SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

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Apoderado: Emilio Ferrero

ASUNTO	Radicación	07-20791
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	

Patente de Invención ⊗

Vía PCT (fase nacional) ⊗ Cap.I ⊗ Cap. II ☐

No. Sol. Internacional PCT/DK2005/000560
Fecha de Presentación Internal. 02/SEP/2005

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios: 106 a 199 Como se radicó inicialmente

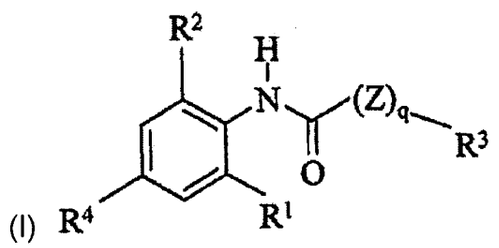
1.2. Reivindicaciones: Folios 200 a 210 Como se radicó inicialmente

1.3. Prioridad: Folio 1: DK PA200401394, 13/sep/2004

2. Objeto de la invención

Título de la solicitud: DERIVADOS DE ANILINA SUSTITUIDOS.

El objeto de la invención son los compuestos derivados de fenil uretano 2,4,6 trisustituido, que caen bajo la fórmula Markush (I):



(I)

-Reivindicaciones 1–12: Un compuesto de la fórmula (I):
-Reivindicación 13: Composiciones que los contienen
-Reivindicaciones 14-20: Uso.

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.):C07D233/15, 333/24, 265/30, C07C237/04, 271728, 233/43, C07D207/22, 295/12, 215/12, C07C311/08, 233/29, 255/60, A61K31/165, A61P25/08

3. De la solicitud de Patente

4.2Reivindicaciones *(artículo 30 de la Decisión 486 de la CA.N.y/o art.22 Tratado PCT.)*

-Tal como aparece reivindicada la materia, es una solicitud basada en un modelismo molecular obtenido mediante ordenador, por lo tanto es muy amplia y especulativa, no hay razones fundadas para creer que un experta de nivel medio será capaz, sobre la base de la información dada en la solicitud tal como fue presentada, de extender la enseñanza particular de la descripción a la totalidad de los campos abarcados en las reivindicaciones; usando los métodos de experimentación de rutina o de análisis, toda vez que la descomunal variabilidad de la fórmula Markush reclamada, no evidencia que cada uno de los compuestos que caen bajo su alcance conserven el efecto de abrir los canales del calcio.

No es racional encontrar sustento técnico real, donde se demuestre que con esa desmedida variabilidad en las potenciales posibilidades de formación de estructuras químicas variables, se consiga el mismo efecto citado. Ya que se trata de "principios activos" que se unen a receptores en seres vivos, y esas tan diversas clases de compuestos no es factible que conserven los mismos efectos de abrir los canales del calcio citados, entonces no aparece el sustento técnico real en la descripción de ese desmedido modelismo de extrapolación, ya que se pretende cubrir toda la química de los derivados fenil uretano 2,4,6 trisustituidos como si jamás en la técnica se hubiese conocido un solo derivado de esa estructura.

-En las reivindicaciones no son aceptadas las denominaciones genéricas para definir los significados de los sustituyentes, tales términos como: *"arilo","heteroarilo* y términos derivados o similares, deberán ser definidos inequívocamente fundados en la descripción, en consideración con el número de átomos de carbono abarcados, en cuanto a los heteroatomos, deben saberse cuales heteroatomos y cuando están involucrados en anillos su tamaño debe estar definido.

-Por lo tanto se debe ajustar el capitulo reivindicatorio de tal manera que la materia reclamada tenga un soporte técnico real, donde aparezca una porción de estructura química reconocible, fija y sobre la cual se encuentre el sustento técnico en la descripción, de tal suerte que sobre ella gire las reivindicaciones, además se debe tener en cuenta que el capitulo reivindicatorio debe conservar la unidad inventiva.

Por consiguiente el capitulo reivindicatorio carece de definición, claridad, concisión y falta de sustento por la descripción, exigidas en las reivindicaciones, por lo tanto no cumplen con el requisito de definición, claridad, concisión y/o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

4. Reivindicaciones relativas a un uso o a un uso distinto *(artículos 14 y 21 D 486 de la C.A.N.)*

-Las reivindicaciones 14-20 reclaman el uso de compuestos y de acuerdo con la legislación colombiana el uso no se considera para protección, como se lee en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina "... Los Países Miembros otorgarán patentes para las invenciones sean de *productos o procedimientos* en todos los campos de la tecnología..."; aquí NO se hace alusión al uso.
Los usos o segundos usos no son patentables, de conformidad con la sentencia del TJAC 89-AI-2000, los usos en general no son patentables.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el estado de la técnica fecha de presentación de la solicitud de la cual se reclama prioridad, 13/sep/2004.
Teniendo en cuenta la fecha indicada se realizó la búsqueda del estado de la técnica, en bases de datos donde esta oficina tiene acceso libre, para búsqueda de documentos relacionados con la materia que se reclama como nueva e inventiva en presente solicitud, encontrándose los siguientes documentos más relevantes:

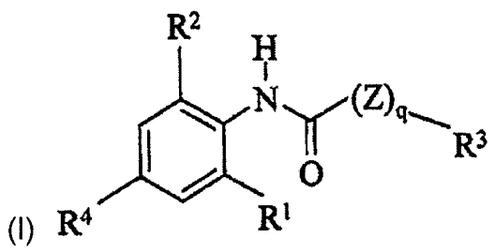
Como la solicitud es tan amplia y especulativa se realizo una búsqueda parcial con base en los ejemplos y se hace un reporte parcial del estado de la técnica.

N°	Documento	Título	Fecha de Publicación*
D1	US3721699	O,N-Diphenil-carbamic acid esters	20-mar-1973
D2	US4063025	4-substituted amino-α-aminomethyl-benzyl alcohol derivatives	13-dic-1977
D3	EP0285219	Method of improving sleep	05-oct-1988
D4	US4145363	4-carbamoylamino-α-aminomethyl-benzyl alcohol derivatives	20-mar-1979
D5	WO0021959	4,5-dihydroisoxazole derivatives and their pharmaceutical use	20-abr-200
D6	Index of subjects, 1949, *J. Chem. Soc.*, 3457		**1949**
D7	Index of subjects, 1951, *J. Chem. Soc.*, 3555		**1951**
D8	CCCCLVII.—The inhibitory effect of substituents in chemical reactions. Part II. The reactivity of the isothiocyano-group in substituted arylthiocarbimides. Donald Wheeler Browne, George Malcolm Dyson, *J. Chem. Soc.*, 3285		**1931**
D9	Index of subjects, 1975, *J. Chem. Soc., Perkin Trans. 1*, 2557		**1975**
D10	Aryl (meth)acrylates and polymers based on them. Vladimir G. Syromyatnikov, Lyudmila P. Paskal', Irina A. Savchenko, *Russ. Chem. Rev.*, 68, 781		**1999**
D11	Chapter 13. Heterocyclic chemistry. R. J. Stoodley, *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.*, **65**, 441		**1968**

6. Análisis de patentabilidad (artículo 14 D486 de la C.A.N.)

6.1. Novedad *(artículo 16 D486 de la C.A.N.)*

La solicitud en estudio reclama los derivados de feniluretano 2,4,6 trisustituido, que caen bajo la fórmula Markush (I):



(I)

-Las anterioridades D1-D6 enseñan derivados feniluretano 2,4,6 trisustituido, que anticipan a describir los compuestos reclamados en la solicitud en estudio, tal como se puede ver en D1 todo el documento especialmente colums.1-6; D2 ver resumen, colums. 3-8; D3 ver ejemplo 1 y 2; D4 columns.1-6, tabla 1; D5 ver 1er párrafo pag. 1, compuesto específico 191; las anterioridades D6-D11 comprenden compuestos específicos de de feniluretano 2,4,6 trisustituido entre los que se encuentran por ejemplo Etil (2-cloro-4,6-dimetilfenil)carbamato o por ejemplo butil (2-chloro-4,6-dimetilfenill)carbamato, no son los únicos compuestos específicos que aparecen en estas anterioridades y que son reclamos en la solicitud en estudio mediante la fórmula Markush (I), por lo tanto las anterioridades destruyen categóricamente la novedad de la solicitud en estudio.

Por lo tanto las solicitud en estudio tampoco cumple con lo exigido en el artículo 16 D486 de la C.A.N.

7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

**Toda solicitud que no posee novedad obviamente no ostenta nivel inventivo.*

Docum. N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	1-20	Novedad
D2	1-20	Novedad
D3	1-20	Novedad
D4	1-20	Novedad
D5	1-20	Novedad
D6	1-20	Novedad
D7	1-20	Novedad
D8	1-20	Novedad
D8	1-20	Novedad
D10	1-20	Novedad
D11	1-20	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiendo que contra él no procede recurso alguno en la vía gubernativa.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha AGO. 2010

CONCEPTO TECNICO No. 2894	**EXAMINADOR TECNICO** Código No.202012

United States Patent [19]

Traber et al.

[11] **3,721,699**

[45] **March 20, 1973**

[54] **O,N-DIPHENYL-CARBAMIC ACID ESTERS**

[75] Inventors: **Walter Traber**, Riehen; **Heinz Hambock**, Binningen; **Anton Georg Weiss**, Benken, all of Switzerland

[73] Assignee: **Ciba-Geigy Corporation**, Ardsley, N.Y.

[22] Filed: **Jan. 26, 1970**

[21] Appl. No.: **5,954**

[52] **U.S. Cl.**.....**260/471 C**, 260/455 A, 424/300

[51] **Int. Cl.**.....**C07c 125/06**

[58] **Field of Search**.....260/471 C

[56] **References Cited**

UNITED STATES PATENTS

3,371,109 2/1968 Baker et al.....260/471 C

Primary Examiner—Henry R. Jiles
Assistant Examiner—L. Arnold Thaxton
Attorney—Karl F. Jorda and Frederick H. Rabin

[57] **ABSTRACT**

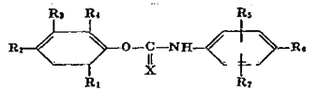
Certain O,N-diphenyl-carbamic acid esters in which one phenyl moiety is substituted in the 2-position by a halogenated phenoxy radical are disclosed as microbicidally active compounds. A method for controlling microorganisms with the aid of such compounds and compositions containing them are also described.

9 Claims, No Drawings

O,N-DIPHENYL-CARBAMIC ACID ESTERS

The present invention concerns new O,N-diphenyl-carbamic acid esters, process for the production of these compounds as well as compositions and methods for the control of microorganisms employing the new carbamic acid esters.

The new O,N-diphenyl-carbamic acid esters (carbanilic acid-phenyl esters) correspond to the Formula I



(I)

In this formula:

R_1 represents a phenoxy radical substituted by at least one and at most three identical or differing halogen atoms,

of the symbols R_2, R_3 and R_4 at least one represents chlorine or bromine, the others each independently represent hydrogen, chlorine or bromine,

R_5 and R_7 each independently represent hydrogen, halogen, lower alkyl, lower alkoxy, lower halogenalkyl, nitro or hydroxy,

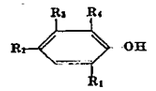
R_6 represents hydrogen, halogen, lower alkyl, lower alkoxy, dialkylamino, hydroxy, and

X represents oxygen or sulfur.

In Formula I, R_1 is in particular one of the following halogenated phenoxy radicals: 4-chlorophenoxy, 4-bromophenoxy, 2,4-dichlorophenoxy, 2,4-dibromophenoxy, 2,4,5-trichlorophenoxy.

Lower alkyl and lower alkoxy radicals R_5 to R_7 have from one to four carbon atoms. As halogenalkyl, trifluormethyl is preferred. The alkyl substituents in a dialkylamino group are radicals having one to four carbon atoms in particular the methyl radical. By halogen represented by R_5, R_6 and/or R_7 is meant fluorine, chlorine, bromine and iodine, especially however, fluorine, chlorine and/or bromine.

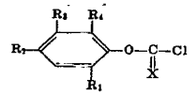
The new O,N-diphenyl-carbamic acid esters are obtained according to the invention, either (a) by converting a phenol of the Formula II



(II)

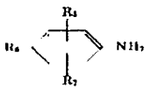
as such or in the Form of one of its alkali metal or alkaline earth metal salts,

with phosgene or thiophosgene into an acid chloride of the Formula III



(III)

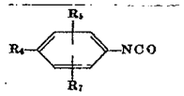
and reacting this with an aniline of the Formula IV



(IV)

or (b) in those cases in which X represents oxygen, by reacting said phenol of Formula II, as such or in the form of one of its alkali metal or alkaline earth metal salts,

with a phenyl isocyanate of the Formula V



(V)

In the Formulas I to V, the symbols R_1 to R_7 and X have the meanings given for Formula I.

The process according to the invention is preferably carried out in the presence of a solvent or diluting agent and of an acid-binding agent (proton acceptor).

Examples of suitable solvents or diluting agents are: hydrocarbons, such as toluene, benzene or ligroine, halogenated hydrocarbons, such as chloroform, carbon tetrachloride or chlorobenzene, amides such as dimethylformamide, ethers and ether-like compounds such as tetrahydrofuran, dioxan or diisopropylether, ketones such as acetone or methyl-ethylketone. Acid-binding agents are preferably organic bases, e.g., tertiary amines such as pyridine, triethylamine etc., inorganic bases such as the hydroxides and carbonates of alkali metals and alkaline earth metals.

In the following examples, the production of some of the diphenyl-carbamic acid esters of Formula I is described. The temperatures are given in degrees centigrade.

EXAMPLE 1

a. About 100 g of phosgene are introduced at 0° into 500 ml of toluene. To this solution there is added dropwise at 0° to 5°, a solution of 289.5 g of 4,2',4'-trichloro-2-hydroxy-diphenyl ether in 700 ml of toluene, and 100 g more of phosgene are introduced. While stirring, a solution of 111.3 g of triethyl amine in 200 ml of toluene is then added to the reaction mixture. After standing for several hours at room temperature, the excess phosgene is removed, the triethylamine-hydrochloride is separated, and the solvent is removed from the filtrate. The residue is fractionated, the 0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-carbonyl chloride boils at 180°–184° and 0.5 Torr.

b. 35.2 g of 0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-carbonyl chloride, dissolved in 300 ml of acetone, are treated dropwise at 15° to 20° with a solution of 32.4 g of 3,5-dichloraniline in 150 ml of acetone. The reaction mixture is then allowed to stand for 3 hours at room temperature, poured onto water, and the precipitate which separates out after several hours is removed by filtration. After recrystallizing several times from cyclohexane and benzene/pteroleum ether, N-(3,5-dichlorophenyl)-carbamic acid-0-[2-(2',4'-di-chlorophenoxyl)-5-chlorophenyl]-ester having a melting point of 132°–134° is obtained.

EXAMPLE 2

a. A solution of 150 g of thiophosgene in 400 ml of chloroform is added to a solution of 289.5 g of 2',4'-dichloro-2-hydroxy-4-chloro-diphenyl ether in 400 ml of chloroform, and cooled to 5°. While stirring vigorously, an aqueous sodium hydroxide solution, 50 g of sodium hydroxide dissolved in 790 ml of water, is

then added dropwise in such a manner that the temperature does not exceed 15°. The reaction mixture is then stirred for 2 hours at room temperature, the organic phase is separated, washed with water, and dried over sodium sulfate. After the solvent is removed by distillation, the residue is fractionated in vacuum. The 2-(2',4'-dichlorophenoxy)-5-chlorophenyl-thiocarbonyl chloride boils at 175°–184° 0.05 Torr. (n_D^{20} = 1.6275).

b. A solution of 24.2 g of 3,5-dimethylaniline in 150 ml of benzene is added dropwise at 5° during 1.5 hours to a solution of 36 g of 0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-thiocarbonylchloride in 150 ml of benzene. The mixture is then stirred for 12 hours at room temperature, shaken out with water, and dried over sodium sulfate. After the solvent has been removed by distillation, the residue of the 0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-thiocarbamic acid-N-(3,5-di-methylphenyl)-ester, recrystallized from benzene/petroleum ether, has a melting point of 102°–104°.

EXAMPLE 3

A solution of 19.8 g of 3-bromo-phenyl-isocyanate in 50 ml of ligroin is added dropwise to a suspension of 30 g of 4'-bromo-4-chloro-2-hydroxy-diphenyl ether in 100 ml of ligroin. After the addition of 2 ml of triethylamine, the mixture is refluxed for 1 hour and then cooled. The precipitate which separates is separated, and recrystallized from benzene/petroleum ether (1:1).

The N-(3-bromophenyl)-carbamic acid-0-[2-(4-bromophenoxy)-5-chlorophenyl]-ester has a melting point of 116°.

The following O,N-diphenyl-carbamic acid esters are prepared from the correspondingly substituted 2-hydroxy-diphenyl ethers or 2-phenoxyphenyl-carbonyl chlorides in accordance with the procedures described in the foregoing examples.

TABLE I

No.	Compound	Melting Point
1	N-(4-fluorophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]- ester	128–130°
2	N-(3-chlorophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	112–113°
3	N-(3-bromophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	99–100°
4	N-(4-chlorophenyl)-thiocarbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	100–102°
5	N-(3-bromophenyl)-thiocarbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	105–107°
6	N-(2,4-dichlorophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	116–117°
7	N-(3,4-dichlorophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	146–147°
8	N-(3-trifluoromethylphenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	82–83°
9	N-(3-trifluoromethyl-4-chlorophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	179–180°
10	N-(3-trifluoromethyl-4-chlorophenyl)-thiocarbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	98–100°
11	N-(3-trifluoromethyl-6-chlorophenyl)-thiocarbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	95–97°
12	N-(4-methylphenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	102–104°
13	N-(4-methylphenyl)-thiocarbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	131–133°
	N-(2-methylphenyl)-thiocarbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	92–96°
	N-(3,5-dimethylphenyl)-thiocarbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	101–102°
	N-(3-methoxyphenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	76–77°
	N-(3-methoxyphenyl)-thiocarbamic acid-0-[2-(4'-chlorophenoxy)-5-chlorophenyl]-ester	84–86°
	N-(4-chlorophenyl)-carbamic acid-0-[2-(4'-bromophenoxy)-5-chlorophenyl]-ester	150–151°
	N-(3-bromophenyl)-carbamic acid-0-[2-(4'-bromophenoxy)-5-chlorophenyl]-ester	116°
	N-(3,4-dichlorophenyl)-carbamic acid-0-[2-(4'-bromophenoxy)-5-chlorophenyl]-ester	142–143°
	N-(3-trifluoromethylphenyl)-carbamic acid-0-[2-(4'-bromophenoxy)-5-chlorophenyl]-ester	84–86°
	N-(2-methylphenyl)-carbamic acid-0-[2-(4'-bromophenoxy)-5-chlorophenyl]-ester	98°
	N-(3-chlorophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-bromophenyl]-ester	116–118°
	N-(2,4-dichlorophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-bromophenyl]-ester	122–124°
	N-(3-trifluoromethyl-4-chlorophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-bromophenyl]-ester	136–138°
	N-(3,5)-bis-(trifluoromethylphenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-bromophenyl]-ester	129°
	N-(3-methoxyphenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-5-bromophenyl]-ester	76°
	N-(3,4-dichlorophenyl)-carbamic acid-0-[2-(4'-bromophenoxy)-5-bromophenyl]-ester	152–154°
	N-(3-trifluoromethylphenyl)-carbamic acid-0-[2-(4'-bromophenoxy)-5-bromophenyl]-ester	88–89°
	N-(3-methylphenyl)-carbamic acid-0-[2-(4'-bromophenoxy)-5-bromophenyl]-ester	114–116°
	N-(4-methoxyphenyl)-carbamic acid-0-[2-(2-(4'-bromophenoxy)-5-bromophenyl]-ester	135–137°
	N-(4-chlorophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-4-bromo-5-chlorophenyl]-ester	155–160°
	N-(3-chlorophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-4-bromo-5-chlorophenyl]-ester	120–121°
	N-(3-bromophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-4-bromo-5-chlorophenyl]-ester	120–121°
	N-(4-bromophenyl)-thiocarbamic acid-0-[2-(4'-chlorophenoxy)-4-bromo-5-chlorophenyl]-ester	127–128°
	N-(3,4-dichlorophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-4-bromo-5-chlorophenyl]-ester	162–163°
	N-(3-trifluoromethyl-4-chlorophenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-4-bromo-5-chlorophenyl]-ester	145–147°
	N-(3-trifluoromethylphenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-4-bromo-5-chlorophenyl]-ester	122–124°
	N-(3-trifluoromethylphenyl)-thiocarbamic acid-0-[2-(4'-chlorophenoxy)-4-bromo-5-chlorophenyl]-ester	75–77°
	N-(4-methylphenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-4-bromo-5-chlorophenyl]-ester	135–138°
	N-(3-metboxyphenyl)-carbamic acid-0-[2-(4'-chlorophenoxy)-4-bromo-5-chlorophenyl]-ester	150–151°
	N-(3,4-dichlorophenyl)-carbamic acid-0-[2-(4'-bromophenoxy)-4,6-dibromophenyl]-ester	162–167°
	N-phenyl-carbamic acid-0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-ester	150–151°
	N-phenyl-thiocarbamic acid-0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-ester	105–107°
	N-(4-fluorophenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	144–146°
	N-(2-chlorophenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	105–107°
	N-(4-chlorophenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	153–154°
	N-(4-chlorophenyl)-thiocarbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	98–101°
	N-(2-bromophenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	110–111°

50	N-(3-bromophenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	126–128°
51	N-(4-bromophenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	159–160°
52	N-(4-bromophenyl)-thiocarbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	106–107°
53	N-(3,4-dichlorophenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	145–147°
54	N-(3,5-dichlorophenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	132–134°
55	N-(3,4-dichlorophenyl)-thiocarbamic acid-0-[2-(2',4' -dichlorophenoxy)-5-chlorophenyl]-ester	99–102°
56	N-(2,4,5-trichlorophenyl)-thiocarbamic acid-0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-ester	80–82°
57	N-(3-trifluoromethyl-4-chlorophenyl)-carbamic acid-0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-ester	125–126°
58	N-(2-methyl-3-chlorophenyl)-carbamic acid-0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-ester	137–138°
59	N-(3-nitro-4-chlorophenyl)-carbamic acid-0-[2',4'-dichlorophenoxy)-5-chlorohenyl]-ester	150–152°
60	N-(2,4,5-trichlorophenyl)-carbamic acid-0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-ester	145–147°
61	N-(3-trifluoromethylphenyl)-carbamic acid-0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-ester	120–121°
62	N-(4-hydroxyphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	149°150°
63	N-(4-ethoxyphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	145–147°
64	N-(3-hydroxyphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	136–137°
65	N-(4-dimethylaminophenyl)-carbamic acid-0-[2-(2',4'-dichlorophenoxy)-5-chorophenyl]-ester	148–149°
66	N-(3,5-bis-trifluoromethyl-phenyl)-carbamic acid-0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-ester	128°
67	N-(2-methylphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	115–118°
68	N-(3-methylphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	137–138°
69	N-(4-methylphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	144–145°
70	N-(2,6-dimethylphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	122–124°
71	N-(3,5-dimethylphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	142–145°
72	N-(4-tert-butylphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	153–154°
73	N-(4-methylphenyl)-thiocarbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	94–96°
74	N-(3-methylphenyl)-thiocarbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	107–109°
75	N-(2-methoxyphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	107–108°
76	N-(3-methoxyphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	109–110°
77	N-(4-methoxyphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	150–151°
78	N-(3-methoxyphenyl)-thiocarbamic acid-0-[2-(2',4'-dichlorophenoxy)-5-chlorophenyl]-ester	96–98°
79	N-(4-fluorophenyl)-carbamic acid-0-[2-(2',4''-trichlorophenoxy)-5-chlorophenyl]-ester	132–134°
80	N-(4-methoxyphenyl)-carbamic acid-0-[2-(2',4'5'-trichlorophenoxy)-5-chlorophenyl]-ester	140–141°
81	N-(3-trifluoromethyl-4-chlorophenyl)-carbamic acid-0-[2-(2',4',5'-trichlorophenoxy)-5-chlorophenyl]-ester	136–137°
82	N-(4-fluorophenyl)-carbamic acid-0-[2-(2',4'5-bromophenyl]-ester	114°
83	N-(3,4-dichlorophenyl)-carbamic acid-0-[2-(2',4'5-bromophenyl]-ester	148–151°
84	N-(3-trifluoromethylphenyl)-carbamic acid-0-[2-(2',4'-dichlorophenoxy)-5-bromophenyl]-ester	114–116°
85	N-(3-trifluoromethyl-4-chlorophenyl)-carbamic acid-0-[2-(2',4'-dichlorophenoxy)-5-bromophenyl]-ester	114–115°
86	N-(3-methoxyphenyl)-carbamic acid-0-[2'2-(2',4'-dichlorophenoxy)-5-bromophenyl]-ester	80–110°
87	N-(3-bromophenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	142–143°
88	N-(2,4-dichlorophenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	126–128°
89	N-(3,5bis-trifluoromethyl-phenyl)-carbamic acid-0-[2-(2',4'-dibromophenoxy)-5-chlorophenyl]-ester	145–146°
90	N-(4-methylphenyl)-carbamic acid-0-[2-(2',4'5-chlorophenyl]-ester	160–161°
91	N-(2-methylphenyl)-carbamic acid-0-[2',4'-dichlorophenoxy)-4-bromo-5-chlorophenyl]-ester	158–160°
92	N-(3-chlorophenyl)-carbamic acid-0-[2-(2',4'4-bromo-5-chlorophenyl]-ester	138–139°
93	N-(4-chlorophenyl)-carbamic acid-0-[2-(2',4'4-bromo-5-chlorophenyl]-ester	184–185°
94	N-(2,4-dichlorophenyl)-carbamic acid-0-[2-(2',4'4-bromo-5-chlorophenyl]-ester	134–135°
95	N-(3,4-dichlorophenyl)-carbamic acid-0-[2-(2',4'4-bromo-5-chlorophenyl]-ester	172–173°
96	N-(2,4,5-trichlorophenyl)-carbamic acid-0-[2-(2',4'-dichlorophenoxy)-4-bromo-5-chlorophenyl]-ester	170–172°
97	N-(2-chlorophenyl)-carbamic acid-0-[2-(2',4'4-bromo-5-chlorophenyl]-ester	150–153°
98	N-(3-trifluoromethyl-6-chlorophenyl)-carbamic acid-0-[2-(2',4'-dichlorophenoxy)-4-bromo-5-chlorophenyl]-ester	140–141°
99	N-(3-bromophenyl)-carbamic acid-0-[2-(2',4'4-bromo-5-chlorophenyl]-ester	144–145°
100	N-(3-trifluoromethyl-4-chlorophenyl)-carbamic acid-0-[2-(2',4'-dichlorophenoxy)-4-bromo-5-chlorophenyl]-ester	151–153°
101	N-(4-methylphenyl)-carbamic acid-0-[2-(2',4'4-bromo-5-chlorophenyl]-ester	148–153°
102	N-(3-methoxyphenyl)-carbamic acid-0-[2-(2',4'4-bromo-5-chlorophenyl]-ester	139–141°

The new carbamic acid esters of Formula I are colorless solids which can be purified by recrystallization. They are only slightly toxic for warm-blooded animals and do not irritate the skin in the concentrations normal for use. The advantage of the new carbamic acid esters to be colorless or to have only a slight intrinsic color makes possible their use in many areas where strongly colored compounds would be unsuitable.

The new diphenyl-carbamic acid esters of Formula I have very good bacterostatic and bactericidal effects against gram-positive and gram-negative bacteria, for example: *Staphylococcus aureus* SG 511 *Staphylococcus aureus Smith*, *Staphylococcus lactis*, in addition *Bacillus mesentericus*, *Bacillus pumilus*, *Bacillus subtilis*, *Coli forms*, *Corynebacterium diphtheriae*, *Clostridium botulinum*, *Clostridium butyricum*, *Clostridium welchii*, *Clos-*

United States Patent [19]

Murakami et al.

[11] **4,063,025**

[45] **Dec. 13, 1977**

[54] **4-SUBSTITUTED AMINO-α-AMINOMETHYLBENZYL ALCOHOL DERIVATIVES**

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[73] Assignee: **Yamanouchi Pharmaceutical Co., Ltd.,** Tokyo, Japan

[21] Appl. No.: **651,738**

[22] Filed: **Jan. 23, 1976**

[30] **Foreign Application Priority Data**

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May 24, 1975 Japan 50-62207

[51] **Int. Cl.**[2] **C07C 125/06**

[52] **U.S. Cl.** ..... **560/29;** 260/553 A; 260/570.6; 424/300; 424/322; 424/330

[58] **Field of Search** ..... 260/471 C, 76–84

[56] **References Cited**

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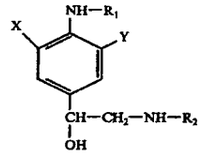
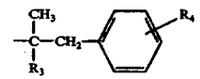
Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Burgess, Ryan and Wayne

[57] **ABSTRACT**

There are disclosed novel 4-substituted amino-α-aminomethylbenzyl alcohol derivatives represented by the formula:



wherein X represents a halogen atom; Y represents a hydrogen atom or a halogen atom; R_1 represents a lower alkyl group, a carbamoyl group, a mono- or di-lower alkyl-substituted carbamoyl group, a phenyl-substituted carbamoyl group, a lower alkoxycarbonyl group, a lower alkoxy-substituted lower alkoxycarbonyl group, a phenyl-substituted lower alkoxycarbonyl group, or a cycloalkyloxycarbonyl group; and R_2 represents a lower alkyl group, a cycloalkyl group, or the group shown by the formula

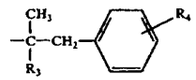


wherein R_3 represents a hydrogen atom or a lower alkyl group and R_4 represents a hydrogen atom, a hydroxy group, or a lower alkoxy group and the pharmaceutically acceptable nontoxic salts thereof.

These compounds are antiasthmatic agents useful for the prophylaxis and treatment of asthma.

10 Claims, No Drawings

yloxycarbonyl group, cyclopentyloxycarbonyl group, cyclopropyloxycarbonyl group, etc. Examples of R_2 are a lower alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, tert-amyl group, etc.; a cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, etc.; and examples of R_3 shown by the formula

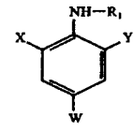


are a hydrogen atom; and a lower alkyl group such as methyl group, ethyl group, isopropyl group, butyl group, etc., and further examples of R_4 are a hydrogen atom; a hydroxy group; and a lower alkoxy group such as methoxy group, ethoxy group, isopropyloxy group, butoxy group, etc.

The preferred homologs of the compounds of this invention are the compounds of formula I in which R_2 is a tert-butyl group. The more preferable homologs of the compounds of this invention are the compounds of in the formula I in which R_1 is a lower alkoxycarbonyl group and R_2 is a tertbutyl group. Also, the most preferred compounds of this invention are the compounds of the formula I in which R_1 in the formula is an ethoxycarbonyl group, R_2 is a tert-butyl group, and X and Y each is a chlorine atom. That is, the practical examples of the most preferred compound of this invention are 3,5-dichloro-4-ethoxycarbonylamino-α-(tert-butylaminomethyl)benzyl alcohol and the pharmaceutically acceptable nontoxic salts thereof.

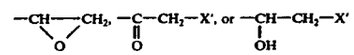
Furthermore, as the pharmaceutically acceptable nontoxic salts of the compounds of this invention, there are the acid addition salts thereof with a mineral acid such as hydrochloric acid, hydro bromic acid, phosphoric acid, etc., or an organic acid such as maleic acid, fumaric acid, acetic acid, etc.

Now, the compound of this invention shown by formula I can be prepared by reacting the compound shown by formula II:



II

wherein X, Y, and R_1 have the same meaning as in formula I and W represents



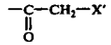
(wherein X' represents a halogen atom)
and the amine shown by formula III

III

wherein R_2 and R_3 have the same meaning as in formula I and, if desired, reducing the reaction product thus obtained.

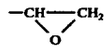
In more detail, at the practice of the aforesaid reaction, the compound of formula II is reacted with an equimolar or excessive amount of the amine of formula III in an organic solvent such as chloroform, isopropyl alcohol, ethanol, acetonitrile, ethyl acetate, dimethyl formamide, etc. In this case, it is preferred for carrying out the reaction smoothly, to add an acid binding agent such as sodium carbonate, potassium carbonate, etc., to the reaction mixture. The reaction usually proceeds sufficiently when carried out for from 30 minutes to 3 hours at room temperature or under heating but the reaction conditions may be properly selected in wide ranges according to the nature of the starting materials. That is, there is no particular limitation about the reaction temperature and reaction period of time but the temperature is preferably from −30° C. to 100° C. and the reaction period of time is preferably from 30 minutes to 48 hours.

When in the aforementioned reaction the compound of formula II wherein W is the group shown by



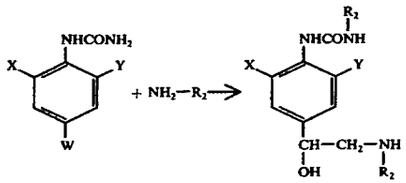
is used as the starting material, the reaction product thus obtained is then reduced. The reduction can be easily carried out by treating the reaction product with a reducing agent such as sodium borohydride, lithium aluminum hydride, etc., in an organic solvent such as methanol, ethanol, ethyl acetate, chloroform, ether tetrahydrofuran, etc., usually at room temperature or, if desired, under ice-cooling.

Further, when the compound of formula II wherein W is the group shown by



is used as the starting material the reaction, it is preferred to heat the compound and the amine of formula III in a sealed tube.

In addition, when the compound of formula II wherein R_1 is a carbamoyl group is used, the reaction is sometimes accompanied by an amine exchange reaction at the same time to form a compound wherein the amino group in the carbamoyl group has been converted into the amine of formula III. This reaction is shown as follows:



The compound of formula I thus prepared may be isolated and purified by known chemical operations such as concentration, recrystallization, column chromatography, etc.

The compound of this invention can be administered orally as, for example, tablets, capsules, etc., or paren-

terally as, for example an intravenous injection, aerosol, etc. Also, when the compound of this invention is orally administered to an adult, the proper dosage thereof is 10-50 μg./day.

The experimental results obtained by testing the bronchodilator activity of the compounds of this invention are shown below together with the comparison results made with NAB 365:

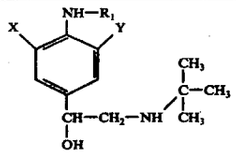
EXPERIMENT I (Anti asthmatic activity)

The experiments were carried out according to the method of Parker et al., (J. Pharmacol. Exptl. Therap., 118, 359–364 (1956)). A guinea pig was placed in a 11 liters glass chamber and exposed to the spasmogen by means of a nebulizer. When 0.1% histamine dihydrochloride was sprayed into the chamber, the guinea pig showed a symptom of dyspnea. Samples were administered subcutaneously to animals 30 min. prior the application of the spasmogen. If the guinea pig showed no asthmatic dyspnoic symptoms, the sample was evaluated to be effective.

ED_{50} was calculated by the method of Litchfield-Wilcoxon (J. Pharmacol. Exptl. Therap., 96, 99–113 (1949) using 4–8 groups and one group consists of 4–8 of guinea pig.

The results are shown in the following Table I.

Table I



Sample	R_1	X	Y		anti-asthmatic activity ED_{50}(μg/Kg)
Known compound					
NAB 365	H	Cl	Cl	hydrochloride	490
Present compound					
Ex. 6	$-C_2H_5$	Cl	Cl	hydrochloride	125–250
Ex. 8	$-COOCH_3$	Br	Br	½ fumarate	125
Ex. 12	$-COOCH(CH_3)_2$	Cl	Cl	hydrochloride	32
Ex. 13	$-COOCH_2-C_6H_5$	Cl	Cl	hydrochloride	125
Ex. 14	$-COOCH_2CH_2OCH_3$	Cl	Cl	hydrochloride	32
Ex. 15	$-CONHCH_3$	Cl	Cl	free base	125–250
Ex. 18	$-COOCH_3$	Br	Cl	½ fumarate	63
Ex. 23	$-COOCH_3$	Cl	H	½ fumarate	63–125

Experiment II

a. Bronchodilator activity, B_2 action

The experiments were carried out according to the method of Konzett and Rossler (Arch. exp. Path. Pharmakol., 195, 11–14 (1940)). Mongorel dogs were anesthetized with pentobarbital Na. Temporary increase in bronchial resistance, measured with transducer connected to a polygraph, were produced by histamine dihydrochloride, 10 μg/Kg injected rapidly intravenously at intervals of 30 min. The test samples were injected intraduodenally and the time-course of antihistamine activity of the sample (the inhibition rate (%) against the control) was obtained.

ED_{50} (μg/Kg) values of β-agonists were obtained from the dose response curve drawn according to the peak effect on each dose. The results are shown in the Table II.

b. Action on heartrate, β_1 action.

Mongorel dogs were anesthetized with pentobarbital Na. Heart rate (HR) was recorded on polygraph. The samples were administered intra-duodenally and the HR was observed at varying intervals after the administration. The time-course of ΔHR (the increased HR against the control) was obtained.

The dose response curve drawn according to the peak response on each dose and the ED_{25} beats/min. (μg/Kg), that is the dose of the sample producing 25 beats/min. increase in heart rate was obtained from the curve. The results are shown in the following Table II.

c. Broncho-selectivity

The broncho-selectivity was obtained by the following equation.

$$\text{Broncho-selectivity} = \frac{ED_{25}\ \text{beats/min. of}\ \beta_1\ \text{action}}{ED_{50}\ \text{of}\ \beta_2\ \text{action}}$$

Table II

Sample	β_2 action i.d. ED_{50} (μg/Kg)	β_1 action i.d. ED_{25} beats/min (μg/Kg)	broncho-selectivity (Ratio of β_1/β_2)
1-(4-amino-3,5-dichlorophenyl)-2-tert-butylamino ethanol hydrochloride (NAB 365)	12.3	5.7	0.46
3,5-dichloro-4-ethoxycarbonylamino-α-(tert-butylaminomethyl)-benzyl alcohol hydrochloride (compound of Ex. 10)	4.5	19.5	4.3

Reference example 1

After gradually adding a solution of 5.5 g. of bromine in 5 ml. of chloroform to a solution of 7.5 g. of 3,5-dichloro-4-methyl-aminoacetophenone in 60 ml. of chloroform with stirring at 40°–50° C., the mixture was further stirred under heating until the color of bromine had disappeared. The white crystals formed were collected by filtration, washed with chloroform, and dried to provide 12.5 g. of a crude product. The crude product was suspended in 50 ml. of chloroform and after adding thereto a saturated aqueous sodium bicarbonate solution followed by shaking, the chloroform layer formed was recovered and dried over anhydrous magnesium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to provide 8.5 g. of 3,5-dichloro-4-methylamino-α-bromoacetophenone having a melting point of 85°–87° C.

Reference example 2

a. A mixture of 4 g. of 3,5-dichloro-4-aminoacetophenone, 12 ml. of phosgene, and 30 ml. of toluene was heated for 24 hours at 150° C. in a sealed tube. The reaction mixture was then cooled and concentrated under reduced pressure to provide 4.0 g. of 2,6-dichloro-4-acetylphenyl isocyanate having a melting point of 82°–84° C.

b. In 50 ml. of toluene was dissolved 3.9 g. of 2,6-dichloro-4-acetylphenyl isocyanate and after adding 2 ml. of absolute methanol to the solution, the mixture was stirred overnight at 100° C. The reaction mixture was cooled and then concentrated under reduced pressure and the residue obtained was recrystallized from a mixture of benzene and n-hexane to provide 4.33 g. of 3,5-dichloro-4-methoxycarbonylaminoacetophenone having a melting point of 107°–109° C.

c. In 30 ml. of chloroform was dissolved 2 g. of 3,5-dichloro-4-methoxycarbonylaminoacetophenone and then a solution of 1.22 g. of bromine in 5 ml. of chloroform was added to the solution with stirring at room temperature. After further stirring the mixture for 30 minutes, the mixture was concentrated under reduced pressure, whereby crystals were formed. The crystals were recrystallized from a mixture of benzene and n-hexane to provide 2.07 g. of 3,5-dichloro-4-methoxycarbonylamino-α-bromoacetophenone having a melting point of 140°–141° C.

Reference example 3

In 14 ml. of absolute methanol was dissolved 0.5 g. of 3,5-dichloro-4-methoxycarbonylamino-α-bromoacetophenone and after cooling the solution to 5° C., 0.05 g. of sodium borohydride was added thereto followed by stirring for one hour. Then, after acidifying the solution by adding thereto 2 ml. of a 1.44 N hydrogen chloride-ethanol solution under cooling, an excessive amount of sodium carbonate was immediately added to the mixture followed by stirring for 10 minutes. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in 30 ml. of chloroform. The solution was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to provide 0.4 g. of 3,5-dichloro-4methoxycarbonylamino-α-bromomethylbenzyl alcohol.

Nuclear magnetic resonance spectra ($CDCl_3$):

δ: 2.92 (d, 1H, >CH—OH), 3.50 (m, 2H, —CH_2Br), 3.73 (s, 3H, —OCH_3), 4.84 (m, 1H, >CH-), 7.36 (s, 2H, H of a benzene ring).

Reference example 4

A solution of 1 g. of bromine in 2 ml. of chloroform was gradually added to a solution of 1.8 g. of 3,5-dibromo-4-methylaminoacetophenone in 20 ml. of chloroform with stirring at 40°–50° C., whereby crystals were formed. The crystals thus formed were recovered by filtration and after adding water to the crystals, the mixture was extracted with benzene. The benzene extract obtained was washed with water and dried over anhydrous magnesium sulfate. The mixture was filtered and the filtrate formed was concentrated under reduced pressure to provide the crystals of 3,5-dibromo-4-methylamino-α-bromoacetophenone. By washing the crystals with isopropylalcohol and drying, 1.7 g. of 3,5-dibromo-4-methylamino-α-bromoacetophenone having a melting point of 87°–89° C. was obtained.

Reference example 5

By following the similar procedure as in Reference example 4 using a solution of 30 ml. of chloroform containing 3.5 g. of 3,5-dichloro-4-ethylaminoacetophenone prepared by dichlorinating p-ethylaminoacetophenone and a solution of 2.5 g. of bromine in 3 ml. of chloroform, 2.7 g. of 3,5-dichloro-4-ethylamino-α-bromoacetophenone having a melting point of 58°–59° C. was obtained.

Reference example 6

By following the similar procedure as in Reference example 2-*a*) using 2 g. of 4-amino-3,5-dibromoacetophenone and 2 g. of phosgene, 2,6-dibromo-4-acetylphenyl isocyanate was obtained and then by treating the product with the similar procedure as in Reference example 2-*b*), 1.7 g. of 3,5-dibromo-4-methoxycarbonylaminoacetophenone having a melting point of 141°–142° C. was obtained.

Furthermore, by following the similar procedure as in Reference example 4 using 1.3 g. of 3,5-dibromo-4-methoxycarbonylaminoacetophenone and 0.6 g. of bro-

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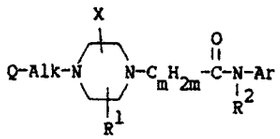
(54) Method of improving sleep.

(57) The use for the manufacture of a medicament for improving sleep and treating sleep disorders of a piperazine derivative of formula



(I),

wherein R^1 is hydrogen or C_{1-6} alkyl;

X is C_{1-6} alkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, aminocarbonyl, mono-and di(C_{1-6} alkyl)-aminocarbonyl, carboxyl, C_{1-6} alkyloxycarbonyl, (aminocarbonyl)C_{1-6} alkyl, [mono-and di(C_{1-6} alkyl)-aminocarbonyl]C_{1-6} alkyl, carboxylC_{1-6} alkyl, (C_{1-6} alkyloxycarbonyl)C_{1-6} alkyl or (hydroxyC_{1-6} alkyl)-aminocarbonyl;

R^2 is hydrogen or C_{1-6} alkyl;

Ar is phenyl, pyridinyl, pyrazolyl, all three being optionally substituted, or a radical of formula

EP 0 285 219 A2

Those of skill in the pertinent art could easily determine what could be an effective sleep-improving amount from the results presented hereinafter. In general it is contemplated that an effective amount would be from 0.001 mg/kg to 100 mg/kg body weight, and more preferably from 0.01 mg/kg to 10 mg/kg body weight.

The following examples are intended to illustrate and not to limit the scope of the invention.

Unless otherwise stated all parts therein are by weight.

EXPERIMENTAL PART

A. Preparation of intermediates

Example 1

a) A mixture of 13.36 parts of 2-chloro-N-[2,6-dimethyl-4-(phenylmethoxy)phenyl]acetamide, 6.76 parts of hexahydro-3,3-dimethylimidazo[1,5-a]pyrazin-1(5H)-one, 7.8 parts of N,N-diethylethanamine and 180 parts of N,N-dimethylformamide was stirred for 20 hours at 70°C. The reaction mixture was evaporated. The residue was taken up in water and the product was extracted twice with dichloromethane. The combined extracts were washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The desired fraction was collected and the eluent was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 11.66 parts (66.8%) of N-[2,6-dimethyl-4-(phenylmethoxy)phenyl]hexahydro-3,3-dimethyl-1-oxoimidazo-[1,5-a]pyrazine-7(8H)-acetamide; mp. 223.8°C (int. 1).

b) A mixture of 11.10 parts of N-[2,6-dimethyl-4-(phenylmethoxy) phenyl]hexahydro-3,3-dimethyl-1-oxoimidazo[1,5-a]pyrazine-7(8H)-acetamide and 100 parts of a hydrochloric acid solution 0.5 N was stirred for 2 hours at reflux temperature. After cooling, the reaction mixture was treated with a sodium hydroxide solution 50%. The product was extracted twice with dichloromethane. The combined extracts were dried, filtered and evaporated. The residue was suspended in 2,2'-oxybispropane. The product was filtered off and dried, yielding 8.19 parts (82.6%) of 3-(aminocarbonyl)-N-[2,6-dimethyl-4-(phenylmethoxy)phenyl]-1-piperazineacetamide (int. 2).

In a similar manner there were also prepared:

3-(aminocarbonyl)-N-(5-fluoro-2-methylphenyl)-1-piperazineacetamide; mp. 168.6°C (int. 3);
3-(aminocarbonyl)-N-(2-chloro-6-methylphenyl)-1-piperazineacetamide; mp. 176.6°C (int. 4);
3-(aminocarbonyl-N-(2,6-dichloro-4-cyanophenyl)-1-piperazineacetamide; mp. 205.5°C (int. 5);
N-(4-acetyl-2,6-dichlorophenyl)-3-(aminocarbonyl)-1-piperazineacetamide (int. 6);
3-(aminocarbonyl)-N-(2,4,6-trichlorophenyl)-1-piperazineacetamide (int. 7);
3-(aminocarbonyl)-N-[4-(aminocarbonyl)-2,6-dichlorophenyl]-1-piperazineacetamide; mp. 256.8°C (int. 8);
3-(aminocarbonyl)-N-(2,6-diethylphenyl)-1-piperazineacetamide; mp. 166.9°C (int. 9);
N-(3-acetyl-2,6-dimethylphenyl)-3-(aminocarbonyl)-1-piperazineacetamide (int. 10);
N-(3-acetyl-2,6-dimethylphenyl)-3-[(methylamino)carbonyl]-1-piperazineacetamide (int. 11) and
N-(2,6-diethylphenyl)-3-(methylaminocarbonyl)-1-piperazineacetamide; mp. 138.1°C (int. 12).

Example 2

A mixture of 15.33 parts of N-methyl-2-piperazinecarboxamide, 27.2 parts of 2-chloro-N-(2,4,6-trichlorophenyl)acetamide, 9.8 parts of N,N-diethylethanamine and 300 parts of 2-methoxyethanol was stirred for 3 hours at 60°C. The reaction mixture was evaporated. The residue was taken up in a small amount of water and treated with sodium carbonate. The product was extracted three times with dichloromethane. The combined extracts were dried, filtered and evaporated. The residue was crystallized from acetonitrile. The product was filtered off (the filtrate was set aside) and dried, yielding a first fraction of 9.27 parts (24.4%) of 3-[(methylamino)carbonyl]-N-(2,4,6-trichlorophenyl)-1-piperazineacetamide.

The filtrate, which was set aside (see above) was evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and 2-propanol (90:10 by volume) as eluent. The desired fraction was collected and the eluent was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding a second fraction of 5.93 parts (15.6%) of 3-[-(methylamino)carbonyl]-N-(2,4,6-trichlorophenyl)-1-piperazineacetamide; mp. 168.9°C.

Total yield: 15.2 parts (40.0%) of 3-[(methylamino)carbonyl]-N-(2,4,6-trichlorophenyl)-1-piperazineacetamide (int. 13).

In a similar manner there were also prepared:

N-(2,6-dimethylphenyl)-3-(hydroxymethyl)-1-piperazineacetamide; mp. 135.1°C (int. 14);

N-(2-acetylphenyl)-3-(aminocarbonyl)-1-piperazineacetamide (int. 15);

N-(4-acetyl-2,6-dichlorophenyl)-3-[(methylamino)carbonyl]-1-piperazineacetamide (int. 16);

N-(3-chloro-2,5,6,7-tetrahydro-2-oxo-1H-1-pyrindin-4-yl)-3-(methylaminocarbonyl)-1-piperazineacetamide (int. 17);

3-[(methylamino)carbonyl]-N-(2,4,6-trimethyl-3-pyridinyl)-1-piperazineacetamide as a residue (int. 18) and

N-(4-acetyl-2,6-dichlorophenyl)-3-methyl-1-piperazineacetamide as a residue (int. 19).

Example 3

a) To a stirred solution of 60 parts of 2-methylpiperazine in 1500 parts of trichloromethane was added dropwise a solution of 46 parts of bis(1,1'-dimethylethyl)dicarbonate in 75 parts of trichloromethane at 10-15°C during 90 minutes. Upon complete addition, stirring was continued for 1 hour at room temperature. The reaction mixture was washed twice with water, dried, filtered and evaporated, yielding 52 parts (100%) of (1,1-dimethylethyl) 3-methyl-1-piperazinecarboxylate as a residue (int. 20).

b) A mixture of 12 parts of (1,1-dimethylethyl) 3-methyl-1-piperazinecarboxylate, 18.7 parts of N-(4-acetyl-2,6-dichlorophenyl)-2-chloroacetamide, 11.8 parts of N,N-diethylethanamine and 230 parts of N,N-dimethylformamide was stirred first for 8 hours at 70°C and then over weekend at room temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted twice with dichloromethane. The combined extracts were washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using trichloromethane as eluent. The desired fraction was collected and the eluent was evaporated, yielding 27 parts (100%) of (1,1-dimethylethyl) 4-[2-[(4-acetyl-2,6-dichlorophenyl)amino]-2-oxoethyl]-3-methyl-1-piperazinecarboxylate as a residue (int. 21).

c) Gaseous hydrogen chloride was bubbled through a mixture of 87 parts of (1,1-dimethylethyl) 4-[2-[(4-acetyl-2,6-dichlorophenyl)amino]-2-oxoethyl]-3-methyl-1-piperazinecarboxylate and 400 parts of methanol. The whole was stirred for 15 minutes at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The whole was treated with an ammonium hydroxide solution and the product was extracted twice with dichloromethane. The combined extracts were dried, filtered and evaporated. The residue was suspended in 2,2'-oxybispropane. The product was filtered off and dried, yielding 15 parts (72.6%) of N-(4-acetyl-2,6-dichlorophenyl)-2-methyl-1-piperazineacetamide (int. 22).

In a similar manner there was also prepared:

N-(3-bromo-6,7-dihydro-5H-1-pyrindin-4-yl)-2-methyl-1-piperazineacetamide (int. 23).

Example 4

a) A mixture of 51 parts of 1,1'-(5-bromo-1-penten-1-ylidene)bis[4-fluorobenzene], 25.4 parts of hexahydro-3,3-dimethylimidazo-[1,5-a] pyrazin-1(5H)-one, 35.5 parts of N,N-diethylethanamine and 270 parts of N,N-dimethylformamide was stirred overnight at 70°C. After evaporation, the residue was taken up in trichloromethane. The organic layer was washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (96:4 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 60 parts (94.0%) of 7-[5,5-bis(4-fluorophenyl)-4-pentenyl]hexahydro-3,3-dimethylimidazo[1,5-a]pyrazin-1(5H)-one as a residue (int. 24).

b) A mixture of 60 parts of 7-[5,5-bis(4-fluorophenyl)-4-pentenyl] hexahydro-3,3-dimethylimidazo[1,5-a]pyrazin-1(5H)-one and 850 parts of a hydrochloric acid solution 0.5 N was stirred for 2 hours at reflux temperature. After cooling, the reaction mixture was treated with potassium carbonate. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 1,1'-oxybisethane. The product was filtered off and dried, yielding 29.5 parts (50%) of 4-[5,5-bis(4-fluorophenyl)-4-pentenyl]-2-piperazinecarboxamide monohydrate; mp. 51.3°C (int. 25).

trichloromethane and methanol, saturated with ammonia (97 3 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 3.3 parts (72.8%) of 4,6-dimethyl-2,5-pyridinediamine as a residue (int. 96).

c) To a stirred solution of 3.3 parts of 4,6-dimethyl-2,5-pyridinediamine in 30 parts of acetic acid were added 4.7 parts of 2-chloroacetyl chloride at room temperature. The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with methylbenzene and neutralised with sodium carbonate. The reaction mixture was filtered over diatomaceous earth and the filtrate was evaporated, yielding 2.6 parts (50.7%) of N-(6-amino-2,4-dimethyl-3-pyridinyl)-2-chloroacetamide as a residue (int. 97).

Example 18

A mixture of 20 parts of N-(4-amino-2,6-dichlorophenyl)acetamide, 10 parts of 2-propanone, 2 parts of a solution of thiophene in methanol 4%, 400 parts of methanol, 5 parts of potassium fluoride and 18 parts of 2-propanol, saturated with hydrogen chloride was hydrogenated in a Parr apparatus and at 50°C with 2 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 15.7 parts (66.7%) of N-[2,6-dichloro-4-[(1-methylethyl)amino]-phenyl]acetamide (int. 98).

Example 19

A mixture of 15.2 parts of N-(2-acetyl-4-nitrophenyl)acetamide, 5 parts of poly(oxymethylene), 1 part of a solution of thiophene in methanol 4% and 200 parts of methanol was hydrogenated in a Parr apparatus and at 50°C with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the reaction mixture was evaporated. The residue was hydrogenated at normal pressure and at 50°C in 6 parts of acetic acid. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from methylbenzene. The product was filtered off and dried in vacuo at 40°C, yielding 10 parts (66.7%) of N-[2-acetyl-4-(dimethylamino)-phenyl]acetamide as a residue (int. 99).

Example 20

a) A mixture of 10.5 parts of 2-chloro-N-(2,6-dichloro-4-cyanophenyl)acetamide, 22 parts of 2-propanol, saturated with hydrogen chloride and 200 parts of methanol was hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in water and treated with a sodium hydroxide solution 50%. The product was extracted twice with dichloromethane. The combined extracts were dried, filtered and evaporated, yielding 10.7 parts (100%) of N-[4-(aminomethyl)-2,6-dichlorophenyl]-2-chloroacetamide as a residue (int. 100).

b) 10.1 Parts of bis(1,1-dimethylethyl) dicarbonate were added dropwise to 10.7 parts of N-[4-(aminomethyl)-2,6-dichlorophenyl]-2-chloroacetamide. Upon complete addition, stirring was continued for 1 hour at room temperature. The reaction mixture was washed with water, dried, filtered and evaporated. The residue was crystallized from methylbenzene. The product was filtered off and dried, yielding 10.08 parts (62.3%) of (1,1-dimethylethyl) [[3,5-dichloro-4-[(2-chloroacetyl) amino]phenyl]methyl]carbamate (int. 101).

c) A mixture of 7 parts of 4-[5,5-bis(4-fluorophenyl)pentyl]-2-piperazinecarboxamide, 6.6 parts of (1,1-dimethylethyl) [[3,5-dichloro-4-[(2-chloroacetyl)amino]phenyl]methyl]carbamate, 2.8 parts of N,N-diethylethanamine and 94 parts of N,N-dimethylformamide was stirred over weekend at 70°C. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted twice with dichloromethane. The combined extracts were washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, (96:4 by volume) as eluent. The desired fractions were collected and the eluent was evaporated, yielding 8.7 parts (80.7%) of (1,1-dimethylethyl) [[4-[[2-[2-(aminocarbonyl)-4-[5,5-bis-(4-fluorophenyl)pentyl]-1-piperazinyl]acetyl]amino]-3,5-dichlorophenyl]methyl]carbamate as a residue (int. 102).

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United States Patent [19]

Murakami et al.

[11] **4,145,363**

[45] **Mar. 20, 1979**

[54] **4-CARBAMOYLAMINO-α-AMINOMETHYLBENZYL ALCOHOL DERIVATIVES**

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[21] Appl. No.: **809,998**

[22] Filed: **Jun. 27, 1977**

Related U.S. Application Data

[62] Division of Ser. No. 651,738, Jan. 23, 1976, Pat. No. 4,063,025.

[30] **Foreign Application Priority Data**

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May 24, 1975 [JP] Japan 50-62207
Dec. 26, 1975 [JP] Japan 50-157348

[51] **Int. Cl.**[2] **C07C 127/17;** A61K 31/17

[52] **U.S. Cl.** ..... **260/553 A;** 260/553 C; 424/322

[58] **Field of Search** ..... 260/553 A, 553 C

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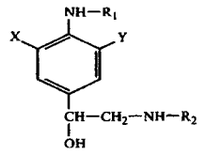
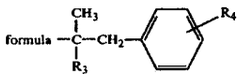
[57] **ABSTRACT**

There are disclosed novel 4-substituted amino-α-aminomethylbenzyl alcohol derivatives represented by the formula:



wherein X represents a halogen atom; Y represents a hydrogen atom or a halogen atom; R_1 represents a lower alkyl group, a carbamoyl group, a mono- or di-lower alkyl-substituted carbamoyl group, a phenyl-substituted carbamoyl group, a lower alkoxycarbonyl group, a lower alkoxy-substituted lower alkoxycarbonyl group, a phenyl-substituted lower alkoxycarbonyl group, or a cycloalkyloxycarbonyl group; and R_2 represents a lower alkyl group, a cycloalkyl group, or the group shown by the



wherein R_3 represents a hydrogen atom or a lower alkyl group and R_4 represents a hydrogen atom, a hydroxy group, or a lower alkoxy group and the pharmaceutically acceptable nontoxic salts thereof.

These compounds are antiasthmatic agents useful for the prophylaxis and treatment of asthma.

3 Claims, No Drawings

4-CARBAMOYLAMINO-α-AMINOMETHYLBENZYL ALCOHOL DERIVATIVES

This is a division of application Ser. No. 651,738, filed Jan. 23, 1976, now U.S. Pat. No. 4,063,025.

BACKGROUND OF THE INVENTION

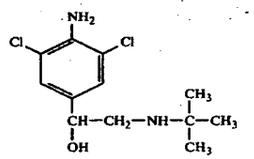
1. Field of the Invention

The present invention relates to novel benzyl alcohol derivatives and more particularly to novel 4-substituted amino-α-aminomethylbenzyl alcohol derivatives and the pharmaceutially accepable nontoxic salts thereof.

2. Description of the Prior Art

Various compounds having bronchodilator activity are known and among them Isoproterenol and Salbutamol are well known as a bronchodilating agent and are commercially available. In the prophylactic treatment of asthma, it is desirable that a medicament showing bronchodilator activity be administered orally. However, although commercially available medicaments show strong bronchodilator activity by parenteral adminstration such as by intravenous injection, or by aerosol adminstration, etc., the bronchodilator activity of these medicaments is not sufficiently strong when they are orally administered. Thus, there has been an urgent need for the discovery of a medicament showing a strong bronchodilator activity by oral adminstration.

Now, recently, it was reported that 1-(4-amino-3,5-dichlorophenyl)-2-tert-butylamino ethanol (referred to as NAB 365) shown by the formula:

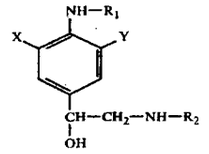


showed a strong bronchodilator activity by oral administration (see, Arzneim, Forsch; 22(5), 861–876(1972)). The report discloses that the bronchodilator activity of NAB 365 by oral administration is about 500 times stronger than that of Isoproterenol and about 100 times stronger than that of Salbutamol.

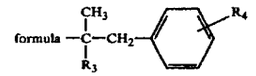
SUMMARY OF THE INVENTION

As a result of various investigations under such a technical level, the inventors have discovered that among the compounds obtained by introducing various substituents to the amino group at the 4-position of NAB 365 the compounds of this invention show a stronger bronchodilator activity than that of NAB 365 by oral administration and further the activity is selective.

According to the present invention, there are provided novel 4-substituted amino-α-aminomethylbenzyl alcohol derivatives shown by formula:



wherein X represents a halogen atom; Y represents a hydrogen atom or a halogen atom; R_1 represents a lower alkyl group, a carbamoyl group, a mono- or di-lower alkyl-substituted carbamoyl group, a phenyl-substituted carbamoyl group, a lower alkoxycarbonyl group, a lower alkoxy-substituted lower alkoxycarbonyl group, a phenyl-substituted lower alkoxycarbonyl group, or a cycloalkyloxycarbonyl group; and R_2 represents a lower alkyl group, a cycloalkyl group, or the group shown by the



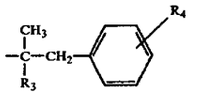
wherein R_3 represents a hydrogen atom or a lower alkyl group and R_4 represents a hydrogen atom, a hydroxy group, or a lower alkoxy group and the pharmaceutially acceptable nontoxic salts of them.

The compounds of this invention are useful as medicaments which show a relatively high activity more effectively to the smooth muscles of respiratory organs than to the cardiac muscles and show directly a bronchodilator activity by stimulation of a β-adrenergic receptor. In particular, the compounds of this invention have a selective bronchodilator activity by oral administration and thus they can be used as an excellent antiasthmatic agent for the prophylaxis and treatment of an asthma.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

As described above, the compounds of this invention are shown by formula I. As suitable examples of the halogen atoms shown by X and Y in the formula, there are illustrated a chlorine atom and a bromine atom. Also, suitable examples of R_1 in said formula are a lower alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, tert-butyl group, amyl group, etc.; a carbamoyl group; a mono- or di-lower alkylcarbamoyl group such as methylcarbamoyl group, dimethylcarbamoyl group, ethylcarbamoyl group, propylcarbamoyl group, isopropylcarbamoyl group, tert-butylcarbamoyl group, diethylcarbamoyl group, ethylmethylcarbamoyl group, etc.; a lower alkoxycarbonyl group such as methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, butoxycarbonyl group, tert-butoxycarbonyl group, amyloxycarbonyl group, etc.; a lower alkoxy-substituted lower alkoxycarbonyl group such as ethoxymethoxycarbonyl group, (2-ethoxy)ethoxycarbonyl group, (2-methoxy)ethoxycarbonyl group, etc.; a phenyl-substituted alkoxycarbonyl group such as benzyloxycarbonyl group, phenethyloxycarbonyl group, α-methylphenethyloxycarbonyl group, etc.; and a cycloalkyloxycarbonyl group such as cyclohex-

yloxycarbonyl group, cyclopentyloxycarbonyl group, cyclopropyloxycarbonyl group, etc. Examples of R_2 are a lower alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, tert-amyl group, etc.; a cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, etc.; and examples of R_3 shown by the formula



are a hydrogen atom; and a lower alkyl group such as methyl group, ethyl group, isopropyl group, butyl group, etc., and further examples of R_4 are a hydrogen atom; a hydroxy group; and a lower alkoxy group such as methoxy group, ethoxy group, isopropyloxy group, butoxy group, etc.

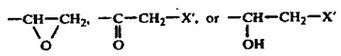
The preferred homologs of the compounds of this invention are the compounds of formula I in which R_2 is a tert-butyl group. The more preferable homologs of the compounds of this invention are the compounds of in the formula 1 in which R_1 is a lower alkoxycarbonyl group and R_2 is a tert-butyl group. Also, the most preferred compounds of this invention are the compounds of the formula 1 in which R_1 in the formula is an ethoxycarbonyl group, R_2 is a tert-butyl group, and X and Y each is a chlorine atom. That is, the practical examples of the most preferred compound of this invention are 3,5-dichloro-4-ethoxycarbonylamino-α-(tert-butylaminomethyl)benzyl alcohol and the pharmaceutially acceptable nontoxic salts thereof.

Furthermore, as the pharmaceutially acceptable nontoxic salts of the compounds of this invention, there are the acid addition salts thereof with a mineral acid such as hydrochloric acid, hydrobromic acid, phosphoric acid, etc., or an organic acid such as maleic acid, fumaric acid, acetic acid, etc.

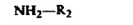
Now, the compound of this invention shown by formula I can be prepared by reacting the compound shown by formula: II

II

wherein X, Y, and R_1 have the same meaning as in formula I and W represents



(wherein X' represents a halogen atom) and the amine shown by formula III

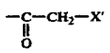


III

wherein R_2 and R_3 have the same meaning as in formula I and, if desired, reducing the reaction product thus obtained.

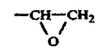
In more detail, at the practice of the aforesaid reaction, the compound of formula II is reacted with an equimolar or excessive amount of the amine of formula III in an organic solvent such as chloroform, isopropyl alcohol, ethanol, acetonitrile, ethyl acetate, dimethyl formamide, etc. In this case, it is preferred for carrying out the reaction smoothly, to add an acid binding agent such as sodium carbonate, potassium carbonate, etc., to the reaction mixture. The reaction usually proceeds sufficiently when carried out for from 30 minutes to 3 hours at room temperature or under heating but the reaction conditions may be properly selected in wide ranges according to the nature of the starting materials. That is, there is no particular limitation about the reaction temperature and reaction period of time but the temperature is preferably from −30° C. to 100° C. and the reaction period of time is preferably from 30 minutes to 48 hours.

When in the aforementioned reaction the compound of formula II wherein W is the group shown by



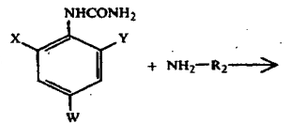
is used as the starting material, the reaction product thus obtained is then reduced. The reduction can be easily carried out by treating the reaction product with a reducing agent such as sodium borohydride, lithium aluminum hydride, etc., in an organic solvent such as methanol, ethanol, ethyl acetate, chloroform, ether, tetrahydrofuran, etc., usually at room temperature or, if desired, under ice-cooling.

Further, when the compound of formula II wherein W is the group shown by



is used as the starting material the reaction, it is preferred to heat the compound and the amine of formula III in a sealed tube.

In addition, when the compound of formula II wherein R_1 is a carbamoyl group is used, the reaction is sometimes accompanied by an amine exchange reaction at the same time to form a compound wherein the amino group in the carbamoyl group has been converted into the amine of formula III. This reaction is shown as follows.

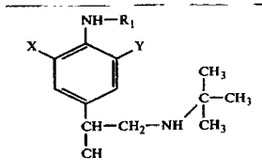


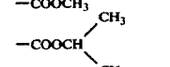
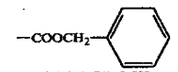
-continued

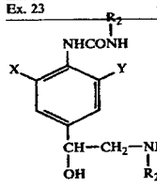
(1949)) using 4–8 groups and one group consists of 4–8 guinea pig.

The results are shown in the following Table I.

Table I



Sample	R_1	X	Y		anti-asthmatic activity ED_{50}(μg/Kg)
Known compound NAB 365	H	Cl	Cl	hydrochloride	490
Present compound					
Ex. 6	$-C_2H_5$	Cl	Cl	hydrochloride	125–250
Ex. 8	$-COOCH_3$	Br	Br	½ fumarate	125
Ex. 12		Cl	Cl	hydrochloride	32
Ex. 13		Cl	Cl	hydrochloride	125
Ex. 14	$-COOCH_2CH_2OCH_3$	Cl	Cl	hydrochloride	32
Ex. 15	$-CONHCH_3$	Cl	Cl	free base	125–250
Ex. 18	$-COOCH_3$	Br	Cl	½ fumarate	63
Ex. 23	$-COOC_3$	Cl	H	½ fumarate	63–125



The compound of formula I thus prepared may be isolated and purified by known chemical operations such as concentration, recrystallization, column chromatography, etc.

The compound of this invention can be administered orally as, for example, tablets, capsules, etc., or parenterally as, for example an intravenous injection, aerosol, etc. Also, when the compound of this invention is orally administered to an adult, the proper dosage thereof is 10–50 μg./day.

The experimental results obtained by testing the bronchodilator activity of the compounds of this invention are shown below together with the comparison results made with NAB 365:

EXPERIMENT I (Anti asthmatic activity)

The experiments were carried out according to the method of Parker et al., (*J. Pharmacol. Exptl. Therap.*, 118, 359–364 (1956)). A guinea pig was placed in a 11 liters glass chamber and exposed to the spasmogen by means of a nebulizer. When 0.1% histamine dihydrochloride was sprayed into the chamber, the guinea pig showed a symptom of dyspnea. Samples were administered subcutaneously to animals 30 min. prior the application of the spasmogen. If the guinea big showed no asthmatic dyspnoic symptoms, the sample was evaluated to be effective.

ED_{50} was calculated by the method of Litchfield-Wilcoxon (*J. Pharmacol. Exptl. Therap.*, 96, 99–113

EXPERIMENT II

(a) Bronchodilator activity, β_2 action

The experiments were carried out according to the method of Konzett and Rossler (Arch. exp. Path. Pharmakol., 195, 11–14 (1940)). Mongrel dogs were anesthetized with pentobarbital Na. Temporary increase in bronchial resistance, measured with transducer connected to a polygraph, were produced by histamine dihydrochloride, 10 μg/Kg injected rapidly intravenously at intervals of 30 min. The test samples were injected intraduodenally and the time-course of antihistamine activity of the sample (the inhibition rate (%) against the control) was obtained.

ED_{50} (μg/Kg) values of α-antagonists were obtained from the dose response curve drawn according to the peak effect on each dose. The results are shown in the Table II.

(b) Action on heartrate, β_1 action

Mongorel dogs were anesthetized with pentobarbital Na. Heart rate (HR) was recorded on polygraph. The samples were administered intra-duodenally and the HR was observed at varying intervals after the administration. The time-course of ΔHR (the increased HR against the control) was obtained.

The dose response curve drawn according to the peak response on each dose and the ED_{25} beats/min. (μg/Kg), that is the dose of the sample producing 25 beats/min. increase in heart rate was obtained from the curve. The results are shown in the following Table II.

(c) Broncho-selectivity

The broncho-selectivity was obtained by the following equation.

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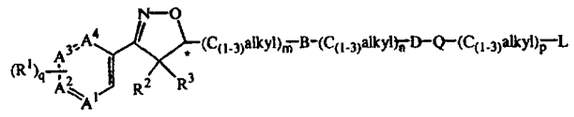


(I)

(57) Abstract

The present invention is concerned with the compounds of formula (I), wherein m, n and p are each independently 0 or 1 and q is 0, 1, 2, 3, 4 or 5; $-A^1=A^2-A^3=A^4-$ is pyridinylidene, pyridazinylidene, pyrimidinylidene, pyrazinylidene or phenylidene; B represents an amide, ketone or oxadiazole; D represents Ar or Het; Q represents a covalent direct bond or a ketone, –N–, –O–, $-CR^5R^6-$, amide, ethenyl, imine, sulfonyl, sulfinyl, 3–oxobutenyl, pyrazole isoxazole or thiazole; L represents Ar or Het; R^1 represents hydrogen, halo, hydroxy $C_{(2-6)}$alkenyl, $C_{(2-6)}$alkynyl, $C_{(3-6)}$cycloalkyl, $C_{(3-6)}$cycloalkenyl, cyano, guanidine, nitro $NR^{17}R^{18}$, an optionally substituted $C_{(1-6)}$alkyl or $C_{(1-6)}$alkyloxy; R^2 and R^3 each independently represent hydrogen, halo, $C_{(1-6)}$alkyloxy or an optionally substituted $C_{(1-6)}$alkyl; R^5 and R^6 each independently represent hydrogen, hydroxy, halo, an optionally substituted $C_{(1-6)}$alkyl, $C_{(2-6)}$alkenyl, $C_{(2-6)}$alkynyl, $C_{(3-6)}$cycloaklyl, $C_{(3-6)}$cycloalkenyl, $C_{(1-6)}$alkyloxy, cyano, $(C=O)R^{25}$, $(C=O)OR^{16}$, $(SO_2)R^{16}$, aminocarbonyloxy, amino $C_{(1-6)}$alkyl, $NR^{17}R^{18}$, N_3, Ar or Het; or R^5 and R^6 together with the carbon atom to which they are attached, form an Ar or Het; Ar represents an optionally substituted $C_{(6-14)}$aryl; Het represents an optionally substituted $C_{(1-14)}$heterocycle; or a *N*–oxide, pharmaceutically acceptable addition salt, quaternary amine or stereochemically isomeric form thereof; the process for their preparation and compositions comprising them. It further relates to their use as a medicine.

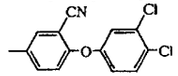
4,5-DIHYDRO-ISOXAZOLE DERIVATIVES AND THEIR PHARMACEUTICAL USE

The present invention is directed to novel isoxazole compounds, methods for their preparation, pharmaceutical compositions comprising these compounds, and their use in therapy, particularly in the prevention and/or treatment of disease states associated with immune cell activation and proliferation .

Higher organisms are characterized by an immune system which protects them against foreign pathogens and endogenous diseases such as tumors and genetic defects. The immune system has developed a series of pathways to protect the host. The primary cells of the immune system are lymphocytes. One class of lymphocytes, T lymphocytes, affects and regulates the cell mediated response of the immune system. They consist of a heterogeneous population of cells with several distinct functional subsets called helper cells, suppressor cells and killer cells.

T lymphocytes are derived from the thymus and circulate through the blood and lymphatic vessels of the body where they can detect and interact with foreign invaders i.e. viruses, allergens, tumors and autoantigens. Upon specific interaction with invading pathogens,
T lymphocytes are activated, resulting in the development of enlarged cells - T cell blasts - which subsequently turn on the machinery for cytokine synthesis, cytokine receptor expression and proliferation. This initiates a cascade of host defense actions involving other lymphocyte subsets.

While the normal immune system is closely regulated, aberrations in the immune response are not uncommon. Many signs and symptoms of infectious, inflammatory and neoplastic diseases evolve as a result of abnormalities in the immune system, especially in T lymphocyte-mediated immunity. Even if these immunocompetent cells are not involved in the initial stage, abnormal regulation of otherwise normal appropriate cellular immune reactions may lead to acute and chronic diseases. These diseases are often of unknown etiology and include systemic rheumatic diseases, organ specific endocrine diseases, inflammatory disease of the gut and skin. The treatments available in relation to said diseases are usually symptomatic or palliative, i.e. most of the drugs prescribed in connection with said diseases are directed at allaying the symptoms and have no curative effect. Thus, a long-felt need exists for an effective means of curing or ameliorating T lymphocyte-mediated pathologies. Such a treatment

Co. No.	Ex. No.	R^6	R^{17}	R^{18}	Physical Data
177	B16b	H	H	4-methoxyphenyl	-
178	B16b	H	H	3-hydroxyphenyl	-
179	B16b	H	H	2-cyanomethyl	-
180	B16b	H	H	6-benzothiazolyl	-
181	B16b	H	H	3-hydroxy-4-methylphenyl	-
182	B16b	H	H	4-chloro-3-methylphenyl	-
183	B16b	H	H	4-carboxy-3-hydroxyphenyl	-
184	B16b	H	H		-
185	B16b	H	H	2,4-difluorophenyl	-
186	B16b	H	H	4-methylphenyl	-
187	B16b	H	H	3,5-dichlorophenyl	-
188	B16b	H	H	3-methoxyphenyl	-
189	B16b	H	H	4-fluorophenyl	-
190	B16b	H	H	3-methylphenyl	-
191	B16b	H	H	3,5-dichloro 4-(methylcarboxyl-amino)phenyl	-
192	B16b	H	H	2-aminocarbonylphenyl	-
193	B16b	H	H	2-methoxyphenyl	-
194	B16b	H	H	2,5-dimethylphenyl	-
195	B16b	H	H	3,4-dichlorophenyl	-
196	B16b	H	H	2,5-dichlorophenyl	-
197	B16b	H	H	3-(trifluoromethyl)phenyl	-
198	B16b	H	H	2-methylphenyl	-
199	B16b	H	H	2,4-dimethylphenyl	-
200	B16b	H	H	4-chloro-2-iodophenyl	-
201	B16b	H	H	2,3-dichlorophenyl	-
202	B16b	H	H	2-(methoxyoxycarbonyl)phenyl	-
203	B16b	H	H	2-hydroxyphenyl	-
204	B16b	H	H	2,4-dimethoxyphenyl	-
205	B17c	H	H	H	[5S-(A)]
206	B17c	H	H	H	[5S-(B)]
207	B16b	CN	H	2-pyridinyl	-
208	B16b	H	H	4-chlorophenyl	-