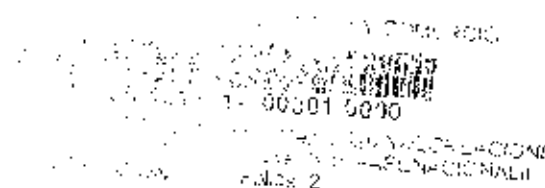


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jlloco@lloredacamacho.com

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____



Re: P1.-F. HOFFMANN-LA ROCHE AG.-Solicitud de Patente de
Invencción en Fase Nacional PCT para "3-AMINO-1-
ARILPROPIL-INDOLES COMO INHIBIDORES DE
RECAPTACIÓN DE MONOAMINAS".-Clase CO7D 209/04.-
Expediente número 06-121.181.-

1. Me refiero a mi solicitud de patente de 30 de Noviembre de 2006.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **578** de 31 de Julio de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo **II**.
4. Anexo me permito acompañar recibo número 07-99.282, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,


ALICIA LLOREDA RICAURTE
T.P. 53.215

332
329

COMISIÓN DE INGENIERÍA DE INDUSTRIA Y COMERCIO
SECRETARÍA DE ECONOMÍA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 000176089-2

RECIBO OFICIAL DE CAJA : 07 - 79,202
CHA : DICIEMBRE 5 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VALOR PAGO
LLORCA Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-4	72074914	07/12/2007	1,994,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	VALOR
1	50005-01-01	SOLICITUDES	
		114 PTO CAP-11 EXAMEN DE PATENTABILIDAD	202,000.00
		TOTAL :	202,000.00

SOM: DOSCIENTOS DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-121181

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 578 DE

FECHA 31 DE JULIO DE 2007 EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL 26 DE OCTUBRE DE 2007

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 X

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

202012

Bogotá, D.C., 9 de enero de 2010

Apoderado: Alicia Lloreda Ricaurte

ASUNTO	Radicación	06-121181
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	2605
	Folios	

Patente de Invención ☒

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

No. Sol. Internacional PCT/EP2005/005734
Fecha de Presentación Intern. 27/may/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: 95 a 275 Como se radicó inicialmente.

1.2. Reivindicaciones: Folios: 276 a 290 Modificado al momento de entraren fase nacional.

Folios: 45 a 64 Modificado en fase internacional.

1.3. Prioridad: Folio 2: US 60/576044, 06/oct/2005

2. Modificaciones no aceptadas (artículo 34 D.486 y art. 22 Tratado PCT)

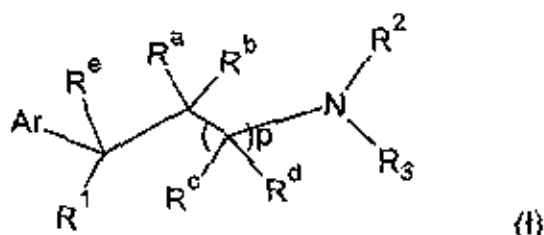
En el oficio (folio 94) mediante el cual el solicitante presentó un capítulo reivindicatorio modificado (folios 276 a 290), no tal como había sido presentado en la solicitud internacional o modificado en dicha fase, el solicitante manifiesta que en ejercicio del derecho conferido por el artículo 28 numeral 1 del tratado PCT, el capítulo reivindicatorio fue modificado al momento de su presentación en fase

nacional. Esta oficina considera que el solicitante hizo una lectura errónea del artículo citado porque dicha modificación no está prevista en el momento de entrada a fase nacional, como lo confirman el artículo 22 y 34 del mismo Tratado, sino tan sólo después de haberse admitido a dicha fase nacional y solo previo diligenciamiento y presentación de un formulario único de correcciones y modificaciones y pago de una tasa (numeral 1.2.1.6 del capítulo quinto, título X de la circular única de la Superintendencia de Industria y Comercio). Puesto que dicho formulario no se presentó y el pago tampoco se efectuó, dicha modificación no podía tomarse en cuenta, mucho menos a la entrada de la fase nacional de PCT.

3. Objeto de la invención

Título de la solicitud: 3-AMINO-1-ARILPROPIL-INDOLES COMO INHIBIDORES DE LA RECAPTACIÓN DE MONOAMINAS.

La presente solicitud tiene múltiples objetos derivados amino-1-arilalquil-arilos de la fórmula Markush (I):



Reivindicaciones 1-6,28,: Un compuesto de la fórmula (I).

Reivindicaciones 7-12: Un Compuesto de la fórmula (II)

Reivindicaciones 13-18: Un Compuesto de la fórmula (III)

Reivindicación 19: Un Compuesto de la fórmula (IV)

Reivindicación 20: Un Compuesto de la fórmula (V)

Reivindicación 21: Un Compuesto de la fórmula (VI)

Reivindicación 22: Un Compuestos de las fórmulas (VIa), (VIb)

Reivindicación 23: Un Compuesto de la fórmula (VII).

Reivindicación 24: Un Compuesto de la fórmula (VIII)

Reivindicación 25: Un Compuesto de la fórmula (IX)

Reivindicación 26: Un Compuesto de la fórmula (X)

Reivindicación 27: Un Compuestos de las fórmulas (XIa), (XIb).

Reivindicación 29: Dos compuestos específicos

Reivindicación 30: Composición que contiene los compuestos.

Reivindicaciones 31-32: Uso

Reivindicación 33: como se describió

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.):
C07D209/04, A61K31/4042.

4. De la solicitud de Patente

4.1. Reivindicaciones (artículo 30 D 486 de la C.A.N.)

Tal como aparece reivindicada la materia, es una solicitud con base en un modelismo molecular obtenido mediante ordenador, por lo tanto es muy amplia y especulativa, no hay razones técnicas fundadas, para creer que un experto del 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 experimentales de rutina o de análisis, toda vez que para la descomunal variabilidad de la fórmula Markush reclamada, no existe evidencia que todas las probabilidades de los compuestos que caen bajo su alcance conserven el efecto como inhibidores de la recaptación de monoaminas..

No es racional encontrar sustento técnico real, donde se demuestre que con esa desmedida variabilidad en posibilidades de enlaces entre múltiples estructuras químicas variables, con sustituyentes mutables 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 como inhibidores de la recaptación de monoaminas citados, por lo tanto no aparece el sustento técnico real en la descripción de ese desmedido modelismo de extrapolación.

Por lo tanto se debe ajustar el capítulo 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 capítulo reivindicatorio debe conservar la unidad inventiva.

Por consiguiente el capítulo reivindicatorio carece de definición, claridad, concisión y falta de estar fundadas enteramente en la descripción, tal como se exige para 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.

5. Unidad de invención (artículo 25 D 486 de la C.A.N.)

La presente solicitud no conserva la unidad de invención. En la reivindicación 1 se encuentra una gran cantidad de grupos de invenciones, es muy engorroso para esta oficina determinarlos, toda vez que no tienen sustento en la descripción.

De la parte que se puede determinar mediante la estructura fija indol, que es única parte sustentada, o sea, está fundada enteramente en la descripción, algunos posibles grupos inventivos pueden ser:

- (i) 3-(2-3-disustituido-1H-indol-1-il)propan-1-amina.
- (ii) 3-(1-3-disustituido-1H-indol-2-il)propan-1-amina
- (iii) 3-(1-2-disustituido-1H-indol-3-il)propan-1-amina

Para cada uno de estos grupos se requiere un examen de patentabilidad independiente.

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

Las reivindicaciones 31 y 32 reclaman el uso de compuestos y de acuerdo con la legislación colombiana el uso no se considera para protección por patente, 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 a que el uso sea patentable.

Los usos o segundos usos no son patentables, de conformidad con la sentencia del TJAC 89-AI-2000, en general los usos no son patentables

7. 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, 01/06/2004.

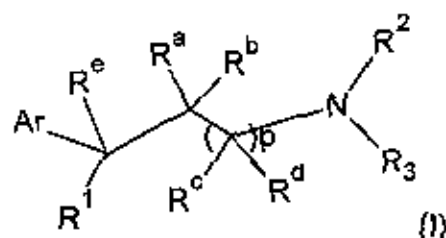
Teniendo en cuenta la fecha indicada se realizó la búsqueda del estado de la técnica, en bases de datos en las que esta oficina tiene acceso libre, en búsqueda de documentos relacionados con la materia que se reclama como nueva e inventiva en presente solicitud, encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de presentación
D1	GB705.652	Manufacture of 3-aminopropane compounds	17-mar-1950
D2	US2708197	Preparation of (hydrixy-3-indole)-alkylamines	10-may-1955
D3	US5023269	3-aryloxy-3-substitutes-propanamines	11-jun-1991

8. Análisis de patentabilidad (según requisito) (artículo 14 D486)

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

La solicitud en estudio reclama los compuestos de la fórmula Markush(I):



-Las anterioridades D1,D2,D3 escriben derivados 3-aryl-3-arylpropanolaminas sustituidas. Las anteriorides D1 y D2 se refieren a derivados indolil-propanaminas que tal como puede verse en la totalidad de D1 y D2, por lo tanto la solicitud de considera una generalización especulativa de estas anterioridades.

-La anterioridad D3 se refiere a 3-fenil o naftil-3-aryl-propanaminas, tal como aparece especialmente en las cols.1-16 y tabla 1. Tal como puede verse la solicitud en

335
338

estudio no es nueva, no cumple con el requisito exigido en el artículo 16 D486 de la C.A.N.

8. Conclusión:

-Se hizo un estudio de patentabilidad parcial, debido a la desmedida extrapolación presentado mediante un modelismo molecular, ya que en la solicitud no aparece el sustento técnico de todas las posibles combinaciones reclamadas mediante la fórmula Markush (I).

Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	1-33	Novedad
D2	1-33	Novedad
D3	1-8	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 60 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 numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


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

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

2,708,197

PREPARATION OF (HYDROXY-3-INDOLE)-ALKYLAMINES

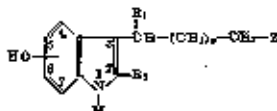
Merrill E. Spear, Kalamazoo Township, Kalamazoo County, Mich., assignor to The Upjohn Company, Kalamazoo, Mich., a corporation of Michigan

Filed Drawing, Application May 24, 1952,
Serial No. 269,872

23 Claims. (Cl. 260-319)

The present invention relates to a novel process for the preparation of organic compounds, and is more particularly concerned with a novel process for the preparation of (hydroxy-3-indole)-alkylamines, and with the products thus produced. This application is a continuation-in-part of my prior filed copending application Serial Number 279,931, filed April 1, 1952, and Serial Number 265,045, filed January 4, 1952, and now abandoned.

The compounds prepared by the novel process of the present invention may be represented by the formula:



wherein R₁ and R₂ represent hydrogen or lower-alkyl, and n is selected from zero or one. Z represents the amine radical

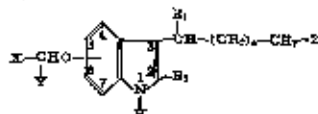


wherein R₃ and R₄ represent hydrogen, alkyl, cycloalkyl, phenyl, and aralkyl. The amine radicals thus represented by Z include such radicals as the unsubstituted amino -NH₂, alkylamino, cycloalkylamino, aralkylamino, phenylamino, dicycloalkylamino, diaralkylamino, dialkylamino, diphenylamino, alkyl aralkylamino, alkyl cycloalkylamino, alkyl phenylamino, aralkyl cycloalkylamino, aralkyl phenylamino, or cycloalkyl phenylamino, and R₃ and R₄ taken together with the nitrogen also represent a monoheterocyclic amine radical selected from five and six atom monoheterocyclic amine radicals, including amine radicals such as piperidyl, morpholyl, thiomorpholyl, pyrrolidyl, or the like.

It is an object of the present invention to provide a novel process for the preparation of (hydroxy-3-indole)-alkylamines and salts thereof. It is a further object of the present invention to provide a novel process for the preparation of (6-hydroxy-3-indole)-alkylamines, (5-hydroxy-3-indole)-alkylamines, (6-hydroxy-3-indole)-alkylamines, (7-hydroxy-3-indole)-alkylamines, acid addition, and quaternary ammonium salts thereof. Other objects of the present invention will be apparent to one skilled in the art to which the invention pertains.

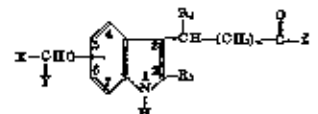
The compounds produced by the novel process of the present invention, the (hydroxy-3-indole)-alkylamines, have demonstrated potent vasoconstrictor qualities. The isolation of serotonin creatinine sulfate, 5-hydroxy-3-(2-aminoethyl)-indole creatinine sulfate, was first announced by Rapport (J. Biol. Chem., 180, 961 (1949)) and the compound was definitely shown to possess vasoconstrictor properties. Similarly other analogs of serotonin, prepared by the novel process of the present invention, such as butotemin, 5-hydroxy-3-12-(N,N-dimethylamino)-ethyl-indole (Karrer, Organic Chemistry, 2nd English edition, Elsevier Publishing Company, New York, page 764), 5-hydroxy-3-[2-(N-methylamino)-ethyl]-indole, and the like, have exhibited similar pharmacological activity.

According to the method of the present invention the (hydroxy-3-indole)-alkylamines are prepared by the debenzylation of the (benzyloxy-3-indole)-alkylamines represented by the formula:



wherein X represents phenyl, halophenyl, lower alkylphenyl, or lower alkylphenyl, Y represents hydrogen, phenyl, halophenyl, lower alkylphenyl, or lower alkylphenyl, and R₃, R₄, n, and Z have the same values as specified above.

The starting compounds for the process of the present invention, the (benzyloxy-3-indole)-alkylamines, are prepared by the reduction of a (benzyloxy-3-indole)-alkanoylamide represented by the formula:



wherein X, Y, R₁, R₂, and n, have the values specified above, and wherein Z represents the amide radical

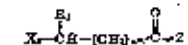


Representative reducing agents include metal hydrides such as lithium aluminum hydride, lithium borohydride, and the like, with lithium aluminum hydride being preferred. The reduction of the (benzyloxy-3-indole)-alkanoylamides can also be accomplished catalytically, in which case platinum is the preferred catalyst. The non-catalytic reduction is usually conducted in an organic solvent, with tetrahydrofuran being preferred, although other well known solvents such as isopropyl ether, ether, N-methylmorpholine, dioxane, and the like may also be used. The reduction of the (benzyloxy-3-indole)-alkanoylamides is usually accomplished at the boiling point of the solvent used, although other temperatures between about zero and 100 degrees may be employed, and preferably zero to 65 degrees centigrade when lithium aluminum hydride is the reducing agent utilized. After a reaction period of from thirty minutes to five hours, the (benzyloxy-3-indole)-alkylamine free bases are readily obtained as heavy non-crystalline oils, or in some instances as crystalline compounds, by hydrolyzing the reaction product with aqueous ether followed by dilute alkali, extracting the alkaline residue with several portions of ether, combining the ether extracts, and concentrating and evaporating the solvent. Other conventional procedures for the hydrolysis may be used if desired, and other organic solvents may be used in place of ether. A preferable manner of procedure, however, resides in reacting the free base, without isolation, with a stoichiometric quantity of an acid, such as hydrochloric, hydrobromic, sulfuric, acetic, tartaric, citric, or the like, to form the (benzyloxy-3-indole)-alkylamine acid addition salt. Similarly a quaternary ammonium salt may also be prepared by reacting the tertiary amine free base

with an alkyl halide or aralkyl halide and such quaternary ammonium salts include the methochloride, ethochloride, benzyl chloride, and the like. In this manner, the free base may be separated as its crystalline salt, e. g., hydrochloride, which usually precipitates from the solution. Alternatively the free base may be isolated by removal of the solvent and admixed with a stoichiometric quantity of an acid, e. g., hydrochloric, to form the corresponding acid addition salt or the isolated tertiary amine free base may be distilled with an alkyl halide or aralkyl halide to form the quaternary ammonium salt of the (benzyloxy-3-indole)-alkylamine employed. The (benzyloxy-3-indole)-alkylamine salts, so obtained, may be removed by filtration and so utilized, or the resulting salt precipitate may be further purified, if desired, by recrystallizing from alcohol-water solutions such as methanol-water, ethanol-water, isopropanol-water, and the like, with ethanol-water being preferred. The (benzyloxy-3-indole)-alkanoylamides are prepared by the Grignard reaction of a benzyloxyindole represented by the formula:



wherein X, Y and R₃ have the same values as specified above, with a haloalkanoylamide represented by the formula:



wherein R₁ represents a halogen i. e., chlorine, iodine, or bromine, and wherein n, R₂, and Z have the values specified above. Representative haloalkanoylamides include the α-haloacetamides, β-haloacetamides, or the like. The starting 3-benzyloxyindoles and 6-benzyloxyindoles may be prepared according to the method of Burton and Stover (J. Chem. Soc. 1937, 1726). An alternative method for the preparation of the 3-benzyloxyindoles involves the reductive cyclization of the 3-benzyloxy-2,2-dimethylstyrenes, as more fully disclosed in my copending application Serial Number 273,149, filed February 23, 1952. The 3-benzyloxy-2,2-dimethylstyrenes are prepared by the dehydration of the 3-benzyloxy-2-nitro-α-[1-(1-nitroalkyl)]benzyl alcohols, as more fully disclosed in my copending application Serial Number 273,148, filed February 23, 1952. The 3-benzyloxy-2-nitro-α-[1-(1-nitroalkyl)]benzyl alcohols are prepared by the condensation of 5-benzyloxy-2-nitrobenzaldehydes with a 1-nitroalkane, as more fully disclosed in my copending application Serial Number 273,147, filed February 23, 1952. The 5-benzyloxy-2-nitrobenzaldehydes are prepared according to the method of Burton (J. Chem. Soc., 1935, 1265) or Portmann and Giovannini (Helv. Chim. Acta, 31, 1341 (1948)). The starting 7-benzyloxyindoles are prepared by the benzylation of a 3-hydroxy-2-nitrobenzaldehyde (Hodgson et al., J. Chem. Soc. 127, 877), with a benzyl halide such as benzyl chloride, para-methylbenzyl bromide, and the like, to produce a 3-benzyloxy-2-nitrobenzaldehyde. The preparation of the 7-benzyloxyindole from the thus-produced 3-benzyloxy-2-nitrobenzaldehyde thereafter follows the identical process utilized in the preparation of the 5-benzyloxyindole as outlined above. In a similar manner the 4-benzyloxyindoles are prepared by the benzylation of a 6-hydroxy-2-nitrobenzaldehyde (Ashley et al., J. Chem. Soc. 1930, 352-393), with a benzyl halide to produce a 6-benzyloxy-2-nitrobenzaldehyde, whereafter the 4-benzyloxyindoles are prepared from the thus-produced 6-benzyloxy-2-nitrobenzaldehyde by the identical process utilized in the preparation of the 5-benzyloxyindole from the starting 5-benzyloxy-2-nitrobenzaldehyde as previously discussed.

The Grignard reaction, for the preparation of (benzyloxy-3-indole)-alkanoylamides, is usually carried out in the presence of an organic solvent, diethyl ether and dibutyl ether being preferred, although other organic solvents, suitable for use in Grignard reactions, such as benzene, toluene, or anisole, can also be employed. In some instances dimethylformamide may also be utilized. A great many Grignard reagents are satisfactory, among them being those prepared from alkyl halides, cycloalkyl halides, aryl halides, and aralkyl halides, the lower-alkyl halides, such as methyl iodide and ethyl iodide being preferred. The preparation of the benzyloxyindole Grignard reagent is usually conducted at the boiling point of the solvent employed, although other temperatures between about zero and 150 degrees centigrade, preferably between about zero and 100 degrees centigrade, may also be used, a longer reaction period being required in the lower temperature ranges. The resulting benzyloxyindolemagnesium halide is then reacted with a haloalkanoylamide, such as the α-haloacetamides, β-haloacetamides, or the like, in the presence of the same organic solvent utilized in the preparation of the Grignard reagent although others may also be used if desired. The reaction of the haloalkanoylamide and the benzyloxyindolemagnesium halide is usually conducted at the boiling point of the solvent employed, although other temperatures between about zero and 150 degrees centigrade, preferably about 100 degrees centigrade may also be used. Upon removal of the organic solvent by distillation, the remaining residue is heated on a steam bath, and a heavy oil is obtained upon cooling. The (benzyloxy-3-indole)-alkanoylamides may then be isolated from the oil, or in some instances the (benzyloxy-3-indole)-alkanoylamides need not be isolated as a crystalline product, in which case the oil may be treated directly with a reducing agent to produce the desired (benzyloxy-3-indole)-alkylamine. One method for the separation of the (benzyloxy-3-indole)-alkanoylamides from the oil involves the addition of an organic solvent, such as ether, chloroform, or benzene, with ether being preferred, to the oil, and hydrolysis of the mixture with dilute acetic acid, whereupon the (benzyloxy-3-indole)-alkanoylamide separates from the mixture. Upon filtration the amide product may be recrystallized from alcohol to a greater degree of purity and may be converted to the amines as previously disclosed.

In the method of the present invention the (hydroxy-3-indole)-alkylamines are prepared by subjecting the (benzyloxy-3-indole)-alkylamines to hydrolysis in the presence of a catalyst which results in a debenylation of the (benzyloxy-3-indole)-alkylamine. The debenylation reaction may also result in the removal of the benzyl radical from the amino group to produce a secondary or primary amino group. The amino group may be re-benzylation, if so desired, by various well known procedures, e. g., benzaldehyde may be added to the debenzylation solution and the mixture refluxed for a short time, whereafter the solution may be hydrogenated in the presence of a platinum oxide catalyst, resulting in a benzylation group. In the hydrogenation reaction the hydrogen pressure employed may range from slightly under atmospheric to about two or three atmospheres, although higher pressures can also be used. The hydrogenation is usually carried out at the temperature of about 25 degrees centigrade (room temperature), but the reaction can also be conducted satisfactorily in a temperature range between about zero degrees centigrade and the boiling point of the solvent employed. The reaction is completed in a period of a few minutes to several hours, with a shorter reaction time, of course, being required at the higher temperatures and greater pressures. Catalysts which may be employed in the reaction include among others palladium black, palladium-barium sulfate, palladium-charcoal, and the like, with a ten percent palladium-charcoal catalyst being preferred.

Other concentrations between about one and fifty percent may also be employed, with a somewhat shorter reaction time being required at the higher concentrations. Organic solvents suitable for the hydrogenolysis include, among others, lower-aliphatic ketones, such as acetone, and alcohols, such as methanol, ethanol, and isopropanol, with ethanol being preferred. The desired (hydroxy-3-indole)-alkylamine can be isolated at this point by filtering to remove the catalyst, concentrating, and evaporating the solvent employed. The isolated (hydroxy-3-indole)-alkylamine is obtained as a non-crystalline, water-insoluble oil which may be readily converted to a more convenient acid addition salt by reaction with a stoichiometric quantity of acid such as hydrochloric, phosphoric, tartaric, citric, acetic, sulfuric, and the like, or by the addition of sulfuric acid and a stoichiometric quantity of creosoline sulfate. Similarly a quaternary ammonium salt may also be prepared by heating the isolated tertiary amine free base in a pressure bottle with an alkyl halide or aralkyl halide, and such quaternary ammonium salts include the methochloride, ethochloride, benzyl chloride, and the like. The resulting (hydroxy-3-indole)-alkylamine salt solution may then be filtered, the filtrate heated, and the (hydroxy-3-indole)-alkylamine salt precipitated therefrom by the addition of an appropriate precipitating agent for the particular desired salt, such as a lower aliphatic ketone, e. g., acetone, diethyl ketone, methyl-isopropyl ketone, methyl-isobutyl ketone, and the like, with acetone as the preferred reagent, to an aqueous solution of serotonin creosoline sulfate, lower-alkyl ethers such as dimethyl, diethyl, methyl-n-butyl, methyl-ethyl, and the like, with diethyl ether being preferred, to an alcoholic solution of serotonin sulfate, hydrochloride, acetate, tartrate, or citrate, the addition of water to an alcoholic solution of serotonin picrate; or by the addition of ether to an alcoholic solution of the quaternary ammonium salt. Lower alcohols such as methanol, ethanol, propanol, isopropanol, butanol, and the like are usually employed as solvents in the precipitation of the picrate, sulfate, hydrochloride, acetate, tartrate, and citrate acid addition salts. Alternatively, the addition salts may be prepared by treating the (hydroxy-3-indole)-alkylamines, without isolation from the reaction mixture, with a stoichiometric quantity of the above-mentioned acids, or with the addition of sulfuric acid and creatinine sulfate, or by the addition of an alkyl or aralkyl halide to the non-isolated tertiary amine free base. An additional alternative procedure for the preparation of the (hydroxy-3-indole)-alkylamine salts involves the direct debenzoylation of an alcoholic solution of a (benzyloxy-3-indole)-alkylamine salt in the presence of the catalyst and hydrogen whereafter the (hydroxy-3-indole)-alkylamine salts are precipitated by the addition of the proper precipitating agent as outlined above. The hydrogenolysis of the (benzyloxy-3-indole)-alkylamines may also be accomplished by reaction with sodium and liquid ammonia, conducted at the boiling point of the liquid ammonia, wherein molecular hydrogen is liberated for the desired hydrogenolysis, but the catalytic procedure is preferred.

The 5-hydroxytryptamines, i. e., serotonin, the primary amine, can also be prepared in an alternative procedure. In the alternative procedure serotonin is prepared by the debenzoylation of a 5-benzyloxytryptamine by the procedure described above. The 5-benzyloxytryptamines are prepared, as disclosed in my copending application Serial Number 260,315, filed December 6, 1951, by reduction of the corresponding 5-benzyloxy-3-indoleacetanilides. The 5-benzyloxyindoleacetanilides are prepared, as disclosed in my copending application Serial Number 257,961, filed November 23, 1951, by a treatment of known 5-benzyloxyindoles as more fully disclosed hereinafter.

The 5-benzyloxyindoleacetanilides are prepared by reacting a 5-benzyloxyindolemagnesium halide, prepared

as described above for the amide process, with a haloacetanilide, such as chloroacetanilide, bromoacetanilide, or iodoacetanilide, with chloroacetanilide being preferred, to produce a 5-benzyloxy-3-indoleacetanilide. The same organic solvent as employed in the Grignard step is usually utilized in the reaction with haloacetanilide although others may be used if desired. The temperature range for the reaction of the haloacetanilide and the 5-benzyloxyindolemagnesium halide is usually between about zero and 100 degrees centigrade, with the reaction ordinarily being conducted at the boiling point of the solvent employed. After refluxing for a period of about one to five hours, the resulting 5-benzyloxy-3-indoleacetanilide is separated by conventional procedure, which, for example, may involve a mild hydrolysis, as with dilute acetic acid, to form a water layer and an ether layer. The ether layer containing the 5-benzyloxy-3-indoleacetanilide can be separated and dried to give an ethereal solution of the 5-benzyloxy-3-indoleacetanilide. From this solution the desired 5-benzyloxy-3-indoleacetanilide can be obtained in high purity by evaporation of solvent removal according to other conventional procedures.

The reduction of the 5-benzyloxy-3-indoleacetanilide is also identical to the lithium aluminum hydride reduction of the amide fully discussed above except that in the nitrate process ether is the preferred solvent.

The following examples will serve to illustrate the process of this invention, but the said invention is not to be considered as limited thereto.

PREPARATION 1.—5-(5-BENZYLOXYINDOLYL)-N-BENZYL-N-METHYLACETAMIDE

To a Grignard reagent prepared from 4.25 grams (0.03 mole) of methyl iodide and 2.4 grams of magnesium in 200 milliliters of ether was added a solution of 5.5 grams (0.025 mole) of 5-benzyloxyindole in 200 milliliters of ether. After heating under reflux for thirty minutes, the mixture was cooled in an ice-bath and a solution of 5.9 grams (0.03 mole) of α -chloro-N-benzyl-N-methylacetamide in 200 milliliters of ether was added thereto. The mixture was stirred and the ether was removed by distillation, whereafter the reddish gummy residue was warmed for three hours on a steam-bath. The mixture was cooled and approximately 500 milliliters of ether was added, followed by the addition with vigorous stirring of a solution of five milliliters of glacial acetic acid and 99 milliliters of water. A light colored solid separated from solution, and after standing overnight the product was collected and recrystallized from isopropanol. The α -3-(5-benzyloxyindolyl)-N-benzyl-N-methylacetamide melted at 151–152 degrees centigrade; yield, 7.5 grams (78 percent).

Anal.—Percent calc. for $C_{21}H_{25}O_2N_2$: C, 78.13; H, 6.29. Found: C, 78.26; H, 6.21.

Other representative 5-benzyloxyindoles which may be utilized in the procedure to prepare the 5-benzyloxyindolemagnesium halides include the 5-benzyloxy-2-alkylindoles, e. g., 5-benzyloxy-2-methylindole, 5-benzyloxy-2-ethylindole, and the like; 5-benzyloxy-2-alkyl-3-alkylbenzyloxyindoles, e. g., 5-(para-methoxybenzyloxy)-indole, 5-(para,para'-dimethylbenzyloxy)-indole, 5-(para,para'-dichlorobenzyloxy)-indole, 5-(para,para'-dibromobenzyloxy)-2-methylindole, and the like; 5-alkoxybenzyloxyindoles, e. g., 5-(para-methoxybenzyloxy)-indole, 5-(para,para'-dimethoxybenzyloxy)-indole, 5-(para,para'-dichlorobenzyloxy)-2-propylindole, and the like.

The preparation of the haloalkanylamides utilized in the process of the present invention involves the addition of an acid halide to ether, cooling in an ice-bath, and adding thereto an amine with vigorous stirring where-

upon a heavy precipitate forms and may be removed by filtration. The precipitate is usually washed with several portions of ether and the combined filtrate then distilled under vacuum to remove the solvent and produce the desirable haloalkanylamide. Other representative haloalkanylamides which can be employed to react with the chosen 5-benzyloxyindolemagnesium halide to produce the desired (5-benzyloxy-3-indole)-alkanylamide include the α -haloacetanilides such as the α -halo-N-alkyl-N-alkylacetanilides, e. g., α -chloro-N-methyl-N-benzylacetamide, α -chloro-N-benzyl-N-isopropylacetamide; α -halo-N,N-dialkylacetanilides, e. g., α -chloro-N,N-dimethylacetamide, α -chloro-N,N-dibutylacetamide, α -iodo-N,N-diethylacetamide; α -halo-N,N-dibenzylacetamide; α -halo-N,N-dicycloalkylacetanilides, e. g., α -chloro-N,N-dicyclohexylacetamide; α -halo-N-alkyl-N-alkyl-N-alkylacetanilides, e. g., α -chloro-N-methyl-N-methyl-N-benzylacetamide, α -halo-N-alkyl-N-cycloalkylacetanilides, e. g., α -chloro-N-benzyl-N-cyclohexylacetamide, α -bromo-N-phenethyl-N-cyclopentylacetamide; α -haloacetylpyrrolidines, e. g., α -chloroacetylpyrrolidine, and the β -halopropionamides, e. g., β -chloro-N,N-diethylpropionamide, β -chloro-N-methyl-N-methyl-N-benzylpropionamide, β -iodopropionylpyrrolidine, and the like.

PREPARATION 2.—5-BENZYLOXY-3-[2-(N-BENZYL-N-METHYLAMINO)-ETHYL]-INDOLE AND SALTS THEREOF

A solution of 3.84 grams (0.01 mole) of α -3-(5-benzyloxyindolyl)-N-benzyl-N-methylacetamide, as obtained in Preparation 1, in 150 milliliters of tetrahydrofuran was added with stirring to a solution of 3.7 grams (0.10 mole) of lithium aluminum hydride in 200 milliliters of tetrahydrofuran. The mixture was heated under reflux for thirty minutes, concentrated to a volume of 75 milliliters, and diluted with 500 milliliters of ether followed by fifty milliliters of five percent sodium hydroxide solution. The ether layer was decanted and the aqueous alkaline residue was extracted with several 300-milliliter portions of ether. To the combined ether solutions of the free 5-benzyloxy-3-[2-(N-benzyl-N-methylamino)-ethyl]-indole was added dilute hydrochloric acid. A white solid separated which was filtered, washed with ether, and recrystallized from ethanol. The yield of 5-benzyloxy-3-[2-(N-benzyl-N-methylamino)-ethyl]-indole hydrochloride melting at 110–112 degrees centigrade was 2.9 grams (71 percent).

Anal.—Percent calc. for $C_{21}H_{25}ON_2 \cdot HCl$: C, 73.79; H, 6.69. Found: C, 73.74; H, 6.69.

In a same manner the following representative (5-benzyloxy-3-indole)-alkylamines and salts may be prepared: 5-benzyloxy-3-[2-(N,N-dibenzylamino)-ethyl]-indole, 5-benzyloxy-3-[2-(N,N-dimethylamino)-ethyl]-indole, 5-benzyloxy-3-[2-(1-piperidino)-ethyl]-indole, 5-(para,para'-dimethylbenzyloxy)-3-[1-methyl-3-(N,N-dibenzylamino)-propyl]-indole, 2-ethyl-5-(para,para'-dichlorobenzyloxy)-3-[2-(N-methyl-N-benzylamino)-ethyl]-indole, 5-(para,para'-dimethoxybenzyloxy)-3-[3-(N-methylamino)-propyl]-indole, 5-benzyloxy-3-[2-(N-benzylamino)-ethyl]-indole, 5-benzyloxy-3-[3-(N,N-dimethylamino)-propyl]-indole, 5-benzyloxy-3-[2-(N,N-dibutylamino)-ethyl]-indole, and the like.

Example 1.—5-Hydroxy-3-[2-(N-methylamino)-ethyl]-indole and salts thereof

To a suspension of 2.64 grams (0.0065 mole) of 5-benzyloxy-3-[2-(N-benzyl-N-methylamino)-ethyl]-indole hydrochloride in 100 milliliters of water was added 25 milliliters of ten percent sodium hydroxide solution followed by 200 milliliters of ether. The mixture was

stirred vigorously until all suspended solid had dissolved, the ether layer was decanted, and the extraction was repeated with three additional 200-milliliter portions of ether. The ether extracts were combined, washed twice with water, dried over potassium carbonate, and the ether removed by distillation. The residue was dissolved in 25 milliliters of absolute ethanol, transferred to a micro-reduction flask and 0.5 gram of ten percent palladium-charcoal catalyst was added. The mixture was shaken with hydrogen at a pressure slightly greater than atmospheric and at a temperature of about 25 degrees centigrade. In about thirty minutes the hydrogen consumption was approximately 110 percent of theory. The reaction mixture was filtered to remove the catalyst and to the solution was added thirty milliliters (0.0065 equivalent) of 0.5 N sulfuric acid. The solution was concentrated to a volume of about five milliliters and a solution of 1.13 grams (0.0035 mole) of creatinine sulfate (neutral salt) in ten milliliters of water was added thereto. The resulting pink solution was filtered through a sintered glass funnel and the flask and funnel were rinsed with water; the final volume of solution was thirty milliliters. The solution was heated to sixty degrees centigrade and eighty milliliters of acetone was added to it with stirring; a heavy buff precipitate of 5-hydroxy-3-[2-(N-methylamino)-ethyl]-indole creatinine sulfate quickly separated. After filtering, drying, and recrystallizing from water-acetone, the product weighed 1.3 grams (fifty percent), and melted at 220–221 degrees centigrade.

Anal.—Percent calc. for $C_{16}H_{19}O_2N_3$: C, 44.88; H, 5.77. Found: C, 45.02; H, 5.55.

In the same manner the following acid addition salts of the 5-hydroxy-3-[2-(N-methylamino)-ethyl]-indole are prepared by reacting the free base with the corresponding acid: hydrochloride, picrate, tartrate, citrate, acetate, and sulfate.

Example 2.—5-Hydroxy-3-[2-(N,N-dimethylamino)-ethyl]-indole and salts thereof

In essentially the same manner as disclosed in Example 1, 5-hydroxy-3-[2-(N,N-dimethylamino)-ethyl]-indole is prepared by debenzoylating 5-benzyloxy-3-[2-(N,N-dimethylamino)-ethyl]-indole, under a hydrogen pressure of two atmospheres, employing a palladium-charcoal catalyst. The 5-hydroxy-3-[2-(N,N-dimethylamino)-ethyl]-indole creatinine sulfate was obtained in fifty percent yield and melted at 141–143 degrees centigrade.

Anal.—Percent calc. for $C_{18}H_{23}O_2N_3$: C, 44.33; H, 6.28; N, 16.16. Found: C, 44.88; H, 6.12; N, 16.17.

Example 3.—5-Hydroxy-3-[2-(N-cyclohexylamino)-ethyl]-indole and salts thereof

In essentially the same manner as given in Example 1, 5-hydroxy-3-[2-(N-cyclohexylamino)-ethyl]-indole is prepared by debenzoylating 5-benzyloxy-3-[2-(N-cyclohexylamino)-ethyl]-indole, under a hydrogen pressure of two atmospheres, employing a palladium-barium sulfate catalyst, and adding a stoichiometric quantity of hydrogen chloride thereto to prepare the 5-hydroxy-3-[2-(N-cyclohexylamino)-ethyl]-indole hydrochloride.

Example 4.—5-Hydroxy-3-[2-(N-phenyl-N-ethylamino)-ethyl]-indole and salts thereof

In essentially the same manner as given in Example 1, 5-hydroxy-3-[2-(N-phenyl-N-ethylamino)-ethyl]-indole is prepared by debenzoylating 5-benzyloxy-3-[2-(N-phenyl-N-ethylamino)-ethyl]-indole, under a hydrogen pressure of two atmospheres, employing a palladium-charcoal catalyst, and adding a stoichiometric quantity of picric acid thereto to prepare the 5-hydroxy-3-[2-(N-phenyl-N-ethylamino)-ethyl]-indole picrate, melting at 185–186 degrees centigrade.

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oxy-3-(2-(N,N-dibenzylamino)-ethyl)-indole by the action of hydrogen in the presence of a palladium catalyst.

13. In a process for the preparation of 5-hydroxytryptamine and addition salts thereof, the step of debenzylating a compound selected from 5-benzoyloxytryptamine and acid addition salts thereof by reacting a 5-benzoyloxytryptamine with a debenzylating agent to produce a 5-hydroxytryptamine.

14. In a process for the preparation of 5-hydroxytryptamine and addition salts thereof, the step of catalytically debenzylating a compound selected from 5-benzoyloxytryptamine and acid addition salts thereof in the presence of hydrogen to produce 5-hydroxytryptamine.

15. In a process for the preparation of 5-hydroxytryptamine and addition salts thereof, the step of debenzylating a compound selected from 5-benzoyloxytryptamine and acid addition salts thereof to produce 5-hydroxytryptamine by the action of hydrogen in the presence of a palladium catalyst.

16. In a process for the preparation of 5-hydroxytryptamine and addition salts thereof, the step of debenzylating 5-benzoyloxytryptamine to produce 5-hydroxytryptamine by the action of hydrogen in the presence of a palladium catalyst.

17. In a process for the preparation of 5-hydroxytryptamine and addition salts thereof, the steps of reducing the nitrile group of a 5-benzoyloxy-3-indoleacetonitrile to an amine group with a reducing agent selected from the group consisting of metal hydrides and hydrogen in the presence of a hydrogenation catalyst, and catalytically debenzylating the thus-formed 5-benzoyloxytryptamine in the presence of hydrogen to produce 5-hydroxytryptamine.

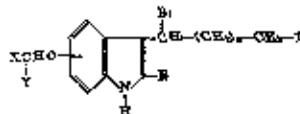
18. In a process for the preparation of 5-hydroxytryptamine and addition salts thereof, the steps of reducing the nitrile group of 5-benzoyloxy-3-indoleacetonitrile to an amine group with a reducing agent selected from the group consisting of metal hydrides and hydrogen in the presence of a hydrogenation catalyst, and catalytically debenzylating the thus-formed 5-benzoyloxytryptamine in the presence of hydrogen to produce 5-hydroxytryptamine.

19. In a process for the preparation of 5-hydroxytryptamine and addition salts thereof, the steps of converting a 5-benzoyloxyindole to a 5-benzoyloxy-3-indoleacetonitrile by mixing said 5-benzoyloxyindole with a Grignard reagent, reacting the thus-produced 5-benzoyloxyindolemagnesium halide with a haloacetonitrile to prepare a 5-benzoyloxy-3-indoleacetonitrile, reducing the nitrile group of the 5-benzoyloxy-3-indoleacetonitrile with a reducing agent selected from the group consisting of metal hydrides and hydrogen in the presence of a hydrogenation catalyst to prepare a 5-benzoyloxytryptamine, and catalytically debenzylating the 5-benzoyloxytryptamine in the presence of hydrogen to produce 5-hydroxytryptamine.

20. In a process for the preparation of 5-hydroxytryptamine and addition salts thereof, the steps of converting 5-benzoyloxyindole to 5-benzoyloxy-3-indoleacetonitrile by mixing said 5-benzoyloxyindole with a Grignard reagent, reacting the thus-produced 5-benzoyloxyindolemagnesium halide with a haloacetonitrile to prepare a 5-benzoyloxy-3-indoleacetonitrile, reducing the nitrile group of the 5-benzoyloxy-3-indoleacetonitrile with a reducing agent selected from the group consisting of metal hydrides and hydrogen in the presence of a hydrogenation catalyst to prepare 5-benzoyloxytryptamine, and

catalytically debenzylating the 5-benzoyloxytryptamine in the presence of hydrogen to produce 5-hydroxytryptamine.

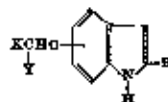
21. In a process for the preparation of (hydroxy-3-indole)-alkylamines including salts thereof, the step of debenzylating a (benzoyloxy-3-indole)-alkylamine having the formula



wherein X is selected from the group consisting of phenyl, halophenyl, lower alkoxyphenyl, and lower alkylphenyl, Y is selected from the group consisting of hydrogen, phenyl, halophenyl, lower alkoxyphenyl and lower alkylphenyl, R and R' are selected from the group consisting of hydrogen and lower alkyl, n is selected from the group consisting of zero and one, and Z is an amino radical, with a debenzylating agent to produce a (hydroxy-3-indole)-alkylamine.

22. In a process for the preparation of (hydroxy-3-indole)-alkylamines including salts thereof, the steps of reducing a compound selected from the group consisting of 5-benzoyloxy-3-indoleacetonitriles and (benzoyloxy-3-indole)-alkanoylamides with a reducing agent selected from the group consisting of metal hydrides and hydrogen in the presence of a hydrogenation catalyst to prepare a (benzoyloxy-3-indole)-alkylamine, and catalytically debenzylating the (benzoyloxy-3-indole)-alkylamine in the presence of hydrogen to produce a (hydroxy-3-indole)-alkylamine.

23. In a process for the preparation of (hydroxy-3-indole)-alkylamines including salts thereof, the steps of mixing a benzoyloxyindole having the formula:



wherein X is selected from the group consisting of phenyl, halophenyl, lower alkoxyphenyl, and lower alkylphenyl, Y is selected from the group consisting of hydrogen, phenyl, halophenyl, lower alkoxyphenyl, and lower alkylphenyl, and R is selected from the group consisting of hydrogen and lower alkyl, with a Grignard reagent, reacting the thus-produced benzoyloxyindolemagnesium halide with a compound selected from the group consisting of a haloalkanoylamide and a haloacetonitrile to produce a compound selected from the group consisting of a (benzoyloxy-3-indole)-alkanoylamide and a 5-benzoyloxy-3-indoleacetonitrile, reducing the thus-produced compounds with a reducing agent selected from the group consisting of metal hydrides and hydrogen in the presence of a hydrogenation catalyst to prepare a (benzoyloxy-3-indole)-alkylamine, and catalytically debenzylating the (benzoyloxy-3-indole)-alkylamine in the presence of hydrogen to produce a (hydroxy-3-indole)-alkylamine.

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- [54] 3-ARYLOXY-3-SUBSTITUTED
PROPANAMINES
- [75] Inventors: David W. Robertson, Greenwood;
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- [73] Assignee: Eli Lilly and Company, Indianapolis,
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- [21] Appl. No.: 499,940
- [22] Filed: Mar. 27, 1990
- Related U.S. Applications Data
- [60] Division of Ser. No. 462,925, Jan. 12, 1990, Pat. No.
4,956,388, which is a continuation of Ser. No. 943,122,
Dec. 22, 1986, abandoned.
- [31] Int. Cl.³ A61K 31/38; A61K 31/44;
C07D 333/16
- [32] U.S. Cl. 514/438; 514/357;
514/363; 514/471; 546/334; 548/205; 549/75;
549/481
- [38] Field of Search 549/75, 491; 546/334;
548/205; 514/438, 471, 357, 363

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[57] ABSTRACT
The present invention provides 3-aryloxy-3-substituted
propanamines capable of inhibiting the uptake of seroto-
nin and norepinephrine.

51 Claims, No Drawings

3-ARYLOXY-3-SUBSTITUTED PROPANAMINES

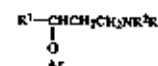
This application is a division of application Ser. No.
07/462,925, filed Jan. 12, 1990, now U.S. Pat. No.
4,956,388, continuation of application Ser. No.
06/945,122, filed on Dec. 22, 1986, now abandoned.

BACKGROUND OF THE INVENTION

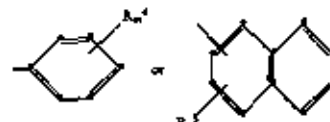
During the past decade, the relationship between
monoamine uptake and a variety of diseases and condi-
tions has been appreciated and investigated. For exam-
ple, the hydrochloride salt of fluoxetine (di-N-methyl-
7-[4-(trifluoromethyl)phenoxy]benzopropylamine) is
a selective serotonin (5-hydroxytryptamine) uptake
inhibitor presently undergoing clinical evaluation for
the treatment of depression, anxiety, appetite suppres-
sion, and other disorders. Similarly, (racemic hydro-
chloride ((-)-N-methyl-8-(2-methylphenoxy)benzo-
propylamine hydrochloride) is a selective inhibitor of
norepinephrine uptake being investigated clinically for
its antidepressant activity. These compounds are among
many taught in U.S. Pat. Nos. 4,018,895, 4,194,009, and
4,314,081 as being potent but selective blockers of the
uptake of a particular monoamine.

SUMMARY OF THE INVENTION

The present invention provides novel 3-aryloxy-3-
substituted propanamines which are potent inhibitors of
both serotonin and norepinephrine uptake. More specifi-
cally, the present invention relates to a compound of the
formula



wherein:
R¹ is C₂-C₇ cycloalkyl, thienyl, halothienyl, (C₁-C₄)
alkylthienyl, furanyl, pyridyl or thiazolyl;



each of R² and R³ independently is hydrogen or methyl;
each R⁴ independently is halo, C₁-C₄ alkyl, C₁-C₃
alkoxy or trifluoromethyl;
each R⁵ independently is halo, C₁-C₄ alkyl or trifluo-
romethyl;
m is 0, 1 or 2;
n is 0 or 1; and
the pharmaceutically acceptable acid addition salts
thereof.

The invention also provides pharmaceutical formula-
tions comprising a compound of the above formula and
a pharmaceutically acceptable carrier, diluent or excipi-
ent thereof.

A further embodiment of the invention are methods
for selectively inhibiting the uptake of serotonin and
norepinephrine, as well as for treating a variety of disor-
ders which have been linked to decreased neurotrans-
mission of serotonin and norepinephrine in mammals
including obesity, depression, alcoholism, pain, loss of

memory, anxiety, smoking, and the like, employing a
compound of the invention.

DETAILED DESCRIPTION OF THE INVENTION

In the above formula, the term C₁-C₄ alkyl represents
a straight or branched alkyl chain bearing from one to
four carbon atoms. Typical C₁-C₄ alkyl groups include
methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl,
sec-butyl and t-butyl.

C₁-C₃ alkoxy represents methoxy, ethoxy, n-
propoxy or isopropoxy.

Halo represents fluoro, chloro, bromo or iodo.

When Ar is naphthalenyl, it can be either 1-naph-
thalenyl or 2-naphthalenyl.

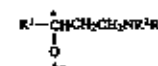
When R¹ is thienyl, it can be either 2-thienyl or 3-thi-
enyl; when R¹ is furanyl, it can be either 2-furanyl or
3-furanyl; when R¹ is pyridyl, it can be either 2-pyridyl,
3-pyridyl or 4-pyridyl; when R¹ is thiazolyl, it can be
either 2-thiazolyl, 4-thiazolyl or 5-thiazolyl.

(C₁-C₄ Alkyl)thienyl represents a thienyl ring mono-
substituted with a C₁-C₄ alkyl substituent. Typical
C₁-C₄ alkylthienyl groups include 4-methyl-2-thienyl,
3-ethyl-2-thienyl, 2-methyl-3-thienyl, 4-propyl-3-thi-
enyl, 3-n-butyl-2-thienyl, 4-methyl-3-thienyl, 3-methyl-
2-thienyl, and the like.

Halothienyl represents a thienyl ring monosubstituted
with a halo substituent. Typical halo-thienyl groups
include 3-chloro-2-thienyl, 4-bromo-3-thienyl, 2-iodo-3-
thienyl, 3-iodo-3-thienyl, 4-fluoro-2-thienyl, 2-bromo-3-
thienyl, 4-chloro-2-thienyl and the like.

While all of the compounds of the present invention
are believed to inhibit the uptake of serotonin and nore-
pinephrine in mammals, there are certain of these com-
pounds which are preferred for such use. Preferably,
R¹ is halothienyl, (C₁-C₄ alkyl)thienyl and especially
thienyl. Further, one of R² and R³ is hydrogen and the
other is methyl. It is also preferred that those com-
pounds wherein both R² and R³ are other than methyl
are preferred for inhibiting the uptake of norepineph-
rine in mammals. Other preferred aspects of the present
invention will be noted hereinafter.

The compounds of the present invention possess an
asymmetric carbon represented by the carbon atom
labeled "C" in the following formula:



As such, the compounds can exist as the individual
stereoisomers as well as the racemic mixture. Accord-
ingly, the compounds of the present invention will in-
clude not only the di-racemates, but also their respec-
tive optically active D- and L-isomers.

As pointed out above, the invention includes the
pharmaceutically acceptable acid addition salts of the
compounds defined by the above formula. Since the
compounds of this invention are amines, they are basic
in nature and accordingly react with any number of
inorganic and organic acids to form pharmaceutically
acceptable acid addition salts. Since the free amines of
the invention are typically oils at room temperature, it is
preferable to convert the free amines to their corre-
sponding pharmaceutically acceptable acid addition
salts, which are routinely solid at room temperature, for

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Analysis calculated for $C_{21}H_{23}NO_5$ Theory: C, 62.83; H, 5.77; N, 3.49; Found: C, 62.70; H, 5.88; N, 3.26.

EXAMPLE 2

N-Methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate

Phenyl chloroformate (794 μ l, 0.0063 mol) was added dropwise to a refluxing solution of N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine (1.79 g, 0.0058 mol) in 100 ml of toluene. The resulting solution was refluxed one and one half hours and cooled to room temperature. The solution was washed (2.5N sodium hydroxide, water, 1N hydrochloric acid, brine), dried over anhydrous sodium sulfate and concentrated in vacuo to give 2.4 g of the crude carbamate. 2N Sodium hydroxide (11.5 ml, 0.058 mol) was added to a solution of the carbamate (2.4 g, 0.0058 mole) in propylene glycol (100 ml). The mixture was heated at 110° C. for 75 minutes. The reaction mixture was diluted with water and extracted with diethyl ether. The organic phase was washed with water and then a saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under vacuum to yield 1.5 g of an oil. Crystallization of the oil as the oxalate salt from ethyl acetate/methanol gave 920 mg (41.3%) of the title compound as a white powder. mp = 136° C.-138.5° C.

Analysis calculated for $C_{20}H_{21}NO_5$ Theory: C, 62.00; H, 5.46; N, 3.62; Found: C, 62.21; H, 5.72; N, 3.57.

EXAMPLE 3

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(5-methyl-2-thienyl)propanamine oxalate

A. 3-Dimethylamino-1-(5-methyl-2-thienyl)-1-propanone hydrochloride

The title compound was prepared according to the general procedure outlined in Example 1 employing 2-acetyl-5-methylthiophene as the starting material to provide 31.3 g (37.4%) of a yellow powder following crystallization from acetone. mp = 145° C.-147° C.

Analysis calculated for $C_{19}H_{21}ClNO_2$ Theory: C, 51.38; H, 6.90; N, 5.99; Found: C, 51.53; H, 6.82; N, 5.66.

B. α -(2-(Dimethylamino)ethyl)-5-methyl-2-thiophene methanol

According to the general procedure set forth in Example 1 using 3-dimethylamino-1-(5-methyl-2-thienyl)-1-propanone hydrochloride as the starting material. The title compound was obtained (50.9%) as an opaque crystalline solid synthesized. mp = 66.5° C.-68° C.

Analysis calculated for $C_{10}H_{17}NOS$ Theory: C, 60.26; H, 8.60; N, 7.03; Found: C, 60.49; H, 8.58; N, 6.91.

C. According to the procedure set forth in Example 1, using α -(2-(dimethylamino)ethyl)-5-methyl-2-thiophene methanol as the starting material N,N-dimethyl-3-(1-naphthalenyloxy)-3-(5-methyl-2-thienyl)propanamine was prepared. The crude material was chromatographed over silica gel (eluent: methylene chloride/methanol) to yield 1.4 g (25.5%) of an oil. Crystallization from ethyl acetate/methanol of a small portion of the oil as the oxalate salt gave the title compound as yellow crystals mp = 151° C.

Analysis calculated for $C_{22}H_{25}NO_5$ Theory: C, 63.59; H, 6.06; N, 3.37; Found: C, 63.36; H, 5.84; N, 3.33.

EXAMPLE 4

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(3-methyl-2-thienyl)propanamine oxalate

A. 3-Dimethylamino-1-(3-methyl-2-thienyl)-1-propanone hydrochloride

The title compound was prepared according to the general procedure set forth in Example 1 using 2-acetyl-3-methylthiophene as the starting material. The crude material was crystallized from acetone to provide 43.4 g (60.7%) of the title compound as a white powder. mp = 157° C.-158° C.

Analysis calculated for $C_{19}H_{21}ClNO_2$ Theory: C, 51.38; H, 6.90; N, 5.99; Found: C, 51.63; H, 7.14; N, 5.82.

B. α -(2-(Dimethylamino)ethyl)-3-methyl-2-thiophene methanol

The title compound was prepared from 3-dimethylamino-1-(3-methyl-2-thienyl)-1-propanone hydrochloride according to the general procedure of Example 1. Crystallization from hexanes yielded 11.38 g (53.7%) of an opaque crystalline solid. mp = 41.5° C.-42.5° C.

Analysis calculated for $C_{10}H_{17}NOS$ Theory: C, 60.26; H, 8.60; N, 7.03; Found: C, 60.80; H, 8.33; N, 6.56.

C. Crude N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(3-methyl-2-thienyl)propanamine, prepared according to the general procedure outlined in Example 1, was chromatographed over silica gel (eluent: methylene chloride/methanol) to yield 10.4 g (74.3%) of an oil. The oil was converted to the oxalate salt and crystallized from ethyl acetate/methanol to give a white powder. mp = 140° C.-141° C.

Analysis calculated for $C_{22}H_{25}NO_5$ Theory: C, 63.59; H, 6.06; N, 3.37; Found: C, 63.85; H, 6.07; N, 3.49.

EXAMPLE 5

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(5-chloro-2-thienyl)propanamine oxalate

A. 3-Dimethylamino-1-(5-chloro-2-thienyl)-1-propanone hydrochloride

The title compound was prepared according to the general procedure of Example 1 using 2-acetyl-5-chlorothiophene as the starting material. Crystallization from acetone gave 14.55 g (36.9%) mp = 170° C.-171° C.

Analysis calculated for $C_{18}H_{19}Cl_2NO_2$ Theory: C, 42.83; H, 5.16; N, 5.51; Found: C, 42.00; H, 5.23; N, 6.30.

B. α -(2-(Dimethylamino)ethyl)-5-chloro-2-thiophene methanol

Three grams of the title compound were prepared from 3-dimethylamino-1-(5-chloro-2-thienyl)-1-propanone hydrochloride according to the general procedure of Example 1 following crystallization from hexanes (38.6%). mp = 76° C.-77° C.

Analysis calculated for $C_{10}H_{15}ClNO_2$ Theory: C, 49.20; H, 6.42; N, 6.37; Found: C, 47.37; H, 6.65; N, 6.40.

C. N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(5-chloro-2-thienyl)propanamine was prepared from α -(2-(dimethylamino)ethyl)-5-chloro-2-thiophene methanol according to the general procedure of Example 1. The crude product was chromatographed over silica gel employing methylene chloride/methanol/ammonium

hydroxide as the eluent to yield 320 mg (3.5%) of an oil. Crystallization of the oil as the oxalate salt from ethyl acetate/methanol gave a brown solid. mp = 134° C.-135° C.

Analysis calculated for $C_{21}H_{23}ClNO_5$ Theory: C, 57.86; H, 5.09; N, 3.21; Found: C, 57.73; H, 5.35; N, 3.30.

EXAMPLE 6

N,N-Dimethyl-3-(4-(trifluoromethyl)-1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate

According to the procedure set forth in Example 1 using 4-(trifluoromethyl)-1-fluoronaphthalene as a starting material, 1.7 g (66.5%) of the title compound as a tan solid was prepared following crystallization from ethyl acetate/methanol. mp = 145° C.-147° C.

Analysis calculated for $C_{22}H_{23}F_3NO_5$ Theory: C, 56.28; H, 4.72; N, 2.98; Found: C, 56.04; H, 4.65; N, 3.23.

EXAMPLE 7

N-Methyl-3-(4-(trifluoromethyl)-1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate

According to the procedure set forth in Example 2 N,N-dimethyl-3-(4-(trifluoromethyl)-1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate was converted to the title compound. Crystallization from ethyl acetate/methanol gave 430 mg (33.8%) of a tan powder. mp = 154° C.-156° C.

Analysis calculated for $C_{21}H_{23}F_3NO_5$ Theory: C, 55.38; H, 4.43; N, 3.08; Found: C, 55.63; H, 4.55; N, 3.27.

EXAMPLE 8

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(3-thienyl)propanamine oxalate

A. 3-Dimethylamino-1-(3-thienyl)-1-propanone hydrochloride

The title compound was prepared according to the procedure of Example 1 using 3-acetylthiophene as a starting material. Crystallization from acetone gave 73.9 g (84.9%) of a tan powder. mp = 143° C.-145° C.

Analysis calculated for $C_{18}H_{21}ClNO_2$ Theory: C, 49.20; H, 6.42; N, 6.37; Found: C, 46.27; H, 6.11; N, 7.00.

B. α -(2-(Dimethylamino)ethyl)-3-thiophene methanol

The title compound was prepared according to the procedure in Example 1 using 3-dimethylamino-1-(3-thienyl)-1-propanone hydrochloride as a starting material. Crystallization from diethyl ether/hexane gave 29.0 g (47.7%) of the title compound as a solid. mp = 61° C.-63° C.

Analysis calculated for $C_{10}H_{17}NOS$ Theory: C, 58.34; H, 8.16; N, 7.56; Found: C, 58.34; H, 8.17; N, 7.72.

C. N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(3-thienyl)propanamine oxalate was prepared according to the procedure of Example 1 using α -(2-(dimethylamino)ethyl)-3-thiophene methanol as a starting material. Crystallization from ethyl acetate/methanol gave 5.88 g (69.8%) of a white powder. mp = 164° C.-165° C.

Analysis calculated for $C_{21}H_{23}NO_5$ Theory: C, 62.83; H, 5.77; N, 3.49; Found: C, 63.12; H, 6.01; N, 3.51.

EXAMPLE 9

N-Methyl-3-(1-naphthalenyloxy)-3-(3-thienyl)propanamine oxalate

The title compound was prepared according to procedure of Example 2 from N,N-dimethyl-3-(1-naphthalenyloxy)-3-(3-thienyl)propanamine. Crystallization

from ethyl acetate/methanol gave 2.97 g (63.6%) of a white powder. mp = 148° C.-150° C.

Analysis calculated for $C_{20}H_{21}NO_5$ Theory: C, 62.00; H, 5.46; N, 3.62; Found: C, 62.23; H, 5.59; N, 3.85.

EXAMPLE 10

N,N-Dimethyl-3-(4-chloro-1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate

To a stirred mixture of 4-chloro-1-naphthol (5.36 g, 0.03 mol), α -(2-(dimethylamino)ethyl)-2-thiophene methanol (5.56 g, 0.03 mol), triphenylphosphine (7.87 g, 0.03 mol) and 75 ml of tetrahydrofuran under a nitrogen atmosphere was added 4.3 ml (0.03 mol) of diethylazodicarboxylate dropwise. Occasional cooling was needed to keep the temperature of the reaction mixture below about 30° C. The resulting solution was stirred at room temperature overnight. The volatile constituents were evaporated under vacuum. The residue was diluted with water and the mixture was basified with 3N sodium hydroxide. The mixture was extracted with diethyl ether, and the organic extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the diethyl ether and preparative HPLC of the residue using a silica column with a methylene chloride/methanol mixture as eluent yielded 3.7 g (34% yield) of the pure free base as an oil. The oxalate salt was prepared from the above free base by treating an ethyl acetate solution of the free base with oxalic acid. The resulting precipitate was recrystallized from ethanol to afford colorless crystals. mp = 155° C. dec.

Analysis calculated for $C_{21}H_{23}ClNO_5$ Theory: C, 57.86; H, 5.09; N, 3.21; Found: C, 57.66; H, 4.94; N, 3.12.

EXAMPLE 11

N-Methyl-3-(4-chloro-1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate

To a stirred solution of N,N-dimethyl-3-(4-chloro-1-naphthalenyloxy)-3-(2-thienyl)propanamine (2.81 g, 8.12 mmol) and 20 ml of toluene heated at 85° C. was added dropwise triethoxyethyl chloroformate (1.89 g, 8.93 mmol). The stirring was continued at 85° C. for three hours, and the resulting solution was cooled in an ice bath. To the mixture was added 0.13 ml of 98% formic acid followed by 0.28 ml of triethylamine. The mixture was stirred at room temperature for 30 minutes. The mixture was poured into water and the resulting mixture was extracted with diethyl ether. The organic extracts were washed successively with a saturated sodium chloride solution, a 2N hydrochloric acid solution and a saturated sodium chloride solution. The organic phase was dried over anhydrous sodium sulfate. The volatile constituents were evaporated under vacuum to yield 3.81 g (92% yield) of the crude carbamate as an oil. To a solution of the crude carbamate in 10.0 ml of DMF was added 98% formic acid (0.69 g, 14.9 mmol). The reaction solution was cooled to about 15° C. under a nitrogen atmosphere. Zinc dust (1.22 g, 18.7 mmol) was next added in portions over a 30 minute period. The mixture was stirred at about 15° C. for one hour and then overnight at room temperature. The reaction mixture was filtered through a sintered glass funnel and the filtrate was diluted with water. The acidic solution was made basic with excess cold ammonium hydroxide and then extracted with diethyl ether. The organic extracts were washed with water followed by a saturated sodium chloride solution. The organic phase was dried over anhydrous sodium sulfate and

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evaporated under vacuum. The residue was purified by preparative HPLC using a silica gel column with a methylene chloride/methanol/ammonium hydroxide (100:5:1, v/v/v) mixture as eluent to give 1.26 g (51% yield) of the free base as an oil.

The oxalate salt was prepared from the free base by treating an ethyl acetate solution of the free base with oxalic acid. The resulting precipitate was crystallized from methanol to afford colorless crystals, mp = 182° C. dec.

Analysis calculated for $C_{20}H_{23}ClNO_5$ Theory: C, 56.94; H, 4.78; N, 3.32; Found: C, 57.22; H, 4.54; N, 3.48.

EXAMPLE 12

N,N-Dimethyl-3-(4-methyl-1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate

N,N-Dimethyl-3-(4-methyl-1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate was prepared in 21% yield by the general procedure described in Example 10. The oxalate salt was made and crystallized from ethanol to afford the title compound as colorless crystals, mp = 151° C. dec.

Analysis calculated for $C_{23}H_{25}NO_5$ Theory: C, 63.59; H, 6.06; N, 3.37; Found: C, 63.29; H, 6.02; N, 3.23.

EXAMPLE 13

N-Methyl-3-(4-methyl-1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate

The free base of the title compound was prepared in 44% yield by the procedure described above in Example 11. The oxalate salt was prepared from the free base by treating an ethyl acetate solution of the free base with maleic acid. The resulting precipitate was recrystallized from ethanol to afford colorless crystals, mp = 174° C. dec.

Analysis calculated for $C_{21}H_{23}NO_5$ Theory: C, 64.62; H, 5.89; N, 3.28; Found: C, 64.49; H, 5.71; N, 3.48.

The following compounds were prepared according to the general procedures outlined in Examples 1 and 2 above.

EXAMPLE 14

(+)-N-Methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine maleate, mp = 118° C.-123° C.

[α]_D²⁵ = +82° ([α]_D²⁵ = +391° at C=1 in methanol). Analysis calculated for $C_{22}H_{23}NO_4$ Theory: C, 63.90; H, 5.61; N, 3.39; S, 7.75; Found: C, 63.78; H, 5.44; N, 3.35; S, 7.64.

EXAMPLE 15

N-Methyl-3-(1-naphthalenyloxy)-3-cyclohexylpropanamine oxalate, mp = 184° C.-185° C.

Analysis calculated for $C_{22}H_{29}NO_5$ Theory: C, 68.20; H, 7.54; N, 3.61; Found: C, 68.36; H, 7.30; N, 3.45.

EXAMPLE 16

N-Methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate, mp = 183° C.-185° C.

Analysis calculated for $C_{22}H_{23}NO_5$ Theory: C, 58.75; H, 5.19; N, 3.21; Found: C, 59.02; H, 4.94; N, 3.47.

EXAMPLE 17

N,N-Dimethyl-3-(4-(trifluoromethyl)phenoxy)-3-(2-furyl)propanamine oxalate, mp = 144.5° C.-145.5° C.

Analysis calculated for $C_{18}H_{19}F_3NO_5$ Theory: C, 53.60; H, 5.00; N, 3.47; Found: C, 53.83; H, 5.22; N, 3.23.

EXAMPLE 18

N,N-Dimethyl-3-(4-(trifluoromethyl)phenoxy)-3-(2-thienyl)propanamine oxalate, mp = 130° C.-131.5° C.

Analysis calculated for $C_{18}H_{19}F_3NO_5$ Theory: C, 51.55; H, 4.81; N, 3.34; Found: C, 51.25; H, 4.91; N, 3.55.

EXAMPLE 19

N,N-Dimethyl-3-(4-(trifluoromethyl)phenoxy)-3-(3-thienyl)propanamine oxalate, mp = 124° C.-125° C.

Analysis calculated for $C_{18}H_{19}F_3NO_5$ Theory: C, 51.55; H, 4.81; N, 3.34; Found: C, 51.35; H, 4.68; N, 3.39.

EXAMPLE 20

N-Methyl-3-(4-(trifluoromethyl)phenoxy)-3-(2-thienyl)propanamine oxalate, mp = 167° C.-168° C. dec.

Analysis calculated for $C_{17}H_{19}F_3NO_5$ Theory: C, 50.37; H, 4.48; N, 3.46; Found: C, 50.40; H, 4.66; N, 3.72.

EXAMPLE 21

N,N-Dimethyl-3-(4-(trifluoromethyl)phenoxy)-3-(2-furyl)propanamine, oil

Analysis calculated for $C_{18}H_{19}F_3NO_4$ Theory: C, 61.34; H, 5.79; N, 4.47; Found: C, 61.07; H, 5.82; N, 4.68.

EXAMPLE 22

N-Methyl-3-(4-(trifluoromethyl)phenoxy)-3-(3-thienyl)propanamine oxalate, mp = 181° C.-182° C.

Analysis calculated for $C_{17}H_{19}F_3NO_5$ Theory: C, 50.37; H, 4.48; N, 3.46; Found: C, 50.49; H, 4.42; N, 3.67.

EXAMPLE 23

N-Methyl-3-(4-(trifluoromethyl)phenoxy)-3-(2-furyl)propanamine oxalate, mp = 98° C.-102° C. dec.

Analysis calculated for $C_{17}H_{19}F_3NO_5$ Theory: C, 52.45; H, 4.66; N, 3.60; Found: C, 52.52; H, 4.45; N, 3.80.

EXAMPLE 24

N,N-Dimethyl-3-(4-methylphenoxy)-3-(2-thienyl)propanamine oxalate, mp = 132.5° C.-133.5° C.

Analysis calculated for $C_{18}H_{21}NO_5$ Theory: C, 59.16; H, 6.34; N, 3.83; Found: C, 59.06; H, 6.12; N, 4.11.

EXAMPLE 25

N,N-Dimethyl-3-(4-chlorophenoxy)-3-(2-thienyl)propanamine oxalate, mp = 118° C.-119° C.

Analysis calculated for $C_{17}H_{19}ClNO_5$ Theory: C, 52.95; H, 5.22; N, 3.63; Found: C, 52.85; H, 5.22; N, 3.48.

EXAMPLE 26

N-Methyl-3-(4-methylphenoxy)-3-(2-thienyl)propanamine oxalate, mp = 152° C.-153° C.

Analysis calculated for $C_{17}H_{19}NO_5$ Theory: C, 58.10; H, 6.02; N, 3.99; Found: C, 58.05; H, 6.04; N, 3.72.

EXAMPLE 27

N-Methyl-3-(4-chlorophenoxy)-3-(2-thienyl)propanamine oxalate, mp = 128° C.-129° C.

Analysis calculated for $C_{16}H_{15}ClNO_5$ Theory: C, 51.68; H, 4.88; N, 3.77; Found: C, 51.60; H, 5.01; N, 3.52.

EXAMPLE 28

N-Methyl-3-(4-methoxyphenoxy)-3-(2-thienyl)propanamine oxalate, mp = 140° C.-143° C.

Analysis calculated for $C_{17}H_{19}NO_5$ Theory: C, 55.57; H, 5.76; N, 3.81; Found: C, 55.31; H, 5.55; N, 4.06.

EXAMPLE 29

N,N-Dimethyl-3-(4-methoxyphenoxy)-3-(2-thienyl)propanamine oxalate, mp = 110° C.-111.5° C.

Analysis calculated for $C_{18}H_{21}NO_5$ Theory: C, 56.68; H, 6.08; N, 3.67; Found: C, 56.43; H, 5.85; N, 3.81.

EXAMPLE 30

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(2-furyl)propanamine oxalate, mp = 153° C.-155.5° C.

Analysis calculated for $C_{22}H_{23}NO_5$ Theory: C, 65.44; H, 6.02; N, 3.63; Found: C, 65.21; H, 5.75; N, 3.78.

EXAMPLE 31

N-Methyl-3-(1-naphthalenyloxy)-3-(2-furyl)propanamine oxalate, mp = 145° C.-146° C.

Analysis calculated for $C_{20}H_{21}NO_5$ Theory: C, 64.68; H, 5.70; N, 3.77; Found: C, 64.79; H, 5.51; N, 3.95.

EXAMPLE 32

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate, mp = 190° C.-191° C. dec.

Analysis calculated for $C_{20}H_{23}NO_5$ Theory: C, 59.69; H, 5.51; N, 3.96; Found: C, 59.99; H, 5.60; N, 7.01.

EXAMPLE 33

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(2-cyclohexyl)propanamine oxalate, mp = 167° C.-169° C.

Analysis calculated for $C_{22}H_{29}NO_5$ Theory: C, 68.80; H, 7.78; N, 3.49; Found: C, 68.53; H, 7.53; N, 3.54.

EXAMPLE 34

N-Methyl-3-(4-(trifluoromethyl)phenoxy)-3-(2-cyclohexyl)propanamine oxalate, mp = 212° C.-213° C.

Analysis calculated for $C_{19}H_{21}F_3NO_5$ Theory: C, 56.29; H, 6.46; N, 3.45; Found: C, 56.19; H, 6.37; N, 3.32.

EXAMPLE 35

N,N-Dimethyl-3-(4-(trifluoromethyl)phenoxy)-3-(2-cyclohexyl)propanamine oxalate, mp = 159° C.-160° C.

Analysis calculated for $C_{20}H_{23}F_3NO_5$ Theory: C, 57.27; H, 6.73; N, 3.34; Found: C, 57.49; H, 6.61; N, 3.20.

EXAMPLE 36

N-Methyl-3-(1-naphthalenyloxy)-3-(3-pyridyl)propanamine oxalate, mp = 98° C. dec.

Analysis calculated for $C_{21}H_{23}N_2O_5$ Theory: C, 65.96; H, 5.80; N, 3.33; Found: C, 66.27; H, 5.67; N, 3.01.

EXAMPLE 37

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(3-pyridyl)propanamine oxalate, mp = 176° C.-178° C.

Analysis calculated for $C_{22}H_{25}N_2O_5$ Theory: C, 66.65; H, 6.10; N, 3.07; Found: C, 66.53; H, 6.36; N, 6.41.

EXAMPLE 38

(+)-N-Methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate, mp = 135° C.-134° C.

Analysis calculated for $C_{20}H_{23}NO_5$ Theory: C, 62.00; H, 5.46; N, 3.62; Found: C, 62.03; H, 5.51; N, 3.87.

EXAMPLE 39

(-)-N-Methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate, mp = 138° C.-138.5° C.

Analysis calculated for $C_{20}H_{23}NO_5$ Theory: C, 62.00; H, 5.46; N, 3.62; Found: C, 61.72; H, 5.32; N, 3.82.

As noted above, the compounds of this invention are useful for inhibiting the uptake of serotonin. Therefore, another embodiment of the present invention is a method for inhibiting serotonin uptake in mammals which comprises administering to a mammal requiring increased neurotransmission of serotonin a pharmacologically effective amount of a compound of the invention.

Compounds of the invention also have the ability to inhibit the uptake of norepinephrine. As such, yet another embodiment of this invention is a method for inhibiting norepinephrine uptake in mammals which comprises administering to a mammal requiring increased neurotransmission of norepinephrine a pharmacologically effective amount of a compound of the invention.

The term "pharmacologically effective amount," as used herein, represents an amount of a compound of the invention which is capable of inhibiting serotonin or norepinephrine uptake. The particular dose of compound administered according to this invention will of course be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes. The compounds of the invention unexpectedly inhibit the uptake of not only serotonin but also norepinephrine in mammals. It is a special feature of the compounds that they have good oral bioavailability without losing their substantial potent inhibiting effect of serotonin and norepinephrine uptake inhibiting effect. It is also a special feature of the compounds of the present invention in that they have been found to demonstrate a low degree of toxicity to mammals. A typical daily dose will contain from about 0.01 mg/kg to about 20 mg/kg of the active compound of this invention. Preferred daily doses will be about 0.05 to about 10 mg/kg, ideally about 0.1 to about 5 mg/kg.

A variety of physiologic functions have been shown to be subject to influence by brain serotonergic and norepinephrinergic neural systems. As such, the compounds of the present invention are believed to have the ability to treat a variety of disorders in mammals associated with these neural systems such as obesity, depression, alcoholism, pain, loss of memory, anxiety and smoking. Therefore, the present invention also provides methods of treating the above disorders at rates set forth above for inhibiting serotonin and norepinephrine uptake in mammals.

The following experiment was conducted to demonstrate the ability of the compounds of the present invention to inhibit the uptake of serotonin and norepinephrine. This general procedure is set forth by Wong et al., in *Drug Development Research* 6:397-403 (1985).

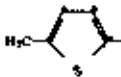
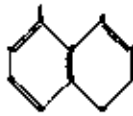
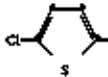
Male Sprague-Dawley rats (110-150 g) from Harlan Industries (Cumberland, IN) were fed a Purina Chow ad libitum for at least 3 days before being used in the studies. Rats were killed by decapitation. Whole brains were removed and dissected. Cerebral cortex was homogenized in 9 volumes of a medium containing 0.32 M sucrose and 10 mM glucose. Crude synaptosomal preparations were isolated after differential centrifugation at 1,000 g for 10 min. and 17,000 g for 28 min. The final pellets were suspended in the same medium and kept in ice until use within the same day.

Synaptosomal uptake of ^3H -serotonin (^3H -5HT) and ^{14}C -norepinephrine (^{14}C -NE) was determined as follows. Cortical synaptosomes (equivalent to 1 mg of protein) were incubated at 37°C . for 5 min in 1 ml of Krebs-bicarbonate medium containing also 10 mM glucose, 0.1 mM iproniazid, 1 mM ascorbic acid, 0.17 mM EDTA, 50 nM ^3H -5HT and 100 nM ^{14}C -NE. The reaction mixture was immediately diluted with 2 ml of ice-chilled Krebs-bicarbonate buffer and filtered under vacuum with a cell harvester (Brandel, Gaithersburg, MD). Filters were rinsed twice with approximately 5 ml of ice-chilled 0.9% saline and were transferred to a counting vial containing 10 ml of scintillation fluid (PCS, Amersham, Arlington Heights, IL). Radioactivity was measured by a liquid scintilla-

tion spectrophotometer. Accumulation of ^3H -5HT and ^{14}C -NE at 4°C . represented the background and was subtracted from all samples.

The results of the evaluation of various compounds of the present invention are set forth below in Table I. In the Table, columns 1-4 identify the structure of the compounds evaluated when taken with the formula set forth in the heading; column 5 identifies the salt form, if any, of the compound evaluated; and columns 6 and 7 provide the concentration of the test compound at 10^{-9}M (nM) needed to inhibit 50% of serotonin (5HT) or norepinephrine, respectively, and is indicated in the Table as IC_{50} . The numbers in parentheses represent percent inhibition at 1000 nM.

TABLE I
INHIBITION OF 5HT AND NOREPINEPHRINE UPTAKE IN VITRO

Compound or Example No.	Ar		R ¹		Salt Form	IC ₅₀ (nM)	
	Ar		R ¹	R ²		5HT	NE
1			CH ₃	CH ₃	oxalate	13	600
2			CH ₃	H	oxalate	17.5	38.5
3			CH ₃	CH ₃	oxalate	35	730
4			CH ₃	CH ₃	oxalate	76	(61)
5			CH ₃	CH ₃	oxalate	82	725

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CPE

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION No. 32734
Por la cual se deniega una patente de invención

Rad. PCT/06-121181

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
en ejercicio de sus facultades legales, en especial de las conferidas en el numeral 38 del artículo 3° del Decreto 1687 de 2010, y

CONSIDERANDO:

PRIMERO: Que mediante escrito radicado en esta Superintendencia el día 30 de noviembre del 2006 con el N° 06-121181-00000-0000, la doctora Alicia Lloreda Ricaurte, en su calidad de apoderada de F. Hoffmann – La Roche AG, presentó la solicitud de patente de invención titulada "3-AMINO-1-ARILPROPIL-INDOLES COMO INHIBIDORES DE RECAPTACIÓN DE MONOAMINAS", correspondiente a la solicitud internacional PCT/EP 2005/005734 de fecha 27 de mayo del 2005, para que se iniciara la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Si la oficina nacional competente encontrara que la invención no es patentable o que no cumple con alguno de los requisitos establecidos en esta Decisión para la concesión de la patente, lo notificará al solicitante. Este deberá responder a la notificación dentro del plazo de sesenta días contados a partir de la fecha de la notificación. Este plazo podrá ser prorrogado por una sola vez por un periodo de treinta días adicionales. (...) Si el solicitante no respondiera a la notificación dentro del plazo señalado, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, la oficina nacional competente denegará la patente"*.

CUARTO: Que de conformidad con lo dispuesto en el artículo 45 antes mencionado, se realizó el examen de fondo y se requirió al solicitante para que presentara respuesta a las observaciones de carácter técnico visibles a folios 331 a 348, formuladas en relación con la patentabilidad o cumplimiento de los requisitos establecidos por la Decisión 486 de la Comisión de la Comunidad Andina, para la concesión de la patente, sin que frente a dicho requerimiento el solicitante se hubiera pronunciado y, en consecuencia, el Despacho procederá a denegar la patente.

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Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION No. 34734

Por la cual se deniega una patente de invención

Rad. PCT/06-121181

RESUELVE:

ARTICULO PRIMERO: Denegar la patente de invención titulada "3-AMINO-1-ARILPROPIL-INDOLES COMO INHIBIDORES DE RECAPTACIÓN DE MONOAMINAS", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Alicia Lloreda Ricaurte, en su calidad de apoderada de F.Hoffmann-La Roche AG, a quien haga sus veces, entregándole copia de la misma y advirtiéndole que contra ella procede el recurso de reposición, ante el Superintendente de Industria y Comercio, el cual podrá ser interpuesto en el momento de la notificación o dentro de los cinco (5) días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los **25 JUN 2010**

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO (E)


GIANCARLO MARCENARO JIMÉNEZ

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