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Señor

SUPERINTENDENTE DELEGADO PARA LA F
DIVISION DE NUEVAS CREACIONES

SUPERINDUSTRIA Y COMERCIO

Radicacion : 00052050 00010000

Fecha (AMD): 2004-08-31 11:51:00

Tramite : 002 PATENTES D 332 PRESENTAC 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 2

E. _____ S. _____ D. _____

Ref: P1.-GRUNENTHAL GmbH.-Expediente No. 00-052.850.-

1. Me refiero al asunto de la referencia.
2. Por medio del presente, atentamente me permito manifestar que hubo un **cambio** de apoderado para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **GRUNENTHAL GmbH**.
3. En consecuencia, atentamente solicito a ese Despacho reconocirme personería en este asunto, de conformidad con la sustitución de poder adjunta, otorgada a favor de la SUSCRITA.
4. Por lo tanto, ruego a usted notificarme de las providencias expedidas dentro de este expediente y notificadas al anterior apoderado, que actualmente se encuentran pendientes de cumplimiento o de respuesta.
5. Solicito a ese Despacho proceder de conformidad.

Atentamente,



ALICIA LLOREDA RICAURTE

T.P. 53215

Código 231

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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. _____ S. _____ D. _____

Ref: P1.-GRUNENTHAL GmbH .-Expediente No.00-052.850.-

Yo, **JOSE ANTONIO LLOREDA**, mayor de edad y vecino de esta ciudad, abogado titulado e inscrito, identificado como aparece al pie de mi firma, actuando en mi carácter de Representante Legal en Bogotá para asuntos relacionados con la propiedad industrial de **GRUNENTHAL GmbH**, sociedad organizada y existente de conformidad con las leyes de Alemania, domiciliada en Aachen, Alemania, tal y como consta en este expediente, atentamente manifiesto a usted que **SUSTITUYO** el poder a mi conferido a la doctora **ALICIA LLOREDA RICAURTE**, abogada titulada e inscrita, identificada con la cédula de ciudadanía No. 39.690.713 de Usaquén, para que continúe representando a la mencionada sociedad en el expediente de la referencia.

De conformidad con el artículo 66 del C.P.C., manifiesto bajo la gravedad de juramento que los demás apoderados citados en el documento otorgado a mi favor no desean ejercer el poder a ellos conferido.

El mencionado apoderado tendrá las mismas facultades a mi conferidas, en especial, renunciar, recibir, sustituir, desistir, presentar recursos, conciliar, transigir, y en fin, para todo lo que se encamine a la correcta defensa de los intereses de la sociedad en cuyo nombre hablo.

NOTARIA SEXTA DE BOGOTA

CONOCIMIENTO Y PRESENTACION PERSONAL

Atentamente,

Bogotá, D.C.

Ante mi **PABLO MENDEZ BARRAJAS**

NOTARIO SEXTO(E) DEL CIRCULO

BOGOTA

Comparece el Sr. **JOSE ANTONIO LLOREDA**

T.P. /10784

Código 231

quien (es) exhibió (eron) la(s) C.C.

JOSE ANTONIO LLOREDA
C.C. No. 17.159.681 de Bogotá



291

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 00-52850

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION** FUE PUBLICADO

EN LA GACETA DE PROPIEDAD INDUSTRIAL No 526, DE FECHA 31 DE **MARZO** DE 2003, EL

TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL 01 DE **JULIO** DE 2003.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO ☒ _____

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2005/09/01

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, D.C., 25 de agosto de 2005

Apoderado: Alicia Lloreda Ricaurte

Oficio: 001 7736

REFERENCIA: Radicación No. 00-52850
Tramite 002
Evento 001
Actuación 430
Folios

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:

Documentos estudiados:

- ◆ Capítulo descriptivo folios 5 a 76;
- ◆ Capítulo reivindicatorio, folios 77 a 112;
- ◆ 1° examen de forma folios 120 y 121;
- ◆ Respuesta técnica al primer examen de forma, folios 122 y 123;
- ◆ Solicitudes de las cuales se reivindica prioridad, folios 124 a 271;
- ◆ 2° examen de forma folio 272;
- ◆ Solicitud del examen de patentabilidad, folios 449 a 451;

Objeto de la invención:

La presente solicitud cuyo título es "DERIVADOS DE 2-BENCIL-3-DIMETILAMINO-1-FENILPROPANO". El objeto de la solicitud son los compuestos derivados de 2-bencil-3-dimetilamino-1-fenilpropano que tiene un actividad farmacológica como analgésico.

El objeto de la invención se puede clasificar según la clasificación internacional como A61K 31/135.

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Claridad de la solicitud:

En el artículo 30 de la decisión 486 de la Comisión de la Comunidad Andina se establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.

-Las reivindicaciones 49 y 50 no es clara, puesto que el encabezado no es consistente con el resto del texto de la reivindicación. Una composición no se puede caracterizar por su uso o por el efecto terapéutico que se desea obtener, una composición se caracteriza por sus elementos constitutivos particulares.

Reivindicaciones de uso:

La Decisión 486 establece: *"Artículo 14.- Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."*

Las reivindicaciones 51 a 63 reclaman el uso de los compuestos...", y el uso no es patentable de acuerdo con el campo de la patentabilidad definido en el artículo en referencia, donde solo se consideran patentables los productos o procesos, en ningún momento se hace alusión a que el uso sea patentable.

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comunidad Andina establece que: *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*.

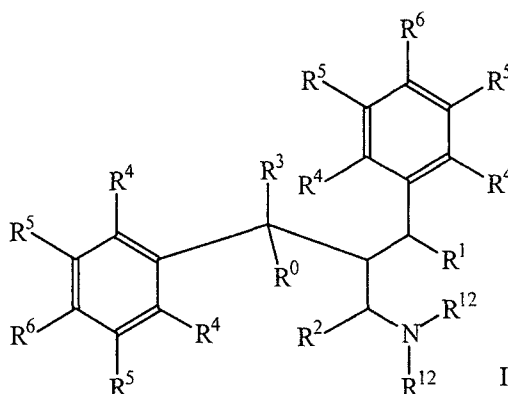
En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio. Reivindicaciones 1 a 48 de los folios 77 a 107, consultada la fuente de información con que cuenta este despacho se encontró los siguientes documentos:

Item	Documento	Fecha de publicación	Título
D1	GB901438	18-jul-1959	Maleamic Acid Derivaives
D2	GB938732	28-nov-1960	Substituted amines and a process for their manufacturate
D3	US3277165	04-oct-1966	Fumaric acid derivatives
D4	US3342829	19-sep-1967	Bis-quaternary salts of triamines and process fro preparing them
D5	WO9856752	17-dic-1998	Compounds active at a novel site on receptor-operated calcium channels usefull for treatmen of neurological disorders and diases

Evaluación de la novedad:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina dispone que: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*.

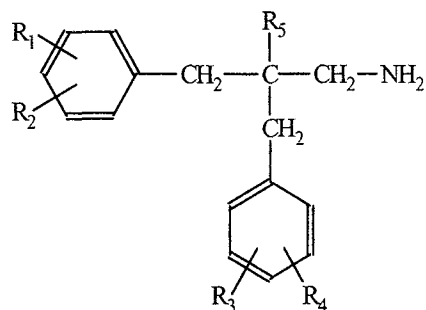
En la solicitud en estudio se reivindica un compuesto que comprende la fórmula (I):



-La anterioridad D1 enseña compuestos derivados de ácido maleámico, especialmente el compuesto específico ácido N-(1-metil-2-benzil-3-fenilpropil)-maleámico (ejemplo 30); es compuesto cae dentro de los compuestos reclamados en la solicitud en estudio, siendo un compuesto específico demuestra que los compuestos de solicitud en estudio representados con la fórmula Markush I no son nuevos.

-La anterioridad D2 enseña los compuestos de fórmula (I)

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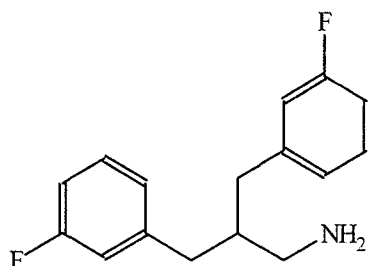


Son propilamina derivados, igualmente se describe compuestos específicos en los ejemplos 3 a 7 de esta anterioridad que caen dentro de la formula Markush de la solicitud en estudio. Por ser compuestos específicos se demuestra que los compuestos de solicitud en estudio representados con la fórmula I Markush no son nuevos.

-La anterioridad D3 enseña compuestos derivados de ácido fumárico, especialmente el compuesto específico fenil-2-benzil-3-butanona (ejemplo 10); es compuesto cae dentro de los compuestos reclamados en la solicitud en estudio, siendo un compuesto específico demuestra que los compuestos de solicitud en estudio representados con la fórmula Markush I no son nuevos.

La anterioridad D4, describe sales de bis-cuaternario de triaminas especialmente el compuesto específico N-[β-(2,4-diclorofenil)-γ-(2,4-diclorofenil)-propil]-N-N-bis-(β-piridiniometil)-amina dicloruro (reivindicación 5); es compuesto que cae dentro de los compuestos reclamados en la solicitud en estudio, siendo un compuesto específico demuestra que los compuestos de solicitud en estudio representados con la fórmula Markush I no son nuevos.

La anterioridad D5 describe compuestos diaril amino sustituidos, especialmente el compuesto de formula específica:



que cae dentro de los compuestos reclamados en la solicitud en estudio, siendo un compuesto específico demuestra que los compuestos de solicitud en estudio representados con la fórmula Markush I no son nuevos.

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No	Documento:	Reivindicaciones afectadas:	Requisito afectado
D1	GB901438	1	NOVEDAD
D2	GB938732	1, 2, 5, 8, 14, 15, 18, 19, 22, 23, 48, 50	NOVEDAD
D3	US3277165	1	NOVEDAD
D4	US3342829	1	NOVEDAD
D5	WO9856752	1	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 la 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 conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5° del título 1° de la Circular Única n°.10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL.

Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 10 SET. 2005

CONCEPTO TÉCNICO No. 1298	EXAMINADOR TÉCNICO Código: 202012
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901438

D1 297
462

Date of Application and filing Complete Specification: April 29, 1959.

No. 14638/59.

Complete Specification Published: July 18, 1962.

Index at acceptance:—Class 2(3), C1E6K(1:3:6:7), C1F1(A1:A2:C2:C4:C5:D2), C1F3(A2:B:D3), C1F4(B:D2:F5), C1H1(A1:B:C2), C2A(2:5:7:12:13:14), C2B3(A2:B:G1:G6:G8:G9), C2B(21:30), C2B46(C2:G1:G5), C2B47(C2:G1:G2:G3:G5), C2C(2:7E), C2R15, C2T(16:18), C3A12(A2:B3:C3:C6), C3A13C(1C:9:10F), C3A14A(2D:7A:8D).

International Classification:—C07c.

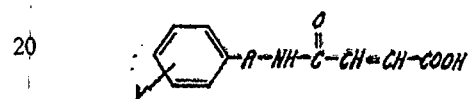
COMPLETE SPECIFICATION

Maleamic Acid Derivatives

We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to derivatives of maleamic acid, and is concerned with certain derivatives in which a hydrogen atom of the amino group of maleamic acid is replaced by a substituted phenylethyl radical or by a substituted or unsubstituted phenylpropyl radical.

The novel compounds of this invention can be illustrated by the following structural formula:



The invention includes the alkali metal salts and simple ester derivatives of the novel acids, i.e., esters in which the carboxyl group is esterified, including those esters derived from the C_{1-10} alcohols. In the above formula, Y is a hydrogen or halogen atom, particularly chlorine or bromine, or a C_{1-10} alkyl or C_{1-10} alkoxy group, and R is an ethylene or propylene radical, each valency of the ethylene or propylene radical being satisfied by one of the following: (a) hydrogen, with the proviso that not more than three of the valencies of an ethylene radical should be

[Price

satisfied by hydrogen, (b) a C_{1-10} , preferably C_{1-6} , straight or branched-chain alkyl radical, such as a methyl, *iso*- or *n*-propyl, *iso*- or *n*-butyl, amyl, or hexyl radical; (c) a saturated alicyclic radical such as cyclopentyl or cyclohexyl radical; (d) a mononuclear aryl or mononuclear aryl- C_{1-10} alkyl radical, either unsubstituted or having a C_{1-10} alkyl, C_{1-10} alkoxy or halogen (preferably chlorine or bromine) substituent attached to the aryl portion in *ortho*, *meta* or *para* position; and (e) a hydroxy group.

The compounds of this invention possess a variety of properties and are especially useful because they inhibit the excretion of penicillin through the kidney tubules thus providing prolonged blood levels of penicillin. Because of this property the new compounds of this invention are useful as adjuvants for use in conjunction with the administration of penicillin to provide an increase in the blood plasma penicillin concentration with a given dose of penicillin, thereby making possible very high penicillin blood levels, or permitting the use of smaller quantities of penicillin for providing a given blood level, or permitting less frequent administration of penicillin while maintaining a penicillin blood level adequate for bactericidal or bacteriostatic purposes.

Some of the compounds additionally enhance the excretion of uric acid from the body and therefore are useful agents in the treatment of gout or gouty arthritis and in alleviating symptoms of these conditions and of complications associated with gout and gouty arthritis.

Additionally, some of the compounds have been found to inhibit the biosynthesis of

PATENT SPECIFICATION

NO DRAWINGS

Inventors: EVERETT MAYNARD SCHULTZ, JOHN BEEH BICKING and
VIRGIL DANIEL WEIBELHAUS

901,438



Date of Application and filing Complete Specification: April 29, 1959.

No. 14638/59.

Complete Specification Published: July 18, 1962.

ERRATA

SPECIFICATION No. 901,438

Page 1, line 44, for "ortho" read "ortho"
Page 5, marginal line No. 50 should read
"49"

Page 5, line 52 } for "N-(2-" read "N-(1-"
Page 8, line 72 }
Page 6, line 19, for "C, 64.96" read
"C, 64.93"

Page 6, line 58, for "yield" read "yields"
Page 7, line 75, insert "comma" after "ether"
Page 8, line 73, delete "comma" after
"(2.5g.)"

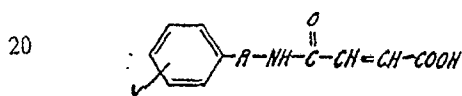
Page 10, line 110 } for "Calcd,"
Page 11, line 54 } read "Calcd."
Page 13, line 1, for "Calcd," read "Calcd."
Page 15, Example 38, insert "Step A"
between lines 14 and 15

Page 15, line 39, delete "The thus" in the
first occurrence

Page 15, line 43, for "Step 8," read "Step
B,"

THE PATENT OFFICE
27th September 1963

The novel compounds of this invention can
be illustrated by the following structural
formula:



The invention includes the alkali metal salts
and simple ester derivatives of the novel acids,
i.e., esters in which the carboxyl group is
esterified, including those esters derived from
25 the C₁₋₁₀ alcohols. In the above formula, Y
is a hydrogen or halogen atom, particularly
chlorine or bromine, or a C₁₋₁₀ alkyl or C₁₋₁₀
alkoxy group, and R is an ethylene or
propylene radical, each valency of the
30 ethylene or propylene radical being satisfied
by one of the following: (a) hydrogen, with
the proviso that not more than three of the
valencies of an ethylene radical should be

[Price]

longed blood levels of penicillin. Because of
this property the new compounds of this in-
vention are useful as adjuvants for use in con-
junction with the administration of penicillin
to provide an increase in the blood plasma
penicillin concentration with a given dose of
55 penicillin, thereby making possible very high
penicillin blood levels, or permitting the use
of smaller quantities of penicillin for providing
a given blood level, or permitting less frequent
administration of penicillin while maintaining
60 a penicillin blood level adequate for
bactericidal or bacteriostatic purposes.

Some of the compounds additionally
enhance the excretion of uric acid from the
body and therefore are useful agents in the
65 treatment of gout or gouty arthritis and in
alleviating symptoms of these conditions and
of complications associated with gout and
gouty arthritis.

Additionally, some of the compounds have
70 been found to inhibit the biosynthesis of

C4: C5: D2),
C2A (2: 5: 7:
C2B46 (C2:
R15, C2T (16:
A14A (2D: 7A:

preferably
1 radical, 35
iso- or n-
saturated
or cyclo-
or mono-
er unsub- 40
alkoxy
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id (e) a 45

possess a
ily useful
penicillin
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Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50;
Found: C, 69.57; H, 5.60; N, 4.48.

EXAMPLE 30.
5 N-(1-Methyl-2-benzyl-3-phenylpropyl)-maleamic Acid.

1-Phenyl-2-benzyl-3-butanone is converted by the Leuckart reaction in substantially the manner described in Example 1, Step B, to 1-phenyl-2-benzyl-3-aminobutane hydrochloride. The hydrochloride salt is converted to the free base, by substantially the procedure described in Example 1, Step

E, b.p. 193—198° C. (15 mm.). The aminobutane thus obtained (4.8 g., 0.02 mole) is dissolved in ether (30 ml.) and reacted with a solution of maleic anhydride (0.02 mole) in ether (30 ml.) yielding 3.5 g. of N-(1-methyl-2-benzyl-3-phenylpropyl)-maleamic acid, m.p. 142—143° C. after crystallization from a mixture of benzene-hexane by the method described in Example 15, Step E. 15 20

Anal. Calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15;
Found: C, 74.77; H, 6.96; N, 4.15.

EXAMPLE 31.
25 N-(1-Benzyl-3-phenylpropyl)-maleamic Acid.

1,4-Diphenyl-2-aminobutane (11.25 g., 0.05 mole) is dissolved in ether (30 ml.) and reacted with a solution of maleic anhydride

(4.9 g., 0.05 mole) in ether (30 ml.) yielding 10.7 g. of N-(1-benzyl-3-phenylpropyl)-maleamic acid, m.p. 133—135° C. after crystallization from a mixture of benzene-hexane by the method described in Example 15, Step E. 30 35

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33;
Found: C, 74.49; H, 6.70; N, 4.35.

EXAMPLE 32.
40 N-(1-*n*-Propyl-3-phenylpropyl)-maleamic Acid.

1-Phenyl-3-hexanone (26.7 g., 0.15 mole) is submitted to a Leuckart reaction in substantially the manner described in Example 1, Step B, yielding 15 g. of 1-phenyl-3-aminohexane hydrochloride. The hydrochloride salt is converted to the free base by

substantially the procedure described in Example 1, Step E, b.p. 142° C. (25 mm.). The aminohexane thus obtained (5.3 g., 0.03 mole) is dissolved in ether (30 ml.) and reacted with a solution of maleic anhydride (0.03 mole) in ether (30 ml.) yielding 2.55 g. of N-(1-*n*-propyl-3-phenylpropyl)-maleamic acid, m.p. 101—102° C. after crystallization from a 5:1 mixture of ether-benzene. 50 55

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09;
Found: C, 69.88; H, 7.61; N, 5.07.

EXAMPLE 33.
60 N-(1,3-Diphenylpropyl)-maleamic Acid.
1,3-Diphenyl-1-aminopropane hydrochloride (7.42 g., 0.03 mole) is converted to an ethereal solution (30 ml.) of the base by substantially the method described in Example 1, Step E. The ethereal solution of the

base thus obtained is reacted with a solution of maleic anhydride (2.94 g., 0.03 mole) in ether (30 ml.) yielding 6.2 g. of N-(1,3-diphenylpropyl)-maleamic acid, m.p. 151—152° C., after crystallization from a 5:2 mixture of alcohol-water. 65 70

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53;
Found: C, 73.87; H, 6.05; N, 4.57.

EXAMPLE 34.
75 N-(1-Isopropyl-3-phenylpropyl)-maleamic Acid.

Step A.
Isopropyl-2-phenylethyl ketone (55 g.) is submitted to the Leuckart reaction in substantially the manner described in Example 1, Step B, to form 1-phenyl-4-methyl-3-

aminopentane hydrochloride. The hydrochloride salt is converted to the free base by substantially the procedure described in Example 1, Step E, yielding (33 g.) of the free base, b.p. 90—95° C. (0.4 mm.). The hydrochloride of the aminopentane is prepared by the usual method and melts at 195—196° C. after crystallization from benzene. 85

PATENT SPECIFICATION

NO DRAWINGS

938.732

DZ
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Date of Application and filing Complete Specification: Nov. 28, 1960.

No. 40880/60.

Application made in Germany (No. F29941 IVb/12q) on Nov. 27, 1959.

Complete Specification Published: Oct. 2, 1963.

© Crown Copyright 1963.

Index at acceptance:—Class 2(3), C1F1(C2:D2), C1F2(C2:C5:D2), C1F4(C2:D2:F3),
C1H1(A1:C2), C1H2(A7:C2).

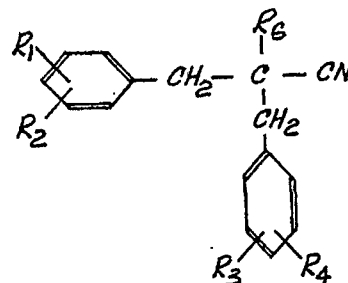
International Classification:—C07c.

COMPLETE SPECIFICATION

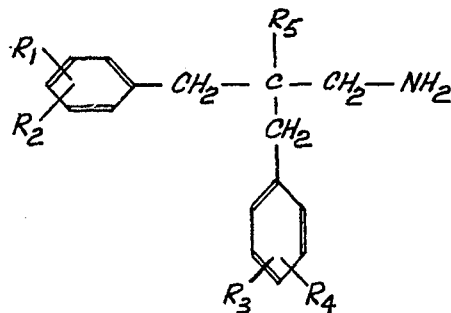
Substituted Amines and a process for their manufacture

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT vormals Meister Lucius & Brüning, a body corporate recognised under German law, of (16) Frankfurt (M)-Hoechst, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 The present invention provides new substituted amines of the formula



30



35

15 in which R_1 and R_3 each represents a halogen atom, R_2 and R_4 each represents a hydrogen atom or a halogen atom and R_5 represents a hydrogen atom, an alkyl group containing 1—5 carbon atoms, a hydroxy-methyl group or a carboxyl group esterified by an alkyl group containing 1—4 carbon atoms, and acid addition salts thereof.

20 The new compounds are easily compatible and exhibit valuable therapeutic properties. They have particularly valuable uses as disinfectants, bacteriostatics and fungistatics.

25 The present invention also provides a process for the manufacture of the new substituted amines corresponding to the above formula, which comprises reducing a nitrite corresponding to the following formula

[Price 4s. 6d.]

in which R_1 , R_2 , R_3 and R_4 have the meanings indicated above and R_6 represents a hydrogen atom, an alkyl group containing 1—5 carbon atoms or a carboxyl group esterified by an alkyl group containing 1—4 carbon atoms, and, if desired, converting the base obtained into the corresponding acid addition salt by treatment with an inorganic or organic acid.

R_1 and R_3 in the above defined starting materials may represent fluorine, chlorine, bromine or iodine, but are advantageously chlorine atoms.

R_2 and R_4 in the above defined starting materials may represent fluorine, chlorine, bromine or iodine as the halogen atoms, but are preferably chlorine atoms. Both benzene nuclei of the starting materials may be substituted by the same or different halogen atoms.

R_6 in the above defined starting materials may represent a hydrogen atom or a straight- or branched-chain alkyl group of low molecular weight containing 1—5 carbon atoms, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl or *n*-amyl. R_6 may, furthermore, represent a carboxyl group esterified by an alkyl group containing 1—4 carbon atoms, the propyl and butyl groups having straight or branched chains.

The following starting materials yield particularly valuable products when used in the process of the present invention: α, α -bis-(4-

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chlorobenzyl) - propionitrile, α,α -bis - (3,4 - dichlorobenzyl)-propionitrile, α - (4 - chlorobenzyl) - β - (4¹ - chlorophenyl) - propionitrile, α - (3,4 - dichlorobenzyl) - β - (3,4-dichlorophenyl) - propionitrile, α - (2,4 - dichlorobenzyl) - β - (2,4 - dichlorophenyl)-propionitrile, α - (3,4 - dichlorobenzyl) - β - (4 - chlorophenyl) - propionitrile, α,α - bis - (3,4 - dichlorobenzyl) - valerionitrile, bis - (4-chlorobenzyl) - cyanoacetic acid methyl ester, bis - (3,4 - dichlorobenzyl) - cyanoacetic acid methyl ester, bis - (3,4 - dichlorobenzyl)-cyanoacetic acid ethyl ester and bis-(2,4-dichlorobenzyl) - cyanoacetic acid *n*-butyl ester.

The starting materials can be prepared in various different ways. They may, for example, be prepared as follows: a nitrile possessing a methylene group in the α -position and a substituted benzylhalide are dissolved in an inert solvent such, for example, as benzene, and a suspension of sodium amide in the same solvent is allowed to react with this solution whereupon the hydrogen atoms of the methylene group vicinal to the cyano group are substituted by two benzyl radicals with the evolution of ammonia. Another way of preparing the nitriles consists, for example, in reacting substituted benzylhalides with the sodium compounds of cyanoacetic acid alkyl esters using the corresponding alcohols as solvents. In this manner there are obtained cyanoacetic acid alkyl esters substituted by two benzyl radicals, the ester groups of which may be hydrolysed, if desired, in an alkaline medium and decarboxylated by dry heating to a temperature within the range of 180—250° C.

The new substituted amines are prepared by reduction in the process of the present invention by the chemical methods which are known to be in actual use or described in the literature on the subject for the reduction of nitriles to the corresponding amines. Thus, for example, the reduction can be carried out by allowing an alkali metal hydride, for example, lithium-aluminium-hydride or sodium-borohydride, to react with the nitrile. The process is preferably carried out with the use of an anhydrous inert solvent. As such solvents there are advantageously used, for example, aliphatic or cyclic ethers, for example, diethyl ether, dioxane, or tetrahydrofuran. The reaction may be carried out at temperatures of 0° C. to 150° C., or preferably at the boiling temperatures of the solvents used. The reaction is advantageously initially carried out while cooling the reactants with ice and then completed by raising the temperature to the boiling temperature of the solvent.

If R_6 in the nitrile subjected to the action of the metal hydride is an esterified carboxyl group, this group may, if desired, simultaneously be reduced in the process of the present invention to the hydroxymethyl group provided that a sufficient quantity of reducing agent is used.

The reduction of the nitriles can be carried out with particular advantage in the process of the present invention by catalytic hydrogenation. In this case the process is preferably carried out in the presence of alcohols or ethers, for example, methanol, ethanol or dioxane as solvent and an excess of ammonia is added in order to avoid the formation of secondary amines. As catalysts there may be used the usual substances, preferably Raney-nickel or Raney-cobalt. The hydrogenation is generally carried out at an elevated hydrogen pressure, advantageously within the range of 50 to 150 atmospheres gauge, and at a moderately elevated temperature, preferably within the range of 40 to 50° C. Under these reaction conditions halogen atoms contained in the starting materials are surprisingly not eliminated in the form of the hydrogen halide. When the reaction temperature is increased beyond the above indicated range, however, partial separation of the halogen sets in.

For working up, the reaction mixture is suitably separated from the catalyst by suction-filtration and the solvent is eliminated by distillation. For the purpose of purification the crude product being contained in the distillation residue is advantageously converted into a corresponding acid addition salt such, for example, as the hydrochloride, and the salt obtained is purified in the usual manner since the distillation of the crude product generally proceeds with decomposition and, therefore, involves a considerable loss of the product.

In general, the new substituted amines are obtained in the form of colourless or yellow viscous oils which can be distilled under reduced pressure with variable serious decomposition occurring. They are therapeutically active in the form of their free bases, and more particularly in the form of their physiologically tolerable acid addition salts which may be obtained in the usual manner by treating the free bases with inorganic or organic acids. As inorganic acids there may be mentioned: hydrohalic acids, for example, hydrochloric or hydrobromic acid, sulphuric acid, phosphoric acid and amidosulphonic acid. As organic acids there may be used, for example, acetic acid, propionic acid, butyric acid, aceturic acid, tartaric acid, succinic acid, malic acid, maleic acid, fumaric acid, sorbinic acid, citric acid, aspartic acid, para-amino-benzoic acid, salicylic acid and ethylene diamine-tetracetic acid.

The acid addition salts which may be obtained by treatment with the acids are mostly colourless crystalline compounds, the solubility of which depends upon both the type of the anion and the number of the halogen atoms contained in the molecule.

The new substituted amines of the present invention possess in addition to a good compatibility valuable therapeutic properties the

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EXAMPLE 2.

2,2-bis-(3¹,4¹-dichlorobenzyl)-propylamine.

115 Grams of α,α -bis-(3,4-dichlorobenzyl)-propionitrile were hydrogenated in a mixture of 2000 cc of dioxane saturated with ammonia and 15—20 grams of Raney-nickel at a temperature ranging between 40° C. and 50° C. and under a pressure of 100 atmospheres gauge until the absorption of hydrogen was complete. The oil remaining after suction-filtration of the catalyst and distillation of the solvent was dissolved in 1500 cc of ether and mixed with 54 cc of alcoholic hydrochloric acid of 21% strength whereupon a salt immediately separated. The product was filtered with suction, washed with water and dried in air; 102 grams were obtained. By recrystallization from 1000 cc of alcohol to which 1000 cc of diisopropyl ether were added prior to the suction-filtration in order to complete the crystallization, there were obtained 71 grams of pure 2,2-bis-(3¹,4¹-dichlorobenzyl)-propylamine-hydrochloride melting at a temperature ranging between 248° C. and 250° C.

In order to obtain the pure free base, the salt was agitated with dilute sodium hydroxide solution and ether until completely dissolved, the ethereal layer was dried over potassium carbonate and the ether was distilled off. The 2,2-bis-(3¹,4¹-dichlorobenzyl)-propylamine was obtained in the form of a light yellow thick oil.

The α,α -bis-(3,4-dichlorobenzyl)-propionitrile serving as starting material was prepared as follows: a suspension of 147 grams of sodium amide of 80% strength in 400 cc of dry benzene was added in small portions, while stirring vigorously, to a solution of 82.5 grams of propionitrile and 586.5 grams of 3,4-dichlorobenzyl-chloride in 1000 cc of dry benzene which had been heated to 50—60° C. After each addition a vigorous reaction could be observed. The reaction mixture was stirred for two hours at the same temperature and then poured into about 1000 cc of iced water. The organic phase was separated and washed with water. After drying over calcium chloride the benzene was distilled off. The residue solidifying in a crystalline form was comminuted in the mortar and triturated with a small quantity of methanol. After suction-filtration there were obtained 370 grams of a yellow-coloured product. After recrystallization from isopropanol, the α,α -bis-(3,4-dichlorobenzyl)-propionitrile was obtained in the form of almost colourless crystals melting at a temperature ranging between 131 and 132° C.

EXAMPLE 3.

2-(4¹-chlorobenzyl)-3-(4¹¹-chlorophenyl)-propylamine.

85 Grams of α -(4-chlorobenzyl)- β -(4¹-chlorophenyl)-propionitrile were dissolved in 800 cc of dioxane saturated with ammonia and the solution was hydrogenated using Raney-

nickel as a catalyst at a temperature ranging between 40° C. and 50° C. and under a pressure of 100 atmospheres gauge. After completion of the hydrogen absorption, the Raney-nickel was removed by suction-filtration and the dioxane was distilled off under a slightly reduced pressure. There remained behind 83 grams of a crude product which was dissolved in 1000 cc of ether and mixed with 40 cc of alcoholic hydrochloric acid of 28% strength whereupon the hydrochloride separated out in solid form. The salt was filtered with suction, washed with ether and dried at a temperature of about 100° C. 82 Grams of 2-(4¹-chlorobenzyl)-3-(4¹¹-chlorophenyl)-propylamine-hydrochloride melting at 163—164° C. were obtained. The melting point even remained constant after recrystallization from a mixture of isopropanol/benzene/diisopropyl ether. The free base, namely 2-(4¹-chlorobenzyl)-3-(4¹¹-chlorophenyl)-propylamine, was obtained from the salt in the usual manner and formed a light yellow thick oil.

The α -(4-chlorobenzyl)- β -(4¹-chlorophenyl)-propionitrile serving as starting material was prepared as follows: into a sodium methylate solution obtained by dissolving 46 grams of sodium in 750 cc of absolute methanol there were added dropwise at room temperature, while mechanically stirring, 110 grams of cyanoacetic acid methyl ester and after mechanically stirring for 30 minutes, 354 grams of 4-chlorobenzylchloride, the temperature being maintained below 35° C. by slight cooling. After completion of the addition, the reaction mixture was further heated for one hour under reflux. Nearly all the methanol was then distilled off and the residue was poured into water whereupon the reaction product solidified. The precipitate was filtered off with suction and washed well with water. 369 Grams of bis-(4-chlorobenzyl)-cyanoacetic acid-methyl ester which melted at a temperature ranging between 110° C. and 112° C. were obtained. By recrystallization from ethanol the product was purified and then melted at 113—115° C.

150 grams of the bis-(4-chlorobenzyl)-cyanoacetic acid methyl ester so obtained were introduced into a solution of 24.2 grams of potassium hydroxide in 450 cc of methanol and the whole mixture was heated for 5 minutes under reflux whereupon a practically complete dissolution took place. The major part of the solvent was then distilled off and the residue was poured into water. The solid product so obtained which consisted of unreacted starting material (27 grams) was filtered with suction after standing for several hours and then after washed with water. The filtrate was acidified whereupon a viscous semi-solid precipitate was formed. After complete deposition, the supernatant aqueous layer was decanted and the viscous residue was treated with diisopropyl-ether whereupon the major part was dissolved.

The undissolved substance was filtered with suction; it was a bis-(4-chlorobenzyl)-malonic acid -monoamide that was obtained in an amount of 15 grams. The filtrate was agitated with water, dried over sodium sulphate and the diisopropyl ether was distilled off. The residue was dissolved in 150 cc of benzene and precipitated again by the addition of 500 cc of petroleum ether. There were obtained 100 grams of a practically colourless bis-(4-chlorobenzyl)-cyanoacetic acid melting at 158—160° C. After recrystallization from benzene the compound melted at 163—164° C.

100 grams of the bis-(4-chlorobenzyl)-cyanoacetic acid obtained were heated to 210° C. (inner temperature) in an open flask. The temperature increased spontaneously to about 260° C. with a vigorous evolution of carbon dioxide. The reaction was completed within a few minutes. The reaction mixture was cooled and simultaneously mixed with 50 cc of alcohol whereupon crystallization took place. After suction-filtration and washing with a small quantity of alcohol, there were obtained 82 grams of colourless α -(4-chlorobenzyl)- β -(4-chlorophenyl)-propionitrile which melted at 102—103° C. The melting point remained constant after recrystallization from alcohol.

EXAMPLE 4.

2-(3¹,4¹-dichlorobenzyl)-3-(3¹¹,4¹¹-dichlorophenyl)-propylamine.

A suspension of 12.6 grams of lithium-aluminium-hydride in 600 cc of dry ether was introduced into the boiling flask of a Soxhlet-extractor and 70 grams of α -(3,4-dichlorobenzyl)- β -(3,4-dichlorophenyl) - propionitrile were introduced into the socket. The mixture was heated at the boil until the nitrile in the socket was dissolved. There were then added carefully and successively 5 cc of water, 3.8 cc of sodium hydroxide solution of 20% strength and 18 cc of water, and the mixture was stirred until the grey precipitate that had at first formed had become colourless. It was filtered with suction and washed well with ether. The filtrate was dried over potassium carbonate and mixed, after filtration, with 19 cc of alcoholic hydrochloric acid of 31% strength. The 2-(3¹,4¹-dichlorobenzyl)-3-(3¹¹,4¹¹-dichlorophenyl) - propylamine - hydrochloride immediately crystallized out. 57 Grams of a colourless product which melted at 200—201° C. were obtained.

The free 2-(3¹,4¹-dichlorobenzyl)-3-(3¹¹,4¹¹-dichlorophenyl)-propylamine was prepared in the usual manner from the hydrochloride. It was a light-yellow, very viscous oil. The oil was distilled under reduced pressure whereupon a part of it passed over with strong decomposition at a temperature ranging between 245° C. with 250° C. under a pressure of 2.5 mm of mercury; the residue remained as a resin.

The acetate of acetic ester/diisopropyl ether

melts at 116—117° C. and the sorbate of acetic acid ethyl ester melts at 139° C.—140° C.

The α - (3,4 - dichlorobenzyl) - β - (3,4-dichlorophenyl) - propionitrile serving as starting material was obtained in the following manner: a sodium-methylate solution was prepared by dissolving 46 grams of sodium in 750 cc of methanol. To this solution there were added dropwise first 110 grams of cyanoacetic acid-methyl ester and, after stirring for 30 minutes, 391 grams of 3,4-dichlorobenzyl-chloride. Finally, the reaction mixture was heated for one hour under reflux whereupon the reaction product crystallized out. When the crystallization did not take place it could be initiated by inoculation. After cooling, the liquid part was removed by suction-filtration, the residue was washed with a small quantity of methanol and the filter cake obtained was stirred with water in order to dissolve out the sodium chloride. The solution was then removed by suction-filtration, the substance was washed with water until no more chlorine ions could be detected and the residue was dried at about 100° C. 350—360 Grams of bis - (3,4 - dichlorobenzyl) - cyanoacetic acid-methyl ester melting at 106—107° C. were obtained. The product could be recrystallized from alcohol for further purification.

348 grams of bis-(3,4-dichlorobenzyl)-cyanoacetic acid-methyl ester were introduced into a solution of 47 grams of potassium hydroxide in 940 cc of methanol and 15 cc of water and the whole mixture was heated for about 5 minutes under reflux. The major part of the methanol was then distilled off and the residue was poured into water. The remainder of unsaponified starting material remains undissolved. It was filtered off with suction (26 grams) and the filtrate was acidified with concentrated hydrochloric acid. The saponification product separated in a semi-solid viscous form but solidified after several hours to give a hard mass. This process could accelerate by inoculation. The product which had been disintegrated in a mortar was suction-filtered and thoroughly washed with water. 260 Grams of bis - (3,4 - dichlorobenzyl) - cyanoacetic acid melting at 170—171° C. were obtained. After recrystallization from acetonitrile, the product melted at 172—174° C.

242 grams of bis-(3,4-dichlorobenzyl)-cyanoacetic acid were heated in an open flask. A vigorous reaction set in at about 180° C. so that the temperature automatically rose to 220—230° C. After a few minutes carbon dioxide evolution was complete. 200 cc of ethanol were added while cooling. The product crystallized out and was suction-filtered. 203 Grams of colourless α -(3,4-dichlorobenzyl) - β - (3,4 - dichlorophenyl) - propionitrile melting at 116—118° C. were obtained. After recrystallization from alcohol, the melting point remained constant.

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EXAMPLE 5.

2-(3¹,4¹-dichlorobenzyl)-3-(3¹¹,4¹¹-dichlorophenyl)-propylamine.

- 90 grams of α -(3,4-dichlorobenzyl)- β -(3,4-dichlorophenyl)-propionitrile prepared as described in Example 4, were dissolved in 800 cc of dioxane, which had been saturated with ammonia, and hydrogenated with the use of Raney-nickel as catalyst at a temperature of 40° C. and under a pressure of 120 atmospheres gauge until the hydrogen absorption was complete. After separation of the catalyst and evaporation of the solvent, the crude amine was dissolved in 500 cc of diisopropyl ether and 33 cc of alcoholic hydrochloric acid of 28% strength were added to the solution. The hydrochloride first separated out as a greasy mass but solidified rapidly. After addition of a further 500 cc of diisopropyl ether, the precipitate was filtered with suction and after-washed with diisopropyl ether. 93 Grams of 2-(3¹,4¹-dichlorobenzyl)-3-(3¹¹,4¹¹-dichlorophenyl)-propylamine-hydrochloride melting at 195—198° C. were obtained. The product obtained was further purified by recrystallization from isopropanol; it then melted at 199—201° C.

EXAMPLE 6.

2-(2¹,4¹-dichlorobenzyl)-3-(2¹¹,4¹¹-dichlorophenyl)-propylamine.

- 72 grams of α -(2,4-dichlorobenzyl)- β -(2,4-dichlorophenyl)-propionitrile were dissolved in 800 cc of dioxane which has been saturated with ammonia and the solution was hydrogenated with the aid of Raney-nickel as catalyst at 50° C. and under pressure of 80—110 atmospheres gauge. After separation from the catalyst and distillation of the solvent, the crude amine was dissolved in 700 cc of diisopropyl ether and mixed with alcoholic hydrochloric acid of 31% strength. The 2-(2¹,4¹-dichlorobenzyl)-3-(2¹¹,4¹¹-dichlorophenyl)-propylamine-hydrochloride separated out immediately in a solid form and was filtered off with suction and after-washed with ether. 78 Grams of the salt which melted at 217—220° C. were obtained. After recrystallization from ethanol/diisopropyl ether, the compound melted at 221—222° C.

- The free 2-(2¹,4¹-dichlorobenzyl)-3-(2¹¹,4¹¹-dichlorophenyl)-propylamine which was a light yellow viscous oil was obtained from the hydrochloride in the usual manner.

- The α -(2,4-dichlorobenzyl)- β -(2,4-dichlorophenyl)-propionitrile serving as starting material was prepared as follows: to a solution of 50 grams of sodium in 810 cc of absolute methanol were successively added dropwise 120 grams of cyanoacetic acid-methyl ester and 425 grams of 2,4-dichlorobenzylchloride and the mixture was then heated for one hour under reflux. Crystallization took place when the mixture was cooled. The residue was filtered off with suction and washed with methanol. The solid filter residue was stirred

with water, suction-filtered again and thoroughly washed with water. 270 Grams of bis-(2,4-dichlorobenzyl)-cyanoacetic acid methyl ester which could be further dried by recrystallization from alcohol were obtained. It melted at 83—84° C.

270 grams of bis-(2,4-dichlorobenzyl)-cyanoacetic acid-methyl ester were introduced into a solution of 37 grams of potassium hydroxide in 725 cc of methanol and 12 cc of water and the whole mixture was heated at the boil for about 5 minutes. The greater part of the solvent was distilled off and the residue was mixed with 2000—3000 cc of water. Except for a small portion all had dissolved. The whole mass was filtered and the filtrate was acidified with concentrated hydrochloric acid. When allowed to stand the precipitating greasy product solidified to a solid mass which, after comminution, was filtered off with suction and washed well with water. 220 Grams of bis-(2,4-dichlorobenzyl)-cyanoacetic acid were obtained which were further purified by recrystallization from benzene and then melted at 172—173° C.

200 grams of bis-(2,4-dichlorobenzyl)-cyanoacetic acid were heated in an open flask until decarboxylation sets in which occurred at an inner temperature of about 180° C. The temperature automatically rose to about 220° C. by reason of the heat evolved in the reaction. The reaction was completed after a few minutes. During cooling, 200 cc of alcohol were added and the reaction mixture was filtered with suction after the completion of the crystallization. 160 Grams of α -(2,4-dichlorobenzyl)- β -(2,4-dichlorophenyl)-propionitrile melting at 93—96° C. were obtained. After recrystallization from alcohol, the nitrile melted at 96—97° C.

EXAMPLE 7.

2-(3¹,4¹-dichlorobenzyl)-3-(4¹¹-chlorophenyl)-propylamine.

100 grams of α -(3,4-dichlorobenzyl)- β -(4-chlorophenyl)-propionitrile were dissolved in 800 cc of dioxane saturated with ammonia and the solution was hydrogenated under a pressure of 100—110 atmospheres gauge and at a temperature ranging between 40 and 50° C. in the presence of Raney-nickel. After the absorption of hydrogen was complete, the catalyst and solvent were separated by suction-filtration and distillation respectively. The crude amine obtained was dissolved in 500 cc of diisopropyl ether, mixed with 40 cc of alcoholic hydrochloric acid of 31% strength and the precipitated salt was filtered off with suction. The 2-(3¹,4¹-dichlorobenzyl)-3-(4¹¹-chlorophenyl)-propylamine-hydrochloride melted at 166—168° C. The yield amounted to 91 grams. By recrystallization from benzene/diisopropyl ether, the product was further purified and then melted at 168—169° C.

By treating the salt with sodium hydroxide

solution and ether, the free 2-(3',4'-dichlorobenzyl) - 3 - (4'' - chloro-phenyl) - propylamine was obtained in usual manner as a light yellow viscous oil.

- 5 The α - (3,4 - dichlorobenzyl) - β - (4-chlorophenyl)-propionitrile used as starting material was prepared as follows: to a solution of 16 grams of sodium in 200 cc of methanol there were added dropwise 155
10 grams of 4-chlorobenzyl-cyanoacetic acid-methyl ester. The mixture was stirred for about 15 minutes and 136 grams of 3,4-dichlorobenzylchloride were then added dropwise. After mechanically stirring for one hour
15 and heating under reflux, the mixture was cooled whereupon crystallization set in. The product was filtered off with suction, washed with methanol, and the residue was stirred with water, thoroughly washed with water on the
20 suction-filter and dried in air. 190 Grams of 3,4 - dichlorobenzyl - 4' - chlorobenzyl-cyano-acetic acid-methyl ester melting at 80—82° C. were obtained. The product was purified by recrystallization from methanol and
25 then melted at 81—82° C.

- 185 Grams of 3,4-dichlorobenzyl-4'-chlorobenzyl-cyano-acetic acid methyl ester were introduced into a solution of 27 grams of potassium hydroxide in 500 cc of methanol and the solution was heated at the boil for several
30 minutes. The major part of the solvent was then distilled off, the residue was poured into water and filtered off after the addition of animal charcoal. The filtrate was acidified with dilute hydrochloric acid whereupon a greasy
35 precipitate was formed which soon solidified when allowed to stand. After comminution, the liquid part was filtered off with suction and the residue was washed well with water. 156 Grams of 3,4 - dichlorobenzyl - 4' - chlorobenzyl - cyanoacetic acid melting at 127—130°
40 C. were obtained

- 145 grams of 3,4-dichlorobenzyl-4'-chlorobenzyl - cyanoacetic acid were decarboxylated
45 by heating to 200—220° C. in an open flask. After termination of the gas evolution, the substance was cooled accompanied by the simultaneous addition of 100 cc of alcohol. The product which crystallized was filtered off
50 with suction. 102 Grams of α -(3,4-dichlorobenzyl)- β -(4 - chlorophenyl) - propionitrile melting at 71—73° C. were obtained. After recrystallization from isopropanol, the product melts at 73—74° C.

55 **EXAMPLE 8.**

2,2-bis-(3',4'-dichlorobenzyl)-pentylamine.

- 125 grams of α,α -bis-(3,4-dichlorobenzyl)-valeronitrile were hydrogenated in the presence of Raney-nickel in 800 cc of dioxane saturated with ammonia under pressure ranging between 100 and 110 atmospheres gauge
60 and at a temperature of 50° C. After completion of the hydrogen absorption, the liquid part was removed from the catalyst by suction-filtration and the solvent was distilled off.
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The remaining oil was dissolved in 500 cc of ethyl acetate. After the addition of 400 cc of alcoholic hydrochloric acid of 31% strength, the 2,2-bis-(3',4' - dichlorobenzyl) - pentylamine-hydrochloride separated out. It was
70 filtered off with suction. 78 Grams of a colourless product were obtained which was further purified by recrystallization from iso-amyl alcohol. The pure salt melted at 243—245° C.
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The free 2,2-bis-(3',4'-dichlorobenzyl)-pentylamine was obtained in the usual manner from this salt by treating it with ether and sodium hydroxide solution. It was a yellowish viscous oil.
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The α,α - bis - (3,4 - dichlorobenzyl)-valeronitrile serving as starting material was obtained as follows: 500 grams of 3,4-dichlorobenzylchloride and 106 grams of butylcyanide were dissolved in 1000 cc of benzene
85 and the solution was heated to a temperature ranging between 50° C. and 60° C. To this solution there were then added in portions a suspension of 125 grams of sodium amide in 500 cc. of benzene. After stirring for one hour
90 at the same temperature, the reaction mixture was mixed with about the same quantity of water, the organic layer was then washed with water until neutral, dried over calcium chloride and the residue remaining after distillation of the solvent was treated with 250 cc of petroleum ether. The nitrile crystallized out and
95 was filtered with suction. 147 Grams of α,α -bis - (3,4 - dichlorobenzyl) - valeronitrile were obtained which was further purified by recrystallization from isopropanol. It then melted at 160—161° C.
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EXAMPLE 9.

β -amino- α,α -bis-(4-chlorobenzyl)propionic acid-methyl ester.

200 grams of bis-(4-chlorobenzyl)-cyanoacetic acid-methyl ester, prepared as described in Example 3, were dissolved in 2000 cc of dioxane saturated with ammonia, and hydrogenated in the presence of Raney-nickel under
110 a pressure ranging between 100 and 120 atmospheres gauge and at a temperature ranging between 40° C. and 50° C. After the hydrogen absorption was completed, the liquid part was removed from the catalyst by suction-filtration
115 and the solvent was removed by distillation. The remaining base was dissolved in 1000 cc of diisopropyl ether and 80 cc of alcoholic hydrochloric acid of 28% strength were added thereto. The precipitated salt was filtered with
120 suction and washed with diisopropyl ether. 192 Grams of β -amino- α,α -bis-(4-chlorobenzyl)-propionic acid-methyl ester hydrochloride which melted at between 194° C. and 195° C. with decomposition were obtained. It was purified
125 by recrystallization from isopropanol and then melted with decomposition at a temperature ranging between 197° C. and 198° C. The free β -amino- α,α -bis-(4-chlorobenzyl)-propionic acid-methyl ester was obtained from
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FUMARAMIC ACID DERIVATIVES

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The portion of the term of the patent subsequent to Dec. 7, 1982, has been disclaimed
10 Claims. (Cl. 260-518)

This invention comprises novel derivatives of fumaramic acid and in particular those derivatives wherein a hydrogen of the amino group of fumaramic acid is replaced by a phenylethyl radical or by a phenylpropyl radical and more particularly by derivatives wherein the ethylene or propylene chain of the phenylethyl or phenylpropyl substituent is additionally substituted by one or more groups such as by a lower alkyl, phenyl, benzyl, and the like radicals, or is substituted by any combination of these radicals.

The novel compounds of this invention can be considered to be phenylalkylfumaramic acids and include the alkali metal salts thereof as well as simple ester derivatives, such as esters derived from the low molecular weight alcohols. In these compounds the phenyl moiety can be unsubstituted or a hydrogen atom can be replaced by halogen, particularly chlorine or bromine. The alkyl moiety is a straight chain alkylene radical having at least two and no more than three carbon atoms in the chain connecting the phenyl radical and the nitrogen of the amino group of fumaramic acid; in other words, the alkyl moiety is an ethylene or propylene radical, each valence of the ethylene or propylene radical being satisfied by one of the following: (a) hydrogen, (b) a lower alkyl radical having from 1 to 10 carbon atoms, and preferably having up to 6 carbon atoms in a straight or branched chain or alicyclic, such as a methyl, iso- or normal-propyl, iso- or normal-butyl, amyl, hexyl, cyclopentyl, cyclohexyl, and the like, (c) a mononuclear aryl, either substituted or unsubstituted, as a phenyl or a halophenyl radical, wherein the halogen is attached in ortho, meta, or para-position and is preferably a chloro- or bromo-substituent, a lower alkyl substituted phenyl or a lower alkoxy substituted phenyl, and the like, or (d) a mononuclear aryl-lower alkyl radical such as an unsubstituted or substituted mononuclear aryl-lower alkyl radical wherein, if substituted, the substituent group can be attached in ortho, meta, or para-position of the aryl nucleus and advantageously can be a halogen, particularly chlorine or bromine, a lower alkyl or a lower alkoxy substituent attached preferably to the benzenoid portion of the benzyl radical, for example.

The compounds of this invention possess a variety of properties and are especially useful because they inhibit the excretion of penicillin through the kidney tubules thus providing prolonged blood levels of penicillin. Because of this property the new compounds of this invention are useful as adjuvants for use in conjunction with the administration of penicillin to provide an increase in the blood plasma penicillin concentration with a given dose of penicillin, thereby making possible very high penicillin blood levels, or permitting the use of smaller quantities of penicillin for providing a given blood level, or permitting less frequent administration of penicillin while maintaining a penicillin blood level adequate for bactericidal or bacteriostatic purposes.

Some of the compounds additionally enhance the excretion of uric acid from the body and therefore are useful agents in the treatment of gout or gouty arthritis and in alleviating symptoms of these conditions and of complications associated with gout and gouty arthritis.

Additionally, some of the compounds have been found to inhibit the biosynthesis of cholesterol in liver homog-

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enates in vitro. They have also been found to lower the incidence and severity of atherosclerotic plaques in the thoracic aorta or estrogen-treated chickens which were treated with these compounds as compared with their estrogen-treated controls, and to lower the plasma level of cholesterol in rats which had been challenged with quantities of saturated fats such as lard, known to produce an increased cholesterol blood level in these animals. Accordingly, these compounds also are potentially useful in lowering blood cholesterol levels in humans which is considered an important function of chemotherapeutic agents in the treatment of atherosclerosis.

The phenalkylfumaramic acids or their salts or simple esters can be administered in conventional dosage forms such as in a capsule, pill or tablet either with or without therapeutically inert materials and with or without other therapeutically active substances or in the form of sterile solutions and the like.

While all of the fumaramic acid derivatives of this invention possess one or more of the above properties to varying degrees, the compounds having a phenylethyl radical attached to the amino nitrogen of fumaramic acid, and especially those phenylethylfumaramic acids which also have attached to the ethylene chain a phenyl or a benzyl radical, with or without a halogen substituent on one or both of the benzenoid nuclei, possess one or more of the above described properties to a marked degree.

The fumaramic acid derivatives of this invention are easily prepared by bringing together a solution of the selected phenylalkylamine and a solution of a lower alkyl ester of fumaryl halide and saponifying the fumaramate ester thus formed. The reaction between the ingredients occurs quite readily at room temperature and the fumaramic ester can then be separated by known conventional methods, as by evaporation of the solvent and the like. Benzene has been found to be an effective solvent for the phenylalkylamine as well as for the ester of fumaryl halide although other solvents could be used in its place.

Some of the phenylalkylamines used in preparing the fumaramic acid derivatives of this invention are new compounds which can readily be prepared by one or another of the many well-known methods for preparing phenylalkylamines. By one such method, a carbonyl compound is converted by means of the Leuckart reaction to the desired phenylalkylamine. This reaction involves heating the carbonyl compound (i.e., a ketone or an aldehyde), with formamide and formic acid preferably under reflux conditions to form the formamide derivative of the desired phenylalkylamine. This compound, after hydrolysis with a mineral acid, such as hydrochloric acid, generally is isolated either (a) as an acid addition salt thereof, such as the hydrochloric salt, which may be insoluble in the reaction medium or (b) by treatment of the reaction medium with alkali, such as sodium hydroxide, to obtain the free base, which then is extracted with a solvent, such as ether, and purified by distillation of the base.

Another method which can be employed to prepare the phenylalkylamines involves the hydrogenation of the selected nitrile in the presence of Raney nickel at elevated temperatures and pressures.

Alternatively the selected nitriles can be reacted with a Grignard reagent thus forming the corresponding ketimine, which is reduced in the presence of a noble metal catalyst, such as platinum or palladium and the like, to the corresponding desired phenylalkylamine.

Another method which can be employed to advantage involves reacting the selected ketone with hydroxylamine thus forming the corresponding ketoxime, which then is

of Example 1 there is obtained ethyl N-(2,2-diphenyl-3-methylbutyl)-fumaramate.

Step C.—The ester obtained above is saponified by substantially the same method described in Example 1, Step F, to give N-(2,2-diphenyl-3-methylbutyl)-fumaramic acid.

Example 10.—N-(1-methyl-2-benzyl-3-phenylpropyl)-fumaramic acid

Step A.—1-phenyl-2-benzyl-3-butanone is converted by the Leuckart reaction in substantially the same manner described in Example 1, Step B, to 1-phenyl-2-benzyl-3-aminobutane hydrochloride. The hydrochloride salt is converted to the free base by substantially the same procedure described in Example 1, Step E, B.P. 193–198° C. (15 mm.).

Step B.—By replacing the free base of the α -isomer employed in Step E of Example 1 by an equimolecular quantity of 1-phenyl-2-benzyl-3-aminobutane, and following substantially the same procedure described in Step E of Example 1 there is obtained ethyl N-(1-methyl-2-benzyl-3-phenylpropyl)-fumaramate.

Step C.—The ester obtained above is saponified by substantially the same method described in Example 1, Step F, to give N-(1-methyl-2-benzyl-3-phenylpropyl)-fumaramic acid.

Example 11.—N-(1-n-propyl-3-phenylpropyl)-fumaramic acid

Step A.—1-phenyl-3-hexanone (26.7 g., 0.15 mole) is submitted to a Leuckart reaction in substantially the same manner described in Example 1, Step B, yielding 15 g. of 1-phenyl-3-aminohexane hydrochloride. The hydrochloride salt is converted to the free base by substantially the same procedure described in Example 1, Step E, B.P. 142° C. (25 mm.).

Step B.—By replacing the free base of the α -isomer employed in Step E of Example 1 by an equimolecular quantity of 1-phenyl-3-aminohexane, and following substantially the same procedure described in Step E of Example 1 there is obtained ethyl N-(1-n-propyl-3-phenylpropyl)-fumaramate.

Step C.—The ester obtained above is saponified by substantially the same method described in Example 1, Step F, to give N-(1-n-propyl-3-phenylpropyl)-fumaramic acid.

Example 12.—N-(1,3-diphenylpropyl)-fumaramic acid

Step A.—By replacing the α -isomer employed in Step E of Example 1 by an equimolecular quantity of 1,3-diphenyl-1-aminopropane hydrochloride, and following substantially the same procedure described in Step E of Example 1 there is obtained ethyl N-(1,3-diphenylpropyl)-fumaramate.

Step B.—The ester obtained above is saponified by substantially the same method described in Example 1, Step F, to give N-(1,3-diphenylpropyl)-fumaramic acid.

Example 13.—N-(1-methyl-2,2,3-triphenylpropyl)-fumaramic acid

Step A.—Sodium acetate trihydrate (6.8 g., 0.05 mole) and hydroxylamine hydrochloride (6.9 g., 0.1 mole) are dissolved in water (18 ml.) and 3,3,4-triphenyl-2-butanone (15.0 g., 0.05 mole) in methanol (100 ml.) is added. The mixture is boiled for two hours after which the alcohol is removed by distillation. On cooling and addition of water, a precipitate is formed. The water is decanted and extracted with ether. The ether layer is removed and used to dissolve the precipitate, then washed with water, the water-washed ether solution dried over sodium sulfate and the ether evaporated. The residue is crystallized from cyclohexane to give 10.1 g. (64%) of 3,3,4-triphenyl-2-butanone oxime, M.P. 118–122° C.

After purification by recrystallization from cyclohexane

and drying at 80° C. in vacuo the oxime melts at 151–153° C.

Analysis.—Calculated for $C_{22}H_{21}NO$: C, 83.77; H, 6.71. Found: C, 83.12; H, 6.74.

Step B.—The ketoxime from Step A (10.0 g.) is added to absolute ethanol (30 ml.) in a rocking, stainless steel-lined pressure vessel. Raney nickel (2 g.) is added and the ketoxime hydrogenated at 80° C. under an initial hydrogen pressure of 800 pounds per square inch during a period of one half hour. After removal of the alcohol and catalyst from the cooled solution, a residue of 3,3,4-triphenyl-2-aminobutane (7.7 g.) remains as a viscous oil which slowly crystallizes.

Step C.—By replacing the free base of the α -isomer employed in Step E of Example 1 by an equimolecular quantity of 3,3,4-triphenyl-2-aminobutane, and following substantially the same procedure described in Step E of Example 1, there is obtained ethyl N-(1-methyl-2,2,3-triphenylpropyl)-fumaramate.

Step D.—The ester obtained above is saponified by substantially the same method described in Example 1, Step F, to give N-(1-methyl-2,2,3-triphenylpropyl)-fumaramic acid.

Example 14.—N-(2-phenylethyl)-fumaramic acid

Fumaryl chloride (4.5 g., 0.03 mole) is dissolved in ether (100 ml.) and sodium bicarbonate (4.5 g., 0.05 mole) is added. 2-phenylethylamine (3.63 g., 0.03 mole) in ether (20 ml.) then is added dropwise with stirring and the mixture kept at 25–30° C. for 16 hours. The solid material that forms is collected by filtration and added to a dilute solution of sodium hydroxide, stirred well and the resulting solution filtered and acidified with hydrochloric acid. A solid, M.P. 195–198° C. (1.2 g.) separates and after crystallizing from a mixture of water and isopropyl alcohol, gives 0.7 g. off N-(2-phenylethyl)-fumaramic acid, M.P. 200–201° C.

Analysis.—Calculated for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.77; H, 6.04; N, 6.37.

While the above examples describe the preparation of certain illustrative compounds falling within the scope of the discovery hereinbefore described, it is to be understood that the invention is not to be limited by or to these examples, nor by the specific reaction conditions described for the preparation of the compounds, but is to be understood to embrace modifications and variations falling within the scope of the appended claims.

What is claimed is:

1. Phenyl-R-fumaramic acid wherein R is an alkylene radical having two to three carbon atoms in a straight chain between the phenyl radical and the nitrogen atom of the fumaramic acid residue each remaining valence of said alkylene radical being satisfied by a radical selected from the class consisting of hydrogen, lower alkyl, phenyl, chloro-phenyl, bromo-phenyl, benzyl, chloro-benzyl and bromo-benzyl.

2. (Halo-phenyl)-R-fumaramic acid wherein R is an alkylene radical having two carbon atoms in a straight chain between the phenyl radical and the nitrogen atom of the fumaramic acid residue, each remaining valence of said alkylene radical being satisfied by only two hydrogen atoms, a lower alkyl, and a halobenzyl radical the halo radical in each instance is selected from the group consisting of chloro and bromo.

3. N - [1 - lower alkyl-2,3-di-(chlorophenyl)propyl]-fumaramic acid.

4. N - (1-methyl-2,3-di-p-chlorophenylpropyl)-fumaramic acid.

5. N - (1-lower alkyl-2-chlorophenyl-3-phenylpropyl)-fumaramic acid.

6. N - (1 - methyl-2-p-chlorophenyl-3-phenylpropyl)-fumaramic acid.

7. N - (1-lower alkyl-2-phenyl-3-chlorophenylpropyl)-fumaramic acid.

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BIS-QUATERNARY SALTS OF TRIAMINES AND PROCESS FOR PREPARING THEM

Manfred Schorr and Rudolf Fussgänger, Frankfurt am Main, Germany, assignors to Farbwerke Hoechst Aktiengesellschaft vormals Meister Lucius & Brüning, Frankfurt am Main, Germany, a corporation of Germany

No Drawing. Filed June 9, 1964, Ser. No. 373,851

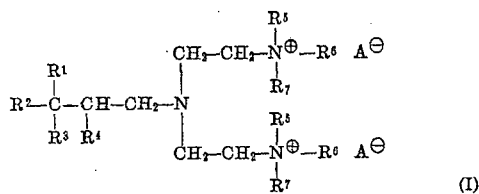
Claims priority, application Germany, June 15, 1963,

F 40,000

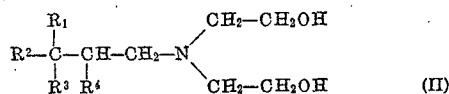
5 Claims. (Cl. 260-296)

The present invention relates to bis-quaternary salts of triamines and to a process for preparing them by reacting reactive esters of bis-(hydroxyethyl)-amines with tertiary amines.

It has been found that bis-quaternary salts of triamines of the Formula I



which compounds possess excellent antibacterial properties, can be prepared by reacting reactive esters of bis-(hydroxyethyl)-amines of the Formula II



with tertiary amines of the Formula III



In the formulae indicated above

- R¹ represents a halosubstituted phenyl radical,
R² and R³ each are hydrogen or a phenyl radical which may be substituted by a halogen atom,
R⁴ represents hydrogen, a halosubstituted phenyl or halo-substituted benzyl radical,
R⁵ is an amino group or an alkyl group of up to 6 carbon atoms,
R⁶ and R⁷ each represent a low molecular alkyl group,
R⁶ and R⁷ together with the nitrogen atom form a saturated heterocyclic ring,
R⁵, R⁶ and R⁷ together with the nitrogen atom form an unsaturated heterocyclic ring, and
A[⊖] is the anion of a non-toxic acid which may also be a component of the radical R⁵.

Alkyl groups in R⁵-position may also be substituted, advantageously by a carboxy, carbonamide, acetyl, lower acyloxy or sulfo group and particularly by a hydroxyl, cyano, lower carbalkoxy, lower acylamino, lower alkoxy and lower alkylmercapto group. The substituents R⁶ and R⁷ may also be substituted if they represent low molecular alkyl groups, advantageously by hydroxyl groups. The saturated and unsaturated heterocyclic rings mentioned above possess preferably 5 to 7 ring members, one of which may also be an oxygen, sulfur or nitrogen atom. Especially piperidine and pyridine enter into consideration, furthermore, morpholine, quinoline, thiazole, benzthiazole or hexamethylene-imine. These heterocyclic rings may also be substituted, advantageously by a lower alkyl, lower alkoxy, lower carbalkoxy, carbonamide or cyano group. As halogen substituents of the radicals R¹, R², R³

2

and R⁴, fluorine, bromine and particularly chlorine enter into consideration. As starting materials for the reaction according to the present invention, the reactive esters of the following bis-(hydroxyethyl)-amines are mentioned as examples:

- 5 N-[γ,γ,γ-tri-(4-chlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- N-[γ-phenyl-γ,γ-bis-(4-chlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- 10 N-[γ-(3-chlorophenyl)-γ,γ-bis-(4-chlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- N-[γ-(3-fluorophenyl)-γ,γ-bis-(4-chlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- 15 N-[γ,γ-bis-(4-fluorophenyl)-γ-(4-chlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- N-[γ,γ-bis-(4-chlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- N-[γ-(3,4-dichlorophenyl)-γ-(4-chlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- 20 N-[γ-(2,4,5-trichlorophenyl)-γ-(4-chlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- N-[β-(2,4,5-trichlorophenyl)-γ-(4-chlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- 25 N-[γ-(4-fluorophenyl)-γ-(4-chlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- N-[β,γ-bis-(4-chlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- N-[β,γ-bis-(3,4-dichlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- 30 N-[β-(4-chlorophenyl)-γ-(2,4-dichlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- N-[β,β-bis-(4-chlorobenzyl)-ethyl]-N,N-bis-(β-hydroxyethyl)-amine
- 35 N-[β,β-bis-(3,4-dichlorobenzyl)-ethyl]-N,N-bis-(β-hydroxyethyl)-amine
- N-[β,β-bis-(2,4-dichlorobenzyl)-ethyl]-N,N-bis-(β-hydroxyethyl)-amine
- N-[β-(4-chlorophenyl)-γ-(4-fluorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- 40 N-[β-(4-chlorophenyl)-γ-(4-bromophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine
- N-[β-(4-chlorophenyl)-γ,γ-bis-(4-chlorophenyl)-propyl]-N,N-bis-(β-hydroxyethyl)-amine.

Tertiary amines which are suitable according to the present invention for the reaction with reactive esters are for example: lower trialkylamines such as trimethylamine, triethylamine, tributylamine, triamylamine or dimethylbutylamine; tertiary alkanol amines such as β-diethylaminoethanol, γ-dimethylaminopropanol or triethanolamine; N,N-disubstituted aminocarboxylic acids and their functional derivatives, such as dimethylamino-acetic acid, γ-piperidino-butyric acid; dimethylamino-acetic acid methyl ester, α-diethylaminopropionitrile, γ-dimethylamino-butyronitrile and dipropylamino-acetic acid amide; asymmetrically disubstituted hydrazines such as N,N-dimethylhydrazine, N,N-bis-(β-hydroxyethyl)-hydrazine, N-amino-piperidine or N-amino-morpholine; saturated nitrogen containing heterocycles such as N-methylhexamethyleneimine, N-ethylpyrrolidine or N-methylpiperidine-carboxylic acid ethyl ether; unsaturated nitrogen containing heterocycles such as pyridine, picoline, lutidine, 3-methoxypyridine, 3-cyano-pyridine, nicotinic acid, isonicotinic acid ethyl ester, nicotinic acid amide, quinoline, thiazole, benzthiazole or 1-alkylbenzimidazole; tertiary amines substituted by alkoxy and alkyl mercapto groups, such as methoxy-ethyl-diethylamine and ethylmercaptoethyl-diethylamine; N,N-disubstituted aminosulfonic acids such as diethyl amino-ethane sulfonic acid and tertiary amines substituted by acyl, acyloxy and acylamino groups such as diethyl-amino-acetone, propionic acid-piperidino ethyl ester and diethylamino-ethyl acetamide.

ammoniummethyl)-amine-dichloride is obtained in the form of a brown viscous oil. The yield is 82.5 grams. The product can be purified by dissolving it repeatedly in ethyl alcohol and reprecipitating it by the addition of diisopropyl ether.

EXAMPLE 9

N-[γ,γ,γ -tri-(4-chlorophenyl)-propyl]-*N,N*-bis-(β -*N'*-acetyl-aminoethyl-N',N'-diethyl-ammoniummethyl)-amine-dichloride

25.8 grams of *N*-[γ,γ,γ -tri-(4-chlorophenyl)-propyl]-*N,N*-bis-(β -chloroethyl)-amine and 15.8 grams of acetic acid β -diethylamino-ethyl amide are dissolved in 120 cc. of alcohol and heated in an autoclave for 4 hours at 120° C. The solvent is then distilled off. As residue there are obtained 30 grams of *N*-[γ,γ,γ -tri-(4-chlorophenyl)-propyl]-*N,N*-bis-(β -*N'*-acetyl-aminoethyl-N',N'-diethyl-ammoniummethyl)-amine-dichloride in the form of a brown, very viscous oil which can be purified by dissolving and reprecipitating it from ethyl alcohol/diisopropyl ether.

EXAMPLE 10

N-[β,β -bis-(3,4-dichlorobenzyl)-ethyl]-*N,N*-bis-(β -pyridiniummethyl)-amine-dichloride

24.5 grams of *N*-[β,β -bis-(3,4-dichlorobenzyl)-ethyl]-*N,N*-bis-(β -chloroethyl)-amine and 7.9 grams of pyridine are dissolved in 120 cc. of ethanol and the mixture is heated in a closed vessel for 2 hours at 120-130° C. After distilling off the alcohol *N*-[β,β -bis-(3,4-dichlorobenzyl)-ethyl]-*N,N*-bis-(β -pyridiniummethyl)-amine-dichloride remains as a light yellow, very viscous oil which can be purified by dissolving it in ethanol and reprecipitating it from diisopropyl ether. The yield is 21 grams.

EXAMPLE 11

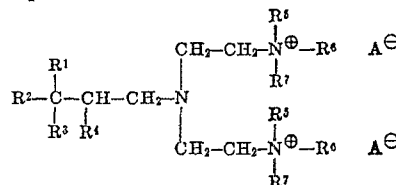
N-[β -(4-chlorophenyl)- γ -(2,4-dichlorophenyl)-propyl]-*N,N*-bis-(β -pyridiniummethyl)-amine-dichloride

A mixture of 37 grams of *N*-[β -(4-chlorophenyl)- γ -(2,4-dichlorophenyl)-propyl]-*N,N*-bis-(β -chloroethyl)-amine, 13.5 grams of pyridine and 120 cc. of ethanol is heated for 4 hours at 120° C. in an autoclave. The alcohol is then completely distilled off and the *N*-[β -(4-chlorophenyl)- γ -(2,4-dichlorophenyl)-propyl]-*N,N*-bis-(β -

pyridiniummethyl)-amine-dichloride is obtained in the form of a viscous brown oil. It is purified by dissolving and reprecipitating it from ethanol/diisopropyl ether. The yield is 31 grams.

5 We claim:

1. A compound of the formula



15 wherein

R^1 is halophenyl;

R^2 and R^3 each are hydrogen, phenyl or halophenyl;

R^4 is hydrogen, halophenyl or halobenzyl;

R^5 , R^6 and R^7 together with N stand for an unsaturated heterocyclic ring system of 6 ring members optionally substituted by a member of the group consisting of lower alkyl, cyano, carboxy, lower carbalkoxy and carbamyl, and

$\text{A}^\ominus$ is the anion of a non-toxic acid.

25 2. *N*-[α,α,α -tri-(4-chlorophenyl)-propyl]-*N,N*-bis-(β -pyridiniummethyl)-amine-dichloride.

3. *N*-[β,β -bis-(3,4-dichlorobenzyl)-ethyl]-*N,N*-bis-(β -pyridiniummethyl)-amine-dichloride.

30 4. *N*-[β -(4-chlorophenyl)- γ -(2,4-dichlorophenyl)-propyl]-*N,N*-bis-(β -pyridiniummethyl)-amine-dichloride.

5. *N*-[β -(2,4-dichlorophenyl)- γ -(2,4-dichlorophenyl)-propyl]-*N,N*-bis-(β -pyridiniummethyl)-amine-dichloride.

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WALTER A. MODANCE, Primary Examiner.

A. ROTMAN, Assistant Examiner.

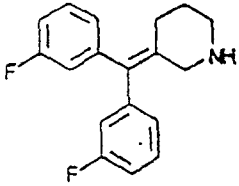
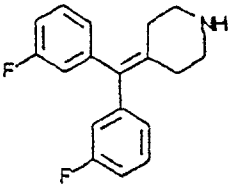
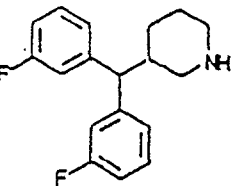
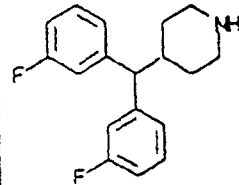
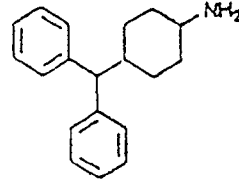
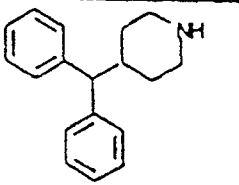
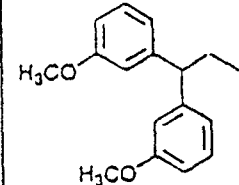
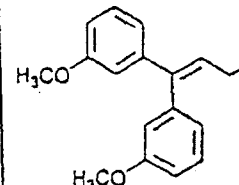
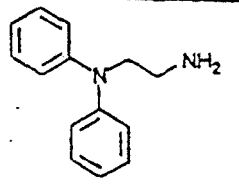
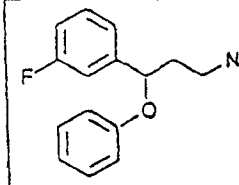
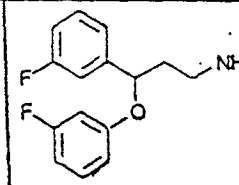
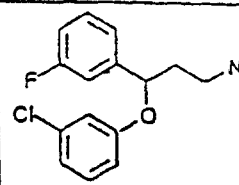
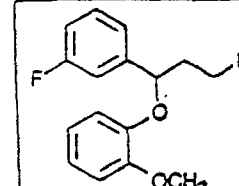
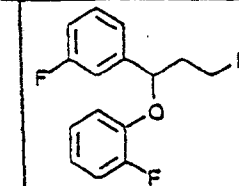
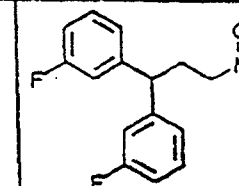
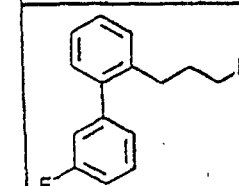
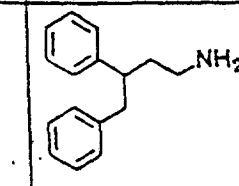
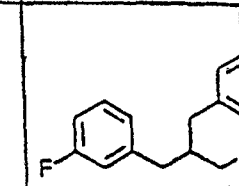
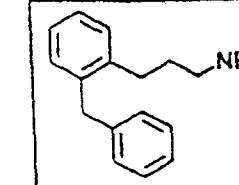
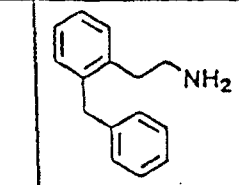
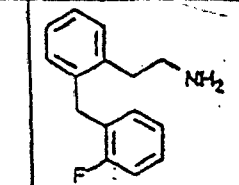
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07C 211/42, 211/32, C07D 311/90, 335/20, 313/12, A61K 31/645	A1	(11) International Publication Number: WO 98/56752 (43) International Publication Date: 17 December 1998 (17.12.98)
(21) International Application Number: PCT/US98/11608 (22) International Filing Date: 11 June 1998 (11.06.98) (30) Priority Data: 08/873,011 11 June 1997 (11.06.97) US (71) Applicant: NPS PHARMACEUTICALS, INC. [US/US]; Suite 240, 420 Chipeta Way, Salt Lake City, UT 84108-1256 (US). (72) Inventors: MUELLER, Alan, L.; 2510 East Skyline Drive, Salt Lake City, UT 84108 (US). MOE, Scott, T.; 6152 South Vinefield Drive, Salt Lake City, UT 84105 (US). (74) Agents: SILVERSTEIN, Sheryl, R. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US).		(81) Designated State: JP. Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: COMPOUNDS ACTIVE AT A NOVEL SITE ON RECEPTOR-OPERATED CALCIUM CHANNELS USEFUL FOR TREATMENT OF NEUROLOGICAL DISORDERS AND DISEASES		
(57) Abstract Method and compositions for treating a patient having a neurological disease or disorder, such as stroke, head trauma, spinal cord injury, spinal cord ischemia, ischemia- or hypoxia-induced nerve cell damage, epilepsy, anxiety, neuropsychiatric or cognitive deficits due to ischemia or hypoxia such as those that frequently occur as a consequence of cardiac surgery under cardiopulmonary bypass, or neurodegenerative diseases such as Alzheimer's Disease, Huntington's Disease, Parkinson's Disease, or amyotrophic lateral sclerosis (ALS).		

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 Compound 109	 Compound 110	 Compound 111
 Compound 112	 Compound 113	 Compound 114
 Compound 115	 Compound 116	 Compound 117
 Compound 118	 Compound 119	 Compound 120
 Compound 121	 Compound 122	 Compound 123
 Compound 124	 Compound 125	 Compound 126
 Compound 127	 Compound 128	 Compound 129

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 0-52850

EDICTO No. 2380

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió **Resolución No. 1489 de 30-ENE-2006**. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "DERIVADOS DE 2-BENCIL-3-DIMETILAMINO-1-FENILPROPANO".

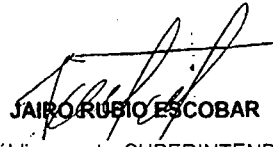
ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Alicia Lloreda Ricaurte, o a quien haga sus veces, en su calidad de apoderada de Grunenthal GmbH., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los

30 ENE. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIRO RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 10-FEB-2006
Secretaría General Ad-Hoc
EDICTO No. 2380

Este edicto se desfija hoy 23-FEB-2006 a las cinco (5:00 p.m.)