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AUSTRALIA
PATENTS ACT 1990
NOTICE OF ENTITLEMENT

We, Otsuka Pharmaceutical Co., Ltd., the applicant/Nominated Person in respect of Application No. 24292/92 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person derives title to the invention from the inventors by assignment.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person made the application listed in the declaration under Article 8 of the PCT, and because that application was the first application made in a Convention country in respect of the invention.

DATED this EIGHTEENTH day of MAY 1993



.....
a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

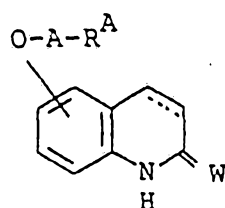
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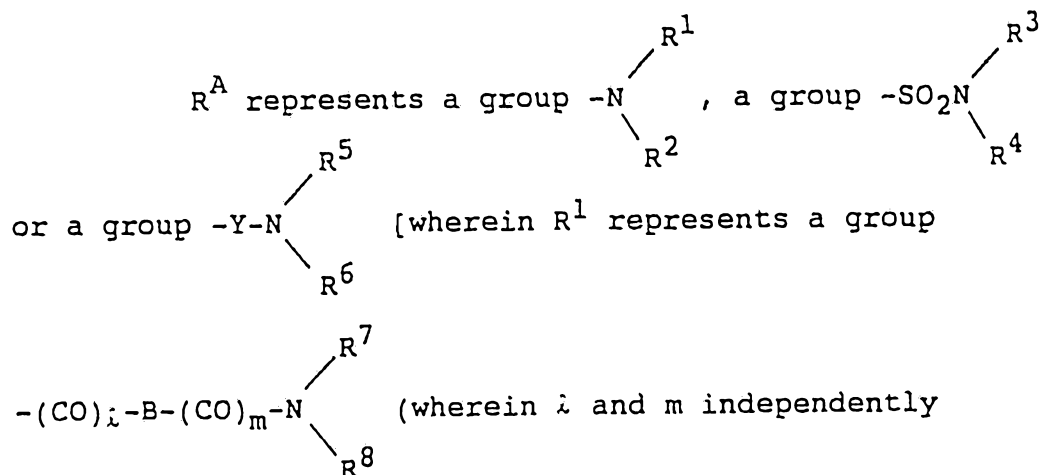
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 (19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 653060

- (54) Title
 CARBOSTYRIL DERIVATIVE AND PLATELET AGGLUTINATION INHIBITOR
- International Patent Classification(s)
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- (57) Claim
1. A carbostyryl derivative represented by general formula (1A)



(1A)

{wherein A represents a lower alkylene group.



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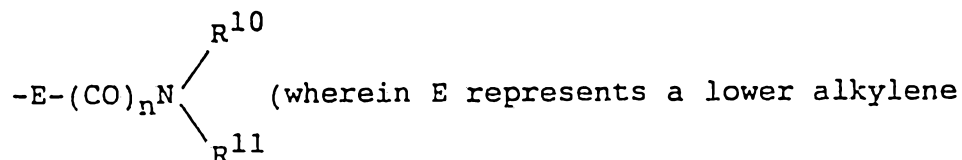
represent 0 or 1; B represents a lower alkylene group; each of R^7 and R^8 , which may be the same or different, represents a hydrogen atom, a lower alkyl group which may have a hydroxyl group, or a lower alkanoyl group; R^7 and R^8 may also form a five- or six-membered saturated heterocyclic ring, together with the nitrogen atom to which they bond and further with or without a nitrogen, oxygen or sulfur atom which may be present between R^7 and R^8 , said heterocyclic ring may have 1-3 substituents selected from the group consisting of a hydroxyl group, a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group, a lower alkyl group-substituted or unsubstituted amino group, a lower alkoxy-lower alkoxy group, an oxo group and a lower alkyl group-substituted or unsubstituted aminocarbonyl group, said heterocyclic ring may also have a lower alkylenedioxy group as a substituent); a lower alkoxy-carbonyl group-substituted lower alkyl group; a carboxy group-substituted lower alkyl group; a lower alkyl group having, as a substituent, a lower alkyl group-substituted or unsubstituted aminocarbonyl group; a hydroxyl group-containing lower alkyl group; an imidazolyl-substituted lower alkyl group; a pyridyl-substituted lower alkyl group; a pyrrolidinyl-lower alkyl group which may have, as substituent(s) on the pyrrolidine ring, 1-3 groups selected from the group consisting of a lower alkyl group, a lower alkoxy-lower alkoxy group

and a hydroxyl group; or a group $-\text{SO}_2-\text{D}-\text{R}^9$ (wherein D represents a lower alkylene group; R^9 represents a five- or six-membered saturated or unsaturated heterocyclic ring residue having 1-3 nitrogen atoms, said heterocyclic ring may have, as a substituent, a hydroxyl group, a lower alkoxy-lower alkoxy group, a lower alkoxy-carbonyl group, or a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group);

R^2 represents a hydrogen atom; a cycloalkyl-lower alkyl group; a cycloalkyl group; a phenyl group; a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a halogen atom, a lower alkyl group, a cyano group, a carboxy group and a lower alkoxy group; a pyridyl-substituted lower alkyl group; a thienyl-substituted lower alkyl group; a cycloalkylcarbonyl group; a benzoyl group; a tetrahydropyranyl-substituted lower alkyl group; a phenyl-lower alkylsulfonyl group; a phenylsulfonyl group; or a cycloalkyl-lower alkylsulfonyl group;

R^1 and R^2 may form a pyrrolidinyll group together with the nitrogen atom to which they bond, said pyrrolidinyll group has 1-2 substituents selected from the group consisting of a hydroxyl group, a lower alkoxy-lower alkoxy group, a lower alkyl group having a lower alkoxy-lower alkoxy group or a hydroxyl group, a lower alkoxy-carbonyl group, a piperidinylcarbonyl group and a cycloalkyl-lower alkyl group-substituted or unsubstituted aminocarbonyl group;

R^3 represents a hydrogen atom; a lower alkyl group which may have a hydroxyl group; a carboxy-substituted lower alkyl group; a lower alkoxy-carbonyl group-substituted lower alkyl group; a group



group which may have a hydroxyl group;

n represents 0 or 1;

each of R^{10} and R^{11} , which may be the same or different, represents a hydrogen atom; a lower alkyl group which may have a hydroxyl group; or a lower alkanoyl group;

R^{10} and R^{11} may also form a five- or six-membered saturated heterocyclic ring, together with the nitrogen atom to which they bond and further with or without a nitrogen, oxygen or sulfur atom which may be present between R^{10} and R^{11} , said heterocyclic ring may have 1-3 substituents selected from the group consisting of a hydroxyl group; an oxo group; a lower alkoxy-lower alkoxy group; a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group; and a lower alkyl-substituted or unsubstituted amino group, said heterocyclic ring may also have a lower alkylenedioxy group as a substituent); or a pyrrolidinyl-lower alkyl group which may have, as substituent(s) on the pyrrolidine ring, 1-3 groups selected from the group consisting of a lower alkyl group, a lower alkoxy-lower alkoxy group and a hydroxyl group;

R^4 represents a hydrogen atom; a cycloalkyl

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group; a cycloalkyl-lower alkyl group; a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a halogen atom, a lower alkyl group and a lower alkoxy group; a phenyl group; a thienyl-substituted lower alkyl group; a pyridyl-substituted lower alkyl group; an imidazolyl-substituted lower alkyl group; or a tetra-hydropyranyl-substituted lower alkyl group;

Y represents a group -NHC- , a group -NHC- or a

group -C- ;

each of R^5 and R^6 , which may be the same or different, represents a hydrogen atom; a lower alkyl group; a cycloalkyl group; a cycloalkyl-lower alkyl group; or a piperidinyllower alkyl group which may have, as a substituent on the piperidinyll ring, a lower alkoxy-lower alkoxy group or a hydroxyl group;

W represents an oxygen atom or a sulfur atom;
the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton represents a single bond or a double bond;

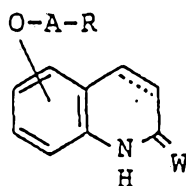
when W is an oxygen atom and R^1 is a hydroxyl group-containing lower alkyl group, R^2 must not be any of a hydrogen atom, a cycloalkyl group and a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a lower alkoxy group and a halogen atom;

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when R^1 and R^2 form a pyrrolidinyl group, the pyrrolidinyl group must not be a pyrrolidinyl group substituted with a hydroxyl group or with a hydroxyl group-containing lower alkyl group }, or a salt thereof.

52. A method for phosphodiesterase inhibition, which uses, as an active ingredient, a carbostyryl derivative represented by general formula (1)



(1)

(wherein A and W have the same definitions as in Claim 1; the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton represents a single bond or a double bond; and R has the same definition as in Claim 51), or a salt thereof.



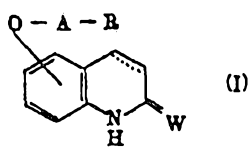
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(51) 国際特許分類 5 C07D 215/22, 215/36, 401/12 C07D 407/12, 409/12, 417/12 A61K 31/47, 31/495, 31/535	A1	(11) 国際公開番号 WO 93/04042 653060 (43) 国際公開日 1993年3月4日 (04.03.1993)
(21) 国際出願番号 PCT JP92/01041 (22) 国際出願日 1992年8月18日 (18.08.92) (30) 優先権データ 特願平3/211268 1991年8月23日 (23.08.91) JP (71) 出願人 (米国を除くすべての指定国について) 大塚製薬株式会社 (OTSUKA PHARMACEUTICAL CO., LTD.) [JP/JP] 〒101 東京都千代田区神田司町二丁目9番地 Tokyo, (JP) (72) 発明者: および (75) 発明者/出願人 (米国についてのみ) 佐藤誠司 (SATO, Seiji) [JP/JP] 〒771-02 徳島県板野郡松茂町笹木野字八上57-1 ハイッ伊達娘 Tokushima, (JP) 湯川浩孝 (YUKAWA, Hirotaka) [JP/JP] 佐藤幹泰 (SATO, Masahiro) [JP/JP] 〒771-01 徳島県徳島市川内町加賀須野463番地の10 Tokushima, (JP) 木原義人 (KIHARA, Yoshito) [JP/JP] 〒772 徳島県鳴門市撫養町立岩字五枚189番地5号 グイラセゾン206 Tokushima, (JP) 古賀信幸 (KOGA, Nobuyuki) [JP/JP] 〒770 徳島県徳島市南蔵本町1丁目16-7 Tokushima, (JP)	西 孝夫 (NISHI, Takao) [JP/JP] 〒771-02 徳島県板野郡北島町太郎八須字外岡2番地の28 Tokushima, (JP) (74) 代理人 弁理士 浅村 皓, 外 (ASAMURA, Kiyoshi et al.) 〒100 東京都千代田区大手町二丁目2番1号 新大手町ビル331 Tokyo, (JP) (81) 指定国 AT (欧州特許), AU, BE (欧州特許), CA, CH (欧州特許), DE (欧州特許), DK (欧州特許), ES (欧州特許), FR (欧州特許), GB (欧州特許), GR (欧州特許), IE (欧州特許), IT (欧州特許), KR, LU (欧州特許), MC (欧州特許), NL (欧州特許), SE (欧州特許), US. 添付公開書類 国際調査報告書	



(54) Title : CARBOSTYRIL DERIVATIVE AND PLATELET AGGLUTINATION INHIBITOR

(54) 発明の名称 カルボスチリル誘導体及び血小板凝集抑制剤

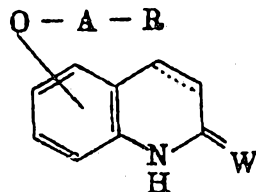


(57) Abstract

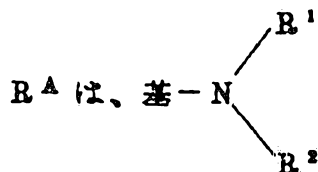
A carbostyryl derivative represented by general formula (I), useful as a platelet agglutination inhibitor, wherein A represents lower alkylene; R¹ represents -NR¹R², wherein R¹ represents lower alkyl substituted with lower alkoxy carbonyl and R² represents hydrogen, cycloalkyl-substituted lower alkyl, etc.; W represents oxygen or sulfur; and a carbon-to-carbon bond between the positions 3 and 4 of the carbostyryl skeleton represents either a single or a double bond.

(57) 要約

本発明によれば、一般式



〔式中、Aは低級アルキレン基



(式中、R¹は低級アルコキシカルボニル基置換低級アルキル基など、R²は、水素原子；シクロアルキル低級アルキル基などを示す。)

Wは、酸素原子又は硫黄原子、カルボスチリル骨格の3，4位の炭素原子間の結合は一重結合または二重結合を示す。〕

本発明のカルボスチリル誘導体は、血小板凝集抑制剤として有用である。

情報としての用途のみ

PCTに基づいて公開される国際出願のパンフレット第1頁にPCT加盟国を同定するために使用されるコード

AT	オーストリア	FI	フィンランド	MR	モーリタニア
AU	オーストラリア	FR	フランス	MW	マラウイ
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BE	ベルギー	GB	イギリス	NO	ノルウェー
BF	ブルキナ・ファソ	GN	ギニア	NZ	ニュージーランド
BG	ブルガリア	GR	ギリシャ	PL	ポーランド
BJ	ベナン	HU	ハンガリー	PT	ポルトガル
BR	ブラジル	IE	アイルランド	RO	ルーマニア
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CG	コンゴ	KP	朝鮮民主主義人民共和国	SE	スウェーデン
CH	スイス	KR	大韓民国	SK	スロヴァキア共和国
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CM	カメルーン	LK	スリランカ	SU	ソヴィエト連邦
CS	チェコスロヴァキア	LU	ルクセンブルク	TD	チャード
CZ	チェコ共和国	MC	モナコ	TG	トーゴ
DE	ドイツ	MG	マダガスカル	UA	ウクライナ
DK	デンマーク	ML	マリ	US	米国
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DESCRIPTION

1 Title of the Invention

Carbostyryl Derivative and Platelets
Aggregation Inhibitory Agent

Field of the Invention

- 5 The present invention relates to a carbostyryl derivative and a platelets aggregation inhibitory agent containing said derivative as an active ingredient.

Background Art

- Compounds having structural formulas similar to
10 that of the carbostyryl derivative of the present invention are disclosed in the following prior art literature (patents).

The prior art by the present applicant

- U.S. Patents Nos. 4070470, 4216220, 4313947,
15 4298739, 4277479, 4435404, 5008274 and 5053514; EP-A-8910919; Japanese Patent Application Kokai (Laid-open) Nos. 50-82218, 50-106977, 50-142576, 50-151881, 54-30180, 54-30183, 54-30184, 55-79371, 57-9780, 57-14574, 57-93962, 57-159778, 58-59980, 56-8319, 57-80322, 52-108980
20 and 63-290821.

The prior art by other applicants

Japanese Patent Application Kokai (Laid-open)



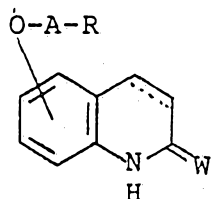
- 1 No. 56-16470 (U.S. Patent No. 4329347); Japanese Patent
Application Kokai (Laid-open) No. 56-36452; Japanese
Patent Application Kokai (Laid-open) No. 59-31753 (EP-A-
96006A); U.S. Patent No. 3994900; BE-A-859415; and EP-A-
5 71150 [Japanese Patent Application Kokai (Laid-open) No.
58-24559].

The structural formulas of the carbostyryl
compounds disclosed in the above prior art literature
10 (patents) are similar to that of the carbostyryl deriva-
tive of the present invention, but are different from the
latter in the side chain structures. Although some of
the carbostyryl compounds disclosed in the prior art
literature, similarly to the carbostyryl derivative of
15 the present invention, have a platelets aggregation
inhibitory activity, the compounds of the prior art
include also those showing different pharmacological
activities such as antithrombotic activity, antihistamin-
ic activity, antiarrhythmic activity, cardiotonicactivi-
20 ty, α - and β -adrenergic blocking activity and the like.

[Disclosure of the Invention]

The carbostyryl derivative of the present
invention is represented by the following general formula
(1)





(1)

1 {wherein A represents a lower alkylene group;

R represents a group $-N \begin{matrix} R^1 \\ R^2 \end{matrix}$, a group $-SO_2N \begin{matrix} R^3 \\ R^4 \end{matrix}$

or a group $-Y-N \begin{matrix} R^5 \\ R^6 \end{matrix}$ [wherein R^1 represents a group

$-(CO)_l-B-(CO)_m-N \begin{matrix} R^7 \\ R^8 \end{matrix}$ (wherein l and m independently

5 represent 0 or 1; B represents a lower alkylene group; each of R^7 and R^8 , which may be the same or different, represents a hydrogen atom, a lower alkyl group which may have a hydroxyl group, or a lower alkanoyl group;

10 R^7 and R^8 may also form a five- or six-membered saturated heterocyclic ring, together with the nitrogen atom to which they bond and further with or without a nitrogen, oxygen or sulfur atom which may be present between R^7 and R^8 , said heterocyclic ring may have 1-3 substituents selected from the group consisting of a hydroxyl group, a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group, a lower alkyl group-substituted or unsubstituted amino group, a lower alkoxy-lower alkoxy group, an oxo group and a lower



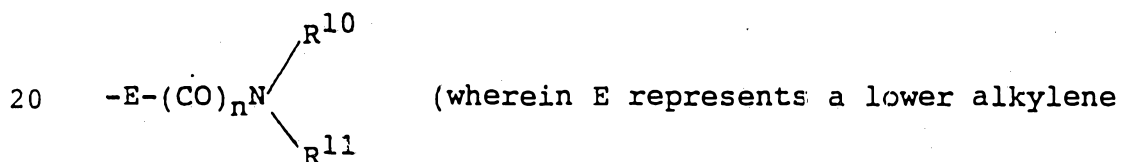
alkyl group-substituted or unsubstituted aminocarbonyl group, said heterocyclic ring may also have a lower alkylenedioxy group as a substituent); a lower alkoxy-carbonyl group-substituted lower alkyl group; a carboxy group-substituted lower alkyl group; a lower alkyl group having, as a substituent, a lower alkyl group-substituted or unsubstituted aminocarbonyl group; a hydroxyl group-containing lower alkyl group; an imidazolyl-substituted lower alkyl group; a pyridyl-substituted lower alkyl group; a pyrrolidinyl-lower alkyl group which may have, as substituent(s) on the pyrrolidine ring, 1-3 groups selected from the group consisting of a lower alkyl group, a lower alkoxy-lower alkoxy group and a hydroxyl group; or a group-SO₂-D-R⁹ (wherein D represents a lower alkylene group; R⁹ represents a five- or six-membered saturated or unsaturated heterocyclic ring residue having 1-3 nitrogen atoms; said heterocyclic ring may have, as a substituent, a hydroxyl group, a lower alkoxy-lower alkoxy group, a lower alkoxy-carbonyl group, or a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group);

R² represents a hydrogen atom; a cycloalkyl-lower alkyl group; a cycloalkyl group; a phenyl group; a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a halogen atom, a lower alkyl group, a cyano group, a carboxy group and a lower alkoxy group;

1 a pyridyl-substituted lower alkyl group; a thienyl-
substituted lower alkyl group; a cycloalkylcarbonyl
group; a benzoyl group; a tetrahydropyranyl-substituted
lower alkyl group; a phenyl-lower alkylsulfonyl group; a
5 phenylsulfonyl group; or a cycloalkyl-lower alkylsulfonyl
group;

R^1 and R^2 may form a pyrrolidiny group
together with the nitrogen atom to which they bond, said
pyrrolidiny group has 1-2 substituents selected from the
10 group consisting of a hydroxyl group, a lower alkoxy-
lower alkoxy group, a lower alkyl group which may have a
lower alkoxy-lower alkoxy group or a hydroxyl group, a
lower alkoxy-carbonyl group, a piperidinylcarbonyl group
and a cycloalkyl-lower alkyl group-substituted or
15 unsubstituted aminocarbonyl group;

R^3 represents a hydrogen atom; a lower alkyl
group which may have a hydroxyl group; a carboxy-
substituted lower alkyl group; a lower alkoxy-carbonyl
group-substituted lower alkyl group; a group



group which may have a hydroxyl group; n represents 0 or
1; each of R^{10} and R^{11} , which may be the same or
different, represents a hydrogen atom; a lower alkyl
group which may have a hydroxyl group; or a lower
25 alkanoyl group; R^{10} and R^{11} may also form a five- or
six-membered saturated heterocyclic ring, together with

1 the nitrogen atom to which they bond and further with or
without a nitrogen, oxygen or sulfur atom which may be
present between R^{10} and R^{11} , said heterocyclic ring may
have 1-3 substituents selected from the group consisting
5 of a hydroxyl group; an oxo group; a lower alkoxy-lower
alkoxy group; a lower alkyl group which may have a lower
alkoxy-lower alkoxy group or a hydroxyl group; and a
lower alkyl-substituted or unsubstituted amino group,
said heterocyclic ring may also have a lower alkylenedioxy
10 group as a substituent.); or a pyrrolidinyl-lower alkyl
group which may have, as substituent(s) on the pyrroli-
dine ring, 1-3 groups selected from the group consisting
of a lower alkyl group, a lower alkoxy-lower alkoxy
group and a hydroxyl group;

15 R^4 represents a hydrogen atom; a cycloalkyl
group; a cycloalkyl-lower alkyl group; a phenyl-lower
alkyl group which may have, as substituent(s) on the
phenyl ring, 1-3 groups selected from the group
consisting of a halogen atom, a lower alkyl group and a
20 lower alkoxy group; a phenyl group; a thienyl-substituted
lower alkyl group; a pyridyl-substituted lower alkyl
group; an imidazolyl-substituted lower alkyl group; or a
tetrahydropyranyl-substituted lower alkyl group;

Y represents a group -NHC- , a group -NHC- or a

$$\begin{array}{c} \parallel \\ \text{O} \end{array}$$

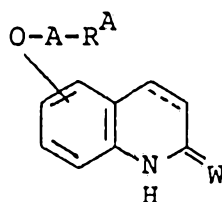
$$\begin{array}{c} \parallel \\ \text{S} \end{array}$$
25 group -C- ;

$$\begin{array}{c} \parallel \\ \text{S} \end{array}$$

- 1 each of R^5 and R^6 , which may be the same or different, represents a hydrogen atom; a lower alkyl group; a cycloalkyl group; a cycloalkyl-lower alkyl group; or a piperidinyl-lower alkyl group which may have, 5. as a substituent on the piperidinyl ring, a lower alkoxy-lower alkoxy group or a hydroxyl group];

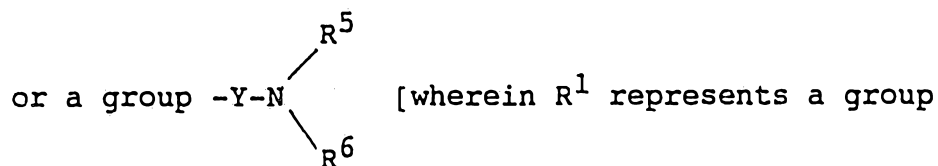
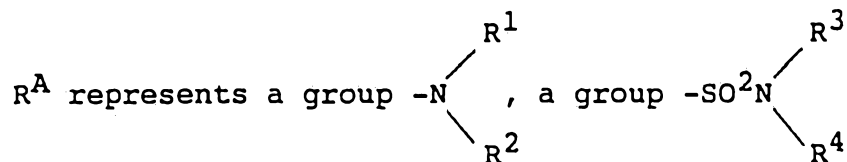
W represents an oxygen atom or a sulfur atom;
the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton represents a 10 single bond or a double bond}.

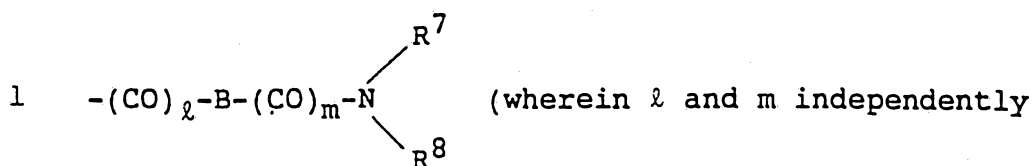
Of the carbostyryl derivatives represented by the above general formula (1), the compounds represented by the following general formula (1A) are novel compounds not disclosed in any literature yet.



(1A)

- 15 {wherein A represents a lower alkylene group.





represent 0 or 1; B represents a lower alkylene group;
each of R^7 and R^8 , which may be the same or different,
represents a hydrogen atom, a lower alkyl group which may
5 have a hydroxyl group, or a lower alkanoyl group;
 R^7 and R^8 may also form a five- or six-membered
saturated heterocyclic ring, together with the nitrogen
atom to which they bond and further with or without a
nitrogen, oxygen or sulfur atom which may be present
10 between R^7 and R^8 , said heterocyclic ring may have 1-3
substituents selected from the group consisting of a
hydroxyl group, a lower alkyl group which may have a
lower alkoxy-lower alkoxy group or a hydroxyl group, a
lower alkyl group-substituted or unsubstituted amino
15 group, a lower alkoxy-lower alkoxy group, an oxo group
and a lower alkyl group-substituted or unsubstituted
aminocarbonyl group, said heterocyclic ring may also have
a lower alkylendioxy group as a substituent); a lower
alkoxycarbonyl group-substituted lower alkyl group; a
20 carboxy group-substituted lower alkyl group; a lower
alkyl group having, as a substituent, a lower alkyl
group-substituted or unsubstituted aminocarbonyl group; a
hydroxyl group-containing lower alkyl group; an
imidazolyl-substituted lower alkyl group; a pyridyl-
25 substituted lower alkyl group; a pyrrolidinyl-lower alkyl
group which may have, as substituent(s) on the pyrroli-



dine ring, 1-3 groups selected from the group consisting of a lower alkyl group, a lower alkoxy-lower alkoxy group and a hydroxyl group; or a group $\text{-SO}_2\text{-D-R}^9$ (wherein D represents a lower alkylene group; R^9 represents a five- or
5 six-membered saturated or unsaturated heterocyclic ring residue having 1-3 nitrogen atoms, said heterocyclic ring may have, as a substituent, a hydroxyl group, a lower alkoxy-lower alkoxy group, a lower alkoxy-carbonyl group, or a lower alkyl group which may have a lower alkoxy-lower
10 alkoxy group or a hydroxyl group));

R^2 represents a hydrogen atom; a cycloalkyl-lower alkyl group; a cycloalkyl group; a phenyl group; a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a halogen atom, a lower alkyl group, a cyano group, a carboxy group and a lower alkoxy group; a pyridyl-substituted lower alkyl group; a thienyl-substituted lower alkyl group; a cycloalkylcarbonyl group; a benzoyl group; a tetrahydropyranyl-substituted lower alkyl group; a phenyl-lower alkylsulfonyl group; a phenylsulfonyl group; or a cycloalkyl-lower alkylsulfonyl group ;

R^1 and R^2 may form a pyrrolidinyl group together with the nitrogen atom to which they bond, said pyrrolidinyl group has 1-2 substituents selected from the group consisting of a hydroxyl group, a lower alkoxy-lower alkoxy group, a lower alkyl group having a lower alkoxy-lower alkoxy group or a hydroxyl group, a lower

- 1 alkoxycarbonyl group, apiperidinylcarbonyl group and a cycloalkyl-lower alkyl group-substituted or unsubstituted aminocarbonyl group;

- 5 R^3 represents a hydrogen atom; a lower alkyl group which may have a hydroxyl group; a carboxy-substituted lower alkyl group; a lower alkoxycarbonyl group-substituted lower

alkyl group; a group $-E-(CO)_nN$ $\begin{matrix} R^{10} \\ R^{11} \end{matrix}$ (wherein E represents

a lower alkylene group which may have a hydroxyl group.

- 10 n represents 0 or 1; each of R^{10} and R^{11} , which may be the same or different, represents a hydrogen atom; a lower alkyl group which may have a hydroxyl group; or a lower alkanoyl group; R^{10} and R^{11} may also form a five- or six-membered saturated heterocyclic ring,
- 15 together with the nitrogen atom to which they bond and further with or without a nitrogen, oxygen or sulfur atom which may be present between R^{10} and R^{11} , said heterocyclic ring may have 1-3 substituents selected from the group consisting of a hydroxyl group; an oxo group; a
- 20 lower alkoxy-lower alkoxy group; a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group; and a lower alkyl-substituted or unsubstituted amino group, said heterocyclic ring may also have a lower alkylendioxy group as a substituent.);
- 25 or a pyrrolidinyl-lower alkyl group which may have, as substituent(s) on the pyrrolidine ring, 1-3 groups

1 selected from the group consisting of a lower alkyl
group, a lower alkoxy-lower alkoxy group and a hydroxyl
group ;

5 R^4 represents a hydrogen atom; a cycloalkyl
group; a cycloalkyl-lower alkyl group; a phenyl-lower
alkyl group which may have, as substituent(s) on the
phenyl ring, 1-3 groups selected from the group consist-
ing of a halogen atom, a lower alkyl group and a lower
alkoxy group; a phenyl group; a thienyl-substituted lower
10 alkyl group; a pyridyl-substituted lower alkyl group; an
imidazolyl-substituted lower alkyl group; or a tetra-
hydropyranyl-substituted lower alkyl group;

Y represents a group -NHC- , a group -NHC- or a
 $\begin{array}{c} \parallel \\ \text{O} \end{array}$ $\begin{array}{c} \parallel \\ \text{S} \end{array}$

-C- ;
 $\begin{array}{c} \parallel \\ \text{S} \end{array}$

15 each of R^5 and R^6 , which may be the same or
different, represents a hydrogen atom; a lower alkyl
group; a cycloalkyl group; a cycloalkyl-lower alkyl
group; or a piperidinyl-lower alkyl group which may have,
as a substituent on the piperidinyl ring, a lower
20 alkoxy-lower alkoxy group or a hydroxyl group];

W represents an oxygen atom or a sulfur atom;

the carbon-to-carbon bond between the 3- and 4-
positions of the carbostyryl skeleton represents a single
bond or a double bond;

25 when W is an oxygen atom and R^1 is a hydroxyl
group-containing lower alkyl group, R^2 must not be any of

1 a hydrogen atom, a cycloalkyl group and a phenyl-lower
alkyl group which may have, as substituent(s) on the
phenyl ring, 1-3 groups selected from the group consist-
ing of a lower alkoxy group and a halogen atom;

5 when R^1 and R^2 form a pyrrolidinyl group, the
pyrrolidinyl group must not be a pyrrolidinyl group
substituted with a hydroxyl group or with a hydroxyl
group-containing lower alkyl group }.

According to the research by the present inven-
10 tors, the carbostyryl derivative represented by the above
general formula (1) or its salt is superior in platelets
aggregation inhibitory activity, phosphodiesterase
inhibitory activity, cardiocontraction increase activity
(positive contraction activity), antiulcerative activity,
15 antiinflammatory activity, brain and peripheral blood
flow increasing activity, platelet plug dissecting
activity, thromboxane A_2 antagonistic activity, etc. The
compound of the present invention is characterized by
having long sustaining times for the above-mentioned
20 activities, low toxicity (the toxicity to heart when used
for cardiac vascular hypertrophy, myocardial disturbance,
etc. is particularly low), and very low circulatory
effects for heart rate increase, blood pressure reduc-
tion, etc. The present compound also has an advantage
25 that it is readily absorbed by intestinal tract and
easily transferred into blood. Thus, the compound of the
present invention can be most suitably used as a prophylactic and treating agent for thrombosis (e.g. cerebral



1 apoplexia, cerebral infarction, myocardial infarction), a
peripheral circulation improving agent, a cerebral
circulation improving agent, an antiinflammatory agent,
an antiasthmatic agent, a prophylactic and treating agent
5 for diabetic complication (e.g. neurosis, nephritis), a
cardiotonic agent and a phosphodiesterase agent.

The compound of the present invention further
has a platelets adhesion inhibitory activity and
therefore can be used, for example, as a prophylactic and
10 treating agent for arteriosclerosis, ischemic heart
disease, chronic arterial embolism, acute or chronic
nephritis, etc.; for the postoperative administration of
blood vessel in percutaneous transluminal coronary
angioplasty (PTCA), etc.; as a prophylactic and treating
15 agent for coronary arterial re-embolism due to indwelling
of stent in blood vessel; and at the time of dialysis
treatment or artificial organ embedding.

Each of the individual groups shown in the
above general formula (1) is as follows.

20 As to the lower alkylene group, there can be
mentioned, for example, straight chain or branched chain
alkylene groups each of 1-6 carbon atoms, such as
methylene, ethylene, methylenemethylene, trimethylene, 2-
methyltrimethylene, 2,2-dimethyltrimethylene, tetra-
25 methylene, pentamethylene, hexamethylene, 2-ethyltri-
methylene, 1-methyltrimethylene and the like.

The lower alkyl group which may have a lower
alkoxy-lower alkoxy group or a hydroxyl group, can be



- 1 exemplified by straight chain or branched chain alkyl
groups each of 1-6 carbon atoms, which may each have 1-3
hydroxyl groups or 1-3 alkoxyalkoxy groups whose alkoxy
portions are each a straight chain or branched chain
5 alkoxy group of 1-6 carbon atoms, such as methyl, ethyl,
propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl,
methoxymethoxymethyl, 2-methoxymethoxyethyl, 3-methoxy-
methoxypropyl, 2,3-dimethoxymethoxypropyl, 2-hydroxy-
ethyl, 3-hydroxypropyl, 4-hydroxybutyl, 2-hydroxybutyl,
10 3-hydroxybutyl, 5-hydroxypentyl, 2-hydroxypentyl, 3-
hydroxypentyl, 4-hydroxypentyl, 6-hydroxyhexyl, 2-
hydroxyhexyl, 3-hydroxyhexyl, 4-hydroxyhexyl, 1-methyl-
2-hydroxyethyl, 2-hydroxypropyl, 1,1-dimethyl-2-
hydroxyethyl, 1,2-dihydroxyethyl, 2,2-dihydroxyethyl,
15 1,3-dihydroxypropyl, 2,3-dihydroxypropyl, 1,2,3-
trihydroxypropyl, 1,4-dihydroxybutyl, 2,4-dihydroxybutyl,
3,4-dihydroxybutyl, 1,2-dihydroxybutyl, 2,3-dihydroxy-
butyl, 1,3-dihydroxybutyl, 2,2-dihydroxybutyl, 1,2,3-
trihydroxybutyl, 2,3,4-trihydroxybutyl, 2,3-dihydroxy-
20 pentyl, 3,4-dihydroxypentyl, 3,5-dihydroxypentyl, 2,3,4-
trihydroxypentyl, 3,4,5-trihydroxypentyl, 2,4,5-trihy-
droxypentyl, 2,3-dihydroxyhexyl, 2,5-dihydroxyhexyl,
2,6-dihydroxyhexyl, 3,4-dihydroxyhexyl, 4,5-dihydroxy-
hexyl, 4,6-dihydroxyhexyl, 5,6-dihydroxyhexyl, 2,3,4-
25 trihydroxyhexyl, 3,4,5-trihydroxyhexyl, 4,5,6-trihy-
droxyhexyl and the like.

As to the lower alkanoyl group, there can be
mentioned, for example, straight chain or branched chain

1 alkanoyl groups each of 1-6 carbon atoms, such as formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl, hexanoyl and the like.

As to the lower alkyl-substituted or unsubstituted amino group, there can be mentioned, for example, amino groups which may each have, as substituent(s), 1-2 straight chain or branched chain alkyl groups each of 1-6 carbon atoms, such as amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, 10 pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino, N-methyl-N-ethylamino, N-ethyl-N-propylamino, N-methyl-N-butylamino, N-methyl-N-hexylamino and the like.

As to the lower alkyl-substituted or unsubstituted aminocarbonyl group, there can be mentioned, for 15 example, aminocarbonyl groups which may have, as substituent(s), 1-2 straight chain or branched chain alkyl groups each of 1-6 carbon atoms, such as aminocarbonyl, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, isopropylamino-carbonyl, butylaminocarbonyl, tert-butylaminocarbonyl, pentylaminocarbonyl, 20 hexylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, dibutylaminocarbonyl, dipentylaminocarbonyl, dihexylaminocarbonyl, N-methyl-N-ethylaminocarbonyl, N-ethyl-N-propylaminocarbonyl, N-methyl-N-butylaminocarbonyl, N-methyl-N-hexylaminocarbonyl and the like. 25

As to the lower alkylenedioxy group, there can

1 be mentioned, for example, straight chain or branched
chain alkylenedioxy groups each of 1-4 carbon atoms, such
as methylenedioxy, ethylenedioxy, trimethylenedioxy,
tetramethylenedioxy and the like.

5 As to the lower alkoxy-carbonyl group-
substituted lower alkyl group, there can be mentioned,
for example, straight chain or branched chain alkoxy-car-
bonylalkyl groups each of 1-6 carbon atoms, whose alkyl
portions are each a straight chain or branched chain
10 alkyl group of 1-6 carbon atoms, such as methoxycar-
bonylmethyl, 3-methoxycarbonylpropyl, 4-ethoxycarbonyl-
butyl, 6-propoxycarbonylhexyl, 5-isopropoxycarbonyl-
pentyl, 1,1-dimethyl-2-butoxycarbonylethyl, 2-methyl-
tert-butoxycarbonylpropyl, 2-pentyloxycarbonylethyl,
15 hexyloxycarbonylmethyl and the like.

The carboxy-lower alkyl group can be
exemplified by carboxyalkyl groups whose alkyl portions
are each a straight chain or branched chain alkyl group
of 1-6 carbon atoms, such as carboxymethyl, 2-carboxy-
20 ethyl, 1-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl,
1,1-dimethyl-2-carboxyethyl, 5-carboxypentyl, 6-carboxy-
hexyl, 2-methyl-3-carboxypropyl and the like.

As to the lower alkyl group having, as a
substituent, a lower alkyl group-substituted or unsubsti-
25 tuted aminocarbonyl group, there can be mentioned
straight chain or branched chain alkyl groups each of 1-6
carbon atoms, each having, a substituent, an amino-
carbonyl group which may have 1-2 straight chain or

- 1 branched chain alkyl groups each of 1-6 carbon atoms,
such as aminocarbonylmethyl, 1-aminocarbonyl-ethyl, 2-
aminocarbonylethyl, 3-aminocarbonylpropyl, 4-
aminocarbonylbutyl, 5-aminocarbonylpentyl, 6-
5 aminocarbonylhexyl, 1,1-dimethyl-2-aminocarbonylethyl,
2-methyl-3-aminocarbonylpropyl, methylaminocarbonyl-
methyl, ethylaminocarbonylmethyl, propylaminocarbonyl-
methyl, isopropylaminocarbonylmethyl, butylamino-
carbonylmethyl, tert-butylaminocarbonylmethyl,
10 pentylaminocarbonylmethyl, hexylaminocarbonylmethyl,
dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl,
diethylaminocarbonylmethyl, dipropylaminocarbonylmethyl,
dibutylaminocarbonylmethyl, dipentylaminocarbonylmethyl,
dihexylaminocarbonylmethyl, N-methyl-N-ethylaminocar-
15 bonylmethyl, N-ethyl-N-propylaminocarbonylmethyl, N-
methyl-N-butylaminocarbonylmethyl, N-methyl-N-hexyl-
aminocarbonylmethyl, 2-methylaminocarbonylethyl, 1-
ethylaminocarbonylethyl, 3-propylaminocarbonylpropyl, 4-
butylaminocarbonylbutyl, 1,1-dimethyl-2-pentylaminocar-
20 bonylethyl, 5-hexylaminocarbonylpentyl, 6-dimethylamino-
carbonylhexyl, 2-diethylaminocarbonylethyl, 1-(N-
methyl-N-hexylamino)carbonylethyl, 3-dihexylamino-
carbonylpropyl, 4-dibutylaminocarbonylbutyl,
2-(N-methyl-N-pentylamino)carbonylethyl and the like.
- 25 As to the hydroxyl group-containing lower alkyl
group can be exemplified by straight chain or branched
chain alkyl groups each of 1-6 carbonyl atoms, each
having 1-3 hydroxyl groups, such as 2-hydroxyethyl, 3-

- 1 hydroxypropyl, 4-hydroxybutyl, 2-hydroxybutyl, 3-hydroxybutyl, 5-hydroxypentyl, 2-hydroxypentyl, 3-hydroxypentyl, 4-hydroxypentyl, 6-hydroxyhexyl, 2-hydroxyhexyl, 3-hydroxyhexyl, 4-hydroxyhexyl,
- 5 1-methyl-2-hydroxyethyl, 2-hydroxypropyl, 1,1-dimethyl-2-hydroxyethyl, 1,2-dihydroxyethyl, 2,2-dihydroxyethyl, 1,3-dihydroxypropyl, 2,3-dihydroxypropyl, 1,2,3-trihydroxypropyl, 1,4-dihydroxybutyl, 2,4-dihydroxybutyl, 3,4-dihydroxybutyl, 1,2-dihydroxybutyl, 2,3-dihydroxybutyl, 1,3-dihydroxybutyl, 2,2-dihydroxybutyl, 1,2,3-trihydroxybutyl, 2,3,4-trihydroxybutyl, 2,3-dihydroxypentyl, 3,4-dihydroxypentyl, 3,5-dihydroxypentyl, 2,3,4-trihydroxypentyl, 3,4,5-trihydroxypentyl, 2,4,5-trihydroxypentyl, 2,3-dihydroxyhexyl, 2,5-dihydroxyhexyl, 2,6-dihydroxyhexyl, 3,4-dihydroxyhexyl, 4,5-dihydroxyhexyl, 4,6-dihydroxyhexyl, 5,6-dihydroxyhexyl, 2,3,4-trihydroxyhexyl, 3,4,5-trihydroxyhexyl, 4,5,6-trihydroxyhexyl and the like.
- 15

As to the imidazolyl-substituted lower alkyl group, there can be mentioned, for example, imidazolyl-alkyl groups whose alkyl portions are each a straight chain or branched chain alkyl group of 1-6 carbon atoms, such as (2-imidazolyl)-methyl, 2-(1-imidazolyl)ethyl, 1-(4-imidazolyl)ethyl, 3-(5-imidazolyl)propyl, 4-(2-imidazolyl)-butyl, 1,1-dimethyl-2-(4-imidazolyl)ethyl, 5-(1-imidazolyl)pentyl, 6-(5-imidazolyl)hexyl, 2-methyl-3-(1-imidazolyl)propyl and the like.

20

25

The pyridyl-substituted lower alkyl group can



1 be exemplified by pyridyl-substituted alkyl groups whose
alkyl portions are each a straight chain or branched
chain alkyl group of 1-6 carbon atoms, such as (2-
pyridyl)methyl, 2-(3-pyridyl)ethyl, 1-(4-pyridyl)ethyl,
5 3-(4-pyridyl)propyl, 4-(2-pyridyl)butyl, 1,1-dimethyl-2-
(3-pyridyl)ethyl, 5-(4-pyridyl)pentyl, 6-(2-pyridyl)-
hexyl, 2-methyl-3-(3-pyridyl)propyl and the like.

The pyrrolidinyl-lower alkyl group which may
have, as substituent(s) on the pyrrolidine ring, 1-3
10 groups selected from the group consisting of a lower
alkyl group, a lower alkoxy-lower alkoxy group and a
hydroxyl group, can be exemplified by pyrrolidinylalkyl
groups whose alkyl groups are each a straight chain or
branched chain alkyl group of 1-6 carbon atoms and which
15 may have, as substituent(s) on the pyrrolidine ring, 1-3
groups selected from the group consisting of a straight
chain or branched chain alkyl group of 1-6 carbon atoms
and a hydroxyl group, such as (2-pyrrolidinyl)methyl, 2-
(3-pyrrolidinyl)ethyl, 1-(2-pyrrolidinyl)ethyl, 3-(2-
20 pyrrolidinyl)propyl, 4-(3-pyrrolidinyl)butyl, 5-(3-
pyrrolidinyl)pentyl, 6-(2-pyrrolidinyl)hexyl, (3-
methoxymethoxy-1-ethoxy-2-pyrrolidinyl)methyl, (1,3-
dimethyl-4-ethoxymethoxy-2-pyrrolidinyl)methyl, 2-(3-
propoxymethoxy-1-pyrrolidinyl)ethyl, 1,1-dimethyl-2-(2-
25 pyrrolidinyl)ethyl, 2-methyl-3-(3-pyrrolidinyl)propyl,
(1-ethyl-4-hydroxy-2-pyrrolidinyl)methyl, 2-(1-methyl-3-
pyrrolidinyl)ethyl, 1-(1-propyl-2-pyrrolidinyl)-ethyl,
3-(1-butyl-4-hydroxy-2-pyrrolidinyl)propyl, 4-(1-pentyl-

- 1 3,4-dihydroxy-3-pyrrolidinyl)butyl, 5-(1-hexyl-3-
pyrrolidinyl)pentyl, 6-(1-methyl-2-pyrrolidinyl)hexyl,
(1,3-dimethyl-4-hydroxy-2-pyrrolidinyl)methyl, 2-(3-
hydroxy-2-pyrrolidinyl)ethyl, (4-hydroxy-2-pyrrolidinyl)-
5 methyl, 3-(5-hydroxy-2-pyrrolidinyl)propyl and the like.

As to the lower alkoxy carbonyl group, there can
be mentioned, for example, alkoxy carbonyl groups whose
alkoxy portions are each a straight chain or branched
chain alkoxy group of 1-6 carbon atoms, such as methoxy-
10 carbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxy-
carbonyl, butoxycarbonyl, pentyloxycarbonyl, hexyloxy-
carbonyl and the like.

As to the cycloalkyl-lower alkyl group, there
can be mentioned, for example, cycloalkylalkyl groups
15 each of 3-8 carbon atoms, whose alkyl portions are each a
straight chain or branched chain alkyl group of 1-6
carbon atoms, such as cyclopropylmethyl, cyclobutyl-
methyl, cyclopentylmethyl, cyclohexylmethyl, cyclo-
heptylmethyl, cyclooctylmethyl, 2-cyclopropylethyl, 1-
20 cyclobutylethyl, 3-cyclopentylpropyl, 4-cyclohexylbutyl,
5-cycloheptylpentyl, 6-cyclooctylhexyl, 2-methyl-3-
cyclohexylpropyl, 2-cyclohexylethyl, 1-cyclohexylethyl
and the like.

As to the cycloalkyl group, there can be
25 mentioned, for example, cycloalkyl groups each of 3-8
carbon atoms, such as cyclopropyl, cyclobutyl,
cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl,
cyclononanyl, cyclodecanyl and the like.

1 The lower alkoxy group can be exemplified by
straight chain or branched chain alkoxy groups each of
1-6 carbon atoms, such as methoxy, ethoxy, propoxy,
isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy and
5 the like.

As to the lower alkyl group, there can be men-
tioned, for example, straight chain or branched chain
alkyl groups each of 1-6 carbon atoms, such as methyl,
ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl,
10 hexyl and the like.

The phenyl-lower alkyl group which may have, as
substituent(s) on the phenyl ring, 1-3 groups selected
from the group consisting of a halogen atom, a lower
alkyl group, a cyano group, a carboxy group and a lower
15 alkoxy group, can be exemplified by phenylalkyl groups
whose alkyl portions are each a straight chain or
branched chain alkyl group of 1-6 carbon atoms and which
may have, as substituent(s) on the phenyl ring, 1-3
groups selected from the group consisting of a halogen
20 atom, a straight chain or branched chain alkyl group of
1-6 carbon atoms, a carboxy group, a cyano group and
a straight chain or branched chain alkoxy group of 1-6
carbon atoms, such as benzyl, 2-phenylethyl, 1-
phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 1,1-
25 dimethyl-2-phenylethyl, 5-phenylpentyl, 6-phenylhexyl,
2-methyl-3-phenylpropyl, 2-chlorobenzyl, 2-(3-
chlorophenyl)ethyl, 1-(4-chlorophenyl)ethyl, 3-(2-
fluorophenyl)propyl, 4-(3-fluorophenyl)butyl, 1,1-

- 1 dimethyl-2-(4-fluorophenyl)ethyl, 5-(2-bromophenyl)-
pentyl, 6-(3-bromophenyl)hexyl, 2-methyl-3-(4-
bromophenyl)propyl, 4-fluorobenzyl, 3-iodobenzyl, 2-(4-
iodophenyl)ethyl, 1-(3,5-dichlorophenyl)ethyl, 3,4-
5 dichlorobenzyl, 2-(3,4-dichlorophenyl)ethyl, 3-(2,6-
dichlorophenyl)propyl, 4-(3,4-dichlorophenyl)butyl, 1,1-
dimethyl-2-(3,4-difluorophenyl)ethyl, 5-(3,5-
dibromophenyl)-pentyl, 6-(3,4,5-trichlorophenyl)hexyl,
4-methylbenzyl, 2-(2-methylphenyl)ethyl, 1-(3-
10 methylphenyl)-ethyl, 3-(3-ethylphenyl)propyl, 4-(2-
ethylphenyl)butyl, 5-(4-ethylphenyl)pentyl, 6-(3-
isopropylphenyl)hexyl, 2-methyl-3-(4-hexylphenyl)propyl,
2-(3,4-dimethylphenyl)ethyl, 2-(2,5-dimethylphenyl)ethyl,
2-(3,4,5-trimethylphenyl)ethyl, 4-methoxybenzyl, 3,4-
15 dimethoxybenzyl, 3,4,5-trimethoxybenzyl, 1-(3-
methoxyphenyl)ethyl, 2-(2-methoxyphenyl)ethyl, 3-(2-
ethoxyphenyl)propyl, 4-(4-ethoxyphenyl)butyl, 5-(3-
ethoxyphenyl)pentyl, 6-(4-isopropoxyphenyl)hexyl, 1,1-
dimethyl-2-(4-hexyloxyphenyl)ethyl, 2-methyl-3-(3,4-
20 dimethoxyphenyl)propyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-
(3,4-diethoxyphenyl)ethyl, 2-(3,4,5-trimethoxyphenyl)-
ethyl, 1-(2,5-dimethoxyphenyl)ethyl, (2-chloro-4-
methoxy)benzyl, 4-cyanobenzyl, 1-(3-cyanophenyl)ethyl,
1-(2-cyanophenyl)propyl, 1-(2,3-dicyanophenyl)butyl, 1-
25 (2,3,4-tricyanophenyl)pentyl, 1-(2,4-dicyanophenyl)hexyl,
4-carboxybenzyl, 1-(3-carboxyphenyl)ethyl, 1-(2-
carboxyphenyl)propyl, 1-(2,4-dicarboxyphenyl)butyl, 1-
(2,4,6-tricarboxyphenyl)pentyl, 1-(2-chloro-4-

1 carboxyphenyl)hexyl, (3-methyl-4-cyano)benzyl and the like.

As to the thienyl-substituted lower alkyl group, there can be mentioned, for example, thienyl-
5 substituted alkyl groups whose alkyl portions are each a straight chain or branched chain alkyl group of 1-6 carbon atoms, such as (2-thienyl)methyl, 2-(3-thienyl)-ethyl, 1-(2-thienyl)ethyl, 3-(2-thienyl)propyl, 4-(3-thienyl)butyl, 1,1-dimethyl-2-(2-thienyl)ethyl, 5-(3-
10 thienyl)pentyl, 6-(2-thienyl)hexyl, 2-methyl-3-(3-thienyl)propyl and the like.

The cycloalkylcarbonyl group can be exemplified by cycloalkylcarbonyl groups each of 3-10 carbon atoms, such as cyclopropylcarbonyl, cyclobutylcarbonyl,
15 cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl, cyclooctylcarbonyl, cyclononanylcabonyl, cyclodecanylcarbonyl and the like.

As to the tetrahydropyranyl-substituted lower alkyl group, there can be mentioned tetrahydropyranyl-
20 substituted alkyl groups whose alkyl portions are each a straight chain or branched chain alkyl group of 1-6 carbon atoms, such as (2-tetrahydropyranyl)methyl, (3-tetrahydropyranyl)methyl, (4-tetrahydropyranyl)methyl, 2-(2-tetrahydropyranyl)ethyl, 2-(3-tetrahydropyranyl)-
25 ethyl, 2-(4-tetrahydropyranyl)ethyl, 1-(2-tetrahydropyranyl)ethyl, 1-(3-tetrahydropyranyl)ethyl, 1-(4-tetrahydropyranyl)ethyl, 3-2-(tetrahydropyranyl)propyl, 3-(3-tetrahydropyranyl)propyl, 3-(4-tetrahydropyranyl)-



1 propyl, 4-(2-tetrahydropyranyl)butyl, 4-(3-
tetrahydropyranyl)butyl, 4-(4-tetrahydropyranyl)butyl,
1,1-dimethyl-2-(2-tetrahydropyranyl)ethyl,
1,1-dimethyl-2-(3-tetrahydropyranyl)ethyl,
5 1,1-dimethyl-2-(4-tetrahydropyranyl)ethyl, 5-(2-
tetrahydropyranyl)pentyl, 5-(3-tetrahydropyranyl)pentyl,
5-(4-tetrahydropyranyl)pentyl, 6-(2-tetrahydropyranyl)-
hexyl, 6-(3-tetrahydropyranyl)hexyl, 6-(4-tetrahydro-
pyranyl)hexyl, 2-methyl-3-(2-tetrahydropyranyl)propyl,
-10 2-methyl-3-(3-tetrahydropyranyl)propyl, 2-methyl-3-(4-
tetrahydropyranyl)propyl and the like.

The phenyl-lower alkylsulfonyl group can be
exemplified by phenylalkylsulfonyl groups whose alkyl
portions are each a straight chain or branched chain
15 alkyl group of 1-6 carbon atoms, such as benzylsulfonyl,
2-phenylethylsulfonyl, 1-phenylethylsulfonyl, 3-
phenylpropylsulfonyl, 4-phenylbutyl-sulfonyl, 1,1-
dimethyl-2-phenylethylsulfonyl, 5-phenylpentylsulfonyl,
6-phenylhexylsulfonyl, 2-methyl-3-phenylpropylsulfonyl
20 and the like.

As to the cycloalkyl-lower alkylsulfonyl group,
there can be mentioned, for example, cycloalkylalkyl-
sulfonyl groups each of 3-8 carbon atoms, whose alkyl
portions are each a straight chain or branched chain
25 alkyl group of 1-6 carbon atom, such as cyclopropyl-
methylsulfonyl, cyclobutylmethylsulfonyl, cyclopentyl-
methylsulfonyl, cyclohexylmethylsulfonyl, cycloheptyl-
methylsulfonyl, cyclooctylmethylsulfonyl, 2-cyclopropyl-

1 ethylsulfonyl, 1-cyclobutylethylsulfonyl, 3-cyclo-
pentylpropylsulfonyl, 4-cyclohexylbutylsulfonyl, 5-
cycloheptylpentylsulfonyl, 6-cyclooctylhexylsulfonyl, 2-
methyl-3-cyclohexylpropylsulfonyl, 2-cyclohexylethylsul-
5 fonyl, 1-cyclohexylethylsulfonyl and the like.

The cycloalkyl-lower alkyl group-substituted or unsubstituted aminocarbonyl group can be exemplified by aminocarbonyl groups which may have, as substituent(s), 1-2 cycloalkylalkyl groups each of 3-8 carbon atoms whose
10 alkyl portions are each a straight chain or branched chain alkyl group of 1-6 carbon atoms, such as aminocarbonyl, cyclohexylmethylaminocarbonyl, cyclopropylmethylaminocarbonyl, cyclobutylmethylaminocarbonyl, cyclopentylmethylaminocarbonyl, cycloheptylmethylamino-
15 carbonyl, cyclooctylmethylaminocarbonyl, (2-cyclopropylethyl)aminocarbonyl, (1-cyclobutylethyl)aminocarbonyl, (3-cyclopentylpropyl)aminocarbonyl, (4-cyclohexylbutyl)aminocarbonyl, (5-cycloheptylpentyl)aminocarbonyl, (6-cyclooctylhexyl)aminocarbonyl, (2-
20 methyl-3-cyclohexylpropyl)aminocarbonyl, (2-cyclohexylethyl)aminocarbonyl, (1-cyclohexylethyl)aminocarbonyl, dicyclohexylmethylaminocarbonyl, N-cyclohexylmethyl-N-cycloheptylmethylaminocarbonyl and the like.

25 The lower alkylene group which may have a hydroxyl group, can be exemplified by the above-mentioned lower alkylene groups and further by straight chain or branched chain alkylene groups each of 1-6 carbon atoms

1 which may have hydroxyl group(s), such as 2-hydroxy-
trimethylene, 2-hydroxytetramethylene, 2,3-dihydroxy-
tetramethylene, 3-hydroxypentamethylene, 3-hydroxy-
tetramethylene, 5-hydroxyhexamethylene and the like.

5 The phenyl-lower alkyl group which may have, as
substituent(s) on the phenyl ring, 1-3 groups selected
from the group consisting of a halogen atom, a lower
alkyl group and a lower alkoxy group, can be exemplified
by phenylalkyl groups whose alkyl portions are each a
10 straight chain or branched chain alkyl group of 1-6
carbon atoms and which may have, as substituent(s) on the
phenyl ring, 1-3 groups selected from the group consist-
ing of a halogen atom, a straight chain or branched chain
alkyl group of 1-6 carbon atoms and a straight chain or
15 branched chain alkoxy group of 1-6 carbon atoms, such as
benzyl, 2-phenylethyl, 1-phenylethyl, 3-phenylpropyl, 4-
phenylbutyl, 1,1-dimethyl-2-phenylethyl, 5-phenylpentyl,
6-phenylhexyl, 2-methyl-3-phenylpropyl, 2-chlorobenzyl,
2-(3-chlorophenyl)ethyl, 1-(4-chlorophenyl)ethyl, 3-(2-
20 fluorophenyl)propyl, 4-(3-fluorophenyl)butyl, 1,1-
dimethyl-2-(4-fluorophenyl)ethyl, 5-(2-bromophenyl)-
pentyl, 6-(3-bromophenyl)hexyl, 2-methyl-3-(4-bromo-
phenyl)propyl, 4-fluorobenzyl, 3-iodobenzyl, 2-(4-
iodophenyl)ethyl, 1-(3,5-dichlorophenyl)ethyl, 3,4-
25 dichlorobenzyl, 2-(3,4-dichlorophenyl)ethyl, 3-(2,6-
dichlorophenyl)propyl, 4-(3,4-dichlorophenyl)butyl, 1,1-
dimethyl-2-(3,4-difluorophenyl)ethyl, 5-(3,5-dibromo-
phenyl)pentyl, 6-(3,4,5-trichlorophenyl)hexyl, 4-



- 1 methylbenzyl, 2-(2-methylphenyl)ethyl, 1-(3-methyl-
phenyl)ethyl, 3-(3-ethylphenyl)propyl, 4-(2-ethyl-
phenyl)butyl, 5-(4-ethylphenyl)pentyl, 6-(3-isopropyl-
phenyl)hexyl, 2-methyl-3-(4-hexylphenyl)propyl, 2-(3,4-
5 dimethylphenyl)ethyl, 2-(2,5-dimethylphenyl)ethyl, 2-
(3,4,5-trimethylphenyl)ethyl, 4-methoxybenzyl, 3,4-
dimethoxybenzyl, 3,4,5-trimethoxybenzyl, 1-(3-
methoxyphenyl)ethyl, 2-(2-methoxyphenyl)ethyl, 3-(2-
ethoxyphenyl)propyl, 4-(4-ethoxyphenyl)butyl, 5-(3-
10 ethoxyphenyl)pentyl, 6-(4-isopropoxyphenyl)hexyl, 1,1-
dimethyl-2-(4-hexyloxyphenyl)ethyl, 2-methyl-3-(3,4-
dimethoxyphenyl)propyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-
(3,4-diethoxyphenyl)ethyl, 2-(3,4,5-trimethoxyphenyl)
ethyl, 1-(2,5-dimethoxyphenyl)ethyl, (2-chloro-4-
15 methoxy)benzyl and the like.

- As to the piperidinyl-lower alkyl group which
may have, as a substituent on the piperidinyl ring, a
lower alkoxy-lower alkoxy group or a hydroxyl group,
there can be mentioned, for example, piperidinylalkyl
20 groups whose alkyl portions are each a straight chain or
branched chain alkyl group of 1-6 carbon atoms and which
may have, as substituent(s) on the piperidinyl ring, 1-3
hydroxyl groups or 1-3 alkoxyalkoxy groups whose alkoxy
portions are each a straight chain or branched chain
25 alkoxy group of 1-6 carbon atoms, such as (4-hydroxy-1-
piperidinyl)methyl, 2-(4-hydroxy-1-piperidinyl)ethyl, 1-
(4-hydroxy-1-piperidinyl)ethyl, 3-(4-hydroxy-1-piperi-
dinyl)propyl, 4-(4-hydroxy-1-piperidinyl)butyl, 5-(4-

1 hydroxy-1-piperidinyl)pentyl, 6-(4-hydroxy-1- piperi-
diny1)-hexyl, 1,1-dimethyl-2-(3-hydroxy-1-piperidinyl)-
ethyl, 2-methyl-3-(2-hydroxy-1-piperidinyl)propyl,
2-(2,4-dihydroxy-1-piperidinyl)ethyl, 3-(2-hydroxy-4-
5 piperidinyl)propyl, (2,4,6-trihydroxy-1-piperidinyl)-
methyl, 1-(2-hydroxy-3-piperidinyl)ethyl, 4-(3-hydroxy-2-
piperidinyl)-butyl, 5-(3-hydroxy-4-piperidinyl)pentyl,
6-(2-hydroxy-3-piperidinyl)hexyl, 2-(4-methoxymethoxy-1-
piperidinyl)ethyl, 3-(4-ethoxymethoxy-1-piperidinyl)
10 propyl, 2-(2,4-dimethoxymethoxy-1-piperidinyl)ethyl and
the like.

The five- or six-membered saturated hetero-
cyclic ring group formed by R^7 and R^8 or by R^{10} and R^{11}
together with the nitrogen atom to which R^7 and R^8 or R^{10}
15 and R^{11} bond and further with or without a nitrogen,
sulfur or oxygen atom which may be present between R^7
and R^8 or R^{10} and R^{11} , can be exemplified by
pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,
thiomorpholinyl, isothiazolidinyl, 3,4,5,6-tetrahydro-
20 1,2-thiazinyl.

The above heterocyclic ring group having 1-3
substituents selected from the group consisting of a
hydroxyl group, a lower alkoxy-lower alkoxy group, a
lower alkyl group which may have a lower alkoxy-lower
25 alkoxy group or a hydroxyl group, a lower alkyl-
substituted or unsubstituted amino group, an oxo group
and a lower alkyl-substituted or unsubstituted
aminocarbonyl group, or having a lower alkylenedioxy

1 group as a substituent, can be exemplified by the above
heterocyclic ring groups each having 1-3 substituents
selected from the group consisting of a hydroxyl group,
an alkoxyalkoxy group whose alkoxy portion is a straight
5 chain or branched chain alkoxy group of 1-6 carbon atoms,
a straight chain or branched chain alkyl group of 1-6
carbon atoms which may have, as substituent(s), 1-3
hydroxyl groups or 1-3 alkoxyalkoxy groups whose alkoxy
portions are each a straight chain or branched chain
10 alkoxy group of 1-6 carbon atoms, an amino group which
may have, as substituent(s), 1-2 straight chain or
branched chain alkyl groups each of 1-6 carbon atoms, an
oxo group, and an aminocarbonyl group which may have, as
substituent(s), 1-2 straight chain or branched chain
15 alkyl groups each of 1-6 carbon atoms, or each having, as
a substituent, a straight chain or branched chain
alkylenedioxy group of 1-4 carbon atoms, such as 4-
hydroxy-1-piperidinyl, 2,6-dimethyl-1-piperidinyl, 4-
methylamino-1-piperidinyl, 4,4-ethylenedioxy-1-
20 piperidinyl, 3,4-dihydroxy-1-pyrrolidinyl, 2-methoxy-
methoxy-methyl-1-pyrrolidinyl, 2-methoxymethoxymethyl-4-
hydroxy-1-pyrrolidinyl, 5-methoxymethoxymethyl-2-oxo-1-
pyrrolidinyl, 4-(2-methoxymethoxyethyl)-1-piperazinyl,
2-hydroxymethyl-1-pyrrolidinyl, 2-dimethylaminocarbonyl-
25 1-pyrrolidinyl, 2-hydroxymethyl-4-hydroxy-1-pyrrolidinyl,
1,1-dioxo-3,4,5,6-tetrahydro-1,2-thiazin-2-yl, 4-(2-
hydroxyethyl)-1-piperazinyl, 4-dimethylamino-1-
piperidinyl, 1,1-dioxo-2-isothiazolidinyl, 3-hydroxy-1-

1 pyrrolidinyl, 2-dimethylamino-1-pyrrolidinyl, 4-
methoxymethoxy-1-piperidinyl, 4-(2-ethoxyethoxy)-1-
piperidinyl, 3-propoxypropoxy-1-pyrrolidinyl, 3-(4-
butoxybutoxy)thiomorpholino, 2-(5-pentyloxy-pentyloxy)-
5 morpholino, 3-(6-hexyloxy-hexyloxy)-3,4,5,6-tetrahydro-
1,2-thiazin-2-yl, 2-oxo-5-hydroxymethyl-1-pyrrolidinyl,
4-methyl-1-piperazinyl, 2,4,6-trimethyl-1-piperidinyl,
3-ethyl-1-pyrrolidinyl, 3-propyl-1-piperazinyl, 3-
methylmorpholino, 5-butyl-2-thiomorpholino, 2-amino-1-
10 pyrrolidinyl, 4-(N-methyl-N-propylamino)-1-piperidinyl,
3-dibutylamino-1-piperazinyl, 3-(N-ethyl-N-pentylamino)-
morpholino, 2-dihexylaminomorpholino, 3-dimethyl-
aminocarbonyl-1-pyrrolidinyl, 3-methylaminocarbonyl-1-
piperidinyl, 2-ethylaminocarbonylmorpholino, 3-
15 propylaminocarbonyl-1-piperazinyl, 3-butylaminocarbonyl-
2-thiomorpholino, 3-pentylaminocarbonyl-3,4,5,6-
tetrahydro-1,2-thiazin-2-yl, 3-hexylaminocarbonyl-2-
isothiazolidinyl, 3-dibutylaminocarbonyl-1-piperazinyl,
4-(N-methyl-N-ethylaminocarbonyl)-1-piperidinyl, 4-
20 hydroxy-2,6-dimethyl-1-piperidinyl, 2-oxo-1-piperazinyl,
3-oxo-1-piperazinyl, 4,4-methylenedioxy-1-piperazinyl and
the like.

The above heterocyclic ring group having 1-3
substituents selected from the group consisting of a
25 hydroxyl group, a lower alkoxy-lower alkoxy group, an oxo
group, a lower alkyl group which may have a lower alkoxy-
lower alkoxy group or a hydroxyl group, and a lower alkyl
group-substituted or unsubstituted amino group, or having

1 a lower alkylenedioxy group as a substituent, can be
exemplified by the above heterocyclic ring groups each
having 1-3 substituents selected from the group
consisting of a hydroxyl group, an alkoxyalkoxy group
5 whose alkoxy portion is a straight chain or branched
chain alkoxy group of 1-6 carbon atoms, a straight chain
or branched chain alkyl group of 1-6 carbon atoms which
may have, as substituent(s), 1-3 hydroxyl groups or 1-3
alkoxyalkoxy groups whose alkoxy portions are each a
10 straight chain or branched chain alkoxy group of 1-6
carbon atoms, an amino group which may have 1-2 straight
chain or branched chain alkyl groups each of 1-6 carbon
atoms, and an oxo group, or each having a straight chain
or branched chain alkylenedioxy group of 1-4 carbon atoms
15 as a substituent, such as 4-hydroxy-1-piperidinyl, 2,6-
dimethyl-1-piperidinyl, 4-methylamino-1-piperidinyl,
4,4-ethylenedioxy-1-piperidinyl, 3,4-dihydroxy-1-
pyrrolidinyl, 2-methoxymethoxymethyl-1-pyrrolidinyl, 2-
methoxymethoxymethyl-4-hydroxy-1-pyrrolidinyl, 5-methoxy-
20 methoxymethyl-2-oxo-1-pyrrolidinyl, 4-(2-methoxymethoxy-
ethyl)-1-piperazinyl, 2-hydroxymethyl-1-pyrrolidinyl, 2-
hydroxymethyl-4-hydroxy-1-pyrrolidinyl, 1,1-dioxo-
3,4,5,6-tetrahydro-1,2-thiazin-2-yl, 4-(2-hydroxyethyl)-
1-piperazinyl, 4-dimethylamino-1-piperidinyl, 1,1-dioxo-
25 2-isothiazolydinyl, 3-hydroxy-1-pyrrolidinyl, 2-dimethyl-
amino-1-pyrrolidinyl, 4-methoxymethoxy-1-piperidinyl, 4-
(2-ethoxyethoxy)-1-piperidinyl, 3-propoxypropoxy-1-
pyrrolidinyl, 3-(4-butoxybutoxy)thiomorpholino, 2-(5-



1 pentyloxy pentyloxy)morpholino, 3-(6-hexyloxyhexyloxy)-
3,4,5,6-tetrahydro-1,2-thiazin-2-yl, 2-oxo-5-
hydroxymethyl-1-pyrrolidinyl, 4-methyl-1-piperazinyl,
2,4,6-trimethyl-1-piperidinyl, 3-ethyl-1-pyrrolidinyl,
5 3-propyl-1-piperazinyl, 3-methylmorpholino, 5-butyl-2-
thiomorpholino, 2-amino-1-pyrrolidinyl, 4-(N-methyl-N-
propylamino)-1-piperidinyl, 3-dibutylamino-1-piperazinyl,
3-(N-ethyl-N-pentylamino)morpholino, 2-dihexylamino-
thiomorpholino, 3-dimethylaminocarbonyl-1-pyrrolidinyl,
10 3-methylaminocarbonyl-1-piperidinyl, 2-ethylamino-
carbonylmorpholino, 4-hydroxy-2,6-dimethyl-1-piperidinyl,
2-oxo-1-piperazinyl, 3-oxo-1-piperazinyl, 4,4-
methylenedioxy-1-piperazinyl and the like.

The five- or six-membered saturated or unsatu-
15 rated heterocyclic ring residue containing 1-3 nitrogen
atoms, can be exemplified by pyrrolyl, 2H-pyrrolyl,
imidazolyl, pyrazolyl, pyridyl, pyridazyl, pyrimidyl,
pyrazyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazolyl,
imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl,
20 piperidinyl, piperazinyl, 1,2,4-triazolyl and 1,3,4-
triazolyl.

The above heterocyclic ring residue having,
assubstituent(s), a hydroxyl group, a lower alkoxyalkoxy
group, a lower alkoxycarbonyl group or a lower alkyl
25 group which may be substituted with a lower alkoxy-lower
alkoxy group or a hydroxyl group, can be exemplified by
the above heterocyclic ring residues each having, as
substituent(s), a hydroxyl group, an alkoxyalkoxy group

1 whose alkoxy portion is a straight chain or branched
chain alkoxy group of 1-6 carbon atoms, a straight chain
or branched chain alkoxycarbonyl group of 1-6 carbon
atoms, or a straight chain or branched chain alkyl group
5 of 1-6 carbon atoms which may have, as substituent(s),
1-3 hydroxyl groups or 1-3 alkoxyalkoxy groups whose
alkoxy portions are each a straight chain or branched
chain alkoxy group of 1-6 carbon atoms, such as 4-
hydroxy-1-piperidinyl, 3-hydroxy-1-piperidinyl,
10 2-hydroxy-1-piperidinyl, 2-methoxycarbonyl-1-
pyrrolidinyl, 2-methoxymethoxymethyl-1-pyrrolidinyl,
2-(2-methoxymethoxyethyl)-1-imidazolyl, 3-methoxy-
methoxymethyl-pyrazolyl, 4-(3-ethoxymethoxypropyl)-2-
pyrimidyl, 4-methoxymethoxymethyl-2-imidazolin-2-yl, 4-
15 ethoxymethoxymethyl-1-pyrazolidinyl, 2-hydroxymethyl-1-
pyrrolidinyl, 2-(2-hydroxyethyl)-1-imidazolyl, 3-
ethoxycarbonyl-1,2,4-triazol-1-yl, 3-hydroxy-1-pyrrolyl,
3-ethoxycarbonyl-2H-pyrrolyl, 3-hydroxymethyl-pyrazolyl,
4-hydroxy-2-pyridyl, 4-ethoxycarbonyl-3-pyridazyl, 4-(3-
20 hydroxypropyl)-2-pyrimidyl, 2-propoxycarbonyl-3-pyrazyl,
2-hydroxy-2-pyrrolinin-1-yl, 4-hydroxymethyl- 2-
imidazolin-2-yl, 2-methoxycarbonyl-1-imidazolidinyl, 3-
methoxymethoxy-1-pyrrolidinyl, 4-(2-ethoxyethoxy)-1-
piperidinyl, 4-methoxymethoxy-1-piperidinyl, 3-hydroxy-
25 2-pyrazolin-1-yl, 4-hydroxymethyl-1-pyrazolidinyl, 4-
ethoxycarbonyl-1-piperazinyl and the like.

The pyrrolidinyl group having 1-2 substituents
selected from the group consisting of a hydroxyl group, a



- 1 lower alkoxy-lower alkoxy group, a lower alkyl group
which may have, as substituent(s), a lower alkoxy-lower
alkoxy group or a hydroxyl group, a lower alkoxy-carbonyl
group, a piperidinylcarbonyl group and a cycloalkyl-lower
5 alkyl group-substituted or unsubstituted aminocarbonyl
group, can be exemplified by pyrrolidinyl groups each
having 1-2 substituents selected from the group
consisting of a hydroxyl group, an alkoxyalkoxy group
whose alkoxy portion is a straight chain or branched
10 chain alkoxy group of 1-6 carbon atoms, a straight chain
or branched chain alkyl group of 1-6 carbon atoms which
may have 1-3 hydroxyl groups or 1-3 alkoxyalkoxy groups
whose alkoxy portions are each a straight chain or
branched chain alkoxy group of 1-6 carbon atoms, a
15 straight chain or branched chain alkoxy-carbonyl group of
1-6 carbon atoms, a piperidinylcarbonyl group and an
aminocarbonyl group which may have 1-2 cycloalkylalkyl
group of 3-8 carbon atoms whose alkyl portion is a
straight chain or branched chain alkyl group of 1-6
20 carbon atoms, such as 2-methoxymethoxymethyl-1-
pyrrolidinyl, 2-methoxymethoxymethyl-4-methoxymethoxy-1-
pyrrolidinyl, 3,4-dihydroxy-1-pyrrolidinyl, 3,4-
dimethoxymethoxy-1-pyrrolidinyl, 2-hydroxymethyl-1-
pyrrolidinyl, 2-methoxycarbonyl-1-pyrrolidinyl, 2-(1-
25 piperidinylcarbonyl)-1-pyrrolidinyl, 2-cyclohexyl-
methylaminocarbonyl-1-pyrrolidinyl, 4-hydroxy-1-
pyrrolidinyl, 2-hydroxymethyl-4-hydroxy-1-pyrrolidinyl,
2-methoxycarbonyl-4-hydroxy-1-pyrrolidinyl, 2-(1-



- 1 piperidinylcarbonyl)-4-hydroxy-1-pyrrolidinyl, 2-cyclohexylmethylaminocarbonyl-4-hydroxy-1-pyrrolidinyl, 3-ethoxycarbonyl-1-pyrrolidinyl, 2-propoxycarbonyl-1-pyrrolidinyl, 3-butoxycarbonyl-1-pyrrolidinyl, 2-pentyloxycarbonyl-1-pyrrolidinyl, 3-hexyloxycarbonyl-1-pyrrolidinyl, 2-hydroxy-1-pyrrolidinyl, 3-hydroxy-1-pyrrolidinyl, 2-cycloheptylmethylaminocarbonyl-1-pyrrolidinyl, 3-cyclooctylmethylaminocarbonyl-1-pyrrolidinyl, 2-cyclopentylmethylaminocarbonyl-1-pyrrolidinyl, 3-cyclopropylmethylaminocarbonyl-1-pyrrolidinyl, 2-cyclobutylmethylaminocarbonyl-1-pyrrolidinyl, 2-(1-piperidinylcarbonyl)-4-methoxycarbonyl-1-pyrrolidinyl, 2-cyclohexylaminocarbonyl-4-methyl-1-pyrrolidinyl, 2-ethyl-4-hydroxy-1-pyrrolidinyl, 4-propyl-1-pyrrolidinyl, 2-hydroxymethyl-4-methoxymethoxy-1-pyrrolidinyl, 2-methoxycarbonyl-4-(2-ethoxyethoxy)-1-pyrrolidinyl, 2-(1-piperidinylcarbonyl)-4-propoxymethoxy-1-pyrrolidinyl, 2-cyclohexylmethylaminocarbonyl-4-butoxymethoxy-1-pyrrolidinyl and the like.

- 20 As to the lower alkoxy-lower alkoxy group, there can be mentioned, for example, alkoxyalkoxy groups whose alkoxy portions are each a straight chain or branched chain alkoxy group of 1-6 carbon atoms, such as methoxymethoxy, 3-methoxypropoxy, 4-ethoxybutoxy, 4-propoxyhexyloxy, 5-isopropoxy-pentyloxy, 1,1-dimethyl-2-butoxyethoxy, 2-methyl-tert-butoxypropoxy, 2-pentyloxyethoxy, hexyloxymethoxy and the like.

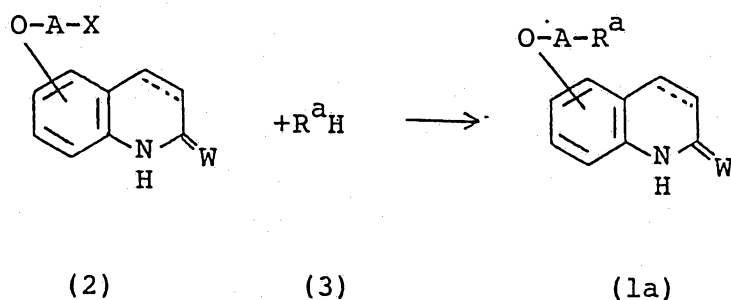
As to the halogen atom, there can be mentioned,



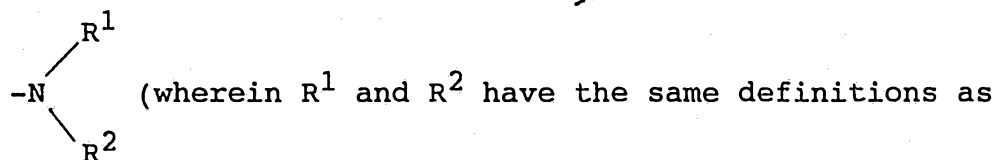
1 for example, a fluorine atom, a chlorine atom, a bromine
atom and an iodine atom.

The carbostyryl derivative represented by the
above general formula (1) can be produced by various
5 processes. It can be easily produced by, for example,
the processes shown by the following reaction formulas.

[Reaction formula-1]



[wherein A, W and the carbon-to-carbon bond between the
3- and 4-positions of the carbostyryl skeleton have the
10 same definitions as given above; R^a represents a group



given above.). X represents a halogen atom, a lower
alkanesulfonyloxy group, an arylsulfonyloxy group or an
aralkylsulfonyloxy group.]

15 The reaction between a compound of general
formula (2) and a compound of general formula (3) is
conducted in an appropriate solvent or in the absence of



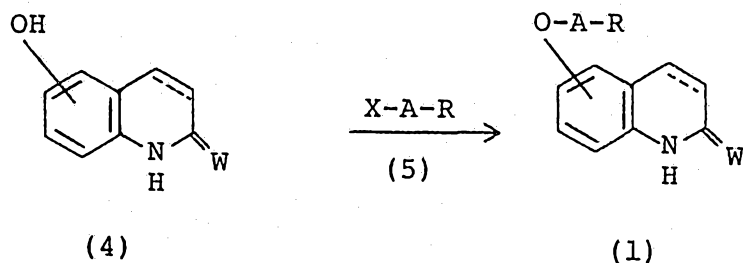
any solvent, in the presence or absence of a basic compound. The reaction is conducted generally at room temperature to 200°C, preferably at room temperature to 150°C, and is complete generally in about 1-30 hours. The solvent used can be exemplified by ethers such as dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, diethyl ether and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride and the like; lower alcohols such as methanol, ethanol, isopropanol and the like; polar solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, pyridine, acetone, actonitrile and the like. The basic compound used can be exemplified by inorganic bases such as potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium hydrogen-carbonate, sodium amide, sodium hydride, potassium hydride and the like; and organic bases such as triethylamine, tripropylamine, pyridine, quinoline and the like. The above reaction proceeds advantageously when an alkali metal iodide (e.g. potassium iodide or sodium iodide) or the like is added to the reaction system. The compound of general formula (3) is added in an amount of generally at least 1 mole, preferably 1-8 moles per mole of the compound of general formula (2).

In the reaction formula 1, the lower alkane-sulfonyloxy group represented by X can be exemplified by



1 methanesulfonyloxy, ethanesulfonyloxy, isopropane-
 sulfonyloxy, propanesulfonyloxy, butanesulfonyloxy,
 tert-butanesulfonyloxy, pentanesulfonyloxy and
 hexanesulfonyloxy. The arylsulfonyloxy group can be
 5 exemplified by substituted or unsubstituted aryl-
 sulfonyloxy groups such as phenylsulfonyloxy, 4-
 methylphenylsulfonyloxy, 2-methylphenylsulfonyloxy, 4-
 nitrophenylsulfonyloxy, 4-methoxyphenylsulfonyloxy, 3-
 chlorophenylsulfonyloxy, α -naphthylphenylsulfonyloxy and
 10 the like. The aralkylsulfonyloxy group can be
 exemplified by substituted or unsubstituted
 aralkylsulfonyloxy groups such as benzylsulfonyloxy, 2-
 phenylethylsulfonyloxy, 4-phenylbutylsulfonyloxy, 4-
 methylbenzylsulfonyloxy, 2-methylbenzylsulfonyloxy, 4-
 15 nitrobenzylsulfonyloxy, 4-methoxybenzylsulfonyloxy, 3-
 chlorobenzylsulfonyloxy, α -naphthylmethylsulfonyloxy and
 the like.

[Reaction formula-2]



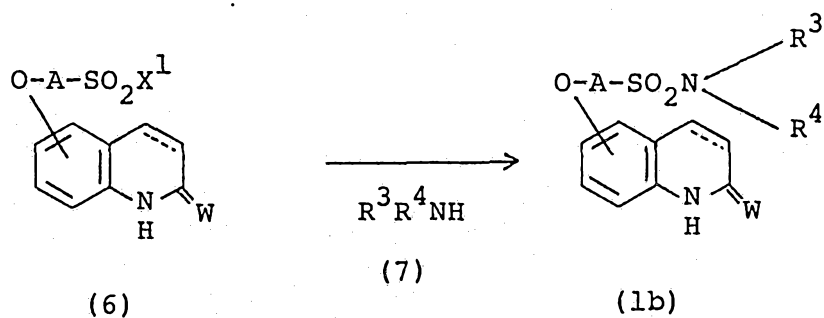
[wherein W, X, A, R and the carbon-to-carbon bond between
 20 the 3- and 4-positions of the carbostyryl skeleton have

the same definitions as given above.]

The reaction between a compound of general formula (4) and a compound of general formula (5) is conducted in an appropriate solvent, preferably using a basic compound as a dehalogenating agent, generally at room temperature to 200°C, preferably at 50-150°C in about 1-30 hours. The appropriate solvent can be exemplified by lower alcohols such as methanol, ethanol, isopropanol and the like; ketones such as acetone, methyl ethyl ketone and the like; ethers such as diethyl ether, dioxane, diethylene glycol dimethyl ether and the like; aromatic hydrocarbons such as toluene, xylene and the like; DMF; DMSO; and hexamethylphosphoric triamide. The basic compound usable as a dehalogenating agent can be exemplified by inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium methoxide, sodium ethoxide, potassium ethoxide, sodium hydroxide, metallic potassium, sodium amide and the like; and organic bases such as pyridine, quinoline, triethylamine, tripropylamine and the like. In the reaction, it is possible to add, as a reaction accelerator, an alkali metal iodide (e.g. potassium iodide or sodium iodide) to the reaction system. The amount of the compound of general formula (5) used has no restriction, but the compound is used in an amount of generally 1-5 moles, preferably 1-2 moles per mole of the compound of general formula (4).



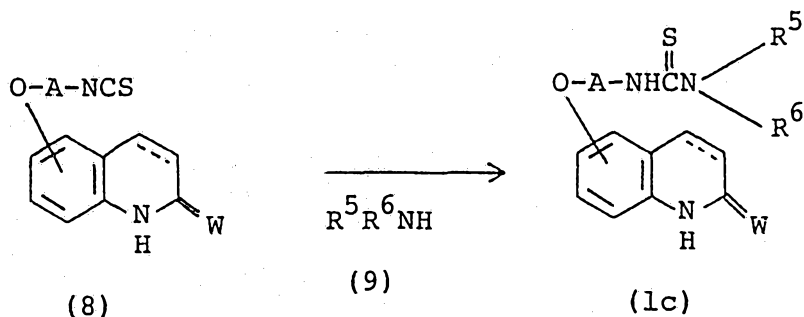
1 [Reaction formula-3]



[wherein A, W, R³, R⁴ and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as given above; x¹ represents a halogen atom].

The reaction between a compound (6) and a compound (7) can be conducted under the same conditions as employed in the reaction between the compound (2) and the compound (3) shown in the Reaction formula-1.

10 [Reaction formula-4]

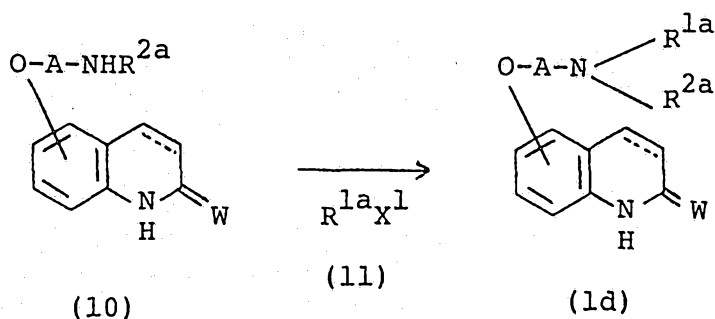


[wherein A, W, R⁵, R⁶ and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as given above.].



- 1 The reaction between a compound (8) and a compound (9) is conducted in the same solvent as used in the reaction between the compound (2) and the compound (3) shown in the reaction formula 1, generally at room temperature to 100°C, preferably at room temperature to about 70°C, and is complete generally in about 0.5-5 hours. The amount of the amine (9) used is generally 1-2 moles, preferably 1-1.5 moles per mole of the compound (8).

10 [Reaction formula-5]



[wherein A, W, R², X¹ and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as given above. R^{1a}

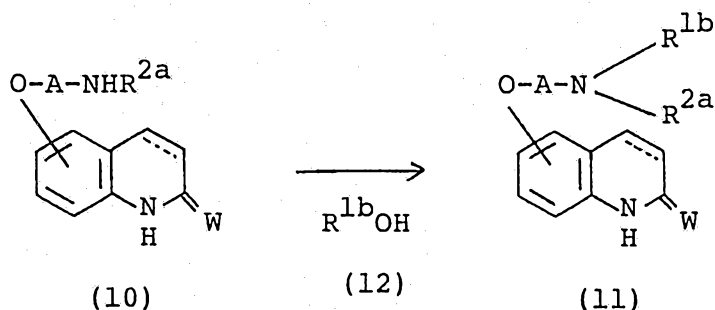
represents a group $-B-(CO)_m-N \begin{matrix} R^7 \\ R^8 \end{matrix}$ (B, m, R⁷ and R⁸ have

- 15 the same definitions as given above); a lower alkoxy-carbonyl-substituted lower alkyl group; a carboxy group-substituted lower alkyl group; a lower allyl group having

1 as a substituent, a lower alkyl group-substituted or
 unsubstituted aminocarbonyl group; a hydroxyl group-
 containing lower alkyl group; an imidazolyl-substituted
 lower alkyl group; a pyridyl-substituted lower alkyl
 5 group; pyrrolidinyl-lower alkyl group which may have, as
 substituent(s) on the pyrrolidine ring, 1-3 groups se-
 lected from the group consisting of a lower alkyl group,
 a lower alkoxy-lower alkoxy group and a hydroxyl group;
 or a group $-SO_2D-R^9$ (wherein D and R^9 have the same
 - 10 definitions as given above.); R^{2a} represents R^2 other
 than the case R^2 and R^1 form a pyrrolidinyl group
 together with the nitrogen atom to which R^2 and R^1
 bond].

The reaction between a compound (10) and a
 15 compound (11) can be conducted under the same conditions
 as employed in the reaction between the compound (2) and
 the compound (3) shown in the Reaction formula 1.

[Reaction formula-6]



[wherein A, W, R^{2a} and the carbon-to-carbon bond between

1 the 3- and 4-positions of the carbostyryl skeleton have
the same definitions as given above; R^{1b} represents a
group $-\text{CO}-\text{B}-(\text{CO})_m-\text{NR}^7\text{R}^8$ (wherein B, m, R^7 and R^8 have the
same definitions as given above].

5 The reaction between a compound of general
formula (10) and a compound of general formula (12) is
conducted in accordance with an ordinary amide bond
formation reaction. In the amide bond formation
reaction, there can be easily used known processes for
10 amide bond formation reaction. For example, there can be
mentioned, (a) a mixed acid anhydride process which
comprises reacting a carboxylic acid (12) with an
alkylhalocarboxylic acid to obtain a mixed acid anhydride
and reacting the anhydride with an amine (10); (b) an
15 active ester process which comprises converting a
carboxylic acid (12) to an active ester such as p-
nitrophenyl ester, N-hydroxysuccinimide ester, 1-
hydroxybenzotriazole ester or the like, and reacting the
active ester with an amine (10); (c) a carbodiimide
20 process which comprises subjecting a carboxylic acid (12)
and an amine (10) to condensation in the presence of an
activating agent such as dicyclohexylcarbodiimide,
carbonyldiimidazole or the like; and (d) other processes,
for example, a process which comprises converting a
25 carboxylic acid (12) to a carboxylic acid anhydride using
a dehydrating agent such as acetic anhydride or the like
and reacting the anhydride with an amine (10), a process
which comprises reacting a carboxylic acid (12) with a



- 1 lower alcohol to form an ester and reacting the ester
with an amine (10) at a high pressure and at a high
temperautre, and a process which comprises converting a
carboxylic acid (12) to an acid halide (a carboxylic acid
5 halide) and reacting the halide with an amine (10).

In the mixed acid anhydride process, the mixed
acid anhydride is obtained by an ordinary Schotten-Baumann
reaction and it is reacted with the amine (10) generally
without being isolated, to obtain a compound of general
10 formula (1f). The Schotten-Baumann reaction is conducted
in the presence of a basic compound. The basic compound
can be any of those generally used in the Schotten-
Baumann reaction, and includes, for example, organic
bases such as potassium carbonate, triethylamine,
15 trimethylamine, pyridine, dimethylaniline, N-methylmor-
pholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-
diazabicyclo[5.4.0]undecene-7 (DBU), 1,4-diazabicyclo-
[2.2.2]octane (DABCO) and the like, and inorganic bases
such as sodium carbonate, potassium hydrogencarbonate,
20 sodium hydrogencarbonate and the like. The reaction is
conducted generally at about -20 to 100°C, preferably at
about 0-50°C, and is complete in 5 minutes to 10 hours,
preferably 5 minutes to 2 hours. The reaction of the
thus obtained mixed acid anhydride with the amine (10) is
25 conducted generally at about -20 to 150°C, preferably at
about 10-50°C, and is complete in 5 minutes to 10 hours,
preferably 5 minutes to 5 hours. The mixed acid
anhydride process is conducted generally in a solvent.

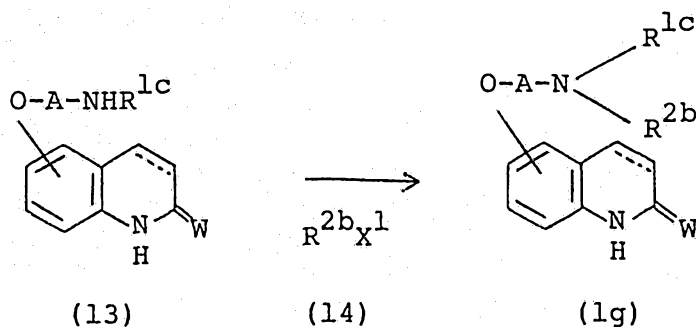


1 Any solvent generally used in the mixed acid anhydride
process can be used. Specific examples of the solvent
are halogenated hydrocarbons such as methylene chloride,
chloroform, dichloroethane and the like; aromatic
5 hydrocarbons such as benzene, toluene, xylene and the
like; ethers such as diethyl ether, tetrahydrofuran,
dimethoxyethane and the like; esters such as methyl
acetate, ethyl acetate and the like; and aprotic polar
solvents such as DMF, DMSO, hexamethylphosphoric triamide
10 and the like. The alkylhalocarboxylic acid used in the
mixed acid anhydride process includes, for example,
methyl chloroformate, methyl bromoformate, methyl
chloroformate, ethyl bromoformate and isobutyl
chloroformate. In the process, the proportions of
15 carboxylic acid (12), alkylhalocarboxylic acid and amine
(10) used are generally each 1 mole, but the first and
second compounds are preferably used each in an amount of
1-1.5 moles per mole of the amine (10).

When there is used the process which comprises
20 reacting a carboxylic acid halide with an amine (10); the
reaction is conducted in an appropriate solvent in the
presence of a basic compound. As to the basic compound,
there can be widely used known compounds. They include,
for example, the basic compounds used in the above
25 Schotten-Baumann reaction, sodium hydroxide, potassium
hydroxide, sodium hydride, potassium hydride, silver
carbonate and alcoholates (e.g. sodium methylate, sodium
ethylate). The solvent includes, for example, the

1 solvents usable in the above mixed acid anhydride
 process, alcohols (e.g. methanol, ethanol, propanol,
 butanol, 3-methoxy-1-butanol, ethyl cellosolve, methyl
 cellosolve), pyridine, acetone, acetonitrile and mixtures
 5 thereof. The proportions of the amine (10) and the
 carboxylic acid halide used are not critical and can be
 selected in wide ranges, but the latter is used in an
 amount of generally about 1 mole, preferably about 1-5
 moles per mole of the former. The reaction is conducted
 10 generally at about -30 to 180°C, preferably at about 0-
 150°C, and is complete generally in about 5 minutes to 30
 hours.

[Reaction formula-7]

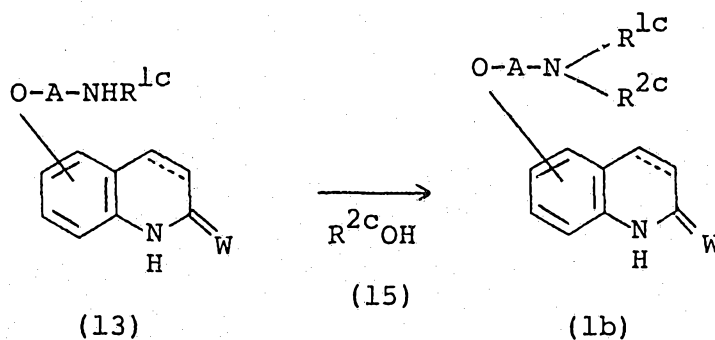


[wherein A, W, X and the carbon-to-carbon bond between
 15 the 3-and 4-positions of the carbostyryl skeleton have
 the same definitions as given above; R^{2b} represents a
 cycloalkyl-lower alkyl group; a cycloalkyl group; a
 phenyl group; a phenyl-lower alkyl group which may have,
 as substituent(s) on the phenyl ring, 1-3 groups selected
 20 from the group consisting of a ^{halogen} halogen atom, a lower

- 1 alkyl group, a cyano group, a carboxy group and a lower alkoxy group; a pyrrolidyl-substituted alkyl group; a thienyl-substituted lower alkyl group; a tetrahydro-pyranyl-substituted lower alkyl group; a phenyl-lower
- 5 alkylsulfonyl group; a phenylsulfonyl group; or acycloalkyl-lower alkylsulfonyl group; R^{1c} represents the above-mentioned R^{1a} and R^{1b}].

The reaction between a compound (13) and a compound (14) can be conducted under the same conditions
 10 as employed in the reaction between the compound (2) and the compound (3) shown in the Reaction formula-1.

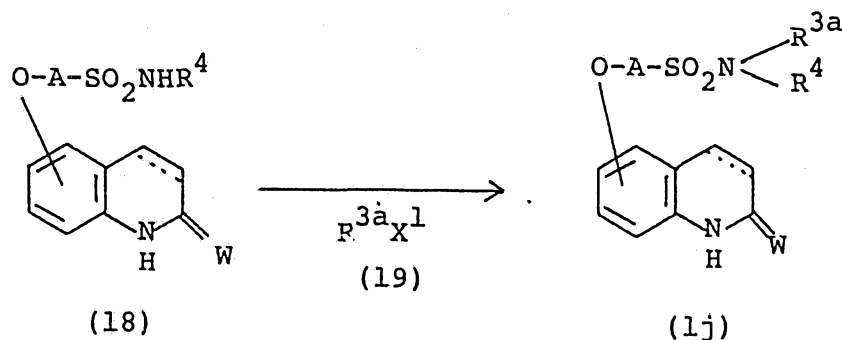
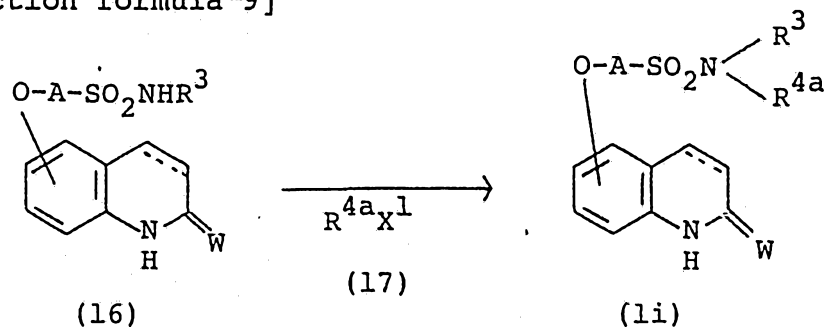
[Reaction formula-8]



[wherein A, W, R^{1c} and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as given above; R^{2c} represents a
 15 cycloalkylcarbonyl group or a benzoyl group.].

The reaction between a compound (13) and a compound (15) can be conducted under the same conditions as employed in the reaction between the compound (10) and
 20 the compound (12) shown in the Reaction formula-6.

1 [Reaction formula-9]

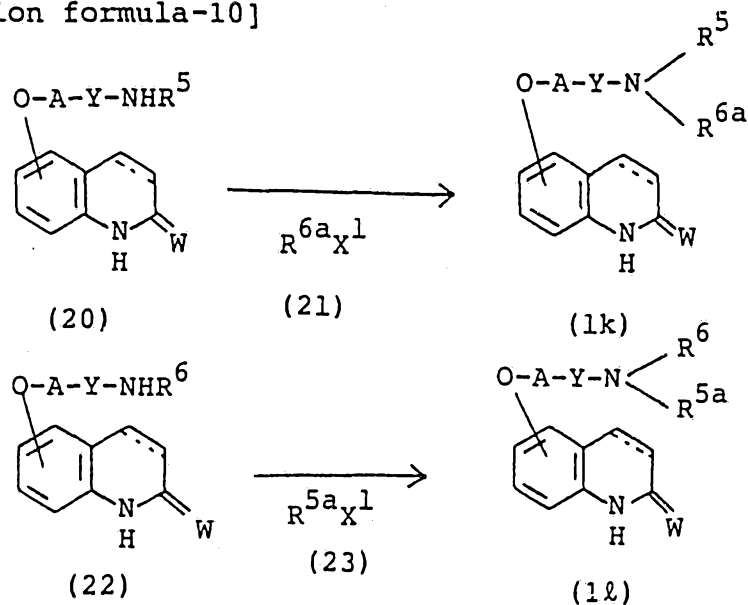


[wherein A, W, X¹, R³, R⁴ and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as given above. R^{3a}

5 represents the above-mentioned R³ other than the case R³ is a hydrogen atom. R^{4a} represents the above-mentioned R^{4a} other than the case R⁴ is a hydrogen atom.]

The reaction between a compound (16) and a compound (17) and the reaction between a compound (18) and a compound (19) can be conducted under the same conditions as employed in the reaction between the compound (2) and the compound (3) shown in the Reaction formula-1.

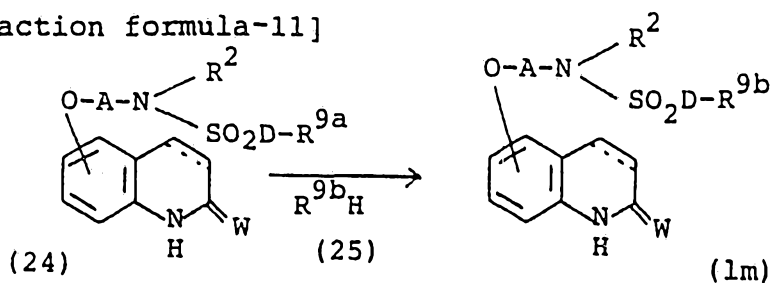
1 [Reaction formula-10]



[wherein A, W, Y, R⁵, R⁶ and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as given above; R^{5a} represents the above-mentioned R⁵ other than the case R⁵ is a hydrogen atom, and R^{6a} represents the above-mentioned R⁶ other than the case R⁶ is a hydrogen atom].

The reaction between a compound (20) and a compound (21) and the reaction between a compound (22) and a compound (23) can be conducted under the same conditions as employed in the reaction between the compound (2) and the compound (3) shown in the Reaction formula-2.

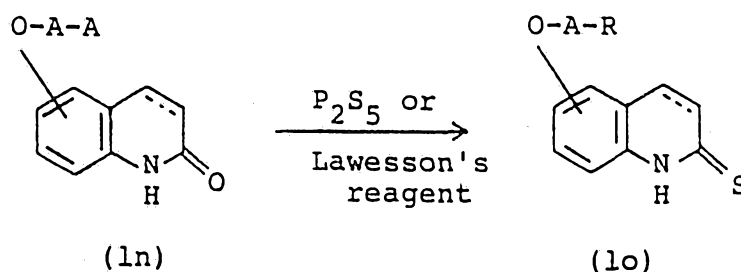
[Reaction formula-11]



- 1 [wherein A, W, R², D and the carbon-to-carbon bond be-
 tween the 3- and 4-positions of the carbostyryl skeleton
 have the same definitions as given above; R^{9a} represents
 a halogen atom; R^{9b} represents a five- or six-membered
 5 saturated or unsaturated heterocyclic ring residue
 containing 1-3 nitrogen atoms, which residue may have, as
 a substituent(s), a hydroxyl group, a lower alkoxy-lower
 alkoxy group, a lower alkoxycarbonyl group or a lower
 alkyl group which may be substituted with a lower
 -10 alkoxy-lower alkoxy group or a hydroxyl group].

The reaction between a compound (24) and a
 compound (25) can be conducted under the same conditions
 as employed in the reaction between the compound (2) and
 the compound (3) shown in the Reaction formula-1.

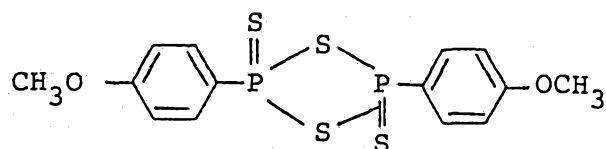
15 [Reaction formula-12]



[wherein A, R and the carbon-to-carbon bond between the
 3- and 4-positions of the carbostyryl skeleton have the
 same definitions as given above].

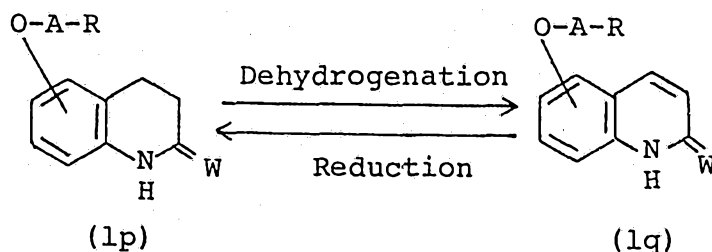
- 20 The reaction between a compound (1n) and phos-
 phorus pentasulfide or a Lawesson's reagent represented

1 by the formula,



is conducted in an ordinary inert solvent such as aromatic hydrocarbon (e.g. benzene, toluene, xylene, chlorobenzene), ether (e.g. diethyl ether, tetrahydrofuran, dioxane), halogenated hydrocarbon (e.g. methylene chloride, chloroform), dimethyl sulfoxide, hexamethylphosphoric triamide or the like. The amount of phosphorus pentasulfide or Lawesson's reagent used is generally 0.2 mole to a large excess, preferably 0.4-2 moles per mole of the compound (1n). The reaction temperature is generally room temperature to 200°C, preferably 50-150°C, and the reaction time is 0.5-50 hours.

[Reaction formula-13]



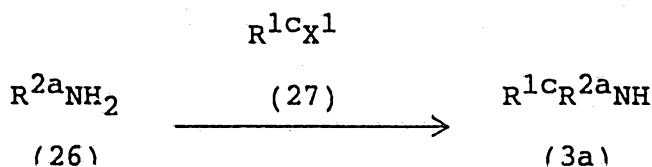
[wherein A, W and R have the same definitions as given above].

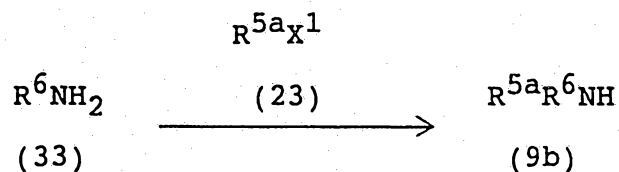
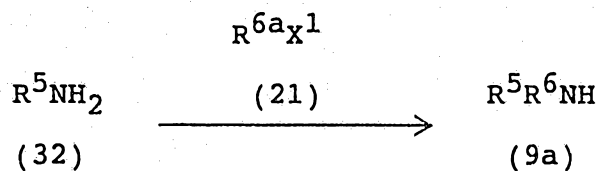
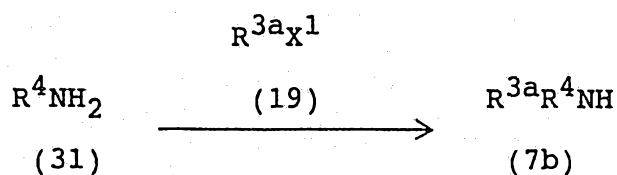
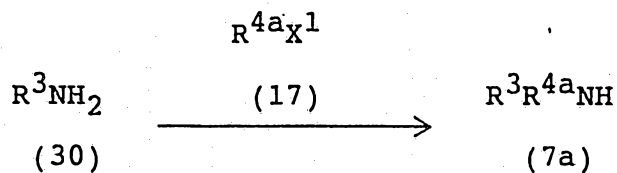
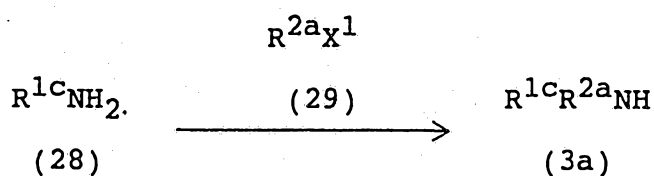
1 The reduction of a compound of general formula
(1q) is conducted under the conditions of ordinary
catalytic reduction. The catalyst used can be
exemplified by metals such as palladium, palladium-
5 carbon, platinum, Raney nickel and the like. Such a
metal is used preferably in an ordinary catalytic amount.
The solvent used includes, for example, alcohols such as
methanol, ethanol, isopropanol and the like; ethers such
as dioxane, tetrahydrofuran and the like; aliphatic
10 hydrocarbons such as hexane, cyclohexane and the like;
esters such as ethyl acetate and the like; and fatty
acids such as acetic acid and the like. The reduction
can be conducted at atmospheric pressure or under
pressure, but is conducted generally at about atmospheric
15 pressure to 20 kg/cm², preferably at atmospheric pressure
to 10 kg/cm². The reaction temperature is generally
about 0-150°C, preferably about room temperature to
100°C.

 The dehydrogenation of a compound of general
20 formula (1p) is conducted in an appropriate solvent,
using an oxidizing agent. The oxidizing agent includes,
for example, benzoquinones such as 2,3-dichloro-5,6-
dicyanobenzoquinone, chloranil (2,3,5,6-tetrachloro-
benzoquinone) and the like; halogenating agents such as
25 N-bromosuccinimide, N-chlorosuccinimide, bromine and the
like; selenium dioxide; palladium-carbon; palladium
black; palladium oxide; and hydrogenation catalysts such
as Raney nickel and the like. The amount of the halogena-

- 1 ting agent used is not critical and can be appropriately
 selected from a wide range, but is used in an amount of
 generally about 1-5 moles, preferably about 1-2 moles per
 mole of the compound of general formula (1p). When a
 5 hydrogenation catalyst is used, it is used in an ordinary
 catalytic amount. The solvent can be exemplified by
 ethers such as dioxane, tetrahydrofuran, methoxyethanol,
 dimethoxyethane and the like; aromatic hydrocarbons such
 as benzene, toluene, xylene, cumene and the like;
 10 halogenated hydrocarbons such as dichloromethane,
 dichloroethane, chloroform, carbon tetrachloride and the
 like; alcohols such as butanol, amyl alcohol, hexanol and
 the like; polar protonic solvents such as acetic acid and
 the like; and polar aprotic solvents such as dimethyl-
 15 formamide, dimethyl sulfoxide, hexamethylphosphoric
 triamide and the like. The reaction is conducted
 generally at about room temperature to 300°C, preferably
 at about room temperature to 200°C, and is complete
 generally in 1-40 hours.
- 20 The compounds (3), (7) and (9) each as starting
 material can be easily produced by, for example, the
 processes shown by the following reaction formulas.

[Reaction formula-14]





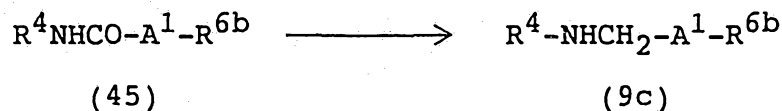
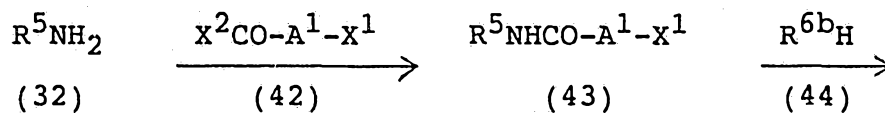
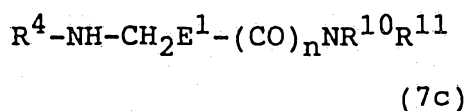
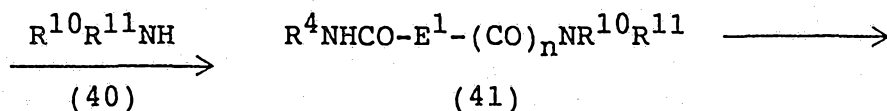
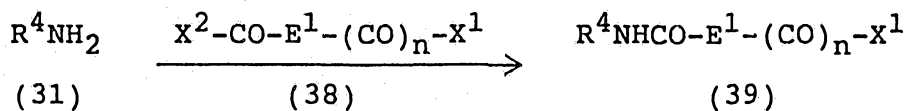
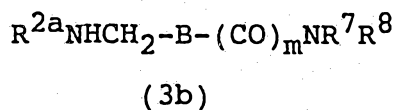
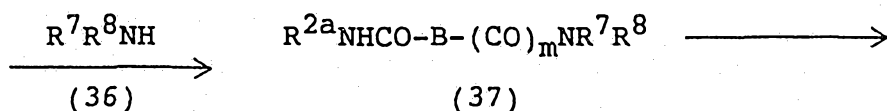
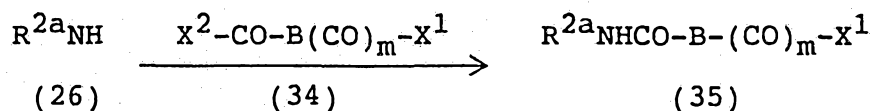
- 1 [wherein R^{2a} , R^{1c} , R^{4a} , R^{3a} , R^{6a} , R^{5a} , R^3 , R^4 , R^5 , R^6 and X^1 have the same definitions as given above].

The reaction between a compound (26) and a compound (27), the reaction between a compound (28) and a compound (29), the reaction between a compound (30) and a compound (17), the reaction between a compound (31) and a compound (19), the reaction between a compound (32) and a compound (21) and the reaction between a



- 1 compound (33) and a compound (23) can be conducted under the same conditions as employed in the reaction between the compound (2) and the compound (3) shown in the Reaction formula-1.

5 [Reaction formula-15]



[wherein R^{2a} , B, m, X^1 , R^7 , R^8 , R^4 , R^{10} , R^{11} and R^5 have the same definitions as given above, X^2 represents a



- 1 halogen atom; E^1 represents a hydroxyl group-substituted
or unsubstituted lower alkylene group; A^1 represents a
lower alkylene group; R^{6b} represents a piperidinyl group
which may have a lower alkoxy-lower alkoxy group or a
5 hydroxyl group as a substituent on the piperidinyl
ring].

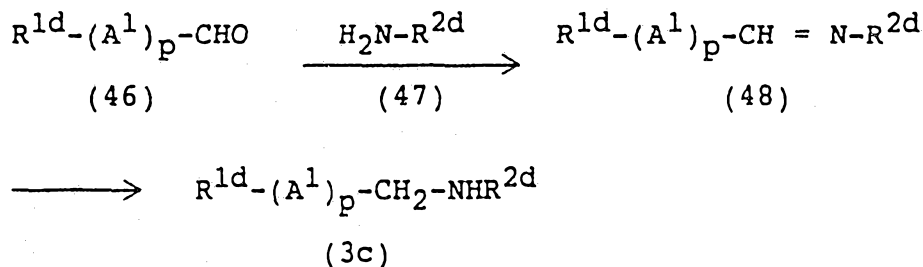
The reaction between a compound (26) and a
compound (34), the reaction between a compound (31) and a
compound (38) and the reaction between a compound (32)
10 and a compound (42) can be conducted under the same
conditions as employed in the reaction between the
compound (2) and the compound (3) shown in the Reaction
formula-1. The reaction between a compound (35) and a
compound (37), the reaction between a compound (39) and a
15 compound (40) and the reaction between a compound (43)
and a compound (44) can also be conducted under the same
conditions as employed in the reaction between the com-
pound (2) and the compound (3) shown in the Reaction
formula-1.

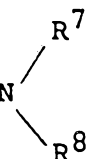
20 The reduction of a compound (37), (41) or (45)
is conducted in an appropriate solvent in the presence of
a hydride and reducing agent. The reducing agent
includes, for example, sodium boron hydride, lithium
aluminum hydride and diborane. The amount of reducing
25 agent used is at least about 1 mole, preferably about 1-3
moles per mole of the starting material. When lithium
aluminum hydride is used as the reducing agent, it is
used in an amount of preferably about the same weight as



1 that of the starting material. The solvent includes, for
 example, water; alcohols such as methanol, ethanol,
 isopropanol and the like; and ethers such as tetra-
 hydrofuran, diethyl ether, diglyme and the like. The
 5 reaction is conducted generally at about -60°C to 150°C,
 preferably at about -30°C to 100°C, and is complete gener-
 ally in about 10 minutes to 15 hours. When lithium
 aluminum hydride or diborane is used as the reducing
 agent, an anhydrous solvent such as diethyl ether,
 10 tetrahydrofuran, diglyme or the like is used preferably.

[Reaction formula-16]



[wherein R^{1d} represents a group $-(\text{CO})_m-\text{N}$  (m, R^7 and R^8

R^8 have the same definitions as given above), a lower
 alkoxy carbonyl group, a carboxy group, a lower alkyl
 15 group-substituted or unsubstituted aminocarbonyl group, a
 hydroxyl group, an imidazolyl group, a pyridyl group or a
 pyrrolidinyl group which may have, as substituent(s) on
 the pyrrolidine ring, 1-3 groups selected from the group
 consisting of a lower alkyl group, a lower alkoxy-lower
 alkoxy group and a hydroxyl group; p represents 0 or 1;



1 R^{2d} represents a cycloalkyl-lower alkyl group, a
cycloalkyl group; a phenyl group, a phenyl-lower alkyl
group which may have, as substituent(s) on the phenyl
ring, 1-3 groups selected from the group consisting
5 of a halogen atom, a lower alkyl group, a cyano group,
a carboxy group and a lower alkoxy group, a pyridyl-
substituted lower alkyl group, a thienyl-substituted
lower alkyl group, a cycloalkylcarbonyl group, a benzoyl
group, a tetrahydropyranyl-substituted lower alkyl group,
10 a phenyl-lower alkylsulfonyl group, a phenylsulfonyl
group or a cycloalkyl-lower alkylsulfonyl group. A¹ has
the same definition as given above 7.

The reaction between a compound of general
formula (46) and a compound of general formula (47) is
15 conducted in an appropriate solvent or in the absence of
any solvent in the presence or absence of a dehydrating
agent. The solvent includes, for example, alcohols such
as methanol, ethanol, isopropanol and the like; aromatic
hydrocarbons such as benzene, toluene, xylene and the
20 like; and aprotic polar solvents such as dimethyl-
formamide, dimethylacetamide, N-methylpyrrolidone and the
like. The dehydrating agent includes, for example,
drying agents ordinarily used in dehydration of solvent,
such as molecular sieve and the like; mineral acids such
25 as hydrochloric acid, sulfuric acid, boron trifluoride
and the like; and organic acids such as p-toluenesulfonic
acid and the like. The reaction is conducted generally
at about room temperature to 200°C, preferably at about

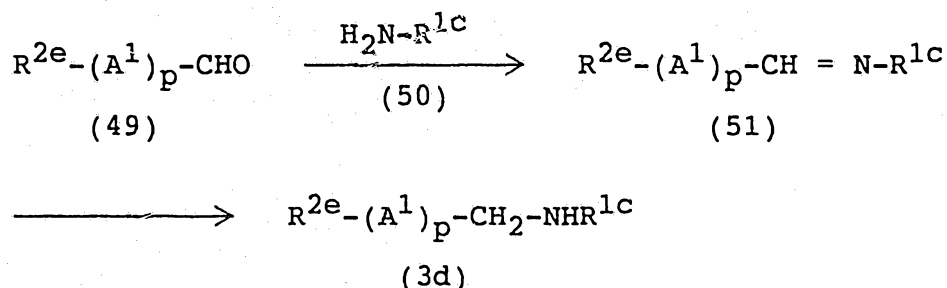


1 room temperature to 150°C, and is complete generally in
about 1-48 hours. The amount of the compound of general
formula (47) used is not critical, but is generally at
least about 1 mole, preferably about 1-15 moles per mole
5 of the compound of general formula (46). The amount of
the dehydrating agent used is generally a large excess
when a drying agent is used, and is a catalytic amount
when an acid used. The thus obtained compound of general
formula (48) is used in the subsequent reduction without
10 being isolated.

The reduction of the compound of general
formula (48) can be conducted by various methods. For
example, there is preferably used a method using a
hydride reducing agent. The hydride and reducing agent
15 includes, for example, lithium aluminum hydride, sodium
boron hydride and diborane. The amount of the reducing
agent used is at least about 1 mole, preferably about 1-
10 moles per mole of the compound of general formula
(48). The reduction is conducted generally in an
20 appropriate solvent such as water, lower alcohol (e.g.
methanol, ethanol, isopropanol), ether (e.g. tetra-
hydrofuran, diethyl ether, diglyme) or the like,
generally at about -60°C to 50°C, preferably at about
-30°C to room temperature for about 10 minutes to 5
25 hours. An anhydrous solvent such as diethyl ether,
tetrahydrofuran, diglyme or the like is preferably used
when there is used, as the reducing agent, lithium
aluminum hydride or diborane.

1 The reduction of the compound of general
 formula (48) can be conducted also by subjecting the
 compound to catalytic hydrogenation in the presence of a
 catalyst in an appropriate solvent. The solvent
 5 includes, for example, water; acetic acid; alcohols such
 as methanol, ethanol, isopropanol and the like; hydro-
 carbons such as hexane, cyclohexane and the like; ethers
 such as dioxane, tetrahydrofuran, diethyl ether, ethylene
 glycol dimethyl ether and the like; esters such as ethyl
 10 acetate, methyl acetate and the like; and aprotic polar
 solvents such as dimethylformamide and the like. The
 catalyst includes, for example, palladium, palladium
 black, palladium-carbon, platinum, platinum oxide, copper
 chromite and Raney nickel. The amount of the catalyst
 15 used is generally about 0.02-1 time the amount of the
 compound of general formula (48). The reaction
 temperature is generally at about -20°C to 150°C,
 preferably at about 0-100°C; the hydrogen pressure is
 generally about 1-10 atm; and the reaction is complete
 20 generally in about 0.5-10 hours.

[Reaction formula-17]

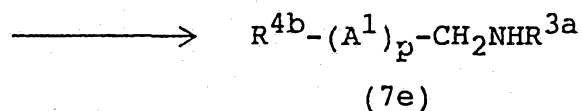
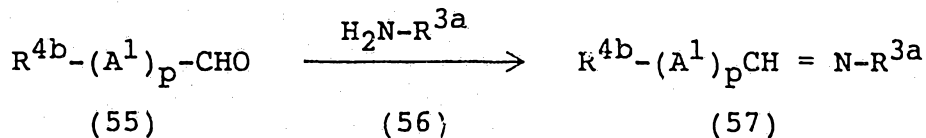
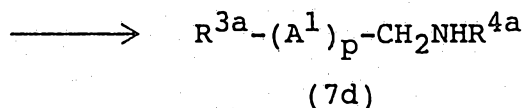
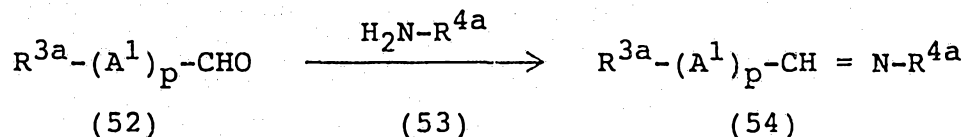


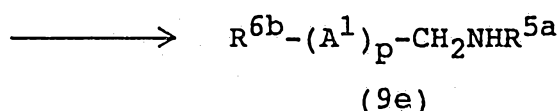
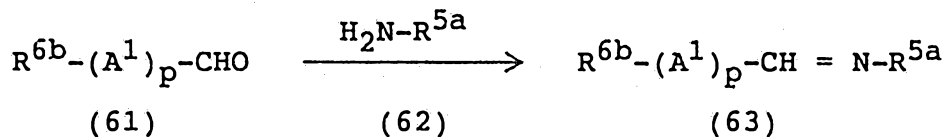
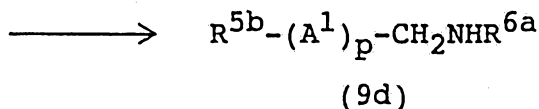
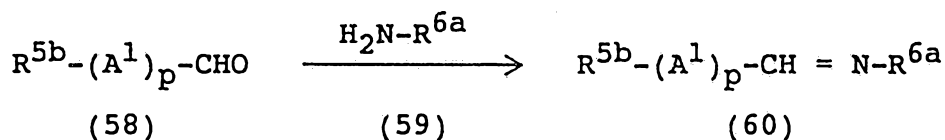
1 [wherein A¹ and p are the same as defined above; R^{2e}
represents a cycloalkyl group, a phenyl group which may
have, as substituent(s) on the phenyl ring, 1-3 groups
selected from the group consisting of a halogen atom, a
5 lower alkyl group, a cyano group, a carboxy group and a
lower alkoxy group, a pyridyl group, a thienyl group or a
tetrahydropyranyl group; R^{1c} has the same definition as
given above.].

The reaction between a compound (49) and a
10 compound (50) can be conducted under the same conditions
as employed in the reaction between the compound (46) and
the compound (47) shown in the reaction formula 16.

The reaction for converting a compound (51) to
a compound (3d) can be conducted under the same condi-
15 tions as employed in the reaction for converting the
compound (48) to the compound (3c).

[Reaction formula-18]





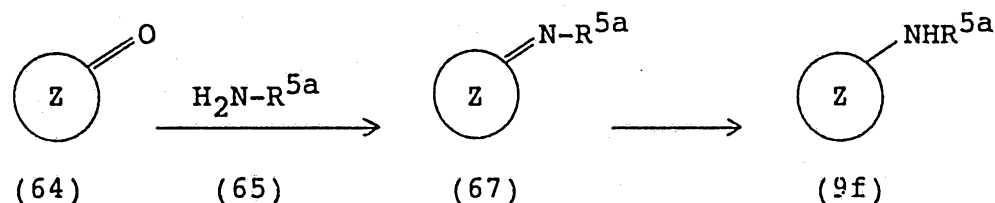
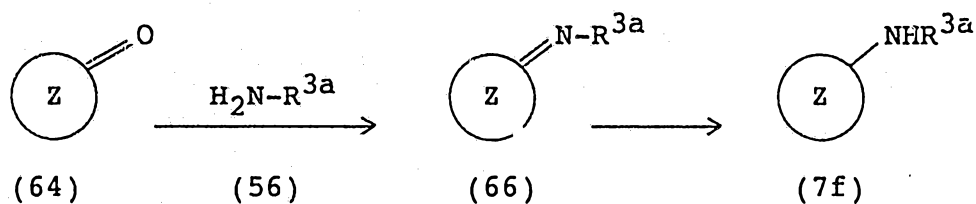
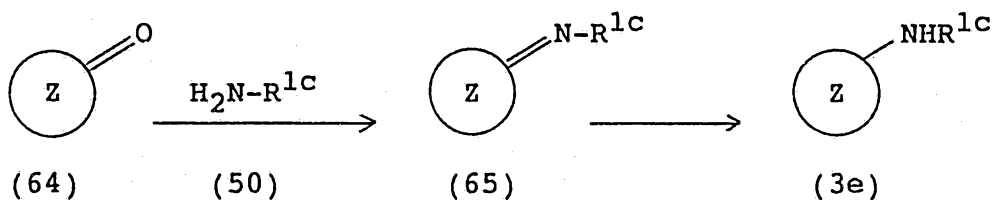
- 1 [wherein R^{3a} , A^1 , p , R^{4a} , R^{5a} and R^{6a} have the same definitions as given above. R^{4b} represents a cycloalkyl group, a phenyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group
- 5 consisting of a halogen atom, a lower alkyl group and a lower alkoxy group, a thienyl group, a pyridyl group, an imidazolyl group or a tetrahydropyranyl group. R^{5b} and R^{6b} independently represent a hydrogen atom, a cycloalkyl group or a piperidinyl group which may have a lower
- 10 alkoxy-lower alkoxy group or a hydroxyl group as a substituent on the piperidinyl ring.]

The reaction between a compound (52) and a compound (53), the reaction between a compound (55) and a compound (56), the reaction between a compound (58) and a compound (59) and the reaction between a compound (61) and a compound (62) can be conducted under the same conditions as employed in the reaction between the

1 compound (46) and the compound (47) shown in the Reaction
formula-16.

The reaction for converting a compound (54) to
a compound (7d), the reaction for converting a compound
5 (57) to a compound (7e), the reaction for converting a
compound (60) to a compound (9d) and the reaction for
converting a compound (63) to a compound (9e) can be
conducted under the same conditions as employed in the
reaction for converting the compound (48) to the compound
10 (3c) shown in the Reaction formula-16.

[Reaction formula-19]



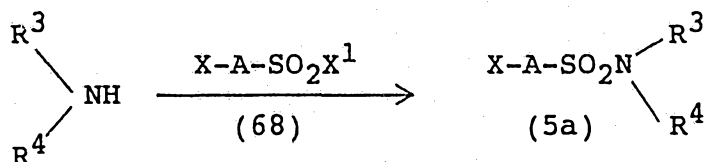
[wherein (Z) represents a cycloalkyl group; $\text{R}^{1\text{c}}$, $\text{R}^{3\text{a}}$
and $\text{R}^{5\text{a}}$ have the same definitions as given above]

1 The reaction between a compound (64) and a
 compound (50), the reaction between a compound (64) and a
 compound 56) and the reaction between a compound (64) and
 a compound (62) can be conducted under the same condi-
 5 tions as employed in the reaction between the compound
 (46) and the compound (47) shown in the Reaction formula-
 16.

 The reaction for converting a compound (65) to
 a compound (3e), the reaction for converting a compound
 10 (66) to a compound (7f) and the reaction for converting a
 compound (67) to a compound (9f) can be conducted under
 the same conditions as employed in the reaction for
 converting the compound (48) to the compound (3c) shown
 in the Reaction formula-16).

15 The compound (5) used as a starting material
 can be produced by, for example, the following processes.

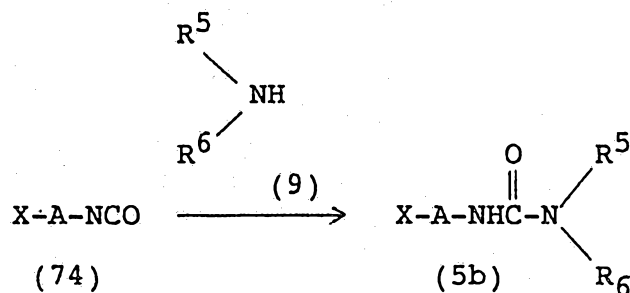
[Reaction formula-20]



[wherein R³, R⁴, X, A and X¹ have the same definitions as
 given above].

20 The reaction between a compound (7) and a com-
 pound (68) can be conducted under the same conditions as
 employed in the reaction between the compound (2) and the
 compound (3) shown in the Reaction formula-1.

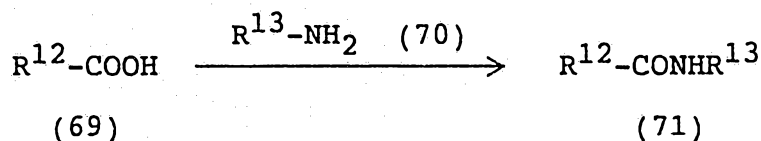
1 [Reaction formula-21]



[wherein X, A, R⁵ and R⁶ have the same definitions as given above].

5 The reaction between a compound (74) and a compound (9) can be conducted under the same conditions as employed in the reaction between the compound (8) and the compound (9) shown in the Reaction formula-4.

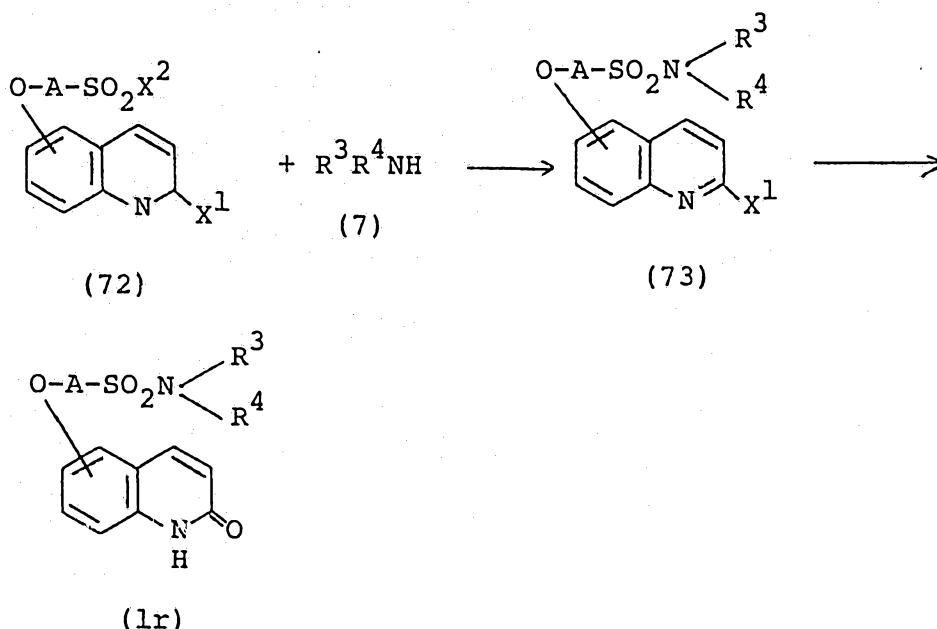
[Reaction formula-22]



10 [wherein R¹² represents a pyrrolidinyll group which may have, as a substituent, a hydroxyl group, a lower alkoxy-lower alkoxy group, a lower alkyl group which may be substituted with a lower alkoxy-lower alkoxy group or a hydroxyl group, a lower alkoxycarbonyl group, a piperidinyllcarbonyl group or an aminocarbonyl group which may
15 be substituted with a cycloalkyl-lower alkyl group. R¹³ represents a cycloalkyl-lower alkyl group or a hydrogen atom].

1 The reaction between a compound (69) and a
 compound (70) can be conducted under the same conditions
 as employed in the reaction between the compound (10) and
 the compound (12) shown in the reaction formula 6. In
 5 the reaction, it is possible to protect the 1-position of
 the pyrrolidine ring with a protecting group, for
 example, a phenyl-lower alkoxy carbonyl group (e.g. a
 benzyloxycarbonyl group), react the protected compound
 with a compound (70) and reduce the reaction product
 - 10 under the same conditions as employed in the reduction of
 the compound (48) by catalytic hydrogenation, shown in
 the Reaction formula-16, to conduct deprotection.

[Reaction formula-23]



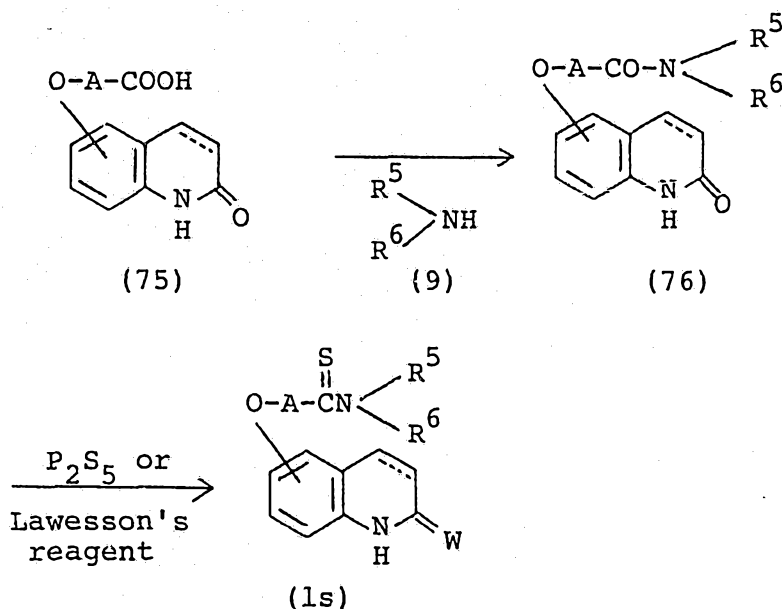
15 [wherein X^1 , X , A , R^3 and R^4 have the same definitions
 as given above].

The reaction between a compound (72) and a

1 compound (7) can be conducted under the same conditions
as employed in the reaction between the compound (2) and
the compound (3) shown in the Reaction formula-1.

The reaction for converting a compound (73) to
5 a compound (1r) can be conducted by heating the compound
(73) in the presence of an acid or a basic compound. The
acid can be exemplified by inorganic acids such as
hydrochloric acid, hydrobromic acid, sulfuric acid,
phosphoric acid and the like, and organic acids such as
10 acetic acid and the like. The basic compound can be
exemplified by inorganic bases such as sodium hydroxide,
potassium hydroxide, sodium carbonate, potassium
carbonate, sodium hydrogencarbonate, potassium hydrogen-
carbonate and the like. The reaction is conducted gene-
15 rally at about 50-150°C, preferably at about 70-120°C,
and is complete generally in about 0.5-24 hours.

[Reaction formula-24]



1 [wherein A, R⁵, R⁶, W and the carbon-to-carbon bond
between the 3- and 4-positions of the carbostyryl
skeleton have the same definitions as given above].

The reaction between a compound (75) and a
5 compound (9) can be conducted under the same conditions
as employed in the reaction between the compound (10) and
the compound (12) shown in the Reaction formula-16.

The reaction between a compound (76) and phos-
phorus pentasulfide or a Lawesson's reagent can be
10 conducted under the same conditions as employed in the
reaction between the compound (1n) and phosphorus
pentasulfide or a Lawesson's reagent, shown in the
Reaction formula-12. In the reaction, there can be
obtained a compound wherein only the carbonyl group of
15 side chain amide group has been subjected to thiocarbony-
lation, or a compound wherein both the carbonyl group of
side chain amide group and the carbonyl group of 2-
position of carbostyryl skeleton have been subjected
to thiocarbonylation.

20 When the compound (1s) is a compound (1)
wherein R⁷ and R⁸ or R¹⁰ and R¹¹ form a five- or six-
membered saturated heterocyclic ring together with the
nitrogen atom to which they bond and further with or
without a nitrogen, oxygen or sulfur atom which may be
25 present between R⁷ and R⁸ or R¹⁰ and R¹¹ and said
heterocyclic ring has a lower alkoxy-lower alkoxy group
as a substituent, a compound (1) wherein R⁹ is a five- or
six-membered saturated or unsaturated heterocyclic ring



1 residue having 1-3 nitrogen atoms and said heterocyclic
ring residue has a lower alkoxy-lower alkoxy group, a
compound (1) wherein R^1 and R^3 form a pyrrolidinyl group
together with the nitrogen atom to which they bond and
5 said pyrrolidinyl group has a lower alkoxy-lower alkoxy
group as a substituent, a compound (1) wherein R^1 or R^3
is a pyrrolidinyl-lower alkyl group which has, as
substituent(s) on the pyrrolidine ring, at least one
lower alkoxy-lower alkoxy group, or a compound (1)
10 wherein R^5 or R^6 is a piperidinyl-lower alkyl group which
has, as substituent(s) on the piperidinyl ring, at least
one lower alkoxy-lower alkoxy group, these compounds (1)
can be converted by hydrolysis, to a compound (1) wherein
 R^7 and R^8 or R^{10} and R^{11} form the above heterocyclic ring
15 group having a hydroxyl group as a substituent, a
compound (1) wherein R^9 is the above heterocyclic ring
group having a substituent, a compound (1) wherein R^1 or
 R^3 is a pyrrolidinyl-lower alkyl group having at least
one hydroxyl group as substituent(s) on the pyrrolidine
20 ring, and a compound (1) wherein R^5 or R^6 is a
piperidinyl-lower alkyl group having at least one
hydroxyl group as substituent(s) on the piperidinyl ring,
respectively.

The above hydrolysis can be conducted under the
25 conditions employed in ordinary hydrolysis. The hydroly-
sis is conducted generally in the presence of a basic
compound, a mineral acid, an organic acid or the like in
an appropriate solvent. The basic compound includes, for

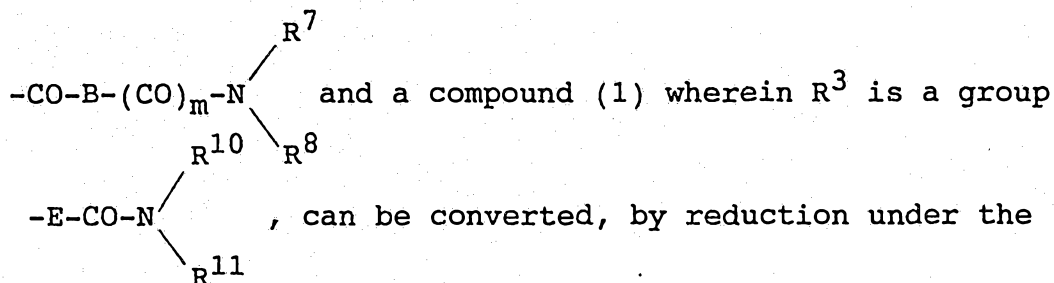
1 example, sodium hydroxide, potassium hydroxide, barium
hydroxide and potassium carbonate; the mineral acid
includes, for example, sulfuric acid, hydrochloric acid
and nitric acid; and the organic acid includes, for
5 example, acetic acid, aromatic sulfonic acids (e.g. p-
toluenesulfonic acid) and Lewis acids (e.g. boron
trichloride). The solvent includes, for example, water;
alcohols such as methanol, ethanol, isopropanol and the
like; ketones such as acetone, methyl ethyl ketone and
10 the like; ethers such as dioxane, tetrahydrofuran,
ethylene glycol dimethyl ether and the like; acetic acid;
and mixtures thereof. The reaction proceeds generally at
about room temperature to 200°C, preferably at about room
temperature to 150°C, and is complete generally in about
15 0.5-30 hours.

A compound (1) wherein R^1 or R^3 is a lower
alkoxycarbonyl group-substituted lower alkyl group, can
be converted by hydrolysis to a compound (1) wherein R^1
or R^3 is a carboxy group-substituted lower alkyl group.

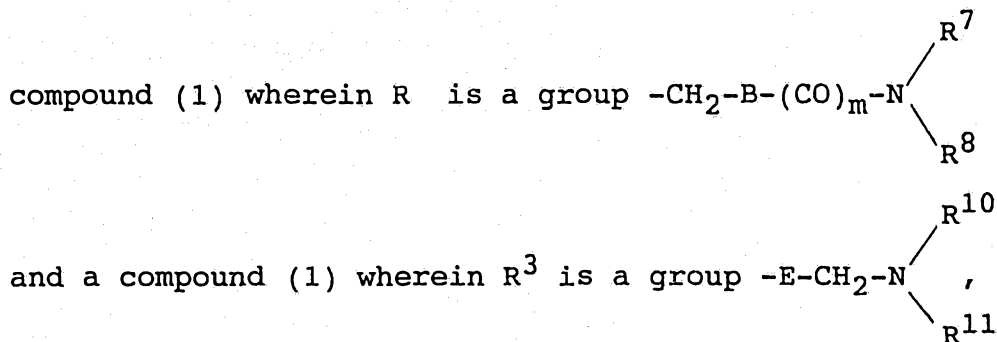
20 The hydrolysis can be carried out in the
presence of an acid or a basic compound in an appropriate
solvent or in the absence of any solvent. The solvent
includes, for example, water; lower alcohols such as
methanol, ethanol, isopropanol and the like; ketones such
25 as acetone, methyl ethyl ketone and the like; ethers such
as dioxane, tetrahydrofuran, ethylene glycol dimethyl
ether and the like; fatty acids such as acetic acid,
formic acid and the like; and mixed solvents thereof.

1 The acid includes, for example, mineral acids such as
hydrochloric acid, sulfuric acid, hydrobromic acid and
the like, and organic acids such as formic acid, acetic
acid, aromatic sulfonic acids and the like. The basic
5 compound includes, for example, metal carbonates such as
sodium carbonate, potassium carbonate and the like, and
metal hydroxides such as sodium hydroxide, potassium
hydroxide, calcium hydroxide and the like. The reaction
proceeds favorably generally at about room temperature to
10 200°C, preferably at about room temperature to 150°C, and
is complete generally in about 0.5-25 hours.

A compound (1) wherein R^1 is a group



15 same conditions as employed in the reduction of the
compound (37) shown in the reaction formula 15, to a



respectively.



1 A compound (1) wherein wherein R^7 and R^8 or R^{10}
and R^{11} form a five- or six-membered saturated hetero-
cyclic ring together with the nitrogen atom to which they
bond and further with or without a nitrogen, oxygen or
5 sulfur atom which may be present between R^7 and R^8 or R^{10}
and R^{11} and said heterocyclic ring has, as a substituent,
a lower alkyl group having at least one lower alkoxy-
lower alkoxy group, a compound (1) wherein R^9 is a five-
or six-membered saturated or unsaturated heterocyclic
10 ring residue having 1-3 nitrogen atoms and said hetero-
cyclic ring residue has a lower alkyl group having at
least one lower alkoxy-lower alkoxy group, and a compound
(1) wherein R^1 and R^2 form a pyrrolidiny1 group together
with the nitrogen atom to which they bond and said
15 pyrrolidiny1 group has, as a substituent, a lower alkyl
group having at least one lower alkoxy-lower alkoxy
group, can be converted, by hydrolysis under the same
conditions as employed in the hydrolysis of each of the
above-mentioned compounds (1) each having a heterocyclic
20 ring having a lower alkoxy-lower alkoxy group as a
substituent, to a compound (1) wherein R^7 and R^8 or R^{10}
and R^{11} form a five- or six-membered saturated
heterocyclic ring together with the nitrogen atom to
which they bond and further with or without a nitrogen,
25 oxygen or sulfur atom which may be present between R^7 and
 R^8 or R^{10} and R^{11} and said heterocyclic ring has, as a
substituent, a lower alkyl group having at least one
hydroxyl group, a compound (1) wherein R^9 is a five- or



1 six-membered saturated or unsaturated heterocyclic ring
residue having 1-3 nitrogen atoms and said heterocyclic
ring residue has a lower alkyl group having at least one
hydroxyl group, and a compound (1) wherein R^1 and R^2 form
5 a pyrrolidinyl group together with the nitrogen atom to
which they bond and said pyrrolidinyl group has, as a
substituent, a lower alkyl group having at least one
hydroxyl group, respectively.

A compound (1) wherein R^3 , R^7 or R^8 is a
10 hydroxyl group-substituted lower alkyl group, can be
converted, by protecting the hydroxyl group with, for
example, a tetrahydropyranyloxy group or a lower
alkylenedioxy group (e.g. a 1,1-dimethylmethylenedioxy
group), subjecting the protected compound to the
15 reactions shown in the reaction formulas 1-22 and
deprotecting the protected group, to a desired compound
(1) wherein R^3 , R^7 or R^8 is a hydroxyl group-
substituted lower alkyl group. The deprotection is
conducted by hydrolysis under the same conditions as
20 employed in the hydrolysis of each of the above-mentioned
compounds (1) each having a heterocyclic ring having a
lower alkoxy-lower alkoxy group as a substituent.

A compound (1) wherein R^7 or R^8 is a hydrogen
atom, can be converted, by protecting the site to which
25 the hydrogen atom bonds, with a lower alkoxycarbonyl
group (e.g. a tert-butoxycarbonyl group), subjecting the
protected compound to the reactions shown in the reaction

- 1 formulas 1-22 and deprotecting the protected group, to a
desired compound (1) wherein R^7 or R^8 is a hydrogen atom.
The deprotection is conducted by hydrolysis under the
same conditions as employed in the hydrolysis of the
5 above-mentioned compound wherein R^1 or R^3 is a lower
alkoxycarbonyl-substituted lower alkyl group.

The carbostyryl derivative represented by
general formula (1) according to the present invention
can be easily converted to an acid addition salt by
10 allowing a pharmaceutically acceptable acid to act on the
derivative. The acid includes, for example, inorganic
acids such as hydrochloric acid, sulfuric acid,
phosphoric acid, hydrobromic acid and the like, and
organic acids such as oxalic acid, maleic acid, fumaric
15 acid, malic acid, tartaric acid, citric acid, benzoic
acid and the like.

The carbostyryl derivative represented by
general formula (1) according to the present invention,
which has an acidic group, can be easily converted to a
20 salt by allowing a pharmaceutically acceptable basic
compound to act on the derivative. The basic compound
includes, for example, sodium hydroxide, potassium
hydroxide, calcium hydroxide, sodium carbonate and
potassium hydrogencarbonate.

25 The products thus obtained in each step can
be isolated and purified by ordinary separation means.
The separation means can be exemplified by solvent
extraction, dilution, recrystallization, column

1 chromatography and preparative thin-layer chromatography.

Needless to say, the compounds of the present invention include optical isomers.

The compound of general formula (1) is
5 generally used in the form of ordinary pharmaceutical preparations. The pharmaceutical preparations are prepared using diluents or excipients ordinarily used, such as filler, bulking agent, binder, humectant, disintegrator, surfactant, lubricant and the like. The
10 pharmaceutical preparations can be used in various forms depending upon the purpose of remedy, and typical forms include tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.), etc. In preparing
15 tablets, various carriers conventionally known in the art can be used. The carriers can be exemplified by excipients such as lactose, white sugar, sodium chloride, grape sugar, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid and the like; binders
20 such as water, ethanol, propanol, simple syrup, grape sugar solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone and the like; disintegrators such as dry starch, sodium alginate,
25 powdered agar, powdered laminaran, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan-fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride, starch, lactose and the like; disinte-



1 gration inhibitors such as white sugar, stearin, cacao
butter, hydrogenated oil and the like; absorption
promoters such as quaternary ammonium salts, sodium
lauryl sulfate and the like; humectants such as glycer-
5 ine, starch and the like; adsorbents such as starch,
lactose, kaolin, bentonite, colloidal silicic acid and
the like; and lubricants such as refined talc, stearic
acid salts, boric acid powder, polyethylene glycol and
the like. The tablets can be prepared, as necessary, in
10 the form of ordinary coated tablets, such as sugar-coated
tablets, enteric coated tablets or film-coated tablets,
or in the form of double-layered tablets or multi-layered
tablets. In preparing pills, various carriers conven-
tionally known in the art can be used. The carriers can
15 be exemplified by excipients such as glucose, lactose,
starch, cacao butter, hardened vegetable oils, kaolin,
talc and the like; binders such as powdered acacia,
powdered tragacanth, gelatin, ethanol and the like; and
disintegrators such as laminaran, agar and the like. In
20 preparing suppositories, various carriers conventionally
known in the art can be used. The carriers can be
exmplified by a polyethylene glycol, cacao butter, a
higher alcohol, a higher alcohol ester, gelatin and a
semi-synthetic glyceride. In preparing injections in the
25 form of solution or suspension, they are sterilized and
preferably isotonic to blood. In preparing these
solutions, pills and suspensions, there can be used all
of the diluents conventionally used in the art, such as

1 water, ethyl alcohol, propylene glycol, ethoxylated
isostearyl alcohol, polyoxyisostearyl alcohol and
polyoxyethylene sorbitan-fatty acid ester. In this case,
the injections may contain sodium chloride, glucose or
5 glycerine in an amount sufficient to make the injections
isotonic, and may further contain a solubilizing agent, a
buffer solution, a soothing agent, etc. all ordinarily
used. The pharmaceutical preparations may furthermore
contain, as necessary, a coloring agent, a preservative, a
10 perfume, a flavoring agent, a sweetening agent and other
drugs.

The amount of the compound of general formula
(1) to be contained in the present pharmaceutical prepa-
ration is not particularly restricted and can be selected
15 in a wide range, and is generally 1-70% by weight,
preferably 1-30% by weight in the pharmaceutical
preparation.

The method for administering the present
pharmaceutical preparation is not particularly restric-
20 ted. The pharmaceutical preparation can be administered
in various methods depending upon the form of prepara-
tion, the age, sex and other conditions of patient, the
degree of disease condition of patient, etc. For
example, tablets, pills, a solution, a suspension, an
25 emulsion, granules or capsules are administered orally.
An injection is intravenously administered singly or in
admixture with an ordinary auxiliary solution of grape
sugar, amino acid or the like, or, as necessary, is



1 singly administered intramuscularly, intradermally,
subcutaneously or intraperitoneally. Suppositories are
administered intrarectally.

The dose of the pharmaceutical preparation of
5 the present invention is appropriately selected depending
upon the administration method, the age, sex and other
conditions of patient, the degree of disease condition of
patient, etc., and is generally about 0.1-10 mg per kg of
body weight per day in terms of the amount of the active
10 ingredient, i.e. the compound (1) of general formula (1).
Preferably, each administration unit form contains the
active ingredient in an amount of 1-200 mg.

[Examples]

Reference Examples, Examples, Pharmacological
15 Test Results and Preparation Examples are shown below.

Reference Example 1

27 g of 1-(2-aminoethyl)-4-methoxymethoxy-
piperidine was dropwise added to a solution of 15 g of
benzaldehyde in 300 ml of ethanol, at room temperature.
20 The mixture was stirred at the same temperature for 1
day. To the reaction mixture was added 5 g of 10% Pd-C,
and the resulting mixture was allowed to absorb hydrogen
at room temperature at atmospheric pressure. After a
reaction was over, the catalyst was removed by filtra-
25 tion. The filtrate was diluted with ethyl acetate. The
dilution was subjected to extraction with 10% hydro-

- 1 chloric acid. The aqueous layer was made alkaline with
an aqueous potassium hydroxide solution and then
subjected to extraction with ethyl acetate. The extract
was washed with water and dried with magnesium sulfate.
5 The solvent was removed by distillation. The resulting
residue was purified by a silica gel column chromato-
graphy (eluant: 10% methanol-chloroform) to obtain 25.50
g of 1-(2-benzylaminoethyl)-4-methoxymethoxypiperidine.

Light yellow oil

- 10 $^1\text{H-NMR}$ (CDCl_3) δ ;
1.35-1.75 (4H, m), 1.75-2.0 (2H, m), 2.0-2.2
(2H, m), 2.47 (2H, t, $J=6.1\text{Hz}$), 2.69 (2H, t,
 $J=6.1\text{Hz}$), 3.37 (3H, s), 3.5-3.7 (1H, m),
3.80 (2H, s), 4.68 (2H, s), 7.2-7.4 (5H, m).

15 Reference Example 2

- 1.7 ml of chloroacetyl chloride was dropwise
added to a solution of 3.0 g of aniline hydrochloride and
7 ml of triethylamine in 30 ml of dichloromethane. The
mixture was stirred at room temperature for 3 hours, then
20 washed with water and a saturated aqueous sodium
hydrogencarbonate solution in this order, and dried with
magnesium sulfate. The solvent was removed by distil-
lation. The resulting residue was crystallized from
ethyl acetate-n-hexane to obtain 2.45 g of N-(2-
25 chloroacetyl)aniline as a light brown solid. A
suspension of 2.45 g of the N-(2-chloroacetyl)-aniline,
2.8 g of 4-methoxymethoxypiperidine, 2.45 g of sodium



1 iodide and 2.3 ml of triethylamine dissolved in 30 ml of
acetonitrile was refluxed for 1.5 hours. The reaction
mixture was diluted with ethyl acetate. The dilution was
washed with water and dried with magnesium sulfate. The
5 solvent was removed by distillation. The resulting
residue was purified by a silica gel column chromatography (eluant : ethyl acetate : n-hexane = 1 : 1) to
obtain 3.64 g of 1-(anilinocarbonylmethyl)-4-methoxymethoxypiperidine as a lightyellow oil.

10 A solution of 3.64 g of 1-(anilinocarbonylmethyl)-4-methoxymethoxypiperidine in 10 ml of tetrahydrofuran was added to a suspension of 630 mg of lithium aluminum hydride in 50 ml of tetrahydrofuran. The
mixture was refluxed for 3 hours. To the reaction
15 mixture were added 1.5 ml of an aqueous solution containing 10% of potassium hydroxide and 1.5 ml of water. The
mixture was diluted with ethyl acetate, and the dilution
was filtered. The solvent in the filtrate was removed by
distillation to obtain 3.41 g of 1-(2-anilinoethyl)-4-methoxymethoxypiperidine.
20

Brown oil

$^1\text{H-NMR}$ (CDCl_3) δ ;

1.6-1.7 (2H, m), 1.9 (2H, m), 2.2 (2H, m),
2.60 (2H, t, $J=6\text{Hz}$), 2.9 (2H, m),
25 3.14 (2H, t, $J=6\text{Hz}$), 3.37 (3H, s),
3.6 (1H, m), 4.69 (2H, s), 6.7 (2H, m),
7.18 (2H, dd, $J=7.3\text{Hz}$, 8.5Hz).

1 Reference Example 3

13.4 g of dicyclohexylcarbodiimide was added,
at room temperature, to a solution of 19.3 g of 1-
benzyloxycarbonyl-4-methoxymethoxy-L-proline, 8.5 ml of
5 cyclohexylmethylamine and 7.5 g of N-hydroxysuccinimide
in 200 ml of dioxane. The mixture was stirred at the
same temperature for 2 hours, then heated at 60°C for 1
hour, and allowed to cool, followed by filtration. The
solvent in the filtrate was removed by filtration. The
10 resulting residue was purified by a silica gel column
chromatography (eluant; 5% methanol/chloroform) to obtain
21.2 g of N-(1-benzyloxycarbonyl-4-methoxymethoxy-L-
prolyl)-N-cyclohexylmethylamine as a light yellow oil.

21.2 g of the obtained N-(1-benzyloxycarbonyl-
15 4-methoxymethoxy-L-prolyl)-N-cyclohexylmethylamine was
dissolved in 200 ml of ethanol. To the solution was
added 2 g of 10% Pd-C. The mixture was subjected to
hydrogenation for 3 hours. The catalyst was removed by
filtration. The solvent in the filtrate was removed by
20 distillation to obtain 14.9 g of N-(4-methoxymethoxy-L-
prolyl)-N-cyclohexylmethylamine.

Light yellow oil

$^1\text{H-NMR}$ (CDCl_3) δ ;

0.9-1.8 (11H, m), 2.0 (1H, m), 2.5 (1H, m),
25 2.96 (8H, dd, $J=3.8\text{Hz}$, 12.5Hz), 3.08 (2H, dd,
 $J=6.5\text{Hz}$, 12.5Hz), 3.24 (1H, d, $J=12.5\text{Hz}$),
3.37 (3H, s), 4.15 (1H, t, $J=8.3\text{Hz}$),
4.3 (1H, m), 4.62 (1H, d, $J=7\text{Hz}$), 4.66 (1H,

1 d, J=7Hz), 7.94 81H, br).

Reference Example 4

Using 3 g of 1-(2-aminoethyl)-4-methoxymethoxy-
piperidine and 2 g of cyclooctanone, 4.3 g of 1-(2-
5 cyclooctylaminoethyl)-4-methoxymethoxypiperidine was
obtained in the same manner as in Reference Example 1.

Light yellow oil

¹H-NMR (CDCl₃) δ;

1.3-2.0 (18H, m), 2.05-2.2 (2H, m),
10 2.44 (2H, t, J=6.1Hz), 2.55-2.85 (5H, m),
3.37(3H, s), 3.5-3.65 (1H, m),
4.68 (2H, s).

Reference Example 5

0.49 ml of 3-chloropropanesulfonyl chloride was
15 dropwise added, at 0°C, to a solution of 1.19 g of 1-(2-
cyclooctylaminoethyl)-4-methoxymethoxypiperidine and 0.67
ml of triethylamine in 10 ml of dichloromethane. The
mixture was stirred at room temperature for 1 day. The
reaction mixture was washed with water and dried with
20 magnesium sulfate. The solvent was removed by
distillation. The resulting residue was purified by
silica gel column chromatography (eluant: 2% methanol/
dichloromethane) to obtain 1.2 g of 1-{2-[N-(3-
chloropropylsulfonyl)-N-cyclooctylamino]-ethyl}-4-
25 methoxymethoxypiperidine.

Light yellow oil

1 ¹H-NMR (CDCl₃) δ;
 1.35-2.05 (18H, m), 2.15-2.35 (4H, m),
 2.57 (2H, t), 2.7-2.9 (2H, m),
 3.16 (2H, t, J=7.6Hz), 3.27 (2H, t,
5 J=7.0Hz), 3.37 (3H, s), 3.55-3.7 (1H, m),
 3.69 (2H, t, J=6Hz), 3.75-3.9 (1H, m),
 4.68 (2H, s).

Reference Example 6

 A solution of 53.3 g of 6-(4-chlorobutoxy)-
10 carbostyryl and 32 g of sodium sulfite dissolved in 500
ml of water and 200 ml of ethanol was refluxed for 1 day.
The solution was allowed to cool and stand for 3 days and
then filtered. The filtrate was made acidic with diluted
15 hydrochloric acid. The solvent was removed by distil-
lation. To the resulting residue was added water, and
the precipitate was collected by filtration to obtain
47.5 g of 6-(4-hydroxysulfonylbutoxy)carbostyryl as a
white powder.

Reference Example 7

20 300 g of phosphorus oxychloride was added to
47.5 g of 6-(4-hydroxysulfonylbutoxy)carbostyryl. The
mixture was refluxed for 5 hours. The phosphorus
oxychloride was removed by distillation under reduced
pressure. The resulting residue was diluted with
25 chloroform. Thereto was added ice, and the organic layer
was separated and dried with magnesium sulfate. The



- 1 solvent was removed by distillation. The residue was crystallized from n-hexane to obtain 48.17 g of 4-(2-chloro-6-quinolyloxy)butylsulfonyl chloride.

White powder

5 Reference Example 8

- 1.75 g of 4-(2-chloro-6-quinolyloxy)butylsulfonyl chloride was added, at 0°C, to a solution of 1.6 g of 1-[2-(2-chlorobenzylamino)ethyl]-4-methoxymethoxy-piperidine and 1 ml of triethylamine in 25 ml dichloro-
10 methane. The mixture was stirred at room temperature for 1 day. The reaction mixture was washed with water and dried with magnesium sulfate. The solvent was removed by distillation. The resulting residue was purified by a silica gel column chromatography (eluant: 3% methanol/
15 dichloromethane) to obtain 2.63 g of 2-chloro-6-[4-{N-(2-chlorobenzyl)-N-[2-(4-methoxymethoxy-1-piperidinyl)-ethyl]aminosulfonyl}butoxy]quinoline.

Light yellow oil

¹H-NMR (CDCl₃) δ;

- 20 7.80-8.05 (2H, m), 7.58 (1H, d, J=7.4Hz),
7.15-7.45 (5H, m), 7.07 (1H, d, J=2.6Hz),
4.65 (2H, s), 4.60 (2H, s), 4.12 (2H, t, J=5.8Hz),
3.45-3.60 (1H, m), 3.10-3.45 (7H, m), 2.60-2.80 (2H, m), 2.44 (2H, t, J=6.2Hz),
25 1.92-2.22 (6H, m), 1.75-1.92 (2H, m), 1.45-1.75 (2H, m).

1 Reference Example 9

 A suspension of 30 g of 6-(4-chlorobutoxy)-
carbostyryl, 103 ml of benzylamine and 33 g of sodium
iodide in 300 ml of dimethylformamide was stirred at 80°C
5 for 8 hours. The reaction mixture was allowed to cool
and then poured into water. The resulting precipitate
was collected by filtration. The precipitate was washed
with water and diethyl ether in this order to obtain 29.1
g of 6-(4-benzylaminobutoxy)carbostyryl.

10 Light yellow powder

Reference Example 10

 1.28 g of 6-(3-aminopropoxy)carbostyryl hydro-
chloride was added, at 0°C, to 10 ml of an aqueous
solution containing 0.3 g of carbon disulfide and 0.4 g
15 of sodium hydroxide. The mixture was stirred at 80°C for
about 2 hours. Thereto was added 0.55 g of ethyl
chlorocarbonate at 35°C. The resulting mixture was
stirred for 30 minutes. The reaction mixture was poured
into water, followed by extraction with ethyl acetate.
20 The filtrate was dried with magnesium sulfate. The
solvent was removed by distillation. To the resulting
residue was added diethyl ether, and the resulting
crystals were collected by filtration and purified by a
silica gel column chromatography (eluant: 3.3% methanol/
25 dichloromethane) to obtain 0.22 g of 6-(3-isothiocyanato-
propoxy)carbostyryl.

1 Reference Example 11

A solution of 3.13 g of 1-[2-(cyclooctylmethyl-amino)ethyl]-4-methoxymethoxypiperidine and 1.0 ml of 3-chloropropaneisocyanate in 20 ml of dichloromethane was
5 stirred at room temperature for 3 hours. The solvent was removed by distillation under reduced pressure to obtain 4.2 g of N-cyclooctylmethyl-N-[2-(4-methoxymethoxy-1-piperidinyl)ethyl]-N'-(3-chloropropyl)urea.

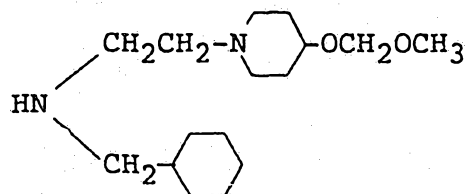
¹H-NMR (CDCl₃) δ;

10 1.15-1.8 (15H, m), 1.85-2.2 (6H, m),
2.25-2.4 (2H, m), 2.51 (2H, t, J=5Hz),
2.75-2.85(2H, m), 3.10 (2H, d, J=7.5Hz),
3.25-3.3 (4H, m), 3.37 (3H, s),
3.55-3.7 (3H, m), 4.68 (2H, s).

15 Using appropriate starting materials, the compounds shown in the following Tables 1-14 were obtained in the same manner as in Reference Examples 1, 2 and 5.

[Table 1]

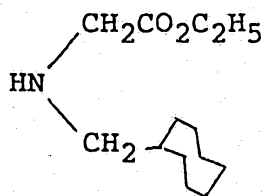
Reference Example 12



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

0.8-2.0(15H, m), 2.13(2H, m), 2.44(4H, m), 2.66(2H, t, $J=6\text{Hz}$), 2.75(2H, m), 3.37(3H, s), 3.57(1H, m), 4.68(2H, s)

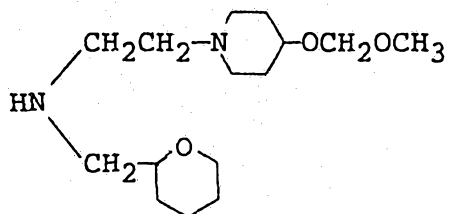
Reference Example 13



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.28(3H, t, $J=7.2\text{Hz}$), 1.4-1.9(15H, m), 2.42(2H, d, $J=6.5\text{Hz}$), 3.39(2H, s), 4.19(2H, q, $J=7.2\text{Hz}$)

Reference Example 14

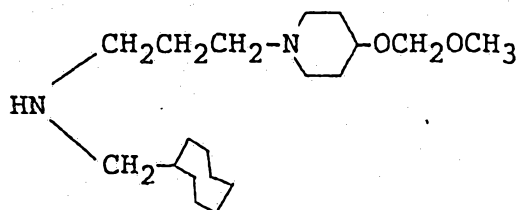


$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.2-2.0(12H, m), 2.1(2H, m), 2.47(2H, t, $J=6.2\text{Hz}$), 2.6-2.8(2H, m), 2.70(2H, t, $J=6.2\text{Hz}$), 3.37(3H, s), 3.42(2H, m), 3.57(1H, m), 3.96(1H, m), 4.68(2H, s)

[Table 2]

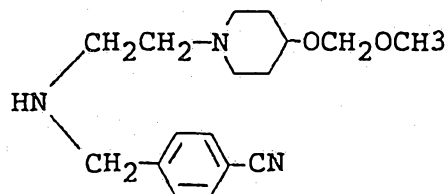
Reference Example 15



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.2-2.0(21H, m), 2.1(2H, m), 2.3-2.7(6H, m),
2.8(2H, m), 3.38(3H, s), 3.6(1H, m), 4.70(2H, s)

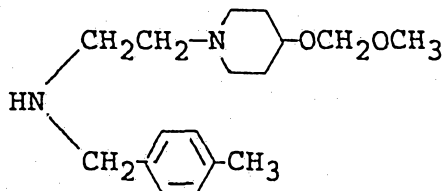
Reference Example 16



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.6(2H, m), 1.9(2H, m), 2.1(2H, m), 2.48(2H, t,
 $J=6\text{Hz}$), 2.67(2H, t, $J=6\text{Hz}$), 2.7(2H, m),
3.37(3H, s), 3.6(1H, m), 3.86(2H, s), 4.68(2H, s),
7.43(2H, d, $J=8\text{Hz}$), 7.61(2H, d, $J=8\text{Hz}$)

Reference Example 17



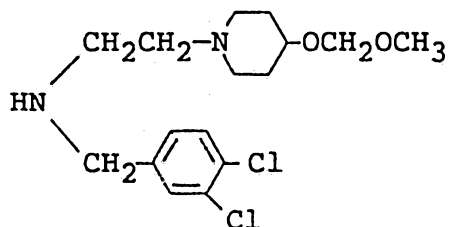
$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.6(2H, m), 1.8(2H, m), 2.1(2H, m), 2.33(3H, s),
2.47(2H, t, $J=6\text{Hz}$), 2.68(2H, t, $J=6\text{Hz}$), 2.7(2H, m),
3.37(3H, s), 3.6(1H, m), 3.76(2H, s), 4.68(2H, s),
7.12(2H, d, $J=8\text{Hz}$), 7.20(2H, d, $J=8\text{Hz}$)



[Table 3]

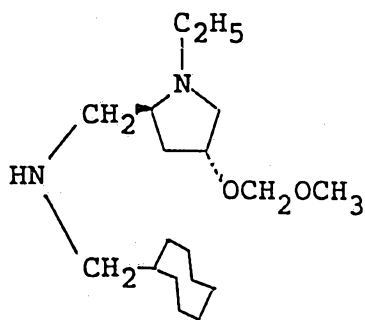
Reference Example 18



¹H-NMR(CDCl₃) δ;

1.6(2H, m), 1.9(2H, m), 2.12(2H, m), 2.47(2H, t, J=6Hz), 2.65(2H, t, J=6Hz), 2.7(2H, m), 3.37(3H, s), 3.6(1H, m), 3.76(2H, s), 4.68(2H, s), 7.15(1H, dd, J=2Hz, 8Hz), 7.38(1H, d, J=8Hz), 7.43(1H, d, J=2Hz)

Reference Example 19

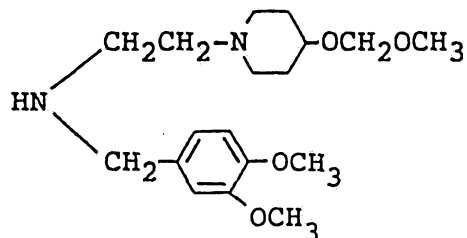


¹H-NMR (CDCl₃) δ;

1.07(3H, t, J=7.2Hz), 1.2-1.7(17H, m), 1.9(2H, m), 2.3(2H, m), 2.40(2H, d, J=6.8Hz), 2.53(1H, dd, J=6.5Hz, 11.5Hz), 2.7-2.9(3H, m), 3.36(3H, s), 3.43(1H, dd, J=6.2Hz, 9.8Hz), 4.2(1H, m), 4.62(1H, d, J=6.8Hz), 4.65(1H, d, J=6.8Hz)

[Table 4]

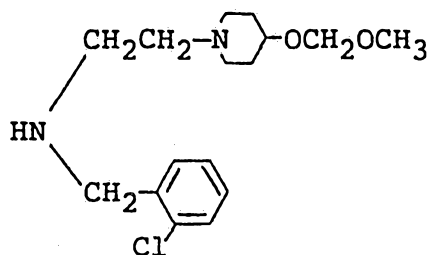
Reference Example 20



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.6(2H, m), 1.8(2H, m), 2.1(2H, m), 2.45(2H, t, $J=6\text{Hz}$), 2.68(2H, t, $J=6\text{Hz}$), 2.7(2H, m), 3.37(3H, s), 3.5(1H, m), 3.75(2H, s), 3.87(3H, s), 3.89(3H, s), 4.68(2H, s), 6.8(3H, m)

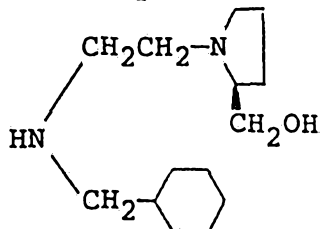
Reference Example 21



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.6(2H, m), 1.8(2H, m), 2.1(2H, m), 2.48(2H, t, $J=6\text{Hz}$), 2.69(2H, t, $J=6\text{Hz}$), 2.7(2H, m), 3.37(3H, s), 3.6(1H, m), 3.89(2H, s), 4.67(1H, s), 7.18-7.24(2H, m), 7.34-7.40(2H, m)

Reference Example 22

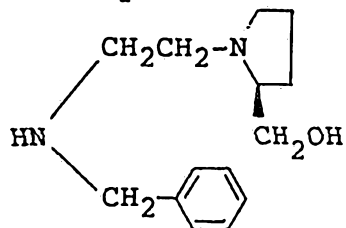


$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

0.80-1.00(2H, m), 1.10-1.90(13H, m), 2.30-2.95(8H, m), 3.10-3.20(1H, m), 3.30-3.40(1H, m), 3.50-3.80(1H, m)

[Table 5]

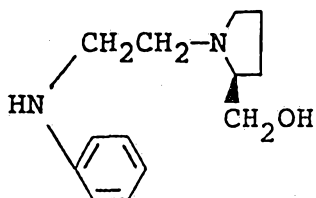
Reference Example 23



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.60-1.95(5H, m), 2.25-3.20(7H, m), 3.35-3.90(4H, m),
7.20-7.40(5H, m)

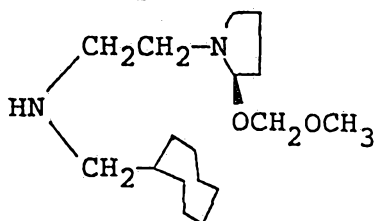
Reference Example 24



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.50-2.00(4H, m), 2.25-2.40(1H, m), 2.55-2.70(2H, m),
3.00-3.65(6H, m), 6.55-6.75(3H, m), 7.10-7.30(2H, m)

Reference Example 25

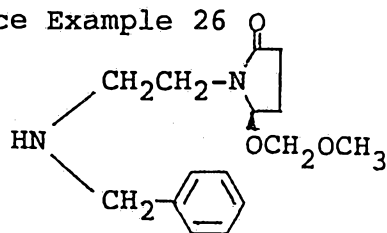


$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.20-2.00(19H, m), 2.15-2.75(7H, m), 2.90-3.20(2H, m),
3.96(3H, s), 3.40-3.60(2H, m), 4.63(2H, s)

[Table 6]

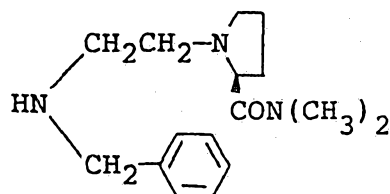
Reference Example 26



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.80-2.65(7H, m), 2.85-3.00(1H, m), 3.25-3.95(9H, m),
4.40-4.70(2H, m), 7.20-7.45(5H, m)

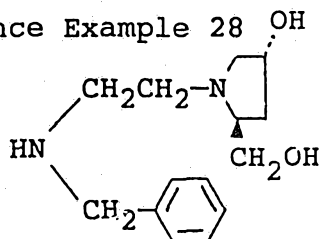
Reference Example 27



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.70-2.15(4H, m), 2.25-2.40(1H, m), 2.60-2.80(4H, m),
2.94(3H, s), 3.04(3H, s), 3.16(1H, brt, $J=6.5\text{Hz}$),
3.36(1H, dd, $J=9\text{Hz}$, 6.5Hz), 3.48(2H, s), 3.75-3.90
(2H, m), 7.20-7.40(5H, m)

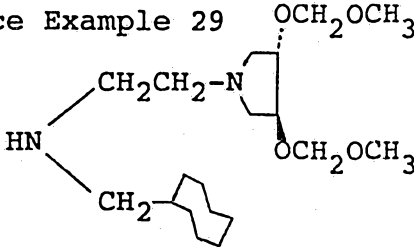
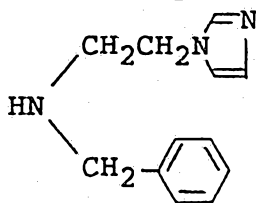
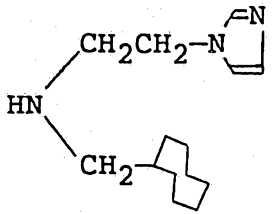
Reference Example 28



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

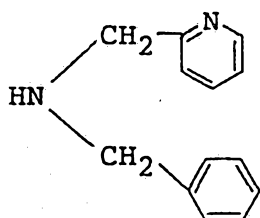
1.75-2.00(2H, m), 2.20-2.80(7H, m), 2.85-3.15(2H, m),
3.25-3.50(2H, m), 3.60-3.80(3H, m), 4.35-4.40(1H, m),
7.20-7.40(5H, m)

[Table 7]

Reference Example 29  $^1\text{H-NMR}(\text{CDCl}_3) \delta;$ 1.20-1.90(15H, m), 2.30-2.70(7H, m), 2.80-2.95(2H, m), 3.37(6H, s), 3.70-3.85(2H, m), 4.13(2H, brs), 4.65(2H, d, J=6.5Hz), 4.71(2H, d, J=6.5Hz)
Reference Example 30  $^1\text{H-NMR}(\text{CDCl}_3) \delta;$ 2.97(2H, t, J=6Hz), 3.77(2H, s), 4.05(2H, t, J=6Hz), 6.95(1H, s), 7.07(1H, s), 7.20-7.45(5H, m), 7.51(1H, s)
Reference Example 31  $^1\text{H-NMR}(\text{CDCl}_3) \delta;$ 1.00-1.70(15H, m), 2.34(2H, d, J=6.5Hz), 2.87(2H, t, J=6Hz), 3.98(2H, t, J=6Hz), 6.89(1H, s), 7.00(1H, s), 7.45(1H, s)

[Table 8]

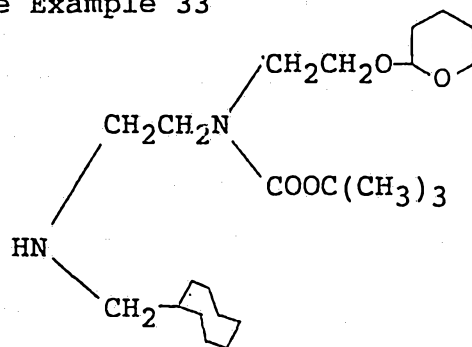
Reference Example 32



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

3.85(2H, s), 3.93(2H, s), 7.10-7.40(7H, m),
7.64(1H, dt, $J=7.5\text{Hz}$, 2Hz), 8.56(2H, brd, $J=5\text{Hz}$)

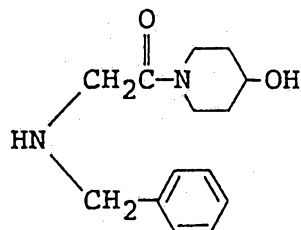
Reference Example 33



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.20-1.80(21H, m), 1.46(9H, s), 2.43(2H, d, $J=6.5\text{Hz}$),
2.76(2H, t, $J=6.5\text{Hz}$), 3.30-3.60(6H, m), 3.75-3.90
(2H, m), 4.59(1H, brs)

Reference Example 34

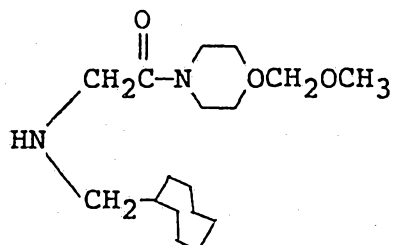


$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.44(2H, brs), 1.76(6H, brs), 3.00-3.20(2H, m),
3.35(2H, s), 3.45-3.60(1H, m), 3.75(2H, s),
3.80-3.95(1H, m), 3.95-4.10(1H, m), 7.15-7.35(5H, m)

[Table 9]

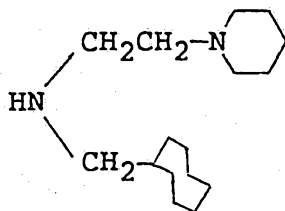
Reference Example 35



¹H-NMR(CDCL₃) δ;

1.15-1.80(15H, m), 1.80-2.00(2H, m), 2.10(2H, brs),
2.43(2H, d, J=6.5Hz), 3.20-3.35(2H, m), 3.38(3H, s),
3.43(2H, s), 3.60-3.70(1H, m), 3.75-3.90(1H, m),
3.90-4.05(1H, m), 4.70(2H, s)

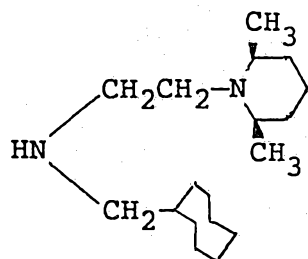
Reference Example 36



¹H-NMR (CDCl₃) δ;

1.20-1.80(21H, m), 2.30-2.45(9H, m),
2.68(2H, t, J=6Hz)

Reference Example 37

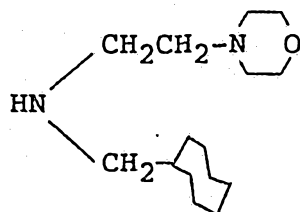


¹H-NMR (CDCl₃) δ;

1.14(6H, d, J=6.5Hz), 1.20-1.80(21H, m),
2.40-2.55(4H, m), 2.60-2.80(4H, m)

[Table 10]

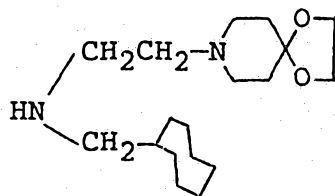
Reference Example 38



¹H-NMR(CDCL₃) δ;

1.20-1.70(14H, m), 2.40-2.85(12H, m), 3.70(4H, t, J=6Hz)

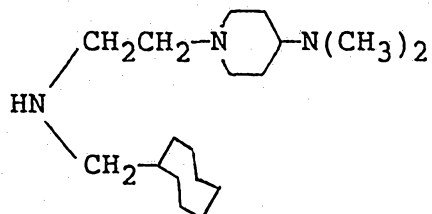
Reference Example 39



¹H-NMR (CDCl₃) δ;

1.20-1.80(19H, m), 2.40-2.60(9H, m),
2.68(2H, t, J=6Hz), 3.95(4H, s)

Reference Example 40



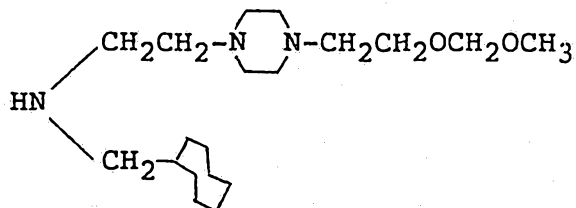
¹H-NMR (CDCl₃) δ;

1.20-2.20(22H, m), 2.27(6H, s), 2.35-2.50(4H, m),
2.67(2H, t, J=6Hz), 2.93(2H, brd, J=12Hz)



[Table 11]

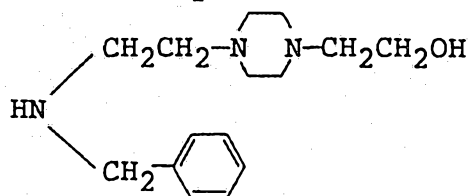
Reference Example 41



$^1\text{H-NMR}(\text{CDCl}_3) \delta;$

1.20-1.80(15H, m), 2.35-2.70(16H, m), 3.36(3H, s),
3.66(2H, t, $J=6\text{Hz}$), 4.64(2H, s)

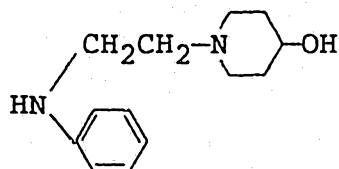
Reference Example 42



$^1\text{H-NMR}(\text{CDCl}_3) \delta;$

1.50-2.00(5H, m), 2.40-2.65(11H, m), 2.70(2H, t,
 $J=6\text{Hz}$), 3.60(2H, t, $J=6\text{Hz}$), 7.20-7.40(5H, m)

Reference Example 43

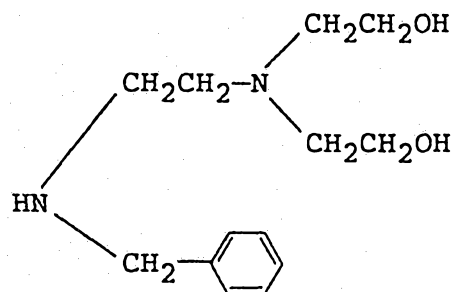


$^1\text{H-NMR}(\text{CDCl}_3) \delta;$

1.40-2.00(10H, m), 2.17(2H, brt, $J=9\text{Hz}$),
2.62(2H, t, $J=6\text{Hz}$), 2.70-2.90(2H, m), 3.15(2H, t,
 $J=6\text{Hz}$), 3.65-3.80(2H, m), 4.30(1H, brs),
6.60-6.75(3H, m), 7.15-7.30(2H, m)

[Table 12]

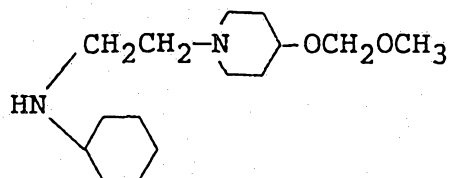
Reference Example 44



$^1\text{H-NMR}(\text{CDCl}_3+\text{D}_2\text{O}) \delta;$

2.60-2.80(8H, m), 3.58(4H, t, $J=5\text{Hz}$), 3.77(2H, s),
7.20-7.50(5H, m)

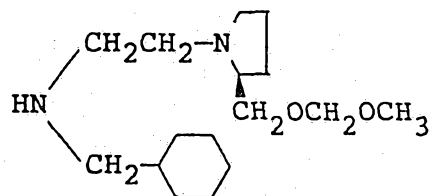
Reference Example 45



$^1\text{H-NMR}(\text{CDCl}_3) \delta;$

1.0-2.0(14H, m), 2.05-2.2(2H, m), 2.3-2.5(3H, m),
2.6-2.8(4H, m), 3.70(3H, s), 3.5-3.65(1H, m),
4.68(2H, s)

Reference Example 46

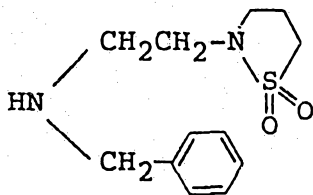


$^1\text{H-NMR}(\text{CDCl}_3) \delta;$

0.8-2.0(15H, m), 2.25(1H, dd), 2.4-2.55(2H, m),
2.55-2.95(4H, m), 3.0-3.15(2H, m), 3.37(3H, s),
3.40-3.55(2H, m), 4.64(2H, s)

[Table 13]

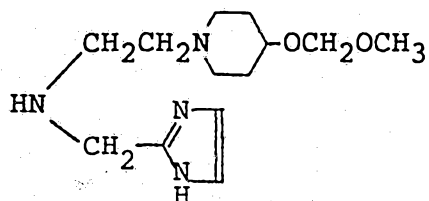
Reference Example 47



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

2.25-2.4(2H, m), 2.84(2H, t, $J=6.3\text{Hz}$), 3.10-3.30(6H, m), 3.82(2H, s), 7.20-7.45(5H, m)

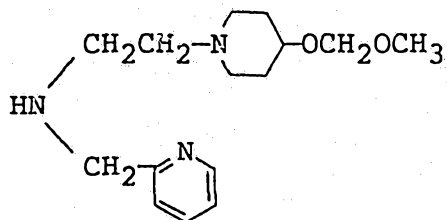
Reference Example 48



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.6-1.75(2H, m), 1.9-2.05(2H, m), 2.15-2.35(2H, m), 2.49(2H, t, $J=9.3\text{Hz}$), 2.7-2.8(4H, m), 3.37(3H, s), 3.6-3.75(1H, m), 3.96(2H, s), 4.68(2H, s), 6.97(2H, s)

Reference Example 49

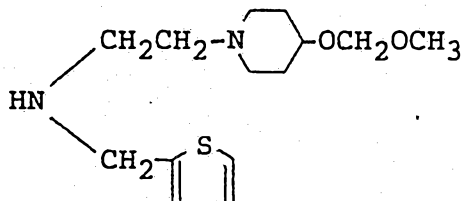


$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.5-1.75(2H, m), 1.8-2.0(2H, m), 2.05-2.2(2H, m), 2.4-2.85(6H, m), 3.37(3H, s), 3.5-3.65(1H, m), 3.93(2H, s), 4.68(2H, s), 7.15(1H, dt, $J=5\text{Hz}$, 2Hz), 7.25(1H, dd), 7.64(1H, dt, $J=5\text{Hz}$, 2Hz), 8.55(1H, dd)

[Table 14]

Reference Example 50



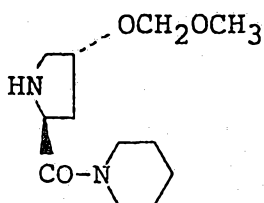
$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.55-1.7(2H, m), 1.8-1.95(2H, m), 2.05-2.15(2H, m),
2.47(2H, t, $J=6\text{Hz}$), 2.65-2.8 (4H, m), 3.36(3H, s),
3.5-3.65(1H, m), 4.0(2H, s), 4.67(2H, s), 6.85-7.0
(2H, m), 7.2(1H, dd, $J=1.5\text{Hz}$, 5Hz)

- 1 Using appropriate starting materials, a compound shown in the following Table 15 were obtained in the same manner as in Reference Example 3.

[Table 15]

Reference Example 51



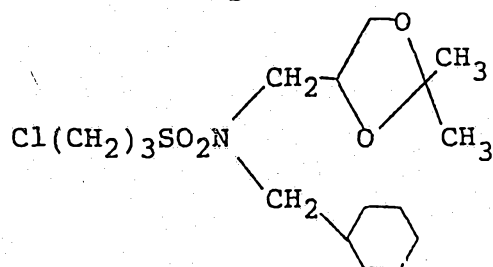
$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.5-1.7(6H, m), 1.87(1H, m), 2.16(1H, ddd, $J=1.9\text{Hz}$,
7.5Hz, 13.2Hz), 2.93(1H, dd, $J=3.5\text{Hz}$, 11.9Hz),
3.39(3H, s), 3.3-3.5(3H, m), 3.6(2H, m),
4.09(1H, t, $J=8\text{Hz}$), 4.3(1H, m), 4.65(2H, s)

1 Using appropriate starting materials, the compounds shown in the following Tables 16-22 were obtained in the same manner as in Reference Example 5.

[Table 16]

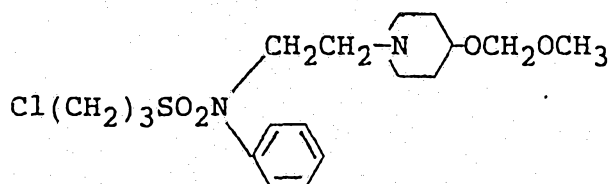
Reference Example 52



$^1\text{H-NMR}$ (CDCl_3) δ ;

0.85-1.05(2H, m), 1.1-1.3(3H, m), 1.35(3H, s),
1.45(3H, s), 1.65-1.85(6H, m), 2.25-2.35(2H, m),
3.05-3.4(6H, m), 3.6-3.75(3H, m), 4.05-4.15(1H, m),
4.25-4.4(1H, m)

Reference Example 53

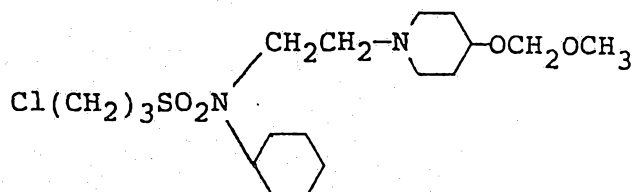


$^1\text{H-NMR}$ (CDCl_3) δ ;

1.55-1.75(2H, m), 1.8-1.95(2H, m), 2.15-2.25(2H, m),
2.31(2H, dd), 2.45(2H, d, $J=6.7\text{Hz}$), 2.65-2.85(2H, m),
3.28(2H, t, $J=7.75\text{Hz}$), 3.36(3H, s), 3.5-3.65(1H, m),
3.66(2H, t, $J=6.3\text{Hz}$), 3.81(2H, t, $J=6.7\text{Hz}$),
4.66(2H, s), 7.3-7.5(5H, m)

[Table 17]

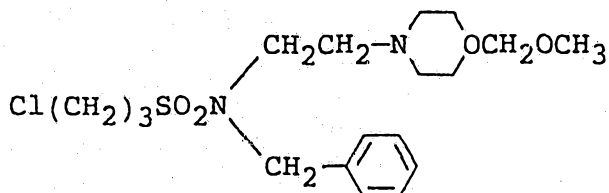
Reference Example 54



^1H -NMR (CDCl_3) δ ;

1.0-2.0(14H, m), 2.15-2.35(4H, m), 2.52(2H, t, $J=7.1\text{Hz}$), 2.25-2.37(2H, m), 3.19(2H, t, $J=7.6\text{Hz}$), 3.30(2H, t, $J=7.7\text{Hz}$), 3.37(3H, s), 3.45-3.65(2H, m), 3.48(2H, t, $J=6.5\text{Hz}$), 4.68(2H, s)

Reference Example 55

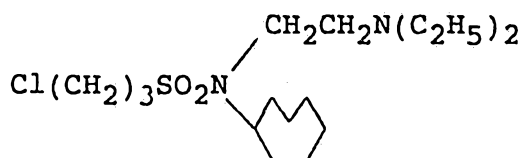


^1H -NMR (CDCl_3) δ ;

1.45-1.7(2H, m), 1.82-1.95(2H, m), 2.05-2.2(2H, m), 2.30-2.35(2H, m), 2.41(2H, t, $J=6.5\text{Hz}$), 2.67-2.8(2H, m), 3.25-3.37(4H, m), 3.37(3H, s), 3.5-3.65(1H, m), 3.69(2H, t, $J=6.2\text{Hz}$), 4.46(2H, s), 4.67(2H, s), 7.30-7.42(5H, m)

[Table 18]

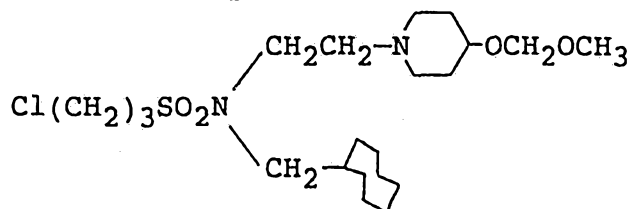
Reference Example 56



$^1\text{H-NMR}(\text{CDCl}_3) \delta$;

1.04(6H, t, $J=7.2\text{Hz}$), 1.37-2.10(12H, m), 2.23-2.35(2H, m), 2.5-2.72(6H, m), 3.1-3.3(4H, m), 3.6-3.75(3H, m)

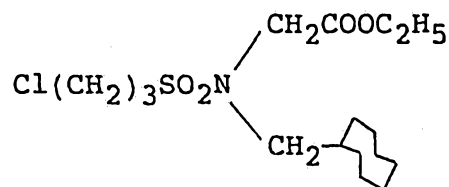
Reference Example 57



$^1\text{H-NMR}(\text{CDCl}_3) \delta$;

1.2-2.1(19H, m), 2.3-2.45(2H, m), 3.16(2H, d, $J=7.6\text{Hz}$), 3.25-3.45(7H, m), 3.55-3.65(1H, m), 3.7(2H, t), 3.8-4.0(2H, m), 4.16(2H, s), 4.70(2H, s)

Reference Example 58

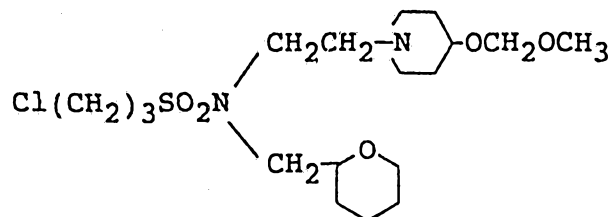


$^1\text{H-NMR}(\text{CDCl}_3) \delta$;

1.18-1.87(18H, m), 2.27-2.42(2H, m), 3.10(2H, d, $J=7.6\text{Hz}$), 3.29(2H, t, $J=7.6\text{Hz}$), 3.68(2H, t, $J=6.3\text{Hz}$), 4.09(2H, s), 4.22(2H, q, $J=7.1\text{Hz}$)

[Table 19]

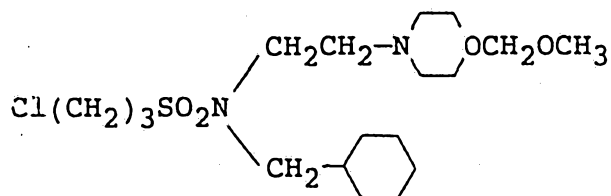
Reference Example 59



$^1\text{H-NMR}$ (CDCl_3) δ ;

1.15-1.7(8H, m), 1.8-1.95(2H, m), 2.15-2.35(4H, m),
2.5-2.65(2H, m), 2.75-2.85(2H, m), 3.2-3.6(12H, m),
3.67(2H, t, $J=6.3\text{Hz}$), 3.9-4.05(1H, m), 4.68(2H, s)

Reference Example 60

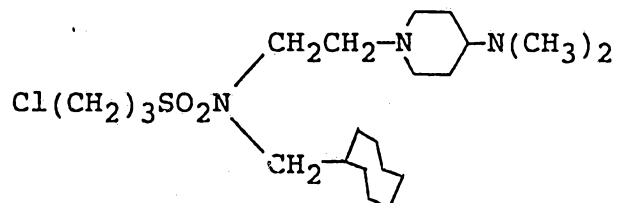


$^1\text{H-NMR}$ (CDCl_3) δ ;

0.85-2.0(15H, m), 2.15-2.4(4H, m), 2.51(2H, t,
 $J=6.7\text{Hz}$), 2.73-2.87(2H, m), 3.0(2H, d, $J=7.4\text{Hz}$),
3.24(2H, t, $J=7.7\text{Hz}$), 3.3-3.45(5H, m),
3.55-3.65(1H, m), 3.68(2H, t, $J=6.2\text{Hz}$),
4.68(2H, s)

[Table 20]

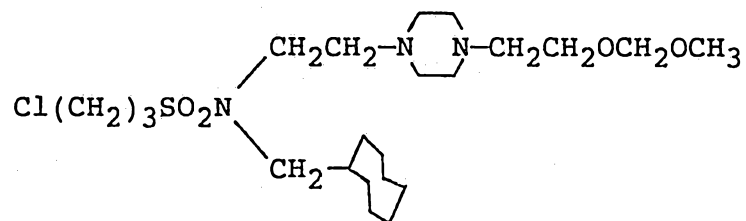
Reference Example 61



$^1\text{H-NMR}$ (CDCl_3) δ ;

1.15-1.9 (31H, m), 1.95-2.1 (2H, m), 2.25-2.35 (8H, m),
2.51 (2H, t, $J=6.8\text{Hz}$), 2.9-3.05 (3H, m),
3.22 (2H, t, $J=7.6\text{Hz}$), 3.34 (2H, t, $J=6.7\text{Hz}$),
3.69 (2H, t, $J=6.2\text{Hz}$)

Reference Example 62

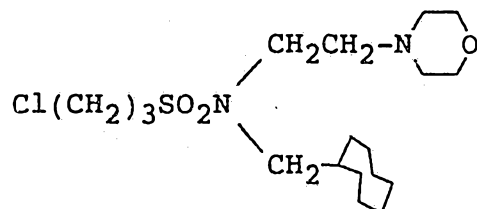


$^1\text{H-NMR}$ (CDCl_3) δ ;

1.18-1.95 (15H, m), 2.2-2.37 (2H, m), 2.4-2.7 (12H, m),
3.01 (2H, d, $J=7.8\text{Hz}$), 3.25 (2H, t, $J=7.6\text{Hz}$),
3.3-3.45 (5H, m), 3.6-3.75 (4H, m), 4.64 (2H, s)

[Table 21]

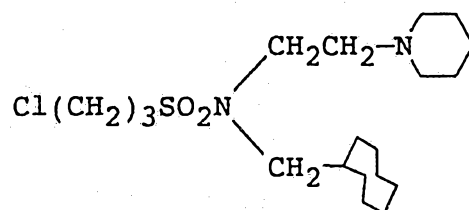
Reference Example 63



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.15-1.9(15h, m), 2.2-2.4(2H, m), 2.4-2.6(6H, m),
3.02(2H, d, $J=7.6\text{Hz}$), 3.26(2h, t, $J=7.7\text{Hz}$),
3.36(2H, t, $J=6.6\text{Hz}$), 3.6-3.8(6H, m)

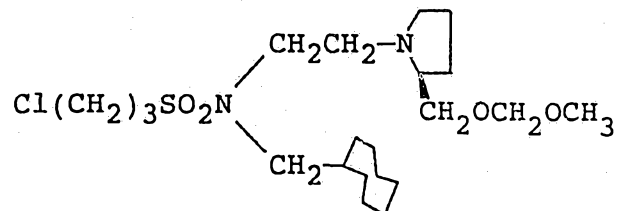
Reference Example 64



$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.15-2.15(21H, m), 2.20-2.65(8H, m), 3.01(2H, d,
 $J=7.6\text{Hz}$), 3.26(2H, t, $J=7.6\text{Hz}$), 3.35(2H, t, $J=6.7\text{Hz}$),
3.68(2H, t, $J=6.2\text{Hz}$)

Reference Example 65

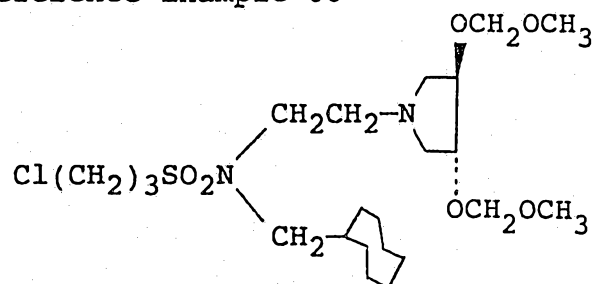


$^1\text{H-NMR}(\text{CDCl}_3)$ δ ;

1.15-2.0(19H, m), 2.1-2.5(4H, m), 2.6-2.75(1H, m),
2.9-3.57(13H, m), 3.68(2H, t, $J=3.8\text{Hz}$),
4.63(2H, s)

[Table 22]

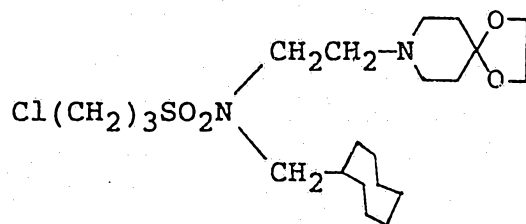
Reference Example 66



$^1\text{H-NMR}$ (CDCl_3) δ ;

1.15-1.8 (15H, m), 2.2-2.35 (2H, m), 2.5-2.8 (4H, m),
2.85-3.05 (4H, m), 3.25-3.4 (10H, m), 3.68 (2H, t,
 $J=6.3\text{Hz}$), 4.12 (2H, t, $J=4.2\text{Hz}$), 4.6-4.75 (4H, m)

Reference Example 67



$^1\text{H-NMR}$ (CDCl_3) δ ;

1.15-1.85 (19H, m), 2.25-2.35 (2H, m), 2.5-2.65 (6H, m),
3.02 (2H, d, $J=7.6\text{Hz}$), 3.24 (2H, t, $J=7.6\text{Hz}$),
3.35 (2H, t, $J=6.6\text{Hz}$), 3.68 (2H, t, $J=6.2\text{Hz}$),
3.95 (4H, s)



1 Example 1

A suspension of 800 mg of 6-(4-bromobutoxy)-carbostyryl, 700 mg of 1-(2-benzylaminoethyl)-4-methoxymethoxypiperidine and 330 mg of sodium hydrogen-
5 carbonate in 20 ml. of dimethylformamide was stirred at 100°C for 6 hours. The reaction mixture was allowed to cool and mixed with water. The resulting mixture was subjected to decantation to obtain an oily substance. The substance was dissolved in chloroform, and the
10 solution was washed with water and dried with magnesium sulfate. The solvent was removed by distillation to obtain 1.07 g of 6-[4-{N-[2-(4-methoxymethoxy-1-piperidinyl)ethyl]-N-dibenzylamino}butoxy]carbostyryl.

¹H-NMR (CDCl₃) δ;

15 1.5-1.9 (8H, m), 2.12 (2H, m), 2.5 (4H, m),
2.6 (2H, m), 2.7 (2H, m), 3.36 (3H, s),
3.6 (1H, m), 3.60 (2H, s), 3.95 (2H, t,
J=6Hz), 4.67 (2H, s), 6.71 (1H, d, J=9.5Hz),
6.93 (1H, d, J=2.5Hz), 7.12 (1H, dd, J=2.5Hz,
20 9Hz), 7.2-7.3 (6H, m).

Example 2

10 ml of 10% hydrochloric acid was added to a solution of 1.07 g of 6-[4-{N-[2-(4-methoxymethoxy-1-piperidinyl)ethyl]-N-benzylamino}butoxy]carbostyryl in 10
25 ml of methanol. The mixture was stirred at room temperature for 1 day. The reaction mixture was washed with chloroform and then made alkaline with a 10% aqueous

1 potassium hydroxide solution, followed by extraction with
chloroform. The extract was washed with water and dried
with magnesium sulfate. The solvent was removed by
distillation. The resulting residue was purified by
5 silica gel column chromatography (eluant: 5% methanol/
chloroform), followed by recrystallization from ethyl
acetate-diethyl ether, to obtain 330 mg of 6-[4-{N-[2-(4-
hydroxy-1-piperidinyl)ethyl]-N-benzylamino}butoxy]-
carbostyryl.

10 White powder
Melting point: 126-131°C

Example 3

5 ml of a 1 N aqueous sodium hydroxide solution
and 5 ml of methanol were added to 795 mg of 6-[4-(N-
15 ethoxycarbonylmethyl-N-cyclooctyl-methyl)butoxy]-
carbostyryl. The mixture was stirred at 50°C for 2
hours. The reaction mixture was neutralized with a 10%
aqueous hydrochloric acid solution. The resulting
precipitate was collected by filtration to obtain 691 mg
20 of 6-[4-(N-carboxymethyl-N-cyclooctylmethyl)butoxy]-
carbostyryl.

White powder
Melting point: 154-155°C

Example 4

25 A suspension of 0.44 g of 6-hydroxycabostyryl,
0.45 g of potassium carbonate and 1.2 g of 1-{2-[N-(3-

1 chloropropylsulfonyl)-N-cyclooctylamino]ethyl}-4-
methoxymethoxypiperidine in 30 ml of dimethylformamide
was stirred at 90°C for 1 day. The reaction mixture was
poured into water, followed by extraction with ethyl
5 acetate. The extract was washed with water and dried
with magnesium sulfate. The solvent was removed by
distillation. The resulting residue was purified by
silica gel column chromatography (eluant: 5% methanol/
dichloromethane) to obtain 0.76 g of 6-[3-{N-[2-(4-
10 methoxymethoxy-1-piperidinyl)ethyl-N-cyclooctylamino-
sulfonyl}propoxy]carbostyryl.

Light yellow oil

¹H-NMR (CDCl₃) δ;

7.75 (1H, d, J=9.5Hz), 7.35 (1H, d, J=9Hz),
15 7.15 (1H, dd, J=9Hz, 2.6Hz), 7.01 (1H, d,
J=2.6Hz), 6.73 (1H, d, J=9.5Hz), 4.68
(2H, s), 4.15 (2H, t, J=5.8Hz), 3.75-3.95
(H, m), 3.58-3.69 (1H, m), 3.37 (3H, s),
3.22-3.35 (4H, m), 2.75-2.90 (2H, m),
20 2.55-2.68 (2H, m), 2.18-2.40 (4H, m),
1.40-2.05 (18H, m).

Example 5

A solution of 2.63 g of 2-chloro-6-[4-{N-(2-
chlorobenzyl)-N-[2-(4-methoxymethoxy-1-piperidinyl)-
25 ethyl]aminosulfonyl}butoxy]quinoline dissolved in 50 ml
of acetic acid was refluxed for 3.5 hours. The solvent
was removed by distillation under reduced pressure to

- 1 obtain crude 6-[4-{N-(2-chlorobenzyl)-N-[2-(4-methoxymethoxy-1-piperidinyl)ethyl]aminosulfonyl}-butoxy]carbostyryl. To the substance were added 10 ml of methanol and 10 ml of a 5% aqueous hydrochloric acid
- 5 solution: The mixture was stirred at room temperature for 1 day and then made alkaline with an aqueous potassium hydroxide solution, followed by extraction with ethyl acetate. The extract was washed with water and dried with magnesium sulfate. The solvent was removed by
- 10 distillation. The resulting residue was purified by silica gel column chromatography (eluant: 10% methanol/dichloromethane) to obtain 1.4 g of 6-[4-{N-(2-chlorobenzyl)-N-[2-(4-hydroxy-1-piperidinyl)ethyl]-aminosulfonyl}butoxy]carbostyryl.
- 15 White powder
- Melting point: 147-152°C

Example 6

- 6.6 ml of 3-chloropropanesulfonyl chloride was dropwise added, at 0°C, to a dichloromethane solution
- 20 containing 8 g of 6-(4-benzylaminobutoxy)carbostyryl and 7.6 ml of triethylamine. The mixture was stirred at room temperature for 1 day. The reaction mixture was washed with 10% hydrochloric acid and water in this order and dried with magnesium sulfate. The solvent was removed by
- 25 distillation. The resulting residue was dissolved in 30 ml of dioxane. To the solution was added 10 ml of a 10% potassium hydroxide solution, followed by stirring at



1 room temperature for 30 minutes. The reaction mixture
was neutralized with 10% hydrochloric acid, followed by
extraction with chloroform. The extract was dried with
magnesium sulfate. The solvent was removed by distil-
5 lation. The resulting residue was crystallized from
diethyl ether to obtain 7.3 g of 6-{4-[N-(3-chloro-
propylsulfonyl)-N-benzylamino]butoxy}carbostyryl.

White powder

¹H-NMR (CDCl₃) δ;

10 1.6-1.7 (4H, m), 2.25-2.35 (2H, m), 3.11
(2H, t, J=7.5Hz), 3.25-3.35 (2H, m),
3.67 (2H, t, J=6.0Hz), 3.9-4.0 (2H, m),
4.44 (2H, s), 6.71 (2H, d, J=9.5Hz),
6.92 (1H, d, J=2.5Hz), 7.09 (2H, dd,
15 J=2.5Hz, 9.0 Hz), 7.3-7.4 (6H, m),
7.73 (1H, d, J=9.5 Hz).

Example 7

1.0 g of 6-{4-[N-(3-chloropropylsulfonyl)-N-
benzylamino]butoxy}carbostyryl and 600 mg of 1,2,4-
20 triazole were stirred at 140°C for 3 hours. The reaction
mixture was diluted with dioxane. The resulting crystals
were collected by filtration and purified by a column
chromatography (eluant: 3% methanol/chloroform). The
purified crystals were recrystallized from ethyl acetate
25 to obtain 327 mg of 6-[4-{N-[3-(1,2,4-triazol-1-yl)-
propylsulfonyl]-N-benzylamino}butoxy]-carbostyryl.

Light yellow powder



1 Melting point: 137-139°C

Example 8

A solution of 6.7 g of 6-(4-chlorobutyl)-
carbostryl, 5 g of 1-(2-aminoethyl)-4-methoxymethoxy-
5 piperidine, 4.0 g of sodium iodide and 2.3 g of sodium
hydrogencarbonate in 30 ml of dimethylformamide was
stirred at 80°C for 4 hours. The reaction mixture was
diluted with chloroform. The dilution was washed with
water and subjected to extraction with 5% hydrochloric
10 acid. The extract was made alkaline with 10% potassium
hydroxide, followed by extraction with chloroform. The
extract was dried with magnesium sulfate. The solvent
was removed by distillation to obtain 9.01 g of 6-{4-[2-
(4-methoxymethoxy-1-piperidinyl)ethyl]aminobutoxy}-
15 carbostryl.

Light yellow oil

¹H-NMR (CDCl₃) δ;

1.5-1.7 (2H, m), 1.75-1.9 (4H, m), 2.15-2.3
(2H, m), 2.6-2.7 (2H, m), 2.7-2.8 (2H, m),
20 2.85-2.95 (4H, m), 3.45 (3H, s), 3.5-3.65
(1H, m), 3.95-4.05 (2H, m), 4.65 (2H, s),
6.64 (1H, d, J=9.5 Hz), 6.91 (1H, d, J=2.5Hz),
7.05 (1H, dd, J=2.5Hz, 9.0Hz), 7.39 81H, d,
J=9.0Hz), 7.70 (1H, d, J=9.5Hz), 8.00 (1H, br).

25 Example 9

A solution of 2.5 g of 6-{4-[2-(4-methoxy-

1 methoxy-1-piperidinyl)ethyl]aminobutoxy}carbostyryl, 1.5
g of cyclohexylmethanesulfonyl chloride and 1.35 ml of
triethylamine in 30 ml of dichloromethane was stirred at
room temperature for 16 hours. The reaction mixture was
5 washed with water and dried with magnesium sulfate. The
solvent was removed by distillation. The resulting
residue was purified by a silica gel column chromatography (eluant: 3% methanol/chloroform) to obtain 620 mg
of 6-[4-{N-[2-(4-methoxymethoxy-1-piperidinyl)ethyl]-N-
10 cyclohexylmethylsulfonylamino}butoxy]carbostyryl.

Light yellow oil

$^1\text{H-NMR}$ (CDCl_3) δ ;

1.0-2.0 (19H, m), 2.1-2.3 (2H, m),
2.4-2.6 (2H, m), 2.7-2.9 (2H, m), 3.2-3.4
15 (4H, m), 3.36 (3H, s), 3.5-3.65 (1H, m),
3.95-4.05 (2H, m), 4.67 (2H, s),
6.71 (1H, d, $J=9.5$), 7.13 (1H, dd, $J=2.5\text{H}$,
9.0Hz), 7.34 (1H, d, $J=9.0\text{Hz}$), 7.75
(1H, d, $J=9.5\text{Hz}$).

20 Example 10

A solution of 0.22 g of 6-(3-isothiocyanatopropoxy)carbostyryl and 0.3 g of 1-[2-(cyclooctylmethylamino)ethyl]-4-methoxymethoxypiperidine in 30 ml of
chloroform was stirred at room temperature for 5 hours.
25 The solvent was removed by distillation under reduced
pressure. The resulting residue was purified by a silica
gel column chromatography (eluant: 3% methanol/dichloro-

1 methane) to obtain 0.36 g of 6-[3-{N-2-(4-methoxymethoxy-
1-piperidinyl)ethyl-N-cyclooctylmethylamino}-
thiocarbonylaminopropoxy]carbostyryl.

Colorless oil

5 Example 11

A solution of 1.6 g of δ -hydroxycarbostyryl,
1.4 g of potassium carbonate and 4.2 g of N-cyclo-
octylmethyl-N-[2-(4-methoxymethoxy-1-piperidinyl)-
ethyl-N-(3-chloropropyl)urea in 20 ml of dimethyl-
10 formamide was stirred at 80°C for 1 day. The reaction
mixture was poured into ice water, followed by extraction
with ethyl acetate. The extract was washed with water
and dried with magnesium sulfate. The solvent was
removed by distillation. The resulting residue was
15 purified by a silica gel column chromatography (eluant:
5% methanol/ dichloromethane) to obtain 0.76 g of
6-[3-{N-[2-(4-methoxymethoxy-1-piperidinyl)ethyl]-N-
cyclooctylmethylamino}carbonylaminopropoxy]carbostyryl.

Brown oil

20 $^1\text{H-NMR}$ (CDCl_3) δ ;

7.73 (1H, d, $J=9.5\text{Hz}$), 7.40 (1H, br),
7.29 (1H, d, $J=11.4\text{ Hz}$), 7.15 (1H, dd,
 $J=11.4\text{ Hz}$, 2.5Hz), 7.01 (1H, d, 2.5Hz),
6.70 (1H, d, $J=9.5\text{ Hz}$), 4.65 (2H, s),
25 4.06 (2H, t, $J=6.2\text{Hz}$), 3.15-3.65 (8H, m),
3.10 (2H, d, $J=7.5\text{Hz}$), 2.65-2.90 (2H, m),
2.35-2.60 (2H, m), 2.10-2.35 (2H, m),

1 1.97-2.10 (2H, t, J=6.5Hz), 1.10-1.97
 (19H, m).

Example 12

 A solution of 0.68 g of 6-[3-(N-cyclohexyl-N-
5 methylaminocarbonyl)propoxy]carbostyryl and 0.81 g of a
Lawesson's reagent in 10 ml of toluene was refluxed for
1.5 hours. The reaction mixture was allowed to cool,
followed by solvent removal by distillation. The
resulting residue was purified by a silica gel column
10 chromatography (eluant: 2% methanol/dichloromethane) to
obtain 0.69 g of 6-[3-(N-cyclohexyl-N-methylaminothio-
carbonyl)propoxy]thiocarbostyryl.

 Yellow powder

 Melting point: 170-172°C

15 Example 13

 A solution of 13.7 g of 6-[3-(N-cyclohexyl-N-
methylaminocarbonyl)propoxy]carbostyryl and 4.45 g of
phosphorus pentasulfide in 200 ml of benzene was refluxed
for 5 hours. The reaction mixture was allowed to cool.
20 The insolubles were removed by filtration. The filtrate
was subjected to distillation to remove the solvent. The
resulting residue was purified by a silica gel column
chromatography (eluant: 5% methanol/dichloromethane) to
obtain 7.2 g of 6-[3-(N-cyclohexyl-N-methylaminothio-
25 carbonyl)propoxy]carbostyryl.

 Yellow powder

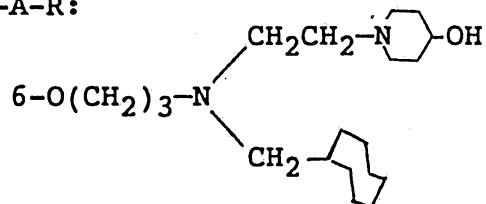
1 Melting point: 167-170°C

 Using appropriate starting materials, the compounds shown in the following Tables 23-56 were obtained in the same manner as in Example 4.

[Table 23]

Example 14

-O-A-R:



W: oxygen atom

Crystal form: white powder

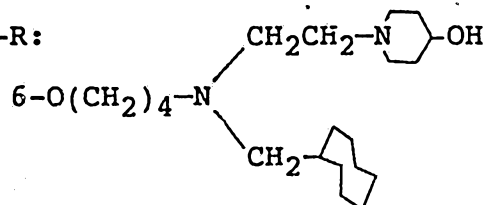
Free form

Melting point: 149-150°

Recrystallization solvent: ethyl acetate - diethyl ether

Example 15

-O-A-R:



W: oxygen atom

Crystal form: white powder

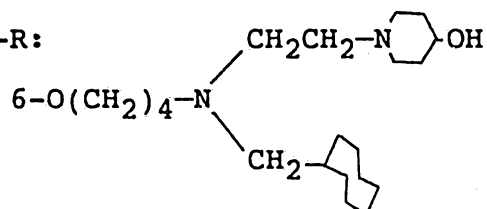
Free form

Melting point: 117-118°C

Recrystallization solvent: ethyl acetate

Example 16

-O-A-R:



W: oxygen atom

Crystal form: white powder

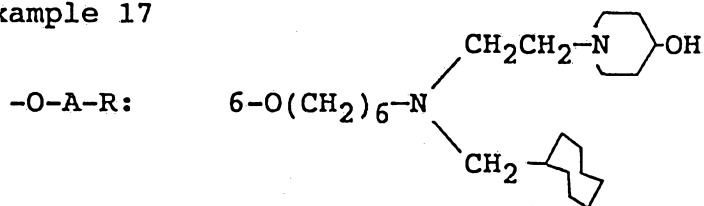
Free form

Melting point: 114.5-116°C

Recrystallization solvent: ethyl acetate - diethyl ether

[Table 24]

Example 17



W: oxygen atom

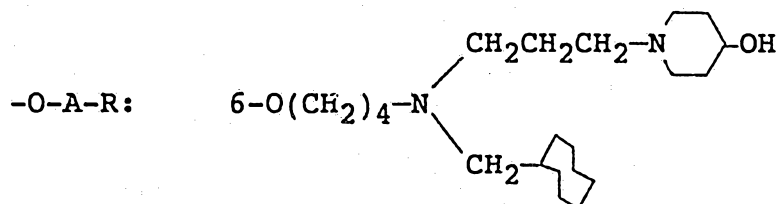
Crystal form: white powder

Free form

Melting point: 69-74°C

Recrystallization solvent: diethyl ether - diisopropyl ether

Example 18



W: oxygen atom

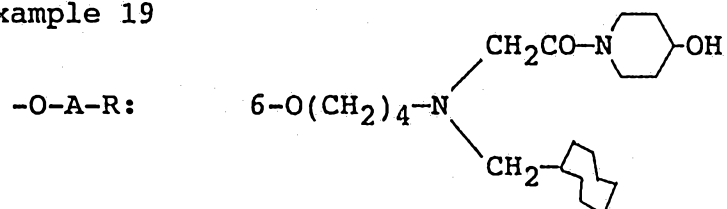
Crystal form: white powder

Free form

Melting point: 124-127°C

Recrystallization solvent: diethyl ether

Example 19



W: oxygen atom

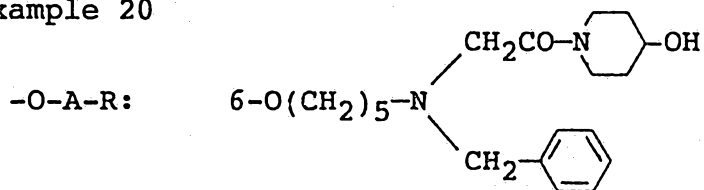
Crystal form: white powder

Free form

Melting point: 129.5-131.5°C

Recrystallization solvent: chloroform - diethyl ether

Example 20



W: oxygen atom

Crystal form: white powder

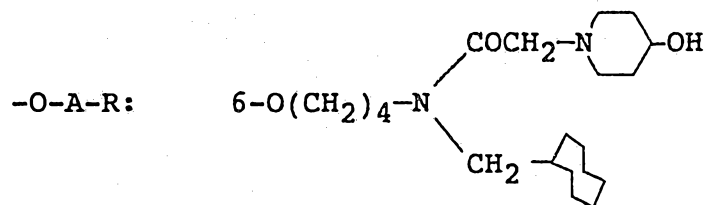
Free form

Melting point: 153.5-162.0°C

Recrystallization solvent: methanol - diisopropyl ether

[Table 25]

Example 21

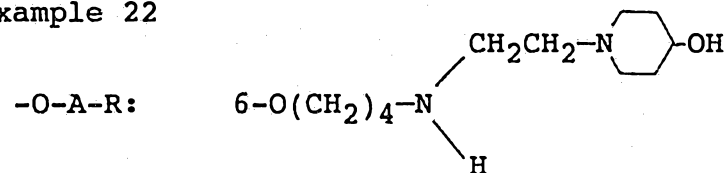


W: oxygen atom

Crystal form: light yellow oil

Free form

Example 22



W: oxygen atom

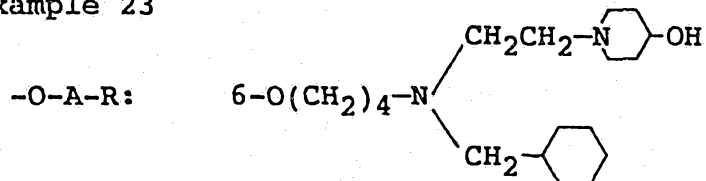
Crystal form: light yellow powder

Free form

Melting point: 96-98°C

Recrystallization solvent: diethyl ether

Example 23



W: oxygen atom

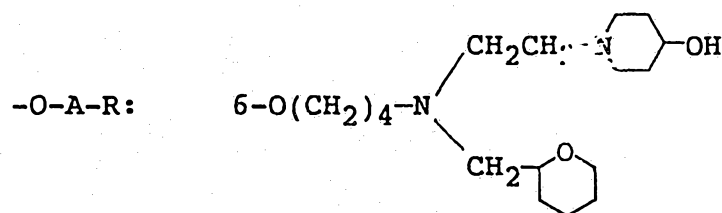
Crystal form: white aciculator

Free form

Melting point: 143-145°C

Recrystallization solvent: ethyl acetate-diethyl ether

Example 24



W: oxygen atom

Crystal form: light yellow powder

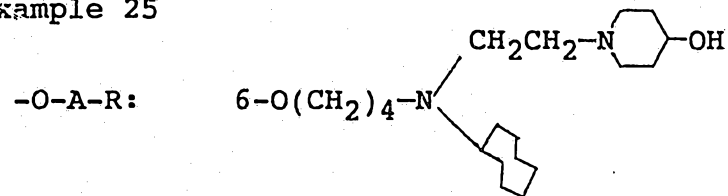
Free form

Melting point: 105-107°C

Recrystallization solvent: ethyl acetate-diethyl ether

[Table 26]

Example 25



W: oxygen atom

Crystal form: light yellow powder

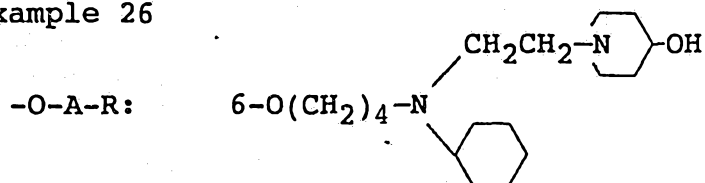
Free form

Melting point: 113-115.5°C

Recrystallization solvent: diethyl ether



Example 26



W: oxygen atom

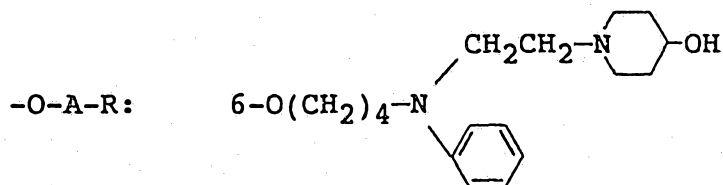
Crystal form: white powder

Free form

Melting point: 148-151°C

Recrystallization solvent: ethyl acetate

Example 27



W: oxygen atom

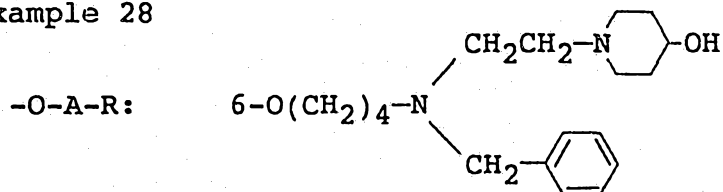
Crystal form: light yellow powder

Free form

Melting point: 116-118°C

Recrystallization solvent: ethyl acetate -
diethyl ether

Example 28



W: oxygen atom

Crystal form: white powder

Free form

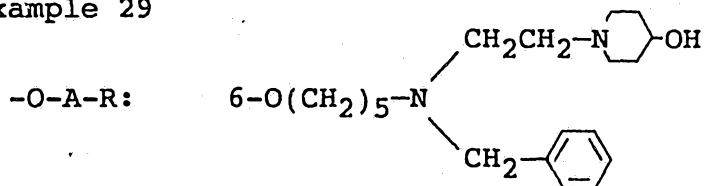
Melting point: 126-131°C

Recrystallization solvent: ethyl acetate-
diethyl ether



[Table 27]

Example 29



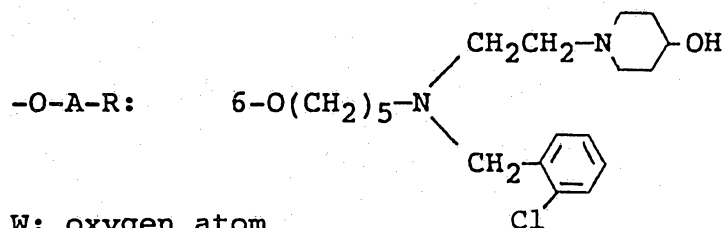
W: oxygen atom

Crystal form: light yellow powder Free form

Melting point: 134-136°C

Recrystallization solvent: ethyl acetate-methanol

Example 30



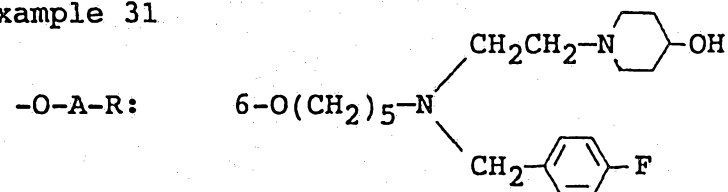
W: oxygen atom

Crystal form: white powder Free form

Melting point: 74°C (decomposed)

Recrystallization solvent: ethyl acetate-diethyl ether

Example 31



W: oxygen atom

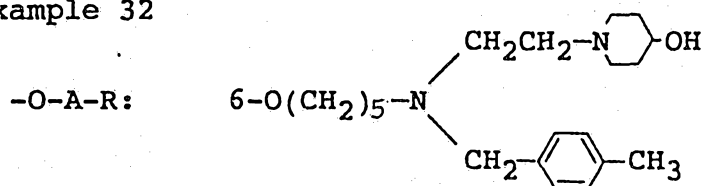
Crystal form: white powder Free form

Melting point: 122-125°C

Recrystallization solvent: methanol - diisopropyl ether



Example 32



W: oxygen atom

Crystal form: white powder

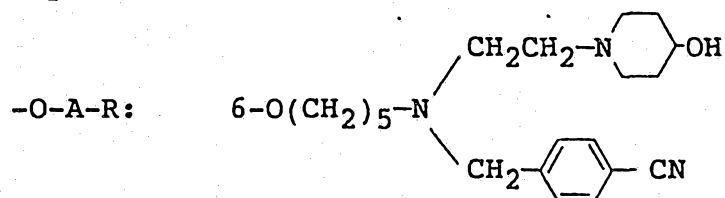
Free form

Melting point: 135-136°C

Recrystallization solvent: ethyl acetate -
diethyl ether

[Table 28]

Example 33



W: oxygen atom

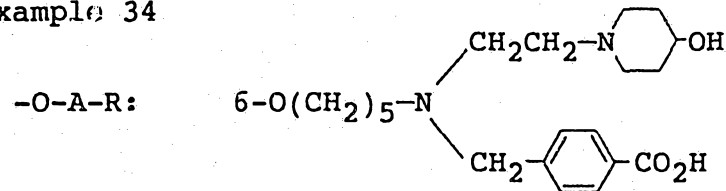
Crystal form: white powder

Free form

Melting point: 131-133°C

Recrystallization solvent: ethyl acetate -
diethyl ether

Example 34



W: oxygen atom

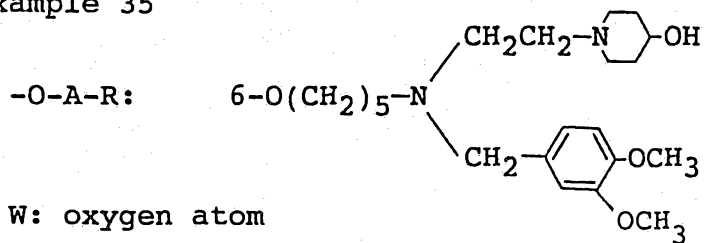
Crystal form: white powder

Free form

Melting point: 217°C (decomposed)



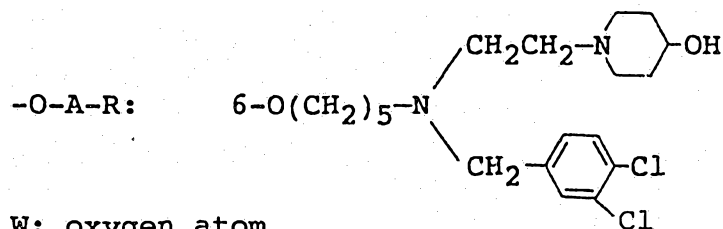
Example 35



W: oxygen atom

Crystal form: light yellow amorphous Free form
NMR (2)

Example 36



W: oxygen atom

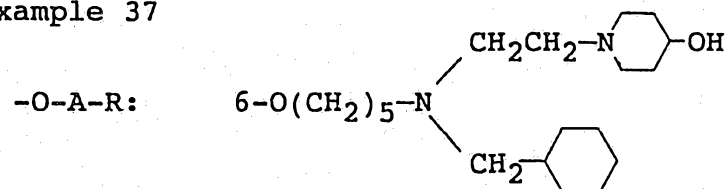
Crystal form: white powder Free form

Melting point: 77°C (decomposed)

Recrystallization solvent: ethyl acetate -
diethyl ether

[Table 29]

Example 37



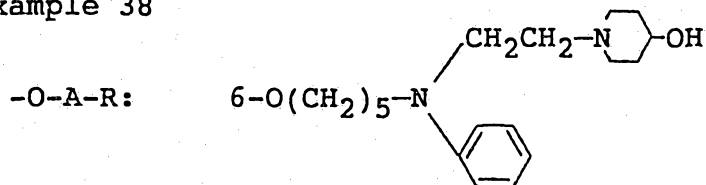
W: oxygen atom

Crystal form: white powder Free form

Melting point: 98.5-101°C

Recrystallization solvent: methanol - diisopropyl
ether

Example 38



W: oxygen atom.

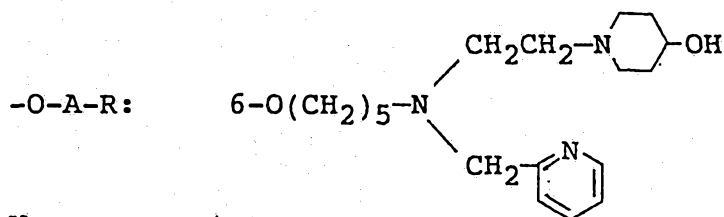
Crystal form: white powder

Free form

Melting point: 128-129.5°C

Recrystallization solvent: methanol -
diisopropyl ether

Example 39

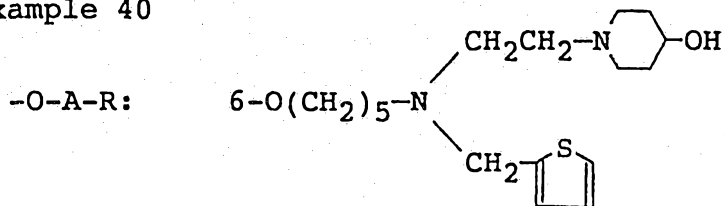


W: oxygen atom

Crystal form: brown oil

Free form
NMR (3)

Example 40



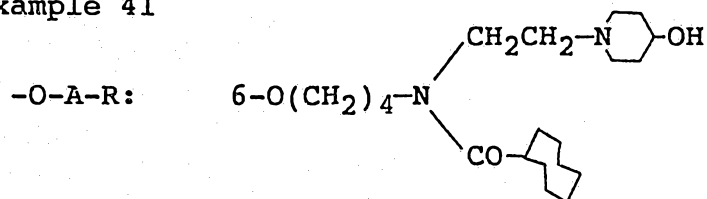
W: oxygen atom

Crystal form: light yellow powder

Free form
NMR (4)

[Table 30]

Example 41



W: oxygen atom

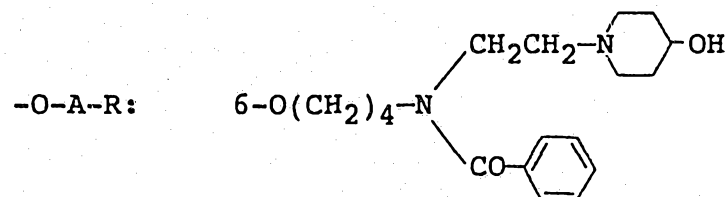
Crystal form: white powder

Free form

Melting point: 139-147°C

Recrystallization solvent: methanol - diethyl ether

Example 42



W: oxygen atom

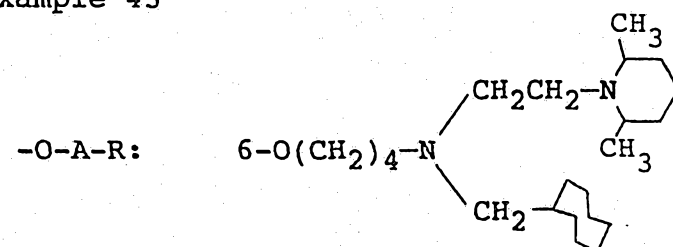
Crystal form: white powder

Free form

Melting point: 165-171°C

Recrystallization solvent: methanol - diethyl ether

Example 43

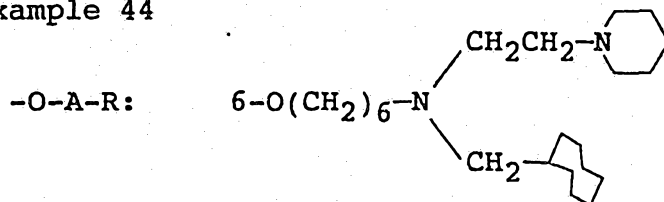


W: oxygen atom

Crystal form: brown caramel-like

Free form
NMR (5)

Example 44



W: oxygen atom

Crystal form: white powder

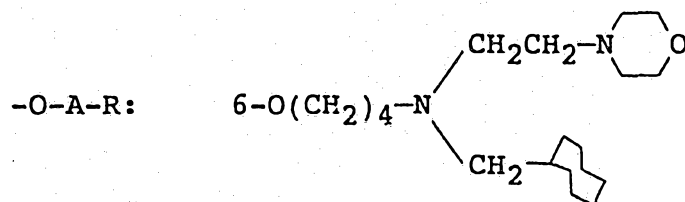
Free form

Melting point: 143-146°C

Recrystallization solvent: dichloromethane -
diisopropyl ether

[Table 31]

Example 45



W: oxygen atom

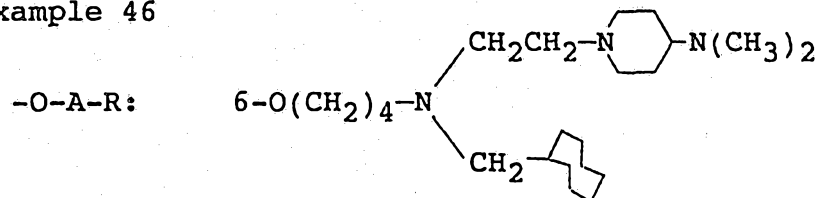
Crystal form: white powder

Free form

Melting point: 130-130.5°C

Recrystallization solvent: dichloromethane -
diisopropyl ether

Example 46



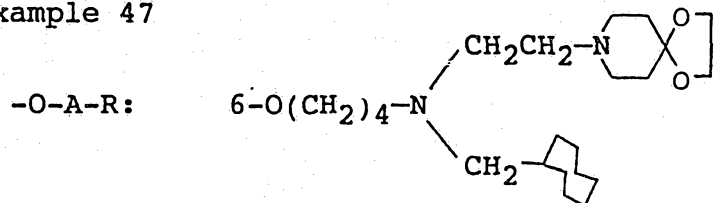
W: oxygen atom

Crystal form: brown caramel-like

Free form
NMR (6)



Example 47



W: oxygen atom

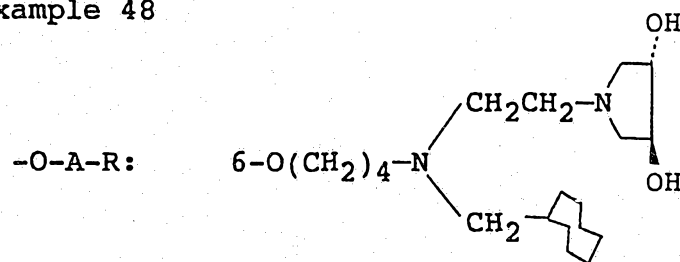
Crystal form: light yellow prisms

Free form

Melting point: 108-109°C

Recrystallization solvent: chloroform -
diisopropyl ether

Example 48



W: oxygen atom

Crystal form: white powder

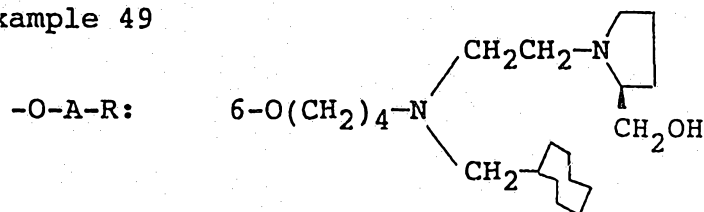
Free form

Melting point: 84.5-97°C

Recrystallization solvent: isopropanol -
diisopropyl ether

[Table 32]

Example 49



W: oxygen atom

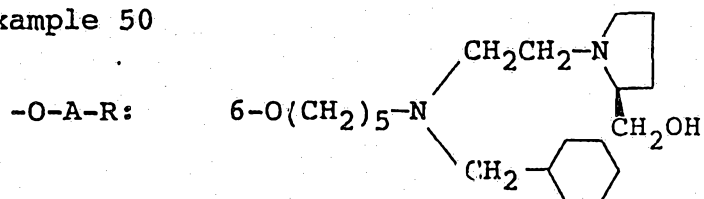
Crystal form: colorless acicular

Free form

Melting point: 126-127.5°C

Recrystallization solvent: dichloromethane -
diisopropyl ether

Example 50

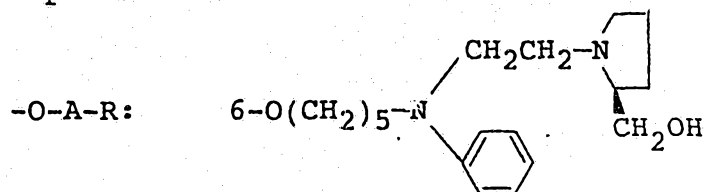


W: oxygen atom

Crystal form: light yellow caramel-like

Free form
NMR (7)

Example 51



W: oxygen atom

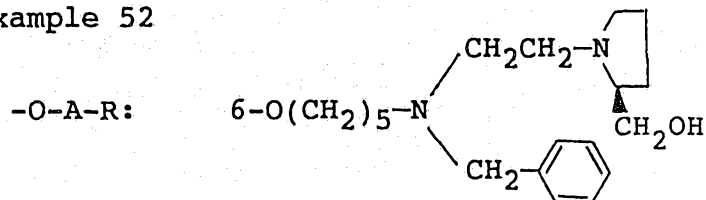
Crystal form: white powder

Free form

Melting point: 96.5-98°C

Recrystallization solvent: methanol - diisopropyl ether

Example 52



W: oxygen atom

Crystal form: white powder

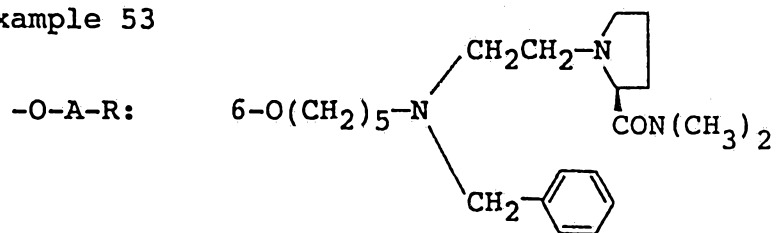
Free form

Melting point: 112-115°C

Recrystallization solvent: methanol - diisopropyl ether

[Table 33]

Example 53

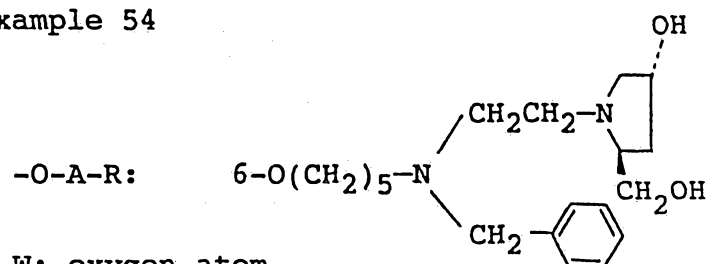


W: oxygen atom

Crystal form: yellow powder

Free form
NMR (8)

Example 54



W: oxygen atom

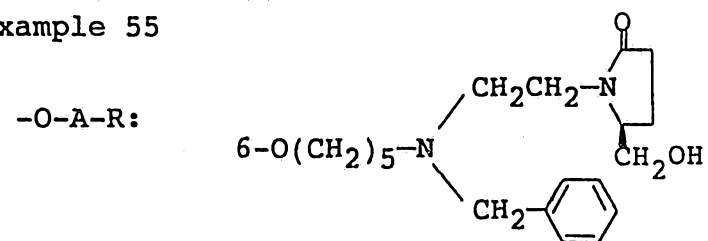
Crystal form: white powder

Free form

Melting point: 106.5-110.5°C

Recrystallization solvent: isopropanol -
diisopropyl ether

Example 55

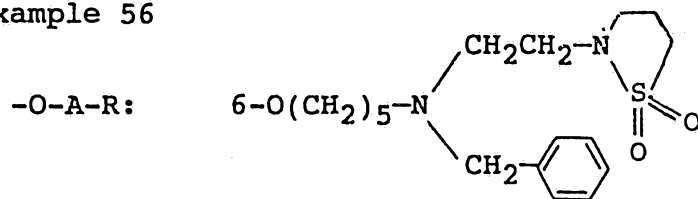


W: oxygen atom

Crystal form: colorless caramel-like

Free form

Example 56



W: oxygen atom.

Crystal form: white powder

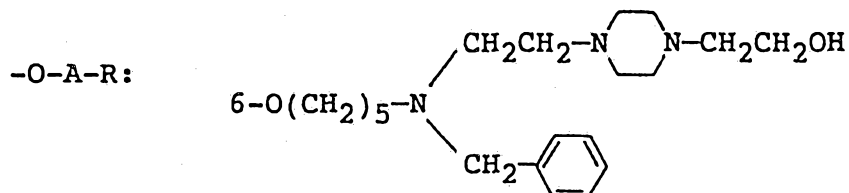
Free form

Melting point: 161-162°C

Recrystallization solvent: methanol

[Table 34]

Example 57

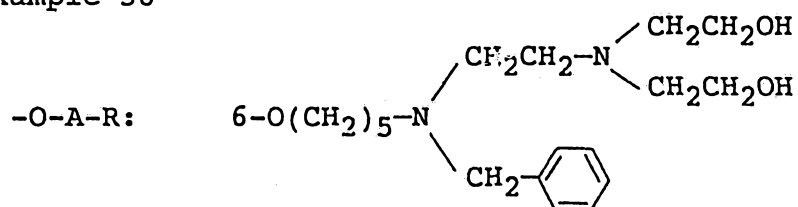


W: oxygen atom

Crystal form: colorless caramel-like

Free form
NMR (10)

Example 58



W: oxygen atom

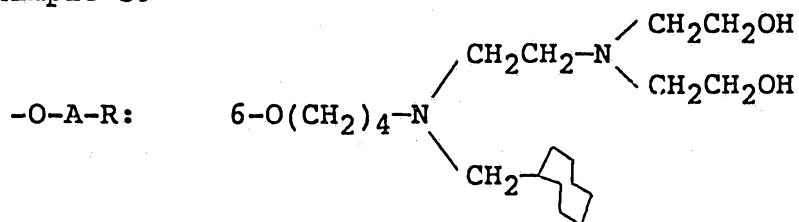
Crystal form: white powder

Free form

Melting point: 118-121°C.5°C



Example 59



W: oxygen atom

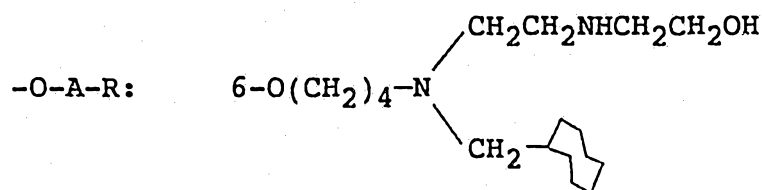
Crystal form: white powder

Free form

Melting point: 107.5-108.5°

Recrystallization solvent: ethyl acetate

Example 60



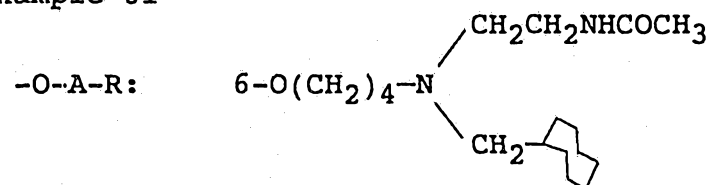
W: oxygen atom

Crystal form: brown caramel-like

Free form

[Table 35]

Example 61



W: oxygen atom

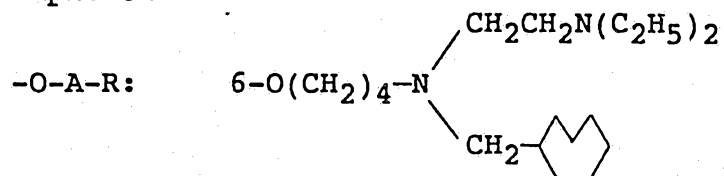
Crystal form: white powder

Free form

Melting point: 83-86°C 31.5°C

Recrystallization solvent: ethyl acetate - diethyl ether

Example 62



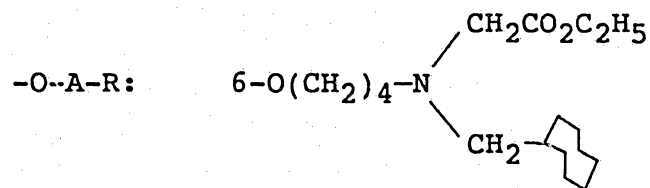
W: oxygen atom

Crystal form: white powder

Free form

Melting point: 123-125°C

Example 63



W: oxygen atom

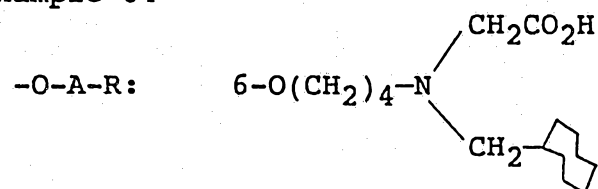
Crystal form: white powder

Free form

Melting point: 98-99°C

Recrystallization solvent: ethyl acetate

Example 64



W: oxygen atom

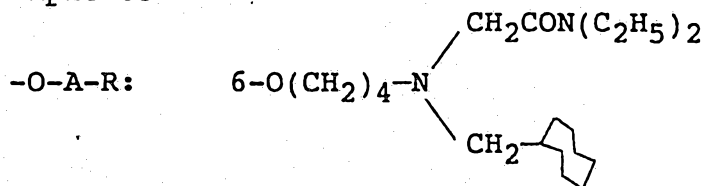
Crystal form: white powder

Free form

Melting point: 154-155°C

[Table 36]

Example 65



W: oxygen atom

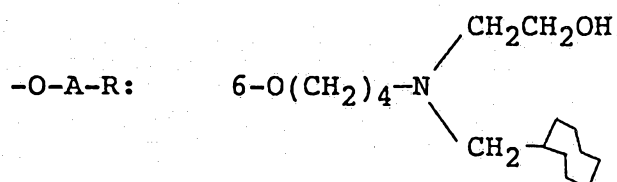
Crystal form: white powder

Free form

Melting point: 116-120°C

Recrystallization solvent: diethyl ether

Example 66



W: oxygen atom

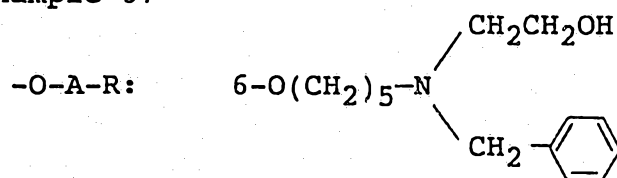
Crystal form: light yellow powder

Free form

Melting point: 95-97°C

Recrystallization solvent: diethyl ether

Example 67



W: oxygen atom

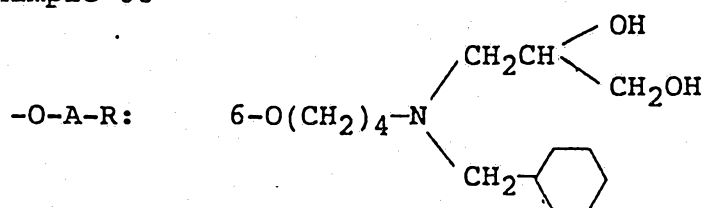
Crystal form: white powder

Free form

Melting point: 168-171°C

Recrystallization solvent: methanol - diisopropyl ether

Example 68



W: oxygen atom

Crystal form: white powder

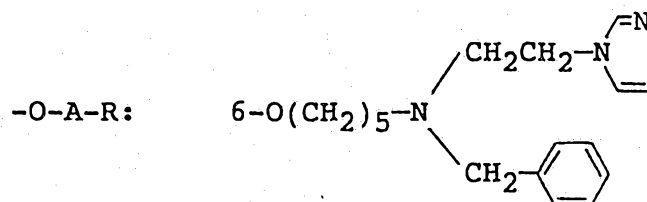
Free form

Melting point: 94-98°C

Recrystallization solvent: ethyl acetate -
diethyl ether

[Table 37]

Example 69

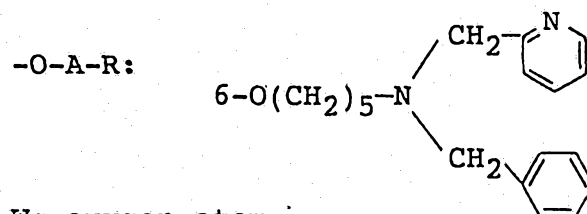


W: oxygen atom

Crystal form: colorless caramel-like

Free form

Example 70



W: oxygen atom

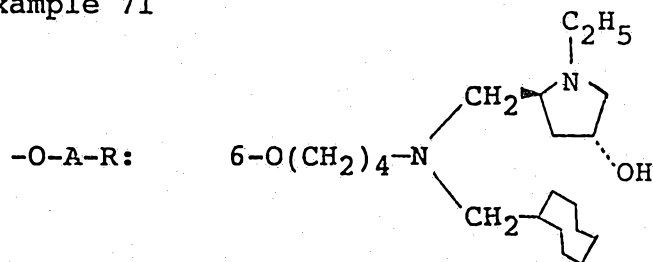
Crystal form: white powder

Free form

Melting point: 124.5-125.5°C

Recrystallization solvent: ethyl acetate

Example 71



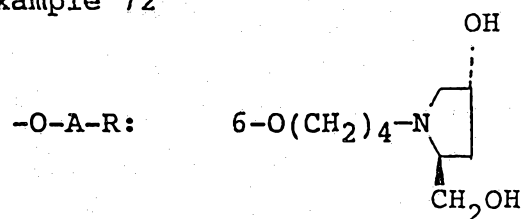
W: oxygen atom

Crystal form: light brown powder Free form

Melting point: 100-102°C

Recrystallization solvent: diethyl ether

Example 72



W: oxygen atom

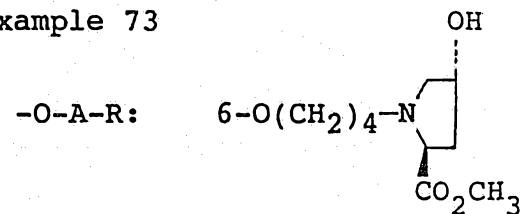
Crystal form: light brown thin plate Free form

Melting point: 164-165°C

Recrystallization solvent: water

[Table 38]

Example 73



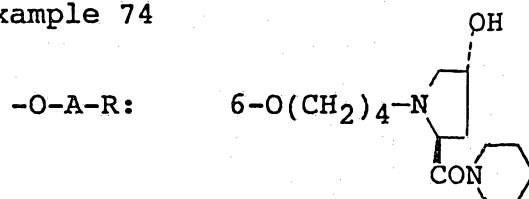
W: oxygen atom

Crystal form: white powder Free form

Melting point: 132-136°C

Recrystallization solvent: ethyl acetate

Example 74



W: oxygen atom

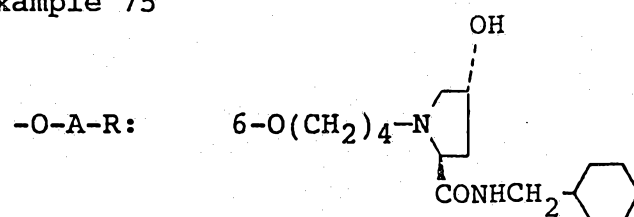
Crystal form: white powder

Free form

Melting point: 173.5-176°C

Recrystallization solvent: methanol - ethyl acetate

Example 75



W: oxygen atom

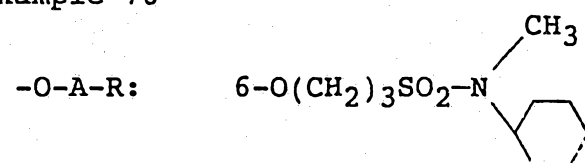
Crystal form: light brown powder

Free form

Melting point: 165-167°C

Recrystallization solvent: methanol - ethyl acetate

Example 76



W: oxygen atom

Crystal form: white powder

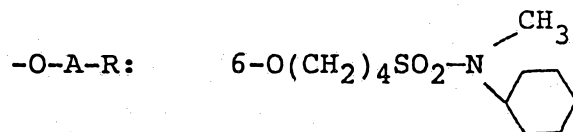
Free form

Melting point: 157-157.5°C

Recrystallization solvent: isopropanol

[Table 39]

Example 77



W: oxygen atom

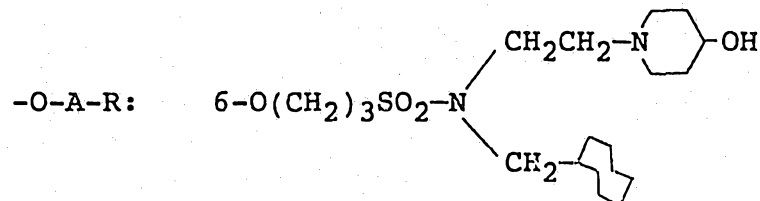
Crystal form: white powder

Free form

Melting point: 179.5°C

Recrystallization solvent: diethyl ether

Example 78



W: oxygen atom

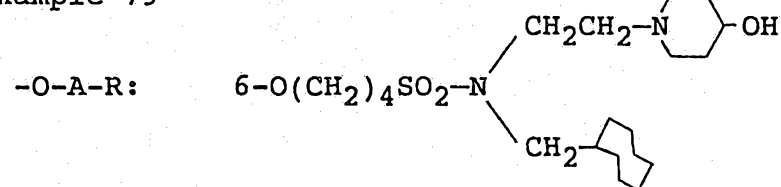
Crystal form: white powder

Free form

Melting point: 181-183°C

Recrystallization solvent: ethanol

Example 79



W: oxygen atom

Crystal form: white powder

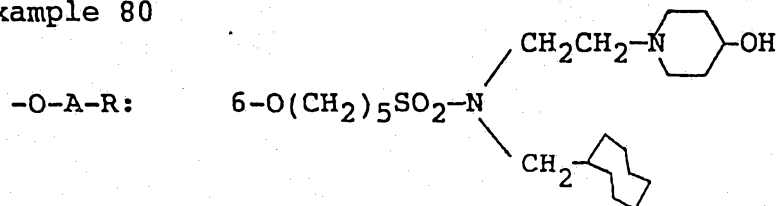
Free form

Melting point: 171-172°C

Recrystallization solvent: ethyl acetate-diethyl ether



Example 80



W: oxygen atom

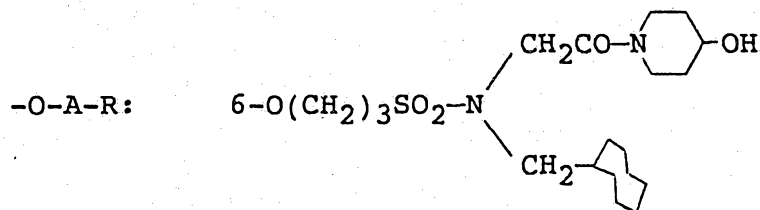
Crystal form: light yellow powder Free form

Melting point: 145-148°C

Recrystallization solvent: ethyl acetate

[Table 40]

Example 81



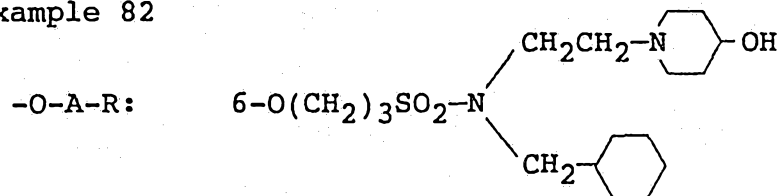
W: oxygen atom

Crystal form: white powder Free form

Melting point: 163.5-167°C

Recrystallization solvent: ethyl acetate-
diethyl ether

Example 82

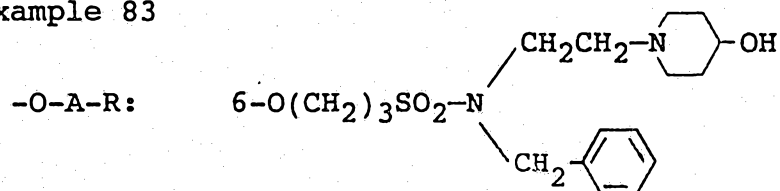


W: oxygen atom

Crystal form: white powder Free form

Melting point: 200-205°C

Example 83



W: oxygen atom

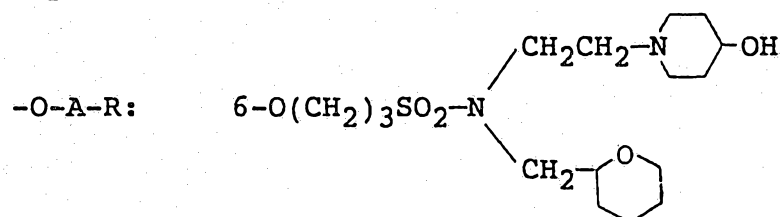
Crystal form: white powder

Free form

Melting point: 189-190.5°C

Recrystallization solvent: ethanol

Example 84



W: oxygen atom

Crystal form: white powder

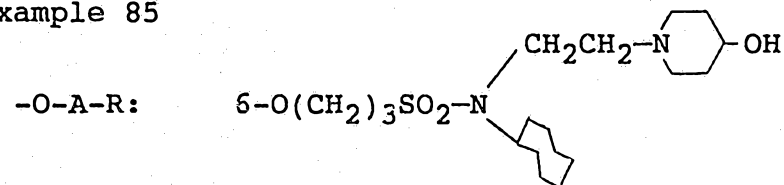
Free form

Melting point: 172-174.5°C

Recrystallization solvent: ethyl acetate-diethyl ether

[Table 41]

Example 85



W: oxygen atom

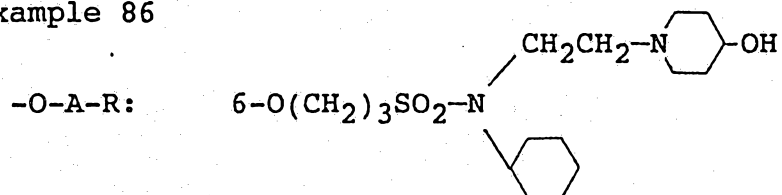
Crystal form: white powder

Free form

Melting point: 182.5-184.5°C

Recrystallization solvent: methanol - diethyl ether

Example 86



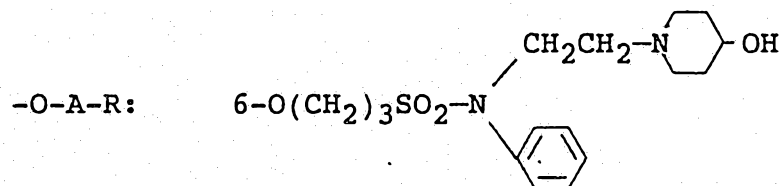
W: oxygen atom

Crystal form: yellow powder

Free form

Melting point: 192-195°C

Example 87



W: sulfur atom

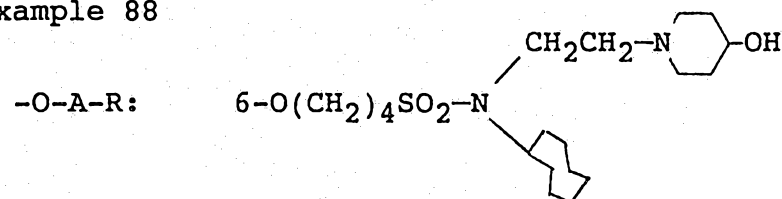
Crystal form: light yellow powder

Free form

Melting point: 164-165.5°C

Recrystallization solvent: diethyl ether

Example 88



W: oxygen atom

Crystal form: white powder

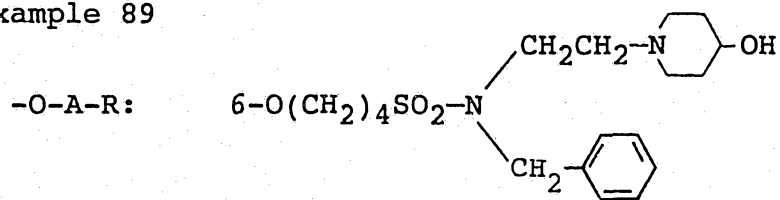
Free form

Melting point: 161-163°C



[Table 42]

Example 89



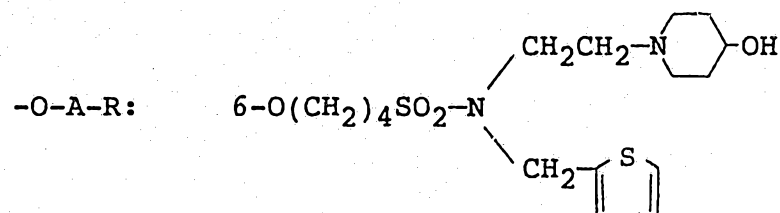
W: oxygen atom

Crystal form: white powder

Free form

Melting point: 165.5-167°C

Example 90



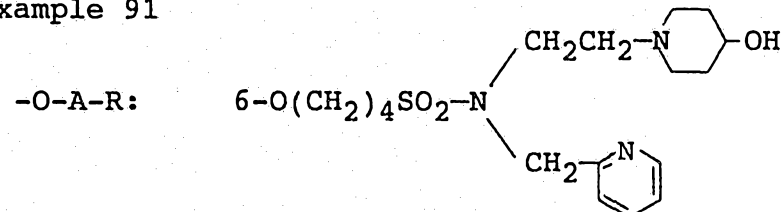
W: oxygen atom

Crystal form: white powder

Free form

Melting point: 129-130.5°C

Example 91



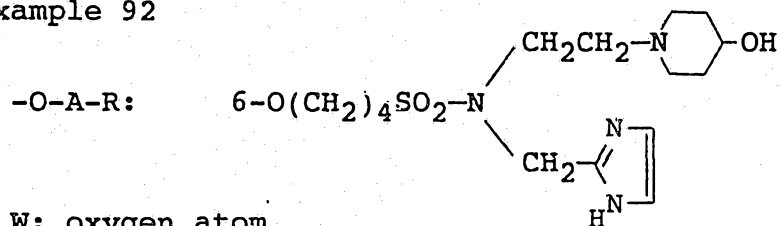
W: oxygen atom

Crystal form: white powder

Free form

Melting point: 98°C

Example 92



W: oxygen atom

Crystal form: white powder

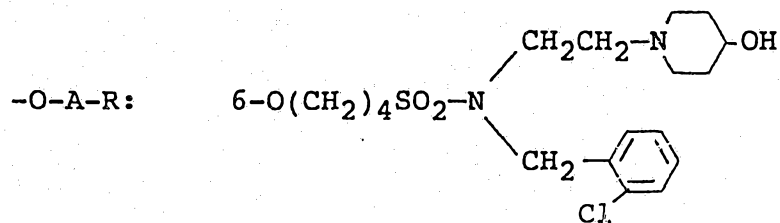
Free form

Melting point: 180°C (decomposed)

Recrystallization solvent: ethanol

[Table 43]

Example 93



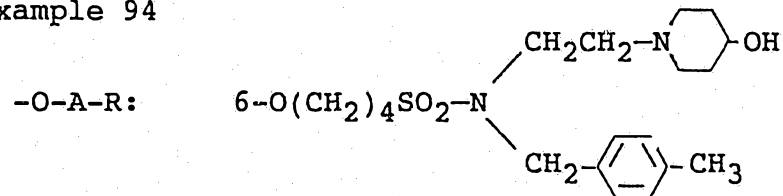
W: oxygen atom

Crystal form: white powder

Free form

Melting point: 147-152°C

Example 94



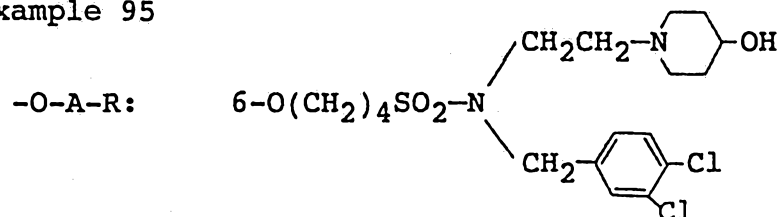
W: oxygen atom

Crystal form: white powder

Free form

Melting point: 164-165°C

Example 95



W: oxygen atom

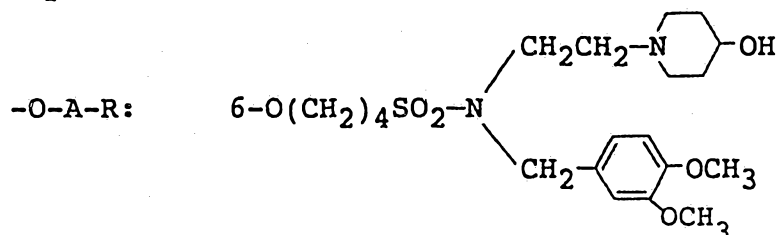
Crystal form: white powder

Free form

Melting point: 169.5-171.5°C

Recrystallization solvent: methanol

Example 96



W: oxygen atom

Crystal form: white powder

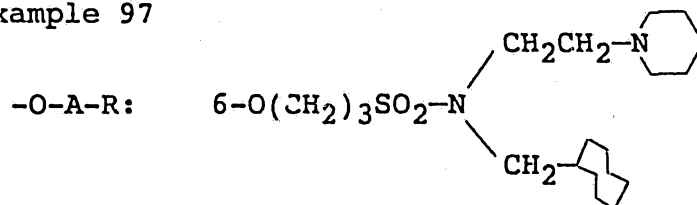
Free form

Melting point: 140-141.5°C

Recrystallization solvent: ethyl acetate

[Table 44]

Example 97



W: oxygen atom

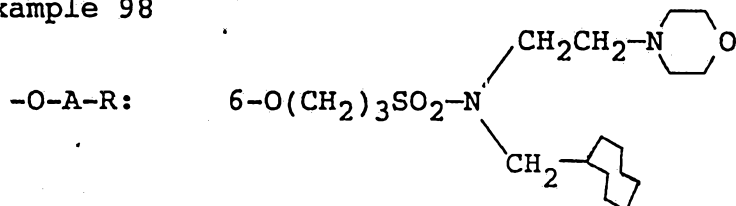
Crystal form: light yellow powder

Free form

Melting point: 154-155°C

Recrystallization solvent: chloroform - diethyl ether

Example 98



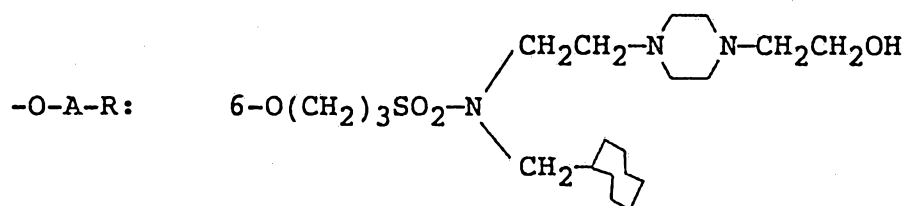
W: oxygen atom

Crystal form: light yellow powder Free form

Melting point: 168.5-169°C

Recrystallization solvent: ethanol

Example 99



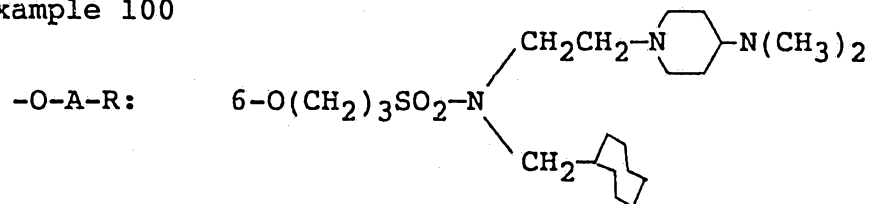
W: oxygen atom

Crystal form: white powder Free form

Melting point: 151.5-154.5°C

Recrystallization solvent: diethyl ether

Example 100



W: oxygen atom

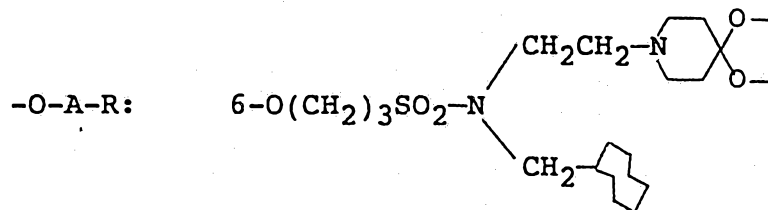
Crystal form: white powder Free form

Melting point: 129.5-130.5°C

Recrystallization solvent: ethyl acetate-diethyl ether

[Table 45]

Example 101



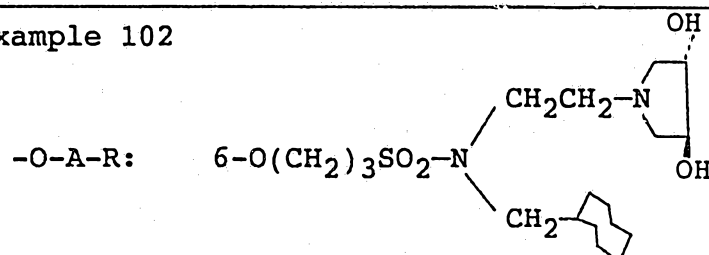
W: oxygen atom

Crystal form: white powder

Free form

Melting point: 154.5-155.5°C

Example 102



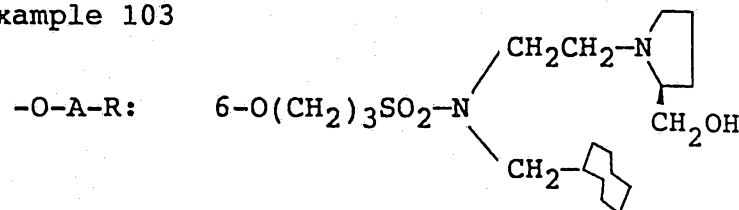
W: oxygen atom

Crystal form: white powder

Free form

Melting point: 107-110°C

Example 103



W: oxygen atom

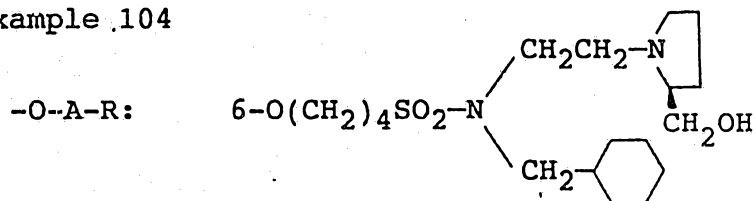
Crystal form: light yellow powder

Free form

Melting point: 129-131°C



Example 104



W: oxygen atom

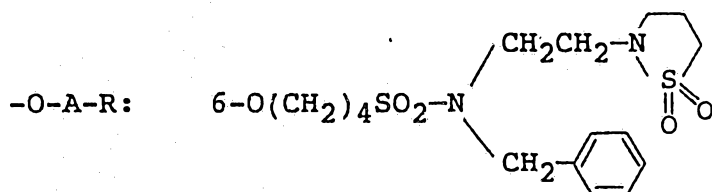
Crystal form: white powder

Free form

Melting point: 163-164.5°C

[Table 46]

Example 105



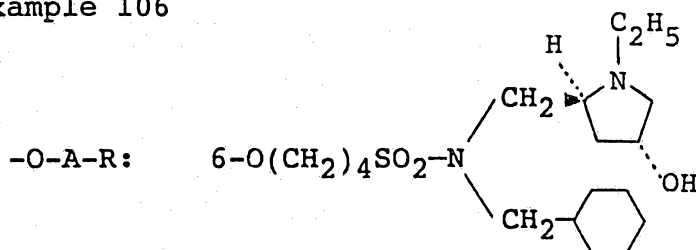
W: oxygen atom

Crystal form: light yellow powder

Free form

Melting point: 156-158.5°C

Example 106



W: oxygen atom

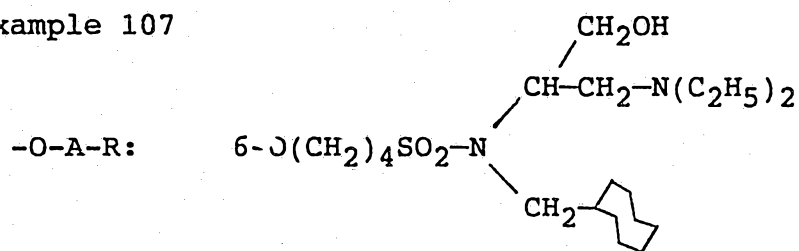
Crystal form: white powder

Free form

Melting point: 141.5-143.5°C



Example 107



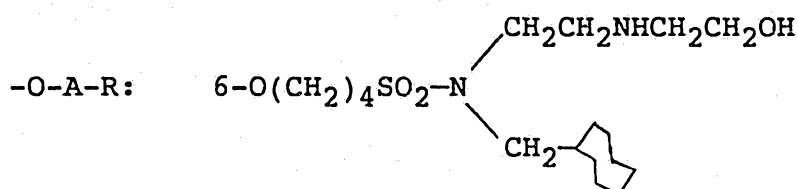
W: oxygen atom

Crystal form: light yellow powder Free form

Melting point: 138.5-141°C

Recrystallization solvent: diethyl ether

Example 108



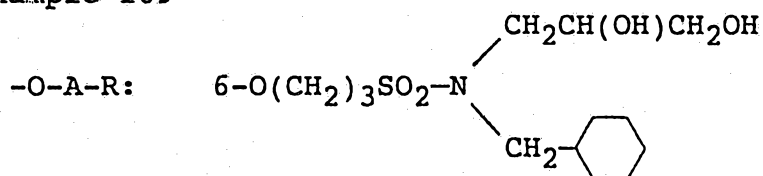
W: oxygen atom

Crystal form: light yellow powder Free form

Melting point: 133-136°C

[Table 47]

Example 109



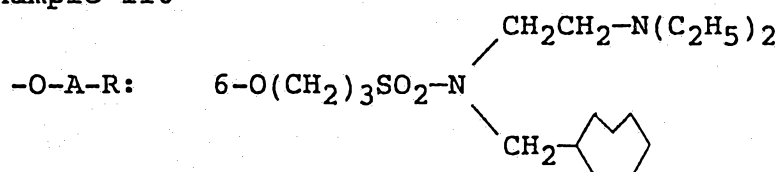
W: oxygen atom

Crystal form: white powder Free form

Melting point: 181.5-183.5°C

Recrystallization solvent: water-ethanol

Example 110



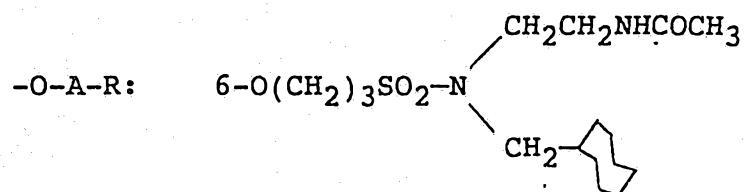
W: oxygen atom

Crystal form: light yellow powder Free form

Melting point: 133-134°C

Recrystallization solvent: diethyl ether

Example 111



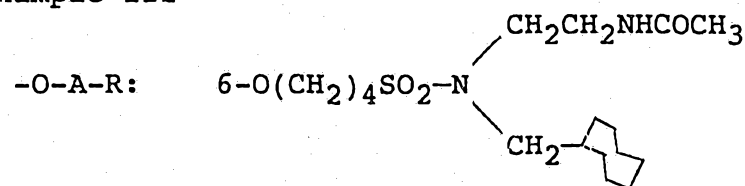
W: oxygen atom

Crystal form: white powder Free form

Melting point: 180-182.5°C

Recrystallization solvent: methanol-diethyl ether

Example 112



W: oxygen atom

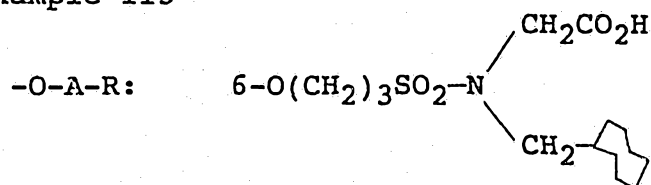
Crystal form: light yellow powder Free form

Melting point: 109°C



[Table 48]

Example 113



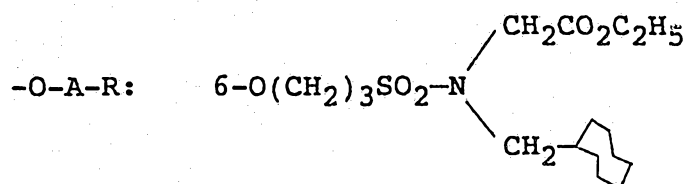
W: oxygen atom

Crystal form: light yellow powder

Free form

Melting point: 141°C (decomposed)

Example 114



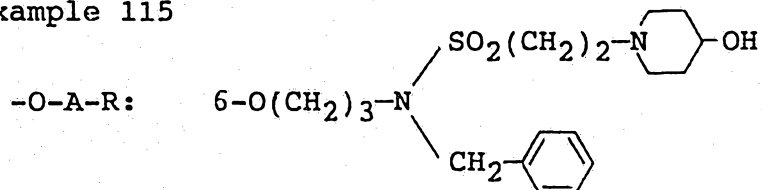
W: oxygen atom

Crystal form: light yellow powder

Free form

Melting point: 128°C

Example 115



W: oxygen atom

Crystal form: light yellow powder

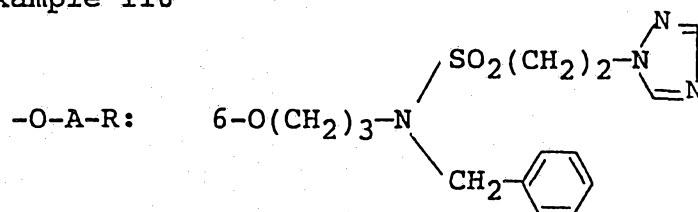
Free form

Melting point: 135-137°C

Recrystallization solvent: methanol



Example 116



W: oxygen atom

Crystal form: white powder

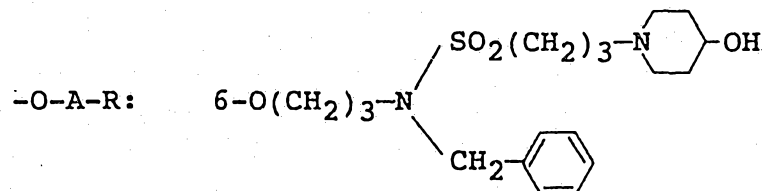
Free form

Melting point: 156-158°C

Recrystallization solvent: ethyl acetate

[Table 49]

Example 117



W: oxygen atom

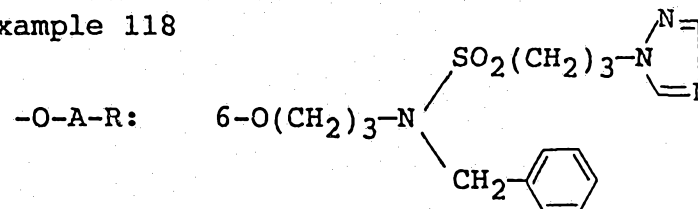
Crystal form: white powder

Free form

Melting point: 143-145°C

Recrystallization solvent: ethyl acetate

Example 118



W: oxygen atom

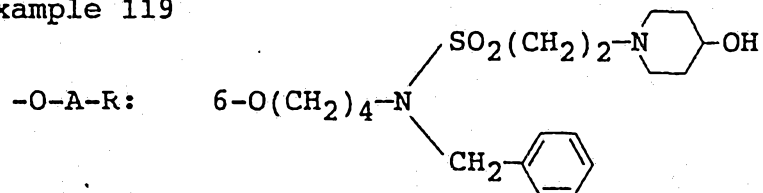
Crystal form: light yellow powder

Free form

Melting point: 130-132°C

Recrystallization solvent: methanol

Example 119



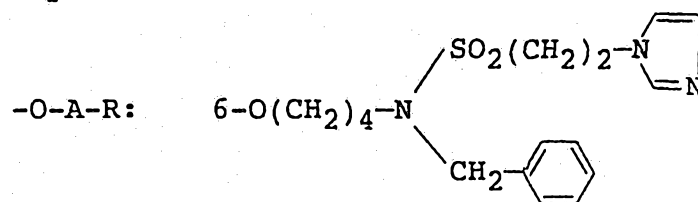
W: oxygen atom

Crystal form: light yellow powder Free form

Melting point: 158-160°C

Recrystallization solvent: ethyl acetate

Example 120



W: oxygen atom

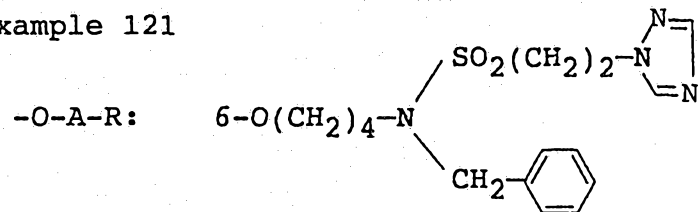
Crystal form: light yellow powder Free form

Melting point: 154-155°C

Recrystallization solvent: ethyl acetate

[Table 50]

Example 121



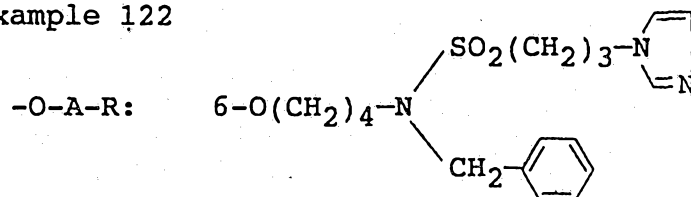
W: oxygen atom

Crystal form: light yellow powder Free form

Melting point: 175-176°C



Example 122



W: oxygen atom

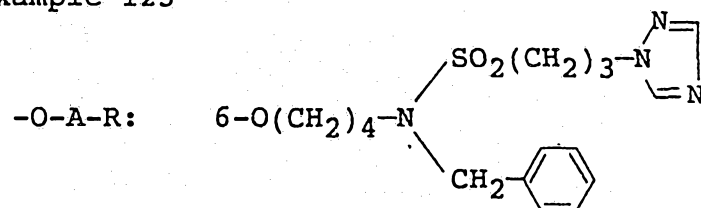
Crystal form: light brown powder

Free form

Melting point: 120-126°C

Recrystallization solvent: ethyl acetate

Example 123



W: oxygen atom

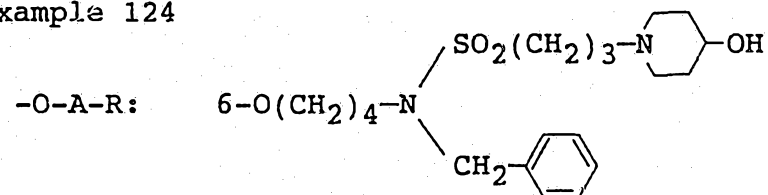
Crystal form: light yellow powder

Free form

Melting point: 137-139°C

Recrystallization solvent: ethyl acetate

Example 124



W: oxygen atom

Crystal form: light yellow powder

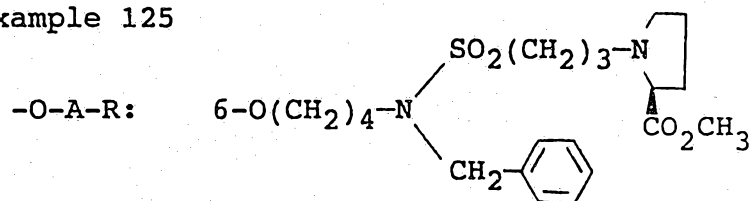
Free form

Melting point: 132-138°C

Recrystallization solvent: ethyl acetate

[Table 51]

Example 125



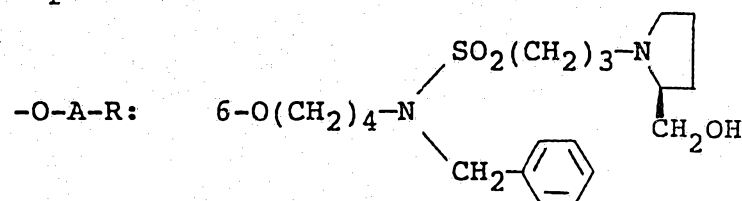
W: oxygen atom

Crystal form: light brown powder Free form

Melting point: 127-129°C

Recrystallization solvent: ethyl acetate

Example 126



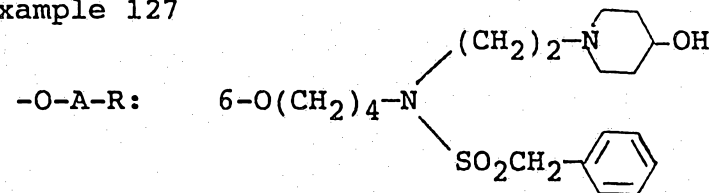
W: oxygen atom

Crystal form: light yellow powder Free form

Melting point: 84-90°C

Recrystallization solvent: diethyl ether

Example 127



W: oxygen atom

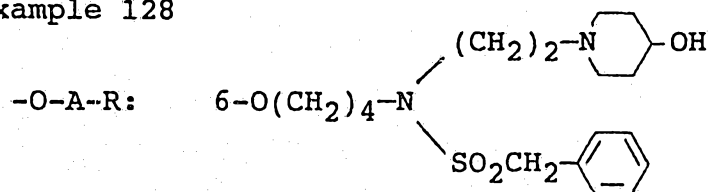
Crystal form: white powder Free form

Melting point: 206-208°C

Recrystallization solvent: methanol



Example 128



W: oxygen atom

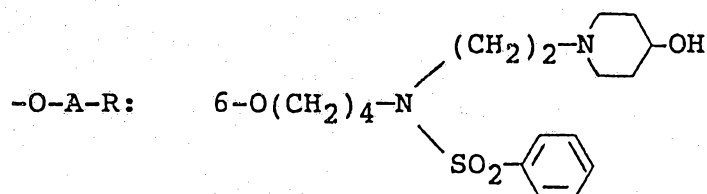
Crystal form: colorless acicular Free form

Melting point: 105-109°C

Recrystallization solvent: ethyl acetate

[Table 52]

Example 129



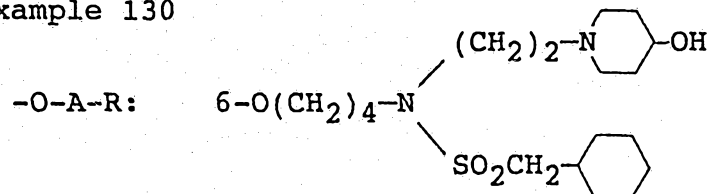
W: oxygen atom

Crystal form: white powder Free form

Melting point: 123-125°C

Recrystallization solvent: methanol

Example 130



W: oxygen atom

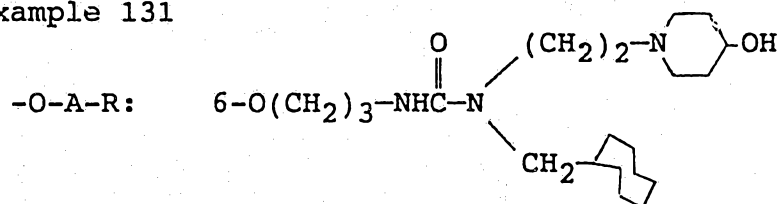
Crystal form: light yellow powder Free form

Melting point: 179-181°C

Recrystallization solvent: ethyl acetate



Example 131

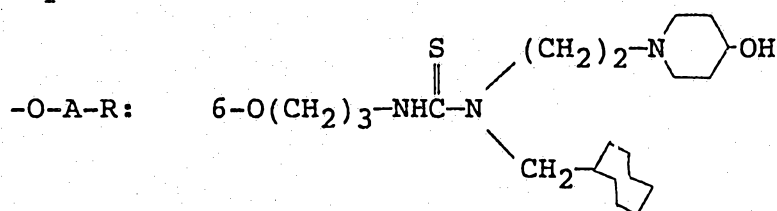


W: oxygen atom

Crystal form: white amorphous

Free form
NMR (13)

Example 132



W: oxygen atom

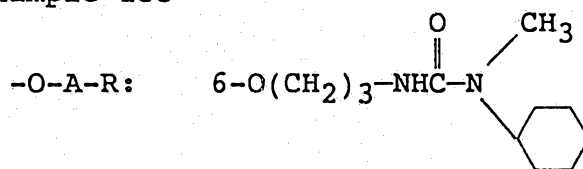
Crystal form: white powder

Free form

Melting point: 138-138.5°C

[Table 53]

Example 133



W: oxygen atom

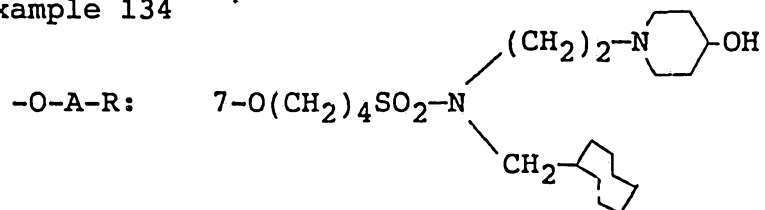
Crystal form: white powder

Free form

Melting point: 156-158.5°C

Recrystallization solvent: diethyl ether

Example 134



W: oxygen atom

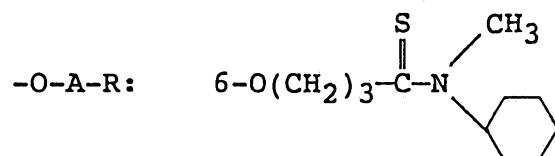
Crystal form: white powder

Free form

Melting point: 138.5-139.5°C

Recrystallization solvent: ethyl acetate

Example 135



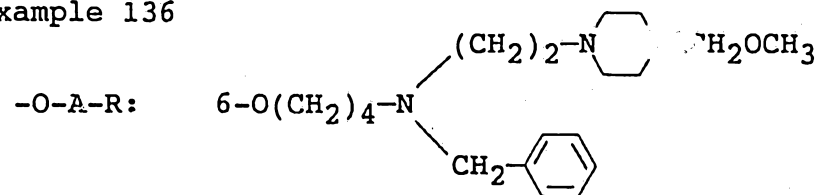
W: oxygen atom

Crystal form: yellow powder

Free form

Melting point: 170-172°C

Example 136



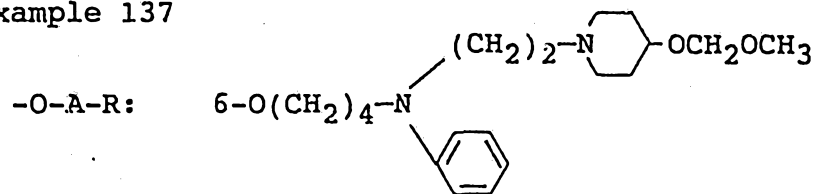
W: oxygen atom

Crystal form: light yellow oil

Free form
NMR (14)

[Table 54]

Example 137

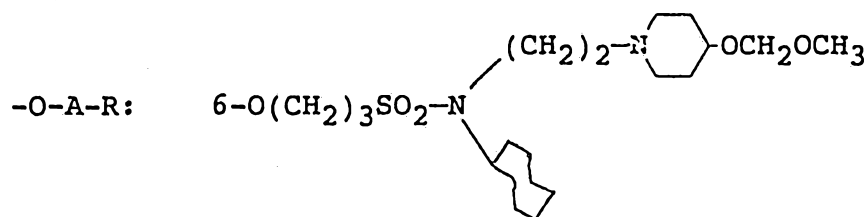


W: oxygen atom

Crystal form: light yellow oil

Free form
NMR (15)

Example 138

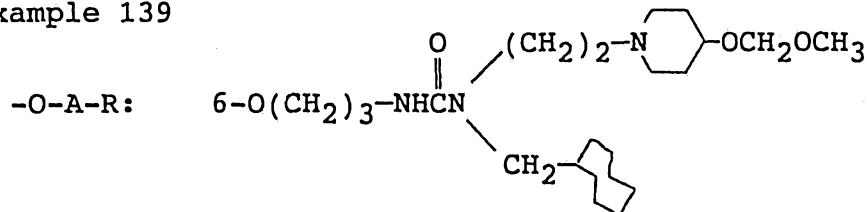


W: oxygen atom

Crystal form: light yellow oil

Free form
NMR (16)

Example 139



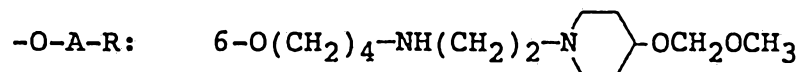
W: oxygen atom

Crystal form: brown oil

Free form
NMR (17)



Example 140



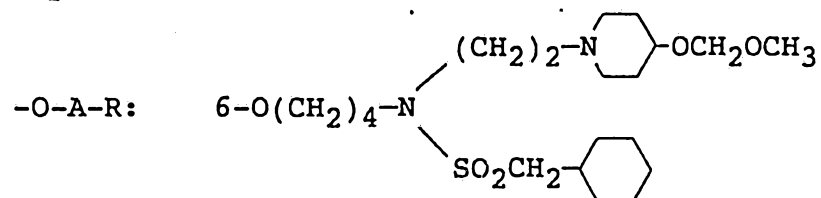
W: oxygen atom

Crystal form: light yellow oil

Free form
NMR (20)

[Table 55]

Example 141

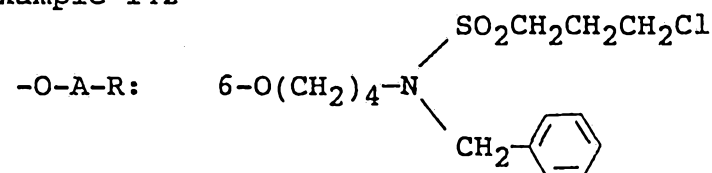


W: oxygen atom

Crystal form: light yellow oil

Free form
NMR (21)

Example 142



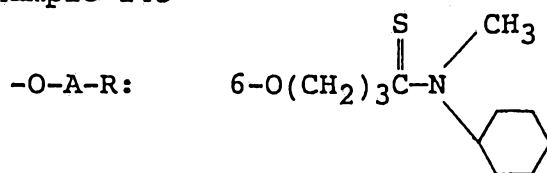
W: oxygen atom

Crystal form: white powder

Free form
NMR (22)



Example 143



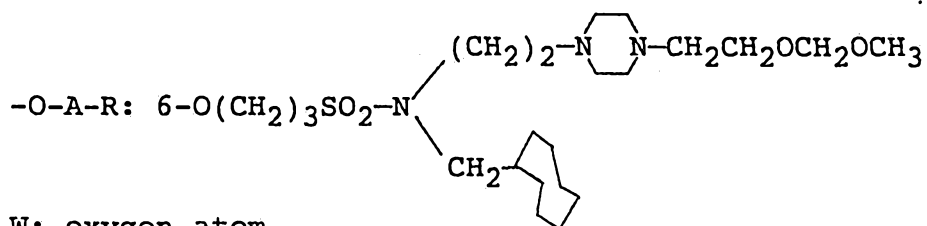
W: oxygen atom

Crystal form: yellow powder

Free form

Melting point: 167-170°C

Example 144



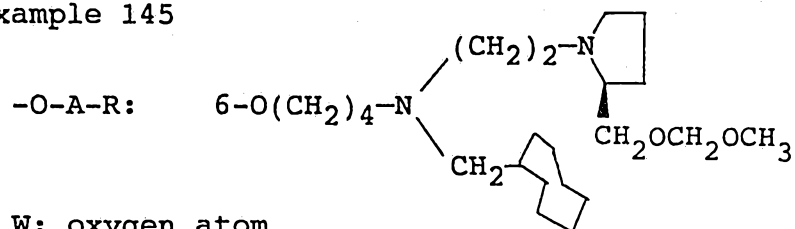
W: oxygen atom

Crystal form: light yellow oil

Free form
NMR (18)

[Table 56]

Example 145



W: oxygen atom

Crystal form: colorless oil

Free form
NMR (19)

1 (1) $^1\text{H-NMR}$ (CDCl_3) δ ;

1.2-2.0 (21H, m), 2.15-2.25 (2H, m), 2.7-2.9
(2H, m), 3.1-3.3 (4H, m), 3.3-3.5 (2H, m), 3.6-3.7 (1H,
m), 3.9-4.1 (2H, m), 6.71 (1H, d, $J=9.5\text{Hz}$), 6.9-7.4 (3H,
5 m), 7.74 (1H, d, $J=9.5\text{Hz}$).

(2) $^1\text{H-NMR}$ (CDCl_3) δ ;

1.4-1.9 (10H, m), 2.1-2.3 (2H, m), 2.45-2.55
(4H, m), 2.6-2.7 (2H, m), 2.7-2.8 (2H, m), 3.54 (2H, s),
3.65-3.75 (2H, m), 3.86 (6H, s), 3.97 (2H, t, $J=6.5\text{Hz}$),
10 6.70 (1H, d, $J=9.5\text{Hz}$), 6.75-6.85 (H, m), 6.91 (H, m),
6.97 (1H, d, $J=2.5\text{ Hz}$), 7.13 (1H, dd, $J=2.5\text{Hz}$, 9.0Hz),
7.29 (1H, d, $J=9.0\text{ Hz}$), 7.73 (1H, d, $J=9.5\text{Hz}$).

(3) $^1\text{H-NMR}$ (CDCl_3) δ ;

1.35-1.7 (6H, m), 1.7-2.0 (4H, m), 2.05-2.25
15 (2H, m), 2.4-2.65 (4H, m), 2.65-2.85 (4H, m), 3.6-3.8
(3H, m), 3.97 (2H, t, $J=6\text{Hz}$), 6.72 (1H, d, $J=9.5\text{Hz}$), 6.97
(1H, d, $J=2.5\text{Hz}$), 7.05-7.2 (2H, m), 7.37 (1H, d, $J=9\text{Hz}$),
7.38-7.58 (1H, m), 7.63 (1H, dt, $J=7.5\text{Hz}$, 1.5Hz), 7.75
(1H, d, $J=9.5\text{Hz}$), 8.41-8.61 (1H, m).

20 (4) $^1\text{H-NMR}$ (CD_3OD) δ ;

1.40-1.95 (10H, m), 2.25 (2H, brt, $J=8.5\text{Hz}$),
2.40-2.90 (8H, m), 3.50-3.70 (1H, m), 3.85 (2H, s), 4.03
(2H, t, $J=6.5\text{Hz}$), 6.60 (1H, d, $J=9.5\text{Hz}$), 6.94 (2H, brs),
7.15-7.35 (4H, m), 7.92 (1H, d, $J=9.5\text{Hz}$).

25 (5) $^1\text{H-NMR}$ (CDCl_3) δ ;

1.15-2.00 (25H, m), 2.20 (2H, brd, $J=6.5\text{Hz}$),
2.45-2.60 (2H, m), 2.85 (2H, brs), 3.05-3.50 (4H, m),
4.01 (2H, t, $J=6.5\text{Hz}$), 6.71 (1H, d, $J=9.5\text{Hz}$), 7.00 (1H,

1 brs), 7.10-7.40 (3H, m), 7.76 (1H, d, J=9.5Hz).

(6) $^1\text{H-NMR}$ (CD_3OD) δ ;

1.15-1.90 (23H, m), 2.01 (2H, brt, J=12Hz),
2.10-2.35 (2H, m), 2.29 (6H, s), 2.35-2.60 (6H, m), 3.01
5 (2H, brd, J=12Hz), 4.06 (2H, t, J=6Hz), 6.61 (1H, d,
J=9.5Hz), 7.15-7.35 (3H, m), 7.92 (1H, d, J=9.5Hz).

(7) $^1\text{H-NMR}$ (CD_3OD) δ ;

0.90-1.10 (2H, m), 1.15-2.15 (19H, m), 2.60-
3.75 (13H, m), 4.07 (2H, t, J=6Hz), 6.62 (1H, d,
10 J=9.5Hz), 7.15-7.35 (3H, m), 7.94 (1H, d, J=9.5Hz).

(8) $^1\text{H-NMR}$ (CD_3OD) δ ;

1.45-2.10 (10H, m), 2.25-2.50 (2H, m), 2.61
(1H, brs), 2.75-3.30 (5H, m), 3.98 (3H, s), 3.03 (3H, s),
3.77 (1H, brs), 4.06 (2H, brs), 4.38 (1H, brd, J=12Hz),
15 6.51 (1H, d, J=9.5Hz), 7.16 (2H, brs), 7.29 (1H, brs),
7.40-7.60 (5H, m), 7.91 (1H, d, J=9.5Hz).

(9) $^1\text{H-NMR}$ (CDCl_3) δ ;

1.40-2.05 (8H, m), 2.15-2.70 (5H, m), 2.90-3.20
(2H, m), 3.35-3.80 (6H, m), 3.97 (2H, t, J=6.5Hz), 6.70
20 (1H, d, J=9.5Hz), 6.98 (1H, d, J=2.5Hz), 7.10-7.60 (6H,
m), 7.74 (2H, d, J=9.5Hz).

(10) $^1\text{H-NMR}$ (CD_3OD) δ ;

1.4-1.9 (6H, m), 2.3-2.7 (16H, m), 3.55-3.75
(4H, m), 4.01 (2H, t, J=6.5Hz), 6.01 (1H, d, J=9.5Hz),
25 7.15-7.45 (8H, m), 7.91 (1H, d, J=9.5Hz).

(11) $^1\text{H-NMR}$ (CD_3OD) δ ;

1.10-1.95 (19H, m), 2.24 (2H, d, J=7Hz), 2.57
(2H, t, J=7Hz), 2.70 (2H, t, J=6Hz), 2.90-3.10 (4H, m),

1 3.74 (2H, t, J=5.5Hz), 4.07 (2H, t, J=6Hz), 6.62 (1H, d, J=9.5Hz), 7.15-7.35 (3H, m), 7.92 (1H, d, J=9.5Hz).

(12) ^1H -NMR (CD_3OD) δ ;

1.30-1.75 (6H, m), 2.46 (2H, t, J=6Hz), 2.77

5 (2H, t, J=6Hz), 3.60 (2H, s), 3.96 (2H, t, J=6Hz), 4.05 (2H, t, J=6Hz), 6.61 (1H, d, J=9.5Hz), 6.91 (1H, s), 7.05 (1H, s), 7.10-7.35 (8H, m), 7.60 (1H, s), 7.91 (1H, d, J=9.5Hz).

(13) ^1H -NMR (CDCl_3) δ ;

10 1.2-1.9 (19H, m), 1.95-2.1 (2H, m), 2.15-2.25 (2H, m), 2.49 (2H, t), 2.7-2.85 (2H, m), 3.1 (2H, d, J=7.5Hz), 3.27 (2H, t), 3.3-3.45 (2H, m), 3.65-3.8 (1H, m), 4.07 (2H, t, J=6Hz), 6.7 (1H, d, J=9.5Hz), 7.00 (1H, d, J=2.5Hz), 7.15 (1H, dd, J=2.5Hz, 9Hz), 7.3 (1H, d, J=9Hz), 7.73 (1H, d, J=9.5Hz).

(14) ^1H -NMR (CDCl_3) δ ;

20 1.5-1.9 (8H, m), 2.12 (2H, m), 2.5 (4H, m), 2.6 (2H, m), 2.7 (2H, m), 3.36 (3H, s), 3.6 (1H, m), 3.60 (2H, s), 3.95 (2H, t, J=6Hz), 4.67 (2H, s), 6.71 (H, d, J=9.5Hz), 6.93 (1H, d, J=2.5Hz), 7.12 (1H, dd, 2.5Hz, 9Hz), 7.2-7.3 (6H, m).

(15) ^1H -NMR (CDCl_3) δ ;

25 1.7-2.0 (8H, m), 2.3 (2H, m), 2.5 (2H, m), 2.8 (2H, m), 3.37 (3H, s), 3.4 (2H, m), 3.5 (2H, m), 3.6 (1H, m), 4.02 (2H, t, J=6Hz), 4.68 (2H, s), 6.63-6.73 (4H, m), 6.97 (1H, d, J=2.5Hz), 7.12-7.23 (3H, m), 7.33 (1H, d, J=9Hz), 7.74 (1H, d, J=9.5Hz).



1 (16) ^1H -NMR (CDCl_3) δ ;

7.75 (1H, d, $J=9.5\text{Hz}$), 7.35 (1H, d, $J=9\text{Hz}$),
7.15 (1H, dd, $J=9\text{Hz}$, 2.6Hz), 7.01 (1H, d, $J=2.6\text{Hz}$), 6.73
(1H, d, $J=9.5\text{Hz}$), 4.68 (2H, s), 4.15 (2H, t, $J=5.8\text{Hz}$),
5. 3.75-3.95 (1H, m), 3.58-3.69 (1H, m), 3.37 (3H, s),
3.22-3.35 (4H, m), 2.75-2.90 (2H, m), 2.55-2.68 (2H, m),
2.18-2.40 (4H, m), 1.40-2.05 (18H, m).

(17) ^1H -NMR (CDCl_3) δ ;

7.73 (1H, d, $J=9.5\text{Hz}$), 7.40 (1H, br), 7.29 (1H,
10 d, $J=11.4\text{Hz}$), 7.15 (1H, dd, $J=11.4\text{Hz}$, 2.5Hz), 7.01 (1H,
d, $J=2.5\text{Hz}$), 6.70 (1H, d, $J=9.5\text{Hz}$), 4.65 (2H, s), 4.06
(2H, t, $J=6.2\text{Hz}$), 3.15-3.65 (8H, m), 3.10 (2H, d,
 $J=7.5\text{Hz}$), 2.65-2.90 (2H, m), 2.35-2.60 (2H, m), 2.10-2.35
(2H, m), 1.97-2.10 (2H, t, $J=5.6\text{Hz}$), 1.10-1.97 (19H, m).

15 (18) ^1H -NMR (CDCl_3) δ ;

1.15-1.85 (15H, m), 2.2-2.4 (2H, m), 2.45-2.8
(4H, m), 2.85-3.1 (4H, m), 3.15-3.4 (10H, m), 4.05-4.2
(4H, m), 4.55-4.7 (4H, m), 6.72 (1H, d, $J=9.5\text{Hz}$), 7.0
(1H, d, $J=2.5\text{Hz}$) 7.15 (1H, dd, $J=2.5\text{Hz}$, 9.0Hz), 7.32 (1H,
20 d, $J=9\text{Hz}$), 7.74 (1H, d, $J=9.5\text{Hz}$).

(19) ^1H -NMR (CDCl_3) δ ;

1.10-2.00 (23H, m), 2.10-2.65 (8H, m), 2.80-
3.25 (2H, m), 3.36 (3H, s), 3.45-3.65 (2H, m), 3.95-4.10
(2H, m), 4.63 (2H, s), 6.70 (1H, d, $J=9.5\text{Hz}$), 6.99 (1H,
25 brs), 7.15 (1H, brd, $J=9\text{Hz}$), 7.31 (1H, d, $J=9\text{Hz}$), 7.74
(1H, d, $J=9.5\text{Hz}$).

(20) ^1H -NMR (CDCl_3) δ ;

1.5-1.7 (2H, m), 1.75-1.9 (4H, m), 2.15-2.3

1 (2H, m), 2.6-2.7 (2H, m), 2.7-2.8 (2H, m), 2.85-2.95 (4H,
m), 3.45 (3H, s), 3.5-3.65 (1H, m), 3.95-4.05 (2H, m),
4.65 (2H, s), 6.64 (1H, d, J=9.5Hz), 6.91 (1H, d,
J=2.5Hz), 7.05 (1H, dd, J=2.5Hz, 9.0Hz), 7.39 (1H, d,
5 J=9.0Hz), 7.70 (1H, d, J=9.5Hz), 8.00 (1H, br).

(21) $^1\text{H-NMR}$ (CDCl_3) δ ;

1.0-2.0 (19H, m), 2.1-2.3 (2H, m), 2.4-2.6 (2H,
m), 2.7-2.9 (2H, m), 3.2-3.4 (4H, m), 3.36 (3H, s), 3.5-
3.65 (1H, m), 3.95-4.05 (2H, m), 4.67 (2H, s), 6.71 (1H,
10 d, J=9.5Hz), 7.13 (1H, dd, J=2.5Hz, 9.0Hz), 7.34 (1H, d,
J=9.0Hz), 7.75 (1H, d, J=9.5Hz).

(22) $^1\text{H-NMR}$ (CDCl_3) δ ;

1.6-1.7 (4H, m), 2.25-2.35 (2H, m), 3.11 (2H,
t, J=7.5Hz), 3.25-3.35 (2H, m), 3.67 (2H, t, J=6.0Hz),
15 3.9-4.0 (2H, m), 4.44 (2H, s), 6.71 (2H, d, J=9.5Hz),
6.92 (1H, d, J=2.5Hz), 7.09 (1H, d, J=2.5Hz, 9.0Hz),
7.3-7.4 (6H, m), 7.73 (1H, d, J=9.5Hz).

Example 146

Using appropriate starting materials, the com-
20 pounds of Examples 4, 14-75, 115-130, 137, 140-142 and
145 were obtained in the same manners as in Examples 1
and 8.

Example 147

Using appropriate starting materials, the com-
25 pounds of Examples 14-18, 20-26, 28-42, 48-52, 54-55,
71-75, 78-96, 99, 102-104, 106, 115, 117, 119, 124, 126-

- 1 132 and 134 were obtained in the same manner as in
Example 2.

Example 148

- Using appropriate starting materials, the com-
5 pound of Example 113 was obtained in the same manner as
in Example 3.

Example 149

- Using appropriate starting materials, the com-
pounds of Examples 76-92, 94-114 and 144 were obtained in
10 the same manner as in Example 5.

Example 150

Using appropriate starting materials, the com-
pounds of Examples 14-71, 76-141 and 143-145 were
obtained in the same manners as in Examples 6 and 9.

- 15 Examples 151

Using appropriate starting materials, the com-
pounds of Examples 115-122 and 124-126 were obtained in
the same manner as in Example 7.

Example 152

- 20 Using appropriate starting materials, the com-
pound of Example 132 was obtained in the same manner as
in Example 10.

1 Example 153

 Using appropriate starting materials, the compounds of Examples 131 and 133 were obtained in the same manner as in Example 11.

5 Phamacological Test I

 The platelets aggregation inhibitory activity of each test compound was measured by the method of Born et al. [J. Physiol., London, 162, 67 (1962)], using Platelets Aggregation Tracer manufactured by Nikoh

10 Bioscience Co., Ltd.

 9 volumes of a blood collected from man was mixed with 1 volume of a 3.8% aqueous sodium citrate solution. Part of the mixture was subjected to centrifugation at 1,100 rpm for 10 minutes to obtain a
15 platelet rich plasma (PRP). The remainder of the mixture was also subjected to centrifugation at 3,000 rpm for 10 minutes to obtain a platelet poor plasma (PPP).

 The number of platelets in the PRP was measured using Coulter Counter manufactured by Coulter Electronics
20 Inc. Then, the PRP was diluted with the PPP so that the number of platelets in the dilution became 300,000, whereby a PRP solution was prepared.

 200 μ l of this PRP solution and 2 ml of a solution containing a test compound at a given concentration
25 were placed in an aggregation measurement cell and heated at 37°C for 1 minute. Thereto was added 20 μ l of adenosine diphosphate (ADP manufactured by Sigma Co.) or

1 a collagen suspension (Collagen Reagent manufactured by
Horm, Hormon-Chemie, GmbH) to induce aggregation of
platelets. The resulting mixture in the cell was
measured for change of transmittance, after which a
5 platelets aggregation curve was prepared. Incidentally,
the concentration of ADP or collagen was selected so that
the final concentration became 7.5 μ M or 20 μ g/ml.

Using the platelets aggregation curve, there
was calculated a maximum aggregation rate (MAR) of
10 platelets using the following formula:

$$\text{MAR} = [(b-a)/(c-a)] \times 100$$

wherein a represents a transmittance of the PRP obtained
in the same manner; c represents a transmittance of the
PPP obtained in the same manner; and b represents a
15 transmittance at the maximum change, of the PRP solution
containing the test compound and the aggregation inducer.

A MAR was also calculated as above, for the
control containing no test compound.

Using the above two MARs, there were calculated
20 platelets aggregation inhibitions (%) of each test com-
pound at various concentrations using the following
formula.

$$\text{Inhibition} = [1 - (\text{MAR of PRP solution containing} \\ \text{test compound}) / (\text{MAR of PRP solution} \\ \text{containing no test compound})] \times 100$$

1 Using the above obtained platelets aggregation
inhibitions (%) of each test compound at various concen-
trations, there was calculated a concentration (IC_{50}) of
each test compound for 50% platelets aggregation inhibi-
5 tion.

The IC_{50} values obtained for some of the com-
pounds obtained in the Examples, each used as a test
compound are shown in Table 57 and Table 58.



[Table 57]

Test compound	IC ₅₀ (μM)		Test compound	IC ₅₀ (μM)	
	ADP	Collagen		ADP	Collagen
Example 15	10	3.6	Example 56	14	7.7
Example 16	6.3	7.4	Example 57	18	17
Example 19	6.1	5.3	Example 58	3.8	4.8
Example 20	2	1.2	Example 60	15	5.3
Example 21	4.2	3.1	Example 61	4.9	6.3
Example 23	8	9.5	Example 62	18	17
Example 24	14	14	Example 64	9	10
Example 26	15	14	Example 65	11	14
Example 27	6.7	7.7	Example 67	4.5	2.9
Example 29	12	6.3	Example 68	15	7.1
Example 30	3.7	2	Example 69	15	9.5
Example 32	4.8	6.1	Example 70	40	22
Example 33	5.6	9.1	Example 71	18	7.4
Example 35	11	11	Example 73	25	6.9
Example 36	11	20	Example 74	17	20
Example 40	13	10	Example 75	9.1	13
Example 41	8.7	11	Example 77	2.1	4.9
Example 42	20	13	Example 78	1.4	0.38
Example 45	22	25	Example 79	1.3	2.5
Example 46	20	20	Example 80	13	15
Example 47	25	29	Example 81	6.1	11
Example 49	6.9	22	Example 82	4.5	3.8
Example 53	11	13	Example 83	11	4.3
Example 55	3.7	2.6	Example 84	9.5	9.1

[Table 74]

Test compound	IC ₅₀ (μM)		Test compound	IC ₅₀ (μM)	
	ADP	Collagen		ADP	Collagen
Example 85	2.1	0.57	Example 106	1.4	0.9
Example 86	8	12	Example 107	3.4	3.2
Example 87	4.7	-	Example 108	2.9	2
Example 88	2.8	1.4	Example 109	4.9	6.3
Example 89	7.7	3.8	Example 110	4.7	8.3
Example 90	5.3	5.4	Example 111	2.2	2.9
Example 93	1.2	2.6	Example 112	0.83	0.69
Example 94	1.4	2.3	Example 114	6.5	4
Example 95	10	7.1	Example 119	20	20
Example 96	8.7	6.5	Example 122	22	29
Example 97	14	18	Example 123	17	9.5
Example 98	9.1	12	Example 126	10	15
Example 99	2.9	3.5	Example 128	25	20
Example 100	13	6.5	Example 130	14	13
Example 101	2.9	3.2	Example 131	2.4	1.3
Example 102	9.5	15	Example 132	2.4	1.8
Example 103	2.6	3.2	Example 133	2.9	-
Example 104	3.5	2.3	Example 135	22	-
Example 105	2.2	1.1	Example 143	3.8	2.3



1 Pharmacological Test II

The heart rate-increasing activity and blood pressure hypotensive activity of each test compound were measured by the following method, using mongrel dogs each weighing 10-20 kg. That is, said dogs were anesthetized by intravenous injection of pentobarbital sodium, then fixed at the back, and tested under artificial respiration. The blood pressures of the dogs were measured by a blood pressure measuring transducer (P23xL manufactured by Gould Statham Instruments, Inc.) via cannula inserted into the femoral artery. The heart rates of the dogs were measured using the pulse wave of the blood pressure of each dog, via a tachometer. The signals of these testing apparatuses were recorded on a thermal pen-type recorder (Recti-Horize 8K manufactured by Nippon Denki-San-ei Sha).

Some of the compounds obtained in the above Examples were used as test compounds. They were dissolved in N,N'-dimethylformamide, and each solution was administered to test dogs via a cannula inserted into the femoral artery of each dog, in such an amount (amount of test compound) of 300 µg/kg. Then, the heart rate of each dog was measured according to the above method and a maximum change in heart rate was calculated.

25 The results are shown in Table 59.



[Table 59]

Test compound	Maximum change in heart rate (beats/minute) dose: 300 mg/kg)
Example 15	1
Example 16	1
Example 19	24
Example 23	-2
Example 27	7
Example 28	0
Example 61	17
Example 62	2
Example 68	30
Example 83	9
Example 85	13
Example 109	16

1 Pharmacological Test III

A blood was collected from a healthy man with normal platelets function by addition of 0.1% disodium ethylenediaminetetraacetate (EDTA.4Na) and immediately
5 subjected to separation of a platelet rich plasma (PRP). The PRP was washed twice with a Tyrode's buffer solution (50 mM TRIS, 0.1% EDTA, Ca (-), Mg (-), 0.14% BSA added, pH = 7.4), and suspended in the buffer solution so that
10 the number of platelets in the resulting suspension became 300,000/ml, to obtain a platelets suspension (EDTA-WP). 4 mg of Type I manufactured by Sigma Co., derived from a bovine skin was dissolved in 0.25 ml of

1 acetic acid (83.5 mM); 8 ml of distilled water was added
thereto; an ultrasonic wave was applied to the mixture at
4°C for 2 minutes; 5 ml of the supernatant liquid was
separated as a collagen solution. Each test compound was
5 dissolved in dimethylformamide (DMF) so as to give a
concentration of at least 2×10^{-12} M when possible, to
prepare a test compound solution. The change in
turbidity of platelets suspension was recorded as a
change in transmitted light emitted from a glass cell
10 containing the suspension, using a platelets aggregation
tracer manufactured by Nikoh Bioscience K.K., generally
used in the test of platelets aggregation function,
whereby the adherence of platelets was measured.
Incidentally, in recording the change in transmitted
15 light, the sensitivity of the recorder was 5 times as
high as that used generally. 200 μ l of the EDTA-WP
was placed in a glass cell exclusively used for the above
platelets aggregation tester. Further, 1 μ l of the test
compound solution was added. The mixture was incubated
20 at room temperature for 5 minutes. Then, the cell was
set in the platelets aggregation tracer and was allowed
to stand for 1 minute until the temperature became 37°C.
Thereafter, about 20 μ l (50 μ g/ml) of the collagen
solution was added, and the adherence of platelets were
25 measured.

The inhibitions (%) of collagen-induced plate-
lets adhesion by each test compound at various concentra-
tions were calculated using the following formula.



$$\text{Inhibition (\%)} = [1 - (\text{platelets adherence when} \\ \text{test compound added}) / \\ (\text{platelets adherence when no} \\ \text{test compound added})] \times 100$$

The results are shown in Table 60.

[Table 60]

<u>Test compound</u>	<u>Dose (μM)</u>	<u>Inhibition (%) of collagen- induced platelets adherence</u>
Example 16	10	48
Example 20	10	49
Example 28	10	48
Example 75	300	57
Example 85	3	50
Example 86	10	47
Example 119	10	40
Example 123	10	39
Example 130	10	43
Example 134	10	45
Example 53	30	35
Example 76	30	35
Example 62	100	54
Example 61	30	35
Example 27	30	40
Example 64	30	31
Example 73	100	36
Example 121	30	38

1 Pharmacological Test IV

The cyclic AMP phosphodiesterase inhibitory activity of the present compound was measured in accordance with the method described in Biochimica et
5 Biophysica Acta Vol. 429, pp. 485-497 (1976) and Biochemical Medicine Vol. 10, pp. 301-311 (1974).

That is, the PRP sample of man used in Pharmacological Test I was subjected to further centrifugation at 3,000 rpm for 10 minutes. To the resulting
10 platelets was added 10 ml of a solution (pH = 7.4) obtained by adding 1 mM of $MgCl_2$ to a TRIS-HCl buffer solution (50 mM). The mixture was subjected to homogenization to grind the platelets in the mixture; then, freezing and thawing were conducted twice, followed by an
15 ultrasonic wave treatment and ultracentrifugation in this order; the resulting supernatant liquid was used as a crude enzyme solution.

The crude enzyme solution was poured into a DEAE-cellulose column buffered with a TRIS-HCl buffer
20 solution (pH = 6.0, 50 mM), and washing and elution was conducted with 30 ml of the same buffer solution. Then, elution was conducted with a sodium acetate-TRIS-HCl buffer solution by a linear gradient method at a flow rate of 0.5 ml/minute to obtain fractions each of 5 ml
25 (total eluate amount = about 300 ml). Thus, there was obtained a fraction having a weak activity of 2 nM/ml/min or less at a high cyclic AMP substrate concentration of 100 μ M and a strong activity of 100 pM/ml/min or more at

1 a low cyclic AMP substrate concentration of 0.4 μ M, and
the fraction was used as a cyclic AMP phosphodiesterase
solution.

5 0.1 ml of one of aqueous solutions containing
each test compound at various concentrations was mixed
with a TRIS-HCl buffer solution (pH = 8.0, 40 mM,
contains 50 μ g of a bovine serum albumin and 4 mM of
MgCl₂) containing 0.4 μ M of cyclic AMP (tritium cyclic
AMP), to prepare 0.2 ml of a substrate solution.

10 To the substrate solution was added 0.2 ml of
the cyclic AMP phosphodiesterase solution. The mixture
was subjected to a reaction at 30°C for 20 minutes to
convert the tritium cyclic AMP to tritium 5'-AMP. The
reaction mixture was immersed in boiling water to
15 terminate the reaction, and then cooled in ice water.
Thereafter was added 0.05 ml of a snake venom (1 mg/ml), and
the mixture was subjected to a reaction at 30°C for 10
minutes to convert the tritium 5'-AMP to tritium
adenosine. The reaction mixture was passed through a
20 cation exchange resin to allow the resin to adsorb the
tritium adenosine. The resulting resin was washed with
distilled water, and elution was conducted with 1.5 ml of
a 3 N ammonia water. The eluate was measured for radio-
activity of tritium adenosine by an ordinary method using
25 a liquid scintillation counter, to determine a phospho-
diesterase activity.

Thus, there were determined the phosphodiester-
ase activities (Vs) of each test compound at various

1 concentrations. Using the Vs and a Vc (the activity of a control, i.e. a water containing no test compound), there was calculated a phosphodiesterase inhibition (%) using the following formula.

5
$$\text{Phosphodiesterase inhibition (\%)} = [(Vc - Vs) / Vc] \times 100$$

Thus, there were calculated the phosphodiesterase inhibitions (%) of each test compound at various concentrations. Using these values, there was determined a 50% phosphodiesterase inhibition concentration (IC₅₀)
10 of each test compound.

In Table 61 are shown the IC₅₀ values of some of the compounds obtained in the Examples, each used as a test compound.

[Table 61]

<u>Test compound</u>	<u>IC₅₀ (μM)</u>
Example 28	0.48
79	Less than 0.1
85	Less than 0.1
89	Less than 0.1
134	0.49
93	Less than 0.1
143	1.44
70	Less than 0.1

1 Preparation Example 1 (Preparation of tablets)

There were prepared, according to the following recipe, 1,000 tablets for oral administration each containing 5 mg of 6-[4-{N-cyclooctylmethyl-N-[2-(4-hydroxy-1-piperidinyl)ethyl]amino}butoxy]carbostyril.

5

Component	Amount (g)
6-[4-{N-cyclooctylmethyl-N-[2-(4-hydroxy-1-piperidinyl)ethyl]amino}butoxy]carbostyril	5
Lactose (Japanese Pharmacopoeia grade)	50
Corn starch (Japanese Pharmacopoeia grade)	25
Crystalline cellulose (Japanese Pharmacopoeia grade)	25
Methyl cellulose (Japanese Pharmacopoeia grade)	1.5
Magnesium stearate (Japanese Pharmacopoeia grade)	1

That is, there were thoroughly mixed 6-[4-{N-cyclooctylmethyl-N-[2-(4-hydroxy-1-piperidinyl)ethyl]-amino}butoxy]carbostyril, lactose, corn starch and crystalline cellulose. The mixture was granulated with a 5% aqueous methyl cellulose solution, and the granules were passed through a 200-mesh sieve and dried carefully. The dried granules were passed through a 200-mesh sieve and mixed with magnesium stearate. The mixture was subjected to press molding to obtain tablets.

10

1 Preparation Example 2 (Preparation of capsules)

There were prepared, according to the following recipe, 1,000 two-piece hard gelatin capsules for oral administration each containing 10 mg of 6-[3-{N-benzyl-

5 N-[2-(4-hydroxy-1-piperidinyl)ethyl]aminosulfonyl}-propoxy]-carbostyryl.

Component	Amount (g)
6-[3-{N-benzyl-N-[2-(4-hydroxy-1-piperidinyl)ethyl]aminosulfonyl}propoxy]-carbostyryl	10
Lactose (Japanese Pharmacopoeia grade)	80
Starch (Japanese Pharmacopoeia grade)	30
Talc (Japanese Pharmacopoeia grade)	5
Magnesium stearate (Japanese Pharmacopoeia grade)	1

That is, the above components were finely ground and thoroughly stirred so as to give a uniform mixture. The mixture was filled into gelatin capsules
10 for oral administration, each having a desired dimension.

Preparation Example 3 (Preparation of injection)

A sterile aqueous solution suitable for parenteral administration was prepared according to the following recipe.



Component	Amount (g)
6-[4-{N-cyclohexylmethyl-N-(2,3-dihydroxypropyl)amino}butoxy]carbostyryl	1
Polyethylene glycol (Japanese Pharmacopoeia grade) (molecular weight: 4,000)	0.3
Sodium chloride (Japanese Pharmacopoeia grade)	0.9
Polyoxyethylene sorbitan monooleate (Japanese Pharmacopoeia grade)	0.4
Sodium metabisulfite	0.1
Methylparaben (Japanese Pharmacopoeia grade)	0.18
Propylparaben (Japanese Pharmacopoeia grade)	0.02
Distilled water for injection	100 ml

- 1 That is, the parabens, sodium metabisulfite and sodium chloride were dissolved in distilled water of about half of the above volume, at 80°C with stirring. The resulting solution was cooled to 40°C. Therein were
- 5 dissolved 6-[4-{N-cyclohexylmethyl-N-(2,3-dihydroxypropyl)amino}butoxy]carbostyryl, polyethylene glycol and polyoxyethylene sorbitan monooleate in this order. To the resulting solution was added distilled water for injection to make a final volume. The solution was
- 10 filtered for sterilization through an appropriate filter paper to prepare an injection.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

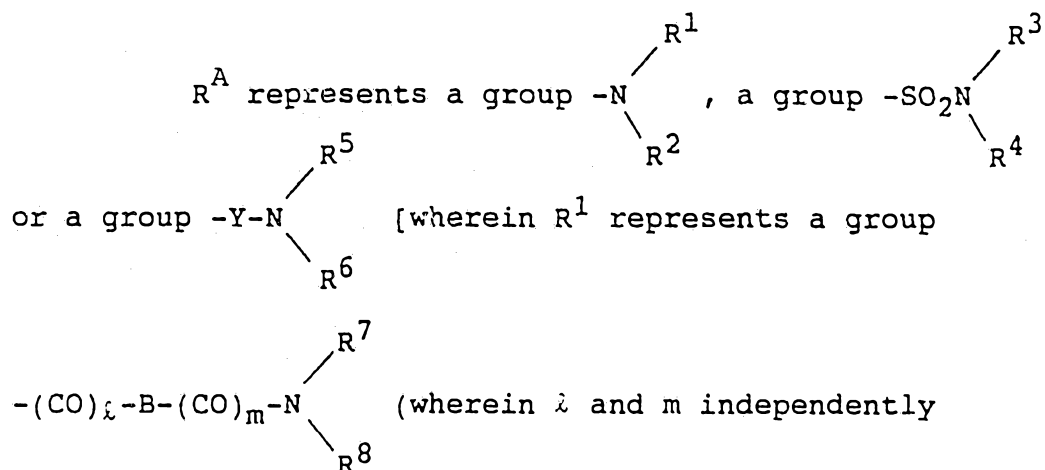


THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A carbostyryl derivative represented by general formula (1A)



{wherein A represents a lower alkylene group.



represent 0 or 1; B represents a lower alkylene group;
 each of R^7 and R^8 , which may be the same or different,
 represents a hydrogen atom, a lower alkyl group which may
 have a hydroxyl group, or a lower alkanoyl group;
 R^7 and R^8 may also form a five- or six-membered
 saturated heterocyclic ring, together with the nitrogen
 atom to which they bond and further with or without a
 nitrogen, oxygen or sulfur atom which may be present
 between R^7 and R^8 , said heterocyclic ring may have 1-3
 substituents selected from the group consisting of a
 hydroxyl group, a lower alkyl group which may have a



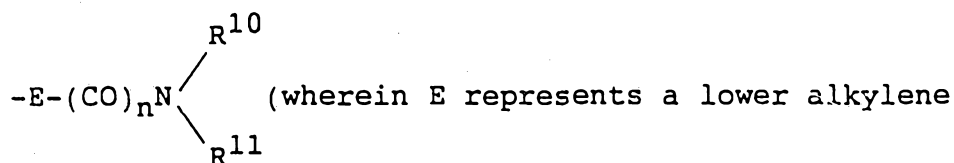
lower alkoxy-lower alkoxy group or a hydroxyl group, a lower alkyl group-substituted or unsubstituted amino group, a lower alkoxy-lower alkoxy group, an oxo group and a lower alkyl group-substituted or unsubstituted aminocarbonyl group, said heterocyclic ring may also have a lower alkylenedioxy group as a substituent); a lower alkoxy-carbonyl group-substituted lower alkyl group; a carboxy group-substituted lower alkyl group; a lower alkyl group having, as a substituent, a lower alkyl group-substituted or unsubstituted aminocarbonyl group; a hydroxyl group-containing lower alkyl group; an imidazolyl-substituted lower alkyl group; a pyridyl-substituted lower alkyl group; a pyrrolidinyl-lower alkyl group which may have, as substituent(s) on the pyrrolidine ring, 1-3 groups selected from the group consisting of a lower alkyl group, a lower alkoxy-lower alkoxy group and a hydroxyl group; or a group $-SO_2-D-R^9$ (wherein D represents a lower alkylene group; R^9 represents a five- or six-membered saturated or unsaturated heterocyclic ring residue having 1-3 nitrogen atoms, said heterocyclic ring may have, as a substituent, a hydroxyl group, a lower alkoxy-lower alkoxy group, a lower alkoxy-carbonyl group, or a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group);

R^2 represents a hydrogen atom; a cycloalkyl-lower alkyl group; a cycloalkyl group; a phenyl group; a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the

group consisting of a halogen atom, a lower alkyl group, a cyano group, a carboxy group and a lower alkoxy group; a pyridyl-substituted lower alkyl group; a thienyl-substituted lower alkyl group; a cycloalkylcarbonyl group; a benzoyl group; a tetrahydropyranyl-substituted lower alkyl group; a phenyl-lower alkylsulfonyl group; a phenylsulfonyl group; or a cycloalkyl-lower alkylsulfonyl group;

R^1 and R^2 may form a pyrrolidinyl group together with the nitrogen atom to which they bond, said pyrrolidinyl group has 1-2 substituents selected from the group consisting of a hydroxyl group, a lower alkoxy-lower alkoxy group, a lower alkyl group having a lower alkoxy-lower alkoxy group or a hydroxyl group, a lower alkoxy-carbonyl group, a piperidinylcarbonyl group and a cycloalkyl-lower alkyl group-substituted or unsubstituted aminocarbonyl group;

R^3 represents a hydrogen atom; a lower alkyl group which may have a hydroxyl group; a carboxy-substituted lower alkyl group; a lower alkoxy-carbonyl group-substituted lower alkyl group; a group



group which may have a hydroxyl group;

n represents 0 or 1;

each of R^{10} and R^{11} , which may be the same or different, represents a hydrogen atom; a lower alkyl group which may have a hydroxyl group; or a lower

alkanoyl group;

R¹⁰ and R¹¹ may also form a five- or six-membered saturated heterocyclic ring, together with the nitrogen atom to which they bond and further with or without a nitrogen, oxygen or sulfur atom which may be present between R¹⁰ and R¹¹, said heterocyclic ring may have 1-3 substituents selected from the group consisting of a hydroxyl group; an oxo group; a lower alkoxy-lower alkoxy group; a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group; and a lower alkyl-substituted or unsubstituted amino group, said heterocyclic ring may also have a lower alkylenedioxy group as a substituent); or a pyrrolidinyl-lower alkyl group which may have, as substituent(s) on the pyrrolidine ring, 1-3 groups selected from the group consisting of a lower alkyl group, a lower alkoxy-lower alkoxy group and a hydroxyl group;

R⁴ represents a hydrogen atom; a cycloalkyl group; a cycloalkyl-lower alkyl group; a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a halogen atom, a lower alkyl group and a lower alkoxy group; a phenyl group; a thienyl-substituted lower alkyl group; a pyridyl-substituted lower alkyl group; an imidazolyl-substituted lower alkyl group; or a tetra-hydropyranyl-substituted lower alkyl group;

Y represents a group -NHC- , a group -NHC- or a

O

S

group $\begin{array}{c} \text{-C-} \\ \parallel \\ \text{S} \end{array}$;

each of R^5 and R^6 , which may be the same or different, represents a hydrogen atom; a lower alkyl group; a cycloalkyl group; a cycloalkyl-lower alkyl group; or a piperidinyl-lower alkyl group which may have, as a substituent on the piperidinyl ring, a lower alkoxy-lower alkoxy group or a hydroxyl group;

W represents an oxygen atom or a sulfur atom;
the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton represents a single bond or a double bond;

when W is an oxygen atom and R^1 is a hydroxyl group-containing lower alkyl group, R^2 must not be any of a hydrogen atom, a cycloalkyl group and a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a lower alkoxy group and a halogen atom;

when R^1 and R^2 form a pyrrolidinyl group, the pyrrolidinyl group must not be a pyrrolidinyl group substituted with a hydroxyl group or with a hydroxyl group-containing lower alkyl group }, or a salt thereof.

2. The carbostyryl derivative or its salt according to Claim 1, wherein W is an oxygen atom.

3. The carbostyryl derivative or its salt according to Claim 1, wherein W is a sulfur atom.

4. The carbostyryl derivative or its salt accord



ing to Claim 2, wherein R^A is a group $-N \begin{matrix} \nearrow R^1 \\ \searrow R^2 \end{matrix}$ (wherein R^1 and R^2 are the same as defined in Claim 1).

5. The carbostyryl derivative or its salt accord-

ing to Claim 2, wherein R^A is a group $-SO_2N \begin{matrix} \nearrow R^3 \\ \searrow R^4 \end{matrix}$ (wherein R^3 and R^4 are the same as defined in Claim 1).

6. The carbostyryl derivative or its salt accord-

ing to Claim 2, wherein R^A is a group $-Y-N \begin{matrix} \nearrow R^5 \\ \searrow R^6 \end{matrix}$ (wherein R^5 and R^6 are the same as defined in Claim 1).

7. The carbostyryl derivative or its salt according to Claim 4, wherein R^1 is a group

$-(CO)_\ell-B-(CO)_m-N \begin{matrix} \nearrow R^7 \\ \searrow R^8 \end{matrix}$ (wherein ℓ , m , B , R^7 and R^8

are the same as defined in Claim 1).

8. The carbostyryl derivative or its salt according to Claim 4, wherein R^1 is a group $-SO_2-D-R^9$ (wherein D and R^9 are the same as defined in Claim 1).

9. The carbostyryl derivative or its salt according to Claim 4, wherein R^1 and R^2 form a pyrrolidinyl group together with the nitrogen atom to which they bond and said pyrrolidinyl group has 1-2 substituents selected from the group consisting of a

hydroxyl group, a lower alkoxy-lower alkoxy group, a lower alkyl group having a lower alkoxy-lower alkoxy group or a hydroxyl group, a lower alkoxycarbonyl group, a piperidinylcarbonyl group and a cycloalkyl-lower alkyl group-substituted or unsubstituted aminocarbonyl group.

10. The carbostyryl derivative or its salt according to Claim 4, wherein R^1 is a lower alkoxycarbonyl group-substituted lower alkyl group, a carboxy group-substituted lower alkyl group, a lower alkyl group having, as a substituent, a lower alkyl group-substituted or unsubstituted aminocarbonyl group; a hydroxyl group-containing lower alkyl group; an imidazolyl-substituted lower alkyl group; a pyridinyl-substituted lower alkyl group, or a pyrrolidinyl-lower alkyl group which may have, as substituent(s) on the pyrrolidine ring, 1-3 groups selected from the group consisting of a lower alkyl group, a lower alkoxy-lower alkoxy group and a hydroxyl group.

11. The carbostyryl derivative or its salt according to Claim 7, wherein R^2 is a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a halogen atom, a lower alkyl group, a cyano group, a carboxy group and a lower alkoxy group.

12. The carbostyryl derivative or its salt according to Claim 7, wherein R^2 is a hydrogen atom, a cycloalkyl-lower alkyl group, a cycloalkyl group, a phenyl group, a pyridyl-substituted lower alkyl group, a



thienyl-substituted lower alkyl group, a cycloalkyl-carbonyl group, a benzoyl group, a tetrahydropyranyl-substituted lower alkyl group, a phenyl-lower alkyl-sulfonyl group, a phenylsulfonyl group or a cycloalkyl-lower alkylsulfonyl group.

13. The carbostyryl derivative or its salt according to Claim 8, wherein R^2 is a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a halogen atom, a lower alkyl group, a cyano group, a carboxy group and a lower alkoxy group.

14. The carbostyryl derivative or its salt according to Claim 8, wherein R^2 is a hydrogen atom, a cycloalkyl-lower alkyl group, a cycloalkyl group, a phenyl group, a pyridyl-substituted lower alkyl group, a thienyl-substituted lower alkyl group, a cycloalkyl-carbonyl group, a benzoyl group, a tetrahydropyranyl-substituted lower alkyl group, a phenyl-lower alkyl-sulfonyl group, a phenylsulfonyl group or a cycloalkyl-lower alkylsulfonyl group.

15. The carbostyryl derivative or its salt according to Claim 9, wherein R^2 is a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a halogen atom, a lower alkyl group, a cyano group, a carboxy group and a lower alkoxy group.

16. The carbostyryl derivative or its salt according to Claim 9, wherein R^2 is a hydrogen atom, a

cycloalkyl-lower alkyl group, a cycloalkyl group, a phenyl group, a pyridyl-substituted lower alkyl group, a thienyl-substituted lower alkyl group, a cycloalkyl-carbonyl group, a benzoyl group, a tetrahydropyranyl-substituted lower alkyl group, a phenyl-lower alkyl-sulfonyl group, a phenylsulfonyl group or a cycloalkyl-lower alkylsulfonyl group.

17. The carbostyryl derivative or its salt according to Claim 10, wherein R^2 is a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a halogen atom, a lower alkyl group, a cyano group, a carboxy group and a lower alkoxy group.

18. The carbostyryl derivative or its salt according to Claim 10, wherein R^2 is a a hydrogen atom, a cycloalkyl-lower alkyl group, a cycloalkyl group, a phenyl group, a pyridyl-substituted lower alkyl group, a thienyl-substituted lower alkyl group, a cycloalkyl-carbonyl group, a benzoyl group, a tetrahydropyranyl-substituted lower alkyl group, a phenyl-lower alkyl-sulfonyl group, a phenylsulfonyl group or a cycloalkyl-lower alkylsulfonyl group.

19. The carbostyryl derivative or its salt according to Claim 11, wherein ℓ is 0; R^7 and R^8 may form a five- or six-membered saturated heterocyclic ring, together with the nitrogen atom to which they bond and further with or without a nitrogen, oxygen or sulfur atom which may be present between R^7 and R^8 ; said heterocyclic

ring may have 1-3 substituents selected from the group consisting of a hydroxyl group, a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group, a lower alkyl group-substituted or unsubstituted amino group, a lower alkoxy-lower alkoxy group, an oxo group and a lower alkyl group-substituted or unsubstituted aminocarbonyl group; and said heterocyclic ring may also have a lower alkylenedioxy group as a substituent.

20. The carbostyryl derivative or its salt according to Claim 11, wherein ℓ is 0 and each of R^7 and R^8 , which may be the same or different, is a hydrogen atom, a lower alkyl group which may have a hydroxyl group, or a lower alkanoyl group.

21. The carbostyryl derivative or its salt according to Claim 12, wherein ℓ is 0; R^7 and R^8 may form a five- or six-membered saturated heterocyclic ring, together with the nitrogen atom to which they bond and further with or without a nitrogen, oxygen or sulfur atom which may be present between R^7 and R^8 ; said heterocyclic ring may have 1-3 substituents selected from the group consisting of a hydroxyl group, a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group, a lower alkyl group-substituted or unsubstituted amino group, a lower alkoxy-lower alkoxy group, an oxo group and a lower alkyl group-substituted or unsubstituted aminocarbonyl group; and said heterocyclic ring may also have a lower alkylenedioxy group as a substituent.

22. The carbostyryl derivative or its salt



according to Claim 12, wherein ℓ is 0 and each of R^7 and R^8 , which may be the same or different, is a hydrogen atom, a lower alkyl group which may have a hydroxyl group, or a lower alkanoyl group.

23. The carbostyryl derivative or its salt according to Claim 11 or 12, wherein ℓ is 1.

24. The carbostyryl derivative or its salt according to any one of Claims 13 to 22, wherein the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton is a single bond.

25. The carbostyryl derivative or its salt according to any one of Claims 13 to 22, wherein the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton is a double bond.

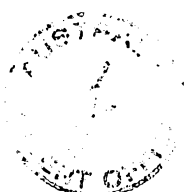
26. The carbostyryl derivative or its salt according to Claim 19 or 21, wherein the heterocyclic ring is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isothiazolidinyl or 3,4,5,6-tetrahydro-1,2-thiazinyl.

27. The carbostyryl derivative or its salt according to Claim 5, wherein R^3 is a group $-E-(CO)_n-N$

$\begin{array}{c} R^{10} \\ \diagup \\ -E-(CO)_n-N \\ \diagdown \\ R^{11} \end{array}$

(wherein E, n, R^{10} and R^{11} are the same as defined as in Claim 1).

28. The carbostyryl derivative or its salt according to Claim 5, wherein R^3 is a hydrogen atom, a lower alkyl group which may have a hydroxyl group, a carboxy-



substituted lower alkyl group, a lower alkoxy-carbonyl group-substituted lower alkyl group, or a pyrrolidinyl-lower alkyl group which may have, as substituent(s) on the pyrrolidine ring, 1-3 groups selected from the group consisting of a lower alkyl group, a lower alkoxy-lower alkoxy group and a hydroxyl group.

29. The carbostyryl derivative or its salt according to Claim 27, wherein R^{10} and R^{11} may form a five- or six-membered saturated heterocyclic ring, together with the nitrogen atom to which they bond and further with or without a nitrogen, oxygen or sulfur atom which may be present between R^{10} and R^{11} ; said heterocyclic ring may have 1-3 substituents selected from the group consisting of a hydroxyl group, an oxo group, a lower alkoxy-lower alkoxy group, a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group, and a lower alkyl-substituted or unsubstituted amino group; and said heterocyclic ring may also have a lower alkylenedioxy group as a substituent.

30. The carbostyryl derivative or its salt according to Claim 27, wherein each of R^{10} and R^{11} , which may be the same or different, is a hydrogen atom, a lower alkyl group which may have a hydroxyl group, or a lower alkanoyl group.

31. The carbostyryl derivative or its salt according to Claim 27 or 28, wherein R^4 is a cycloalkyl group, a cycloalkyl-lower alkyl group, a phenyl-lower alkyl group which may have, as substituent(s) on the

phenyl ring, 1-3 groups selected from the group consisting of a halogen atom, a lower alkyl group and a lower alkoxy group, or a thienyl-substituted lower alkyl group.

32. The carbostyryl derivative or its salt according to Claim 27 or 28, wherein R^4 is a hydrogen atom, a phenyl group, a pyridyl-substituted lower alkyl group, an imidazolyl-substituted lower alkyl group or a tetrahydropyranyl-substituted lower alkyl group.

33. The carbostyryl derivative or its salt according to Claim 29, wherein the heterocyclic ring is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isothiazolidinyl or 3,4,5,6-tetrahydro-1,2-thiazinyl.

34. The carbostyryl derivative or its salt according to any ^{one} of Claims 28, 29 and 30, wherein the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton is a single bond.

35. The carbostyryl derivative or its salt according to any ^{one} of Claims 28, 29 and 30, wherein the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton is a double bond.

36. The carbostyryl derivative or its salt according to Claim 6, wherein Y is a group -NHC-.



37. The carbostyryl derivative or its salt according to Claim 6, wherein Y is a group -NHC- or a group





38. The carbostyryl derivative or its salt according to Claim 36 or 37, wherein the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton is a single bond.

39. The carbostyryl derivative or its salt according to Claim 36 or 37, wherein the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton is a double bond.

40. 6-[4-{N-[2-(4-hydroxy-1-piperidinyl)ethyl]-N-benzylamino}butoxy]carbostyryl

41. 6-{4-[N-(4-hydroxy-1-piperidinyl)carbonylmethyl]-N-benzylamino}butoxy}carbostyryl

42. 6-[5-{N-[2-(4-hydroxy-1-piperidinyl)ethyl]-N-(2-chlorobenzyl)amino}pentyloxy]carbostyryl

43. 6-[3-{N-[2-(4-hydroxy-1-piperidinyl)ethyl]-N-cyclooctylamino}sulfonylpropoxy]carbostyryl

44. 6-[4-{N-[2-(4-hydroxy-1-piperidinyl)ethyl]-N-[(2-thienyl)methyl]amino}sulfonylbutoxy]carbostyryl

45. 7-[4-{N-[2-(4-hydroxy-1-piperidinyl)ethyl]-N-cyclooctylmethylamino}sulfonylbutoxy]carbostyryl

46. 6-[4-{N-[2-(4-hydroxy-1-piperidinyl)ethyl]-N-(2-chlorobenzyl)amino}sulfonylbutoxy]carbostyryl

47. 6-[3-{N-[2-(4-hydroxy-1-piperidinyl)ethyl]-N-cyclooctylmethylamino}carbonylaminopropoxy]carbostyryl

48. A platelets aggregation inhibitory agent containing, as an active ingredient, a carbostyryl



derivative represented by general formula (1A)



(wherein A, R^A and W have the same definitions as given in Claim 1, and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton is a single bond or a double bond), or a salt thereof.

49. A phosphodiesterase inhibitory agent containing, as an active ingredient, a carbostyryl derivative represented by general formula (1A)



(wherein A, R^A and W have the same definitions as given in Claim 1, and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton is a single bond or a double bond), or a salt thereof.

50. A platelets adhesion inhibitory agent containing, as an active ingredient, a carbostyryl derivative represented by general formula (1A)

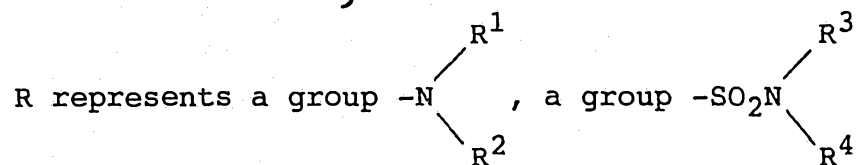


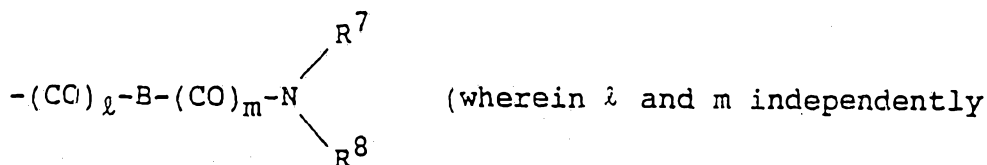
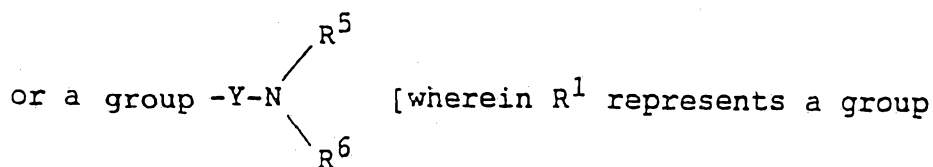
(wherein A, R^A and W have the same definitions as given in Claim 1, and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton is a single bond or a double bond), or a salt thereof.

51. A method for platelets aggregation inhibition, which uses, as an active ingredient, a carbostyryl derivative represented by general formula (1)



{wherein A and W have the same definitions as given in Claim 1; and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton represents a single bond or a double bond;





represent 0 or 1; B represents a lower alkylene group; each of R^7 and R^8 , which may be the same or different, represents a hydrogen atom, a lower alkyl group which may have a hydroxyl group, or a lower alkanoyl group;

- 10 R^7 and R^8 may also form a five- or six-membered saturated heterocyclic ring, together with the nitrogen atom to which they bond and further with or without a nitrogen, oxygen or sulfur atom which may be present between R^7 and R^8 , said heterocyclic ring may have 1-3 substituents selected from
- 15 the group consisting of a hydroxyl group, a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group, a lower alkyl group-substituted or unsubstituted amino group, a lower alkoxy-lower alkoxy group, an oxo group and a lower alkyl group-substituted or
- 20 unsubstituted aminocarbonyl group, said heterocyclic ring may also have a lower alkylendioxy group as a substituent); a lower alkoxy-carbonyl group-substituted lower alkyl group; a carboxy group-substituted lower alkyl group; a lower alkyl group having, as a substituent, a
- 25 lower alkyl group-substituted or unsubstituted aminocarbonyl group; a hydroxyl group-containing lower alkyl group; an



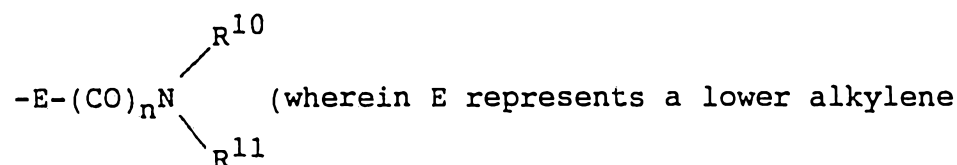
imidazolyl-substituted lower alkyl group; a pyridyl-substituted lower alkyl group; a pyrrolidinyl-lower alkyl group which may have, as substituent(s) on the pyrrolidine ring, 1-3 groups selected from the group consisting of a lower alkyl group, a lower alkoxy-lower alkoxy group and a hydroxyl group; or a group $\text{-SO}_2\text{-D-R}^9$ (wherein D represents a lower alkylene group; R^9 represents a five- or six-membered saturated or unsaturated heterocyclic ring residue having nitrogen atoms, said heterocyclic ring may have, as a substituent, a hydroxyl group, a lower alkoxy-lower alkoxy group, a lower alkoxy-carbonyl group, or a lower alkyl group which may have a lower alkoxy-lower alkoxy group or a hydroxyl group).

R^2 represents a hydrogen atom; a cycloalkyl-lower alkyl group; a cycloalkyl group; a phenyl group; a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a halogen atom, a lower alkyl group, a cyano group, a carboxy group and a lower alkoxy group; a pyridyl-substituted lower alkyl group; a thienyl-substituted lower alkyl group; a cycloalkylcarbonyl group; a benzoyl group; a tetrahydropyranyl-substituted lower alkyl group; a phenyl-lower alkylsulfonyl group; a phenylsulfonyl group; or a cycloalkyl-lower alkylsulfonyl group;

R^1 and R^2 may form a pyrrolidinyl group together with the nitrogen atom to which they bond, said pyrrolidinyl group has 1-2 substituents selected from the

group consisting of a hydroxyl group, a lower alkoxy-
lower alkoxy group, a lower alkyl group which may have a
lower alkoxy-lower alkoxy group or a hydroxyl group, a
lower alkoxycarbonyl group, a piperidinylcarbonyl group
and a cycloalkyl-lower alkyl group-substituted or unsub-
stituted aminocarbonyl group;

R^3 represents a hydrogen atom; a lower alkyl
group which may have a hydroxyl group; a carboxy-
substituted lower alkyl group; a lower alkoxycarbonyl
group-substituted lower alkyl group; a group



group which may have a hydroxyl group; n represents 0 or
1; each of R^{10} and R^{11} , which may be the same or
different, represents a hydrogen atom; a lower alkyl
group which may have a hydroxyl group; or a lower
alkanoyl group; R^{10} and R^{11} may also form a five- or
six-membered saturated heterocyclic ring, together with
the nitrogen atom to which they bond and further with or
without a nitrogen, oxygen or sulfur atom which may be
present between R^{10} and R^{11} , said heterocyclic ring may
have 1-3 substituents selected from the group consisting
of a hydroxyl group; an oxo group; a lower alkoxy-lower
alkoxy group; a lower alkyl group which may have a lower
alkoxy-lower alkoxy group or a hydroxyl group; and a
lower alkyl-substituted or unsubstituted amino group,
said heterocyclic ring may also have a lower alkylendioxy

group as a substituent); or a pyrrolidinyl-lower alkyl group which may have, as substituent(s) on the pyrrolidine ring, 1-3 groups selected from the group consisting of a lower alkyl group, a lower alkoxy-lower alkoxy group and a hydroxyl group;

R^4 represents a hydrogen atom; a cycloalkyl group; a cycloalkyl-lower alkyl group; a phenyl-lower alkyl group which may have, as substituent(s) on the phenyl ring, 1-3 groups selected from the group consisting of a halogen atom, a lower alkyl group and a lower alkoxy group; a phenyl group; a thienyl-substituted lower alkyl group; a pyridyl-substituted lower alkyl group; an imidazolyl-substituted lower alkyl group; or a tetrahydropyranyl-substituted lower alkyl group;

Y represents a group -NHC- , a group -NHC- or a group -C- ;

$$\begin{array}{ccc} \parallel & & \parallel \\ \text{O} & & \text{S} \end{array}$$

each of R^5 and R^6 , which may be the same or different, represents a hydrogen atom; a lower alkyl group; a cycloalkyl group; a cycloalkyl-lower alkyl group; or a piperidinyl-lower alkyl group which may have, as a substituent on the piperidinyl ring, a lower alkoxy-lower alkoxy group or a hydroxyl group]}, or a salt thereof.

52. A method for phosphodiesterase inhibition, which uses, as an active ingredient, a carbostyryl derivative represented by general formula (1)





(wherein A and W have the same definitions as in Claim 1; the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton represents a single bond or a double bond; and R has the same definition as in Claim 51), or a salt thereof.

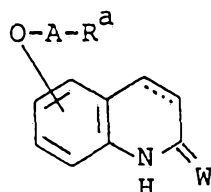
53. A method for platelets adhesion inhibition, which uses, as an active ingredient, a carbostyryl derivative represented by general formula (1)



(wherein A and W and have the same definitions as in Claim 1; the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton represents a single bond or a double bond; and R has the same definition as in Claim 51), or a salt thereof.

54. A process for producing a compound (1a) represented by general formula (1a)

5



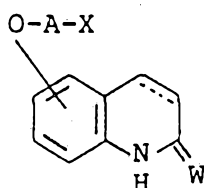
(1a)

[wherein A and W have the same definitions as in Claim 1;

10 R^a represents a group $-N \begin{matrix} R^1 \\ R^2 \end{matrix}$ (wherein R^1 and R^2

have the same definitions as in Claim 1); and the carbon-to-carbon bond of the 3- and 4-positions of the carbostyryl skeleton is the same as mentioned above], by reacting a

15 compound (2) represented by a compound (2)



(2)

20

(wherein A, W and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as given above; and X represents a halogen atom, a lower alkanesulfonyloxy group, an arylsulfonyloxy group or an aralkylsulfonyloxy group) with a compound (3) represented by general formula (3)



(wherein R^a has the same definition as given above) in an appropriate solvent or in the absence of any solvent in the presence or absence of a basic compound.

55. A process for producing a compound (1) represented by general formula (1)



(wherein A, R, W and the carbon-to-carbon bond between the 3-and 4-positions of the carbostyryl skeleton have the same definitions as in Claim 51), by reacting a compound (4) represented by general formula (4)



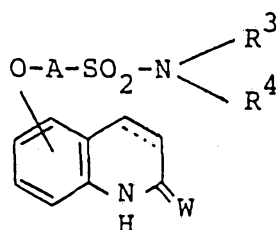
(wherein W and the carbon-to-carbon bond between the 3-and 4-positions of the carbostyryl skeleton have the same definitions as given above) with a compound (5) represented by general formula (5)



(wherein X, A and R have the same definitions as in Claims 1 and 51) in an appropriate solvent in the presence of a basic compound used as a dehalogenating agent.

56. A process for producing a compound (1b) represented by general formula (1b)

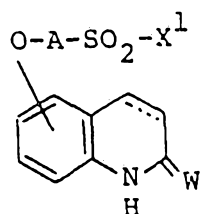
10



(1b)

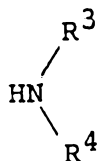
15 (wherein A, W, R³ and R⁴ and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as in Claim 1), by reacting a compound (6) represented by general formula (6)

20



(6)

25 (wherein A, W and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as in Claim 1; and X represents a halogen atom) with a compound (7) represented by general formula (7)

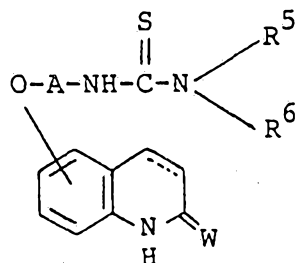


(7)

5 (wherein R^3 and R^4 have the same definitions as in Claim 1)
in an appropriate solvent or in the absence of any solvent
in the presence or absence of a basic compound.

57. A process for producing a carbostyryl derivative (1c)
represented by general formula (1c)

10

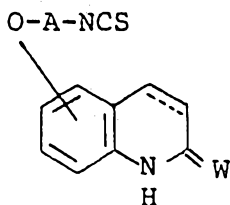


(1c)

15

(wherein A, R^5 , R^6 and the carbon-to-carbon bond between
the 3- and 4-positions of the carbostyryl skeleton have the
same definitions as in Claim 1), by reacting a compound (8)

20 represented by general formula (8)



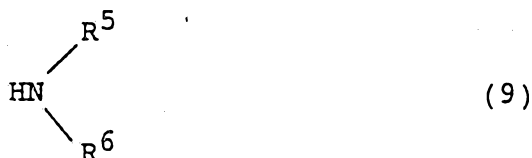
(8)

25

(wherein A, W and the carbon-to-carbon bond between the

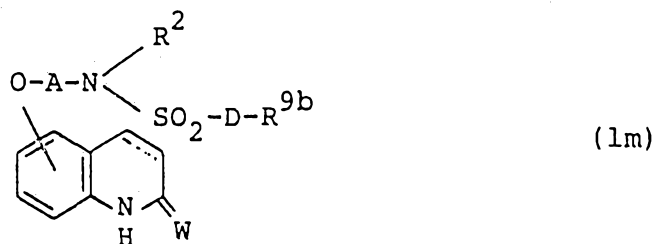


3- and 4-positions of the carbostyryl skeleton have the same definitions as in Claim 1) with a compound (9) represented by general formula (9)



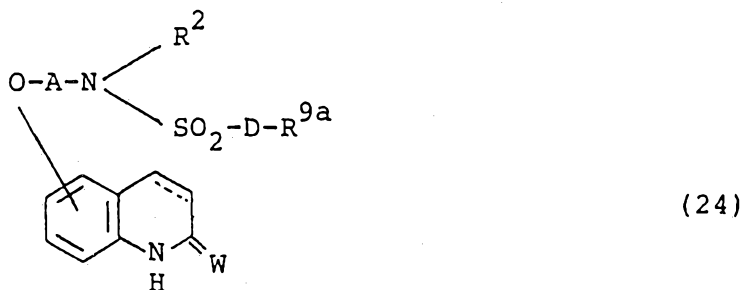
(wherein R^5 and R^6 have the same definitions as given above) in an appropriate solvent.

58. A process for producing a carbostyryl derivative (1m) represented by general formula (1m)



(wherein A, W, R^2 , and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as in Claim 1; D represents a lower alkylene group; and R^{9b} represents a five- or six-membered saturated or unsaturated heterocyclic ring residue containing 1-3 nitrogen atoms, which residue may have, as substituent(s), a hydroxyl group, a lower alkoxy-lower alkoxy group, a lower alkoxycarbonyl group or a lower alkyl group which may be substituted with a

lower alkoxy-lower alkoxy group or a hydroxyl group), by reacting a compound (24) represented by general formula (24)

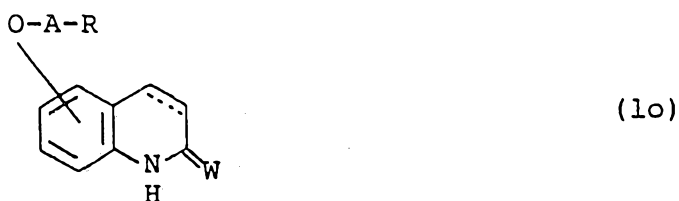


(wherein A, R², D and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as given above; and R^{9a} represents a halogen atom) with a compound (25) represented by general formula (25)



(wherein R^{9b} has the same definition as given above) in an appropriate solvent or in the absence of any solvent in the presence or absence of a basic compound.

59. A process for producing a carbostyryl derivative (10) represented by general formula (10)

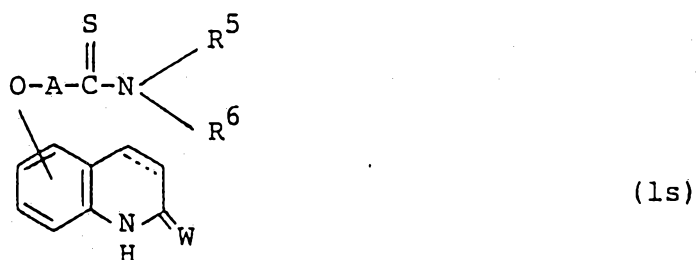


(wherein A, R and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as in Claim 1), by reacting a compound (1n) represented by general formula (1n)



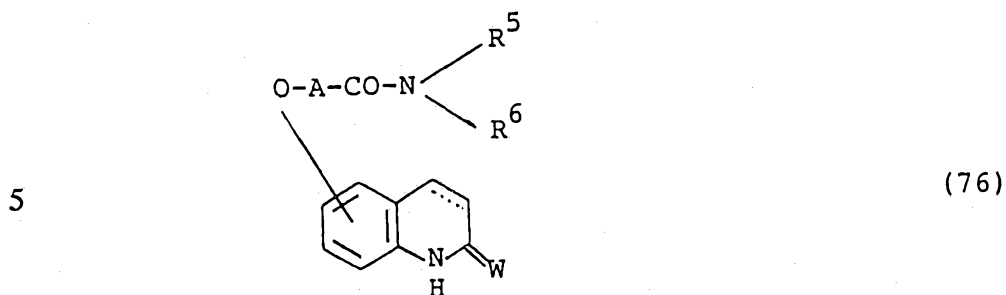
(wherein A, R and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as given above) with P₂S₅ or a Lawesson's reagent.

60. A process for producing a carbostyryl derivative (1s) represented by general formula (1s)



(wherein A, R⁵, R⁶, W and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton have the same definitions as in Claim 1), by reacting a compound (76) represented by general formula (76)





(wherein A, R⁵, R⁶, W and the carbon-to-carbon bond between
10 the 3- and 4-positions of the carbostyryl skeleton have the
same definitions as given above) with P₂S₅ or a Lawesson's
reagent.

61. Carbostyryl derivatives represented by general formula
15 (1A), processes for their preparation or agents containing
them, substantially as hereinbefore described with
reference to the Examples.

62. Processes for the preparation of carbostyryl
20 derivatives represented by the general formula (I) or
methods involving carbostyryl derivatives represented by
the general formula (I), substantially as hereinbefore
described with reference to the Examples.

25 DATED this 19th day of July, 1994.

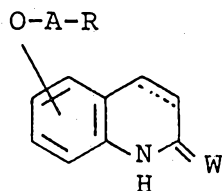
OTSUKA PHARMACEUTICAL CO., LTD.

By Its Patent Attorneys

DAVIES COLLISON CAVE

Abstract

The present invention provides a carbostyryl derivative represented by the following general formula



(wherein A, R and W have the same definitions as given above; and the carbon-to-carbon bond between the 3- and 4-positions of the carbostyryl skeleton represents a single bond or a double bond.).

Said carbostyryl derivative is useful as a platelets aggregation inhibitory agent.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP92/01041

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int. Cl ⁵ C07D215/22, 215/36, 401/12, 407/12, 409/12, 417/12, A61K31/47, 31/495, 31/535		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC	C07D215/22, 215/36, A61K31/47, 31/495, 31/535	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	JP, A, 48-103589 (Otsuka Pharmaceutical Co., Ltd.), December 25, 1973 (25. 12. 73), & DE, A, 2302027 & US, A, 3910924	1-26, 40-42
Y	JP, A, 49-48683 (Otsuka Pharmaceutical Co., Ltd.), May 11, 1974 (11. 05. 74), & DE, A, 2302027 & US, A, 4256890	1-26, 40-42, 54
Y	JP, A, 50-151881 (Otsuka Pharmaceutical Co., Ltd.), December 6, 1975 (06. 12. 75), (Family: none)	1-26, 40-42
Y	JP, A, 53-21176 (Otsuka Pharmaceutical Co., Ltd.), February 27, 1978 (27. 02. 78), (Family: none)	1, 27-35, 43-46, 48-50, 56
Y	JP, A, 54-5981 (Otsuka Pharmaceutical Co., Ltd.), January 17, 1979 (17. 01. 79),	1, 36-39, 47-50, 54, 55
¹⁰ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
October 13, 1992 (13. 10. 92)		November 2, 1992 (02. 11. 92)
International Searching Authority		Signature of Authorized Officer
Japanese Patent Office		

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	& DE, A, 2825048 & US, A, 4298739	
Y	JP, A, 54-12385 (Otsuka Pharmaceutical Co., Ltd.), January 30, 1979 (30. 01. 79), & DE, A, 2825048 & US, A, 4298739	1, 36-39, 47-50, 54, 55
Y	JP, A, 54-115383 (Otsuka Pharmaceutical Co., Ltd.), September 7, 1979 (07. 09. 79), & DE, A, 2825048 & US, A, 4298739	1, 36-39, 47-50, 54, 55
Y	JP, A, 54-132581 (Dr. Karl Thomae GmbH.), October 15, 1979 (15. 10. 79),	1, 27-35, 43-46, 48,

V ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

- 1 ☒ Claim numbers 51-53 because they relate to subject matter not required to be searched by this Authority, namely:

A treatment method by man's physical cure.

- 2 ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- 3 ☐ Claim numbers , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This international Searching Authority found multiple inventions in this international application as follows:

- 1 ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
- 2 ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
- 3 ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
- 4 ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	& DE, A, 2806721 & US, A, 4329347	50, 54-56
Y	JP, A, 54-163825 (Otsuka Pharmaceutical Co., Ltd.), December 26, 1979 (26. 12. 79), (Family: none)	1, 37-39, 47, 49, 54, 55
Y	JP, A, 55-79370 (Otsuka Pharmaceutical Co., Ltd.), June 14, 1980 (14. 06. 80), (Family: none)	1, 37-39, 47-50, 55
Y	JP, A, 56-122356 (Otsuka Pharmaceutical Co., Ltd.),	1, 37-39, 47-50, 55

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers , because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim numbers , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET		
	September 25, 1981 (25. 09. 81), & WO, A, 8102421 & US, A, 4435404	
Y	JP, A, 57-2274 (Otsuka Pharmaceutical Co., Ltd.), January 7, 1982 (07. 01. 82), (Family: none)	1, 37-39, 47-50, 54, 55
Y	JP, A, 57-14574 (Otsuka Pharmaceutical Co., Ltd.), January 25, 1982 (25. 01. 82), (Family: none)	1, 37-39, 47-50, 54, 55
	JP, A, 63-290821 (Otsuka Pharmaceutical	1-26, 40-42,
☐ V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹		
This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:		
☐ Claim numbers , because they relate to subject matter not required to be searched by this Authority, namely:		
☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:		
☐ Claim numbers , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).		
☐ VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²		
This International Searching Authority found multiple inventions in this international application as follows:		
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☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:		
☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:		
☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.		
Remark on Protest		
☐ The additional search fees were accompanied by applicant's protest.		
☐ No protest accompanied the payment of additional search fees.		

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Co., Ltd.),
November 28, 1988 (28. 11. 88),
(Family: none)

54, 55

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers , because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

国 際 調 査 報 告

国際出願番号PCT/JP 92/01041

I. 発明の属する分野の分類		
国際特許分類 (IPC) Int. Cl ⁸ C 07 D 215/22, 215/36, 401/12, 407/12, 409/12, 417/12, A 61 K 31/47, 31/495, 31/535		
II. 国際調査を行った分野		
調 査 を 行 っ た 最 小 限 資 料		
分 類 体 系	分 類 記 号	
IPC	C 07 D 215/22, 215/36, A 61 K 31/47, 31/495, 31/535	
最小限資料以外の資料で調査を行ったもの		
III. 関連する技術に関する文献		
引用文献の カテゴリ	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	請求の範囲の番号
Y	JP, A, 48-103589 (大塚製薬株式会社), 25. 12月. 1973 (25. 12. 73) & DE, A, 2302027 & US, A, 3910924	1-26, 40-42
Y	JP, A, 49-48683 (大塚製薬株式会社), 11. 5月. 1974 (11. 05. 74) & DE, A, 2302027 & US, A, 4256890	1-26, 40-42, 54
Y	JP, A, 50-151881 (大塚製薬株式会社), 6. 12月. 1975 (06. 12. 75), (ファミリーなし)	1-26, 40-42, ~~51, 53~~
Y	JP, A, 53-21176 (大塚製薬株式会社), 27. 2月. 1978 (27. 02. 78), (ファミリーなし)	1, 27-35, 43- 46, 48-50, 56
Y	JP, A, 54-5981 (大塚製薬株式会社), 17. 1月. 1979 (17. 01. 79)	1, 36-39, 47- 50, 54, 55
※引用文献のカテゴリ 「A」 特に関連のある文献ではなく、一般的技術水準を示すもの 「E」 先行文献ではあるが、国際出願日以後に公表されたもの 「L」 優先権主張に疑義を提起する文献又は他の文献の発行日 若しくは他の特別な理由を確立するために引用する文献 (理由を付す) 「O」 口頭による開示、使用、展示等に関する文献 「P」 国際出願日前で、かつ優先権の主張の基礎となる出願の 日の後に公表された文献 「T」 国際出願日又は優先日の後に公表された文献であって出 願と矛盾するものではなく、発明の原理又は理論の理解 のために引用するもの 「X」 特に関連のある文献であって、当該文献のみで発明の新 規性又は進歩性がないと考えられるもの 「Y」 特に関連のある文献であって、当該文献と他の1以上の 文献との、当業者にとって自明である組合せによって進 歩性がないと考えられるもの 「&」 同一パテントファミリーの文献		
IV. 認 証		
国際調査を完了した日	国際調査報告の発送日	
13. 10. 92	1992. 10. 22	
国際調査機関	雇用のある職員	4C 7019
日本国特許庁 (ISA/JP)	特許庁審査官	佐 野 整 博 ®

第2ページから続く情報

(III欄の続き)

	& DE, A, 2825048 & US, A, 4298739	
Y	JP, A, 54-12385 (大塚製薬株式会社), 30. 1月. 1979 (30. 01. 79) & DE, A, 2825048 & US, A, 4298739	1, 36-39, 47-50, 54, 55
Y	JP, A, 54-115383 (大塚製薬株式会社), 7. 9月. 1979 (07. 09. 79) & DE, A, 2825048 & US, A, 4298739	1, 36-39, 47-50, 54, 55

V. ☒ 一部の請求の範囲について国際調査を行わないときの意見

次の請求の範囲については特許協力条約に基づく国際出願等に関する法律第8条第3項の規定によりこの国際調査報告を作成しない。その理由は、次のとおりである。

1. ☒ 請求の範囲 51-53 は、国際調査をすることを要しない事項を内容とするものである。

人の身体の治療による処置方法である。

2. ☐ 請求の範囲 _____ は、有効な国際調査をすることができる程度にまで所定の要件を満たしていない国際出願の部分に係るものである。

3. ☐ 請求の範囲 _____ は、従属請求の範囲でありかつ PCT 規則 6.4(a)第2文の規定に従って起草されていない。

VI. ☐ 発明の単一性の要件を満たしていないときの意見

次に述べるようにこの国際出願には二以上の発明が含まれている。

- ☐ 追加して納付すべき手数料が指定した期間内に納付されたので、この国際調査報告は、国際出願のすべての調査可能な請求の範囲について作成した。
- ☐ 追加して納付すべき手数料が指定した期間内に一部分しか納付されなかったので、この国際調査報告は、手数料の納付があった発明に係る次の請求の範囲について作成した、
請求の範囲 _____
- ☐ 追加して納付すべき手数料が指定した期間内に納付されなかったので、この国際調査報告は、請求の範囲に最初に記載された発明に係る次の請求の範囲について作成した、
請求の範囲 _____
- ☐ 追加して納付すべき手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加して納付すべき手数料の納付を怠らなかった。

追加手数料異議の申立てに関する注意

- ☐ 追加して納付すべき手数料の納付と同時に、追加手数料異議の申立てがされた、
- ☐ 追加して納付すべき手数料の納付に際し、追加手数料異議の申立てがされなかった、

Ⅲ. 関連する技術に関する文献 (第2ページからの続き)

出願番号	引用文献名及び一部の箇所が関連するときは、その関連する箇所の表示	請求の範囲の番号
Y	JP, A, 54-132581 (ドクトル・カール・トーマー・ゲゼルシャフト・ミット・ベシュレンクテル・ハフツング), 15. 10月. 1979 (15. 10. 79) & DE, A, 2806721 & US, A, 4329347	1, 27-35, 43-46, 48, 50, 54-56
Y	JP, A, 54-163825 (大塚製薬株式会社), 26. 12月. 1979 (26. 12. 79), (ファミリーなし)	1, 37-39, 47, 49, 54, 55
Y	JP, A, 55-79370 (大塚製薬株式会社), 14. 6月. 1980 (14. 06. 80), (ファミリーなし)	1, 37-39, 47-50, 55
Y	JP, A, 56-122356 (大塚製薬株式会社), 25. 9月. 1981 (25. 09. 81) & WO, A, 8102421 & US, A, 4435404	1, 37-39, 47-50, 55
Y	JP, A, 57-2274 (大塚製薬株式会社), 7. 1月. 1982 (07. 01. 82), (ファミリーなし)	1, 37-39, 47-50, 54, 55
Y	JP, A, 57-14574 (大塚製薬株式会社), 25. 1月. 1982 (25. 01. 82), (ファミリーなし)	1, 37-39, 47-50, 54, 55
Y	JP, A, 63-290821 (大塚製薬株式会社), 28. 11月. 1988 (28. 11. 88), (ファミリーなし)	1-26, 40-42, 54, 55