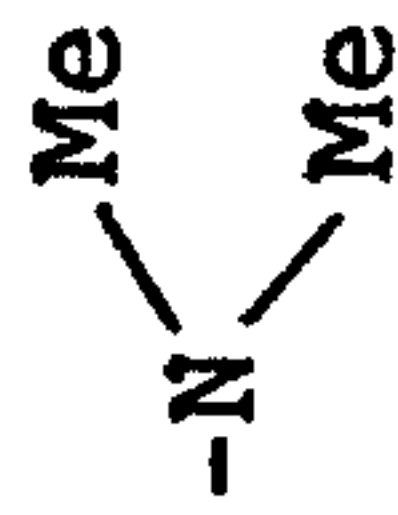
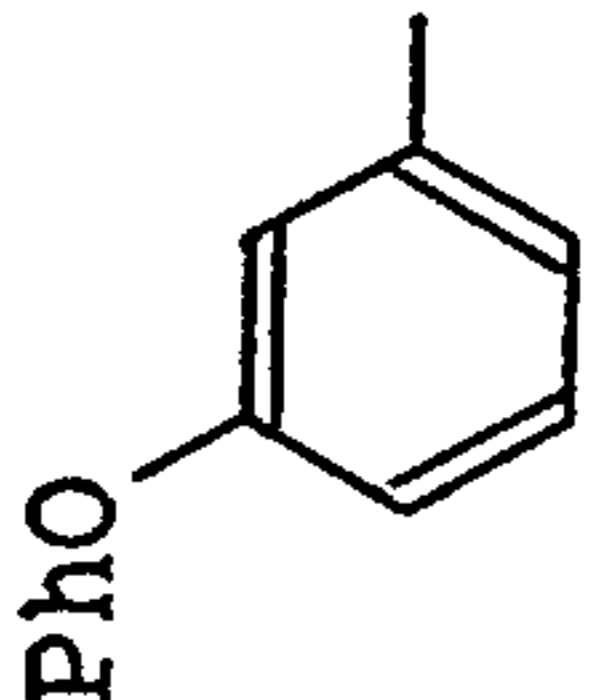
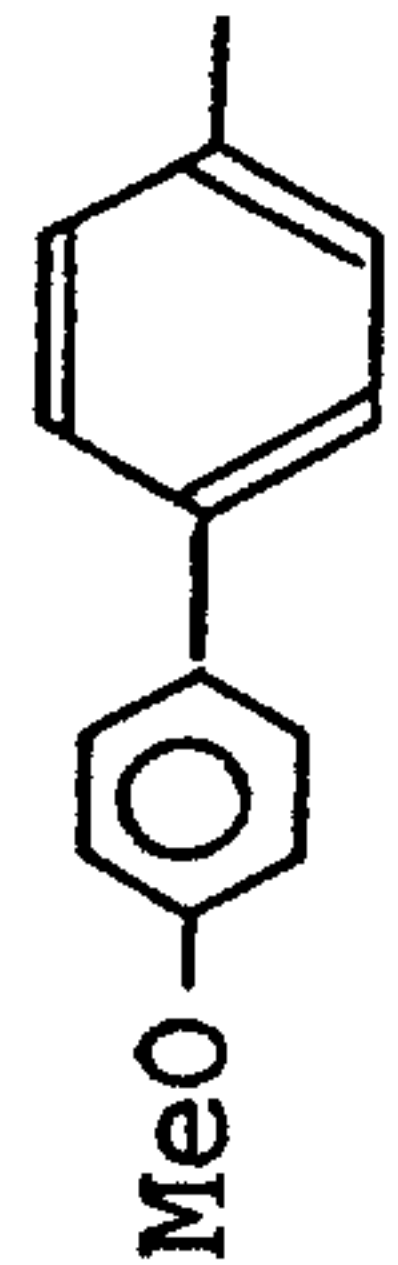
52		H	H	H	H	H	H	H		1	1	HCl	149.5-151 [Me ₂ CO]
53		"	"	"	"	"	"	"	"	"	"	"	140-141 [EtOH- Et ₂ O]
54		"	"	"	"	"	"	"	"	"	"	"	174.5-176.5 [MeCN]
55		"	"	"	"	"	"	"	"	"	"	"	229-231 [MeCN]

Table 5 (cont'd)

[illegible]

Table 5 (cont'd)

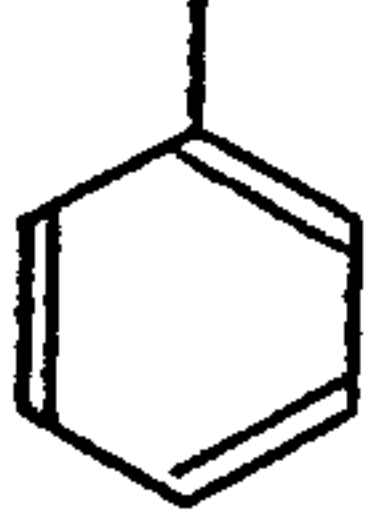
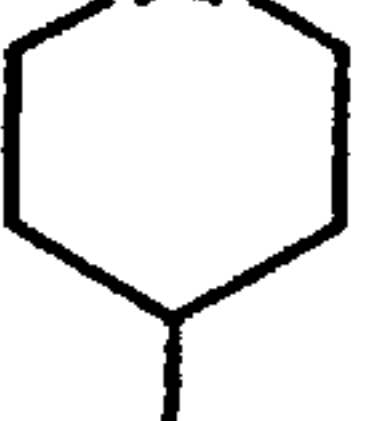
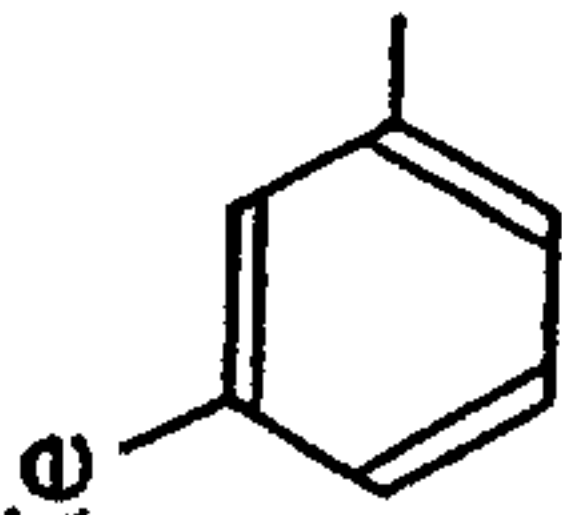
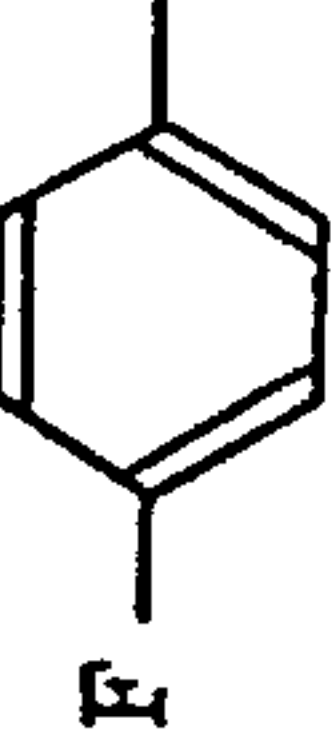
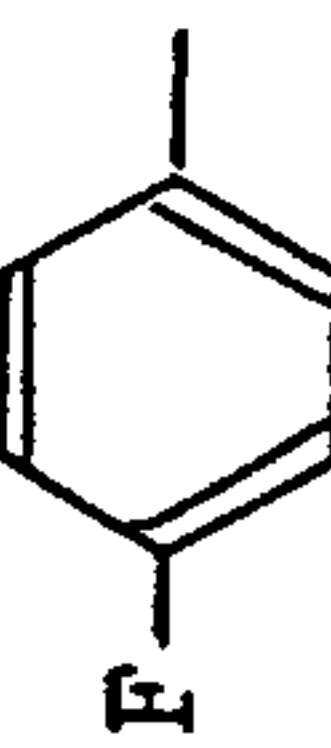
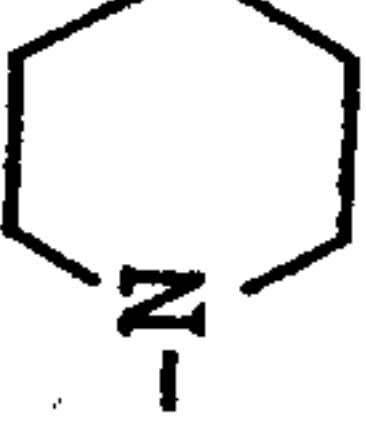
60		H	H	H	H	H	H	H		1	1	-	Oily
61		"	"	"	"	"	"	"	"	"	"	"	"
62		"	"	"	"	"	"	"	"	"	"	"	50-52
63		"	"	"	"	"	"	"		"	"	HCl	160-161 [EtOH- Et ₂ O]

Table 5 (cont'd)

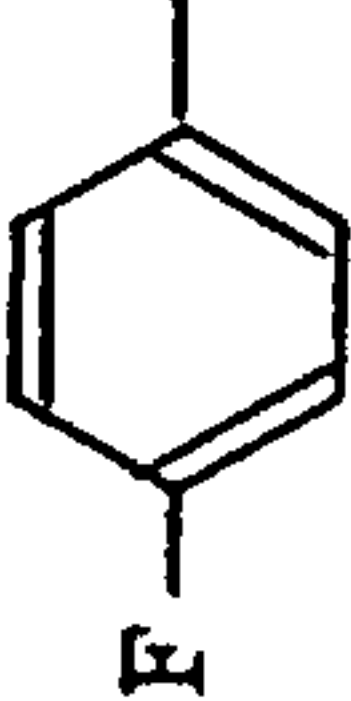
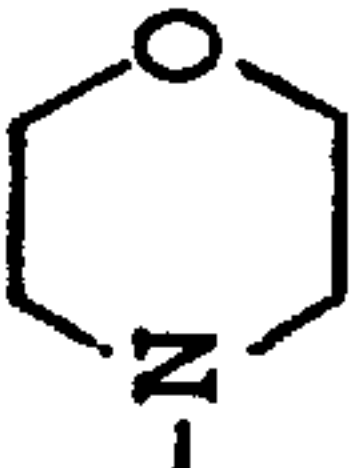
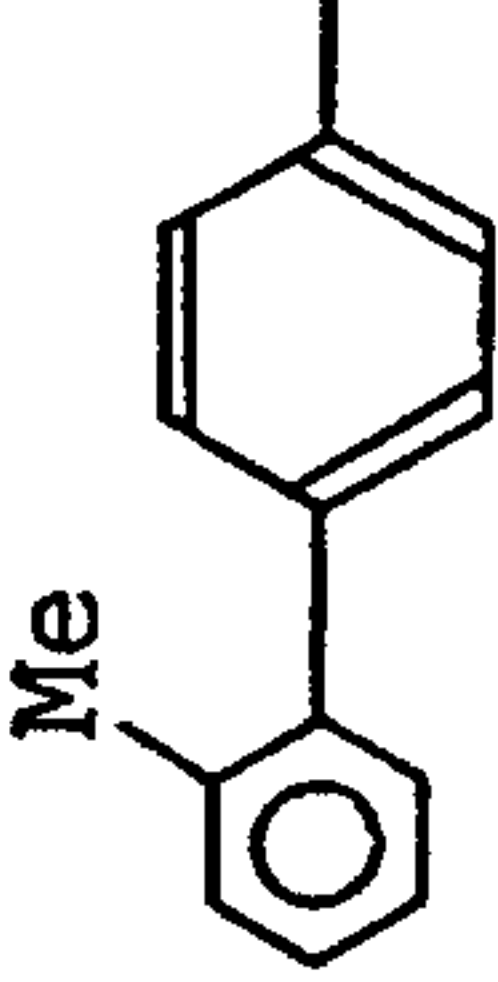
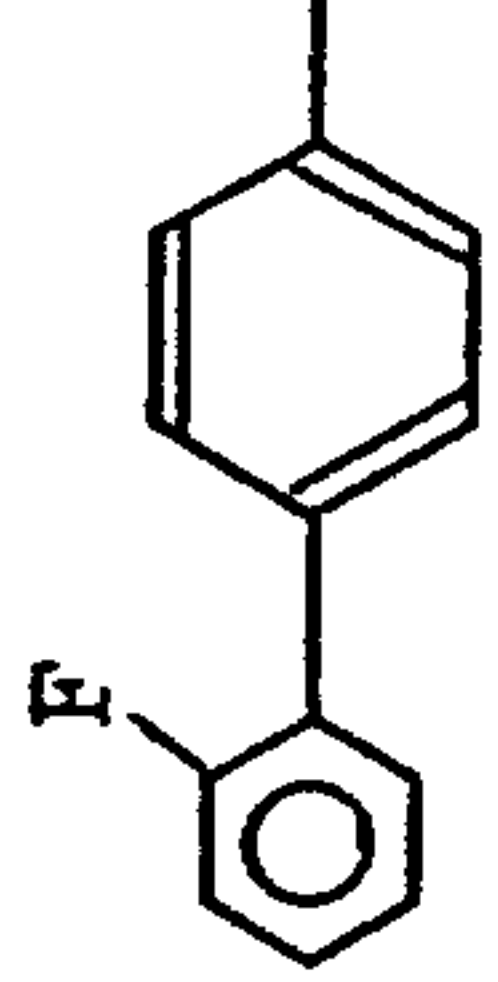
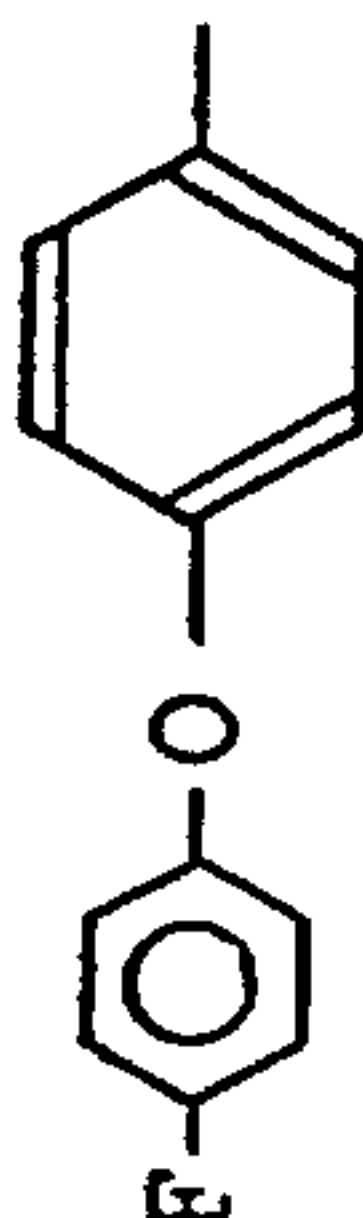
64		H	H	H	H	H	H		1	1	HCl	151-152.5 [EtOH- Et ₂ O]
65		"	"	"	"	"	"		"	"	"	223-225 [EtOH-IPA]
66		"	"	"	"	"	"	"	"	"	"	215-216 [MeOH-EtOH]
67		"	"	"	"	"	"	"	"	"	"	180.5-181.5 [MeCN]

Table 5 (cont'd)

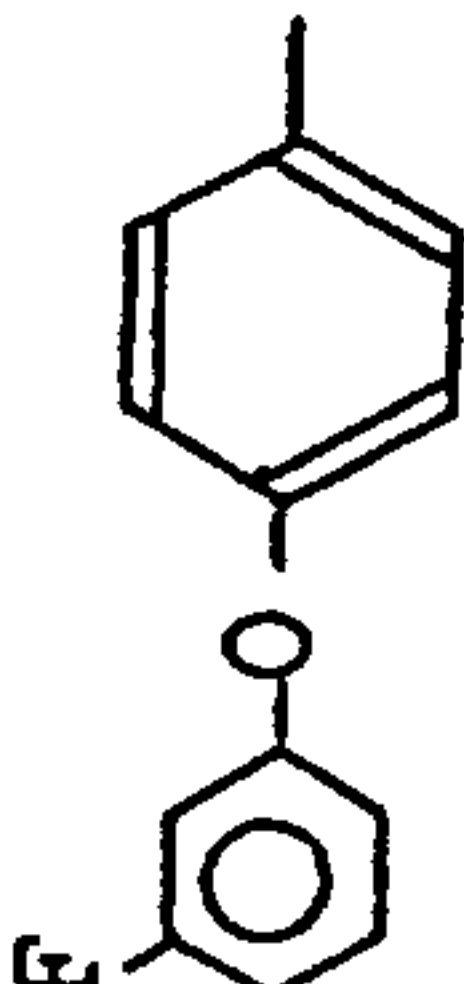
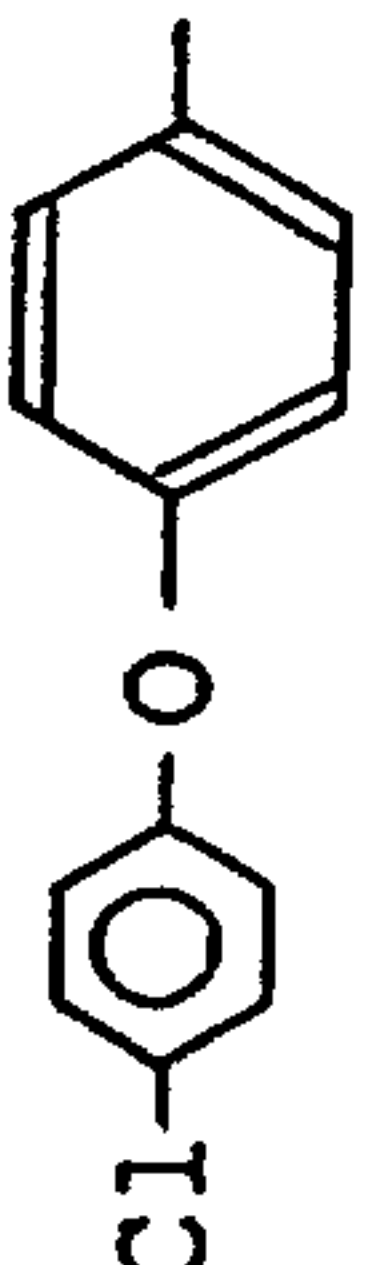
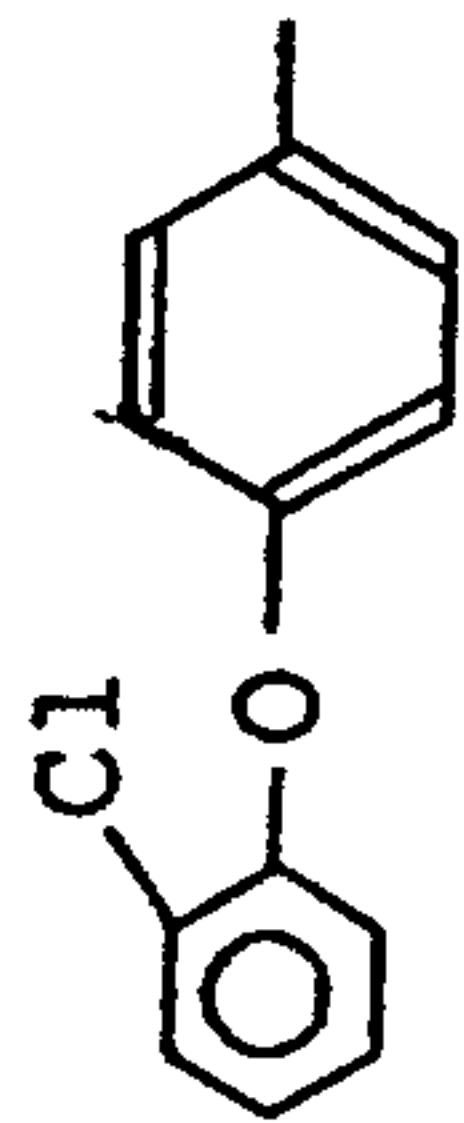
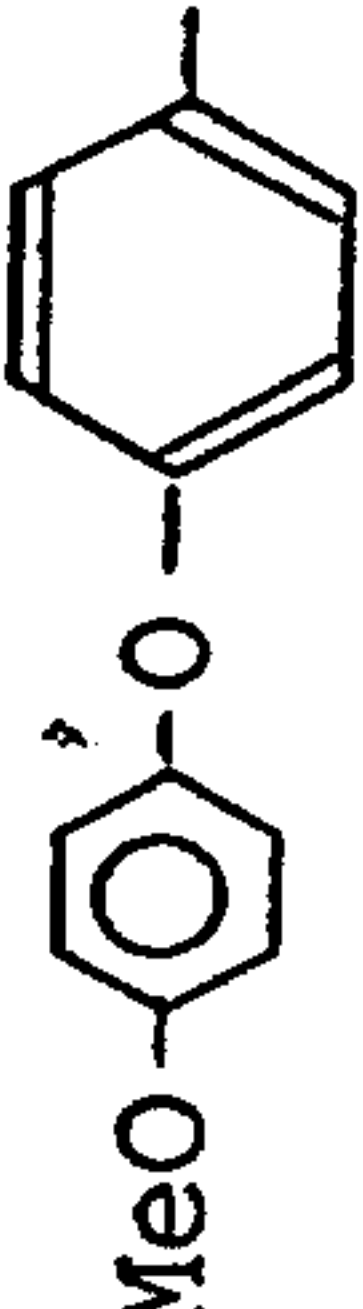
68		H	H	H	H	H	H	H	-N(Me) ₂	1	1	HCl	168.5-169.5 [IPA]
69		"	"	"	"	"	"	"	"	"	"	"	177.5-178.5 [MeCN]
70		"	"	"	"	"	"	"	"	"	"	"	194.5-195 [MeCN]
71		"	"	"	"	"	"	"	"	"	"	"	162-162.5 [IPA]

Table 5 (cont'd)

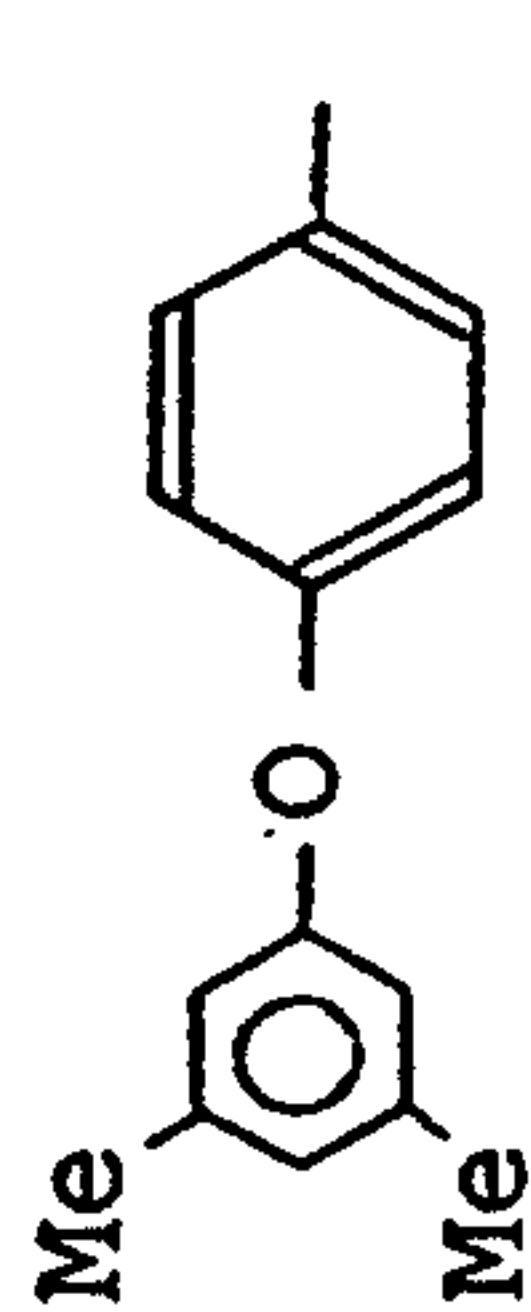
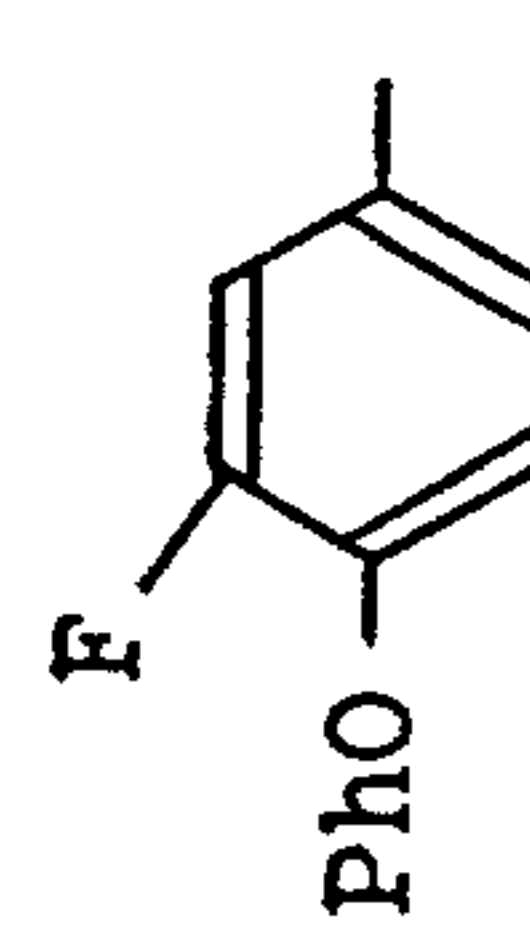
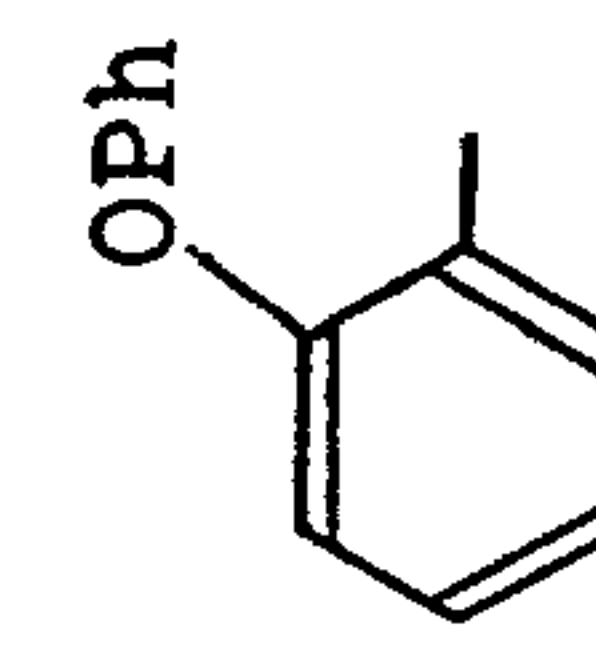
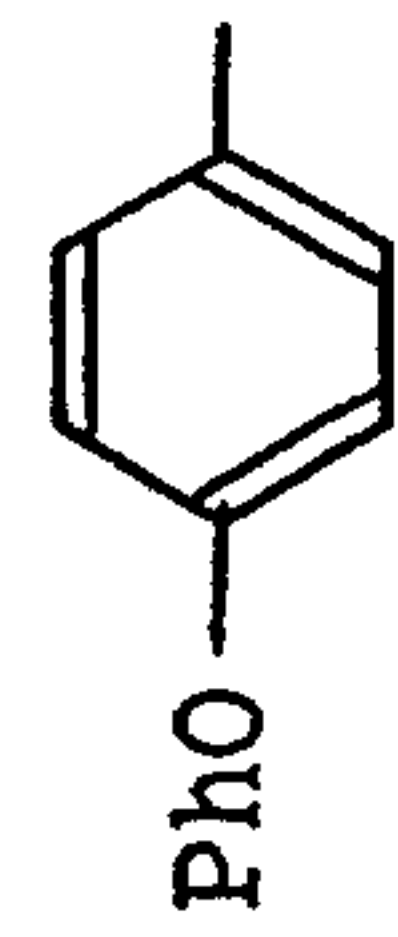
72		H	H	H	H	-N(Me)Me	1	1	HCl	171-172 [IPA]
73		"	"	"	"	"	"	"	"	162-162.5 [IPA]
74		"	"	"	"	"	"	"	"	147.5-148.5 [Me ₂ CO- Et ₂ O]
75		"	"	"	"	"	2	"	-	Oily

Table 5 (cont'd)

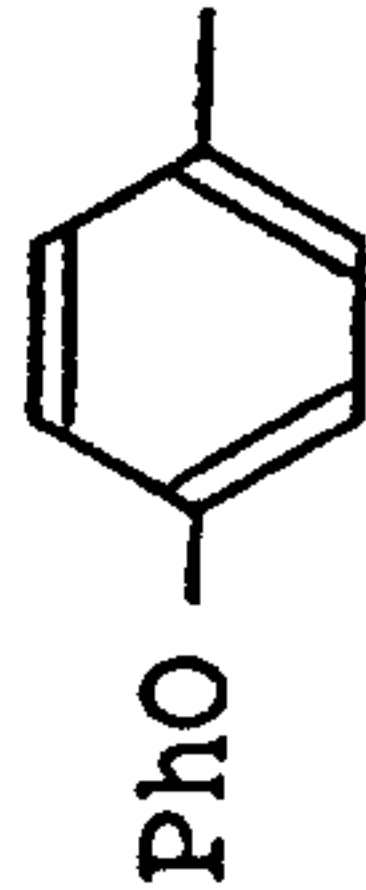
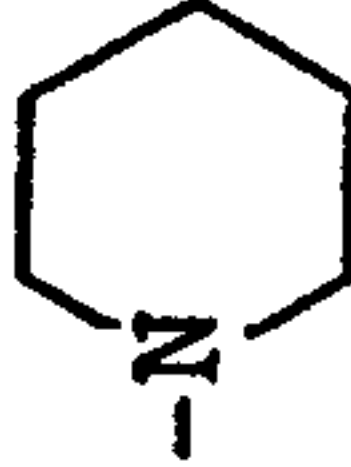
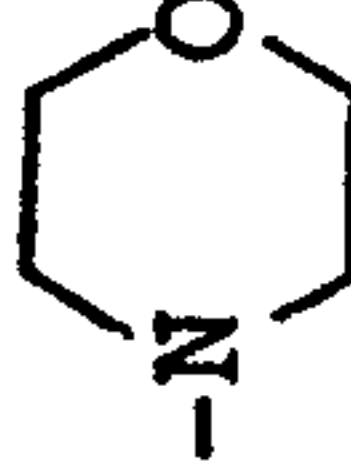
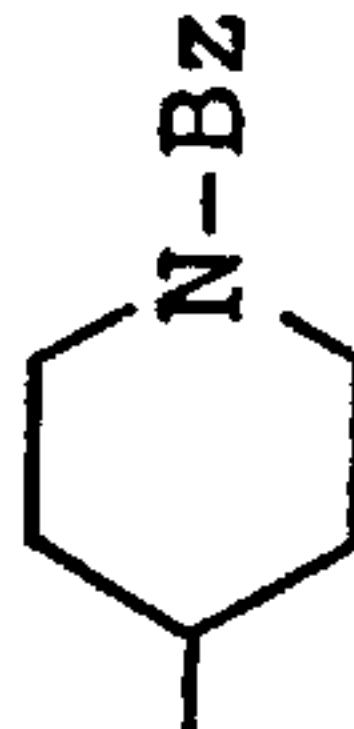
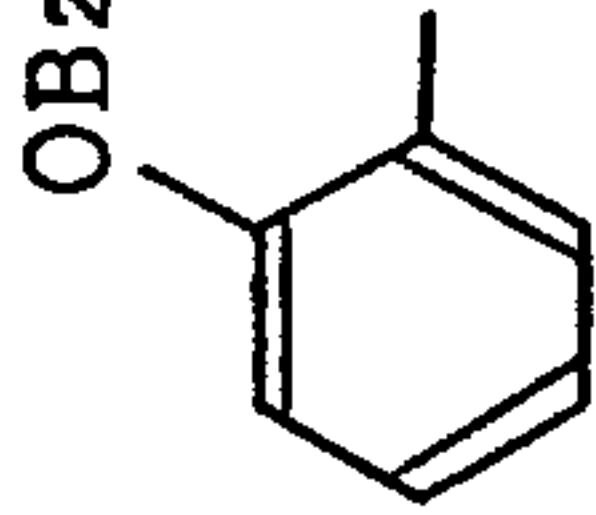
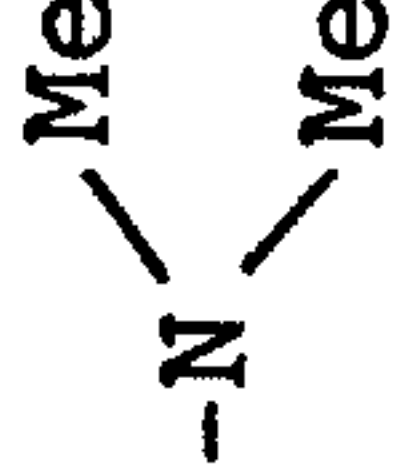
76		H	H	H	H	H	H		1	1	HCl	160-160.5 [IPA]
77	"	"	"	"	"	"	"		"	"	"	192.5-193 [MeCN]
78	"	"	"	"	"	"	"		"	"	-	Oily
79		"	"	"	"	"	"		"	"	HCl	124-125 [MeCN]

Table 5 (cont'd)

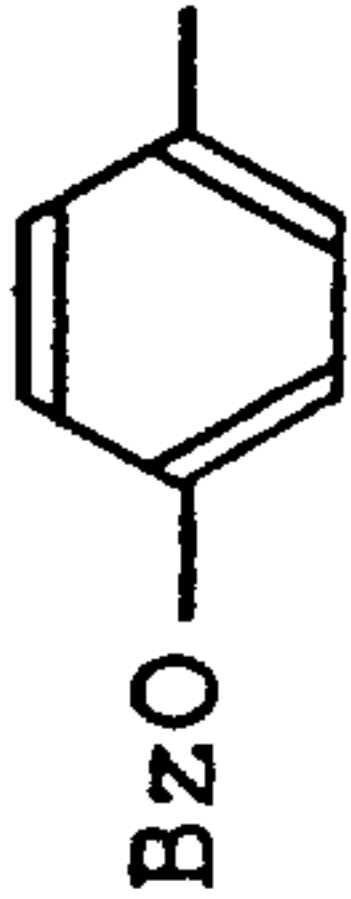
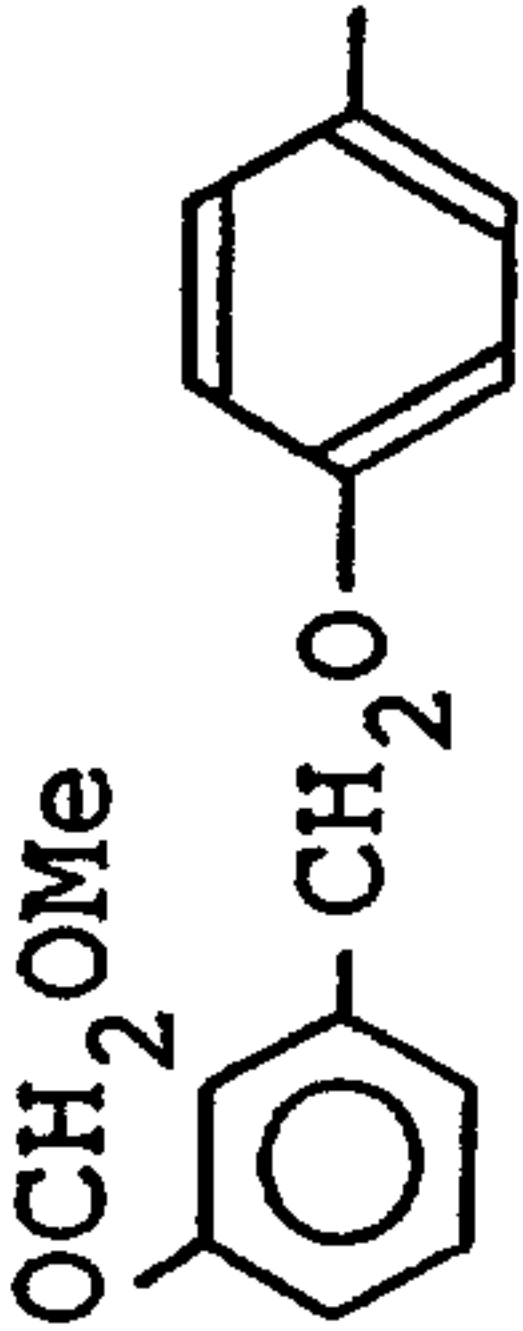
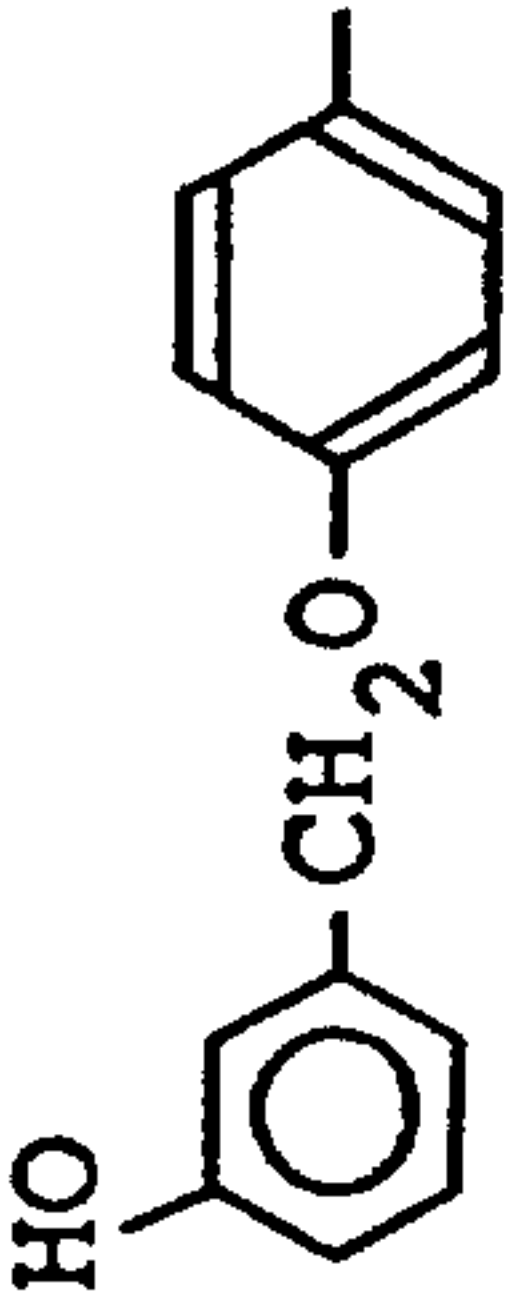
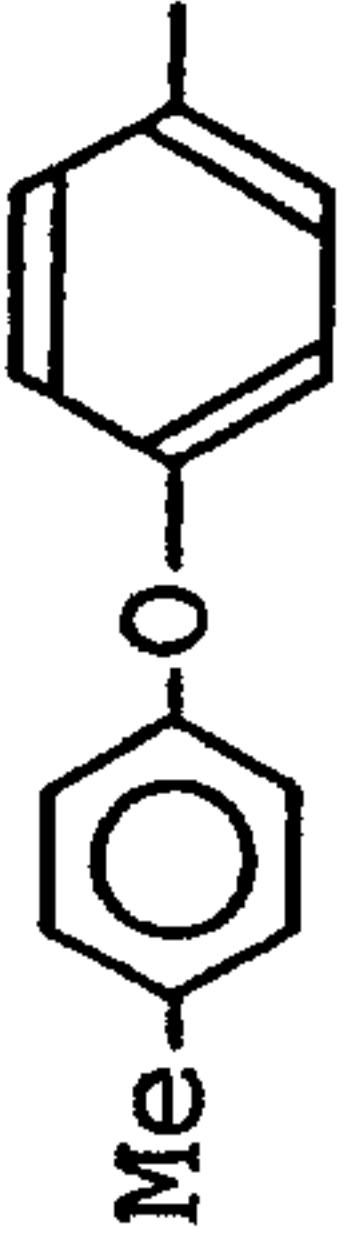
80		H	H	H	H	-N<MeMe	2	1	-	121.5-123 [AcOEt- Et ₂ O]
81		"	"	"	"	"	1	"	"	Oily
82 ^{*C}		"	"	"	"	"	"	"	HCl	179-181 [EtOH]
83		"	"	"	"	"	"	"	"	189.5-190 [IPA]

Table 5 (cont'd)

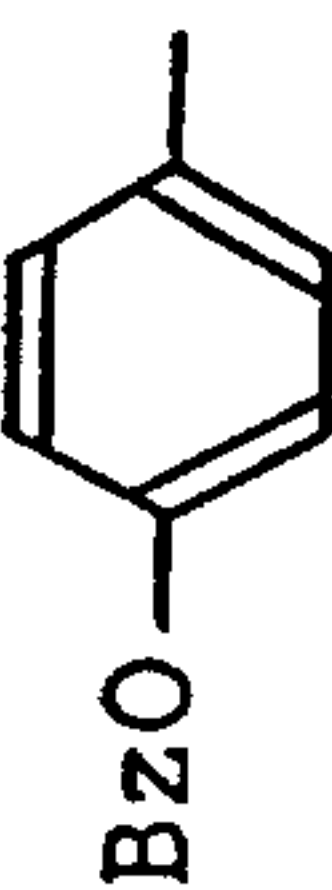
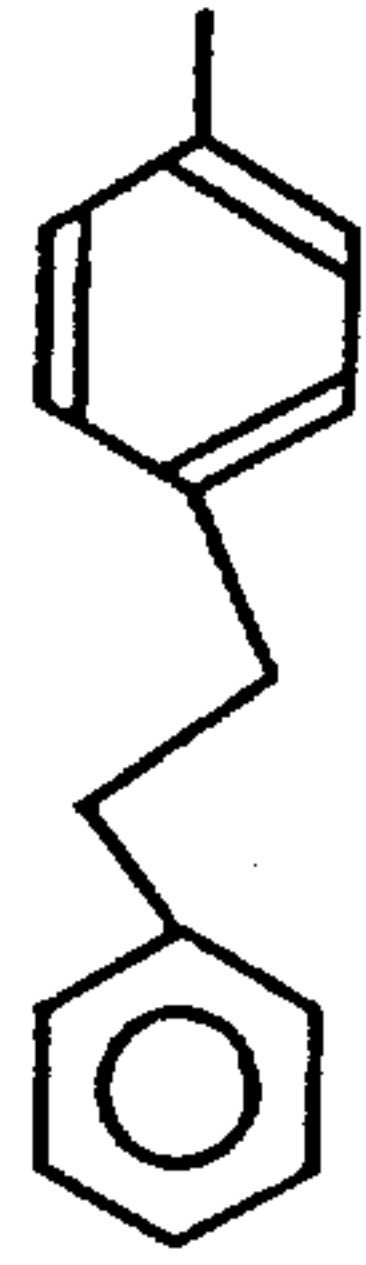
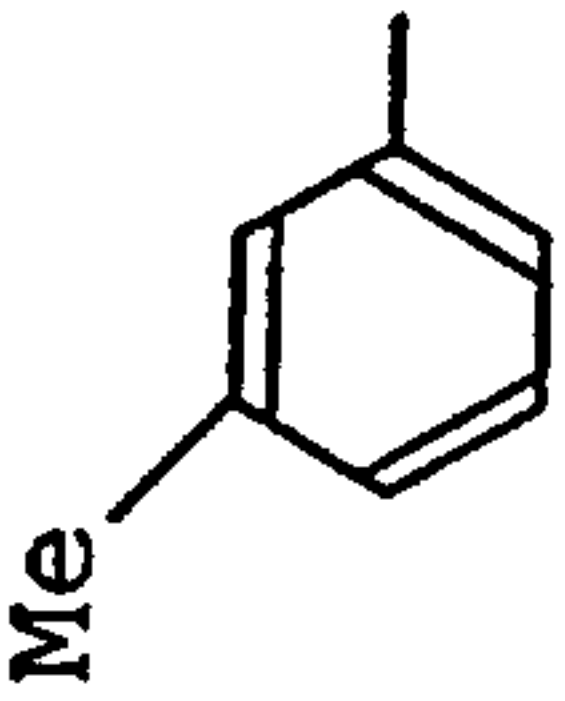
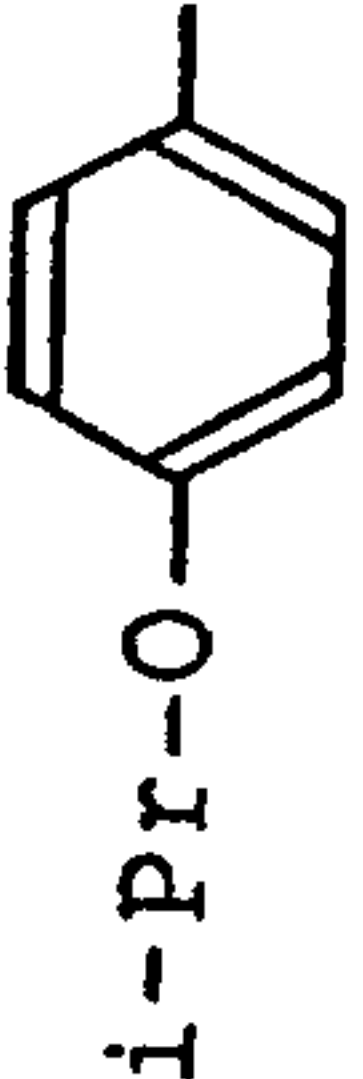
88		H	H	H	H	H	H	H	-N(Et) ₂	1	1	-	Oily
89		"	"	"	"	"	"	"	-N(Me) ₂	"	"	HCl	222.5-223.5 [EtOH]
90		"	"	"	"	"	"	"	-N(Et) ₂	"	"	-	Oily
91		"	"	"	"	"	"	"	-N(Me) ₂	"	"	HCl	204.5-205 [EtOH- Me ₂ CO]

Table 5 (cont'd)

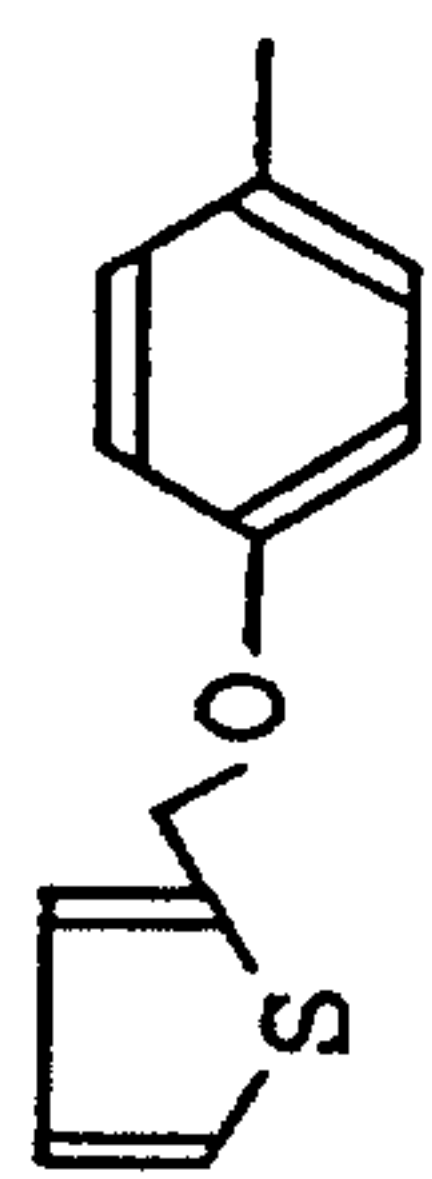
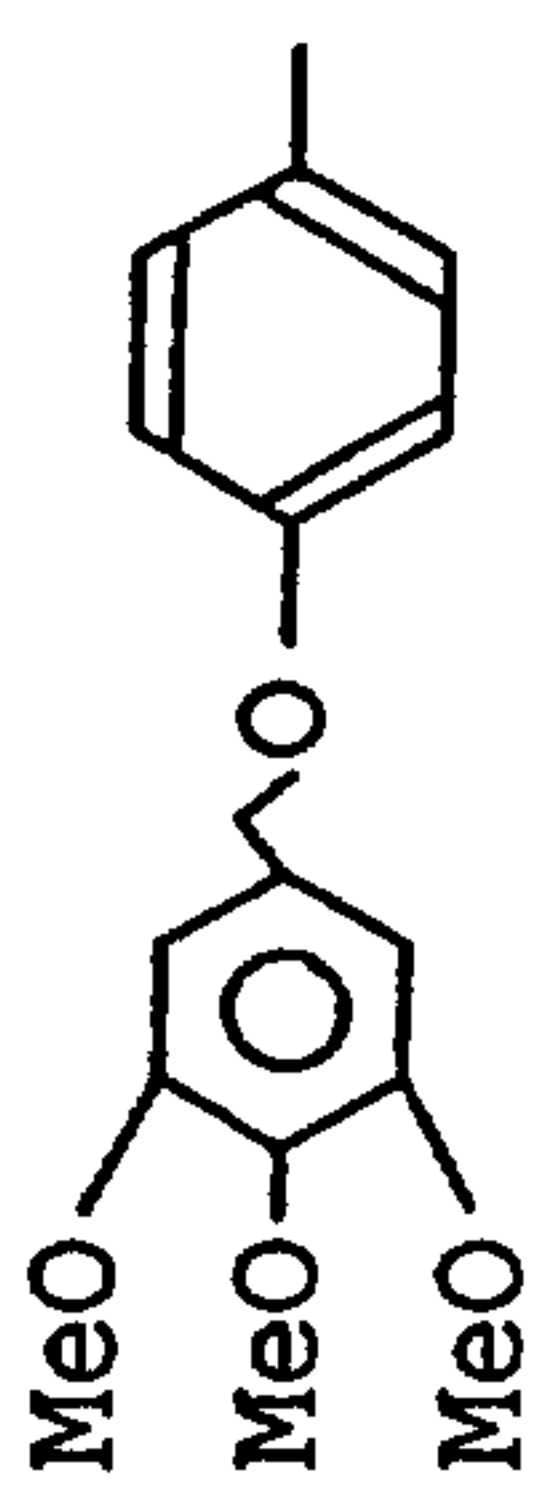
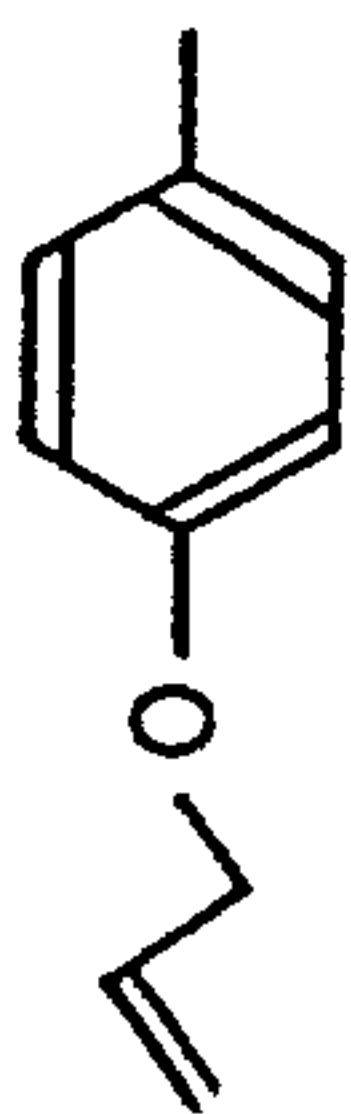
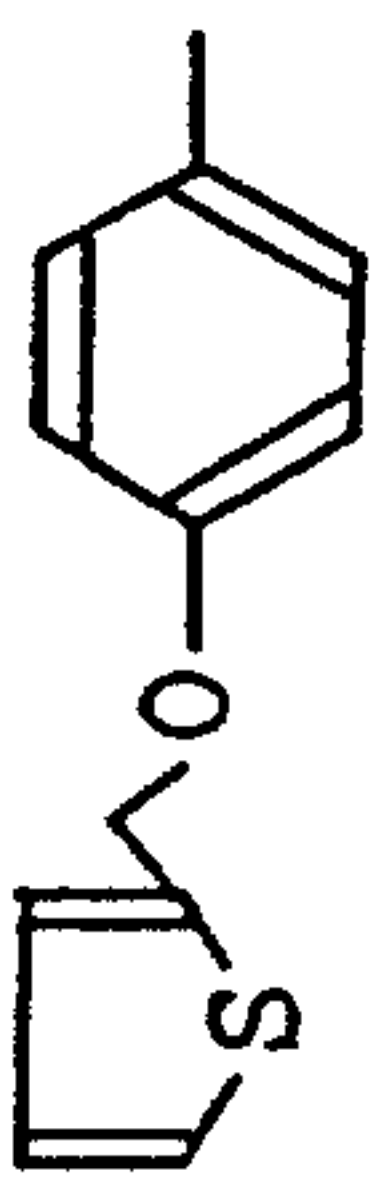
92		H	H	H	H						Me -N Me	1	1	HCl	168.5-169 [EtOH- AcOEt]
93		"	"	"	"	"	"	"	"	"	"	"	"	"	193-194 [EtOH- AcOEt]
94		"	"	"	"	"	"	"	"	"	"	"	"	"	154.5-156 [MeCN]
95		"	"	"	"	"	"	"	"	"	"	"	"	"	168.5-169.5 [EtOH- AcOEt]

Table 5 (cont'd)

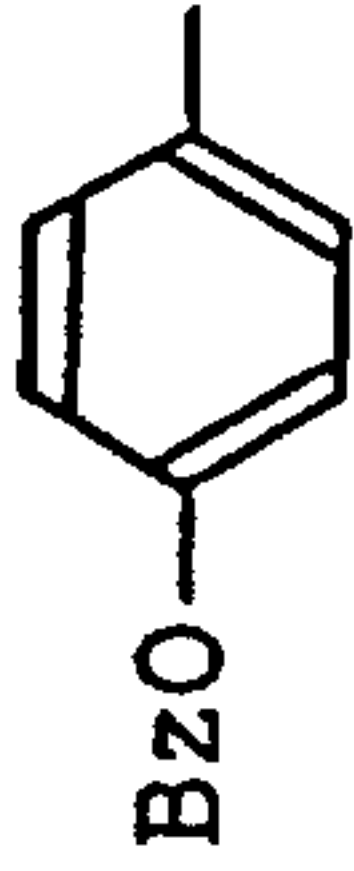
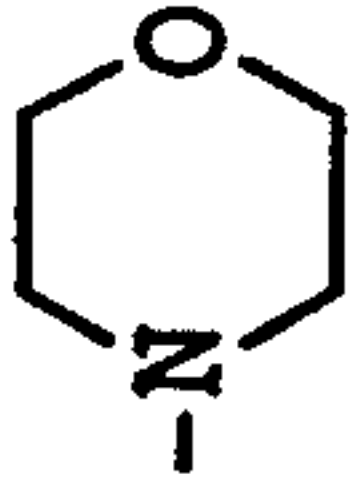
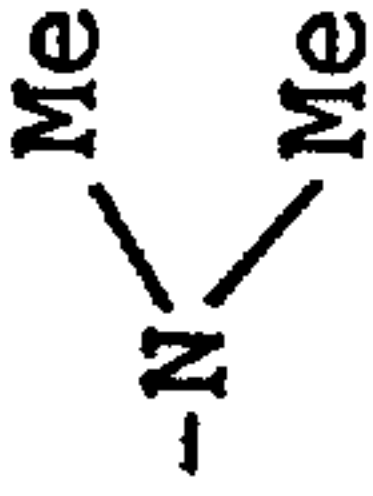
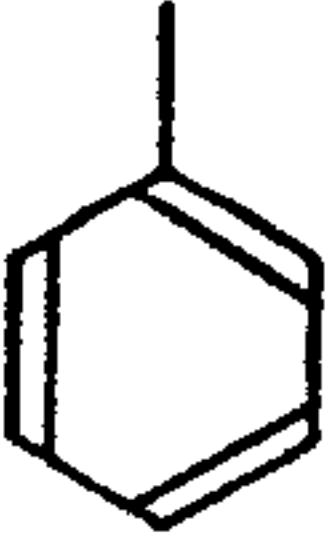
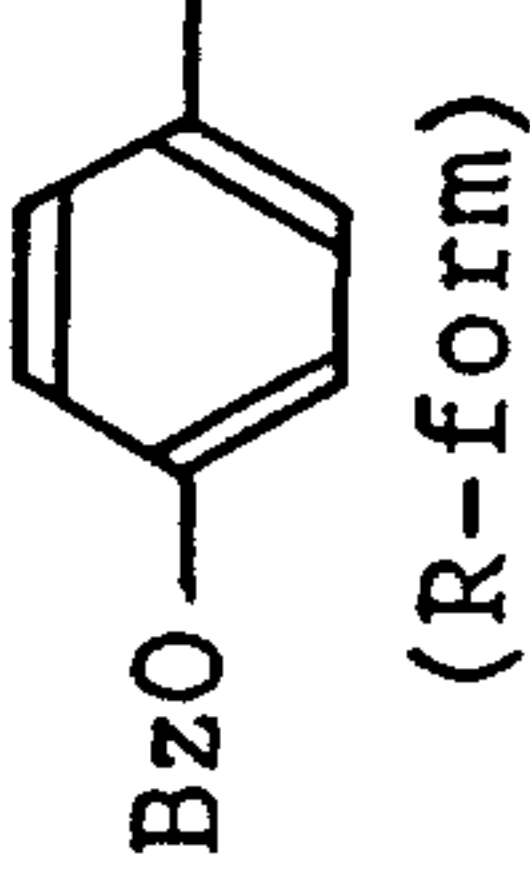
100		H	H	H	H	H	H		1	1	HCl	170-170.5 [EtOH- Me ₂ CO]
101		"	"	"	"	"	"		"	"	"	199-199.5 [EtOH]
102 ^{*d}		"	"	"	"	"	"	-NH ₂	"	"	1/2 Fumaric acid	181-182.5
103 ^{*e}		"	"	"	"	"	"		"	"	HCl	194-194.5 [EtOH- Me ₂ CO]

Table 5 (cont'd)

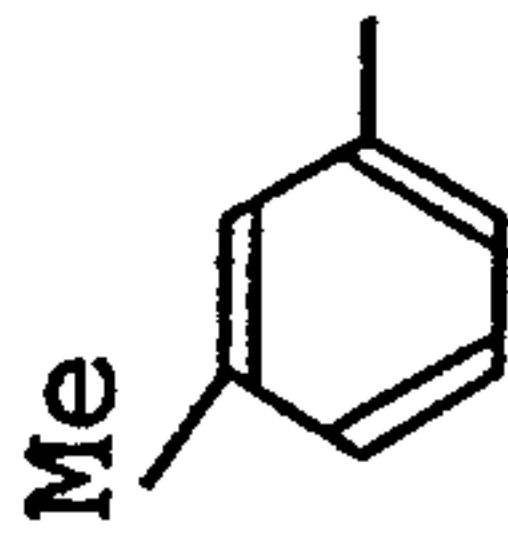
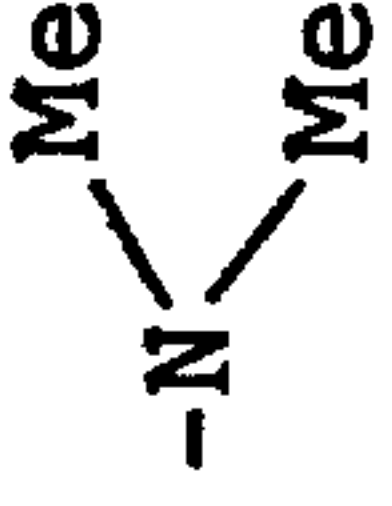
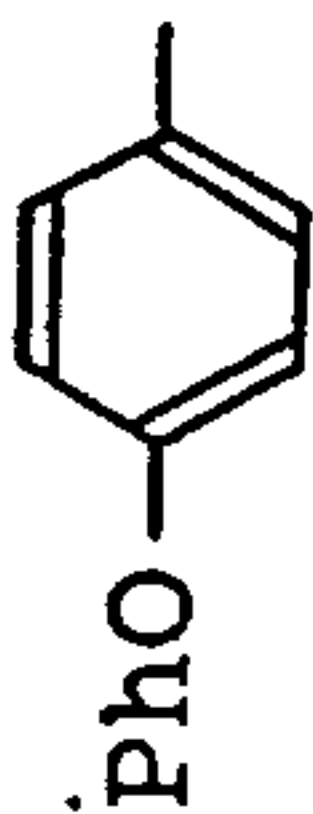
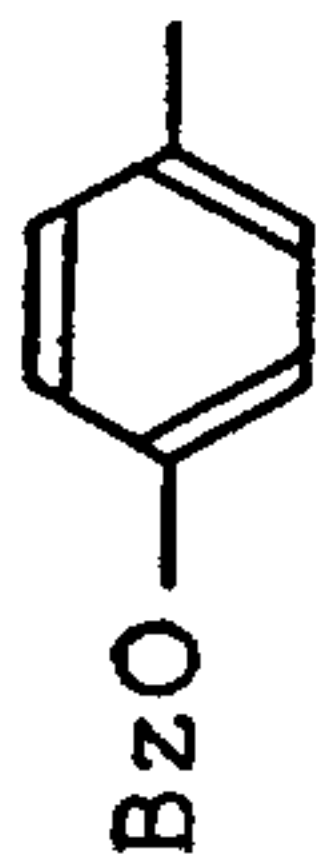
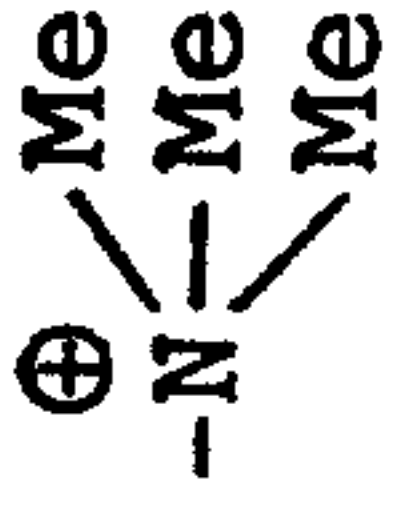
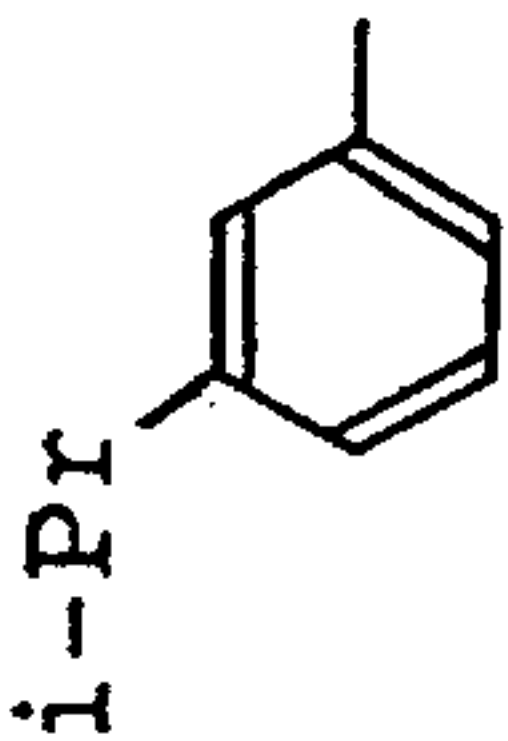
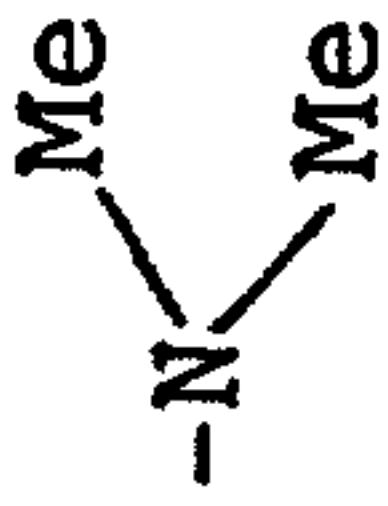
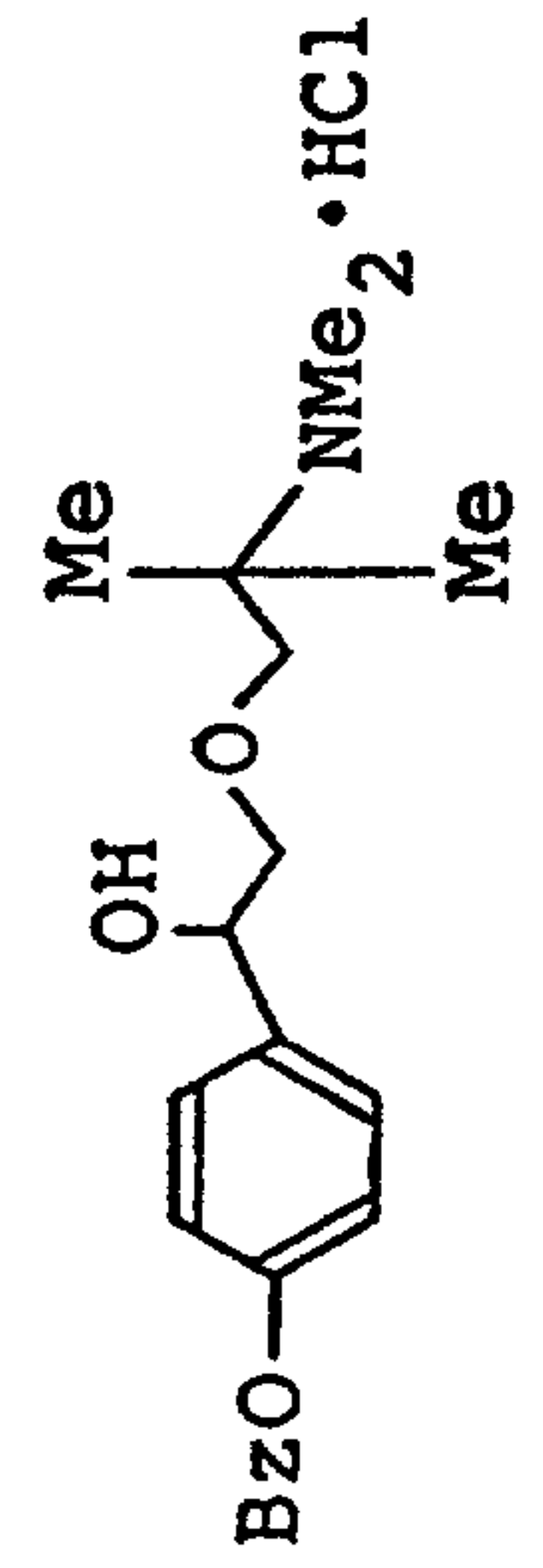
108 ^{*j}	 Me (S-form)	H	H	H	H	H	H	 Me -N Me	1	1	HCl	163-164.5 [EtOH- Me ₂ CO]
109 ^{*k}	 PhO (S-form)	"	"	"	"	"	"	"	"	"	"	187.5-188.5 [MeCN]
110 ^{*h}	 BzO	"	"	"	"	"	"	 Me -N [⊕] Me Me	"	"	1/2 1,5- Naphtha- lenedi- sulfonic acid	168-170 (decomp.)
111	 i-Pr	"	"	"	"	"	"	 Me -N Me	"	"	-	Oily

Table 5 (cont'd)

112		171-173 [EtOH- Et ₂ O]
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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 trityl 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)

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Production Example 4

A mixture of 5.00 g of 1-benzyl-4-hydroxy-piperidine, 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.

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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:

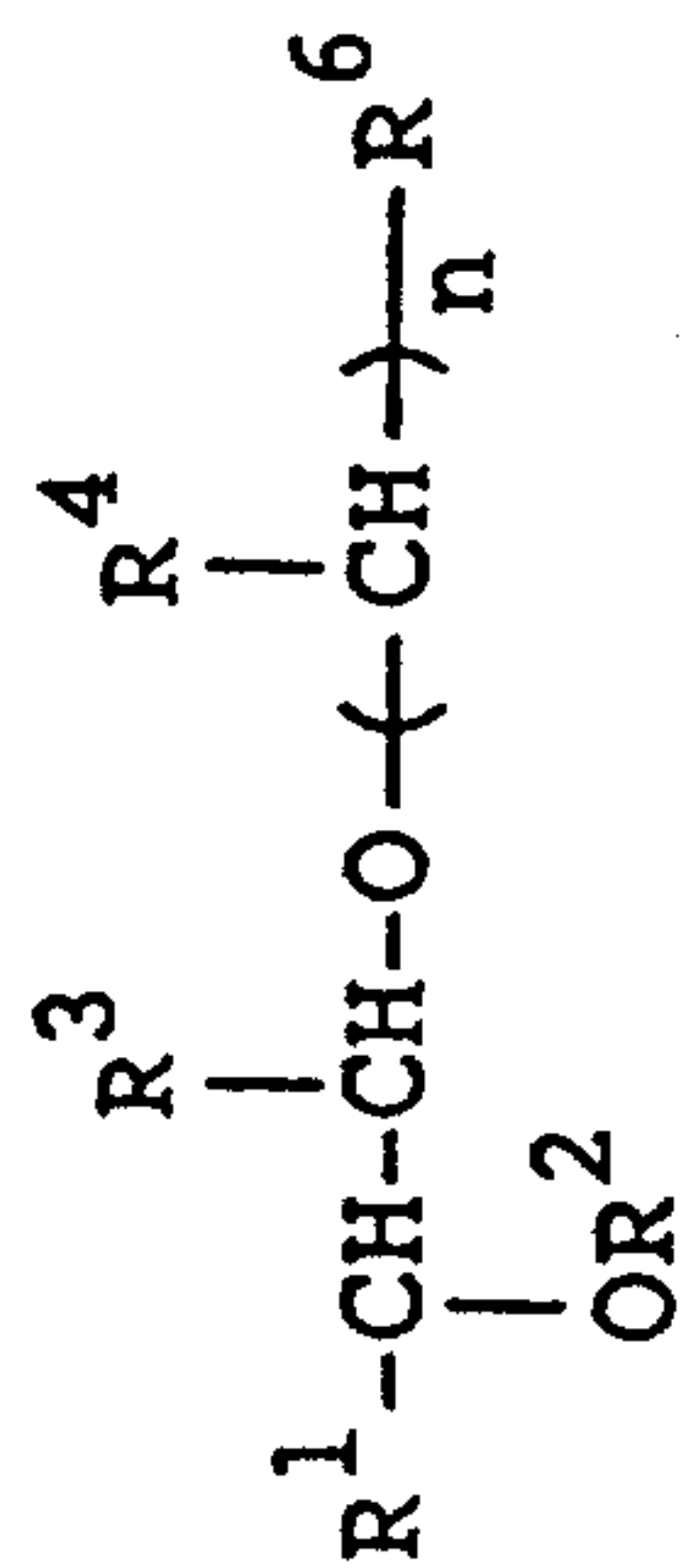


Table 6

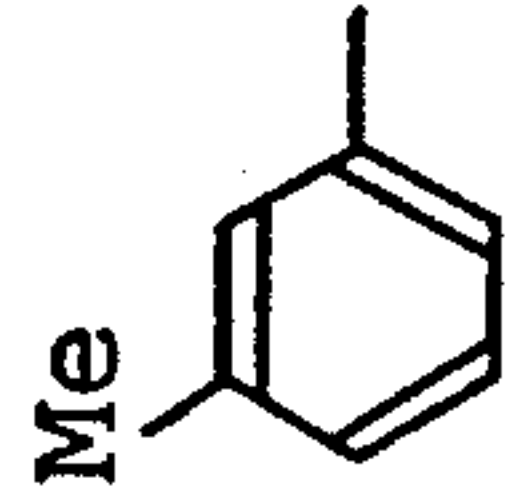
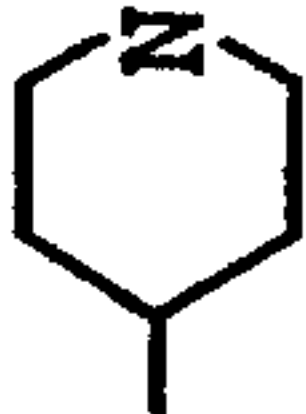
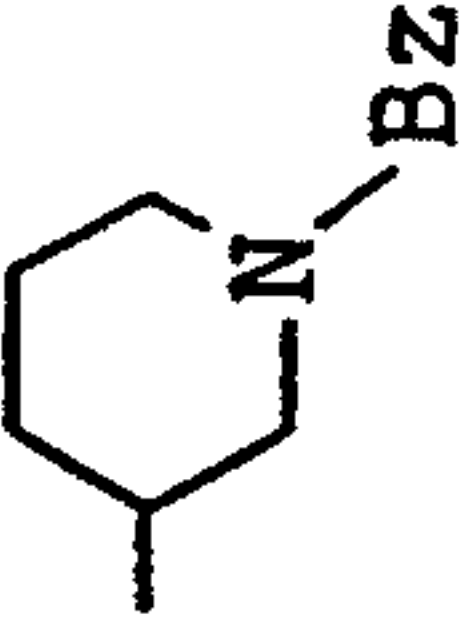
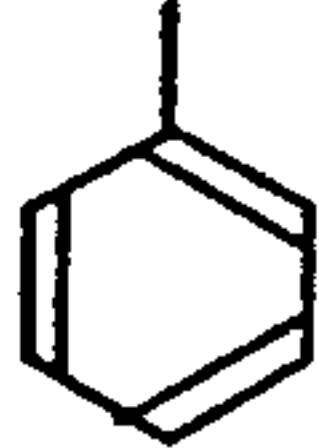
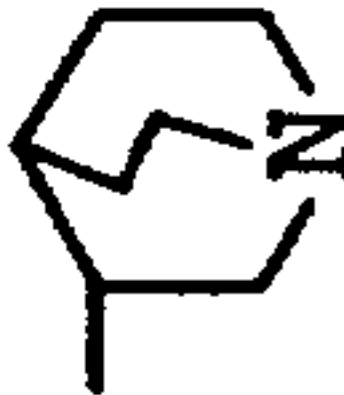
Compound No.	R ¹	R ²	R ³	R ⁴	R ⁶	n	Addition salt	Melting point (°C)
114		H	H	-		0	HCl	180-181.5 [IPA]
115	"	"	"	"		"	"	202-204
116		"	"	"		"	-	119-120

Table 6 (cont'd)

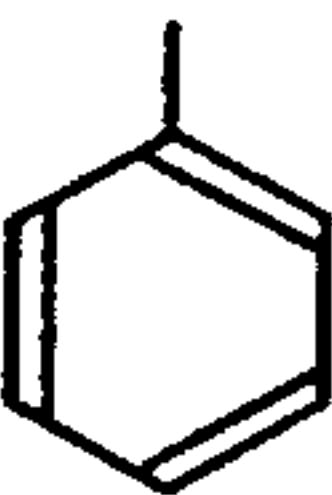
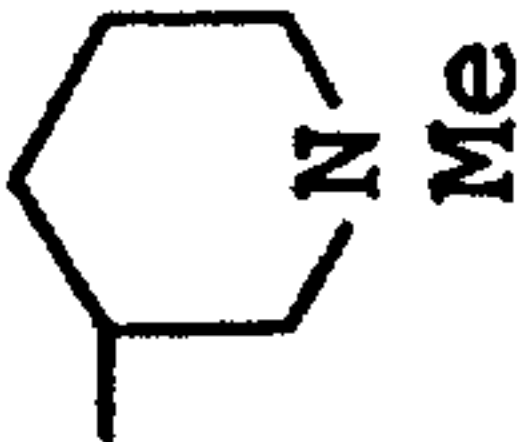
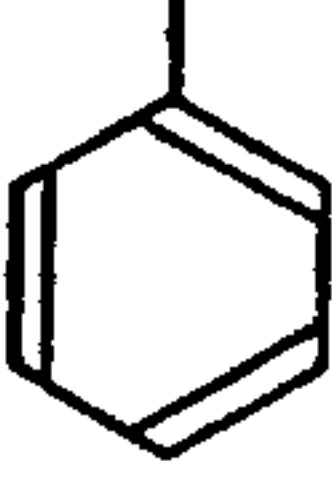
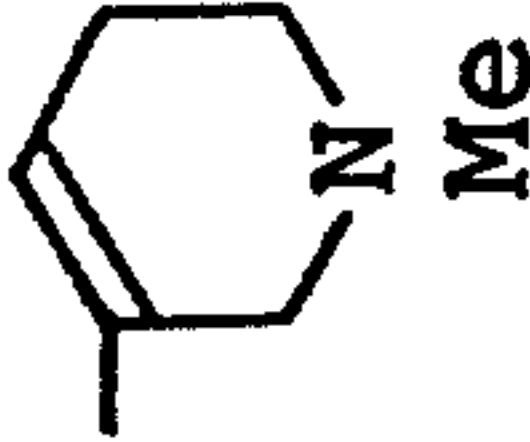
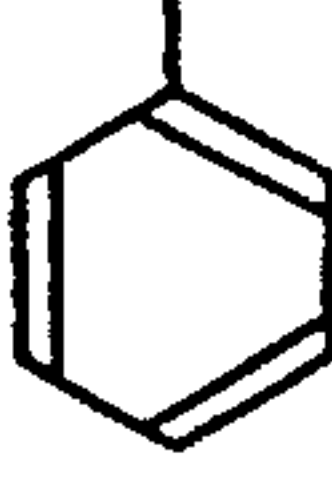
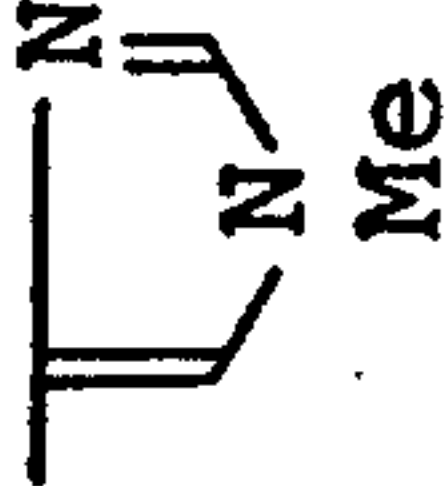
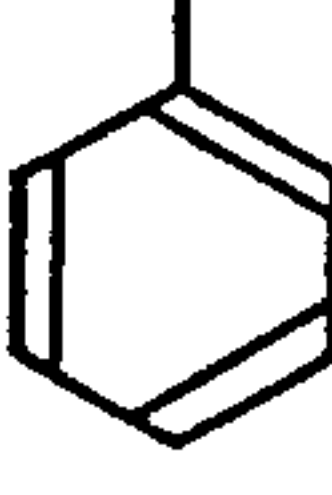
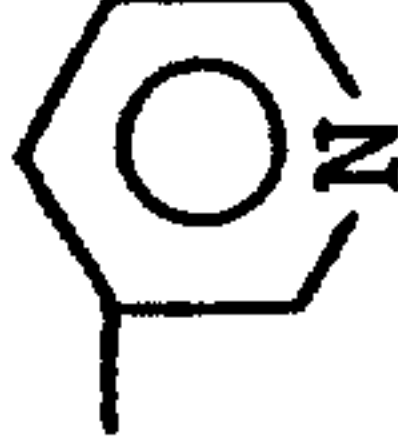
117		H	H	H		1	HCl	153-155 [Me ₂ CO- EtOH]
118		"	"	"		"	"	Oily
119		"	"	"		"	-	92-95
120		"	"	"		"	HCl	Oily

Table 6 (cont'd)

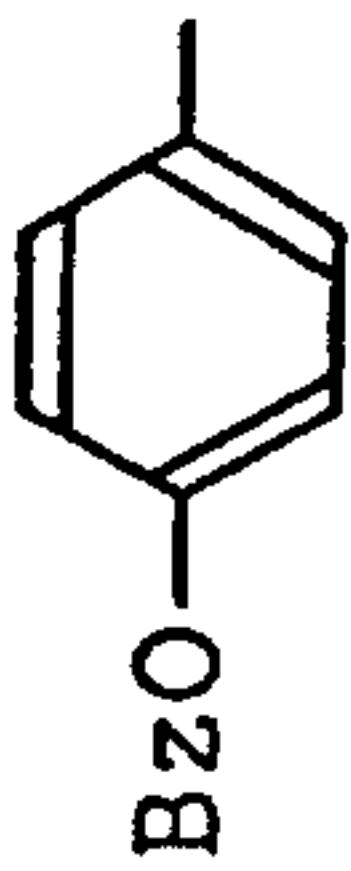
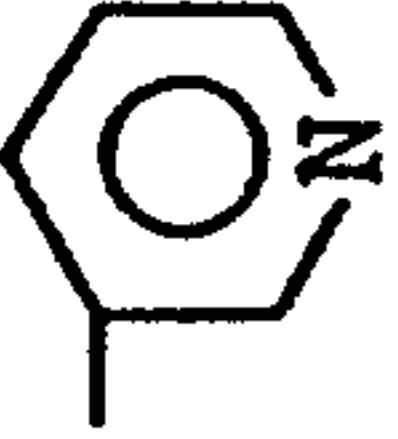
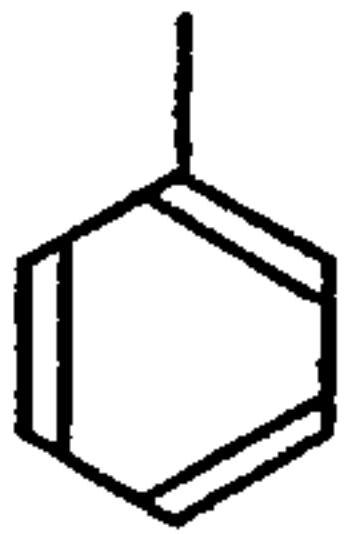
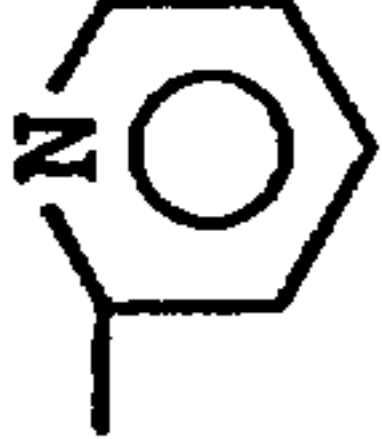
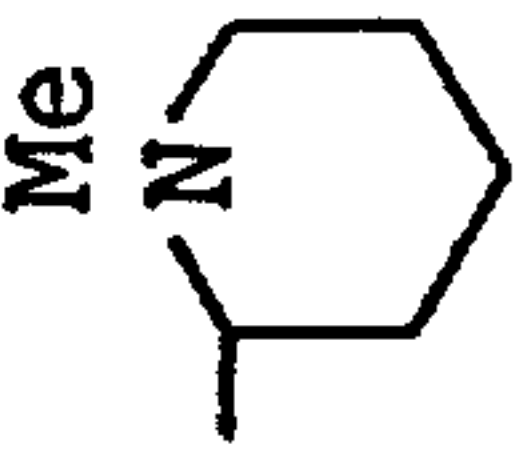
121		H	H	H			1	-	78-81 [AcOEt-IPE]
122		"	"	"	"		"	HCl	129.5-131.5 [AcOEt-IPE]
123	"	"	"	"	"		"	"	157.5-159.5
124	"	"	"	"	"		"	"	137-138.5 [Me ₂ CO]

Table 6 (cont'd)

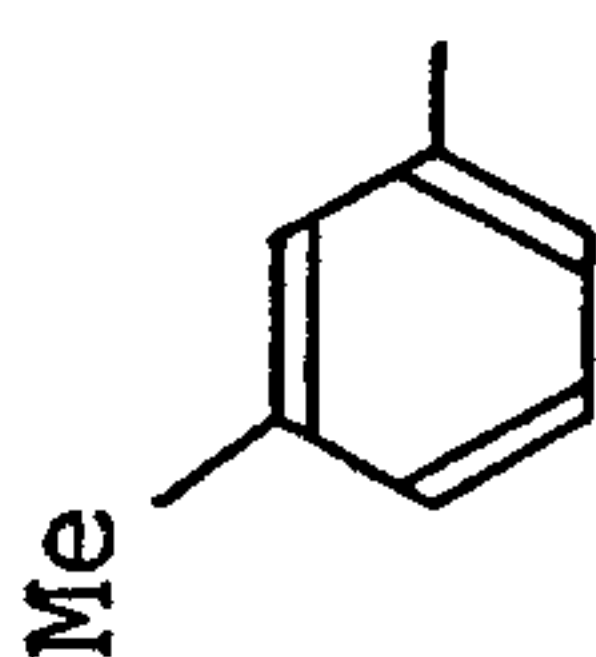
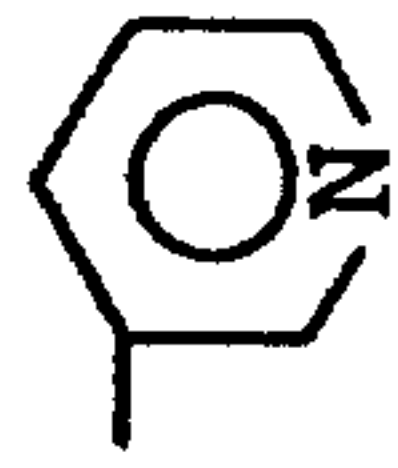
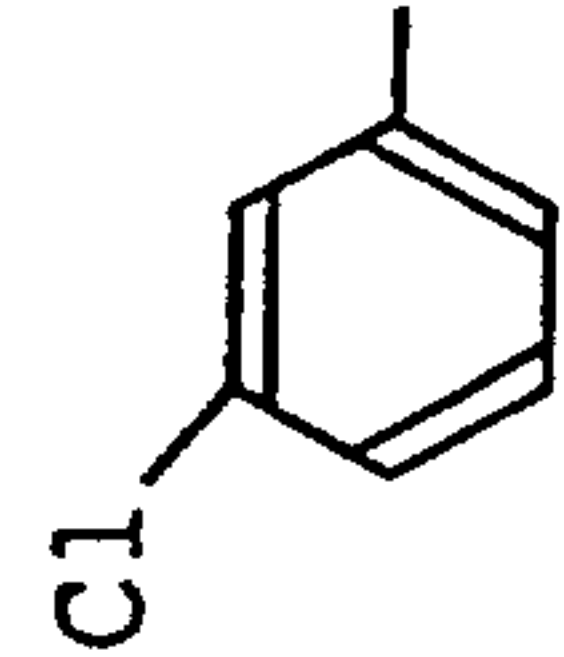
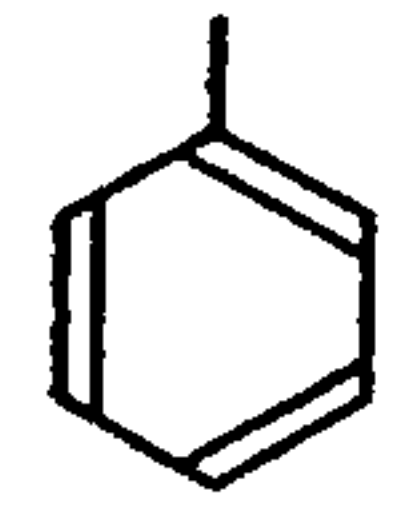
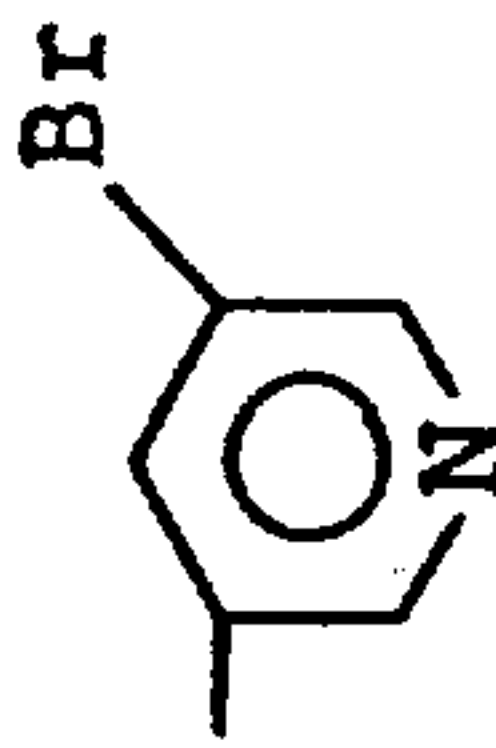
125		H	H	H		1	HCl	Oily
126		"	"	"	"	"	"	"
127		"	"	"		"	"	"
128	"	"	"	"		"	-	"

Table 6 (cont'd)

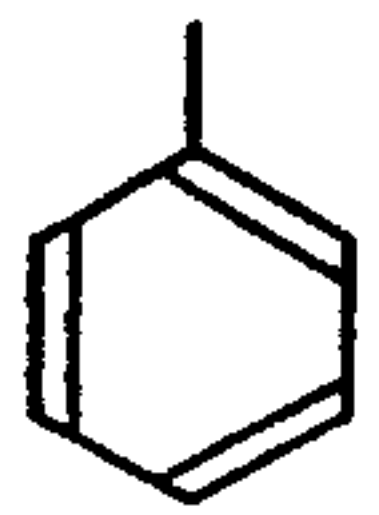
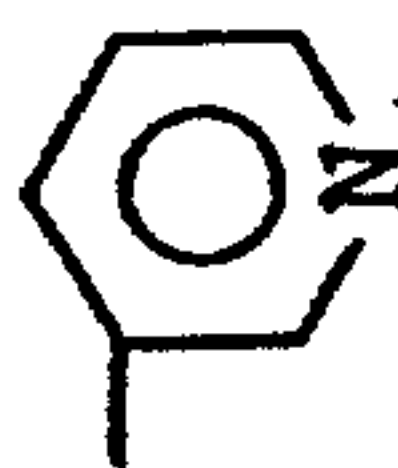
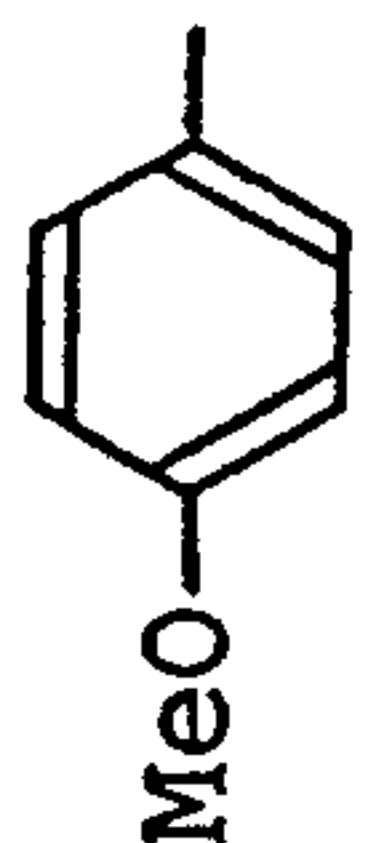
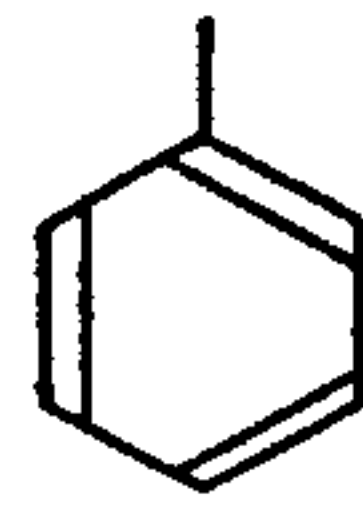
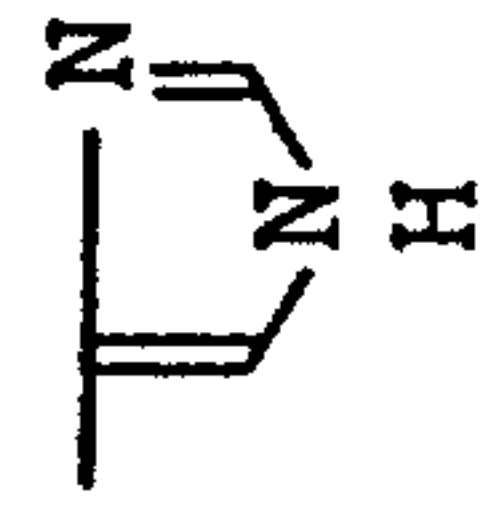
129*1	 (S-form)	H	H	H			1	-	61-61.5 [EtOH-IPE]
130*2	" (R-form)	"	"	"		"	"	"	61-61.5 [EtOH-IPE]
131	 MeO	"	"	"		"	"	"	71.5-72 [EtOH-IPE]
132*3		"	"	"			"	"	118-119.5

Table 6 (cont'd)

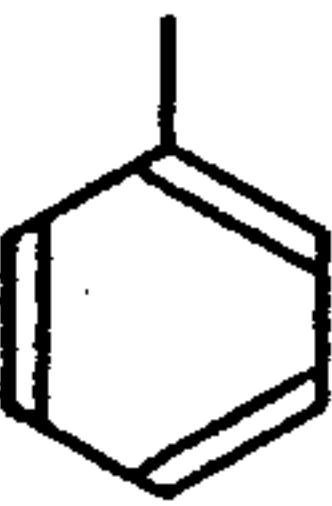
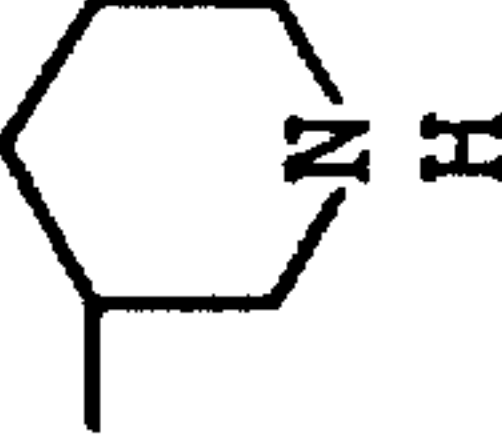
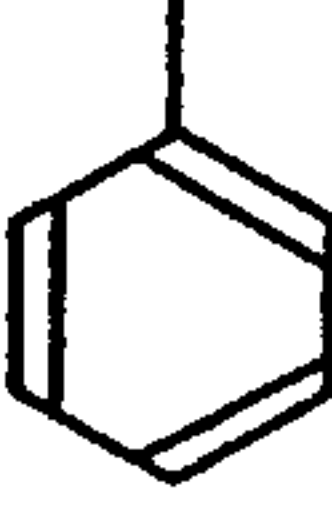
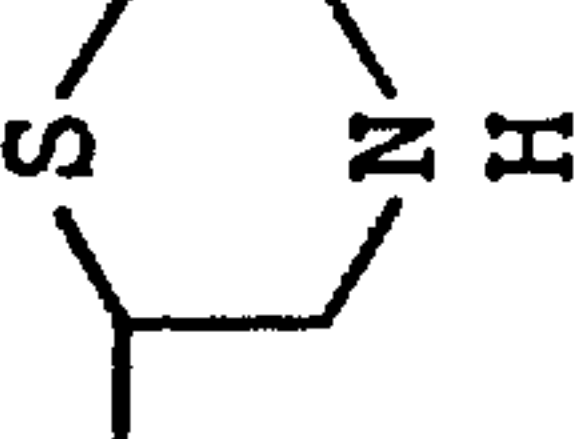
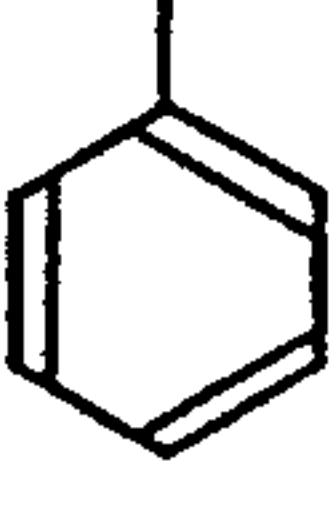
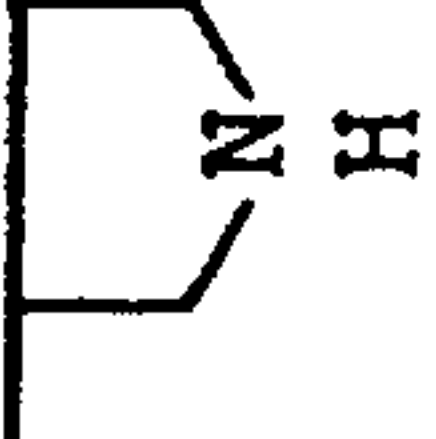
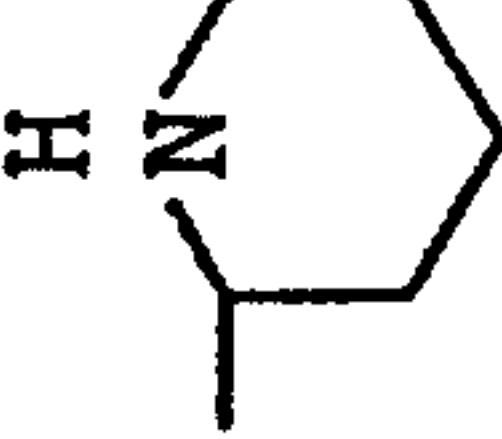
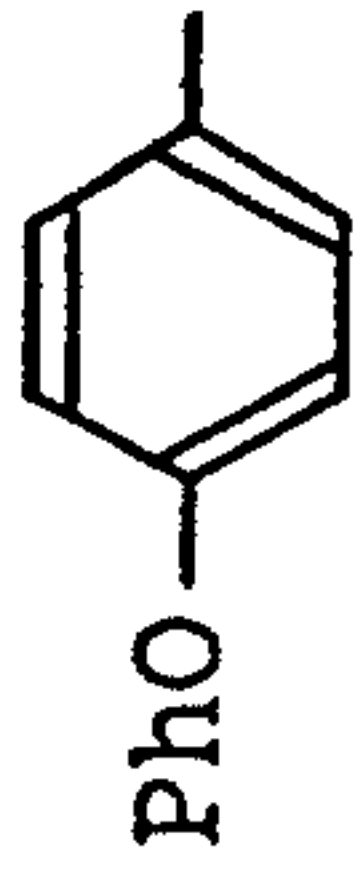
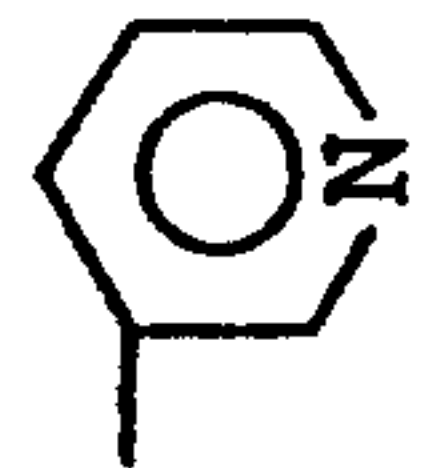
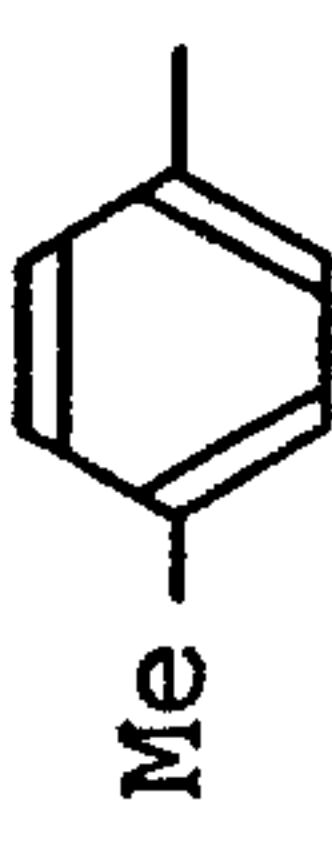
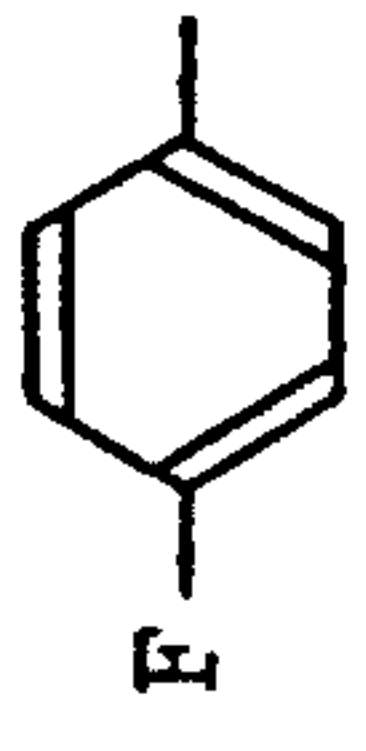
133*3		H	H	H	H		1	HCl	147.5-149 [IPA- AcOEt]
134*3	 (1R-form)	"	"	"	"		"	"	Oily
135*3		"	"	"	"		"	"	104.5-106.5 [IPA- AcOEt]
136*3	"	"	"	"	"		"	"	220-221 [EtOH- AcOEt]

Table 6 (cont'd)

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

Table 6 (cont'd)

141		H	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-hydroxymethyl-morpholine, 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:

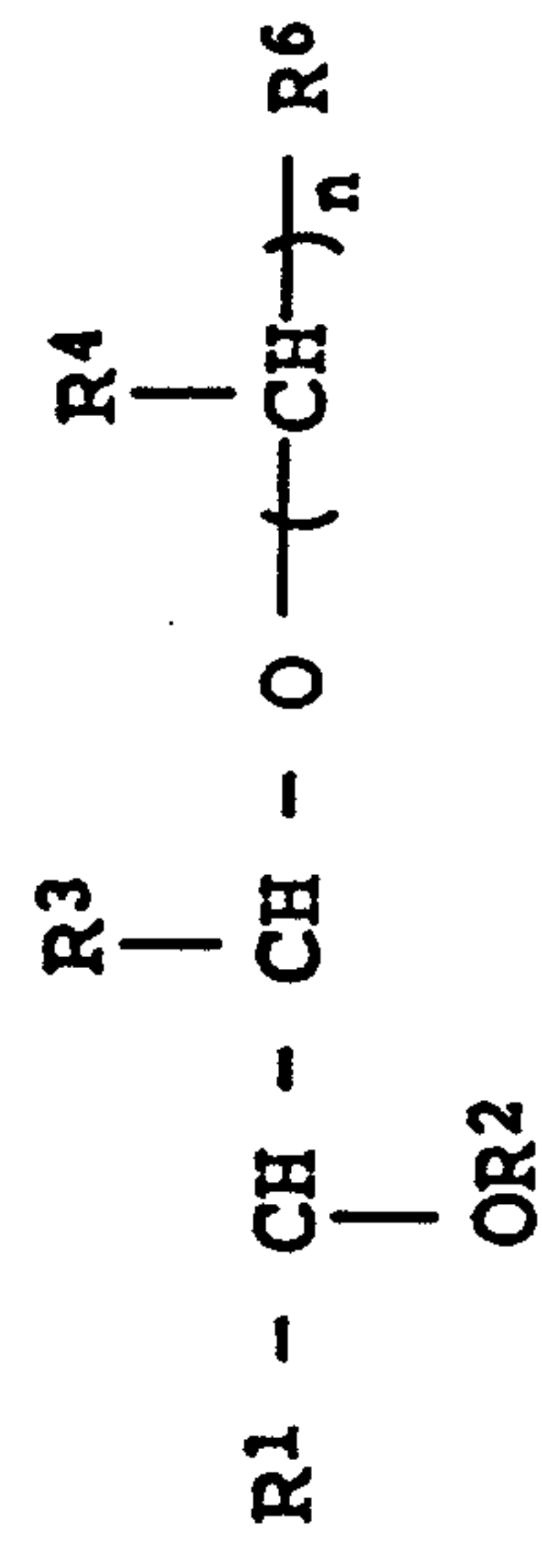
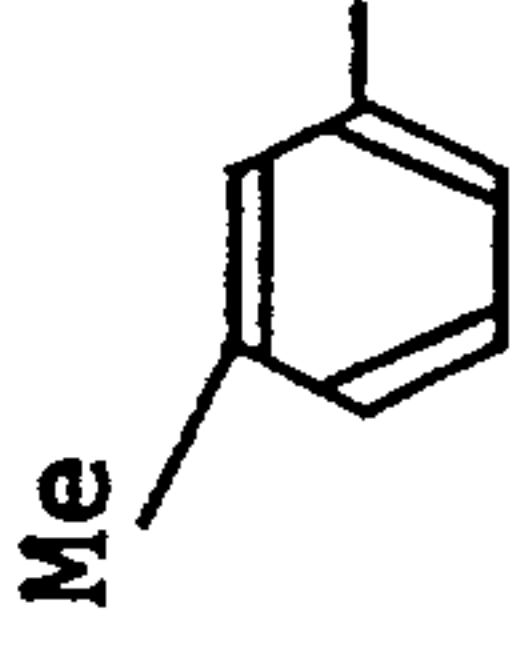
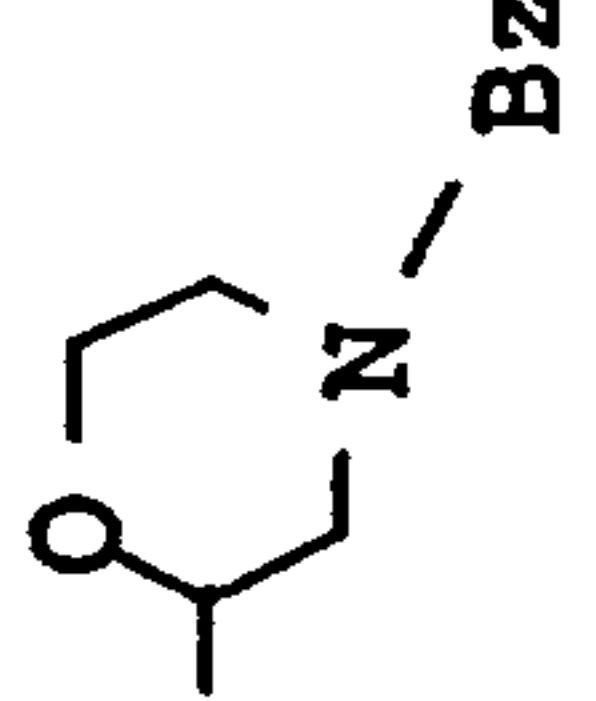
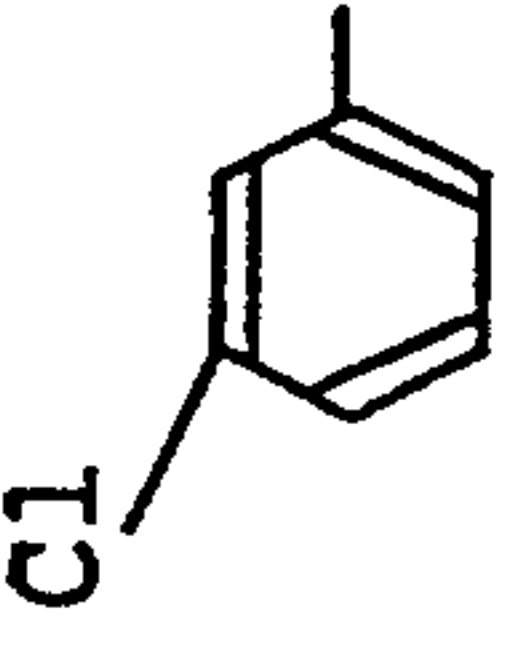
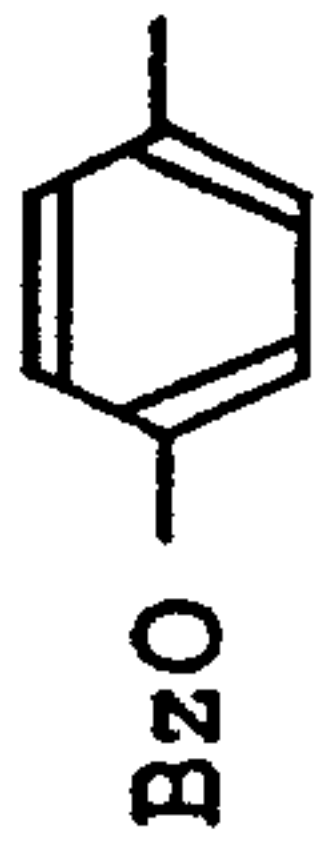
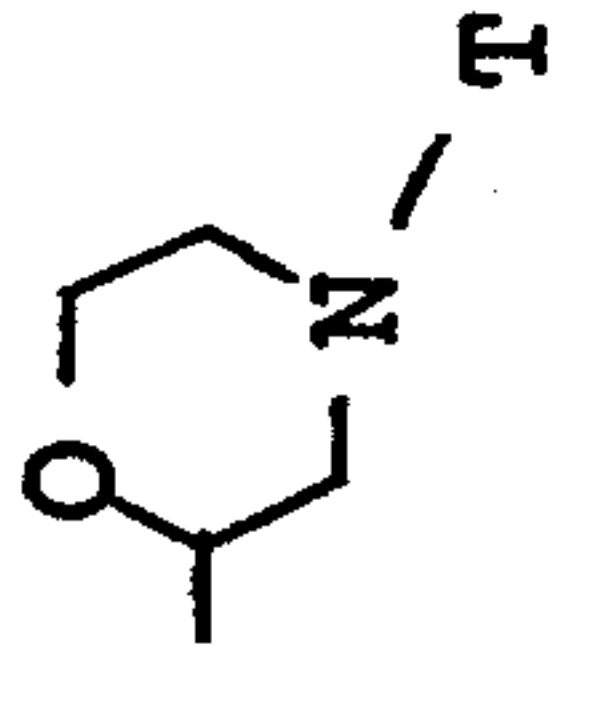
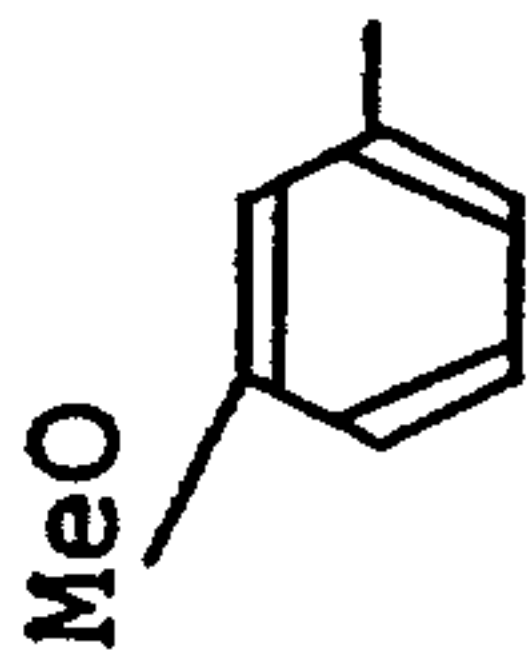
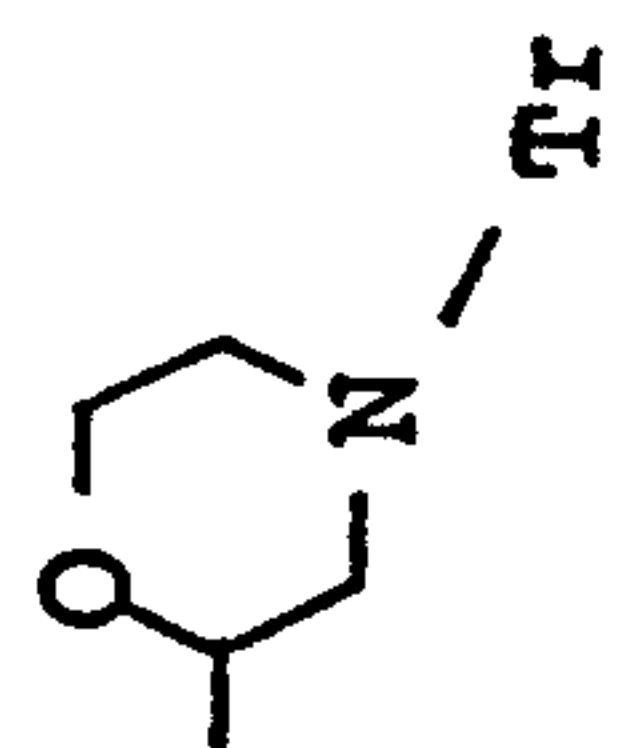
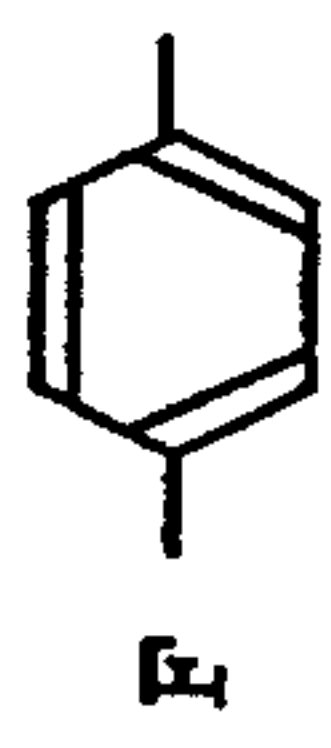


Table 7

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		"	"	"	"	"	"	"	"

1 (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
5 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
10 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
15 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
20 in the same manner.

In Table 8, R¹, R², R³, R⁴, R⁶ and n each show
a substituent or integer used in the following formula:

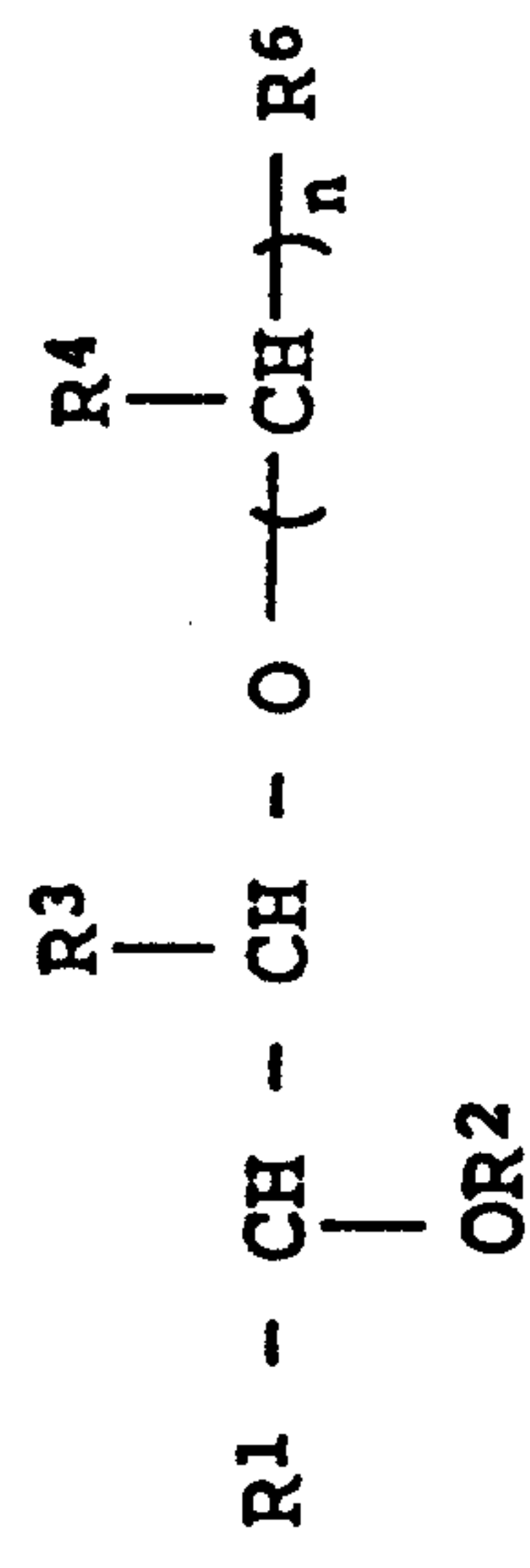
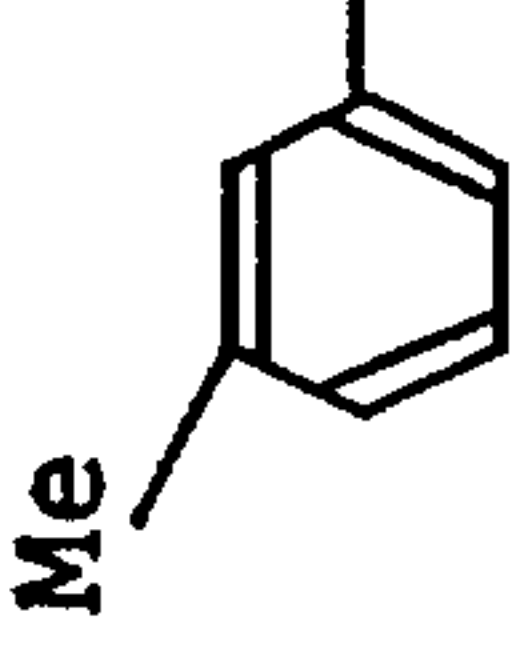
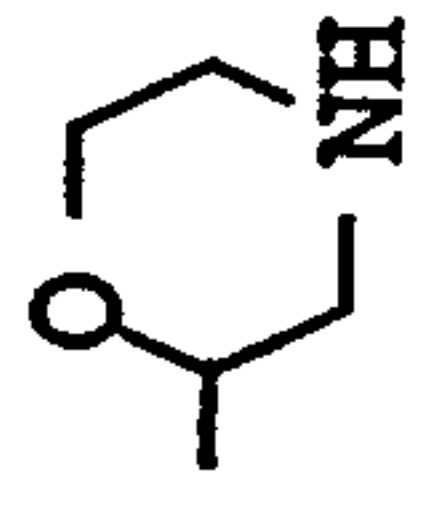
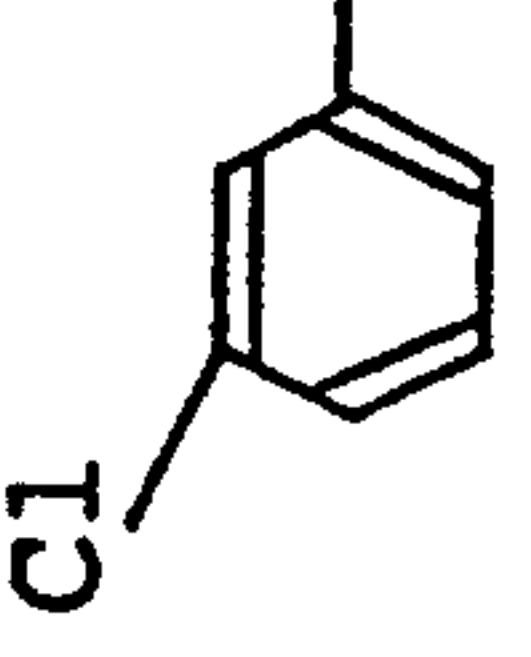
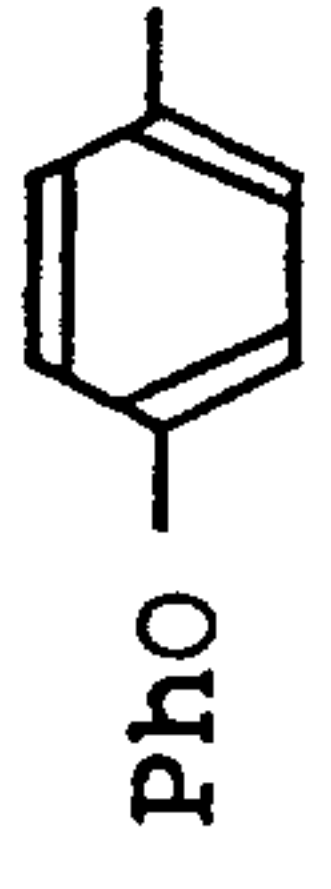


Table 8

Compound No.	R	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 ₂ CO]

1 (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.
5 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
10 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
15 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.
20 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).

25 Melting point: 122-123.5°C [EtOH]

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

21 60270

- 1 In Table 9, R¹, R², R³, R⁴, R⁶ and n each show a substituent or integer used in the following formula:

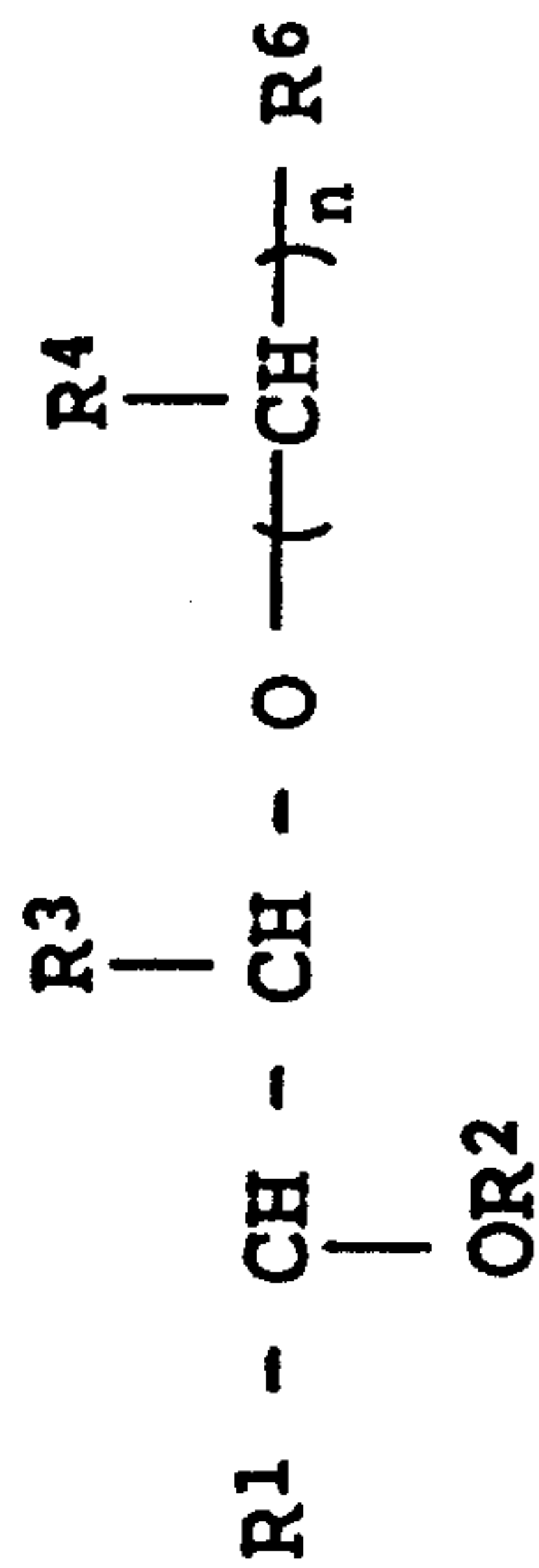
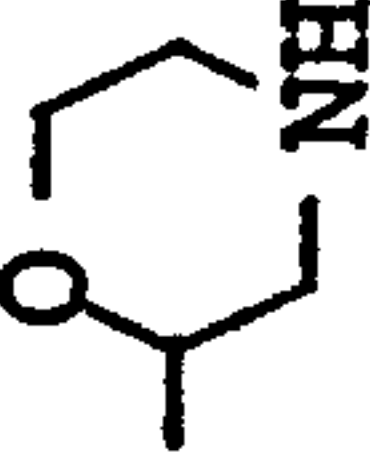


Table 9

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]

1 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
5 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
10 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-
15 (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
20 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
25 with 6 N hydrochloric acid. The organic layer was
separated, washed with a saturated aqueous sodium
hydrogencarbonate solution and water in this order, and
dried over anhydrous magnesium sulfate. The solvent was

1 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-
5 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
10 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
15 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
20 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
25 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 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
5 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
10 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 anhydrous magnesium sulfate. The
15 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
20 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
25 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

1 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
5 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
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
15 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
20 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-chloro-
phenyl)-2-[2-(4-methylpiperazin-1-yl)ethoxy]ethanol
25 dihydrochloride (compound No. 158).

Melting point: 211-213°C [MeOH-EtOH]

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

 In Table 10, R¹, R², R³, R⁴, R⁶ and n each show
a substituent or integer used in the following formula:

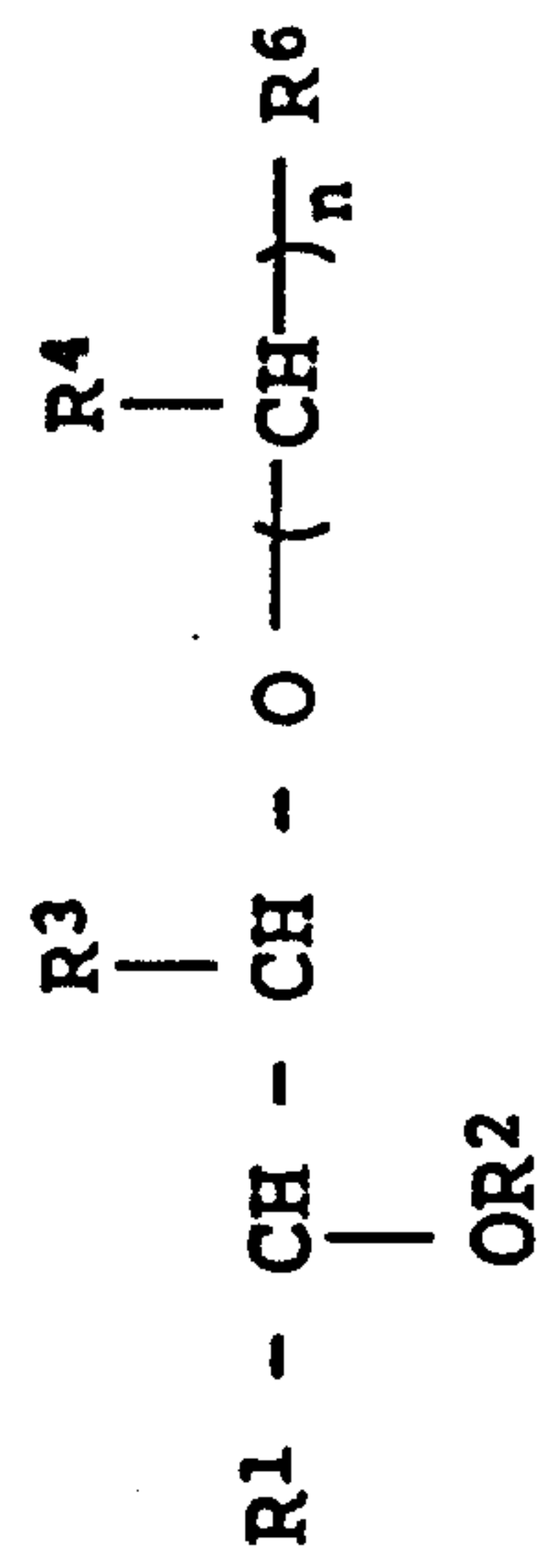
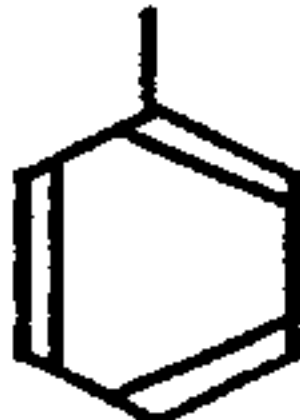
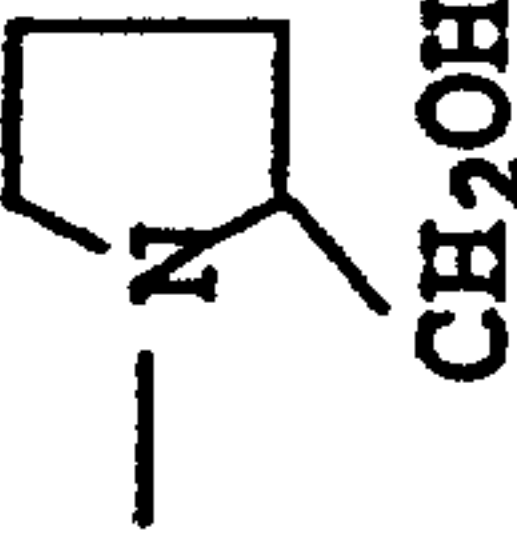
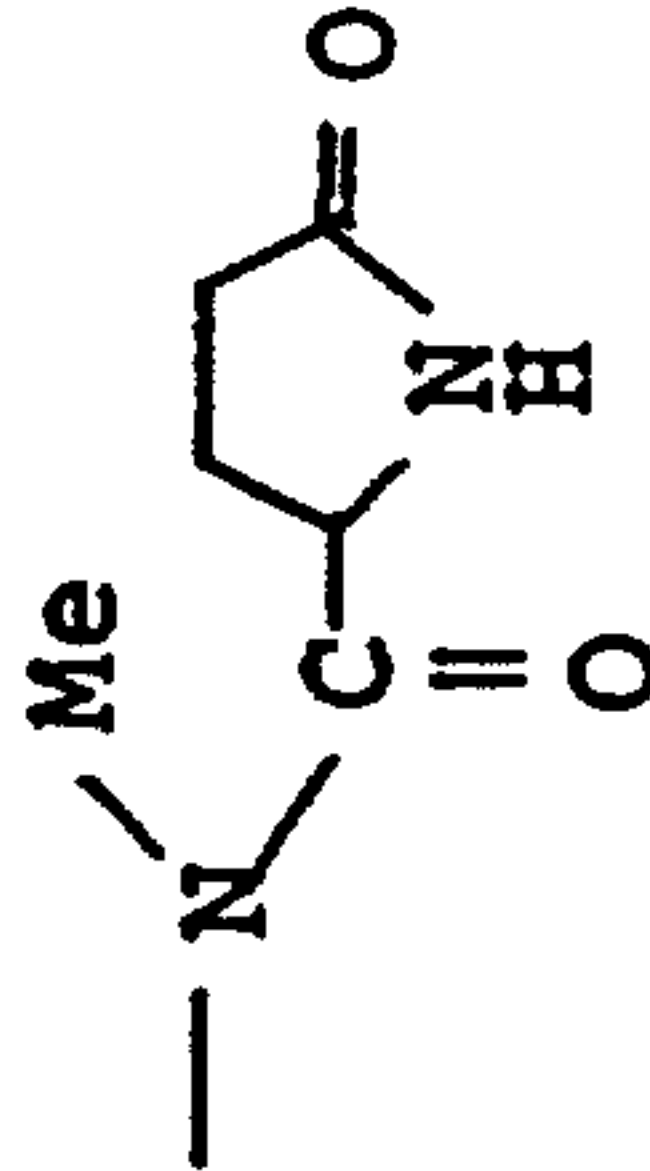
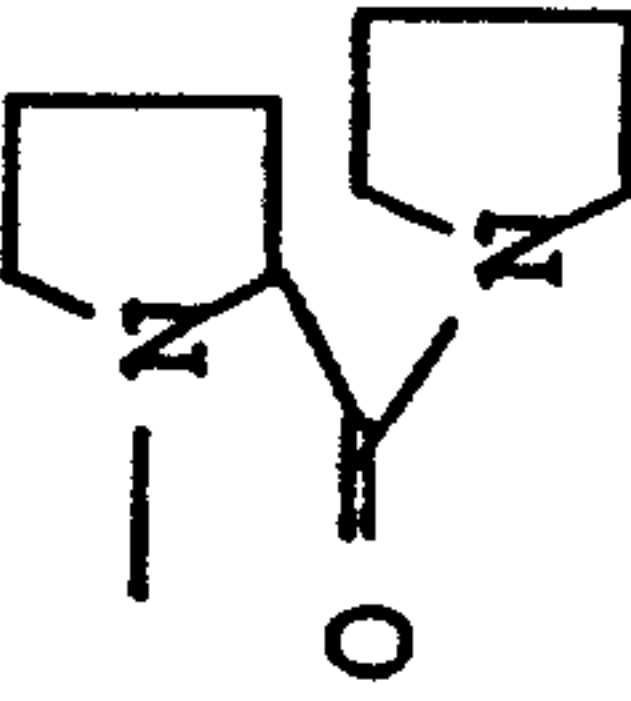
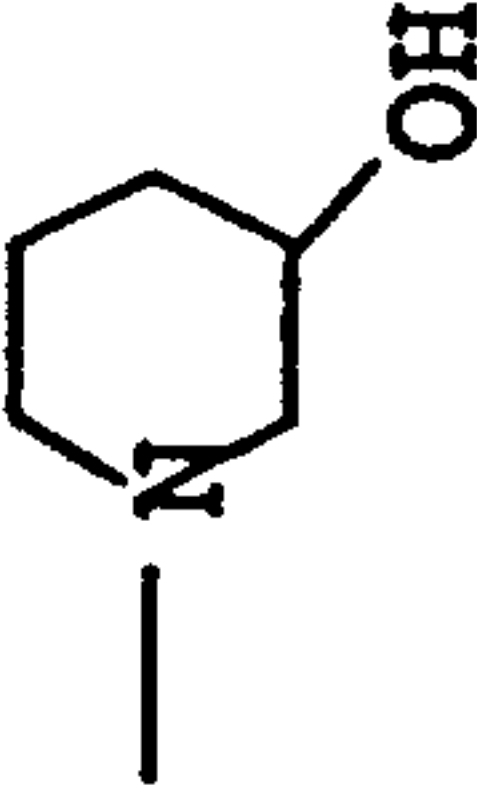
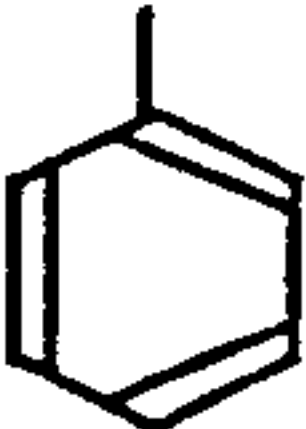
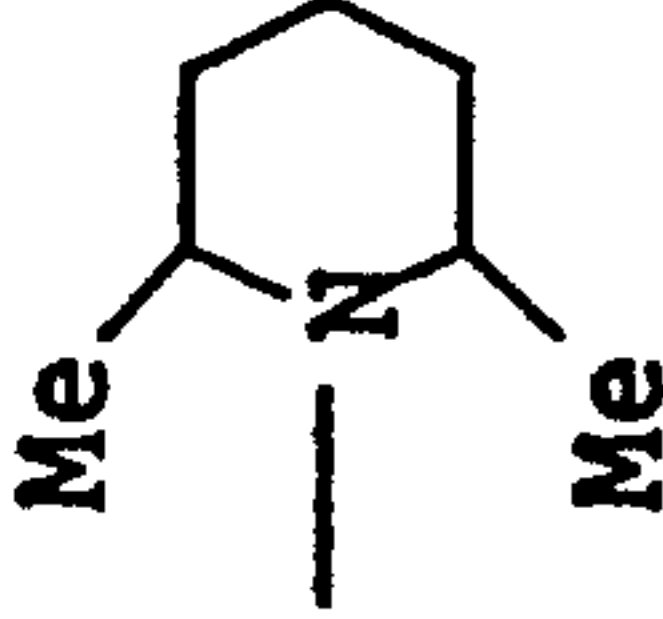
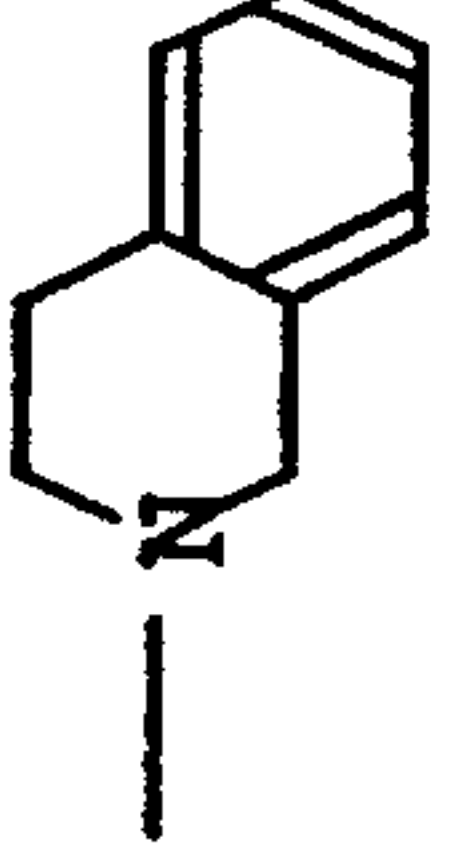
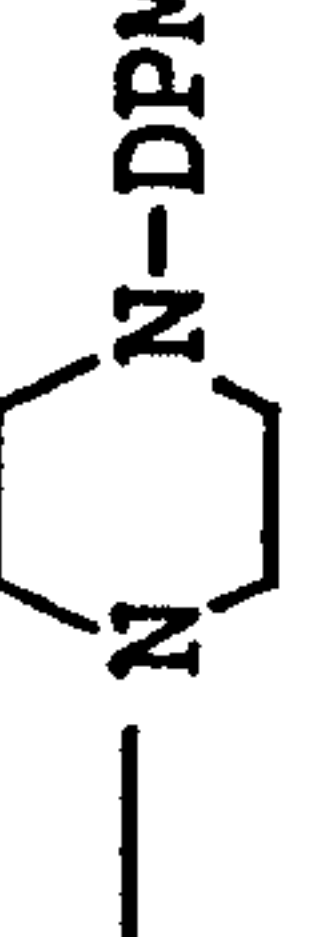


Table 10

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)

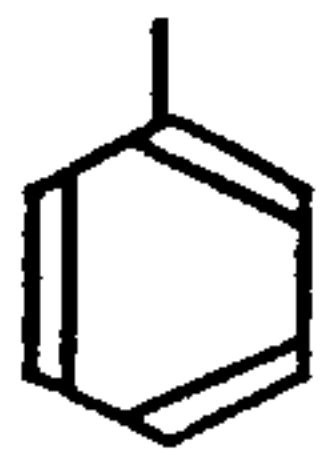
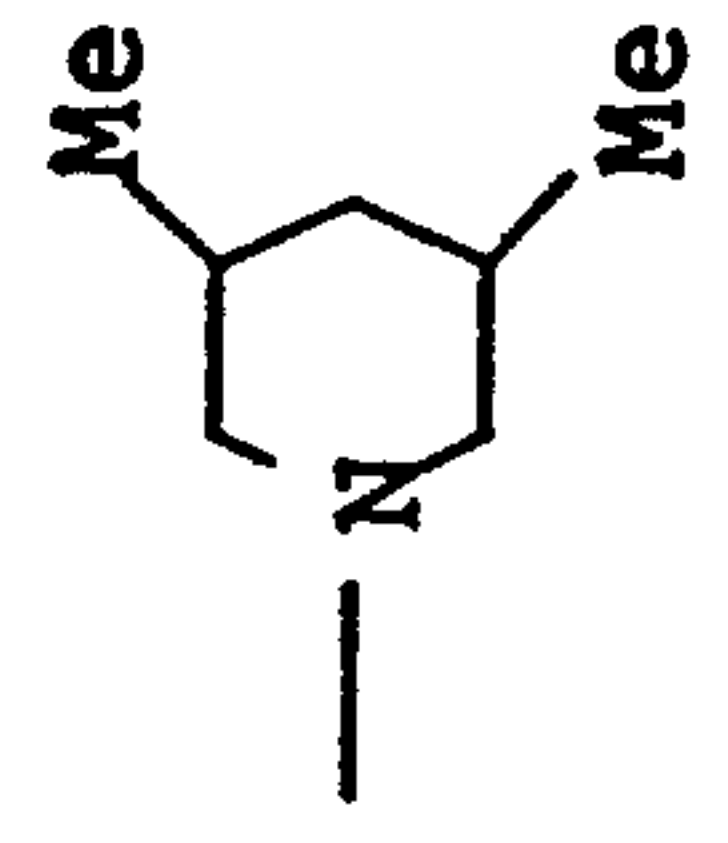
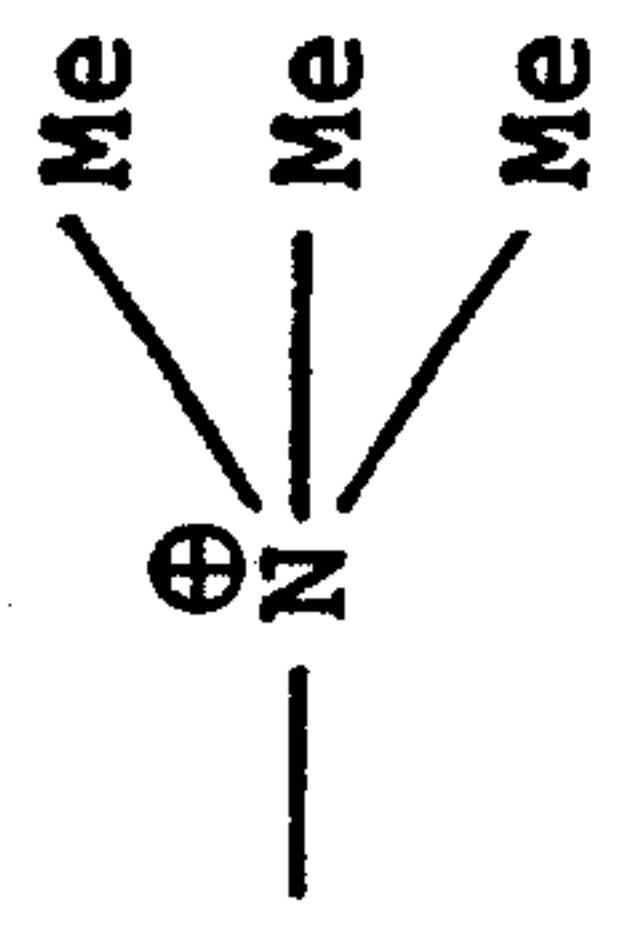
163		H	H	H		2	-	Oily
164	"	"	"	"		"	HCl	164.5 - 166.5
165	"	"	"	"		"	"	169-171 [EtOH]
166	"	"	"	"		"	2HCl	169-171 [CH ₂ Cl ₂ - EtOH]
167	"	"	"	"		"	-	104.5 - 105.5 [EtOH]

- Cont'd -

3

21 60270

Table 10 (Cont'd)

168		H	H	H		2	-	Oily
169 ^{*a}	"	"	"	"		"	1/2 1,5-Naphthalenedisulfonic acid	208-210 [MeOH-Et ₂ O]

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

1 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
5 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-
10 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.

15 In Table 11, R¹, R², R³, R⁴, R⁶ and n each show a substituent or integer used in the following formula:

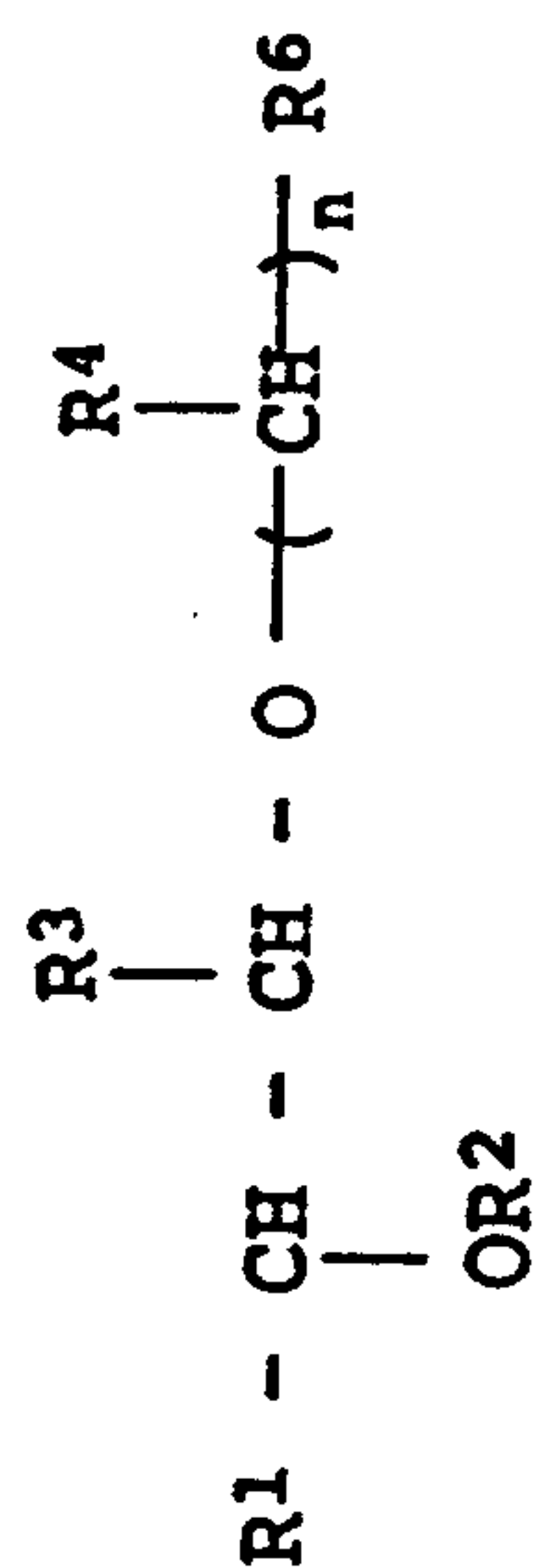
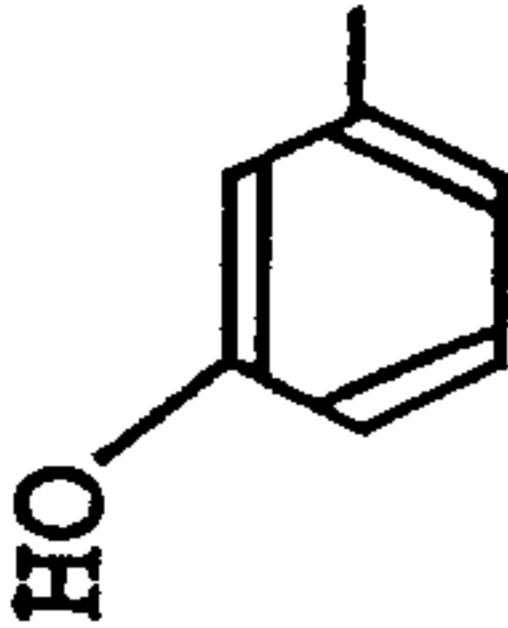
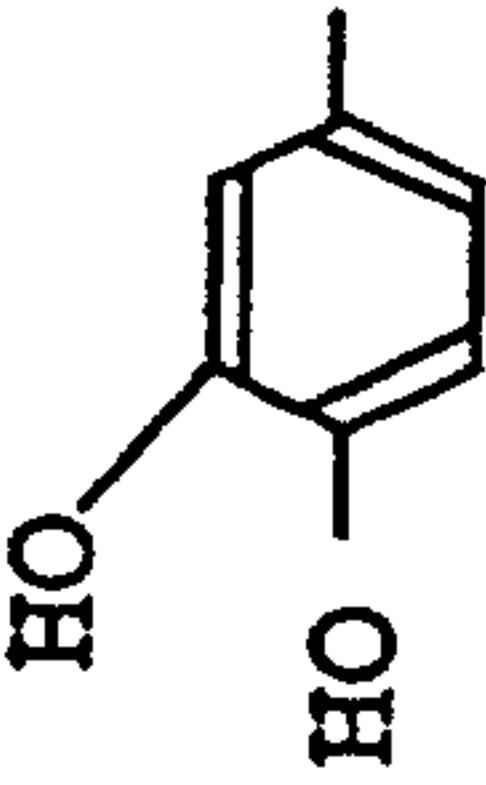
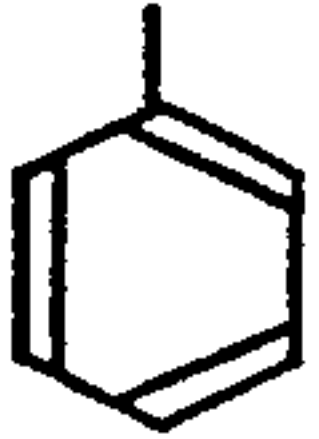
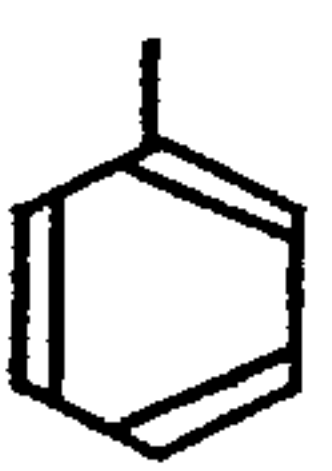
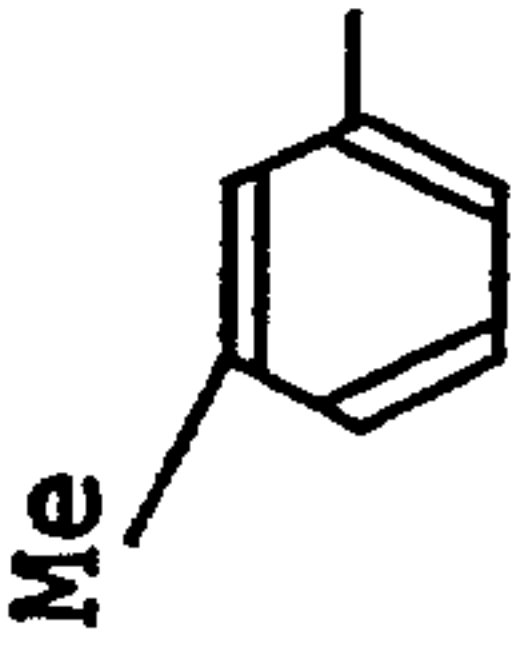
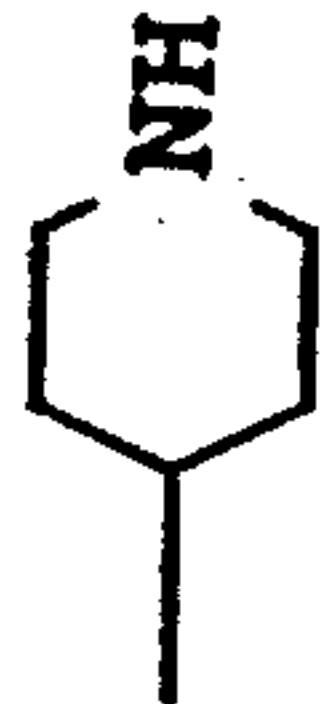
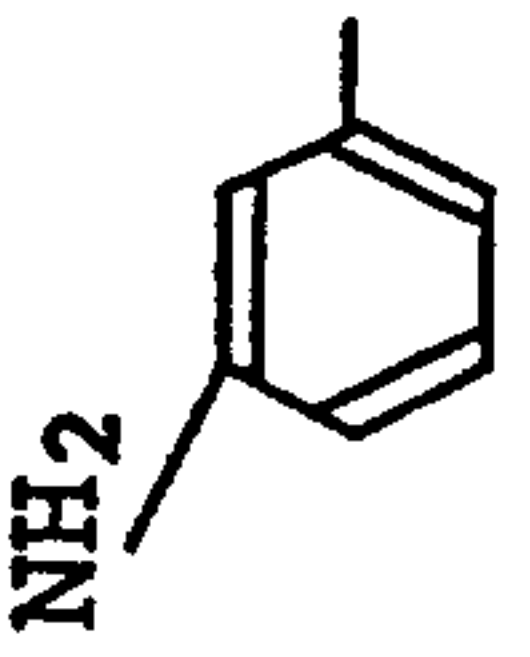


Table 11

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

1 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
5 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
10 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:
15 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.

20 In Table 12, R¹, R², R³, R⁴, R⁶ and n each show a substituent or integer used in the following formula:

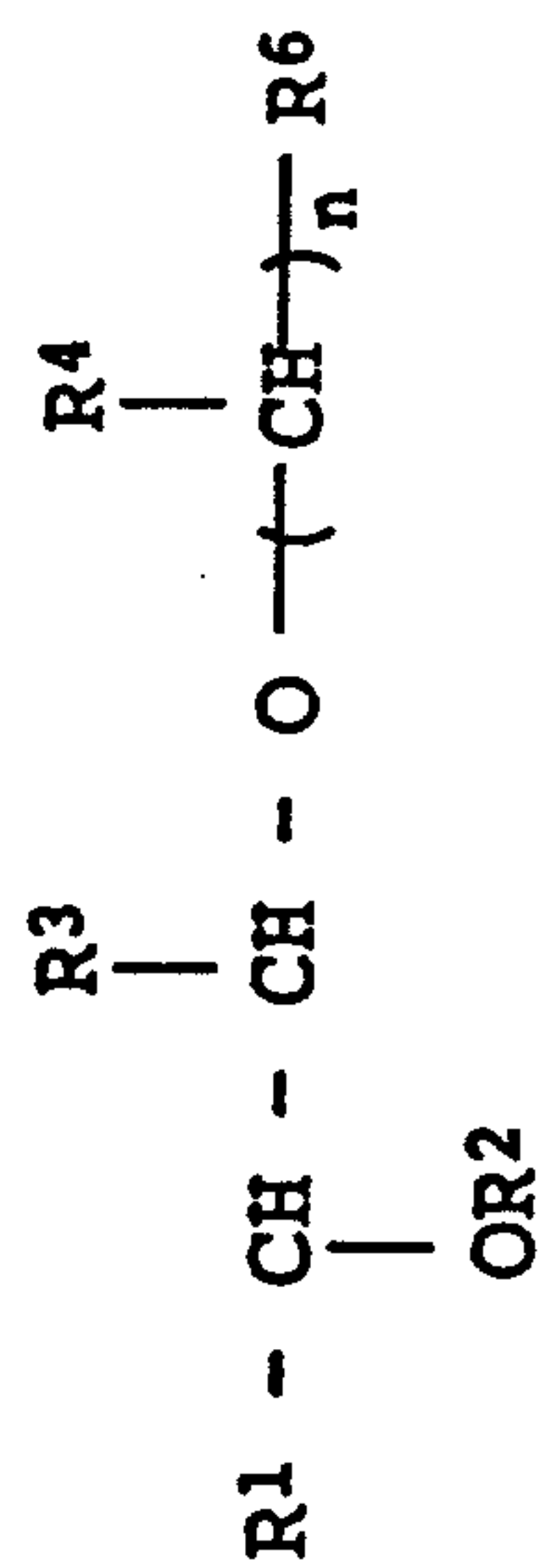
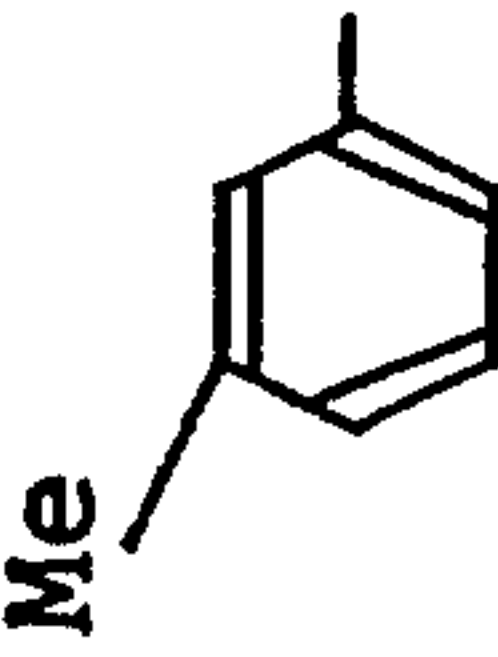
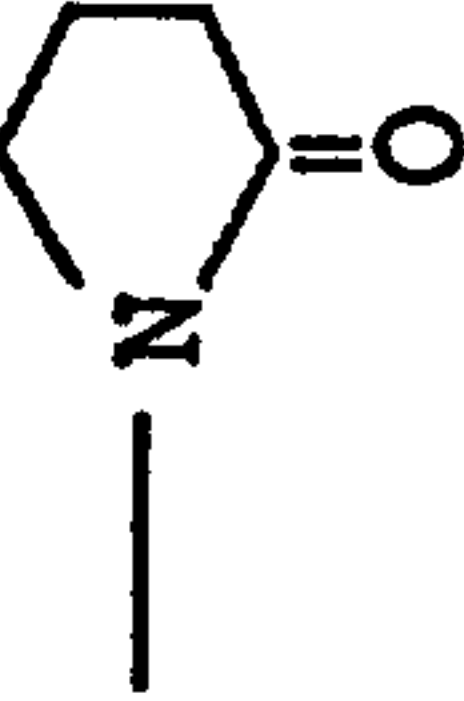
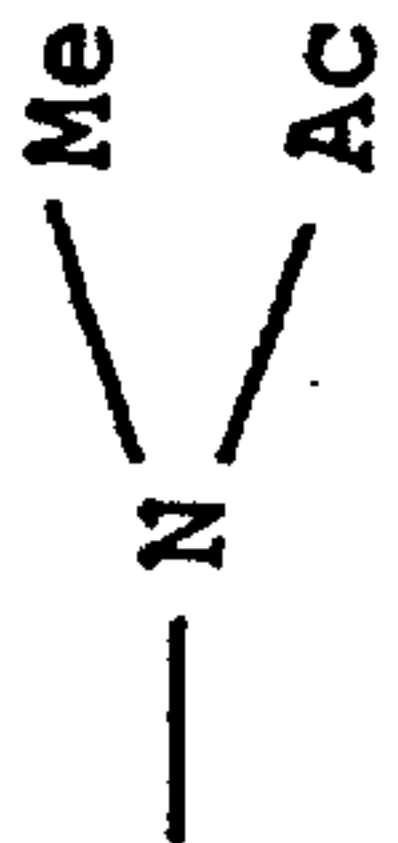
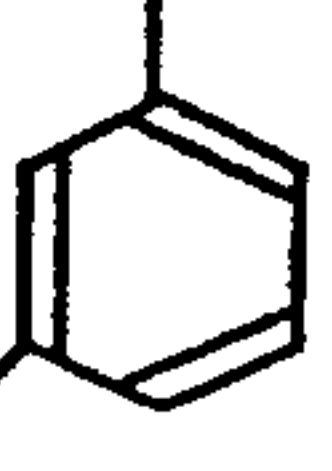
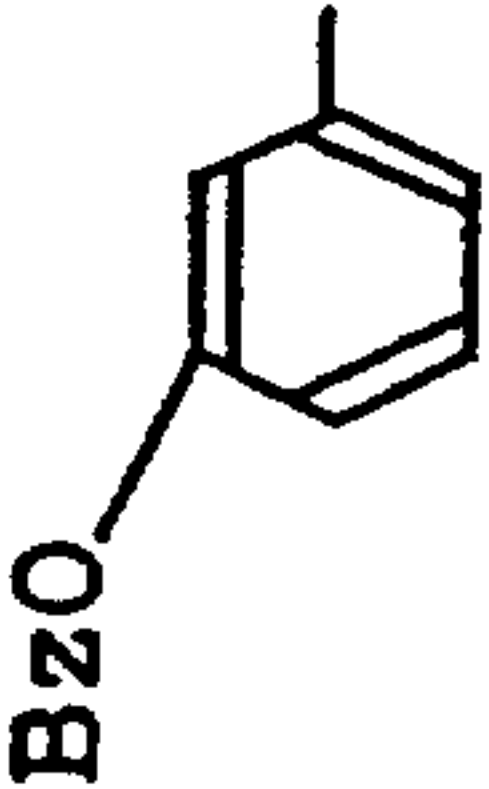
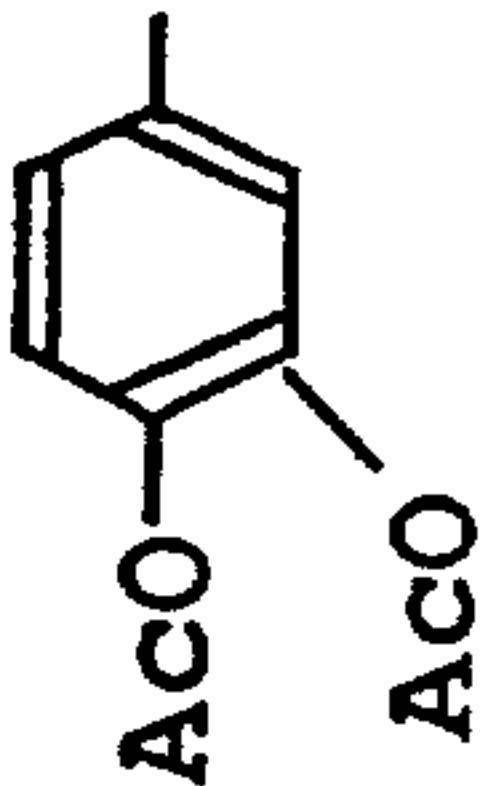
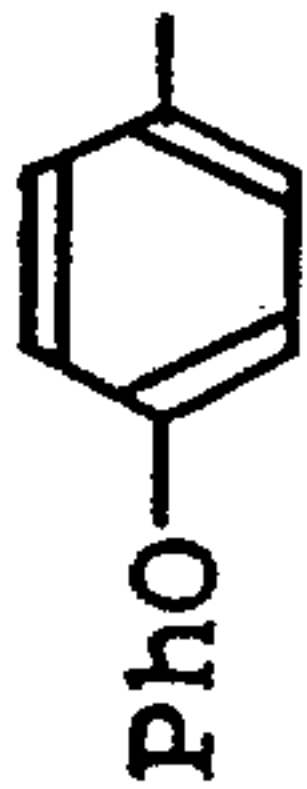
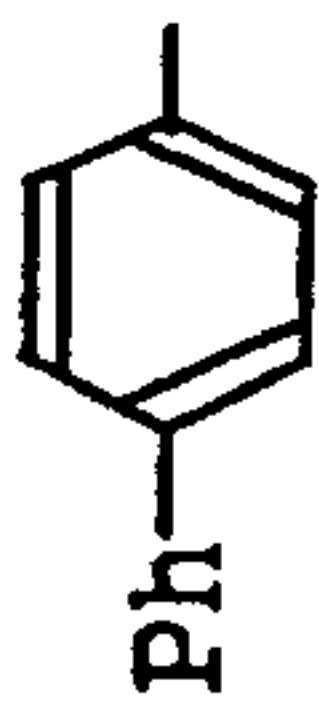


Table 12

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	PhSO ₂ NH 	"	"	"		"	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 [Me2CO]
185		"	"	"	"	"	"	Oily
186		"	"	"	"	"	-	Oily
187		"	"	"	"	"	"	144.5 - 146.5 [EtOH-Et2O]

- Cont'd -

Table 12 (Cont'd)

188		Ac	H	H		1	HCl	Oily
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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.

1 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
5 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
10 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
15 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
20 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 [Me₂CO]

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

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

Production Example 10

- 5 (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
10 resulting mixture was stirred for 30 minutes at the same
temperature. The reaction mixture was cooled to room
temperature 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.
15 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
20 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-
25 hydroxyethoxy)ethanol.

Melting point: 116.5-117°C [MeCN]

1 (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-toluene-sulfonyl chloride.
5 The resulting mixture was heated to 0°C and stirred for
15 hours at the same temperature. The reaction 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
10 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
15 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-
20 toluenesulfonyl)oxyethoxy]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
25 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

- 1 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-tetrahydro-
5 pyranyloxy)-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.
10 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 aqueous layer was
extracted twice each with 20 ml of diethyl ether. The
extracts were combined with the previously separated
15 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.
20 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
25 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

- 1 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]

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

In Table 13, R¹, R², R³, R^{4a}, R^{4b}, R⁶, na and nb each show a substituent or integer used in the following formula:

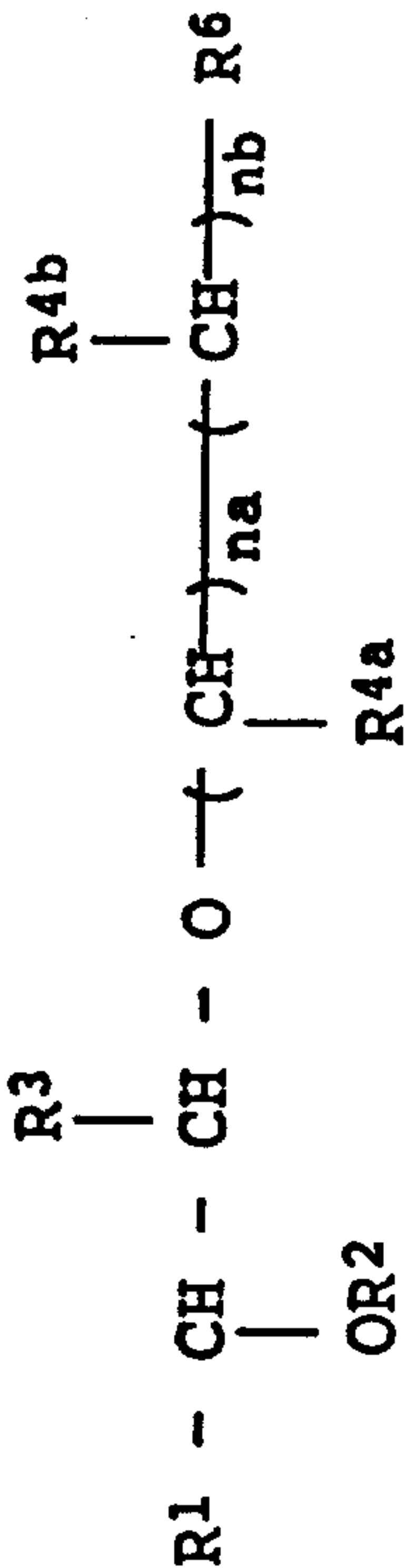


Table 13

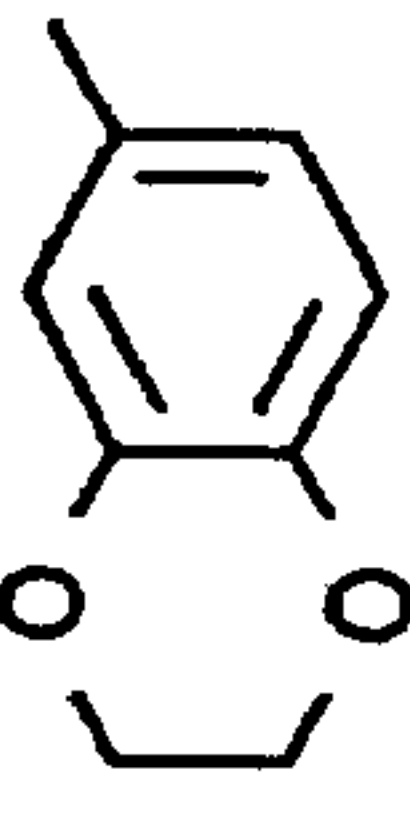
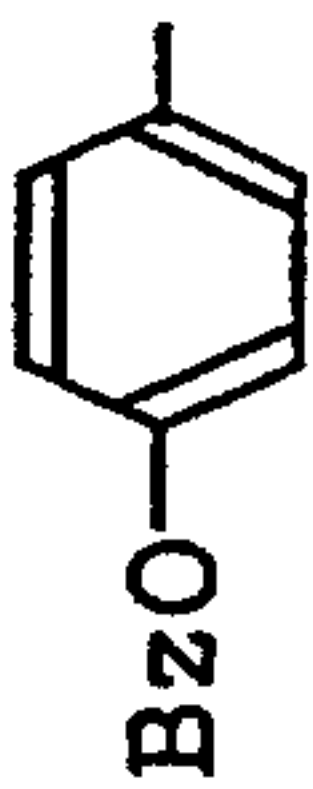
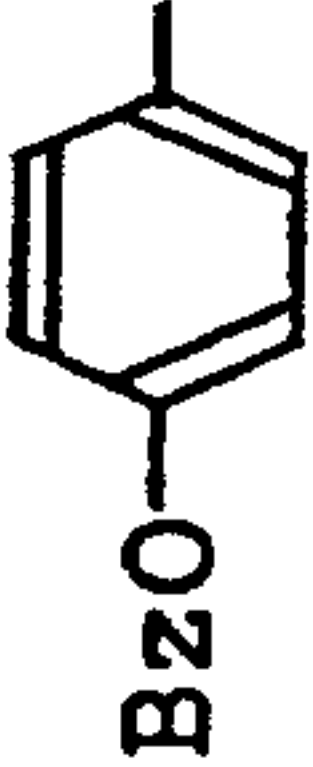
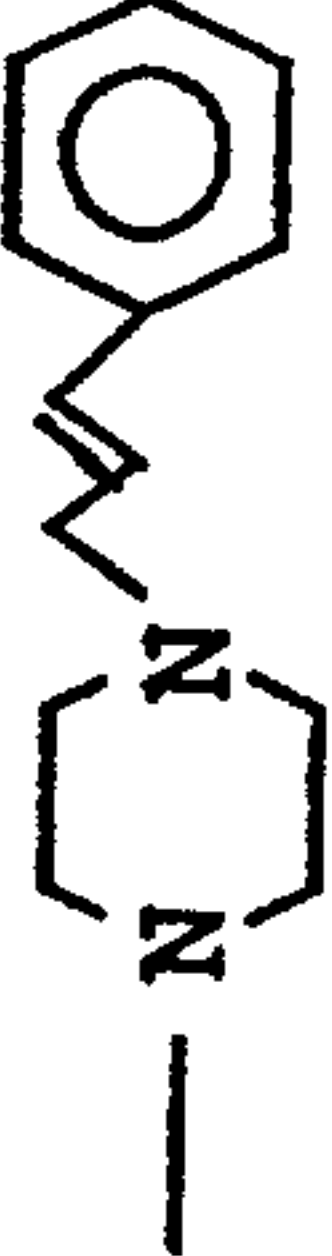
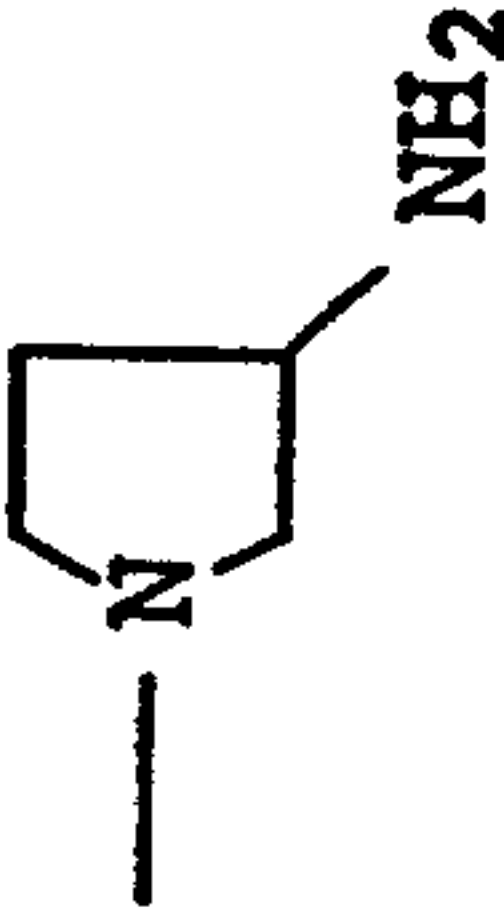
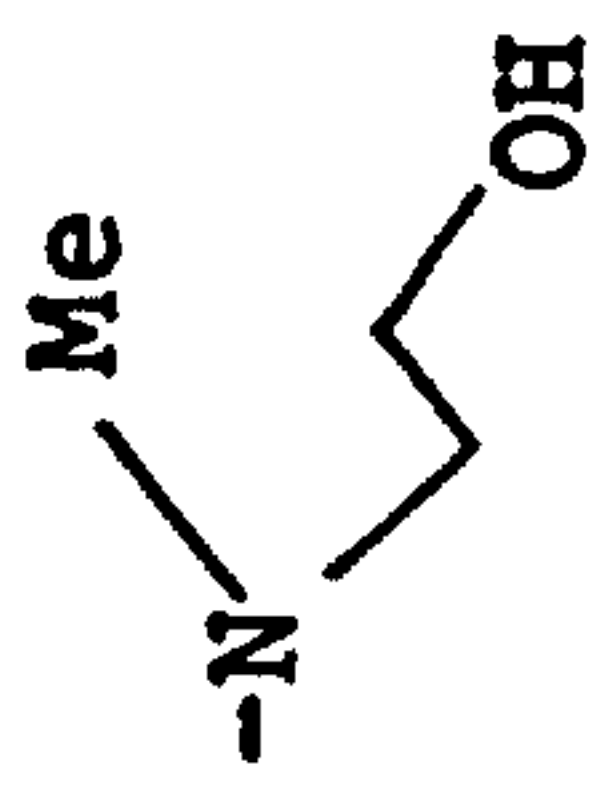
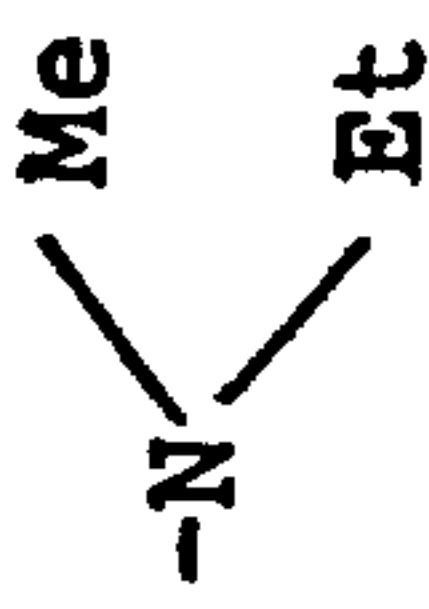
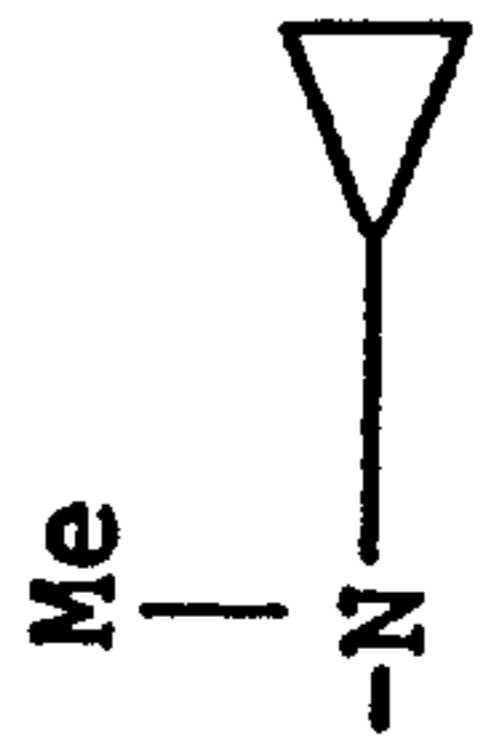
Compound No.	R1	R2	R3	R4a	R4b	R6	na	nb	Addition salt	Melting point (°C)
192		H	H	H	H	-NMe H	1	1	HCl	158-158.5 [IPA]
193	"	"	"	"	"	-N-i-Pr H	"	"	"	170-170.5 [EtOH]
194		"	"	"	"		"	"	"	180-181 [EtOH-AcOEt]
195		"	"	"	"		"	"	2HCl	178-180.5 [MeCN-Et2O]

Table 13 (Cont'd)

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

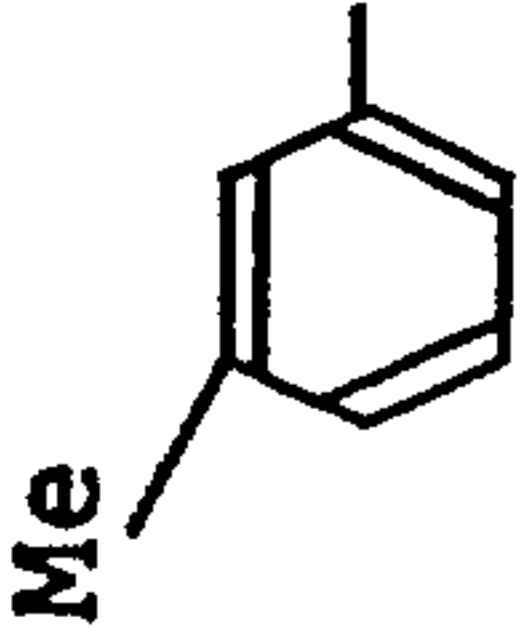
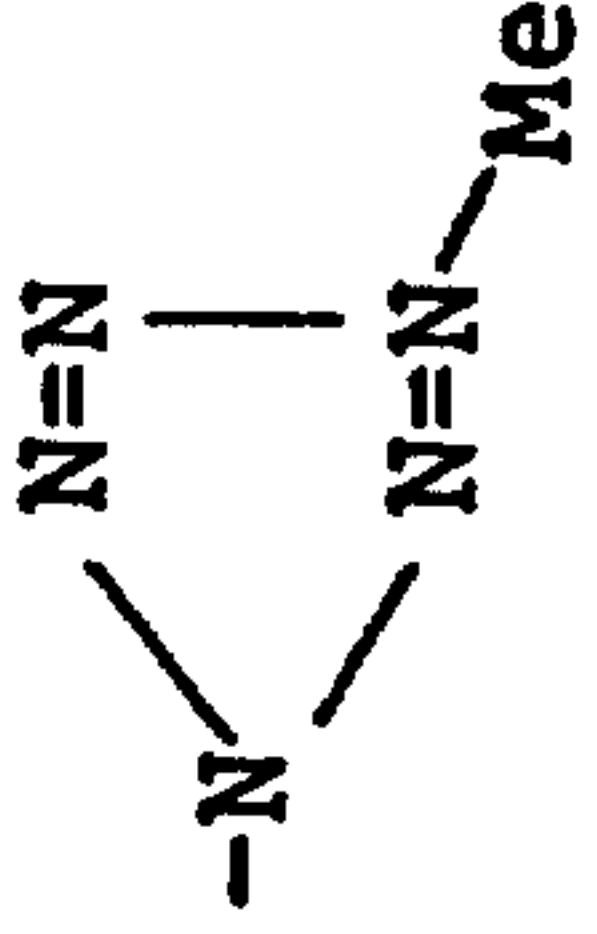
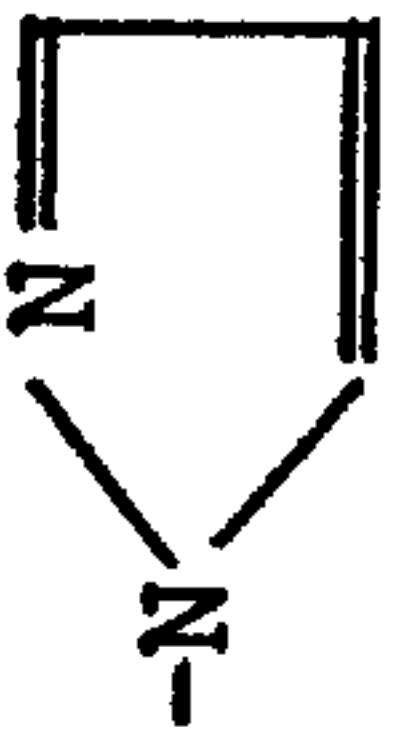
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Table 13 (Cont'd)

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

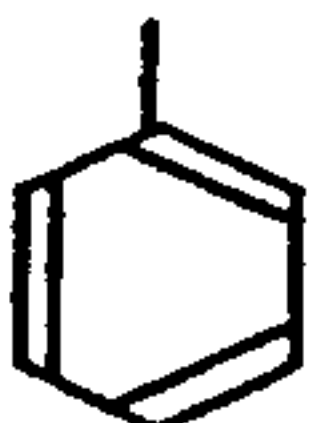
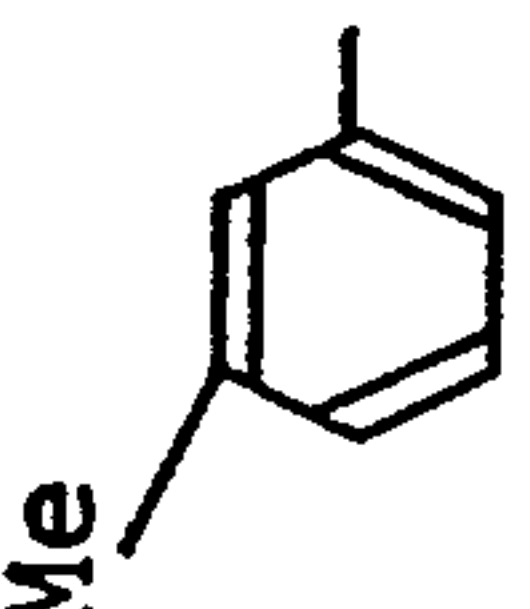
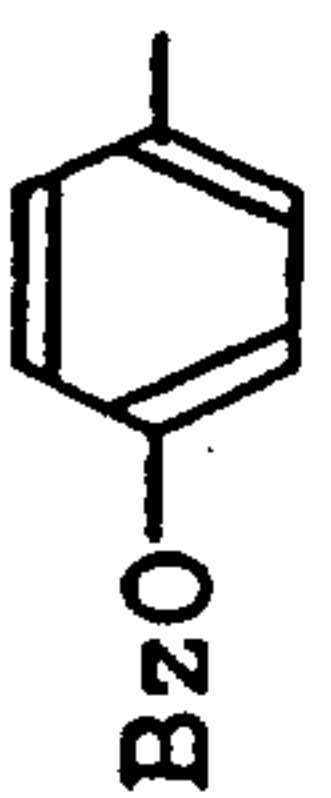
- Cont'd -

Table 13 (Cont'd)

206		H	H	H	H	H		1	1	-	Oily
207	"	"	"	"	"	"		"	"	"	"
208	"	"	"	"	"	"		"	"	HCl	148.5 - 149.5 [IPA- AcOEt]
209		"	"	"	"	"	"	"	"	"	173.5 - 175.5 [EtOH- Me2CO]
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	"	"	"	-N Me 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.

1 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
5 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
10 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
15 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 separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by
20 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 obtain 450 mg of 2-[(1-methylimidazol-5-yl)methoxy]-1-phenylethanol (compound
25 No. 214).

Melting point: 102-105°C

1 The following compound was obtained in the
same manner.

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

5 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
10 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
15 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
20 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
25 solvent was removed by distillation under reduced
pressure. The residue thus obtained was purified by

- 1 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} : $\nu_{\text{C=O}}$ 1635

5 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-hydroxymethylmorpholine was dissolved in 5 ml of ethanol. To the solution was added 5 ml of a 5.9 N 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

1 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
5 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
10 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
15 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
20 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: $[\alpha]_D^{27} = -10.9^\circ$ (C=1, CHCl₃)

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

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

1 Optical rotation: $[\alpha]_D^{27} = +10.9^\circ$ (C=1, CHCl₃)

(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
5 by (S)-2-phenyloxirane and (S)-4-trityl-2-hydroxy-
methylmorpholine, 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-
10 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
15 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
20 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
25 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

- 1 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
5 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: $[\alpha]_D^{24} = +19.9^\circ$ (C=1, CHCl₃)

- 10 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: $[\alpha]_D^{25} = -21.7^\circ$ (C=1, CHCl₃)

- 15 (1S,2'R)-1-phenyl-2-[(morpholin-2-yl)methoxy]ethanol
maleate (compound No. 220)

Melting point: 136-136.5°C [EtOH]

Optical rotation: $[\alpha]_D^{25} = +22.2^\circ$ (C=1, CH₃OH)

- 20 (1R,2'R)-1-phenyl-2-[(morpholin-2-yl)methoxy]ethanol
oxalate (compound No. 221)

Melting point: 131-132.5°C [EtOH]

Optical rotation: $[\alpha]_D^{25} = -20.4^\circ$ (C=1, CH₃OH)

1 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: $49.5-50.5^{\circ}\text{C}$ [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

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1 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
5 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
10 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).

15 Melting point: 173.5-174.5°C [EtOH]

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

In Table 14, R¹, R², R³, R^{4a}, R^{4b}, R⁶, na and
nb each show a substituent or integer used in the
20 following formula:

Table 14

[illegible]

1 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-
5 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
10 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
15 solution, 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
20 was dissolved in 200 ml of acetone. Into the solution
was blown hydrogen chloride gas with ice cooling. The
resulting crystals were collected by filtration, washed
with acetone, and dried to obtain 22.7 g of 2-[2-(N,N-
dimethylamino)ethoxy]-1-(1-naphthyl)ethanol
25 hydrochloride (compound No. 228).

 Melting point: 196-197°C [EtOH]

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

 In Table 15, R¹, R², R³, R^{4a}, R^{4b}, R⁶, n^a and
n^b each show a substituent or integer used in the
5 following formula:

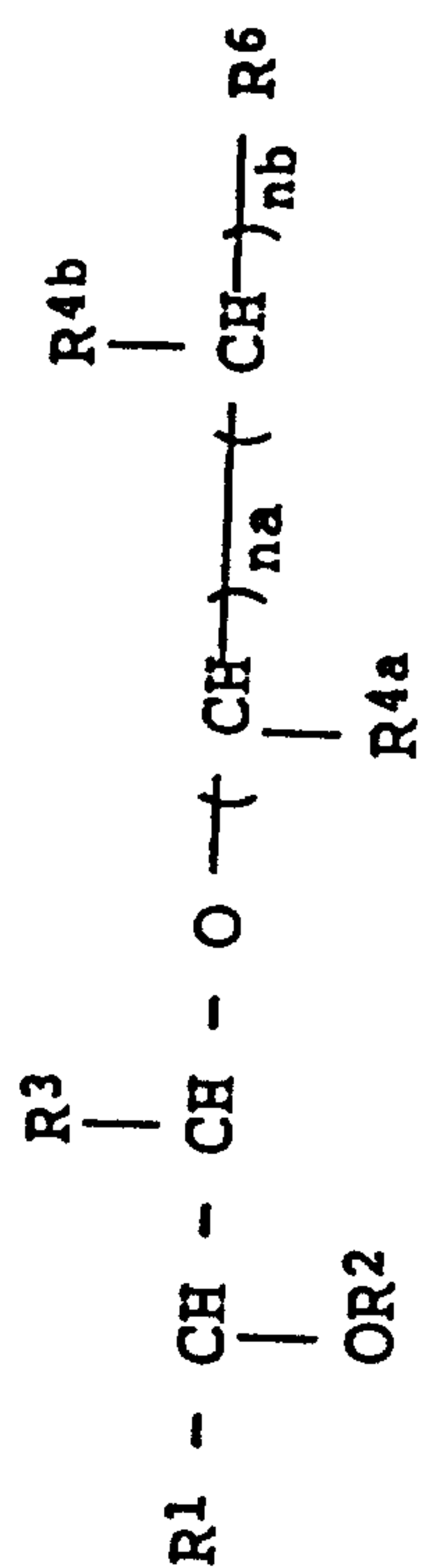


Table 15

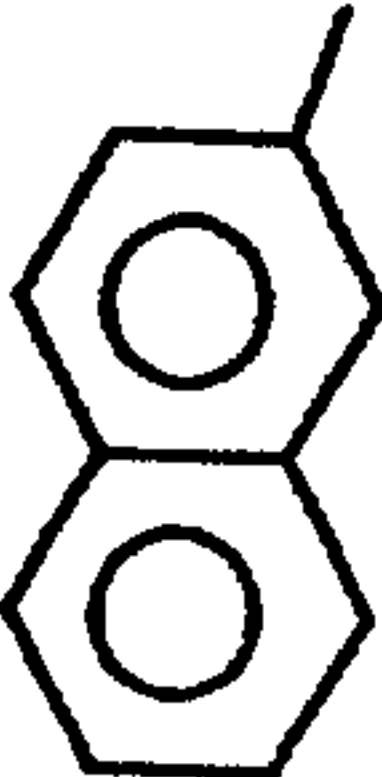
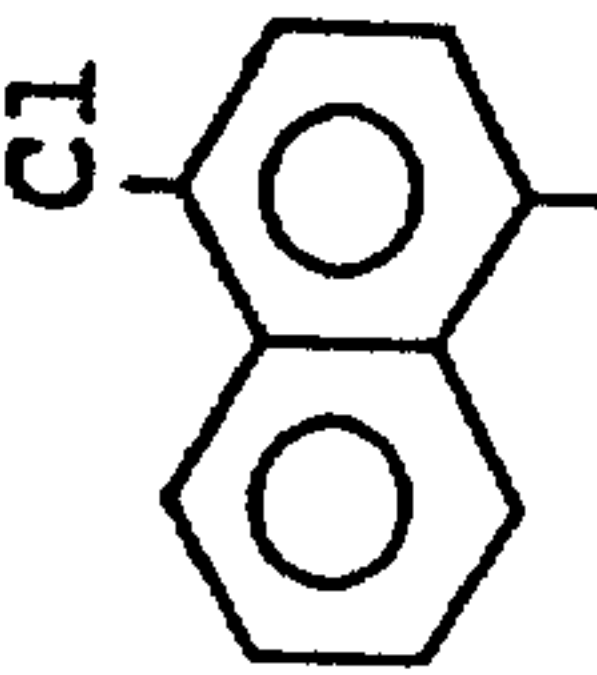
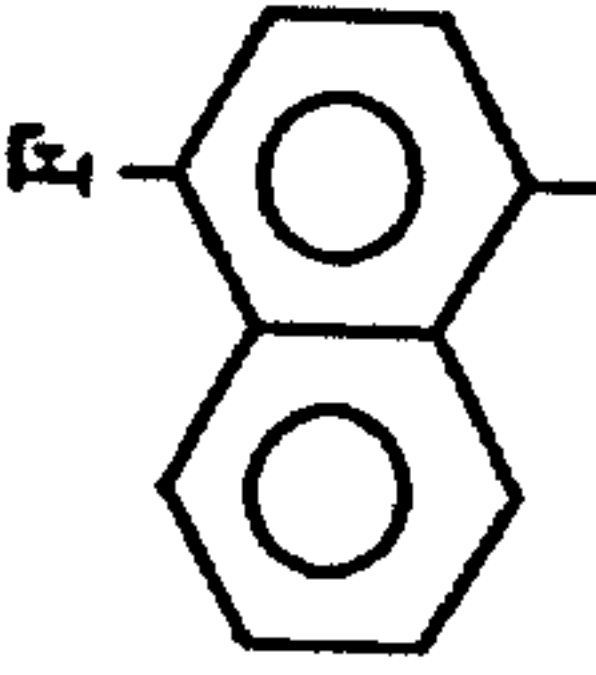
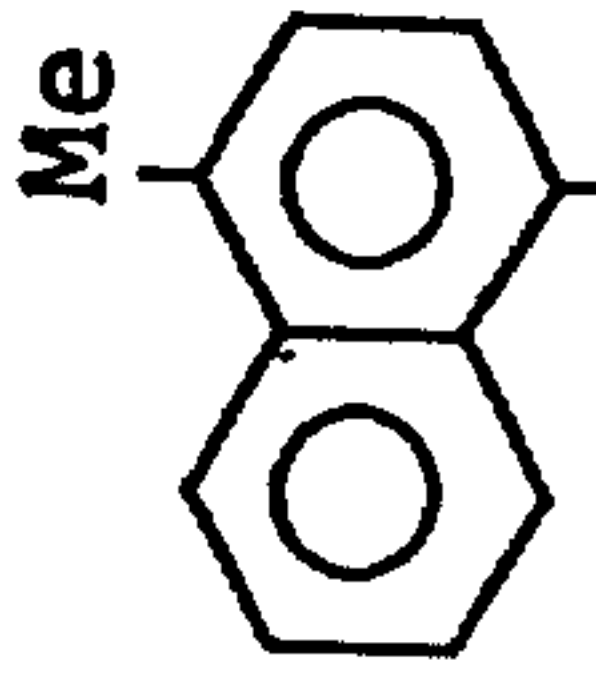
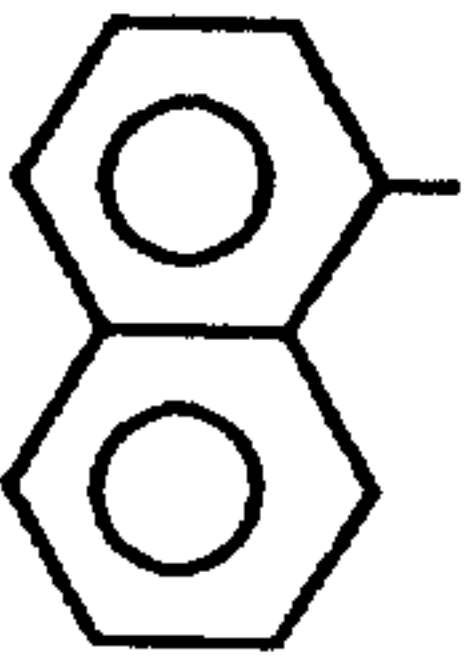
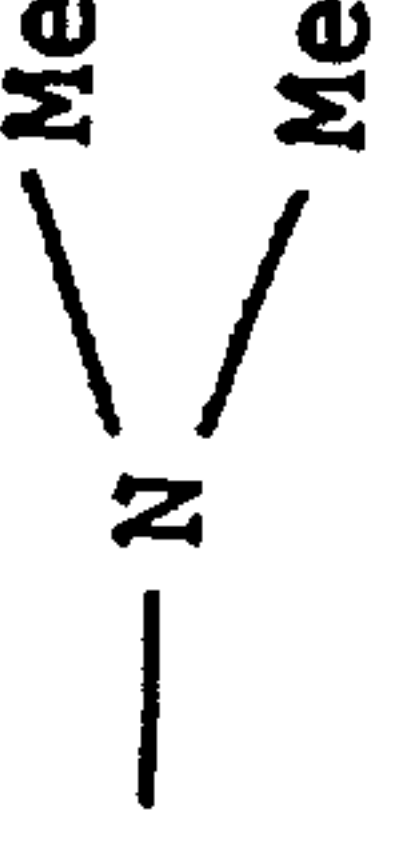
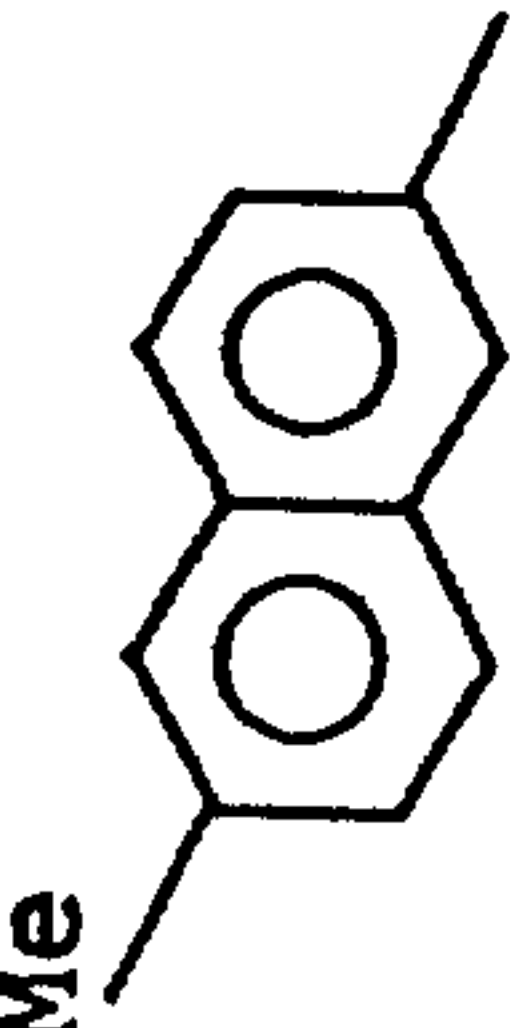
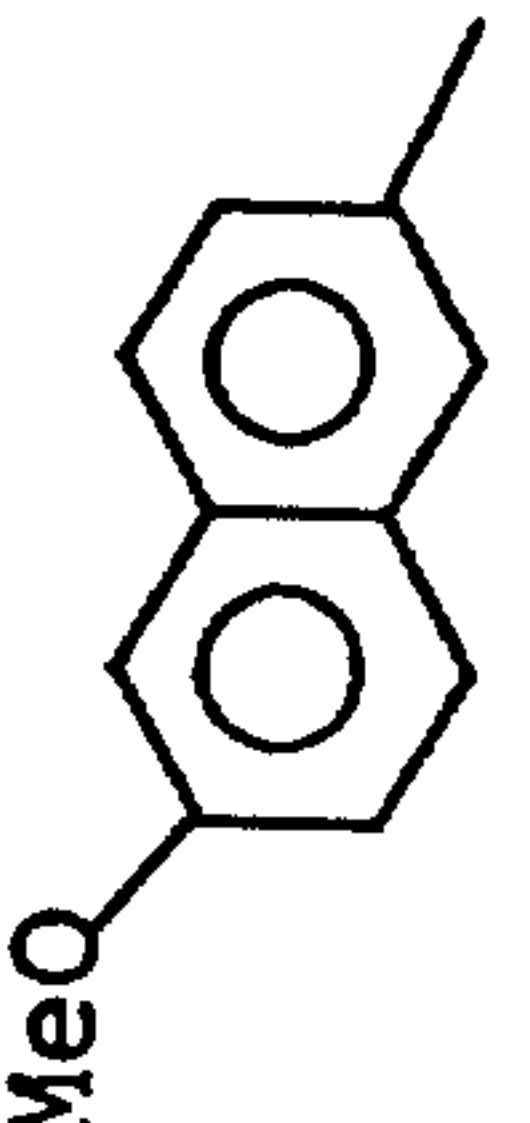
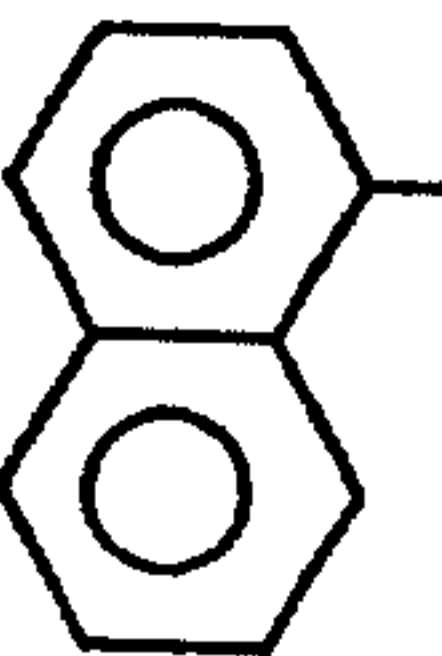
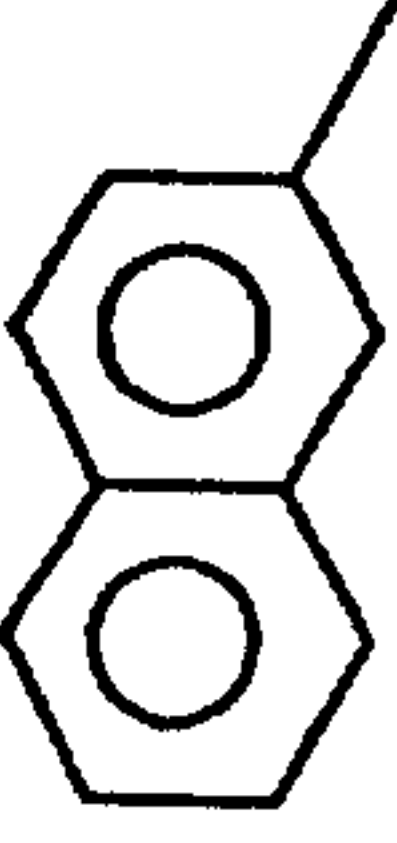
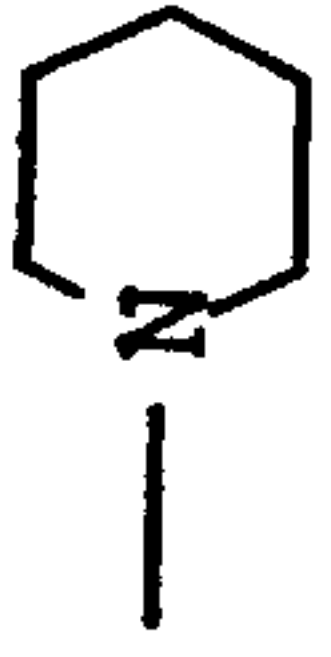
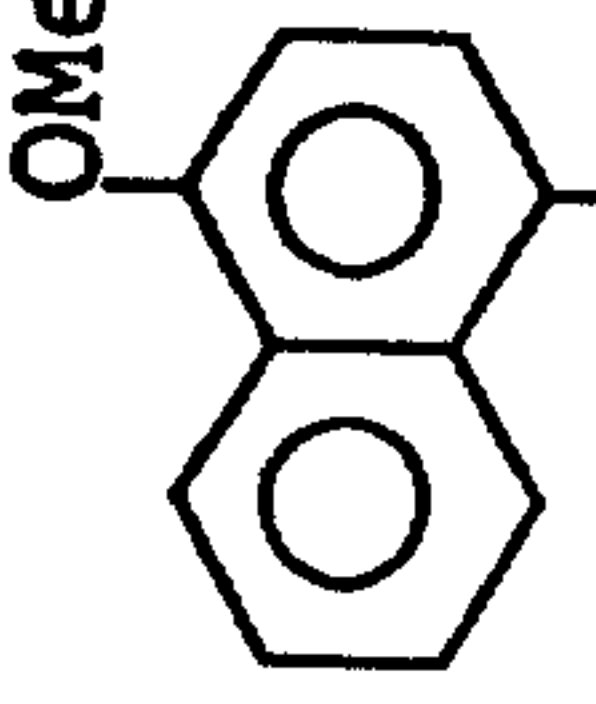
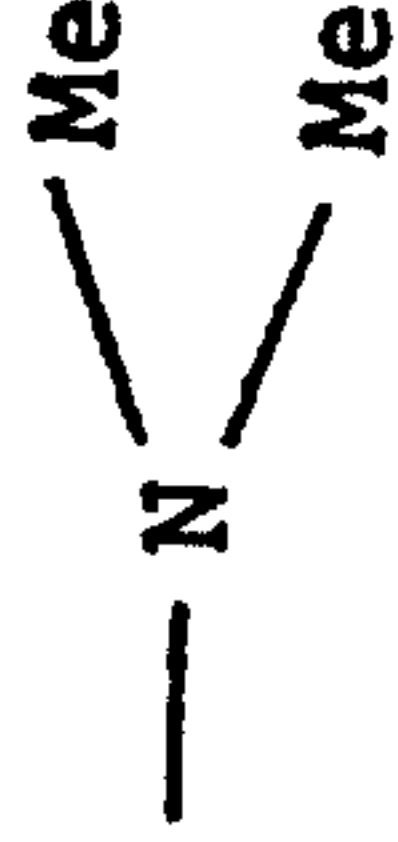
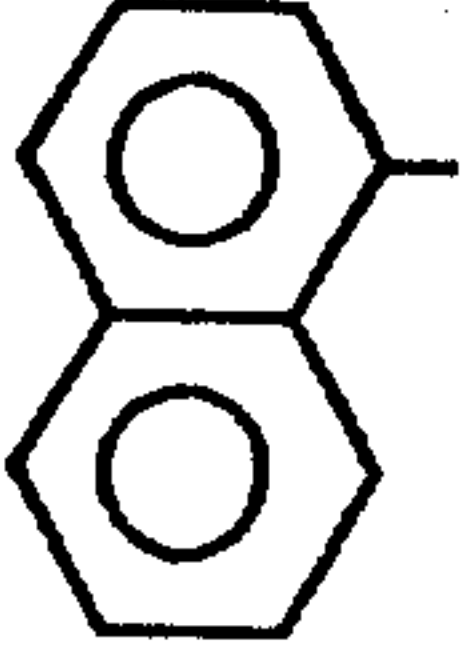
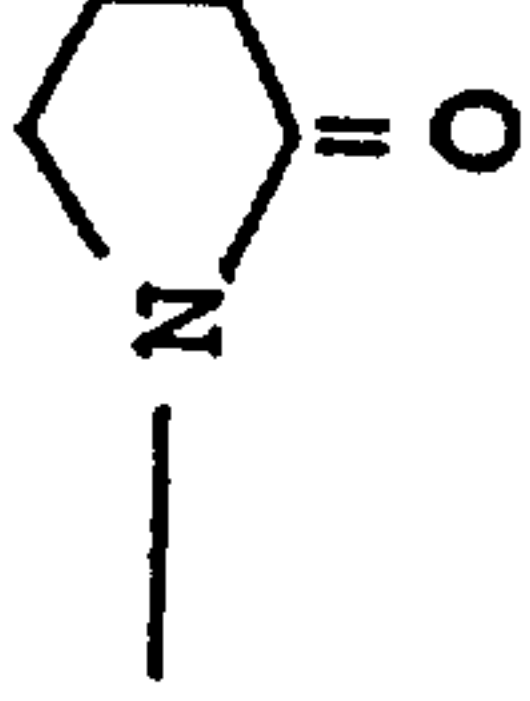
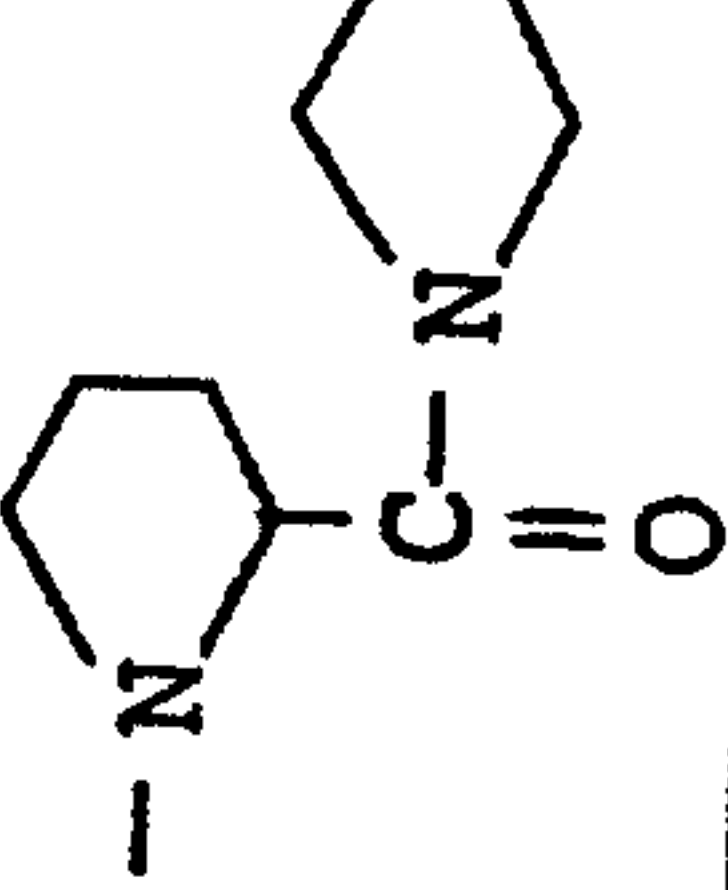
Compound No.	R1	R2	R3	R4a	R4b	R6	na	nb	Addition salt	Melting point (°C)
229		H	H	H	H		1	1	HCl	193-194 [EtOH]
230		"	"	"	"	"	"	"	"	149-150 [Me2CO-EtOH]
231		"	"	"	"	"	"	"	"	178-179 [Me2CO-EtOH]
232		"	"	"	"	"	"	"	"	184-185 [Me2CO-EtOH]

Table 15 (Cont'd)

233*		H	H	H	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 ₂ O]

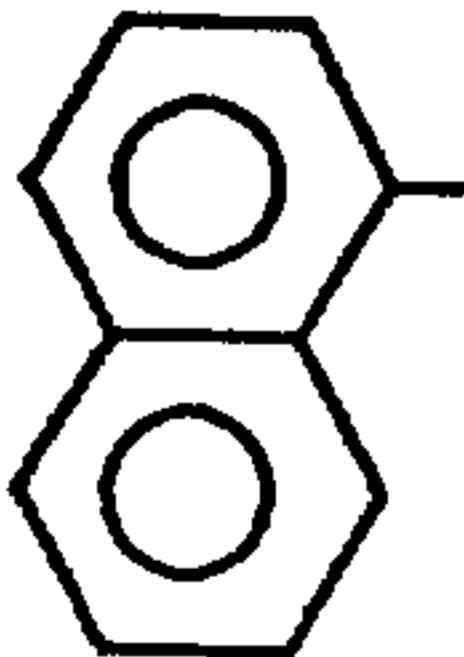
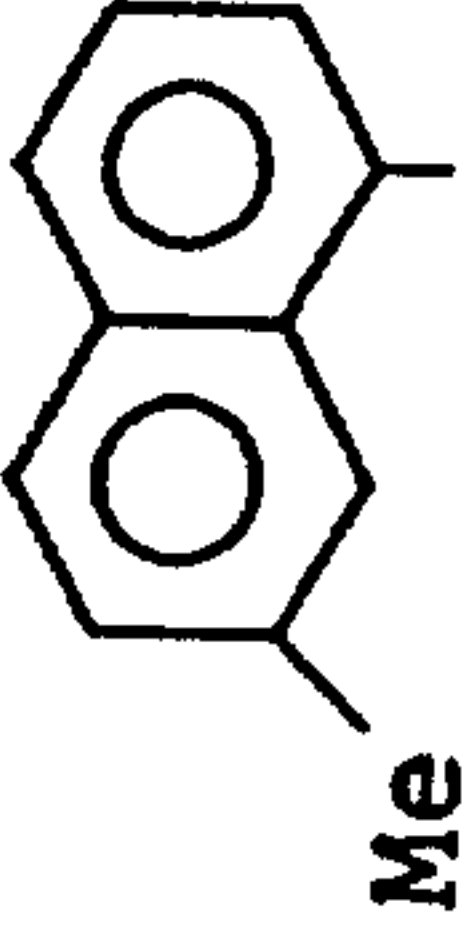
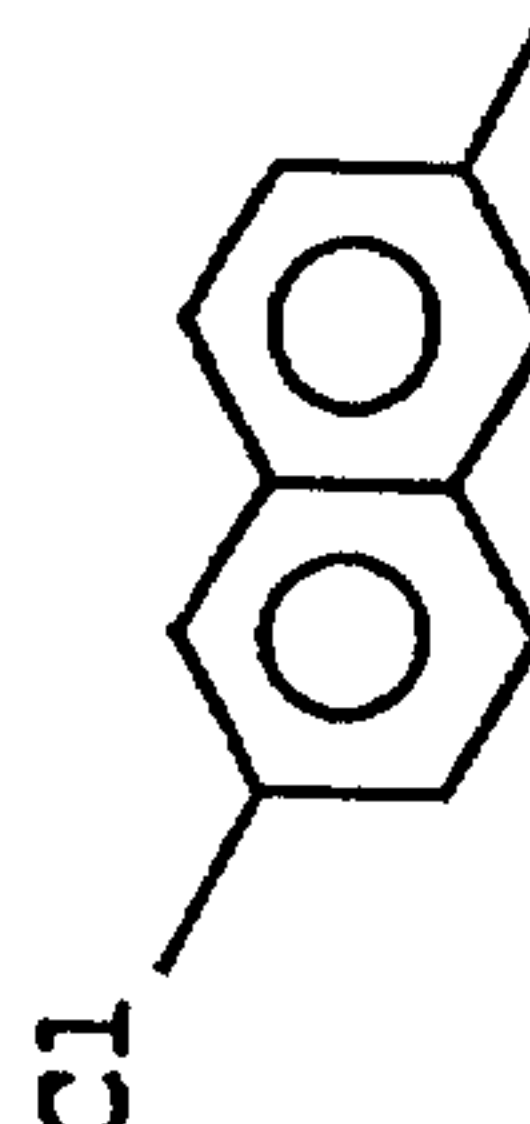
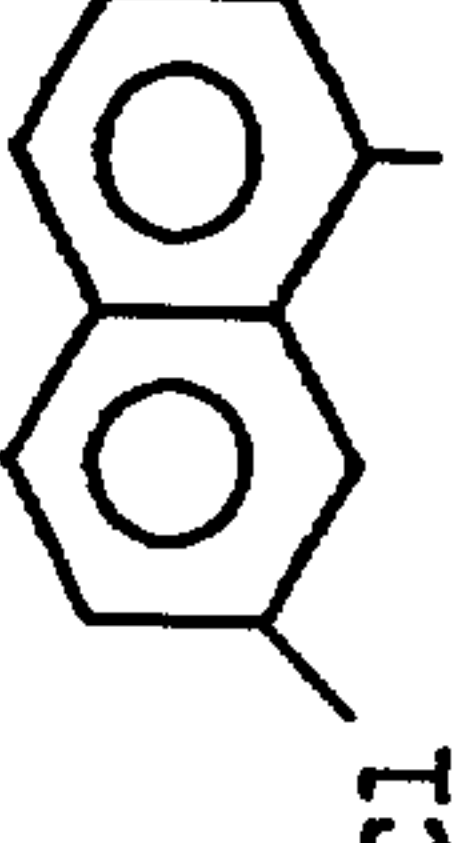
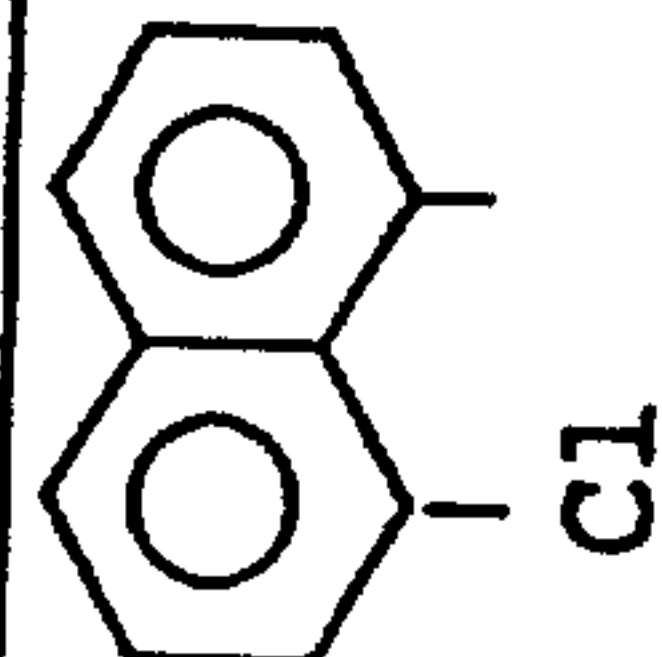
- Cont'd -

Table 15 (Cont'd)

238		H	H	H	H	H		1	1	HCl	156.5-158 [EtOH-Et ₂ O]
239		"	"	"	"	"		"	"	"	157-158 [IPA]
240*		"	"	"	"	"		1	1	-	Oily
241*	"	"	"	"	"	"		"	"	"	"
242*	"	"	"	"	"	"		"	"	"	"

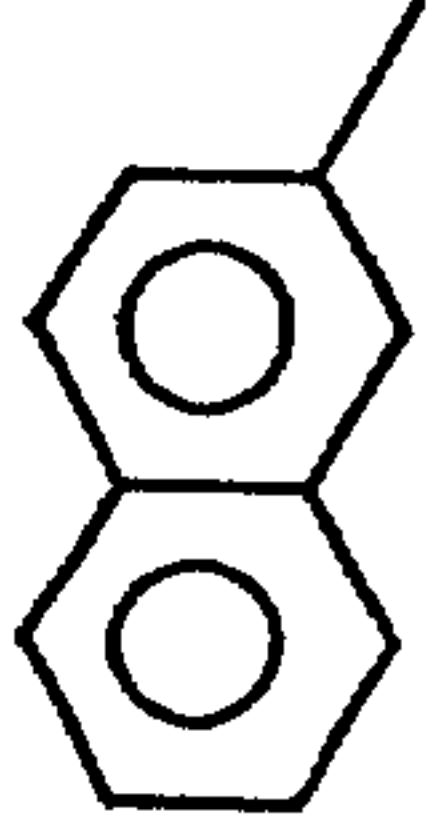
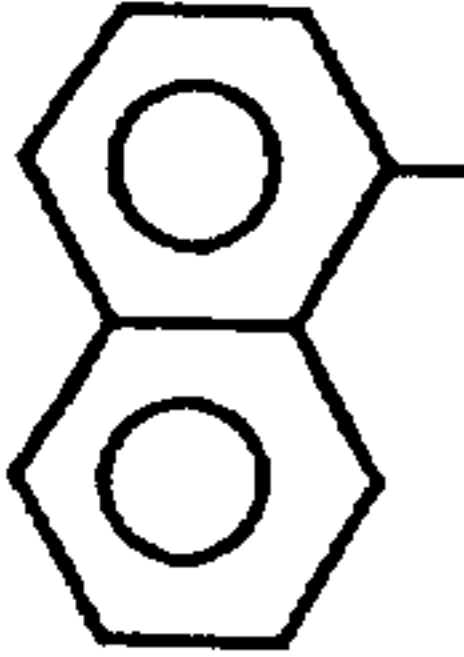
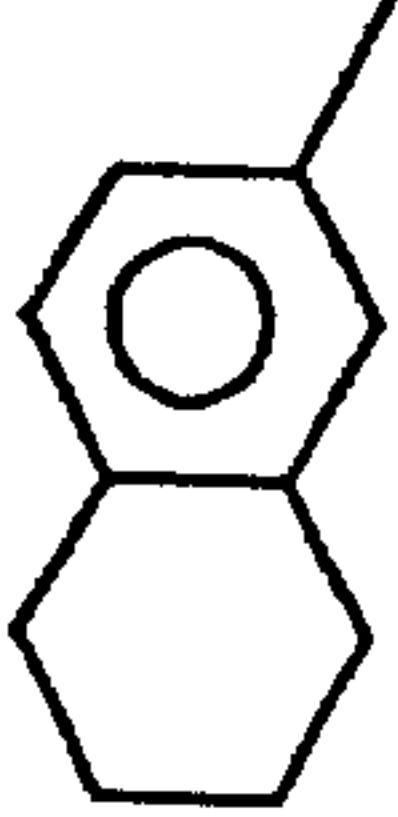
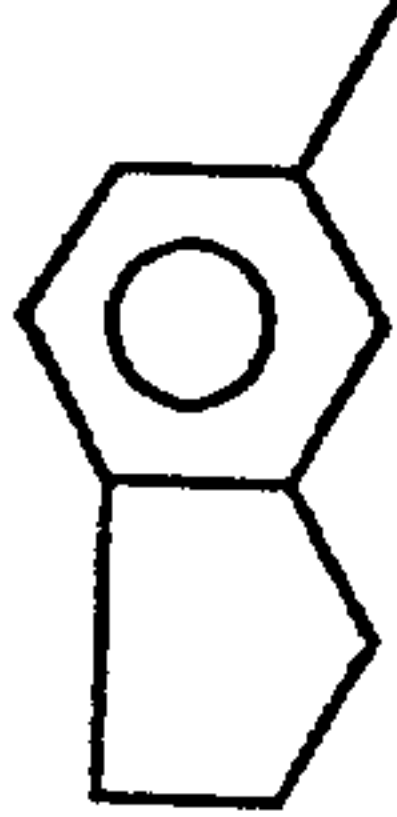
- Cont'd -

Table 15 (Cont'd)

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

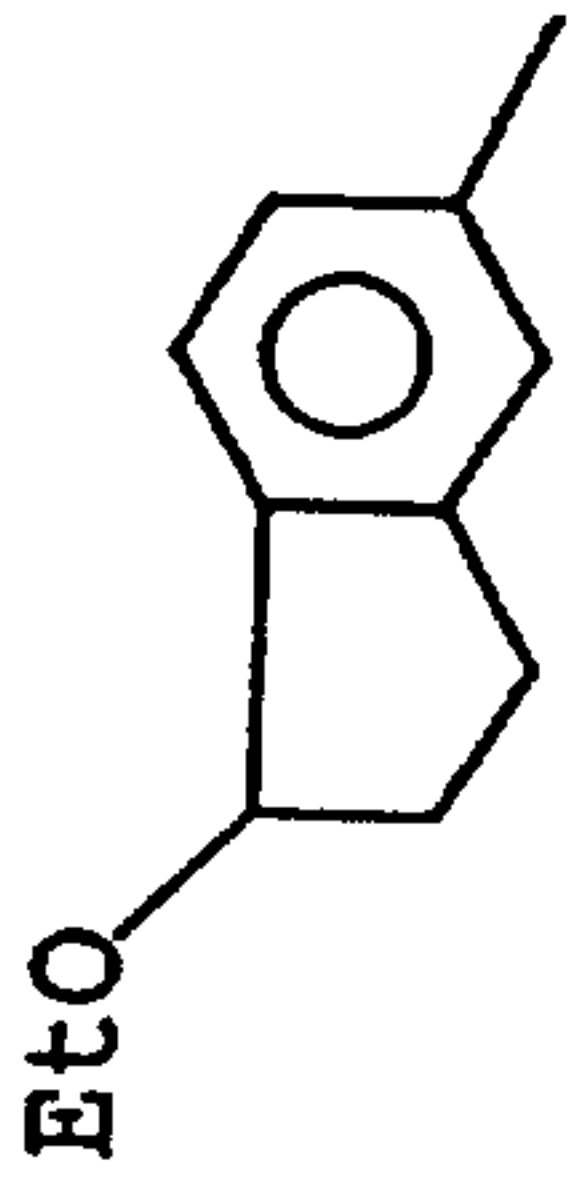
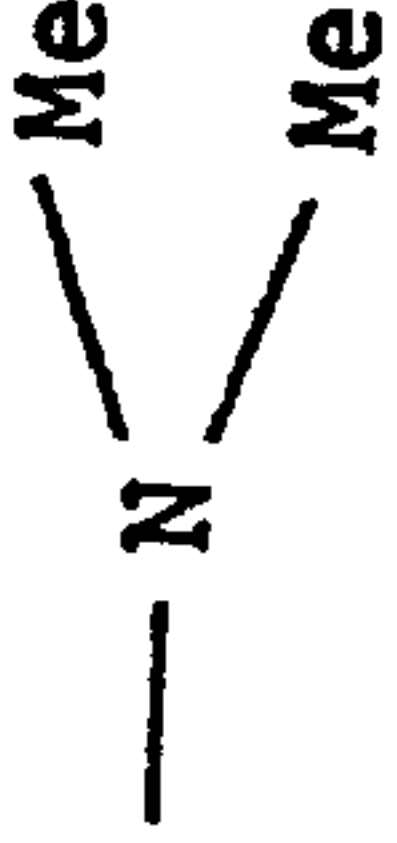
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Table 15 (Cont'd)

248		H	H	H	H	H	H		1	1	HCl	100.5 - 101.5 [IPA- AcOEt]
249		"	Me	"	"	"	"		"	"	"	186.5-188 [EtOH- Me2CO]
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	H		1	1	HCl	157-159 [IPA]
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Note: *: These compounds were not subjected to a step of converting into a hydrochloride.

1 Production Example 16

(1) A mixture of 6.0 g of 2-hydroxymethyl-4-trityl-morpholine, 1.0 g of potassium tert-butoxide and 6 ml of dimethyl sulfoxide was heated to 80°C. Thereto
5 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
10 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
15 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).

20 (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 hydrogen chloride-ethanol solution with ice cooling. The mixture was stirred for 2 hours at room temperature
25 to effect reaction. After the completion of the reaction, the solvent was removed by distillation under

1 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
5 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
10 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
15 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).

20 Melting point: 141-144°C [EtOH]

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

Production Example 17

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

1 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
5 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
10 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)
15 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.

20 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
25 allowed to stand at 0-5°C for 24 hours and further at
room temperature for 4 hours. The reaction mixture

- 1 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.
- 5 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, and dried over anhydrous magnesium sulfate.
- 10 The solvent was removed by distillation under reduced pressure. The residue thus obtained was purified by column chromatography (eluent: toluene/ethyl acetate = 10/1) to obtain 6.3 g of colorless, oily 1-(1-naphthyl)-2-[2-(p-toluenesulfonyloxy)ethoxy]ethanol.
- 15 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
- 20 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
- 25 mixture was cooled, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed by

1 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-
5 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-
10 (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
15 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
20 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
25 (eluant: chloroform/ethanol = 10/1) to obtain 3.36 g
of colorless, oily 2-[2-(4-methylpiperazin-1-yl)ethoxy]-

1 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-
5 (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
10 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
15 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.
20 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
25 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

1 dihydrochloride (compound No. 259).

Melting point: 230.5-231.5°C [MeOH]

Production Example 18

The same procedure as in (4) and (5) of
5 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).

10 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
15 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
20 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.
25 The organic layer was extracted twice each with 10 ml of water. The extracts were combined with the previously

1 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
5 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
10 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-
15 (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.

20 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:

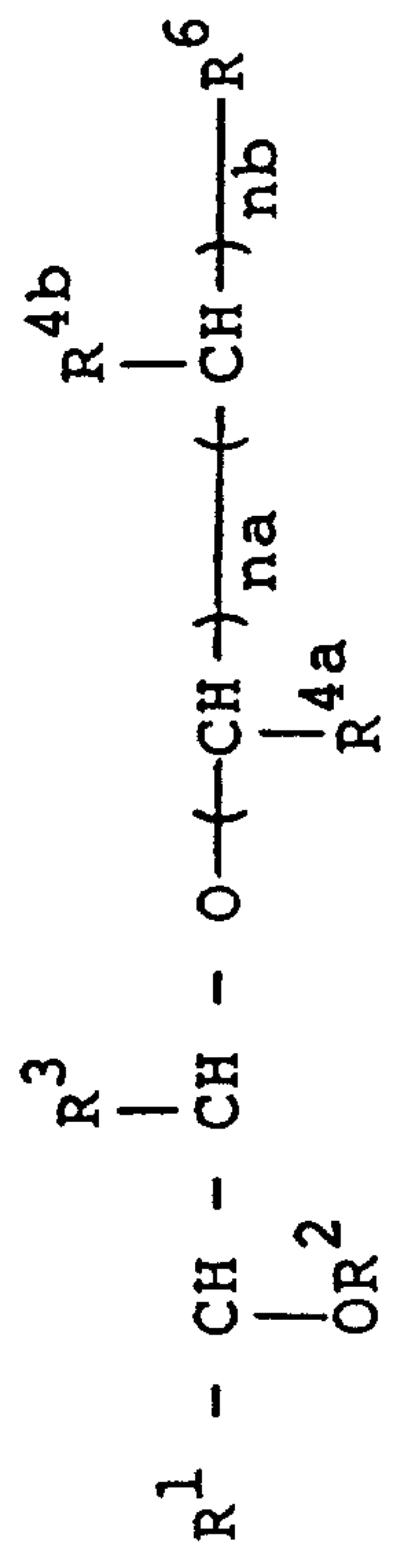
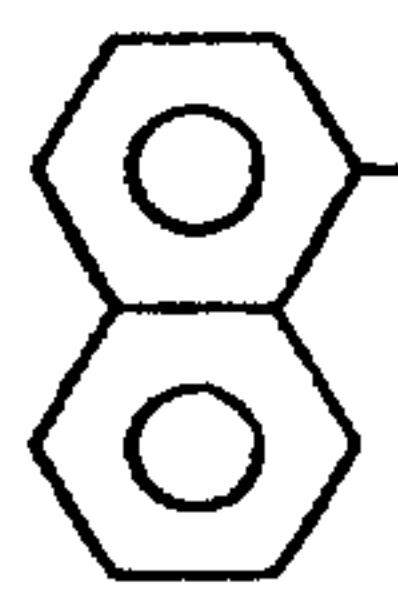
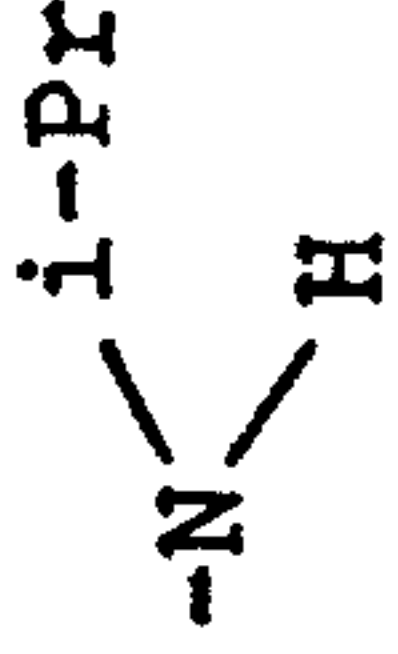
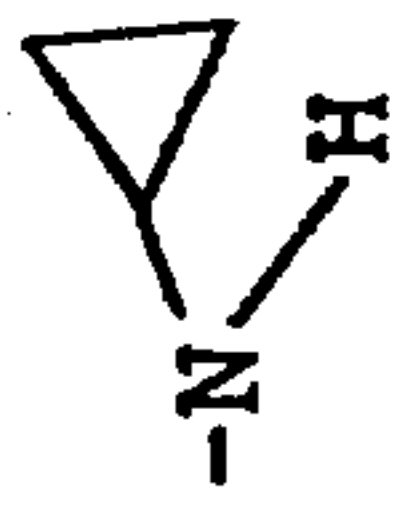
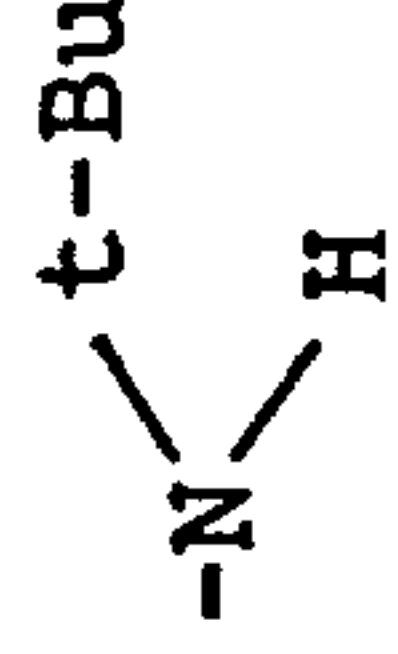
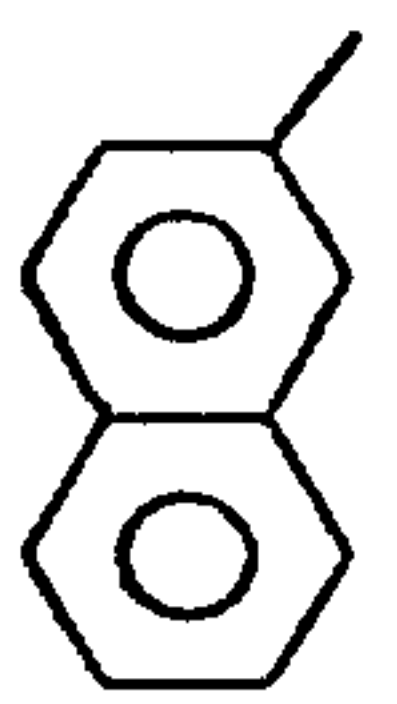
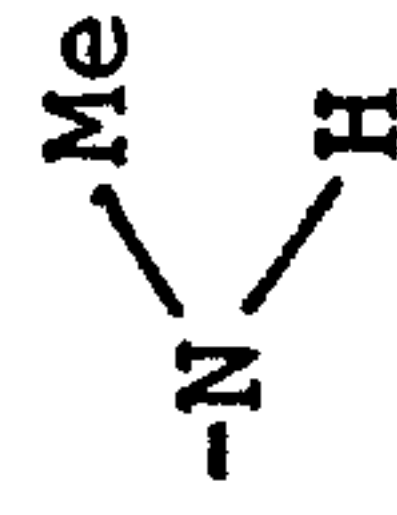
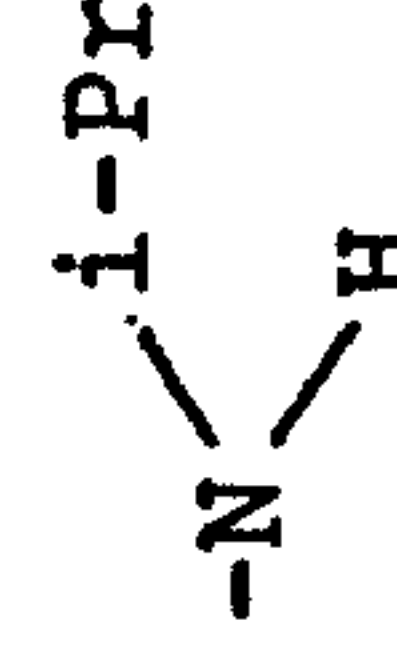


Table 16

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]

1 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.

15 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.

20 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.

25 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

- 1 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.
- 5 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]

10 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
- 15 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 refluxed for 2.5 hours. The
- 20 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
- 25 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

1 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
5 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 chromato-
10 graphy (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
15 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).

20 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,
25 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

1 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
5 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
10 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
15 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
20 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
25 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]

1 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
5 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
10 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:

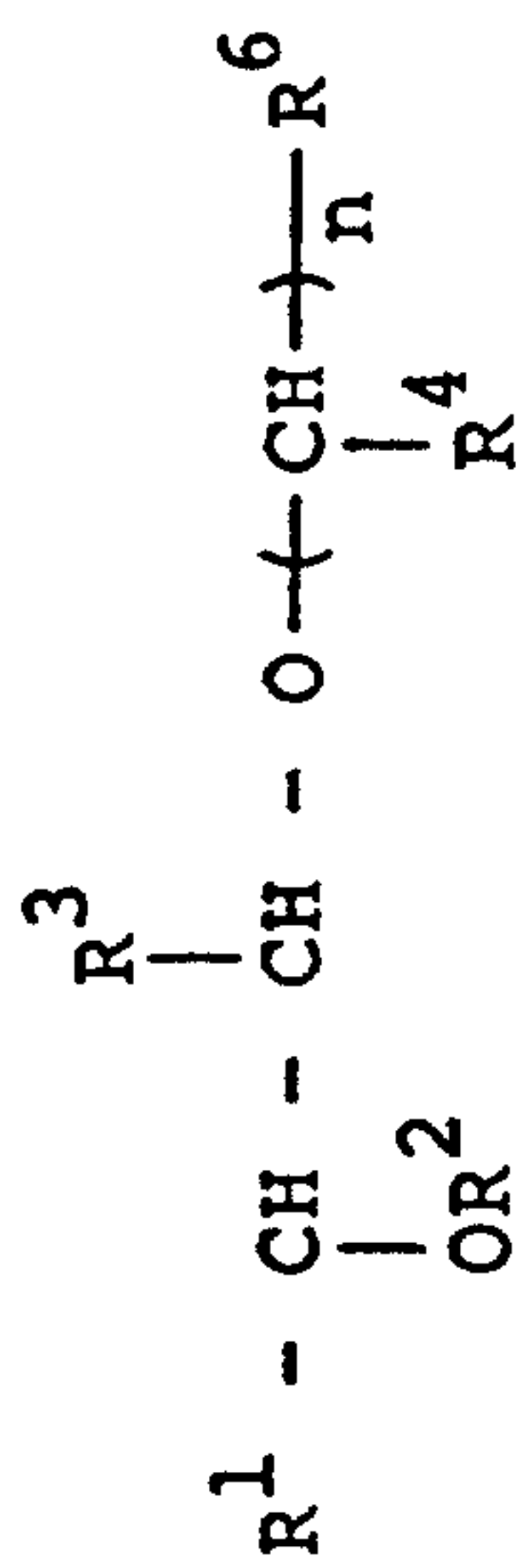
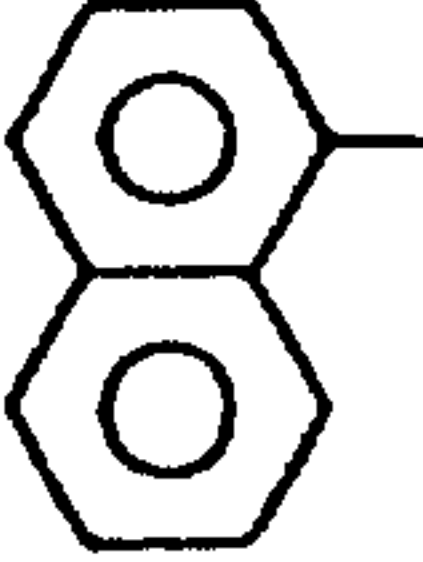
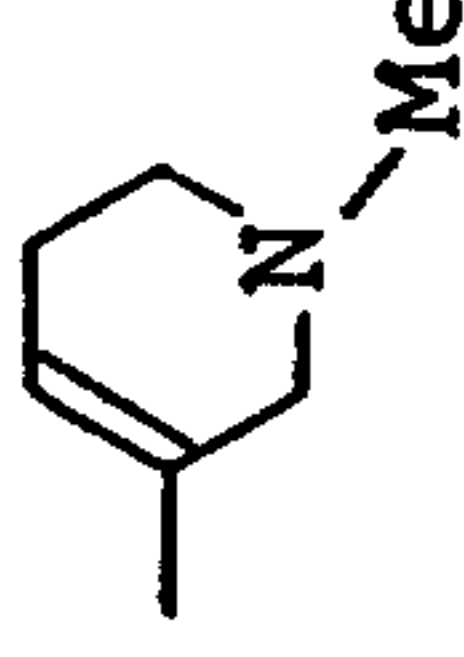
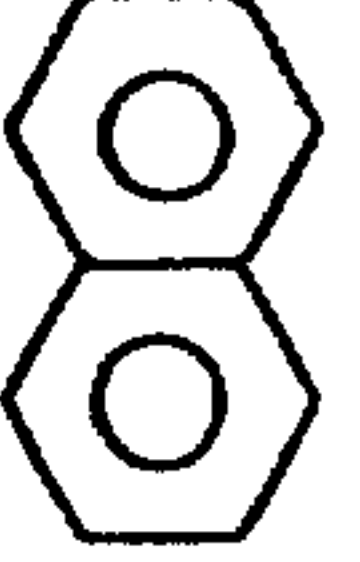


Table 17

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]

1 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
5 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 dihydro-
10 chloride (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
15 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--
20 general formula:

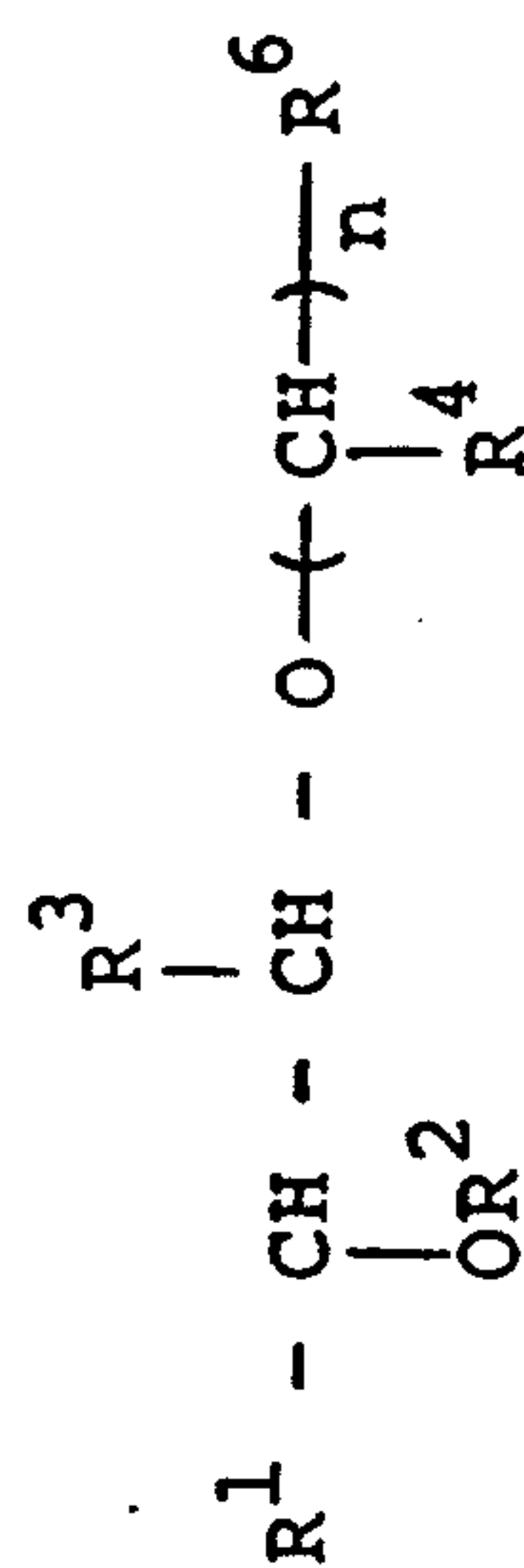
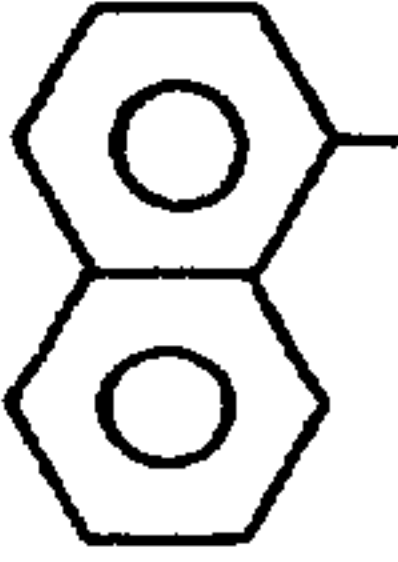
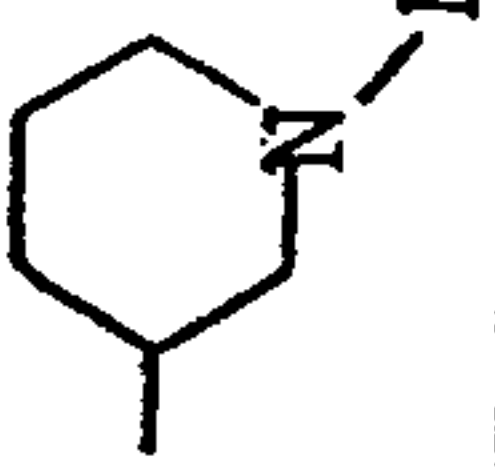
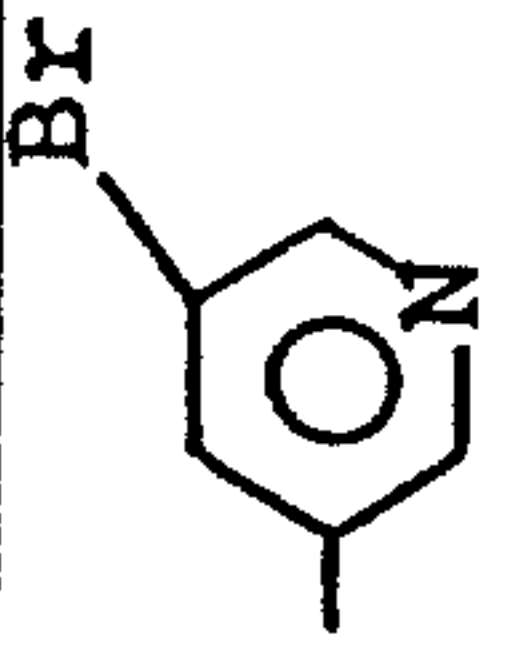


Table 18

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 ₂ O]
276	"	"	"	"		"	"	143-146
277	"	"	"	-		0	"	151.5-154 [EtOH-Et ₂ O]
278	"	"	"	H		1	"	154-156 [EtOH-IPA]

1 Production Example 26

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

- 5 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:

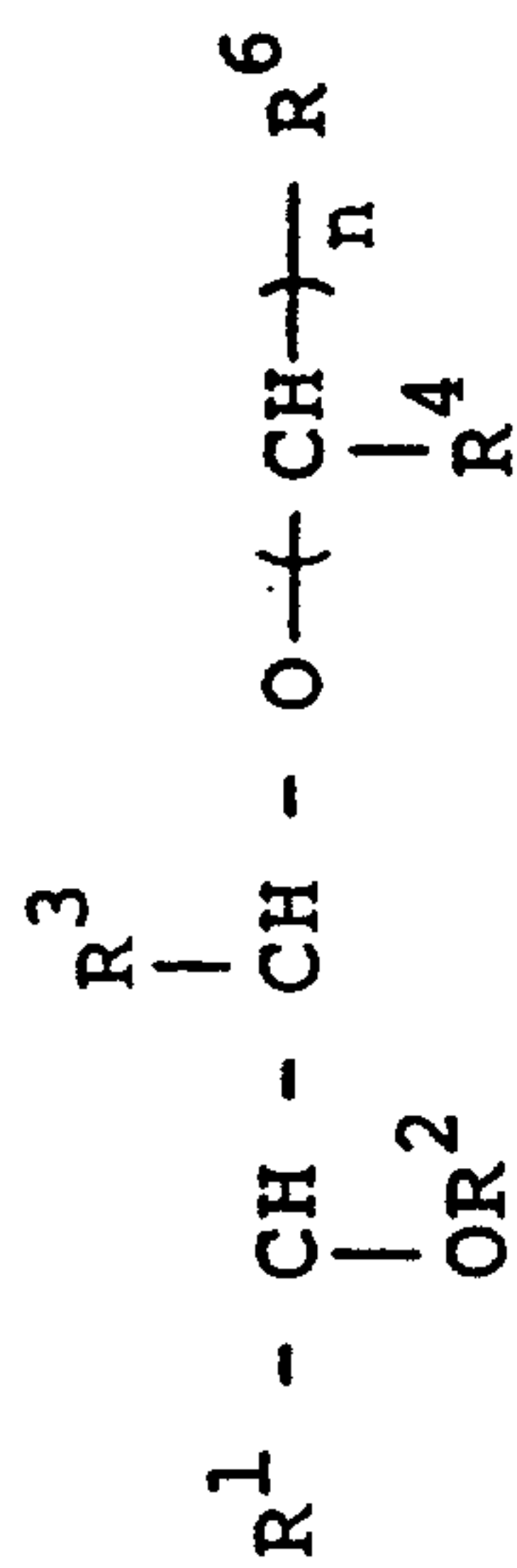
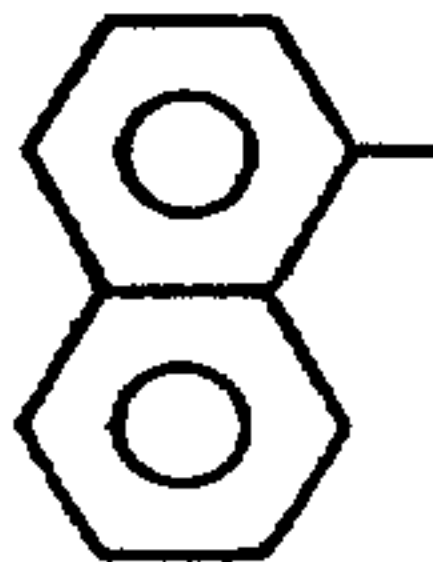
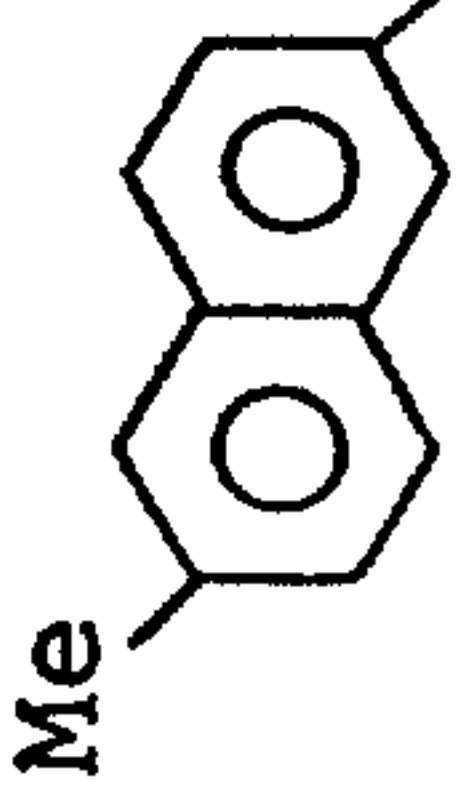


Table 19

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 ₂ CO-AcOEt]
282		"	"	"	"	"	-	138-139 [Me ₂ CO-AcOEt]

1 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
5 (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
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
15 of ammonium chloride. The 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 chloride. The solvent was--
20 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
25 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.

1 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
5 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
10 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
15 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
20 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-H₂O]

 1-(6-Benzyloxy-2-naphthyl)-2-[2-(N,N-dimethyl-
25 amino)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

1 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
5 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
10 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
15 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
20 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
25 crystals 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

1 No. 286).

Melting point: 157-158°C [MeCN]

Production Example 30

A mixture of 2.0 g of 1-acetoxy-1-(6-
5 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
10 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-
15 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-
20 2-naphthyl)-2-[2-(N,N-dimethylamino)ethoxy]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
25 with 10 ml of chloroform. The extracts were combined
with the previously separated organic layer. The combined

1 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
5 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
10 was purified by column chromatography (eluent:
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]-
15 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
20 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).

25 Melting point: 150-158.5°C

1 Production Example 33

A mixture of 150 mg of 2-[2-(N,N-dimethyl-amino)ethoxy]-1-(8-nitro-1-naphthyl)ethanol oxalate, 150 mg of 5% palladium-carbon and 3 ml of methanol was
5 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
10 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
15 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-
20 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]

25 Production Example 34

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

1 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).

5 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-
10 [4-(N,N-dimethylamino)-1-naphthyl]-2-[2-(N,N-dimethyl-
amino)ethoxy]ethanol dihydrochloride (compound No. 292).

Production Example 36

13 ml of ethanol was added to 1.3 g of 1-[4-
N-dimethylamino)-1-naphthyl]-2-[2-(N,N-dimethylamino)-
15 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
20 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
25 reduced pressure to obtain 1.3 g of oily 1-ethoxy-1-
[4-(N,N-dimethylamino)-1-naphthyl]-2-[2-(N,N-dimethyl-

1 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
5 were added, at room temperature, 570 mg of pyridinium p-toluenesulfonate and 4.5 ml of 3,4-dihydro-2H-pyran. The resulting mixture was stirred at the same temperature for 3 hours. The reaction mixture was added to
10 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)
15 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 anhydrous tetra-
hydrofuran under a nitrogen atmosphere. To the solution
20 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
25 room temperature and added to a mixture of 100 ml of ice water, 100 ml of diethyl ether and 2 g of ammonium

1 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
5 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
10 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).

15 (4) A mixture of 2.5 g of 2-[2-(N,N-dimethyl-
amino)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
20 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 =
25 10/1) to obtain 1.9 g of oily 1-acetoxy-2-[2-(N,N-
dimethylamino)ethoxy]-1-[1-(tetrahydropyran-2-yloxy)-

1 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 temperature. 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

1 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-
5 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.
10 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: chloro-
form/methanol = 20/1) to obtain a yellow oily product.
15 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-dimethyl-
20 amino)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
25 Production Example 22, 1-[(1-hydroxy)indan-5-yl]-2-
[2-(N,N-dimethylamino)ethoxy]ethanol hydrochloride

1 (compound No. 299) was obtained.

Melting point: 150-152°C [IPA]

Production Example 39

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

Production Example 40

10 The compound obtained from 2-[2-(6-methyl-
naphthyl)]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 hydro-
chloride in Production Example 22, to obtain oily
15 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
20 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:

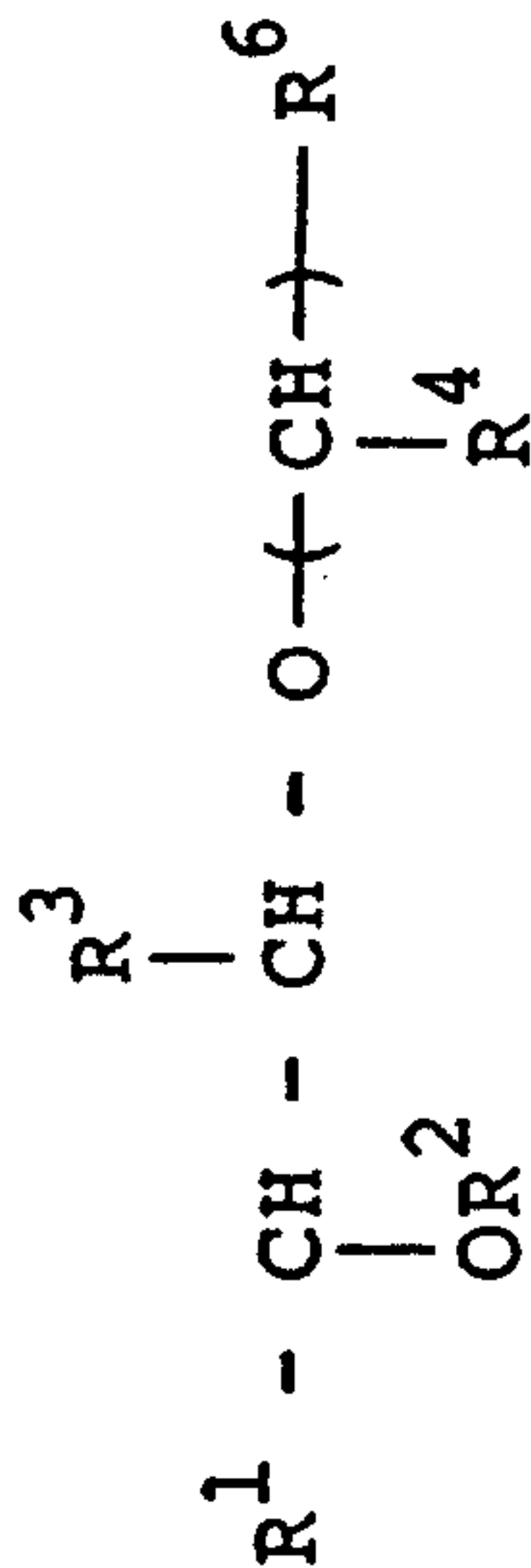


Table 20

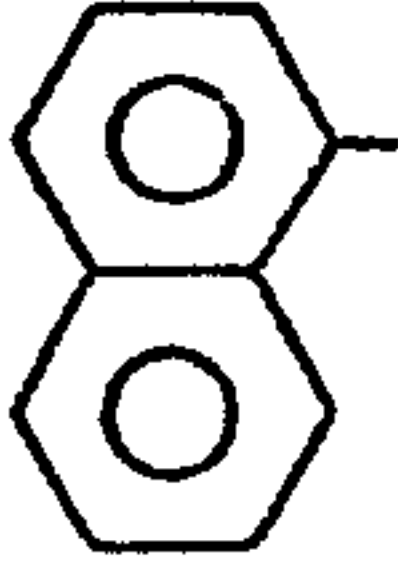
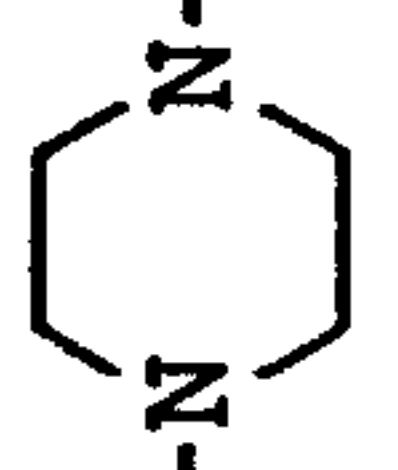
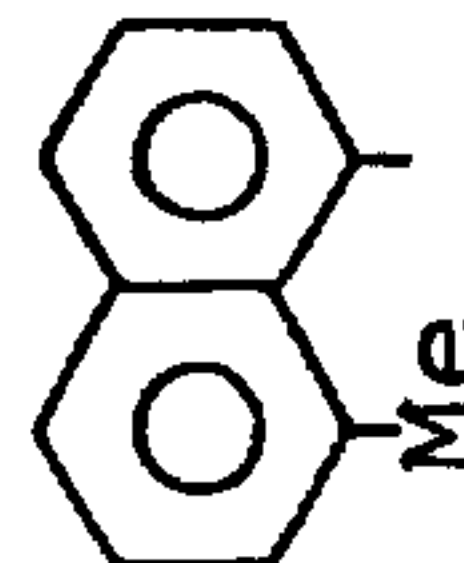
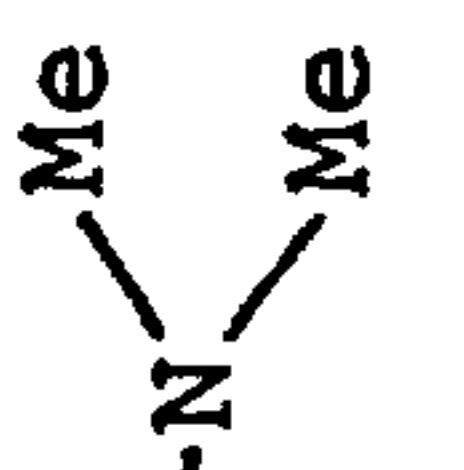
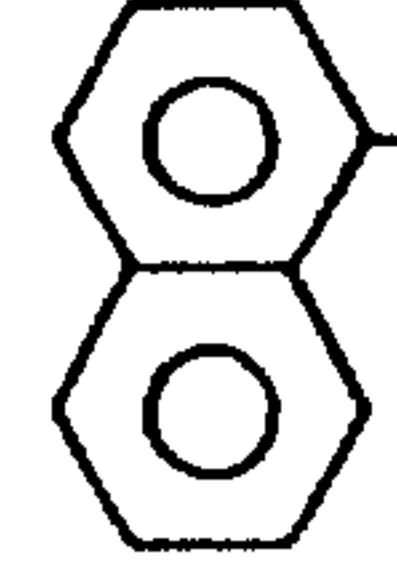
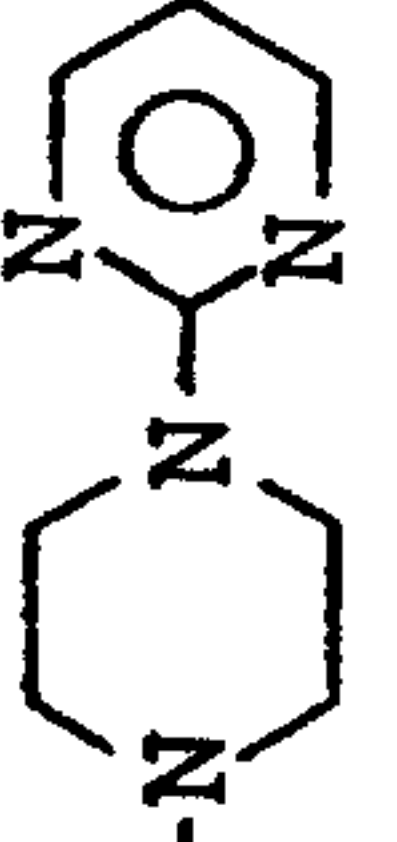
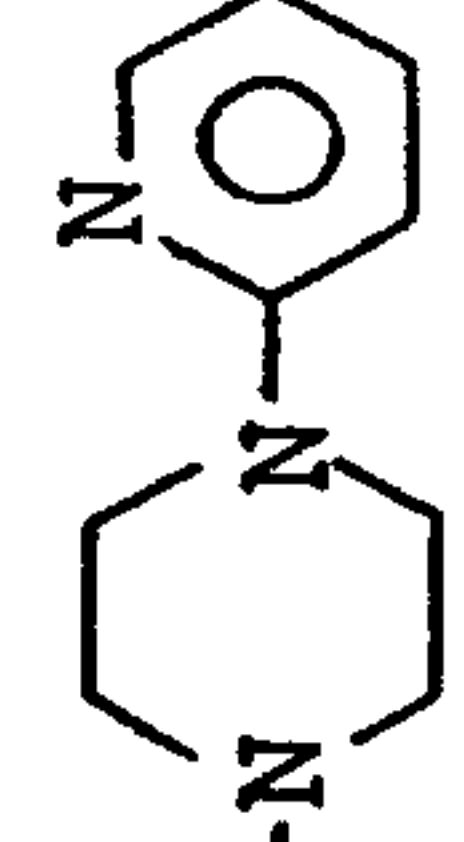
Compound No.	R ¹	R ²	R ³	R ⁴	R ⁶	n	Addition salt	Melting point (°C)
302		H	H	H		2	2HCl	237-238 (decomp.) [EtOH-H ₂ O]
303		"	"	"		"	HCl	191-191.5 [IPA]
304		"	"	"		"	2HCl	175-176.5 (decomp.) [EtOH]
305	"	"	"	"		"	"	122-124 [EtOH]

Table 20 (Cont'd)

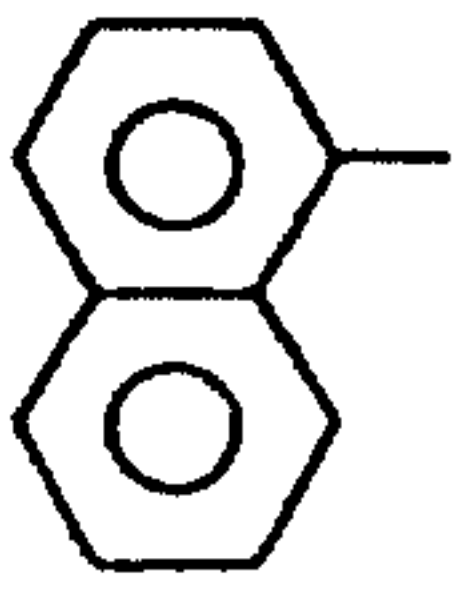
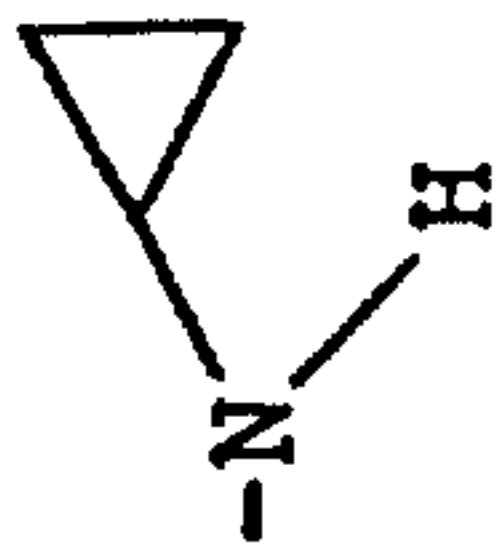
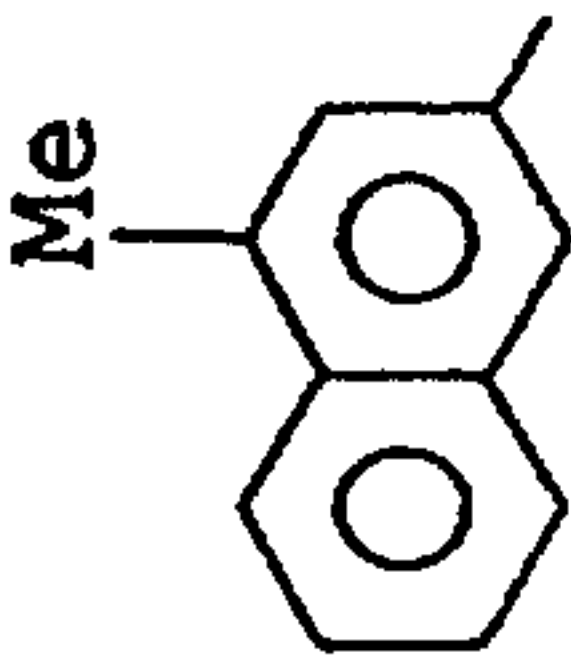
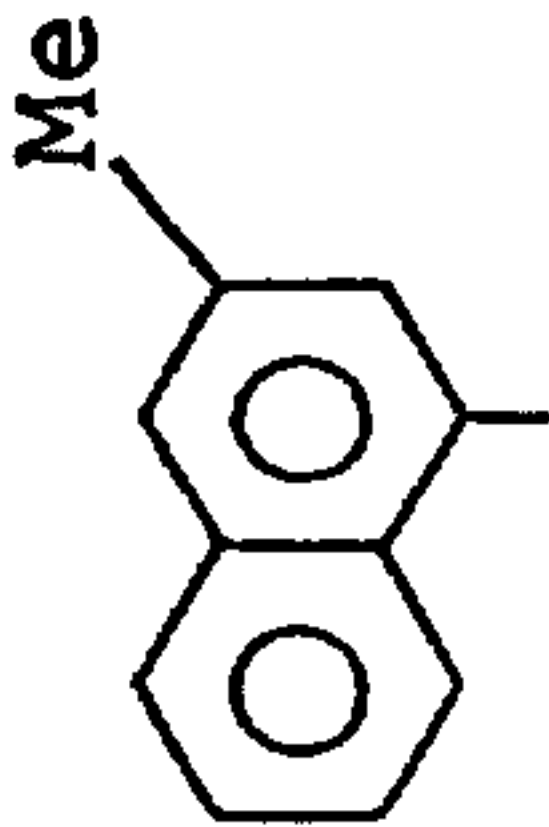
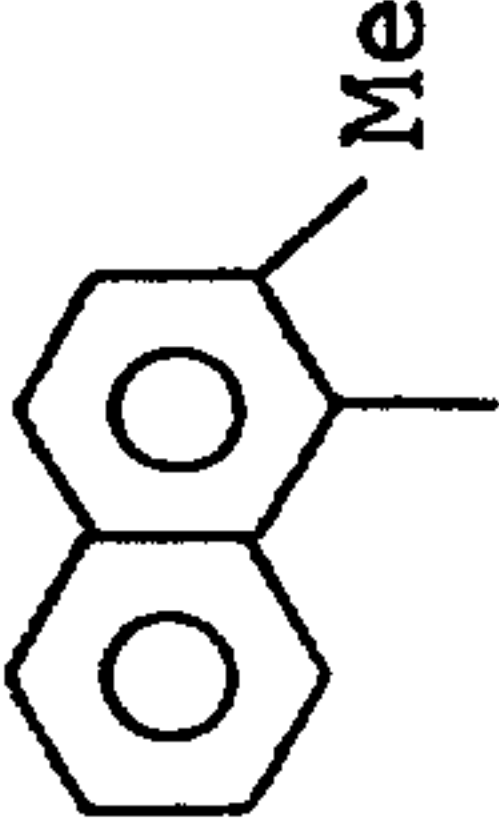
306		H	H	H	-N ^{Me} ₂	3	-	119-120 [AcOEt]
307	"	"	"	"	-N ^{i-Pr} ₂	"	HCl	139-140.5 [EtOH-AcOEt]
308	"	"	"	"		"	"	111.5-112 [EtOH-AcOEt]
309		"	"	"	-N ^{Me} ₂	2	"	186-187 [EtOH-AcOEt]

Table 20 (Cont'd)

310		H	H	H	-N<MeMe	2	HCl	160-161.5 [EtOH-AcOEt]
311		"	"	"	"	"	"	149-150 [EtOH-Me ₂ CO]

1 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 drop-
5 wise 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
10 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
15 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,
20 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 hydrogen chloride-ethanol
25 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

21 60270

- 1 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-Me₂CO]

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

In Table 21, R¹, R², R³, R⁴, R⁶ and n each show a substituent or integer used in the following formula:

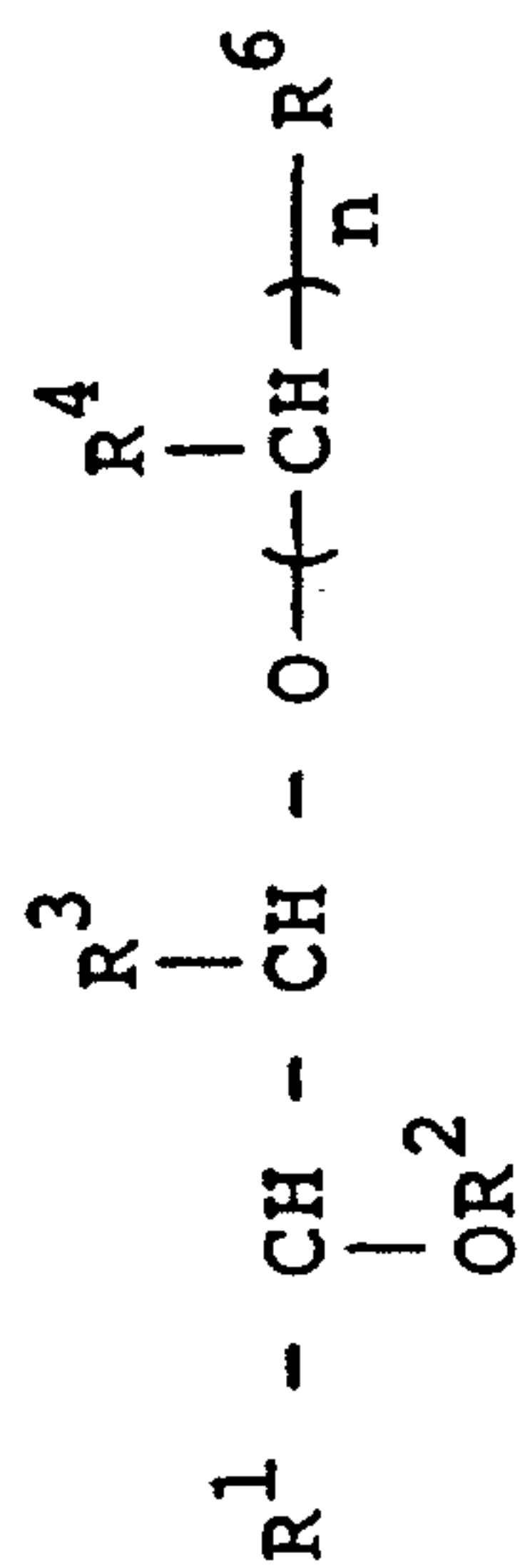


Table 21

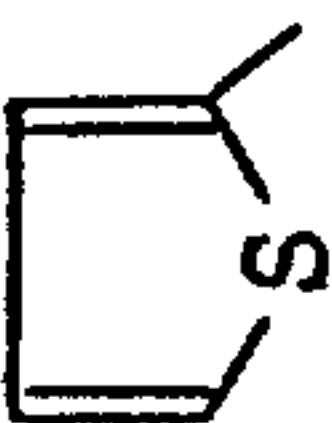
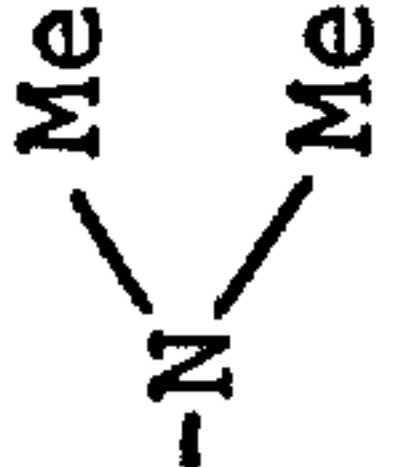
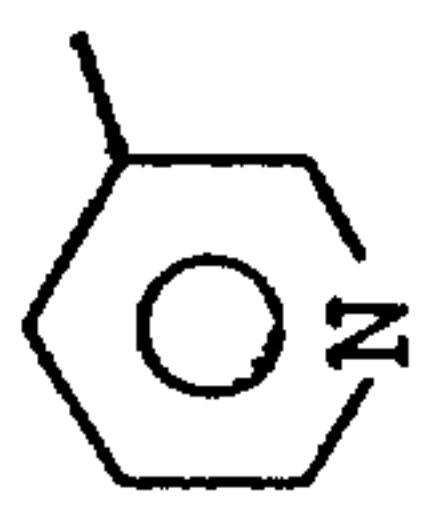
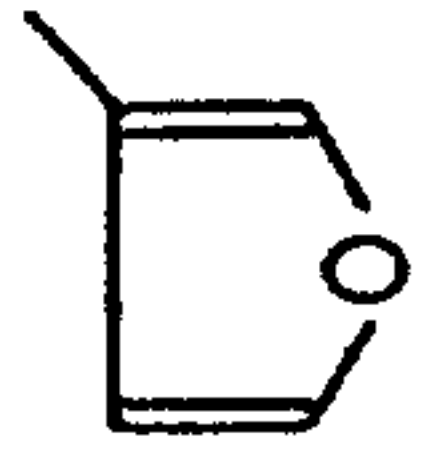
Compound No.	R ¹	R ²	R ³	R ⁴	R ⁶	n	Addition salt	Melting point (°C)
313		H	H	H		2	HCl	139-141
314		"	"	"	"	"	"	165.5-166 [EtOH-Et ₂ O]
315		"	"	"	"	"	2HCl	143-146 [EtOH]
316		"	"	"	"	"	HCl	128.5-130 [EtOH]

Table 21 (Cont'd)

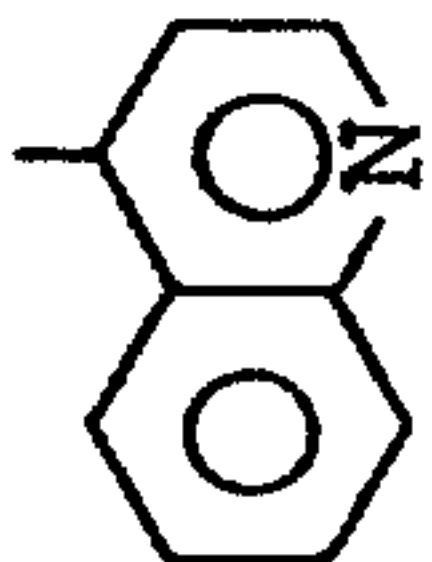
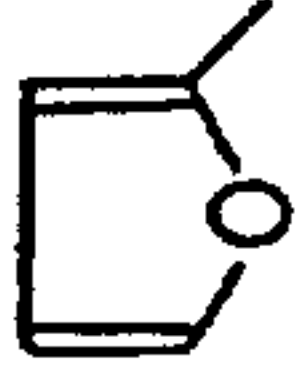
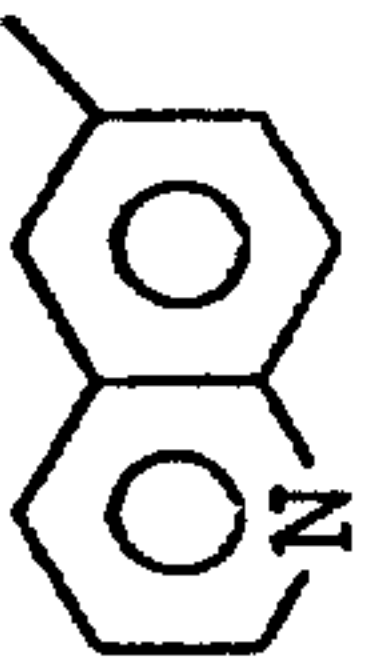
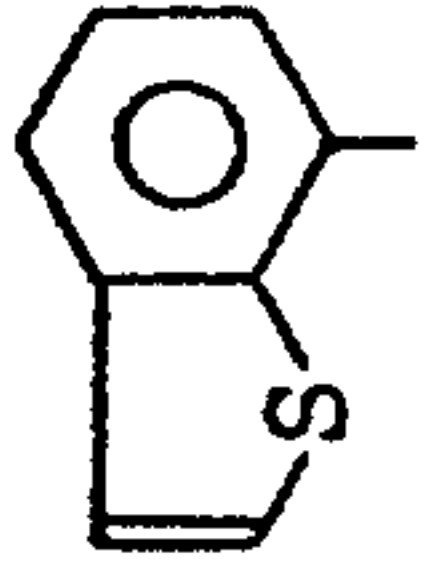
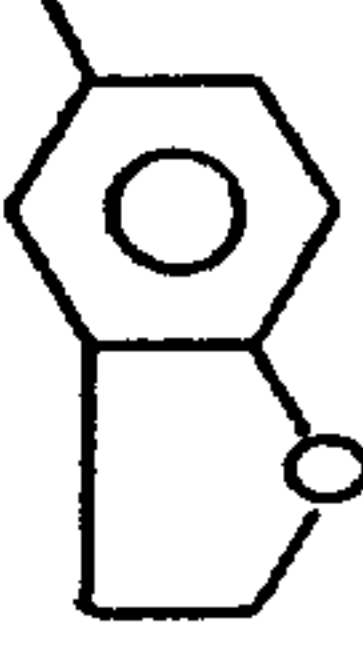
317		H	H	H	-N<Me Me	2	2HCl	185-185.5 [EtOH-IPA]
318		"	"	"	"	"	HCl	128-130
319		"	"	"	"	"	Fumaric acid	136-136.5 [IPA]
320		"	"	"	"	"	HCl	166.5-167.5 [IPA-ACOEt]
321		"	"	"	"	"	"	168.5-169.5 [IPA]

Table 21 (Cont'd)

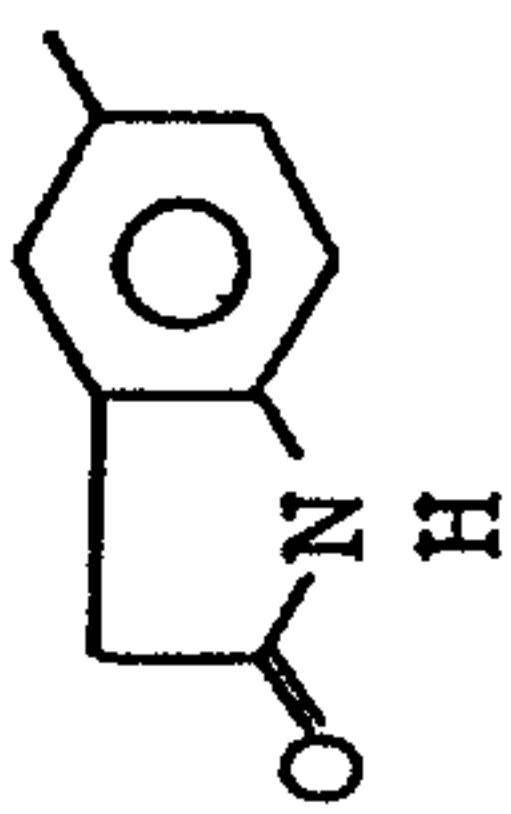
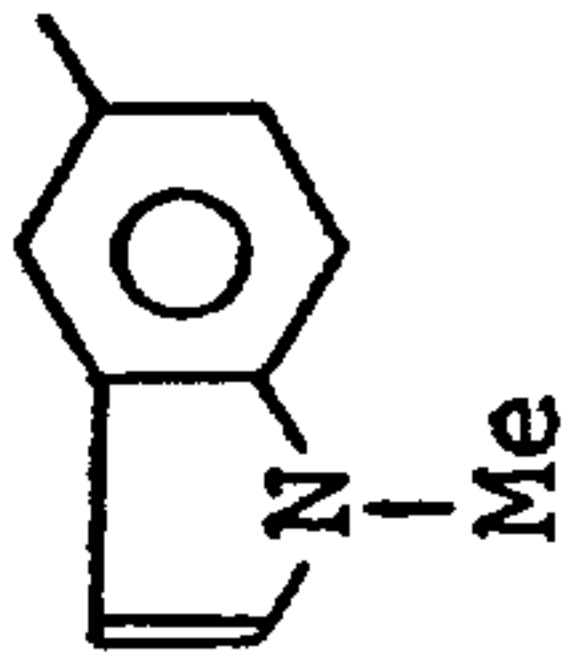
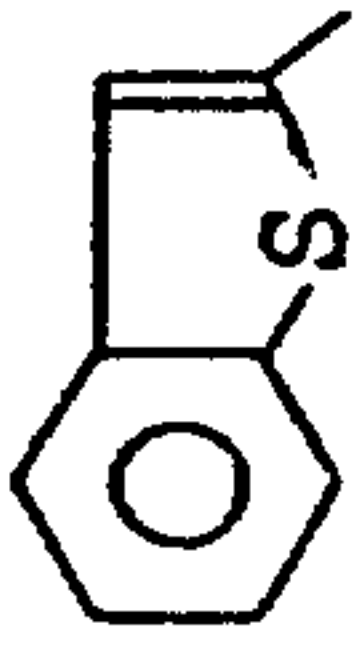
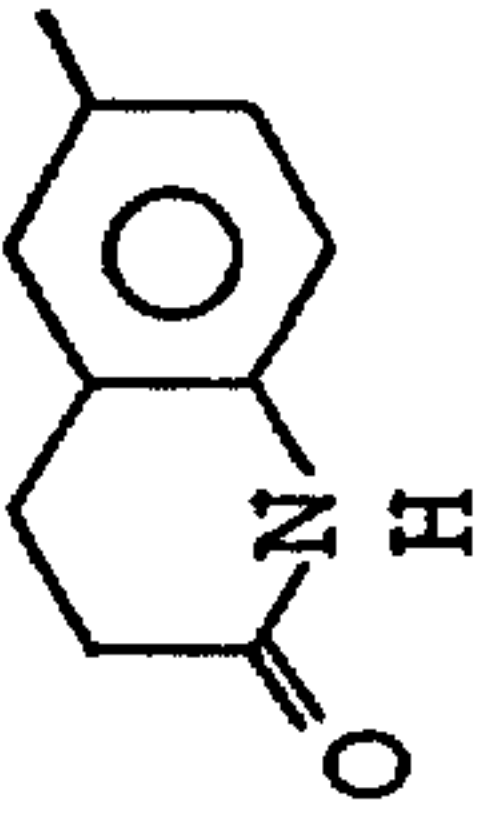
322		H	H	H	-N<Me<Me	2	HCl	169-170
323		"	"	"	"	"	-	Oily
324		"	"	"	"	"	"	188.5-189 [EtOM-ACOEt]
325		"	"	"	"	"	"	168-169.5 [IPA-ACOEt]
326		"	"	"	"	"	"	169-172 [EtOH]

Table 21 (Cont'd)

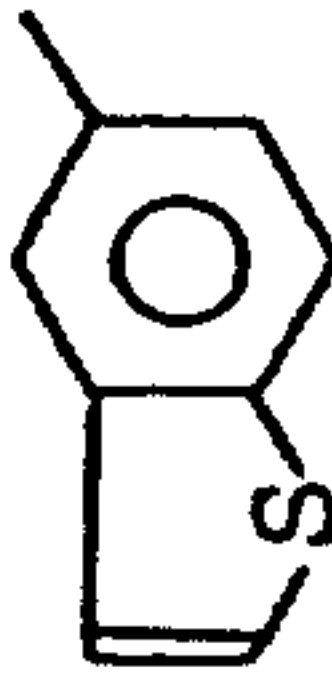
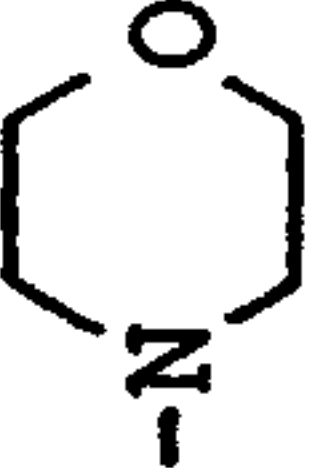
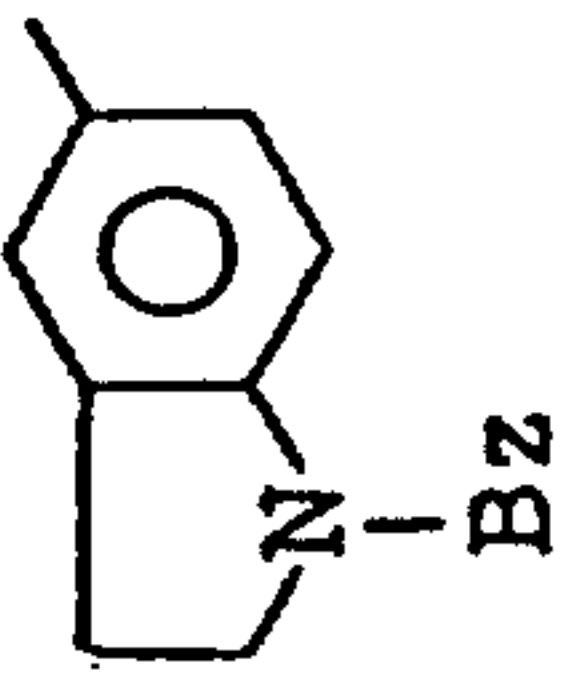
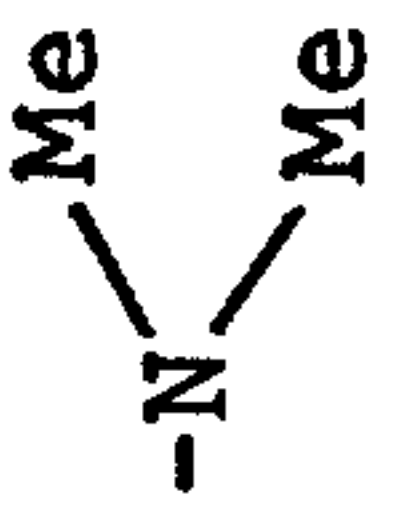
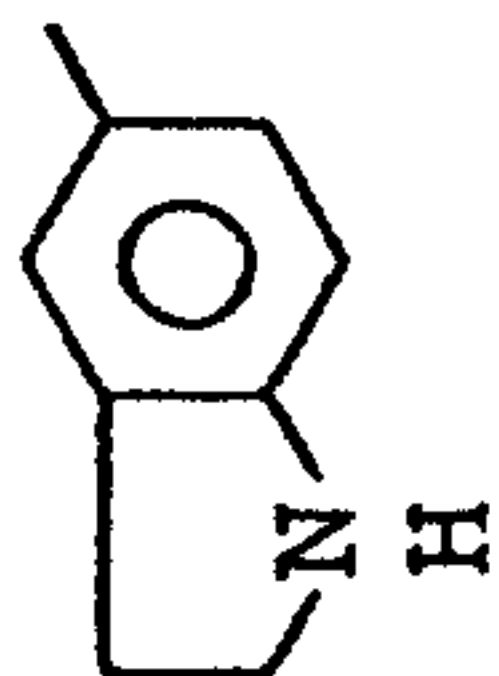
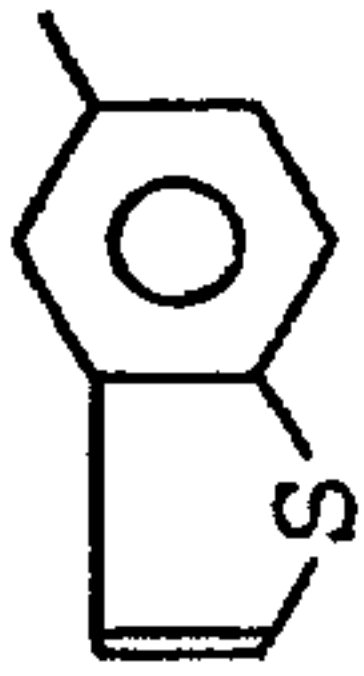
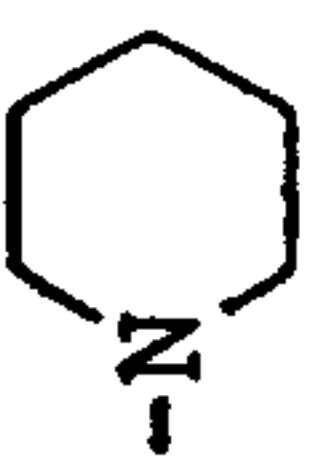
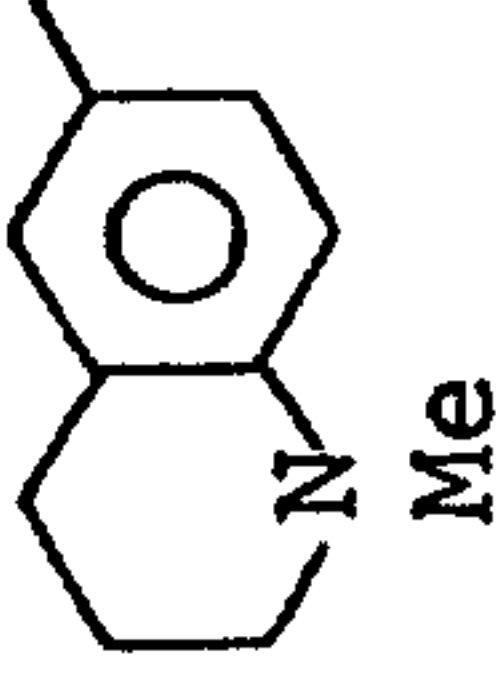
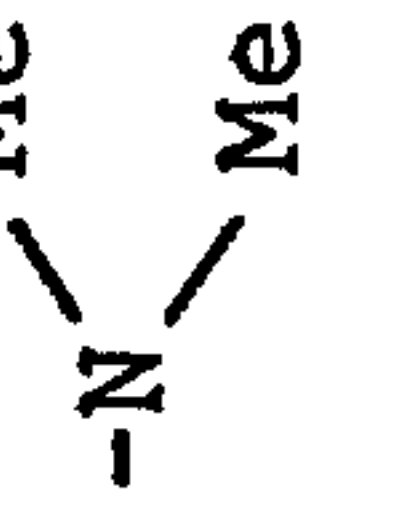
327		H	H	H		2	HCl	166.5-167.5 [EtOH-Me ₂ CO]
328		"	"	"		"	-	Oily
329		"	"	"	"	"	2HCl	"
330		"	"	"		"	HCl	167.5-169
331		"	"	"		"	2HCl	Oily

Table 21 (Cont'd)

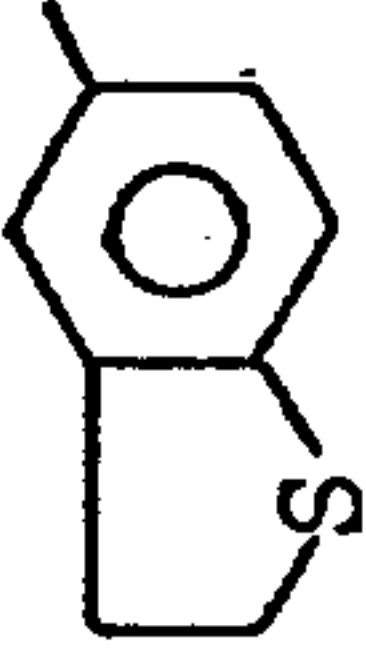
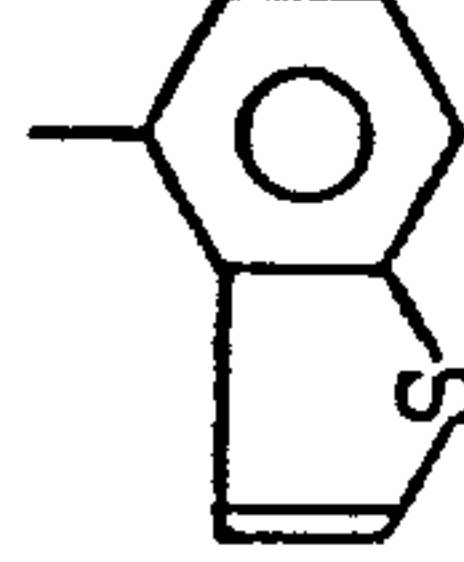
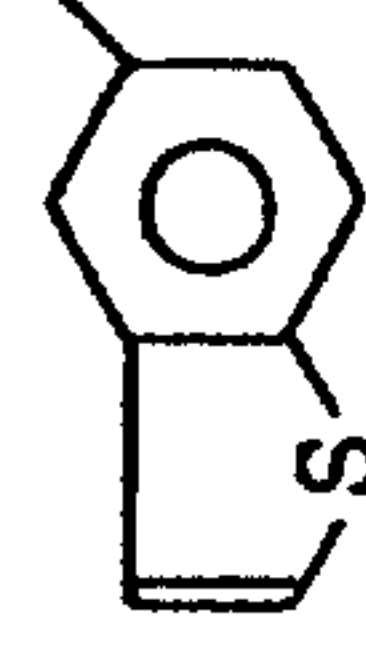
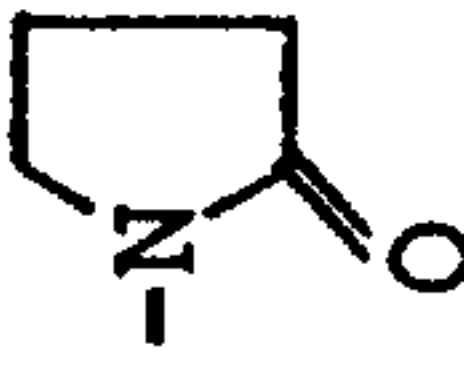
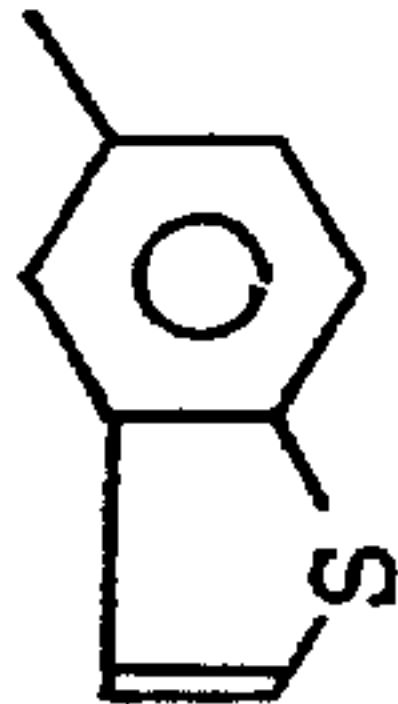
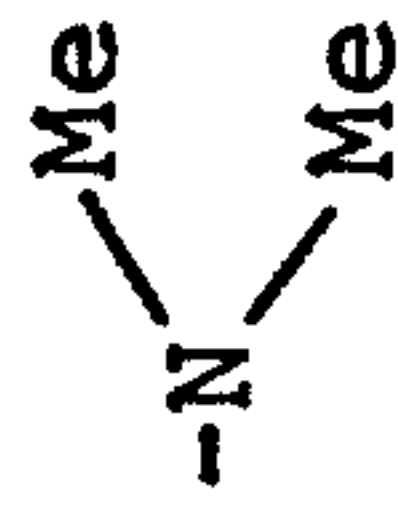
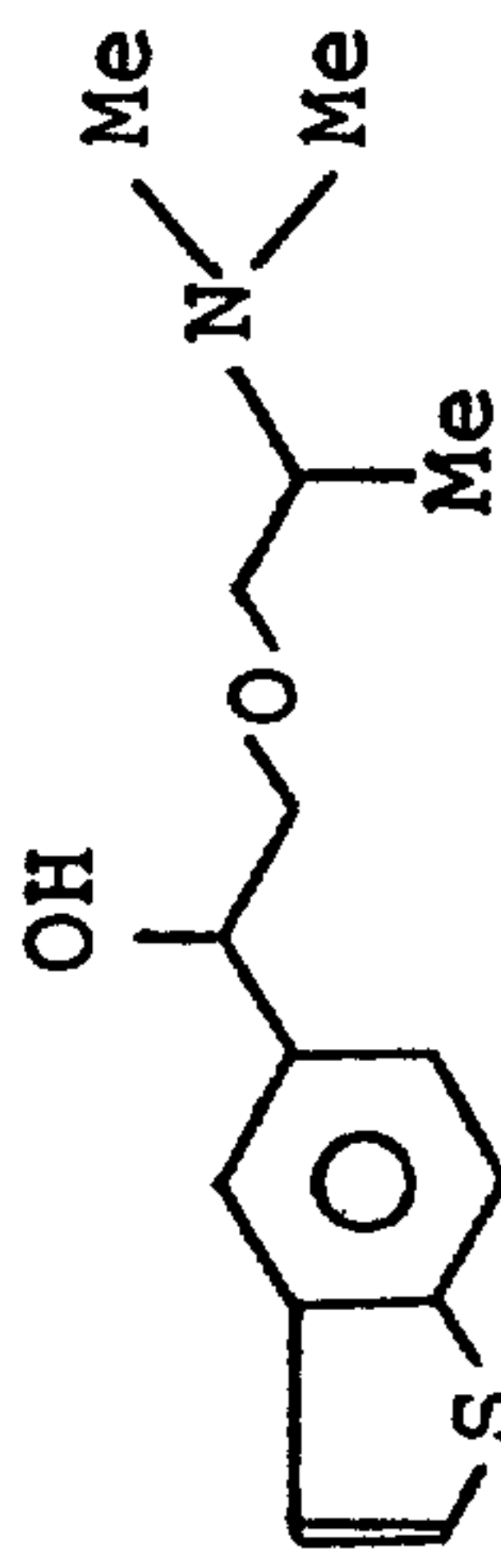
332		H	H	H	-N(Me)Me	2	HCl	207.5-210 [EtOH]
333		"	"	"	"	"	"	190.5-192 [EtOH-IPA]
334		"	"	"	"	"	"	171-172 [IPA-ACOEt]
335		"	"	"		"	-	Oily
336	"	"	"	"	-N(Me)Me	3	-	81.5-85

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.

1 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
5 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
10 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
15 over anhydrous magnesium sulfate. The solvent was
removed by distillation under reduced pressure. The
residue thus obtained was purified by column chromato-
graphy (eluant: chloroform/ethanol = 50/1) to obtain
0.56 g of 1-(benzo[b]furan-5-yl)-2-(pyridin-3-yl-methoxy)-
20 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
25 show a substituent or integer used in the following
formula:

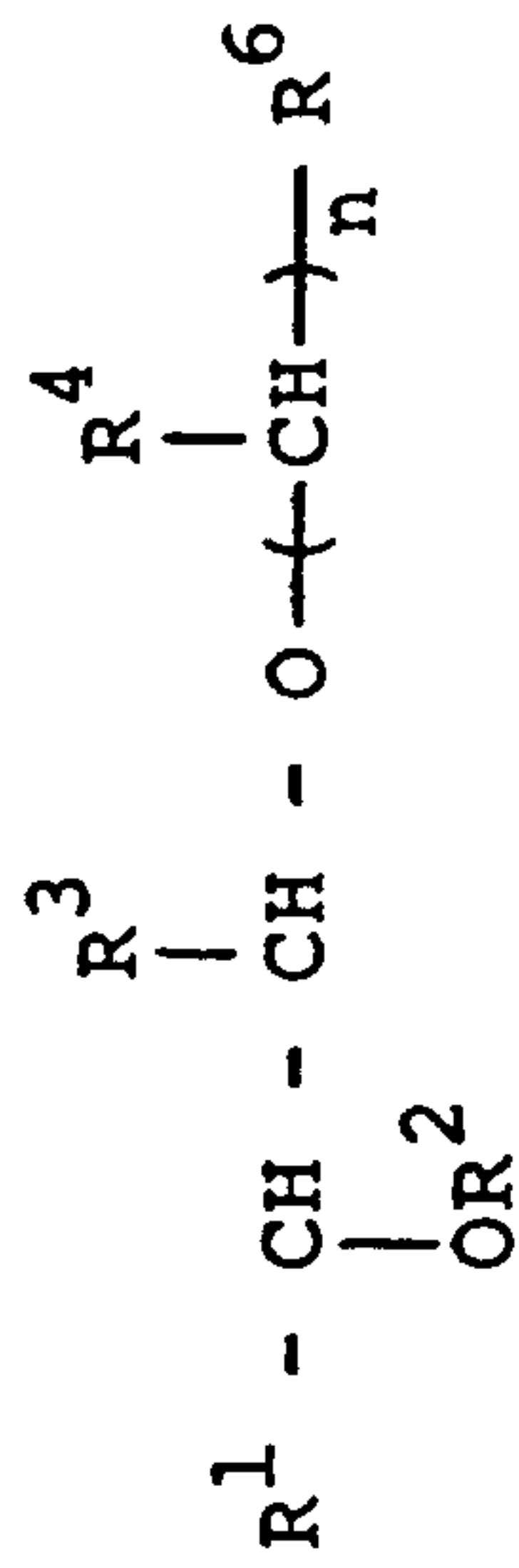


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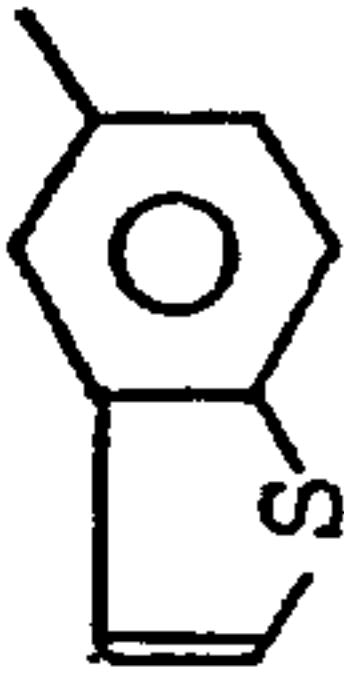
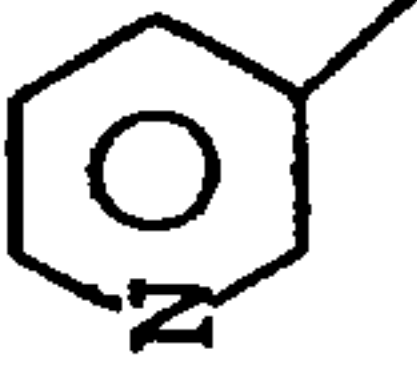
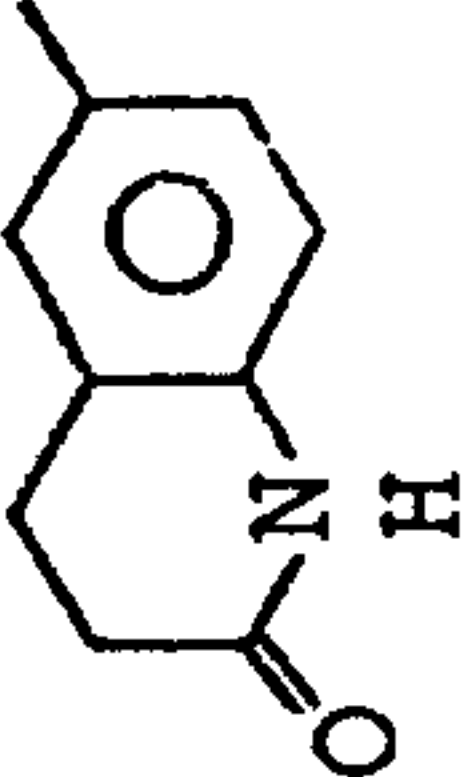
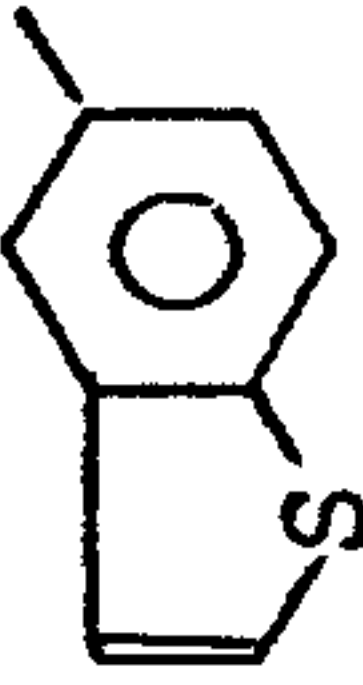
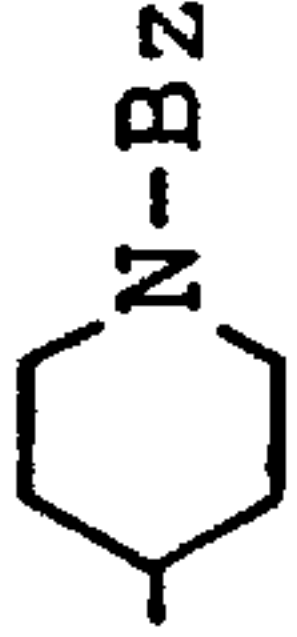
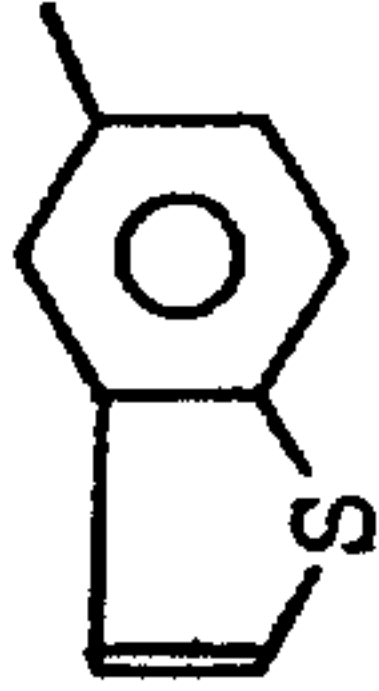
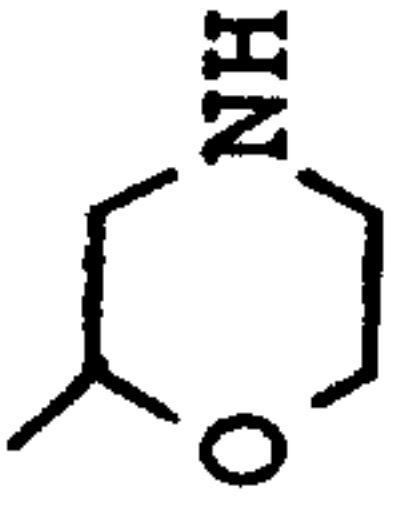
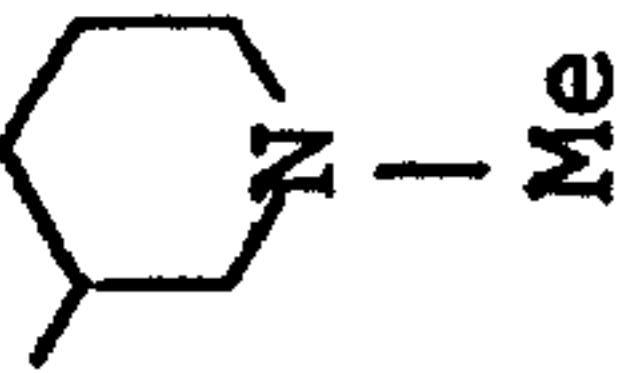
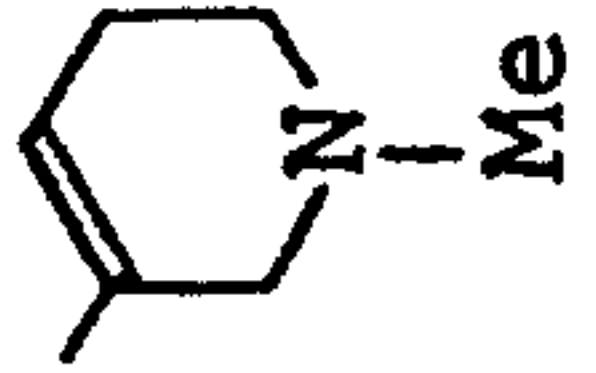
Compound No.	R ¹	R ²	R ³	R ⁴	R ⁶	n	Addition salt	Melting point (°C)
340		H	H	H		1	-	106.5-107.5 [AcOEt-IPE]
341		"	"	"	"	"	HCl	Oily
342		"	"	"		2	-	"

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]

1 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

1 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
5 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
10 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.

15 (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 dis-
solved in 40 ml of methylene chloride. The mixture was
20 stirred at the same temperature 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]-
25 thiophen-5-yl)-1-(2-tetrahydropyranyloxy)-2-[2-(p-
toluenesulfonyloxy)ethoxy]ethane.

1 (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
5 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
10 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
15 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%
20 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
25 magnesium sulfate. The solvent was removed by distil-
lation 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

1 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
5 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-Me₂CO]

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

In Table 23, R¹, R², R³, R⁴, R⁶ and n each
show a substituent or integer used in the following
formula:

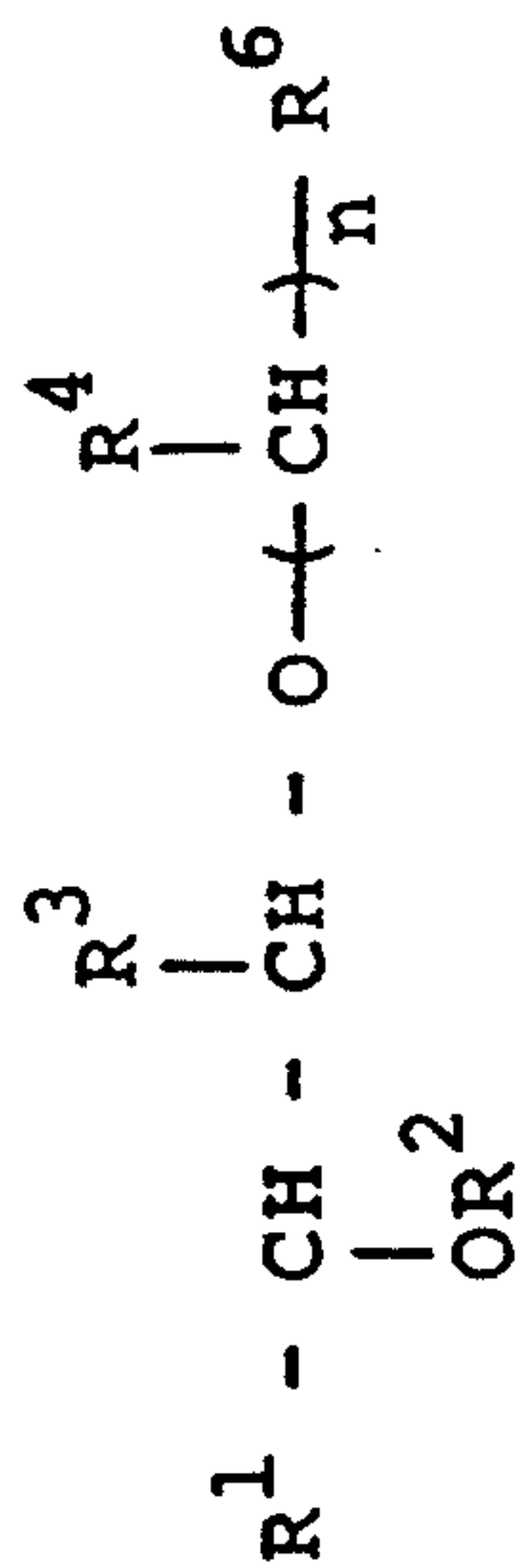


Table 23

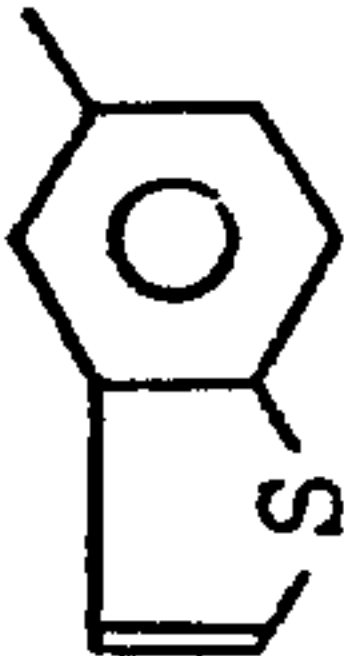
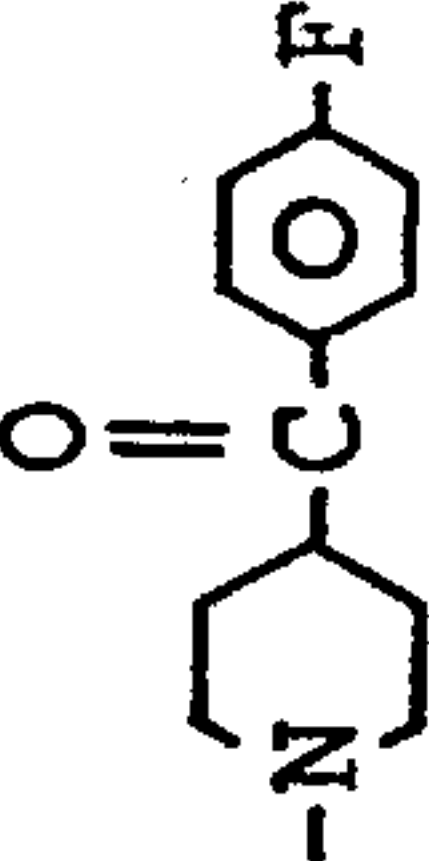
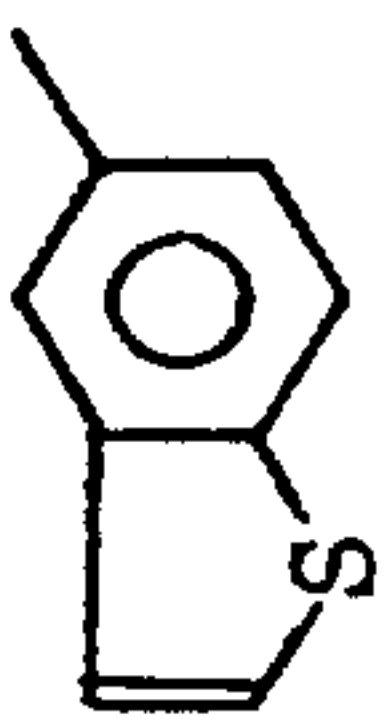
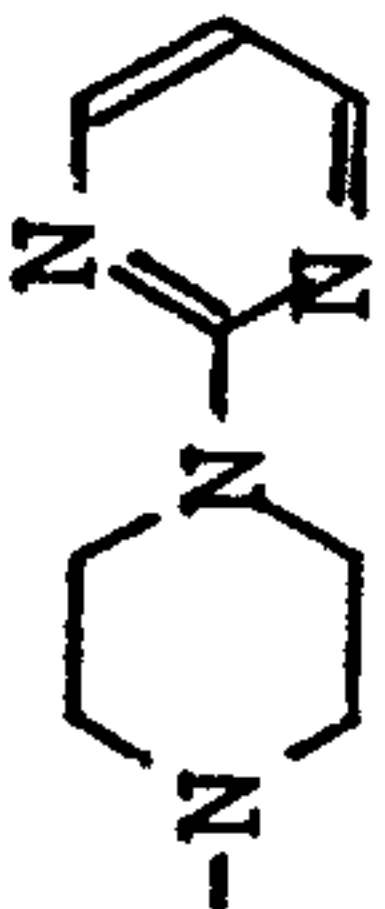
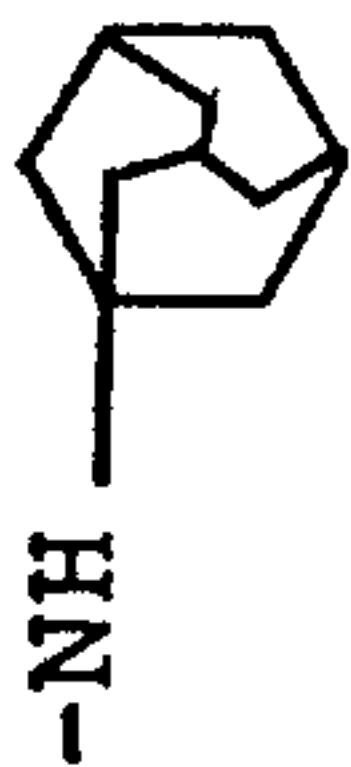
Compound No.	R ¹	R ²	R ³	R ⁴	R ⁶	n	Addition salt	Melting point (°C)
348		H	H	H		2	HCl	196.5-197.5 [EtOH-Me ₂ CO]
349	"	"	"	"		"	2HCl	232-234 [MeOH-Me ₂ CO]
350	"	"	"	"		"	HCl	219.5-220 [EtOH-ACOEt]

Table 23 (Cont'd)

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

1 Production Example 45

- (1) The same procedure as in Production Example 43 was repeated, except that 2-(benzo[b]furan-5-yl)-oxirane and the 3-pyridinemethanol were replaced by 5 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 10 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 15 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.)

20 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 25 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

1 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
5 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 distil-
lation under reduced pressure. To the residue thus
10 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
15 50 ml of ethyl acetate and 30 ml of water. The result-
ing 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
20 aqueous layer. To the combined aqueous layer was
added 50 ml of methylene chloride and 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
25 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]

1 (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
5 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-
10 (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)-
15 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,
20 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

25 0.46 g of 1-(benzo[b]thiophen-5-yl)-2-(2-
aminoethoxy)ethanol was dissolved in a mixture of 5 ml

1 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
5 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
10 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
15 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
20 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
25 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]-

- 1 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

- 5 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.
- 10 The resulting mixture was stirred at the same tem-
perature 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
- 15 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
- 20 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 distil-
lation under reduced pressure. The residue thus obtained
- 25 was purified by column chromatography (eluant:
chloroform/ethanol = 10/1). The resulting oily product
was dissolved in 3 ml of ethanol. To the solution

1 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
5 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).

10 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
15 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
20 2 g of ammonium chloride. The resulting mixture was
adjusted to pH 2 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
25 was separated, washed with water and a saturated
aqueous sodium chloride solution in this order, and
dried over anhydrous magnesium sulfate. The solvent

1 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

1 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
5 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
10 show a substituent or integer used in the following
formula:

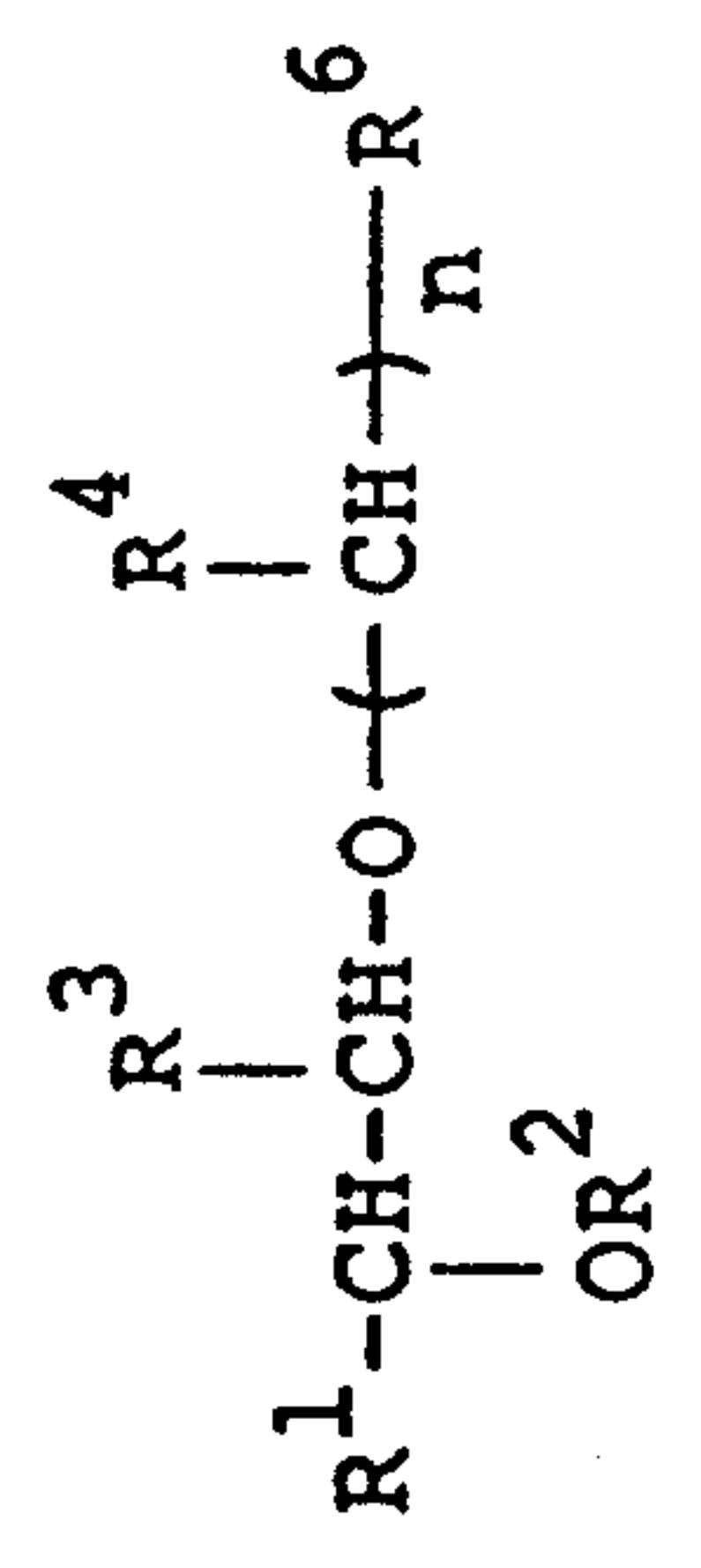


Table 24

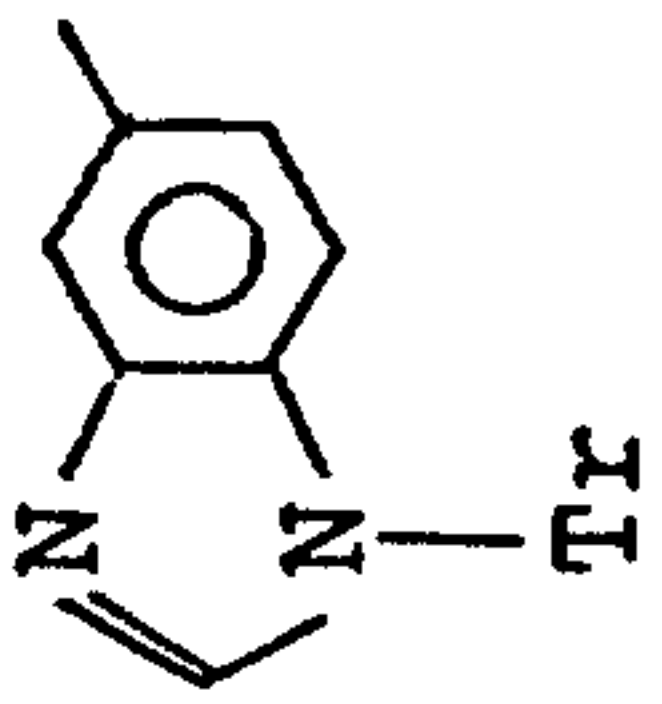
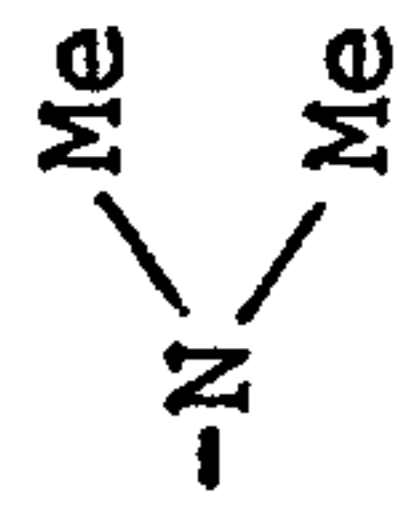
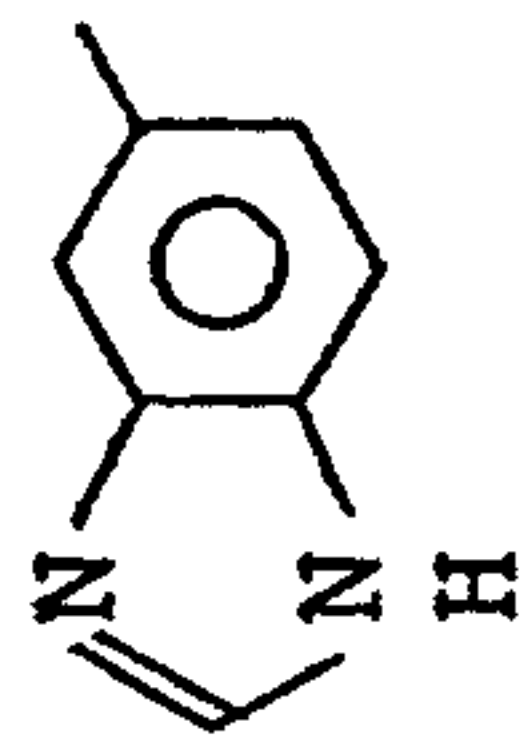
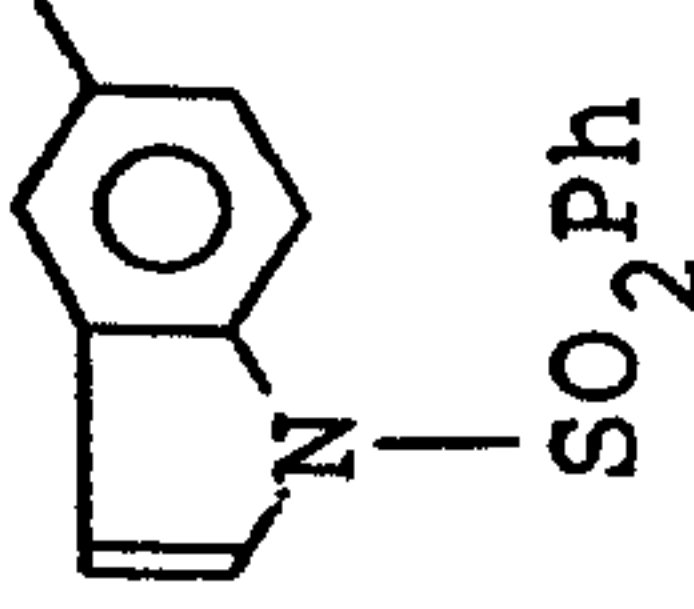
Compound No.	R ¹	R ²	R ³	R ⁴	R ⁶	n	Addition salt	Melting point (°C)
362		H	H	H		2	-	Oily
*1 363		"	"	"	"	"	2HCl	185-186.5 [EtOH-AcOEt]
364		"	"	"	"	"	-	Oily

Table 24 (Cont'd)

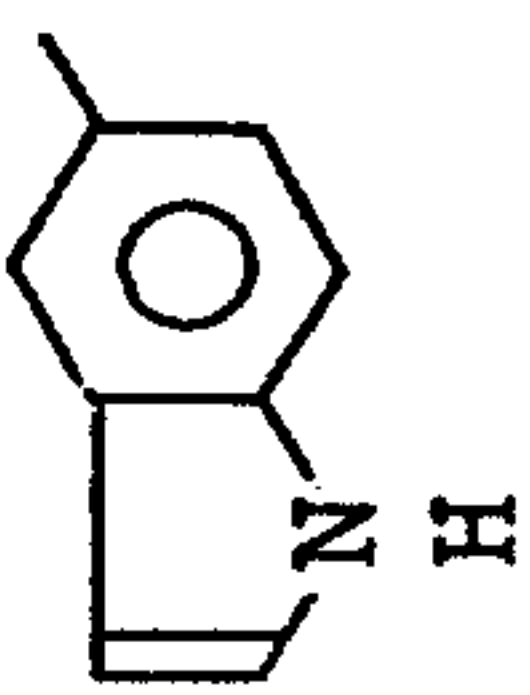
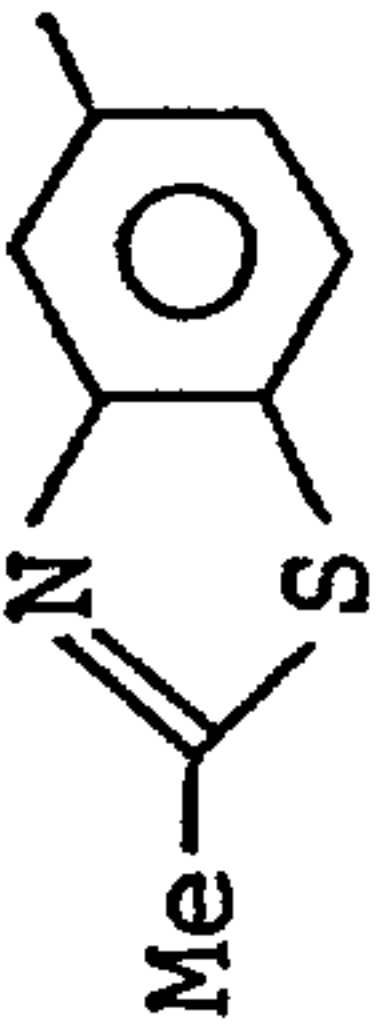
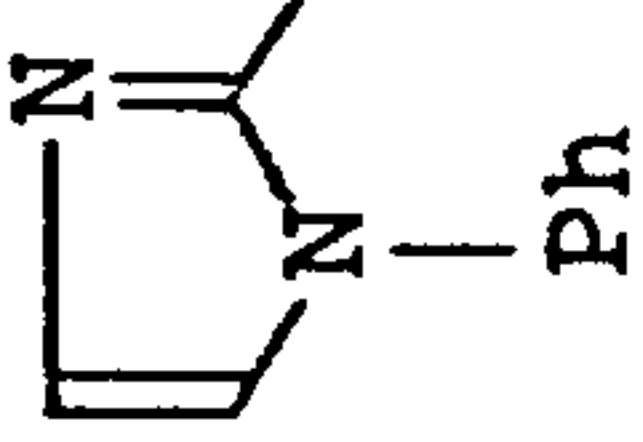
365 *2		H	H	H	-N<Me Me	"	2	-	Oily
366		"	"	"	"	"	"	HCl	175-176 [EtOH-AcOEt]
367		"	"	"	"	"	"	2HCl	Oily
368		"	"	"	"	"	"	HCl	182.5-183 [EtOH-AcOEt]

Table 24 (Cont'd)

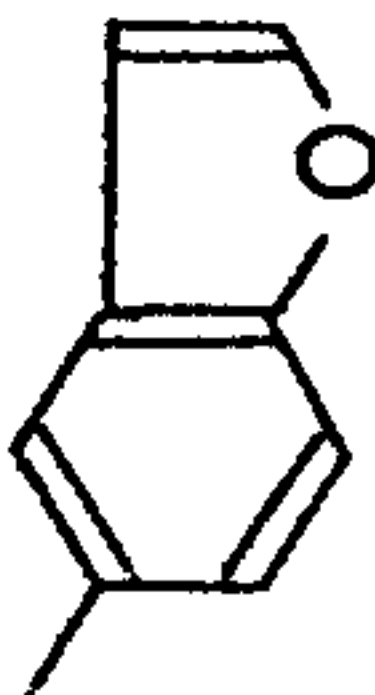
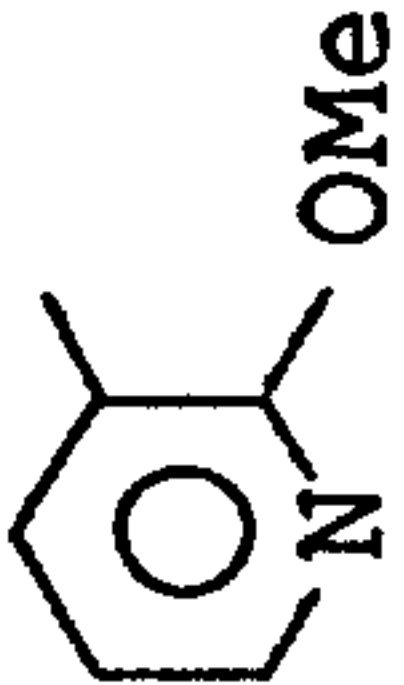
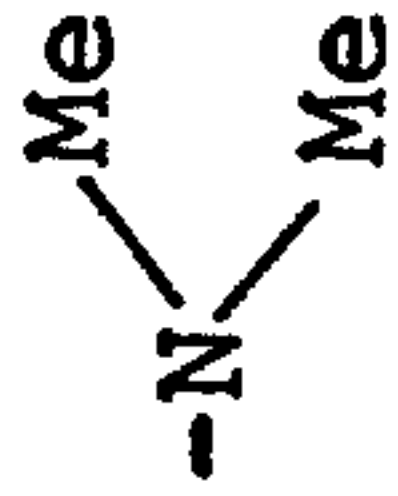
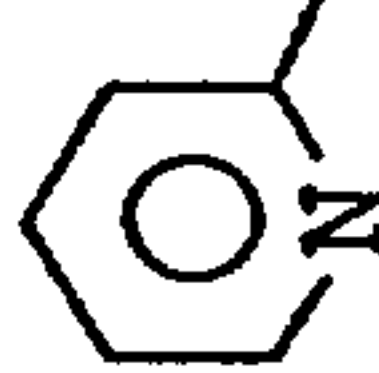
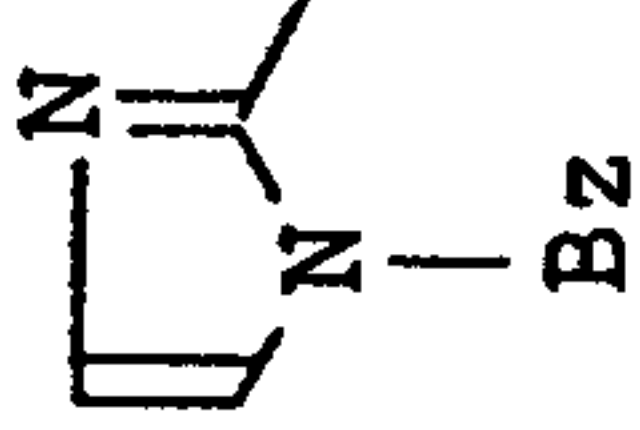
369		H	H	H	-NH ₂	2	1/2 Fumaric acid	170-173
370		"	"	"		"	2HCl	116-117 [EtOH-Me ₂ CO]
371		"	"	"	"	"	"	179-179.5 [EtOH-AcOEt]
372		"	"	"	"	"	"	155-156 [EtOH-AcOEt]

Table 24 (Cont'd)

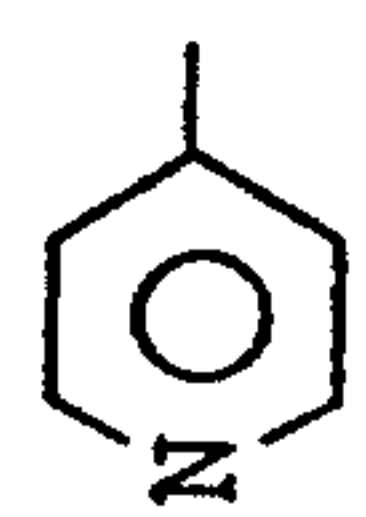
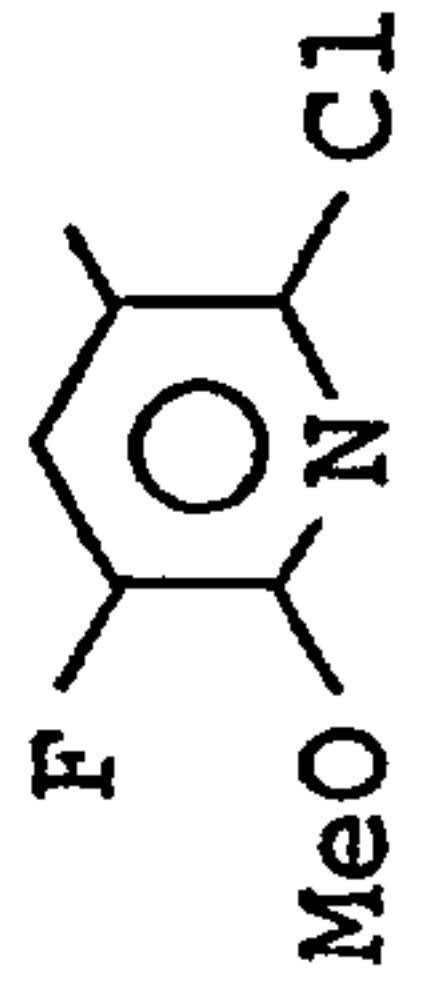
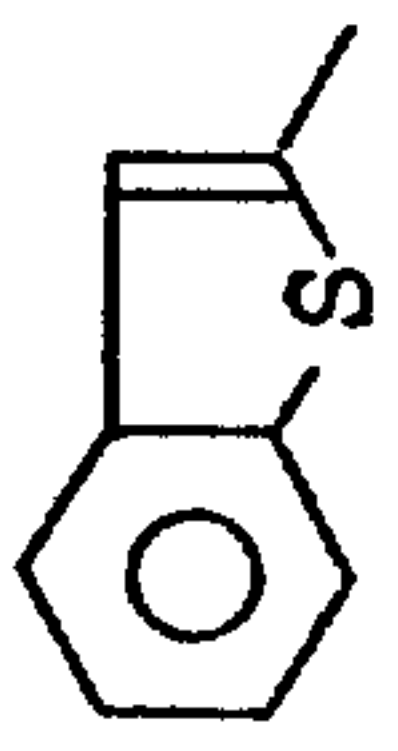
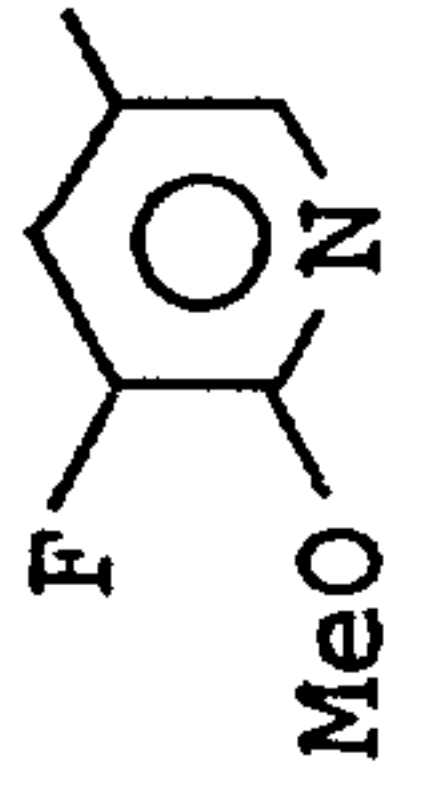
373		H	H	H	-N(Me) ₂	2	2HCl	184-186 [EtOH-AcOEt]
374		"	"	"	"	"	HCl	196-197 [MeOH]
375		"	"	"	-N(Me)H	"	"	193-193.5 [EtOH-AcOEt]
*3 376		"	"	"	-N(Me) ₂	"	"	162-163 [IPA]

Table 24 (Cont'd)

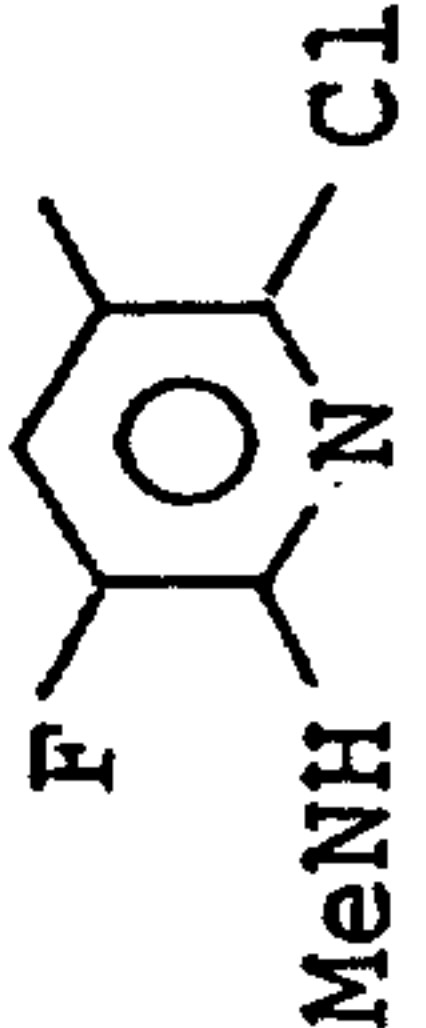
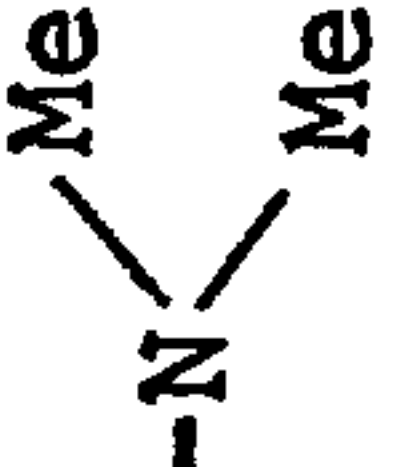
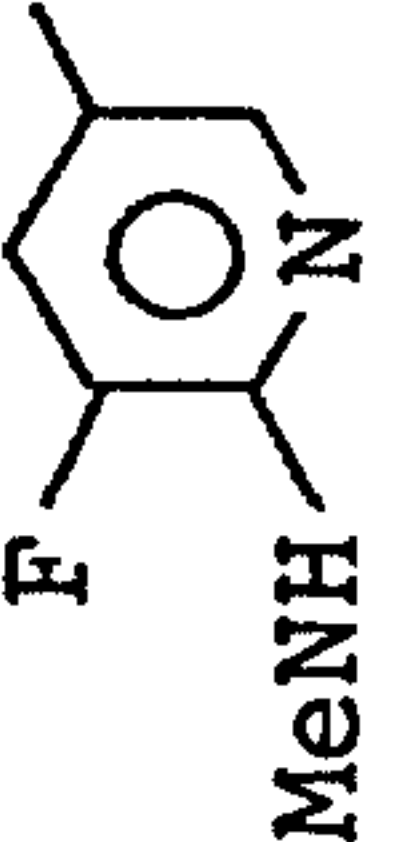
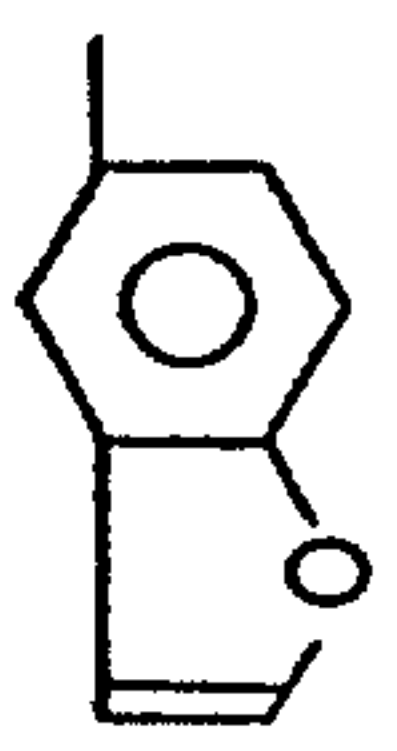
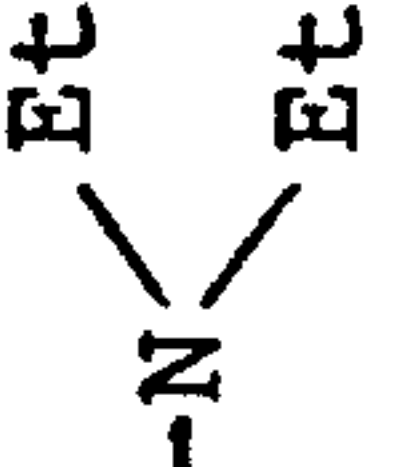
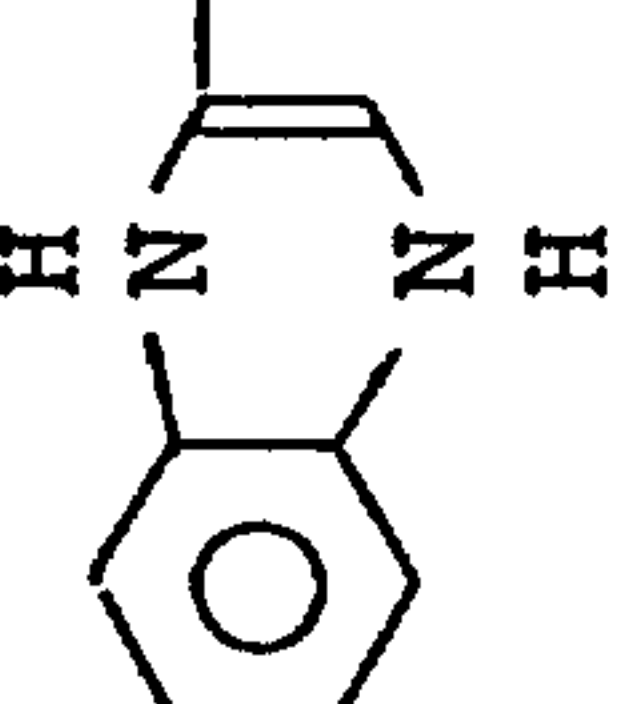
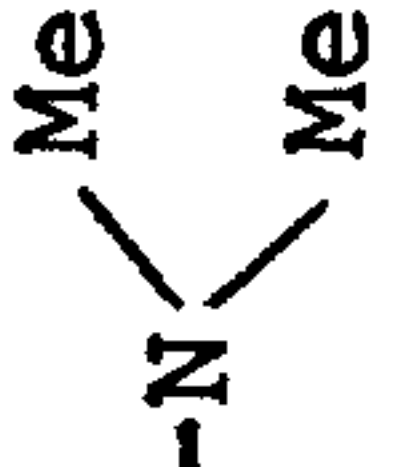
377		H	H	H		2	HCl	153.5-154 [IPA]
378		"	"	"	"	"	2HCl	176-179
379		"	"	"		"	-	Oily
380		"	"	"		"	"	"

Table 24 (Cont'd)

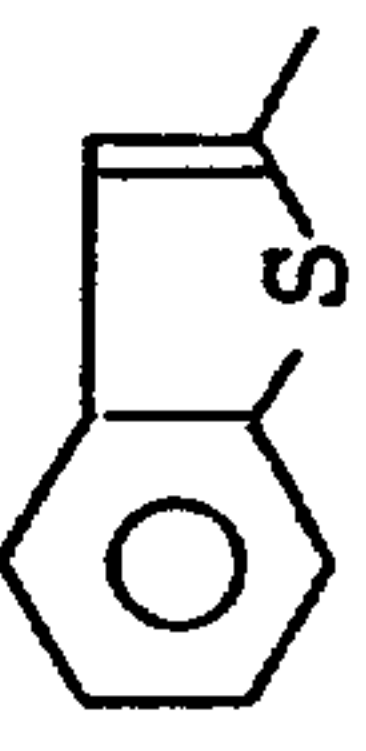
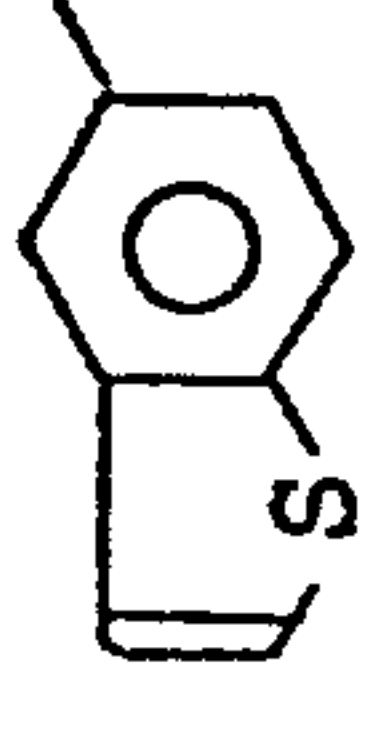
381		H	H	H	-N	2	HCl	194.5-195 [EtOH-AcOEt]
382		"	"	"	-N	3	-	109-111 [AcOEt]
383	"	"	"	"	-N	"	HCl	133.5-134.5 [EtOH-AcOEt]
384	"	"	"	"	-N	"	"	136.5-139.5 [EtOH-AcOEt]

Table 24 (Cont'd)

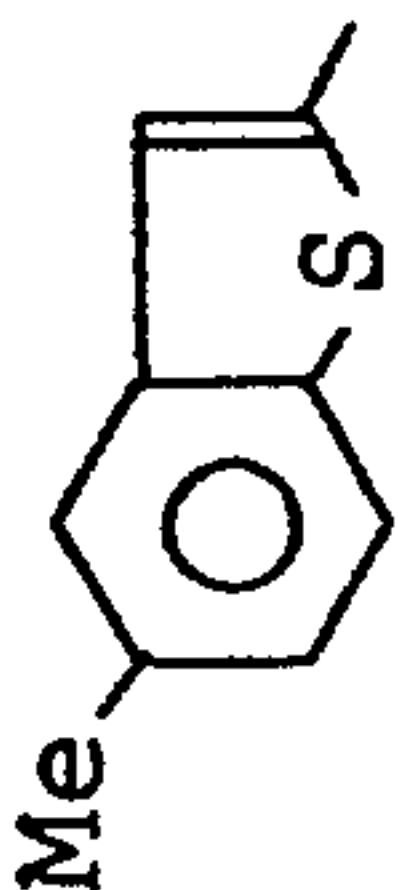
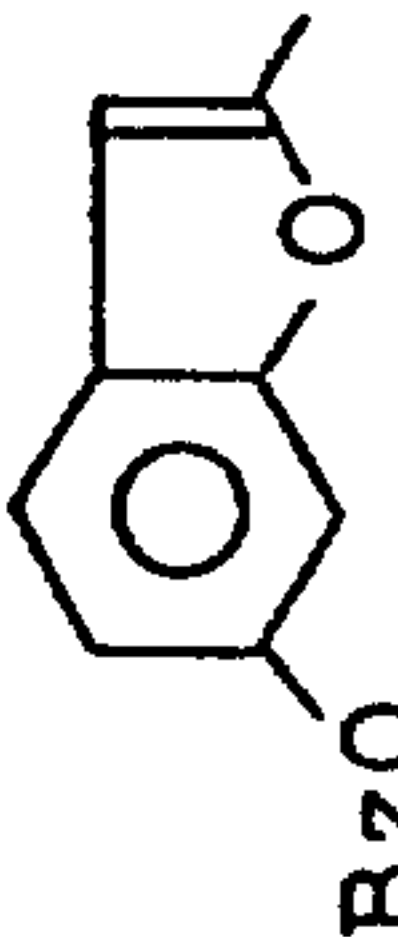
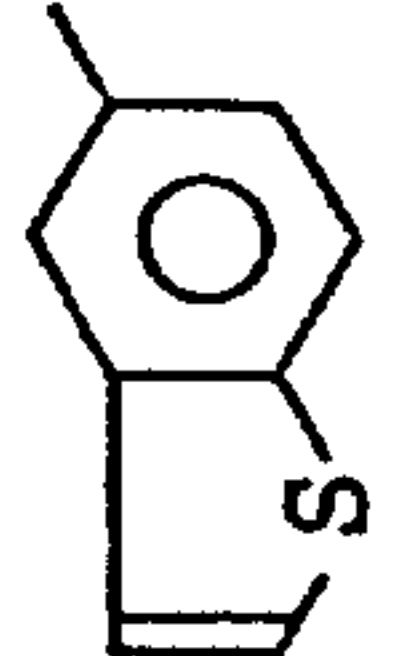
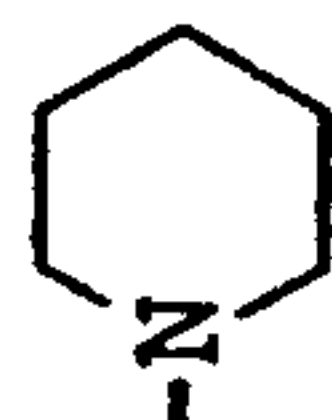
385		H	H	H	-N(Me) ₂	2	HCl	193-193.5 [EtOH-AcOEt]
386		"	"	"	"	"	"	171.5-172 [EtOH-AcOEt]
387		"	"	"		3	"	137.5-139.5 [EtOH-AcOEt]
388	"	"	"	"	-N(Et) ₂	2	"	138.5-139 [EtOH-AcOEt]

Table 24 (Cont'd)

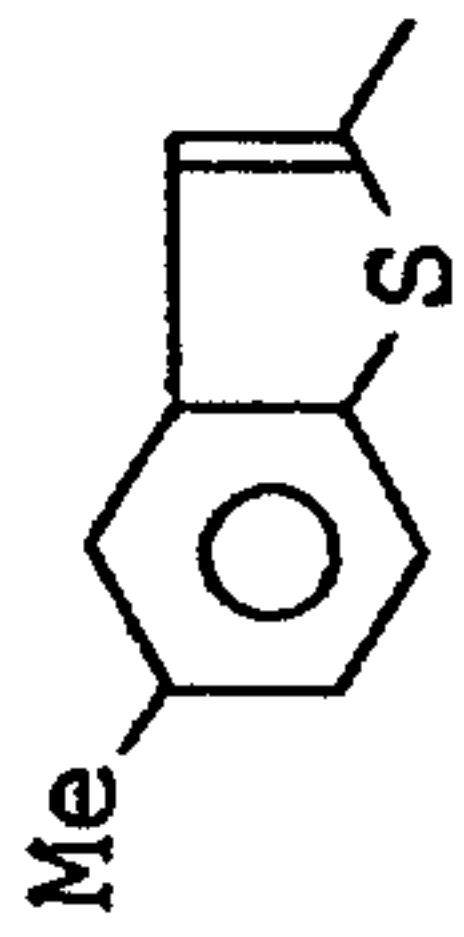
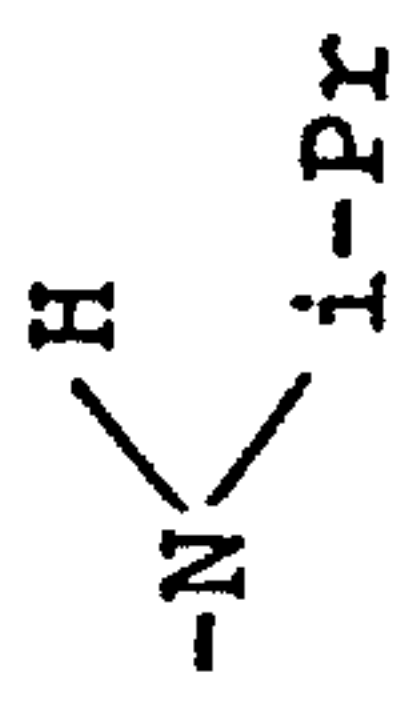
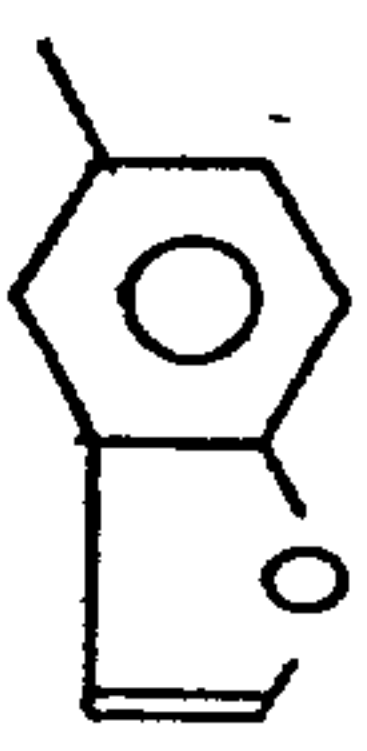
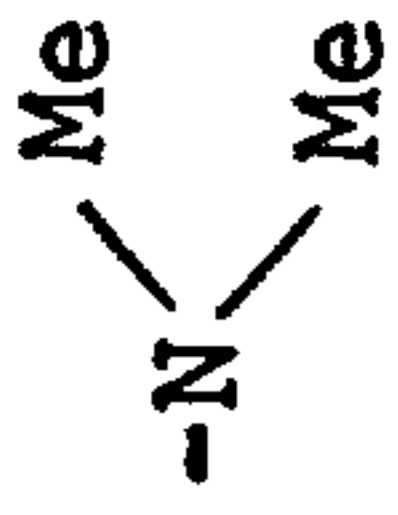
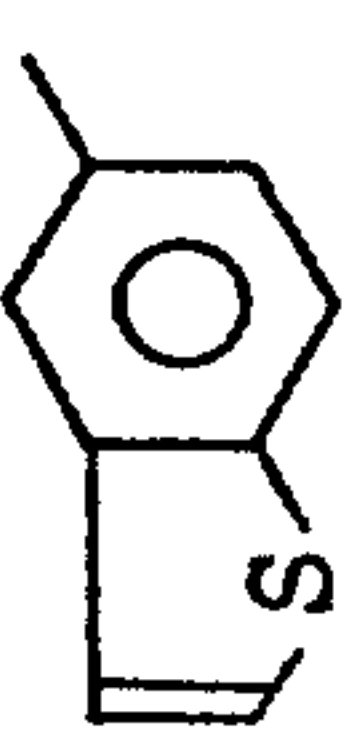
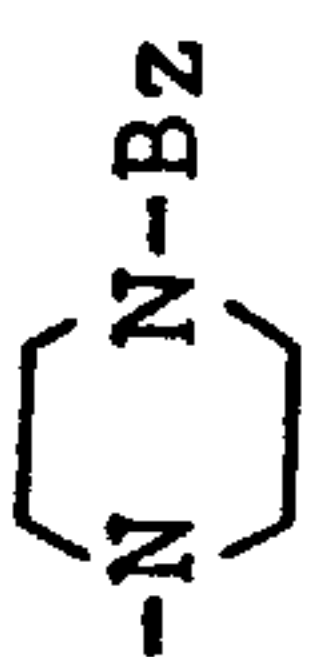
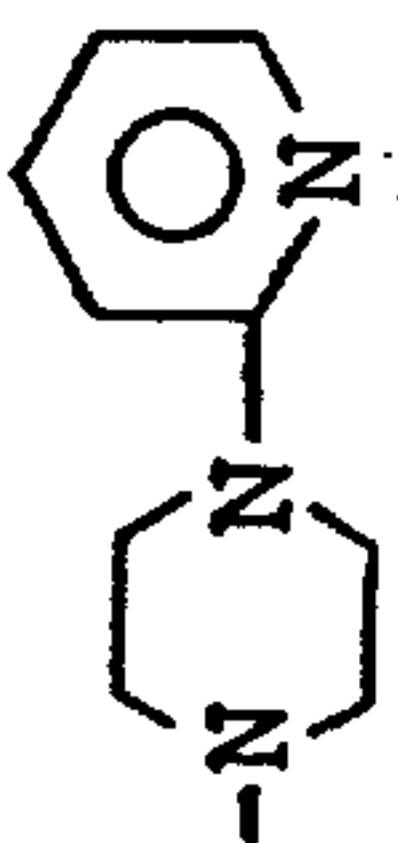
389		H	H	H		2	HCl	184-184.5 [EtOH-AcOEt]
390		"	"	"		3	-	68.5-69.5 [Hexane]
391		"	"	"		2	2HCl	250-252.5 (decomp.) [MeOH-H ₂ O]
392	"	"	"	"		"	"	155-157 [EtOH]

Table 24 (Cont'd)

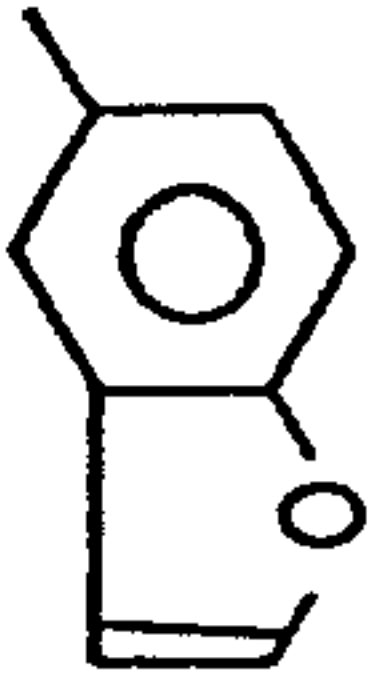
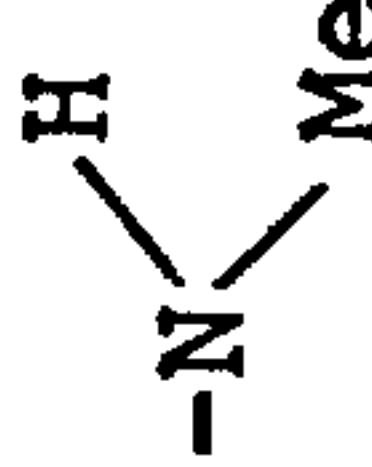
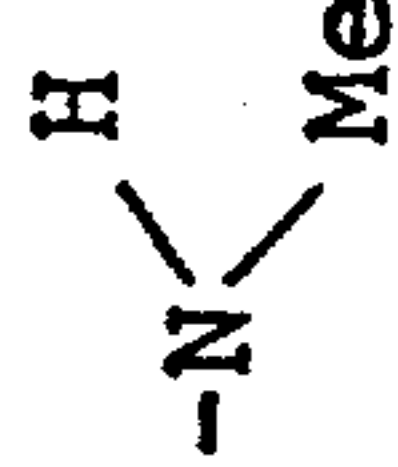
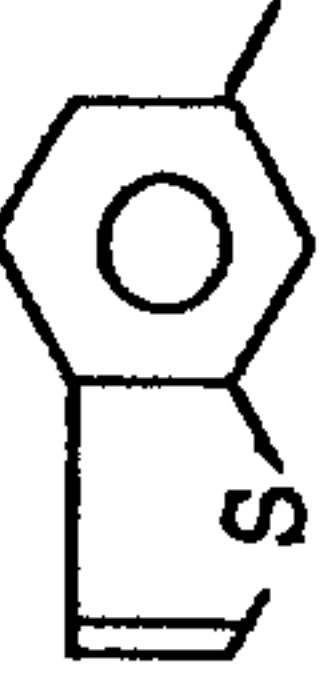
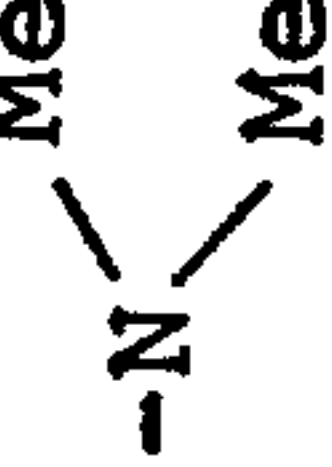
393		H	H	H		3	-	65-67.5 [IPA-IPE]
394	"	"	"	"		2	2HCl	234-234.5 [MeOH-AcOEt]
395	"	"	"	"		"	HCl	178-180.5 [IPA-AcOEt]
396		"	"	"		3	-	52-53 [IPE]

Table 24 (Cont'd)

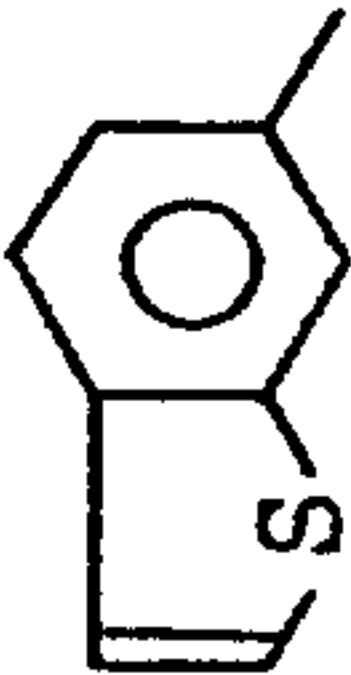
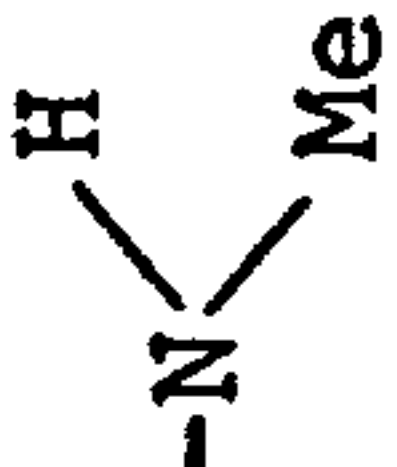
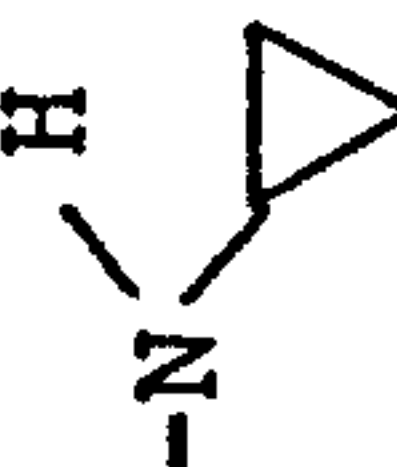
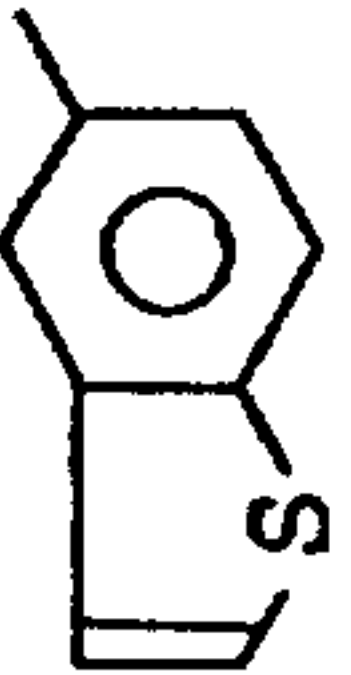
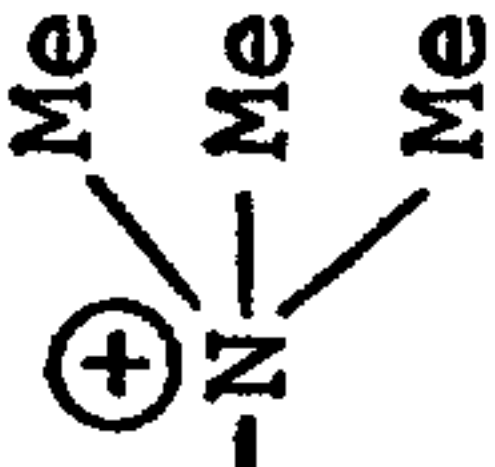
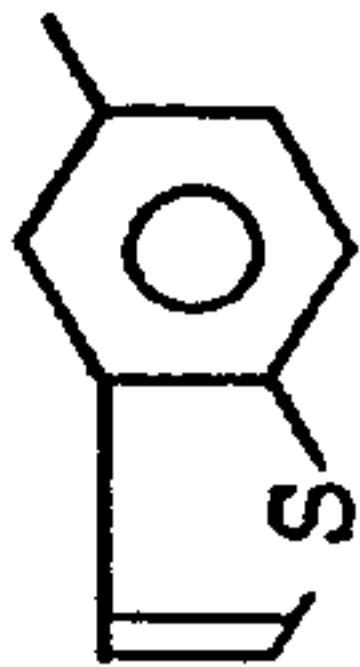
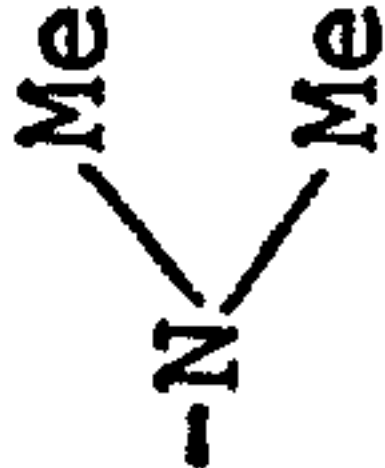
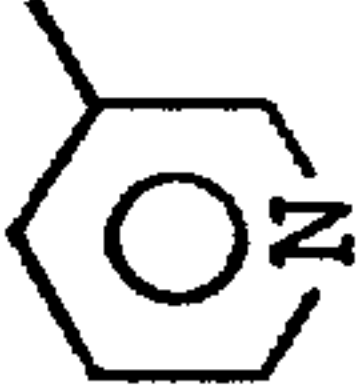
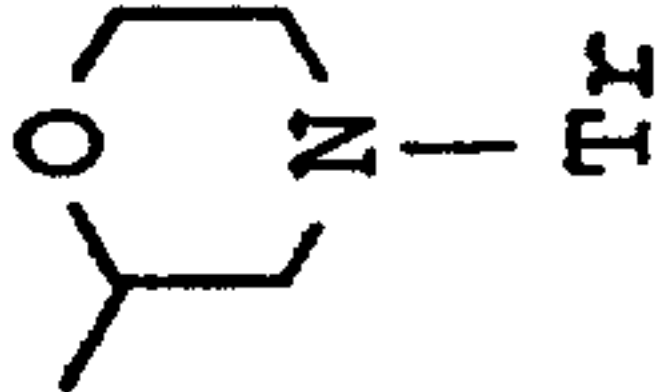
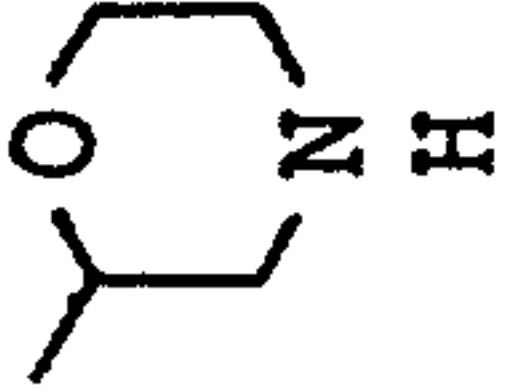
397		H	H	H		3	-	81.5-83 [IPA-IPE]
398	"	"	"	"	"	2	HCl	196-198 [EtOH-ACOEt]
399	"	"	"	"		"	"	190-192.5 [EtOH-ACOEt]
400		"	"	"		"	1/2 1,5-naphthalene-disulfonic acid	Amorphous

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.

1 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 hydrogen-carbonate 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)-

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1 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
5 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
10 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
15 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
20 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
25 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

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1 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
5 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
10 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 =
15 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} : $\nu_{\text{C=O}}$ 1740

(2) A mixture of 3.2 g of 1-acetoxy-1-(6-
20 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
25 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.

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1 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 chloro-
form. The extract was combined with the previously
5 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 distil-
lation under reduced pressure. The residue thus
obtained was purified by column chromatography (eluant:
10 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} : $\nu_{\text{C=O}}$ 1740

(3) In 3.5 ml of benzene was dissolved 0.65 g of
15 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
20 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 an ordinary
method to obtain 0.58 g of oily 1-acetoxy-1-(6-N-
25 ethylcarbamoyloxybenzo[b]furan-2-yl)-2-[2-(N,N-
dimethylamino)ethoxy]ethane hydrochloride (compound No.
408).

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

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

Example 1 (Tablets)

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

20 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 tablest each weighing 175 mg and having

* Trade mark

1 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
5 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	
10	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
15	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
20 components ②. The resulting mixture was charged into No. 3 gelatin capsules in an amount of 150 mg per capsule to obtain capsules.

* Trade mark

1 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

10 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)

15 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

20 The above components were dissolved in 1.5 ml

- 1 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)

- 5 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:

10	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	

- 15 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.

20 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)-

- 1 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-
- 5 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 fumarate
- 10 (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
- 15 tablets each containing 50 mg of one of the above compounds.

Example 7 (Capsules)

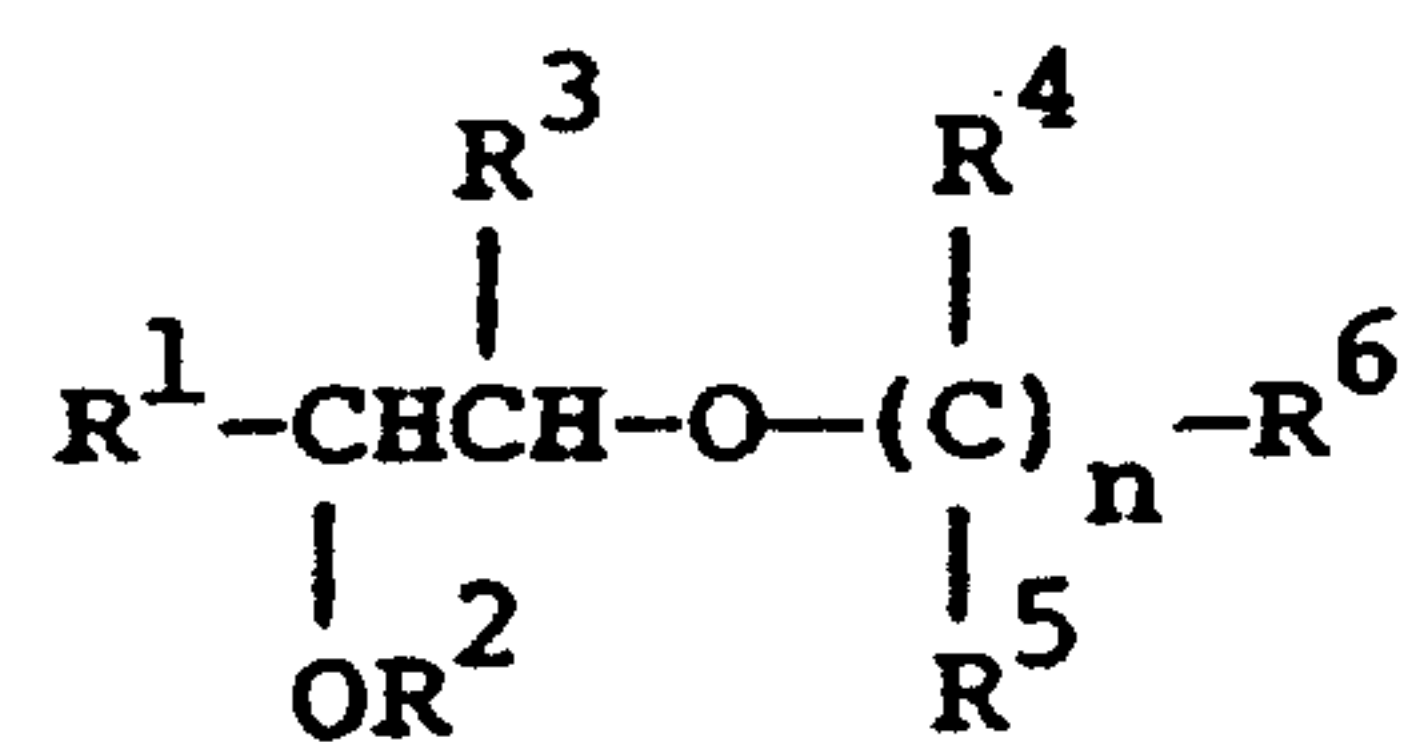
- 2-[2-(N,N-dimethylamino)ethoxy]-1-(3-methylphenyl)ethanol hydrochloride (compound No. 15), 2-
- 20 [(1-methylimidazol-5-yl)methoxy]-1-(4-benzyloxyphenyl)-ethanol (compound No. 215), 2-[2-(N,N-dimethylamino)-ethoxy]-1-(1-naphthyl)ethanol hydrochloride (compound No. 228), 2-[2-(N,N-dimethylamino)ethoxy]-1-(2-naphthyl)ethanol hydrochloride (compound No. 229),
- 25 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
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.

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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A pharmaceutical composition for treating or preventing cerebrovascular dementia, senile dementia, Alzheimer's dementia, sequelae of ischemic encephalopathy or cerebral apoplexy, comprising:
a 1,2-ethanediol derivative represented by the following general formula, a pharmaceutically acceptable salt thereof, or an optical isomer or racemate thereof:



wherein

R¹ represents an unsubstituted or C₁₋₆ alkyl-substituted phenyl group;

R² represents a hydrogen atom, or a C₁₋₆ alkyl, C₁₋₆ acyl, benzyl, or tetrahydropyranyl group;

R³ represents a hydrogen atom or a C₁₋₆ alkyl group;

nR⁴'s and nR⁵'s, independently, represent hydrogen atoms or C₁₋₆ alkyl groups, wherein n is zero or an integer of 1 to 6; and

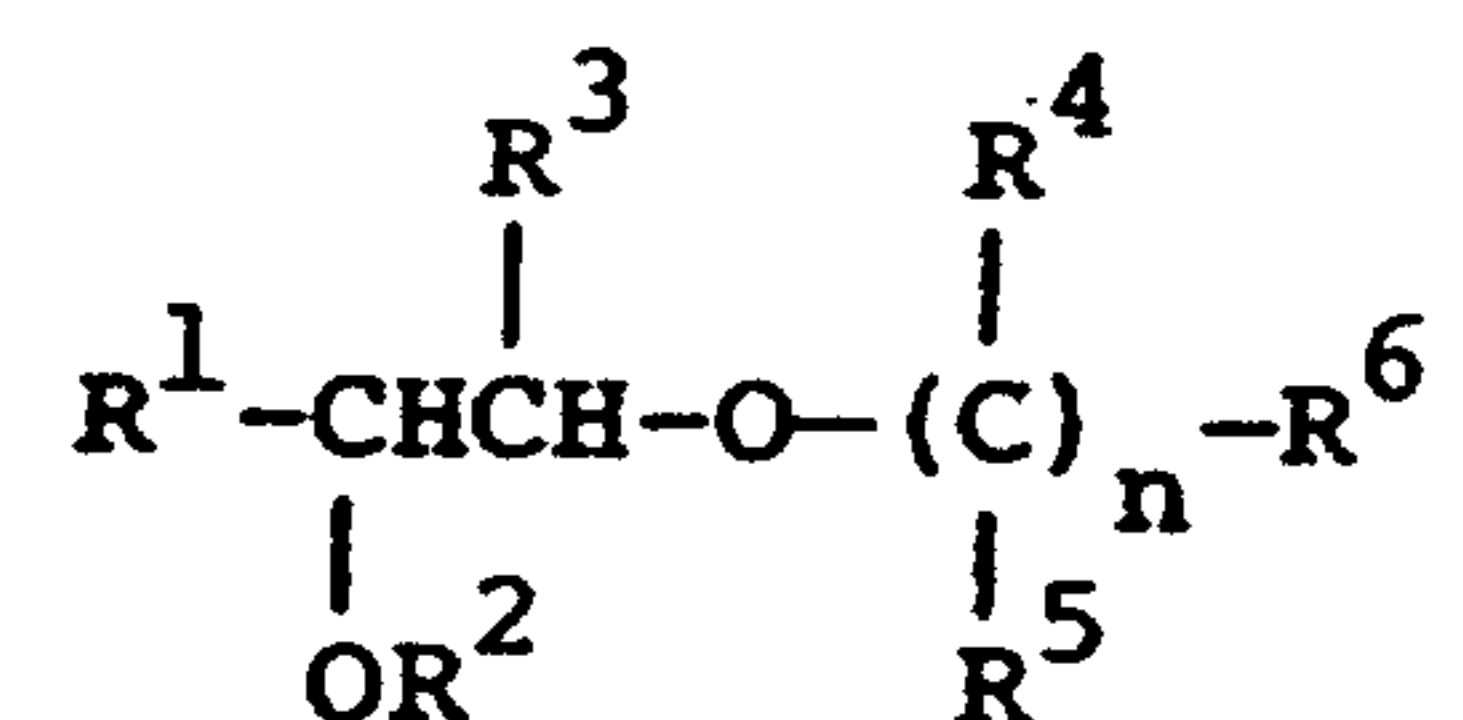
R⁶ represents an ammonio, di-C₁₋₆ alkylamino, pyrrolidinyl, piperidyl or morpholinyl group, and a pharmaceutically-acceptable carrier.

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2. A pharmaceutical composition as defined in claim 1, wherein said derivative is 2-[2-(N,N-dimethylamino)ethoxy]-1-(3-methylphenyl)-ethanol, a pharmaceutically-acceptable salt thereof, or an optical isomer or racemate thereof.

3. Use of a composition as defined in claim 1 or 2, for treating or preventing cerebrovascular dementia, senile dementia, Alzheimer's dementia, sequelae of ischemic encephalopathy or cerebral apoplexy.

4. A cerebral function-improving composition comprising a 1,2-ethanediol derivative represented by the following general formula, a pharmaceutically-acceptable salt thereof, or an optical isomer or racemate thereof:



wherein R^1 , R^2 , R^3 , $n\text{R}^4$'s, $n\text{R}^5$'s, R^6 and n are as defined in claim 1, and a pharmaceutically-acceptable carrier.

5. A cerebral function-improving composition comprising a 1,2-ethanediol derivative as defined in claim 2, and a pharmaceutically-acceptable carrier.

6. Use of a composition as defined in claim 4 or 5, for improving cerebral function.