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NOTICE OF ENTITLEMENT

Name(s) of Applicant(s): Sankyo Company Limited
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~~I~~/WE the above-named Applicant(s) in respect of an invention, entitled

NITROXYALKYLAMIDE DERIVATIVE

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SANKYO COMPANY, LIMITED

Yoshibumi Kawamura — 21 April 1994

Signature(s) of/on behalf of the Applicant(s) — Date

Yoshibumi Kawamura
Representative Director and President

*Full Name(s) of Signatory(s) — *Position(s) Held.

* For corporations only.

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NITROXYALKYLAMIDE DERIVATIVES

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(57)

The present invention relates to nitroxyalkylamide derivatives and pharmaceutically acceptable salts thereof having excellent vasodilator activity for the collateral vessels and anti-anginal action.

CLAIM

1. Nitroxyalkylamide derivatives having the general formula:

$$R^1\text{-}(A)_n\text{-}CONH\text{-}B\text{-}ONO_2 \qquad (I)$$

[in this formula, R^1 represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms

.../2

selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a phenyl group optionally substituted with a C_1-C_4 alkyl group, with a C_1-C_4 alkoxy group or with a halogen atom; a halogen atom; a hydroxy group; an amino group; a mono- or di-C_1-C_4 alkylamino group; and a nitro group); A represents a C_1-C_4 alkylene group; B represents a C_1-C_4 alkylene group; and n represents 0 or 1; provided that, when n is 0, R^1 represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group; and further provided that when R^1 represents a 3-oxazole group, then it is not substituted by a halomethylene group, a mesyloxymethylene group or a tosyloxymethylene group], or pharmaceutically acceptable salts thereof.

12. Phenyl N-(2-nitroxyethyl)carbamate.

13. N-(2-Nitroxyethyl)phenoxyacetamide.

14. N-(2-Nitroxyethyl)-2-chlorophenoxyacetamide.

15. N-(2-Nitroxyethyl)-2-phenoxypropanamide.

16. N-(2-Nitroxyethyl)-5-methyl-4-chloro-3-isoxazolyloxyacetamide.

17. N-(2-Nitroxyethyl-5-phenyl-3-isoxazolyloxy-acetamide.

18. N-(2-Nitroxyethyl)-5-methyl-3-isoxazolyloxy-acetamide.

19. N-(2-Nitroxyethyl)-5-methyl-4-bromo-3-isoxazolyloxyacetamide.

20. N-(2-Nitroxyethyl)-3-isoxazolyloxyacetamide.

21. N-(2-Nitroxyethyl)-5-phenyl-4-bromo-3-isoxazolyloxyacetamide.

22. N-(2-Nitroxyethyl)-4-bromo-3-isoxazolyloxy-acetamide.

23. N-(2-Nitroxyethyl)-4-chloro-3-isoxazolyloxy-acetamide.

24. N-(2-Nitroxyethyl)-1,4-benzodioxane-2-carboxamide.

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添付公開書類 国際調査報告書

662939

(54) Title : NITROXYALKYLAMIDE DERIVATIVE

(54) 発明の名称 ニトロキシアルキルアミド誘導体

(57) Abstract

Constitution: a nitroxyalkylamide derivative represented by the general formula (I): R^1-(A)n-COHN-B-ONO_2, wherein R^1 represents optionally substituted heterocyclic, heterocyclic oxy, aryloxy or arylthio; A represents C_1-C_4 alkylene; B represents C_1-C_4 alkylene; and n represents 0 or 1. Effect: this compound is excellent in collateral vasodilatory and antianginal activities and hence is useful as a remedy for angina pectoris.

M&C FOLIO: 66518/FP-9220 WANGDOC: 2390H

DESCRIPTION

Nitroxyalkylamide derivatives

[Technical field]

The present invention relates to nitroxyalkylamide derivatives and pharmaceutically acceptable salts thereof having excellent vasodilator activity for the collateral vessels and anti-anginal action.

[Background art]

At present, nitroglycerin is most frequently used clinically as a therapeutic agent for cardiovascular diseases, particularly for angina pectoris.

This agent, however, has some faults such as being susceptible to undergoing the first-pass effect and having a short duration of action. Furthermore, side effects occur, such as headache and dizziness and tachycardia caused by hypotension. Against this background, therapeutic agents for angina pectoris which undergo no first-pass effect and have fewer side effects during clinical treatment have been desired.

Nitroxyalkylamide derivatives having anti-anginal action have been disclosed, for example, in U.S. Patent No. 4200640 and Japan Kokai Hei 2-134316. However, in the latter Kokai, there is no specific description.

[Disclosure of Invention]

The present inventors have eagerly studied for many years the synthesis of nitroxy compounds and the

pharmacological actions thereof.

As a result, they have found that compounds having a nitroxyalkylamide group have excellent vasodilator action on the collateral vessels, have fewer side effects and are useful as therapeutic agents for angina pectoris; they thus completed the present invention.

[Constitution of Invention]

The present invention relates to nitroxyalkylamide derivatives having the general formula:

$$R^1\text{-}(A)_n\text{-}CONH\text{-}B\text{-}ONO_2 \qquad (I)$$

[in this formula, R^1 represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group (the substituents are selected from the group consisting of C_1-C_4 alkyl groups; C_1-C_4 alkoxy groups; phenyl groups optionally substituted with a C_1-C_4 alkyl group, with a C_1-C_4 alkoxy group, or with halogen atom(s); halogen atoms; hydroxy groups; amino groups; mono- or di-C_1-C_4 alkylamino groups; and nitro groups); A represents a C_1-C_4 alkylene group; B represents a C_1-C_4 alkylene group; and n represents 0 or 1;

provided that, when n is 0, R^1 represents a 5- or

6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group]

or pharmaceutically acceptable salts thereof; a preventive and therapeutic agent for angina pectoris comprising the nitroxyalkylamide derivatives or pharmaceutically acceptable salts thereof mentioned above as an active ingredient: and preparation of the nitroxyalkylamide derivatives or pharmaceutically acceptable salts thereof mentioned above.

The 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; or the heterocyclic moiety in a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms, each represented by R^1, may be a saturated or unsaturated heterocyclic group and includes, for example, the tetrahydrofuryl, tetrahydrothienyl, tetrahydropyranyl, pyrrolidyl, piperidyl, imidazolidinyl, imidazolinyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolinyl, furyl, thienyl, pyrrolyl, oxazolyl, oxadiazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl,

imidazolyl, pyrazolyl, triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, benzo-1,4-dioxanyl, indolyl, quinolyl or quinazolinyl group; preferably a 5- or 6-membered heterocyclic group containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; more preferably 1,4-dioxanyl, furyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl or benzo-1,4-dioxanyl; still more preferably furyl, thienyl, oxazolyl, isoxazolyl, thiazolyl or benzo-1,4-dioxanyl; and particularly preferably furyl, thienyl, isoxazolyl or benzo-1,4-dioxanyl.

The aryl moiety in an optionally substituted C_6-C_{10} aryloxy group or in an optionally substituted C_6-C_{10} arylthio group, each represented by R^1, may be, for example a phenyl or naphthyl group; preferably a phenyl group.

The alkyl moiety in a C_1-C_4 alkyl group, in a C_1-C_4 alkoxy group or in a C_1-C_4 alkylamino group, each included in R^1, may be, for example a methyl, ethyl, propyl, isopropyl or butyl group; preferably a methyl or ethyl group; and particularly preferably a methyl group.

The halogen atom included in R^1, may be for example a fluorine, chlorine, bromine or iodine atom; preferably a fluorine, chlorine or bromine atom.

The C_1-C_4 alkylene group represented by A or B, may be, for example a methylene, ethylene, propylene, trimethylene or tetramethylene group; preferably a C_1-C_2 alkylene group for A, and a C_2-C_3 alkylene group (particularly C_2) for B.

When compound (I) is basic, it can be converted into

its pharmaceutically acceptable acid addition salts by any conventional means. As examples of such acid addition salts, there may be mentioned salts with a mineral acid such as hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid; salts with a carboxylic acid such as acetic acid, benzoic acid, oxalic acid, maleic acid, fumaric acid, tartaric acid or citric acid; and salts with a sulfonic acid such as methanesulfonic acid, benzenesulfonic acid or p-toluenesulfonic acid.

In addition, when asymmetric carbon atom(s) exist in the molecule of compound (I), the present invention includes its racemic and optical isomers.

Of the compounds having the general formula (I); preferred ones are:

1) Compounds where R^1 is a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted phenoxy group or an optionally substituted phenylthio group (the substituents are selected from the group consisting of C_1-C_4 alkyl groups, C_1-C_2 alkoxy groups, phenyl groups, halogen atoms, di-C_1-C_2 alkylamino groups and nitro groups);

2) Compounds where A is a C_1-C_2 alkylene group; and

3) Compounds where B is a C_2-C_3 alkylene group (particularly a C_2 alkylene group).

More preferable ones are:

4) Compounds where R^1 is an optionally substituted furyl, furyloxy, thienyl, thienyloxy, isoxazolyl, isoxazolyloxy, phenoxy, phenylthio or 1,4-dibenzodioxanyl group (the substituents are selected from the group consisting of C_1-C_2 alkyl groups, phenyl, fluorine, chlorine, bromine, dimethylamino and nitro groups);

5) Compounds where A is a methylene or methylmethylene group; and

6) Compounds where B is an ethylene group.

Particularly preferred ones are:

7) Compounds where R^1 is a phenoxy group and n is 0; or R^1 is a phenoxy group, a chlorophenoxy group, an optionally substituted isoxazol-3-yloxy group (the substituents are selected from the group consisting of methyl, phenyl, chlorine and bromine) or a 1,4-benzodioxanyl group, n is 1 and A is a methylene or methylmethylene group.

Preferable compounds represented by the general formula (I) can be exemplified specifically in Table 1.

Table 1

$R^1-(A)_n-CONH-B-ONO_2$ (I)

Cpd. No.	R^1	A	n	B
1	PhO-	-	0	$(CH_2)_2$
2	2-Me-PhO-	-	0	$(CH_2)_2$
3	3-Me-PhO-	-	0	$(CH_2)_2$
4	4-Me-PhO-	-	0	$(CH_2)_2$
5	4-MeO-PhO-	-	0	$(CH_2)_2$
6	2-Cl-PhO-	-	0	$(CH_2)_2$
7	3-Cl-PhO-	-	0	$(CH_2)_2$
8	4-Cl-PhO-	-	0	$(CH_2)_2$
9	PhO-	CH_2	1	$(CH_2)_2$
10	2-Me-PhO-	CH_2	1	$(CH_2)_2$
11	3-Me-PhO-	CH_2	1	$(CH_2)_2$
12	4-Me-PhO-	CH_2	1	$(CH_2)_2$
13	4-MeO-PhO-	CH_2	1	$(CH_2)_2$
14	2-Cl-PhO-	CH_2	1	$(CH_2)_2$
15	3-Cl-PhO-	CH_2	1	$(CH_2)_2$
16	4-Cl-PhO-	CH_2	1	$(CH_2)_2$
17	$2-NO_2$-PhO-	CH_2	1	$(CH_2)_2$
18	$2-NO_2$-PhO-	CH(Me)	1	$(CH_2)_2$
19	PhO-	CH(Me)	1	$(CH_2)_2$
20	PhO-	CH(Me)	1	$(CH_2)_3$
21	PhO-	CH(Et)	1	$(CH_2)_2$
22	PhO-	CH(Pr)	1	$(CH_2)_2$
23	2-Fur	-	0	$(CH_2)_2$
24	5-Br-2-Fur	-	0	$(CH_2)_2$
25	$5-NO_2$-2-Fur	-	0	$(CH_2)_2$
26	2-Thi	-	0	$(CH_2)_2$

27	3-Me-2-Thi	-	0	$(CH_2)_2$
28	5-Me-4-Cl-3-Isox-O-	CH_2	1	$(CH_2)_2$
29	5-Ph-3-Isox-O-	CH_2	1	$(CH_2)_2$
30	5-Me-3-Isox-O-	CH_2	1	$(CH_2)_2$
31	5-Me-4-Br-3-Isox-O-	CH_2	1	$(CH_2)_2$
32	3-Isox-O-	CH_2	1	$(CH_2)_2$
33	5-Ph-4-Br-3-Isox-O-	CH_2	1	$(CH_2)_2$
34	4-Br-3-Isox-O-	CH_2	1	$(CH_2)_2$
35	4-Cl-3-Isox-O-	CH_2	1	$(CH_2)_2$
36	PhS-	CH_2	1	$(CH_2)_2$
37	4-Cl-PhS-	CH_2	1	$(CH_2)_2$
38	3-(Me_2N)-PhO-	CH_2	1	$(CH_2)_2$
39	5-Ph-4-Cl-3-Isox-O-	CH_2	1	$(CH_2)_2$
40	3-Fur	-	0	$(CH_2)_2$
41	3-Thi	-	0	$(CH_2)_2$
42	1,4-Bezdiox-2-	-	0	$(CH_2)_2$
43	2-Cl-PhO-	CH(Me)	1	$(CH_2)_2$
44	3-Cl-PhO-	CH(Me)	1	$(CH_2)_2$
45	4-Cl-PhO-	CH(Me)	1	$(CH_2)_2$
46	PhO-	CH(iPr)	1	$(CH_2)_2$
47	4-Cl-PhO-	$C(Me)_2$	1	$(CH_2)_2$
48	2-MeO-PhO-	CH_2	1	$(CH_2)_2$
49	3-(Me_2N)-PhO-	CH_2	1	$(CH_2)_2$
50	4-F-PhO-	CH_2	1	$(CH_2)_2$
51	4-F-PhO-	CH(Me)	1	$(CH_2)_2$
52	3-Br-PhO-	CH_2	1	$(CH_2)_2$
53	4-Br-PhO-	CH_2	1	$(CH_2)_2$
54	4-Br-PhO-	CH(Me)	1	$(CH_2)_2$
55	4-(Me_2N)-PhO-	CH_2	1	$(CH_2)_2$
56	4-(Me_2N)-PhO-	CH(Me)	1	$(CH_2)_2$
57	5-Ph-2-Fur	-	0	$(CH_2)_2$
58	5-Me-2-Fur-	-	0	$(CH_2)_2$
59	5-Cl-2-Fur-	-	0	$(CH_2)_2$
60	5-Ph-2-Thi-	-	0	$(CH_2)_2$
61	5-Br-2-Thi-	-	0	$(CH_2)_2$

62	5-Cl-2-Thi-	-	0	$(CH_2)_2$
63	5-Me-4-F-3-Isox-O-	CH_2	1	$(CH_2)_2$
64	5-Me-4-Br-3-Isox-O-	CH_2	1	$(CH_2)_2$
65	5-Me-4-F-3-Isox-O-	CH(Me)	1	$(CH_2)_2$
66	5-Me-4-Br-Isox-O-	CH(Me)	1	$(CH_2)_2$
67	5-Me-4-Cl-3-Isox-O-	CH(Me)	1	$(CH_2)_2$
68	5-Ph-4-F-3-Isox-O-	CH_2	1	$(CH_2)_2$
69	5-Ph-4-Cl-3-Isox-O-	CH_2	1	$(CH_2)_3$
70	5-Ph-4-F-3-Isox-O-	CH(Me)	1	$(CH_2)_2$
71	5-Ph-4-Br-3-Isox-O-	CH(Me)	1	$(CH_2)_2$
72	5-Ph-4-Cl-3-Isox-O-	CH(Me)	1	$(CH_2)_2$

In Table 1 above, abbreviations of groups are:

Bezdiox: Benzodioxanyl
Et: Ethyl
Fur: Furyl
Isox: Isoxazolyl
Me: Methyl
Ph: Phenyl
Pr: Propyl
Thi: Thienyl.

In Table 1 above, there may be mentioned as preferred compounds: Nos. 1, 2, 3, 4, 6, 8, 9, 11, 14, 15, 16, 19, 21, 23, 26, 28, 29, 30, 31, 32, 33, 34, 35, 36, 38, 39, 42, 43, 44, 45, 47, 63, 65, 66, 67 and 72; and as more preferred compounds, there may be mentioned:

Compound No. 1: Phenyl N-(2-nitroxyethyl)carbamate

Compound No. 9: N-(2-Nitroxyethyl)phenoxyacetamide

Compound No. 14: N-(2-Nitroxyethyl)-2-chlorophenoxy-acetamide

Compound No. 19: N-(2-Nitroxyethyl)-2-phenoxypropanamide

Compound No. 28: N-(2-Nitroxyethyl)-5-methyl-4-chloro-3-isoxazolyloxyacetamide

Compound No. 29: N-(2-Nitroxyethyl)-5-phenyl-3-isoxazolyloxyacetamide

Compound No. 30: N-(2-Nitroxyethyl)-5-methyl-3-isoxazolyloxyacetamide

Compound No. 31: N-(2-Nitroxyethyl)-5-methyl-4-bromo-3-isoxazolyloxyacetamide

Compound No. 32: N-(2-Nitroxyethyl)-3-isoxazolyloxy-acetamide

Compound No. 33: N-(2-Nitroxyethyl)-5-phenyl-4-bromo-3-isoxazolyloxyacetamide

Compound No. 34: N-(2-Nitroxyethyl)-4-bromo-3-isoxazolyl-oxyacetamide

Compound No. 35: N-(2-Nitroxyethyl)-4-chloro-3-isoxazolyloxyacetamide and

Compound No. 42: N-(2-Nitroxyethyl)-1,4-benzodioxane-2-carboxamide.

Compounds having the general formula (I) of the present invention can easily be prepared by the following methods.

Method A

$$\underset{(II)}{R^1a\text{-}(A)_n\text{-}CO_2H} + \underset{(III)}{H_2N\text{-}B\text{-}ONO_2}$$

Step A 1

$$\underset{(I)}{R^1\text{-}(A)_n\text{-}CONH\text{-}B\text{-}ONO_2}$$

In the above formulae, R^1, A, B and n have the same meanings as mentioned already and R^1a represents the same meaning as R^1 except that the amino or monoalkylamino group in R^1 is optionally protected.

The amino- or monoalkylamino-protecting group is not particularly restricted provided that it is one of those commonly employed in the field of organic synthesis. For example, the t-butoxycarbonyl or a haloacetyl (such as chloroacetyl, bromoacetyl or iodoacetyl) groups may be mentioned.

Method A is for preparing Compound (I).

Step A1 is for preparing a compound having the general formula (I), and is carried out by reacting a compound having the general formula (II) or its reactive derivative with a compound having the general formula (III) in an inert solvent and then, if desired, by removing the amino- or monoalkylamino-protecting group. For example, the reaction is conducted by the acid halide method, the mixed acid anhydride method, the active ester method or the condensation method.

The acid halide method is conducted by reacting a compound having the general formula (II) with a

halogenating agent and then reacting the resulting acid halide with a compound having the general formula (III) in an inert solvent and in the presence or absence of a base.

The base which may be employed may be, for example an organic amine such as triethylamine, N-methylmorpholine or 4-dimethylaminopyridine; an alkali metal hydrogencarbonate such as sodium hydrogencarbonate or potassium hydrogencarbonate; or an alkali metal carbonate such as sodium carbonate or potassium carbonate; preferably an organic amine.

The inert solvent which may be employed is not particularly limited provided that it does not participate in the reaction, and it may be, for example a hydrocarbon such as hexane, cyclohexane, benzene, toluene or xylene; a halohydrocarbon such as dichloromethane, 1,2-dichloroethane or carbon tetrachloride; an ether such as diethyl ether, tetrahydrofuran or dioxane; a ketone such as acetone; an amide such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone or hexamethylphosphoramide; or a sulfoxide such as dimethyl sulfoxide; preferably a hydrocarbon, a halohydrocarbon, an ether or an amide.

The reaction temperature varies depending on the starting compounds (II) and (III), and the kind of the solvent employed, but it is usually from -20°C to 150°C for both reactions of the halogenating agent with the Compound (II) and the acid halide with the Compound (III); preferably around room temperature for the reaction of the halogenating agent with the Compound (II) and from 0°C to 100°C for the reaction of the acid halide with the Compound (III). The reaction time varies depending on the reaction temperature etc., but

it is from 30 minutes to 24 hours (preferably from 1 hour to 16 hours).

The mixed acid anhydride method is conducted by reacting a C_1-C_4 alkyl halocarbonate or a di-C_1-C_4 alkyl cyanophosphate with the Compound (II) and then by reacting the resulting acid anhydride with the Compound (III).

The reaction for preparing an acid anhydride is conducted by reacting a C_1-C_4 alkyl halocarbonate, such as ethyl chlorocarbonate or isobutyl chlorocarbonate, or a di-C_1-C_4 alkyl cyanophosphate, such as diethyl cyanophosphate, with the Compound (II). The reaction is preferably conducted in an inert solvent and in the presence of a base.

The base and inert solvent which may be employed are the same as those used in the acid halide method mentioned above.

The reaction temperature varies depending on the starting Compound (II) and the kind of solvent employed, but it is usually from -20°C to 50°C (preferably from 0°C to 30°C). The reaction time varies depending on the reaction temperature etc., but it is from 30 minutes to 24 hours (preferably from 1 hour to 16 hours).

The reaction of the resulting acid anhydride with the Compound (III) is preferably conducted in an inert solvent and in the presence or absence of a base. The base and inert solvent which may be employed are the same as those used in the acid halide method mentioned above.

The reaction temperature varies depending on the starting Compound (III) and the kind of solvent

employed, but it is usually from -20°C to 100°C (preferably from 0°C to near room temperature). The reaction time varies depending on the reaction temperature etc., but it is from 30 minutes to 24 hours (preferably from 1 hour to 16 hours).

On the other hand, by using the acid anhydride of Compound (II), which can be obtained from the Compound (II) and/or from any reactive derivative of the Compound (II), Compound (I) can be prepared using a similar reaction to that mentioned above. Compound (I) can be also prepared by the simultaneous presence of Compound (II) with Compound (III) in the presence of di-(C_1-C_4)alkyl cyanophosphate.

The active ester method is conducted by reacting the Compound (II) directly with the Compound (III) in the presence of a condensation agent [for example, dicyclohexyl carbodiimide, carbonyldiimidazole or 1-(N,N-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride]. This reaction is conducted in a similar manner to that for preparing the active ester mentioned above.

After completion of the reaction, the desired product of the reaction can be recovered from the reaction mixture by conventional means. For example, the crystals which separated are collected by filtration; or, after addition of water, the reaction mixture is extracted with a water-immiscible organic solvent, such as ethyl acetate, and dried, and then the solvent is distilled off to obtain the desired compound. If necessary, it can be further purified by a conventional method, such as recrystallization or column chromatography.

Removal of the amino- or monoalkylamino-protecting

group, which is conducted if desired, is carried out after the reaction above according to any conventional method commonly employed in the field of organic synthesis.

Where the protecting group is t-butoxycarbonyl, it can be removed by reacting a corresponding compound with an acid (for example, a mineral acid such as hydrochloric acid, sulfuric acid or nitric acid; or an organic acid such as acetic acid, trifluoroacetic acid, methanesulfonic acid or p-toluenesulfonic acid) in an inert solvent (for example, an ether such as diethyl ether, tetrahydrofuran or dioxane; a halohydrocarbon, such as dichloromethane or 1,2-dichloroethane; or an aromatic hydrocarbon, such as benzene, toluene or xylene) at from 0°C to 50°C (preferably at around room temperature) for from 30 minutes to 5 hours (preferably from 1 hour to 2 hours). Where the protecting group is a haloacetyl group, it can be removed by reacting a corresponding compound with thiourea in an inert solvent (for example, an amide such as dimethylformamide or dimethylacetamide; or a sulfoxide such as dimethyl sulfoxide) at from 0°C to 50°C (preferably at around room temperature) for from 30 minutes to 5 hours (preferably from 1 hour to 2 hours).

After completion of the reaction, the desired product of each reaction can be recovered from the reaction mixture by conventional means. For example, after neutralization of the reaction mixture, if necessary, the crystals which separated are collected by filtration; or, after addition of water, the reaction mixture is extracted with a water-immiscible organic solvent such as ethyl acetate and dried, and then the solvent is distilled off to obtain the desired compound. If necessary, it can be further purified by a conventional method such as recrystallization or column

chromatography.

The starting compound (II) of Method A is known or is easily prepared by any known method [for example, J. Prakt. Chem., [2] 19, 396 (1879)].

Method B

$$\underset{(II)}{R^1a\text{-}(A)_n\text{-}CO_2H} + \underset{(IV)}{H_2N\text{-}B\text{-}OH} \quad \underline{\text{Step B1}} \rightarrow$$

$$\underset{(V)}{R^1\text{-}(A)_n\text{-}CONH\text{-}B\text{-}OH} \quad \underline{\text{Step B2}} \rightarrow$$

$$\underset{(I)}{R^1\text{-}(A)_n\text{-}CONH\text{-}B\text{-}ONO_2}$$

In the above formulae, R^1, R^1a, A, B and n have the same meanings as mentioned already.

Method B is an alternative method for preparing a Compound (I).

Step B1 is for preparing a compound having the general formula (V), and is carried out by reacting a compound having the general formula (II) or its reactive derivative with a compound having the general formula (IV) in an inert solvent. For example, the reaction is conducted by the acid halide method, the mixed acid anhydride method, the active ester method or the condensation method in a similar manner to that in Step A 1.

Step B 2 is for preparing a compound having the

general formula (I), and is carried out by reacting a compound having the general formula (V) with a nitrating agent in the presence or absence of an inert solvent.

The nitrating agent which may be employed may be, for example fuming nitric acid, nitrocollidinium tetrafluoroboron, thionyl chloride nitrate, thionyl nitrate or nitronium tetrafluoroboron; preferably fuming nitric acid, nitrocollidinium tetrafluoroboron or thionyl chloride nitrate.

The inert solvent which may be employed is not particularly limited provided that it does not participate in the reaction and it may be, for example, a hydrocarbon such as hexane, cyclohexane, benzene, toluene or xylene; a halohydrocarbon such as dichloromethane, 1,2-dichloroethane or carbon tetrachloride; an ether such as diethyl ether, tetrahydrofuran or dioxane; a ketone such as acetone; a polar solvent such as acetonitrile, N,N-dimethyl-formamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, hexamethylphosphoramide or dimethyl sulfoxide; preferably a hydrocarbon, a halohydrocarbon, an ether or a polar solvent.

The reaction temperature varies depending on the starting compound (V) and the kind of nitrating agent employed, but is is usually from -20°C to 50°C, preferably around room temperature. The reaction time varies depending on the reaction temperature etc., but it is from 30 minutes to 24 hours (preferably from 1 hour to 16 hours).

After completion of the reaction, the desired product of the reaction can be obtained from the reaction mixture by conventional means. For example, the crystals which separated are collected by

filtration; or, after addition of water, the reaction mixture is extracted with a water-immiscible organic solvent such as ethyl acetate and dried, and then the solvent is distilled off to obtain the desired compound. If necessary, it can be further purified by a conventional method such as recrystallization or column chromatography.

[Effect of Invention]

Compounds having the general formula (I) of the present invention mentioned above exhibited much stronger vasodilator activity for collateral vessels than nicorandil (U.S. Patent No. 4200640) on tests carried out using the carotid collateral vessel system in an anesthesized dog. Therefore, the compounds are very useful as a preventive and therapeutic agent for angina pectoris.

Test Example 1

(Test method for vasodilator activity for collateral vessels)

Beagle dogs (male) weighing from 9 to 13 kg were anesthesized with 30 mg/kg of pentobarbital intravenously and the experiment was carried out under artificial respiration. To measure the left carotid artery pressure, a polyethylene cannula (atom venous catheter 2F) was inserted in a retrograde manner into one branch of the left thyroidal artery. The left carotid artery, upstream of the pressure measuring site, was occluded with an arterial forceps for one minute to measure the pressure immediately before the occlusion (P) and the pressure reduction in the peripheral vessels (ΔP). Next, a test sample was administered through a polyethylene canula which was inserted into the femoral

vein, and the left carotid artery was occluded again for one minute after 5, 15, 30, 45 and 60 minutes, respectively, to measure the pressure immediately before the occlusion (P') and the pressure reduction in the peripheral vessels (ΔP'). The vasodilator activity for the collateral vessels (Collateral Index = CI) was determined by the following equation. Table 2 shows the result.

$$100 - (\Delta P'/P') \times 100 / (\Delta P/P)$$

Table 2

Compound	CI (60)*) (%), 0.1 mg/kg, iv
Compound of Example 1	31
Compound of Example 20	36
Compound of Example 23	19
Compound of Example 26	21
Compound of Example 32	20
Compound of Example 35	20
Nicorandil **)	7.2***)

*) The mean CI value during 60 minutes
**) The compound of U.S. Patent No. 4200640
***) Intravenous administration at a dose of 0.3 mg/kg

[Possible exploitation in industry]

As mentioned above, the compounds having the formula (I) of the present invention have an excellent vasodilator activity for the collateral vessels and are very useful as preventive and therapeutic agents (in particular as a therapeutic agent) for angina pectoris.

When the Compound (I) is used as a therapeutic agent for angina pectoris, it can be administered orally or parenterally per se or as a pharmaceutical composition in the form of powders, granules, tablets, capsules, injections etc., which may be obtained by mixing the compound with a suitable pharmaceutically acceptable carrier, vehicle, diluent etc. The dosage varies depending on the nature of the disease to be treated and administration method, but it is usually from 1 mg to 1000 mg, preferably from 5 mg to 300 mg, for oral administration; and from 0.1 mg to 100 mg, preferably from 0.5 mg to 50 mg, for intravenous administration; and such a dose of the drug is desirably administered from 1 to 3 times a day depending on the conditions.

[The best mode for carrying out the invention]

The present invention will be described below more specifically by Examples but these examples do not limit the scope of the present invention.

Example 1

Phenyl N-(2-nitroxyethyl)carbamate
(Exemplified compound No. 1)

0.4 ml of triethylamine was added to a suspension of 0.5 g of diphenyl carbonate and 0.4 g of 2-nitroxy-ethylamine nitrate in 10 ml of acetonitrile. The mixture was stirred at room temperature for 2 hours and was then allowed to stand overnight at room temperature. The solvent was distilled off under reduced pressure, water was added to the residue, and it was extracted with ethyl acetate 3 times. The extracts were dried over magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography through silica gel

(eluent; hexane : ethyl acetate = 5:1) to give 0.22 g of the title compound as colorless powdery crystals.

m.p.: 61-62°C

NMR spectrum ($CDCl_3$) δppm:
3.45-3.80 (2H, m), 4.60 (2H, t, J=6 Hz), 5.10-5.70 (1H, br.s), 7.00-7.50 (5H, m)

Example 2

N-(2-Nitroxyethyl)phenoxyacetamide
(Exemplified compound No. 9)

1.5 ml of triethylamine and 0.7 ml of diethyl cyanophosphate were added to a suspension of 0.65 g of phenoxyacetic acid and 0.6 g of 2-nitroxyethylamine nitrate in 20 ml of tetrahydrofuran with ice-cooling. The mixture was stirred at room temperature for 2 hours and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography through silica gel (eluent; hexane : ethyl acetate = 1:1) and then recrystallized from diisopropyl ether to give 0.27 g of the title compound as colorless needles.

m.p.: 61-62°C

NMR spectrum ($CDCl_3$) δppm:
3.58-3.82 (2H, m), 4.45-4.70 (4H, m), 6.80-7.50 (6H, m)

Example 3

N-(2-Nitroxyethyl)-3-methylphenoxyacetamide
(Exemplified compound No. 11)

Following a similar treatment to that in Example 2 and using 0.71 g of 3-methylphenoxyacetic acid and 0.6 g of 2-nitroxyethylamine nitrate, 0.50 g of the title compound was obtained as colorless powdery crystals (solvent for recrystallization; hexane).

m.p.: 40-42°C

NMR spectrum (DMSO-d_6) δppm:
2.29 (3H, s), 3.35-3.65 (2H, m), 4.47 (2H, s), 4.59 (2H, t, J=6 Hz), 6.70-7.30 (4H, m), 8.15-8.50 (1H, br.s)

Example 4

N-(2-Nitroxyethyl)-2-chlorophenoxyacetamide
(Exemplified compound No. 14)

Following a similar treatment to that in Example 2 and using 0.79 g of 2-chlorophenoxyacetic acid and 0.6 g of 2-nitroxyethylamine nitrate, 0.31 g of the title compound was obtained as colorless acicular prisms (solvent for recrystallization; diisopropyl ether).

m.p.: 57-58°C

NMR spectrum (DMSO-d_6) δppm:
3.42-3.65 (2H, m), 4.60 (2H, t, J=6 Hz), 4.63 (2H, s), 6.86-7.55 (4H, m), 8.00-8.40 (1H, br.s)

Example 5

N-(2-Nitroxyethyl)-3-chlorophenoxyacetamide
(Exemplified compound No. 15)

Following a similar treatment to that in Example 2 and using 0.79 g of 3-chlorophenoxyacetic acid and 0.6 g of 2-nitroxyethylamine nitrate, 0.28 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 62-64°C

NMR spectrum (DMSO-d_6) δppm:
3.40-3.65 (2H, m), 4.57 (2H, s), 4.60 (2H, t, J=6 Hz), 6.85-7.48 (4H, m), 8.15-8.55 (1H, br.s)

Example 6

N-(2-Nitroxyethyl)-4-chlorophenoxyacetamide
(Exemplified compound No. 16)

Following a similar treatment to that in Example 2 and using 0.79 g of 4-chlorophenoxyacetic acid and 0.6 g of 2-nitroxyethylamine nitrate, 0.16 g of the title compound was obtained as colorless plates (solvent for recrystallization; diisopropyl ether).

m.p.: 86-88°C

NMR spectrum (DMSO-d_6) δppm:
3.39-3.65 (2H, m), 4.53 (2H, s), 4.60 (2H, t, J=6 Hz), 7.05 (2H, d, J=9 Hz), 7.35 (2H, d, J=9 Hz), 8.15-8.55 (1H, br.s)

Example 7

N-(2-Nitroxyethyl)-2-(2-nitrophenoxy)propanamide (Exemplified compound No. 18)

Following a similar treatment to that in Example 2 and using 0.75 g of 2-(2-nitrophenoxy)propionic acid and 0.6 g of 2-nitroxyethylamine nitrate, 0.45 g of the title compound was obtained as pale yellow needles (solvent for recrystallization; diisopropyl ether).

m.p.: 65-67°C

NMR spectrum ($CDCl_3$) δppm:
1.67 (3H, d, J=6 Hz), 3.55-3.85 (2H, m), 4.57 (2H, t, J=6 Hz), 4.97 (1H, q, J=6 Hz), 7.00-8.10 (5H, m)

Example 8

N-(2-Nitroxyethyl)-2-(2-chlorophenoxy)propanamide (Exemplified compound No. 43)

Following a similar treatment to that in Example 2 and using 0.71 g of 2-(2-chlorophenoxy)propionic acid and 0.6 g of 2-nitroxyethylamine nitrate, 0.43 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 56-58°C

NMR spectrum ($CDCl_3$) δppm:
1.63 (3H, d, J=6 Hz), 3.53-3.80 (2H, m), 4.57 (2H, t, J=6 Hz), 4.75 (1H, q, J=6 Hz), 6.85-7.52 (5H, m)

Example 9

N-(2-Nitroxyethyl)-2-(3-chlorophenoxy)propanamide (Exemplified compound No. 44)

Following a similar treatment to that in Example 2 and using 0.71 g of 2-(3-chlorophenoxy)propionic acid and 0.6 g of 2-nitroxyethylamine nitrate, 0.58 g of the title compound was obtained as colorless acicular prisms (solvent for recrystallization; diisopropyl ether).

m.p.: 67-69°C

NMR spectrum ($CDCl_3$) δppm:
1.57 (3H, d, J=6 Hz), 3.50-3.78 (2H, m), 4.53 (2H, t, J=6 Hz), 4.70 (1H, q, J=6 Hz), 6.70-7.40 (5H, m)

Example 10

N-(2-Nitroxyethyl)-2-(4-chlorophenoxy)propanamide (Exemplified compound No. 45)

Following a similar treatment to that in Example 2 and using 0.71 g of 2-(4-chlorophenoxy)propionic acid and 0.60 g of 2-nitroxyethylamine nitrate, 0.51 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 69-71°C

NMR spectrum ($CDCl_3$) δppm:
1.57 (3H, d, J=6 Hz), 3.50-3.80 (2H, m), 4.40-4.85 (3H, m), 6.70-7.45 (5H, m)

Example 11

N-(2-Nitroxyethyl)-2-phenoxy-3-methylbutanamide (Exemplified compound No. 46)

Following a similar treatment to that in Example 2 and using 0.47 g of 2-phenoxy-3-methylbutyric acid and 0.40 g of 2-nitroxyethylamine nitrate, 0.46 g of the title compound was obtained as colorless powdery crystals (solvent for recrystallization; diisopropyl ether).

m.p.: 76-77°C

NMR spectrum ($CDCl_3$) δppm:
1.08 (3H, d, J=6 Hz), 2.03-2.55 (1H, m), 3.47-3.73 (2H, m), 4.30-4.58 (3H, m), 6.60 (1H, br.s), 6.80-7.48 (5H, m)

Example 12

N-(2-Nitroxyethyl)-2-phenoxypentanamide (Exemplified compound No. 22)

Following a similar treatment to that in Example 2 and using 0.69 g of 2-phenoxyvaleric acid and 0.60 g of 2-nitroxyethylamine nitrate, 0.55 g of the title compound was obtained as colorless acicular prisms (solvent for recrystallization; diisopropyl ether).

m.p.: 68-70°C

NMR spectrum ($CDCl_3$) δppm:
0.80-2.10 (7H, m), 3.45-3.73 (2H, m), 4.30-4.70 (3H, m), 6.50-7.45 (6H, m)

Example 13

N-(2-Nitroxyethyl)-2-phenoxybutanamide
(Exemplified compound No. 21)

Following a similar treatment to that in Example 2 and using 0.64 g of 2-phenoxybutyric acid and 0.60 g of 2-nitroxyethylamine nitrate, 0.55 g of the title compound was obtained as colorless acicular prisms (solvent for recrystallization; diisopropyl ether).

m.p.: 59-61°C

NMR spectrum ($CDCl_3$) δppm:
2.03 (3H, t, J=6 Hz), 1.78-2.20 (2H, m), 3.50-3.78 (2H, m), 4.35-4.70 (3H, m), 6.60-7.48 (6H, m)

Example 14

N-(2-Nitroxyethyl)-2-phenoxypropanamide
(Exemplified compound No. 19)

Following a similar treatment to that in Example 2 and using 0.71 g of 2-phenoxypropionic acid and 0.60 g of 2-nitroxyethylamine nitrate, 0.49 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 74-75°C

NMR spectrum ($CDCl_3$) δppm:
1.45 (3H, d, J=6 Hz), 3.25-3.63 (2H, m), 4.54 (2H, t, J=6 Hz), 4.70 (1H, q, J=6 Hz), 6.80-7.50 (5H, m), 8.08-8.55 (1H, br.s)

Example 15

N-(2-Nitroxyethyl)phenylthioacetamide
(Exemplified compound No. 36)

Following a similar treatment to that in Example 2 and using 0.72 g of phenylthioacetic acid and 0.60 g of 2-nitroxyethylamine nitrate, 0.57 g of the title compound was obtained as colorless powdery crystals (solvent for recrystallization; diisopropyl ether).

m.p.: 63-65°C

NMR spectrum ($DMSO-d_6$) δppm:
3.30-3.52 (2H, m), 3.66 (2H, s), 4.50 (2H, t, J=6 Hz), 7.10-7.48 (5H, m), 8.20-8.55 (1H, br.s)

Example 16

N-(2-Nitroxyethyl)-2-methyl-2-(4-chlorophenoxy)propanamide
(Exemplified compound No. 47)

Following a similar treatment to that in Example 2 and using 0.91 g of 2-methyl-2-(4-chlorophenoxy)-propionic acid and 0.60 g of nitroxyethylamine nitrate, 0.21 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 81-82°C

NMR spectrum ($CDCl_3$) δppm:
1.50 (6H, s), 3.52-3.80 (2H, m), 4.57 (2H, t, J=6 Hz), 6.80-7.32 (5H, m)

Example 17

N-(2-Nitroxyethyl)-2-methoxyphenoxyacetamide (Exemplified compound No. 48)

Following a similar treatment to that in Example 2 and using 0.77 g of 2-methoxyphenoxyacetic acid and 0.60 g of nitroxyethylamine nitrate, 0.27 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 63-64°C

NMR spectrum ($CDCl_3$) δppm:
3.55-3.80 (2H, m), 3.90 (3H, s), 4.48-4.68 (4H, m), 6.80-7.15 (4H, m), 7.25-7.75 (1H, br.s)

Example 18

N-(2-Nitroxyethyl)-3-dimethylaminophenoxyacetamide (Exemplified compound No. 38)

Following a similar treatment to that in Example 2 and using 0.83 g of 3-dimethylaminophenoxyacetic acid and 0.60 g of nitroxyethylamine nitrate, 0.50 g of the title compound was obtained as pale yellow acicular prisms (solvent for recrystallization; diisopropyl ether).

m.p.: 62-63°C

NMR spectrum (DMSO-d_6) δppm:
2.90 (6H, s), 3.40-3.70 (2H, m), 4.26 (2H, s), 4.60 (2H, t, J=6 Hz), 6.20-6.50 (3H, m), 6.95-7.25 (1H, m), 8.15-8.50 (1H, br.s)

Example 19

N-(2-Nitroxyethyl)-5-methyl-3-isoxazolyloxyacetamide (Exemplified compound No. 30)

Following a similar treatment to that in Example 2 and using 0.40 g of 5-methyl-3-isoxazolyloxyacetic acid and 0.43 g of nitroxyethylamine nitrate, 0.23 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 93-94°C

NMR spectrum ($CDCl_3$) δppm:
2.37 (3H, s), 3.57-3.85 (2H, m), 4.60 (2H, t, J=6 Hz), 4.73 (2H, s), 5.73 (1H, s), 6.50-7.00 (1H, br.s)

Example 20

N-(2-Nitroxyethyl)-5-methyl-4-chloro-3-isoxazolyloxyacetamide (Exemplified compound No. 28)

Following a similar treatment to that in Example 2 and using 0.68 g of 5-methyl-4-chloro-3-isoxazolyloxyacetic acid and 0.60 g of nitroxyethylamine nitrate, 0.63 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 88-89°C

NMR spectrum ($CDCl_3$) δppm:
2.37 (3H, s), 3.60-3.85 (2H, m), 4.60 (2H, t, J=6 Hz), 4.80 (2H, s), 6.40-6.90 (1H, br.s)

Example 21

N-(2-Nitroxyethyl)-5-phenyl-3-isoxazolyloxyacetamide (Exemplified compound No. 29)

Following a similar treatment to that in Example 2 and using 0.78 g of 5-phenyl-3-isoxazolyloxyacetic acid and 0.60 g of nitroxyethylamine nitrate, 0.58 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 113-114°C

NMR spectrum ($CDCl_3$) δppm:
3.60-3.85 (2H, m), 4.60 (2H, t, J=6 Hz), 4.83 (2H, s), 6.25 (1H, s), 6.55-7.00 (1H, br.s), 7.35-7.85 (1H, m)

Example 22

N-(2-Nitroxyethyl)-4-chloro-3-isoxazolyloxyacetamide (Exemplified compound No. 35)

Following a similar treatment to that in Example 2 and using 0.43 g of 4-chloro-3-isoxazolyloxyacetic acid and 0.41 g of nitroxyethylamine nitrate, 0.21 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 88-89°C

NMR spectrum ($CDCl_3$) δppm:
3.55-3.83 (2H, m), 4.58 (2H, t, J=6 Hz), 4.80 (2H, s), 6.50-7.00 (1H, br.s), 8.23 (1H, s)

Example 23

N-(2-Nitroxyethyl)-4-bromo-3-isoxazolyloxyacetamide (Exemplified compound No. 34)

Following a similar treatment to that in Example 2 and using 0.78 g of 4-bromo-3-isoxazolyloxyacetic acid and 0.60 g of nitroxyethylamine nitrate, 0.44 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 98-99°C

NMR spectrum ($CDCl_3$) δppm:
3.60-3.88 (2H, m), 4.61 (2H, t, J=6 Hz), 4.83 (2H, s), 6.50-7.00 (1H, br.s), 8.26 (1H, s)

Example 24

N-(2-Nitroxyethyl)-5-phenyl-4-chloro-3-isoxazolyloxyacetamide (Exemplified compound No. 39)

Following a similar treatment to that in Example 2 and using 0.70 g of 5-phenyl-4-chloro-3-isoxazolyloxyacetic acid and 0.46 g of nitroxyethylamine nitrate, 0.42 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 138-139°C

NMR spectrum ($CDCl_3$) δppm:
3.60-3.90 (2H, m), 4.62 (2H, t, J=6 Hz), 4.87 (2H, s), 6.60-7.00 (1H, br.s), 7.40-8.10 (5H, m)

Example 25

N-(2-Nitroxyethyl)-5-methyl-4-bromo-3-isoxazolyloxy-acetamide (Exemplified compound No. 31)

Following a similar treatment to that in Example 2 and using 472 mg of 5-methyl-4-bromo-3-isoxazolyloxy-acetic acid and 338 mg of nitroxyethylamine nitrate, 265 mg of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 87-88°C

NMR spectrum ($CDCl_3$) δppm:
2.38 (3H, s), 3.73 (2H, dd, J=6, 11 Hz), 4.61 (2H, t, J=6 Hz), 4.79 (2H, s), 6.68 (1H, br.s)

Example 26

N-(2-Nitroxyethyl)-3-isoxazolyloxyacetamide (Exemplified compound No. 32)

Following a similar treatment to that in Example 2 and using 286 mg of 3-isoxazolyloxyacetic acid and 338 mg of nitroxyethylamine nitrate, 250 mg of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 67-69°C

NMR spectrum ($CDCl_3$) δppm:
3.72 (2H, dd, J=6, 11 Hz), 4.60 (2H, t, J=6 Hz), 4.79 (2H, s), 6.08 (1H, d, J=2 Hz), 6.71 (1H, br.s), 8.20 (1H, d, J=2 Hz)

Example 27

N-(2-Nitroxyethyl)-3-furancarboxamide
(Exemplified compound No. 40)

Following a similar treatment to that in Example 2 and using 0.48 g of 3-furancarboxylic acid and 0.60 g of nitroxyethylamine nitrate, 0.50 g of the title compound was obtained as colorless plates (solvent for recrystallization; diisopropyl ether).

m.p.: 80-82°C

NMR spectrum ($CDCl_3$) δppm:
3.73 (2H, dd, J=6, 11 Hz), 4.63 (2H, t, J=6 Hz), 6.52 (1H, br.s), 6.69 (1H, s), 7.46 (1H, s), 8.00 (1H, s)

Example 28

N-(2-Nitroxyethyl)-3-thiophenecarboxamide
(Exemplified compound No. 41)

Following a similar treatment to that in Example 2 and using 0.55 g of 3-thiophenecarboxylic acid and 0.60 g of nitroxyethylamine nitrate, 0.27 g of the title compound was obtained as colorless plates (solvent for recrystallization; diisopropyl ether).

m.p.: 100-102°C

NMR spectrum (DMSO-d_6) δppm:
3.60 (2H, dd, J=6, 11 Hz), 4.67 (2H, t, J=6 Hz), 7.40-7.68 (2H, m), 8.16 (1H, m), 8.40-8.65 (1H, br.s)

Example 29

N-(2-Nitroxyethyl)-5-bromo-2-furancarboxamide (Exemplified compound No. 24)

Following a similar treatment to that in Example 2 and using 0.68 g of 5-bromo-2-furancarboxylic acid and 0.60 g of nitroxyethylamine nitrate, 0.22 g of the title compound was obtained as pale yellow acicular prisms (solvent for recrystallization; diisopropyl ether).

m.p.: 61-63°C

NMR spectrum ($CDCl_3$) δppm:
3.77 (2H, dd, J=6, 11 Hz), 4.63 (2H, t, J=6 Hz), 6.46 (1H, d, J=4 Hz), 6.63 (1H, br.s), 7.10 (1H, d, J=4 Hz)

Example 30

N-(2-Nitroxyethyl)-5-nitro-2-furancarboxamide (Exemplified compound No. 25)

Following a similar treatment to that in Example 2 and using 0.56 g of 5-nitro-2-furancarboxylic acid and 0.60 g of nitroxyethylamine nitrate, 0.25 g of the title compound was obtained as yellow plates (solvent for recrystallization; diisopropyl ether).

m.p.: 102-104°C

NMR spectrum ($CDCl_3$) δppm:
3.83 (2H, dd, J=6, 11 Hz), 4.67 (2H, t, J=6 Hz), 7.00 (1H, br.s), 7.20-7.48 (2H, m)

Example 31

N-(2-Nitroxyethyl)-3-methyl-2-thiophenecarboxamide (Exemplified compound No. 27)

Following a similar treatment to that in Example 2 and using 0.60 g of 3-methyl-2-thiophenecarboxylic acid and 0.60 g of nitroxyethylamine nitrate, 0.35 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 74-76°C

NMR spectrum (DMSO-d_6) δppm:
2.42 (3H, s), 3.63 (2H, dd, J=6, 11 Hz), 4.67 (2H, t, J=6 Hz), 6.97 (1H, d, J=5 Hz), 7.59 (1H, d, J=5 Hz), 8.13 (1H, br.s)

Example 32

N-(2-Nitroxyethyl)-1,4-benzodioxane-2-carboxamide (Exemplified compound No. 42)

Following a similar treatment to that in Example 2 and using 0.91 g of 1,4-benzodioxane-2-carboxylic acid and 0.85 g of nitroxyethylamine nitrate, 0.45 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 69-71°C

NMR spectrum ($CDCl_3$) δppm:
3.55-3.83 (2H, m), 4.07-4.35 (1H, m), 4.45-4.86 (4H, m), 6.60-7.25 (5H, br.s)

Example 33

N-(2-Nitroxyethyl)-2-furancarboxamide
(Exemplified compound No. 23)

Following a similar treatment to that in Example 2, using 0.34 g of 2-furancarboxylic acid and 0.50 g of nitroxyethylamine nitrate and using diphenylphosphoryl azide instead of ethyl cyanophosphate, 0.35 g of the title compound was obtained as colorless needles (solvent for recrystallization; diisopropyl ether).

m.p.: 88-89°C

NMR spectrum (DMSO-d_6) δppm:
3.57 (2H, dd, J=6, 11 Hz), 4.63 (2H, t, J=6 Hz), 6.67 (1H, m), 7.13 (1H, d, J=4 Hz), 7.87 (1H, s), 8.60 (1H, br.s)

Example 34

N-(2-Nitroxyethyl)-2-thiophenecarboxamide
(Exemplified compound No. 26)

Following a similar treatment to that in Example 33 and using 0.38 g of 2-thiophenecarboxylic acid and 0.50 g of nitroxyethylamine nitrate, 0.27 g of the title compound was obtained as colorless plates (solvent for recrystallization; diisopropyl ether).

m.p.: 102-103°C

NMR spectrum (DMSO-d_6) δppm:
3.60 (2H, dd, J=6, 11 Hz), 4.66 (2H, t, J=6 Hz), 7.10-7.30 (1H, m), 7.70-7.88 (1H, m), 8.70 (1H, br.s)

Example 35

N-(2-Nitroxyethyl)-5-phenyl-4-bromo-3-isoxazolyloxy-acetamide (Exemplified compound No. 33)

Following a similar treatment to that in Example 2 and using 0.53 g of 5-phenyl-4-bromo-3-isoxazolyloxy-acetic acid and 0.30 g of nitroxyethylamine nitrate, 0.44 g of the title compound was obtained as colorless needles (solvent for recrystallization; ethanol).

m.p.: 145-146°C

NMR spectrum (DMSO-d_6) δppm:
3.30-3.65 (2H, m), 4.60 (2H, t, J=6 Hz), 4.82 (2H, s), 7.50-7.73 (3H, m), 7.85-8.13 (2H, m), 8.20-8.70 (1H, br.s)

CLAIMS

1. Nitroxyalkylamide derivatives having the general formula:

$$R^1-(A)_n-CONH-B-ONO_2 \qquad (I)$$

[in this formula, R^1 represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a phenyl group optionally substituted with a C_1-C_4 alkyl group, with a C_1-C_4 alkoxy group or with a halogen atom; a halogen atom; a hydroxy group; an amino group; a mono- or di-C_1-C_4 alkylamino group; and a nitro group); A represents a C_1-C_4 alkylene group; B represents a C_1-C_4 alkylene group; and n represents 0 or 1; provided that, when n is 0, R^1 represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or

an optionally substituted C_6-C_{10} arylthio group; and further provided that when R^1 represents a 3-oxazole group, then it is not substituted by a halomethylene group, a mesyloxymethylene group or a tosyloxymethylene group], or pharmaceutically acceptable salts thereof.

2. Compounds according to Claim 1 in which R^1 is a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted phenoxy group or an optionally substituted phenylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_2 alkoxy group, a phenyl group; a halogen atom; a di-C_1-C_2 alkylamino group; and a nitro group).

3. Compounds according to Claim 1 in which A is a C_1-C_2 alkylene group.

4. Compounds according to Claim 1 in which B is a C_2-C_3 alkylene group.

5. Compounds according to Claim 1 in which R^1 is a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted phenoxy group or an optionally substituted

phenylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_2 alkoxy group, a phenyl group; a halogen atom; a di-C_1-C_2 alkylamino group; and a nitro group); A is a C_1-C_2 alkylene group; and B is a C_2-C_3 alkylene group.

6. Compounds according to Claim 1 in which R^1 is an optionally substituted furyl, furyloxy, thienyl, thienyloxy, isoxazolyl, isoxazolyloxy, phenoxy, phenylthio or 1,4-dibenzodioxanyl group (the substituents are selected from the group consisting of a C_1-C_2 alkyl group, phenyl, fluorine, chlorine, bromine, dimethylamino and nitro groups).

7. Compounds according to Claim 1 in which A is a methylene or methylmethylene group.

8. Compounds according to Claim 1 in which B is an ethylene group.

9. Compounds according to Claim 1 in which R^1 is an optionally substituted furyl, furyloxy, thienyl, thienyloxy, isoxazolyl, isoxazolyloxy, phenoxy, phenylthio or 1,4-dibenzodioxanyl group (the substituents are selected from the group consisting of a C_1-C_2 alkyl group, phenyl, fluorine, chlorine, bromine, dimethylamino and nitro groups); A is a methylene or methylmethylene group; and B is an ethylene group.

10. Compounds according to Claim 1 in which R^1 is a phenoxy group and n is 0; or R^1 is a phenoxy group, a chlorophenoxy group, an optionally substituted isoxazol-3-yloxy group (the substituents are selected from the group consisting of methyl, phenyl, chlorine and bromine) or a 1,4-benzodioxanyl group, n is 1 and A

is a methylene or methylmethylene group.

11. Compounds according to Claim 1 in which R^1 is a phenoxy group and n is 0; or R^1 is a phenoxy group, a chlorophenoxy group, an optionally substituted isoxazol-3-yloxy group (the substituents are selected from the group consisting of methyl, phenyl, chlorine and bromine) or a 1,4-benzodioxanyl group, n is 1, A is a methylene or methylmethylene group and B is an ethylene group.

12. Phenyl N-(2-nitroxyethyl)carbamate.

13. N-(2-Nitroxyethyl)phenoxyacetamide.

14. N-(2-Nitroxyethyl)-2-chlorophenoxyacetamide.

15. N-(2-Nitroxyethyl)-2-phenoxypropanamide.

16. N-(2-Nitroxyethyl)-5-methyl-4-chloro-3-isoxazolyloxyacetamide.

17. N-(2-Nitroxyethyl-5-phenyl-3-isoxazolyloxy-acetamide.

18. N-(2-Nitroxyethyl)-5-methyl-3-isoxazolyloxy-acetamide.

19. N-(2-Nitroxyethyl)-5-methyl-4-bromo-3-isoxazolyloxyacetamide.

20. N-(2-Nitroxyethyl)-3-isoxazolyloxyacetamide.

21. N-(2-Nitroxyethyl)-5-phenyl-4-bromo-3-isoxazolyloxyacetamide.

22. N-(2-Nitroxyethyl)-4-bromo-3-isoxazolyloxy-acetamide.

23. N-(2-Nitroxyethyl)-4-chloro-3-isoxazolyloxy-acetamide.

24. N-(2-Nitroxyethyl)-1,4-benzodioxane-2-carboxamide.

25. A preventive and therapeutic agent for angina pectoris comprising a nitroxyalkylamide derivative having the general formula:

$$R^1-(A)_n-CONH-B-ONO_2 \qquad (I)$$

[in this formula, R^1 represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a phenyl group optionally substituted with a C_1-C_4 alkyl group, with a C_1-C_4 alkoxy group or with halogen atom; a halogen atom; a hydroxy group; an amino group; a mono- or di-C_1-C_4 alkylamino group; and a nitro group); A represents a C_1-C_4 alkylene group; B represents a C_1-C_4 alkylene group; and n represents 0 or 1; provided that, when n is 0, R^1 represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally

condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group] or a pharmaceutically acceptable salt thereof, as the active ingredient.

26. A preventive and therapeutic agent for angina pectoris according to Claim 25 in which R^1 is a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted phenoxy group or an optionally substituted phenylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_2 alkoxy group, a phenyl group; a halogen atom; a di-C_1-C_2 alkylamino group; and a nitro group).

27. A preventive and therapeutic agent for angina pectoris according to Claim 25 in which A is a C_1-C_2 alkylene group.

28. A preventive and therapeutic agent for angina pectoris according to Claim 25 in which B is a C_2-C_3 alkylene group.

29. A preventive and therapeutic agent for angina pectoris according to Claim 25 in which R^1 is a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted phenoxy group or an optionally substituted phenylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_2 alkoxy group, a phenyl group; a halogen atoms; a di-C_1-C_2 alkylamino group; and a nitro group); A is a C_1-C_2 alkylene group; and B is a C_2-C_3 alkylene group.

30. A preventive and therapeutic agent for angina pectoris according to Claim 25 in which R^1 is an optionally substituted furyl, furyloxy, thienyl, thienyloxy, isoxazolyl, isoxazolyloxy, phenoxy, phenylthio or 1,4-dibenzodioxanyl group (the substituents are selected from the group consisting of a C_1-C_2 alkyl group, phenyl, fluorine, chlorine, bromine, dimethylamino and nitro groups).

31. A preventive and therapeutic agent for angina pectoris according to Claim 25 in which A is a methylene or methylmethylene group.

32. A preventive and therapeutic agent for angina pectoris according to Claim 25 in which B is an ethylene group.

33. A preventive and therapeutic agent for angina pectoris according to Claim 25 in which R^1 is an

optionally substituted furyl, furyloxy, thienyl, thienyloxy, isoxazolyl, isoxazolyloxy, phenoxy, phenylthio or 1,4-dibenzodioxanyl group (the substituents are selected from the group consisting of a C_1-C_2 alkyl group, phenyl, fluorine, chlorine, bromine, dimethylamino and nitro groups), A is a methylene or methylmethylene group and B is an ethylene group.

34. A preventive and therapeutic agent for angina pectoris according to Claim 25 in which R^1 is a phenoxy group and n is 0; or R^1 is a phenoxy group, a chlorophenoxy group, an optionally substituted isoxazol-3-yloxy group (the substituents are selected from the group consisting of methyl, phenyl, chlorine and bromine) or a 1,4-benzodioxanyl group, n is 1 and A is a methylene or methylmethylene.

35. A preventive and therapeutic agent for angina pectoris according to Claim 25 in which R^1 is a phenoxy group and n is 0; or R^1 is a phenoxy group, a chlorophenoxy group, an optionally substituted isoxazol-3-yloxy group (the substituents are selected from the group consisting of methyl, phenyl, chlorine and bromine) or a 1,4-benzodioxanyl group, n is 1, A is a methylene or methylmethylene group and B is an ethylene group.

36. A preventive and therapeutic agent for angina pectoris according to Claim 25 in which the active ingredient is selected from the group consisting of phenyl N-(2-nitroxyethyl)carbamate, N-(2-nitroxyethyl)phenoxyacetamide, N-(2-nitroxyethyl)-2-chlorophenoxyacetamide, N-(2-nitroxyethyl)-2-phenoxypropanamide, N-(2-nitroxyethyl)-5-methyl-4-chloro-3-isoxazolyloxy-acetamide,

N-(2-nitroxyethyl)-5-phenyl-3-isoxazolyloxyacetamide,
N-(2-nitroxyethyl)-5-methyl-3-isoxazolyloxyacetamide,
N-(2-nitroxyethyl)-5-methyl-4-bromo-3-isoxazolyloxyacetamide,
N-(2-nitroxyethyl)-3-isoxazolyloxyacetamide,
N-(2-nitroxyethyl)-5-phenyl-4-bromo-3-isoxazolyloxyacetamide,
N-(2-nitroxyethyl)-4-bromo-3-isoxazolyloxyacetamide,
N-(2-nitroxyethyl)-4-chloro-3-isoxazolyloxyacetamide and
N-(2-nitroxyethyl)-1,4-benzodioxane-2-carboxamide.

37. A process for preparing a nitroxyalkylamide derivative having the general formula:

$$R^1-(A)_n-CONH-B-ONO_2 \qquad (I)$$

[in this formula, A, B and n have the same meanings as mentioned below and R^1 represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a phenyl group optionally substituted with a C_1-C_4 alkyl group, with a C_1-C_4 alkoxy group or with halogen atom; a halogen atom; a hydroxy group; an amino group; a mono- or di-C_1-C_4 alkylamino group; and a nitro group);

provided that, when n is 0, R^1 represents a 5- or

6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group.]

or pharmaceutically acceptable salts thereof,

by reacting a compound having the general formula:

$$R^1a\text{-}(A)_n\text{-}CO_2H \qquad (II)$$

[in this formula, R^1a represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a phenyl group optionally substituted with a C_1-C_4 alkyl group, with a C_1-C_4 alkoxy group or with halogen atom; a halogen atom; a hydroxy group; an optionally protected amino group; an optionally protected mono-C_1-C_4 alkylamino group; di-C_1-C_4 alkylamino group; and a nitro group); A represents a

C_1-C_4 alkylene group; and n represents 0 or 1;

provided that, when n is 0, R^1 represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group]

or its reactive derivative

with a compound having the general formula:

$$H_2N\text{-}B\text{-}ONO_2 \qquad (III)$$

(in this formula, B represents a C_1-C_4 alkylene group)

and, if desired, removing an amino- or mono-(C_1-C_4) alkylamino-protecting group.

38. A process for preparing a compound according to Claim 37 in which R^1 is a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen

and sulfur atoms; an optionally substituted phenoxy group or an optionally substituted phenylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_2 alkoxy group, a phenyl group; a halogen atom; a di-C_1-C_2 alkylamino group; and a nitro group).

39. A process for preparing a compound according to Claim 37 in which A is a C_1-C_2 alkylene group.

40. A process for preparing a compound according to Claim 37 in which B is a C_2-C_3 alkylene group.

41. A process for preparing a compound according to Claim 37 in which R^1 is a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted phenoxy group or an optionally substituted phenylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_2 alkoxy group, a phenyl group; a halogen atom; a di-C_1-C_2 alkylamino group; and a nitro group); A is a C_1-C_2 alkylene group; and B is a C_2-C_3 alkylene group.

42. A process for preparing a compound according to Claim 37 in which R^1 is an optionally substituted furyl, furyloxy, thienyl, thienyloxy, isoxazolyl, isoxazolyloxy, phenoxy, phenylthio or 1,4-dibenzodioxanyl group (the substituents are selected from the group consisting of a C_1-C_2 alkyl group,

phenyl, fluorine, chlorine, bromine, dimethylamino and nitro groups).

43. A process for preparing a compound according to Claim 37 in which A is a methylene or methylmethylene group.

44. A process for preparing a compound according to Claim 37 in which B is an ethylene group.

45. A process for preparing a compound according to Claim 37 in which R^1 is an optionally substituted furyl, furyloxy, thienyl, thienyloxy, isoxazolyl, isoxazolyloxy, phenoxy, phenylthio or 1,4-dibenzodioxanyl group (the substituents are selected from the group consisting of a C_1-C_2 alkyl group, phenyl, fluorine, chlorine, bromine, dimethylamino and nitro groups); A is a methylene or methylmethylene group; and B is an ethylene group.

46. A process for preparing a compound according to Claim 37 in which R^1 is a phenoxy group and n is 0; or R^1 is a phenoxy group, a chlorophenoxy group, an optionally substituted isoxazol-3-yloxy group (the substituents are selected from the group consisting of methyl, phenyl, chlorine and bromine) or a 1,4-benzodioxanyl group, n is 1 and A is a methylene or methylmethylene.

47. A process for preparing a compound according to Claim 37 in which R^1 is a phenoxy group and n is 0; or R^1 is a phenoxy group, a chlorophenoxy group, an optionally substituted isoxazol-3-yloxy group (the substituents are selected from the group consisting of methyl, phenyl, chlorine and bromine) or a 1,4-benzodioxanyl group, n is 1, A is a methylene or methylmethylene and B is an ethylene group.

48. A process for preparing a compound according to Claim 37 in which the compound (I) is phenyl N-(2-nitroxyethyl)carbamate.

49. A process for preparing a compound according to Claim 37 in which the compound (I) is N-(2-nitroxyethyl)-phenoxyacetamide.

50. A process for preparing a compound according to Claim 37 in which the compound (I) is N-(2-nitroxyethyl)-2-chlorophenoxyacetamide.

51. A process for preparing a compound according to Claim 37 in which the compound (I) is N-(2-nitroxyethyl)-2-phenoxypropanamide.

52. A process for preparing a compound according to Claim 37 in which the compound (I) is N-(2-nitroxyethyl)-5-methyl-4-chloro-3-isoxazolyloxyacetamide.

53. A process for preparing a compound according to Claim 37 in which the compound (I) is N-(2-nitroxyethyl)-5-phenyl-3-isoxazolyloxyacetamide.

54. A process for preparing a compound according to Claim 37 in which the compound (I) is N-(2-nitroxyethyl)-5-methyl-3-isoxazolyloxyacetamide.

55. A process for preparing a compound according to Claim 37 in which the compound (I) is N-(2-nitroxyethyl)-5-methyl-4-bromo-3-isoxazolyloxyacetamide.

56. A process for preparing a compound according to Claim 37 in which the compound (I) is N-(2-nitroxyethyl)-3-isoxazolyloxyacetamide.

57. A process for preparing a compound according to

Claim 37 in which the compound (I) is N-(2-nitroxyethyl)-5-phenyl-4-bromo-3-isoxazolyloxyacetamide.

58. A process for preparing a compound according to Claim 37 in which the compound (I) is N-(2-nitroxyethyl)-4-bromo-3-isoxazolyloxyacetamide.

59. A process for preparing a compound according to Claim 37 in which the compound (I) is N-(2-nitroxyethyl)-4-chloro-3-isoxazolyloxyacetamide.

60. A process for preparing a compound according to Claim 37 in which the compound (I) is N-(2-nitroxyethyl)-1,4-benzodioxane-2-carboxamide.

61. A process for preparing a nitroxyalkylamide derivative having the general formula:

$$R^1\text{-}(A)_n\text{-}CONH\text{-}B\text{-}ONO_2 \qquad (I)$$

(in this formula, R^1, A, B and n have the same meanings as mentioned below)

or pharmaceutically acceptable salts thereof,

by reacting a compound having the general formula:

$$R^1a\text{-}(A)_n\text{-}CO_2H \qquad (II)$$

[in this formula, R^1a represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms

selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a phenyl group optionally substituted with a C_1-C_4 alkyl group, with a C_1-C_4 alkoxy group or with halogen atom; a halogen atom; a hydroxy group; an optionally protected amino group; an optionally protected mono-C_1-C_4 alkylamino group; a di-C_1-C_4 alkylamino group; and a nitro group); A represents a C_1-C_4 alkylene group; and n represents 0 or 1;

provided that, when n is 0, R^1 represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of oxygen and sulfur atoms, a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group] or its reactive derivative

with a compound having the general formula:

$$H_2N\text{-}B\text{-}OH \qquad (IV)$$

(in this formula, B represents a C_1-C_4 alkylene group)

and, if desired, removing an amino- or mono-(C_1-C_4) alkylamino-protecting group, to prepare a compound having the general formula:

$$R^1\text{-}(A)_n\text{-}CONH\text{-}B\text{-}OH \qquad (V)$$

[in this formula, A, B and n have the same meanings as mentioned above and R^1 represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a phenyl group optionally substituted with a C_1-C_4 alkyl group, with a C_1-C_4 alkoxy group or with halogen atom(s); a halogen atom; a hydroxy group, an amino group; a mono- or di-C_1-C_4 alkylamino group; and a nitro group);

provided that, when n is 0, R^1 represents a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted C_6-C_{10} aryloxy group; or an optionally substituted C_6-C_{10} arylthio group.];

and then reacting the resulting compound (V) with a nitrating agent.

62. A process for preparing a compound according to Claim 61 in which R^1 is a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heterocyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted phenoxy group or an optionally substituted phenylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_2 alkoxy group, a phenyl group; a halogen atom; a di-C_1-C_2 alkylamino group; and a nitro group).

63. A process for preparing a compound according to Claim 61 in which A is a C_1-C_2 alkylene group.

64. A process for preparing a compound according to Claim 61 in which B is a C_2-C_3 alkylene group.

65. A process for preparing a compound according to Claim 61 in which R^1 is a 5- or 6-membered heterocyclic group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; a 5- or 6-membered heteroyclic-oxy group (which may be optionally substituted or optionally condensed with a phenyl ring) containing from 1 to 2 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms; an optionally substituted phenoxy group or an optionally substituted phenylthio group (the substituents are selected from the group consisting of a C_1-C_4 alkyl group, a C_1-C_2 alkoxy group, a

phenyl group; a halogen atom; a di-C_1-C_2 alkylamino group; and a nitro group); A is a C_1-C_2 alkylene group; and B is a C_2-C_3 alkylene group.

66. A process for preparing a compound according to Claim 61 in which R^1 is an optionally substituted furyl, furyloxy, thienyl, thienyloxy, isoxazolyl, isoxazolyloxy, phenoxy, phenylthio or 1,4-dibenzodioxanyl group (the substituents are selected from the group consisting of a C_1-C_2 alkyl group, phenyl, fluorine, chlorine, bromine, dimethylamino and nitro groups).

67. A process for preparing a compound according to Claim 61 in which A is a methylene or methylmethylene group.

68. A process for preparing a compound according to Claim 61 in which B is an ethylene group.

69. A process for preparing a compound according to Claim 61 in which R^1 is an optionally substituted furyl, furyloxy, thienyl, thienyloxy, isoxazolyl, isoxazolyloxy, phenoxy, phenylthio or 1,4-dibenzodioxanyl group (the substituents are selected from the group consisting of a C_1-C_2 alkyl group, phenyl, fluorine, chlorine, bromine, dimethylamino and nitro group); A is a methylene or methylmethylene group; and B is an ethylene group.

70. A process for preparing a compound according to Claim 61 in which R^1 is a phenoxy group and n is 0; or R^1 is a phenoxy group, a chlorophenoxy group, an optionally substituted isoxazol-3-yloxy group (the substituents are selected from the group consisting of methyl, phenyl, chlorine and bromine) or a 1,4-benzodioxanyl group, n is 1 and A is a methylene or

methylmethylene.

71. A process for preparing a compound according to Claim 61 in which R^1 is a phenoxy group and n is 0; or R^1 is a phenoxy group, a chlorophenoxy group, or an optionally substituted isoxazol-3-yloxy group (the substituents are selected from the group consisting of methyl, phenyl, chlorine and bromine) or a 1,4-benzodioxanyl group, n is 1, A is a methylene or methylmethylene group and B is an ethylene group.

72. A process for preparing a compound according to Claim 61 in which the compound (I) is phenyl N-(2-nitroxyethyl)carbamate.

73. A process for preparing a compound according to Claim 61 in which the compound (I) is N-(2-nitroxyethyl)-phenoxyacetamide.

74. A process for preparing a compound according to Claim 61 in which the compound (I) is N-(2-nitroxyethyl)-2-chlorophenoxyacetamide.

75. A process for preparing a compound according to Claim 61 in which the compound (I) is N-(2-nitroxyethyl)-2-phenoxypropanamide.

76. A process for preparing a compound according to Claim 61 in which the compound (I) is N-(2-nitroxyethyl)-5-methyl-4-chloro-3-isoxazolyloxyacetamide.

77. A process for preparing a compound according to Claim 61 in which the compound (I) is N-(2-nitroxyethyl)-5-phenyl-3-isoxazolyloxyacetamide.

78. A process for preparing a compound according to Claim 61 in which the compound (I) is N-(2-nitroxyethyl)-

5-methyl-3-isoxazolyloxyacetamide.

79. A process for preparing a compound according to Claim 61 in which the compound (I) is N-(2-nitroxyethyl)-5-methyl-4-bromo-3-isoxazolyloxyacetamide.

80. A process for preparing a compound according to Claim 61 in which the compound (I) is N-(2-nitroxyethyl)-3-isoxazolyloxyacetamide.

81. A process for preparing a compound according to Claim 61 in which the compound (I) is N-(2-nitroxyethyl)-5-phenyl-4-bromo-3-isoxazolyloxyacetamide.

82. A process for preparing a compound according to Claim 61 in which the compound (I) is N-(2-nitroxyethyl)-4-bromo-3-isoxazolyloxyacetamide.

83. A process for preparing a compound according to Claim 61 in which the compound (I) is N-(2-nitroxyethyl)-4-chloro-3-isoxazolyloxyacetamide.

84. A process for preparing a compound according to Claim 61 in which the compound (I) is N-(2-nitroxyethyl)-1,4-benzodioxane-2-carboxamide.

ABSTRACT

[Constitution]

Nitroxyalkylamide derivatives having the general formula:

$$R^1\text{-}(A)_n\text{-}CONH\text{-}B\text{-}ONO_2 \qquad (I)$$

[R^1: an optionally substituted heterocyclic, heterocyclic-oxy, aryloxy or arylthio group;
A: a C_1-C_4 alkylene group;
B: a C_1-C_4 alkylene group;
n: 0 or 1].

[Effect]

The compounds of the present invention have an excellent vasodilator action for collateral vessels and an anti-anginal action, and are useful as therapeutic agents for angina pectoris.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP92/01419

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^5 C07C235/22, A61K31/16
A61K31/34, A61K31/38, A61K31/41, C07D261/08, C07D261/12,
C07D307/54, C07D307/58, C07D333/24, C07D333/32
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^5
C07C235/22, A61K31/16, A61K31/34, A61K31/38, A61K31/41,
C07D261/08,C07D261/12,C07D307/54,C07D307/58,C07D333/24,C07D333/32

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, A, 63-233962 (Beringer Mannheim GmbH.), September 29, 1988 (29. 09. 88), & DE, A, 3705622 & EP, A, 280951	1-84
Y	JP, A, 61-148151 (Beringer Mannheim GmbH.), July 5, 1986 (05. 07. 86), & DE, A, 3443998 & EP, A, 192829 & US, A, 4801596	1-84

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* 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 when the document is taken alone
"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

Date of the actual completion of the international search	Date of mailing of the international search report
January 25, 1993 (25. 01. 93)	February 16, 1993 (16. 02. 93)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

国際調査報告

国際出願番号 PCT/JP 92/01419

A. 発明の属する分野の分類（国際特許分類（IPC））

Int. Cl' C07C235/22, A61K31/16, A61K31/34, A61K31/38, A61K31/41, C07D261/08, C07D261/12,

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int. Cl' C07C235/22, A61K31/16, A61K31/34, A61K31/38 A61K31/41, C07D261/08, C07D261/12,

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAS ONLINE

C. 関連すると認められる文献

引用文献のカテゴリー*	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	関連する請求の範囲の番号
Y	JP, A, 63-233962（ベーリンガー・マンハイム・ゲゼルシヤフト・ミット・ベシユレンクテル・ハフツング）29. 9月. 1988（29. 09. 88）&DE, A, 3705622&EP, A, 280951	1-84
Y	JP, A, 61-148151（ベーリンガー・マンハイム・ゲゼルシヤフト・ミット・ベシユレンクテル・ハフツング）5. 7月. 1986（05. 07. 86）&DE, A, 3443998&EP, A, 192829	1-84

☑ C欄の続きにも文献が列挙されている。 ☐ パテントファミリーに関する別紙を参照。

* 引用文献のカテゴリー
「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、展示等に言及する文献
「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文献

国際調査を完了した日
25. 01. 93

国際調査報告の発送日 16.02.93

名称及びあて先
日本国特許庁（ISA/JP）
郵便番号100
東京都千代田区霞が関三丁目4番3号

特許庁審査官（権限のある職員）
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4H 7106

電話番号 03-3581-1101 内線

様式PCT/ISA/210（第2ページ）（1992年7月）

C（続き），　関連すると認められる文献

引用文献のカテゴリー＊	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	関連する請求の範囲の番号
	&US, A, 4801596	

A．発明の属する分野の分類

C07D307/54，C07D307/58，C07D333/24，
C07D333/32

B．調査を行った分野

C07D307/54，C07D307/58，C07D333/24，
C07D333/32

（第2ページの続き）