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ABOGADOS

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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REF: Expediente No. **05-003430**
Patente de Invención: **"COMPUESTOS DEL 1-FENIL-2-DIMETILAMINO-METIL-CICLOHEXANO, PARA LA TERAPIA DE SINTOMATOLOGIA DEPRESIVA, DOLOR E INCONTINENCIA"**
Titular: **GRUNENTHAL GMBH**

DESTINO: 444

HUMBERTO RUBIO CAMACHO, mayor de edad, domiciliado en Bogotá, D.C., identificado con la cédula de ciudadanía número 17'192.062 de Bogotá, abogado graduado portador de la Tarjeta Profesional No. 50.007 expedida por el Consejo Superior de la Judicatura, actuando en carácter de Apoderado de **GRUNENTHAL GMBH**, domiciliado en Zieglerstrasse 6, 52078 Aachen, Alemania; encontrándome dentro de la debida oportunidad procesal para dar respuesta al auto proferido por su Despacho, mediante Oficio No.2170 y Concepto Técnico No. 373, notificado por fijación en lista de 20 de febrero de 2009, me permito manifestar y anexar:

I.- Manifiesto y Anexo:

1. Modificaciones a las reivindicaciones

1.1 El examinador considera que el objeto esencial de la invención se circunscribe a los metabolitos de la sustancia química 2-(2-dimetilamino-metil-ciclohexil)-fenol, es decir, se orienta hacia los productos biotransformados y aislados de un ser vivo. Me permito manifestar que el solicitante no comparte la posición tomada por el examinador, toda vez que se esta interpretando esta solicitud como la reivindicación de un metabolito y su síntesis biológica (lo cual no se encuentra *descrito* en ningún párrafo del capítulo descriptivo)

Es decir, el examinador considera que el solicitante tiene la intención de proteger un compuesto obtenido gracias a un proceso metabólico, es decir, biotransformación gracias al uso de maquinaria enzimática. Se entiende que esta conclusión se desprende del uso de la palabra "metabolito" en el capítulo descriptivo, más este no es el objetivo de la solicitud, lo cual estimamos que queda absolutamente claro en los

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ejemplos que describen la síntesis de los compuestos descritos, ya que ningún ejemplo describe etapas del metabolismo.

En vista que el uso de la palabra metabolito resulta confuso para el perito, hemos modificado esta expresión por "compuesto". Creemos que esta modificación no significa ampliación de contenido ya que en el capítulo descriptivo están claramente descritos los pasos de síntesis "sintética" y no metabólica de los compuestos reivindicados.

Sobre los ejemplos 10 y 11 del capítulo descriptivo, insistimos en que estos se refieren al rastreo de los compuestos reivindicados (y a la posibilidad de identificar y de aislar los mismos), tanto *in vitro* como *in vivo* (luego de ser administrados en un ratón), y no al aislamiento de metabolitos propios del metabolismo del individuo experimental.

Respetuosamente le solicitamos al examinador realizar un examen de la presente solicitud de acuerdo a los compuestos del nuevo capítulo reivindicatorio, pues consideramos que su interpretación se ha hecho equívocamente y enfocada a metabolito y su síntesis biológica.

Para facilidad del examinador al momento de evaluar la altura inventiva y novedad que efectivamente poseen las composiciones de la presente solicitud, y atendiendo la buena sugerencia del examinador y las recomendaciones formuladas en el primer examen técnico sobre la patentabilidad de la invención llevado a cabo, estamos presentando un Capítulo Descriptivo y Reivindicatorio, que reemplaza el presentado con la solicitud inicial, que se encuentra íntegramente sustentada, es novedosa, inventiva y es susceptible de aplicación industrial.

Para finalizar, me permito dirigir la atención de ese Despacho al hecho de que un indicio adicional de la existencia de **nivel inventivo** de la presente solicitud, radica en la concesión del privilegio de invención que ha realizado la oficina de **PERU** para la materia objeto de la presente solicitud, adicional a la solicitud presentada en CHILE. Considero pertinente señalar que aunque el solicitante reconoce la autonomía y soberanía de ese Despacho, también considera que no puede pasarse en alto el hecho que para las oficinas en que esta solicitud fue presentada (Chile y **Perú**) en ninguno de estos países se presentó esta confusión (metabolito-compuestos), y que los peritos interpretaron correctamente el objetivo de la materia reivindicada, y que su concepto universal como el **Nivel Inventivo** haya sido considerado satisfecho por las enseñanzas de la presente solicitud, lo cual constituye un claro indicio de la patentabilidad de la misma, mas si consideramos su concesión en Perú, conforme lo establecido en la **Decisión 486 de la Comunidad Andina**, legislación vigente en Colombia.

De manera atenta solicito a su Despacho, tener en cuenta todos y cada una de las consideraciones expuestas anteriormente, al momento de estudiar el presente caso.

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II. Anexo:

Nuevo capitulo descriptivo

Nuevo capitulo reivindicatorio.

III. Petición:

Conforme a lo anterior, una vez atendidos los requerimientos y exigencias del examinador y al tener en cuenta el nuevo capitulo descriptivo y reivindicatorio, así como los argumentos expuestos, solicito muy respetuosamente a su Despacho, continuar el trámite de rigor y de ser el caso se hagan las correspondientes observaciones con el ánimo de hacer lo pertinente dentro del presente trámite.

Atentamente,



HUMBERTO RUBIO CAMACHO

C.C. 17'192.062 de Bogotá

**T.P. 50.007 Consejo Superior
de la Judicatura**

COD. 4134

05/1249/P000286

B-15

**COMPUESTOS DEL 1-FENIL-2-DIMETILAMINO-METIL-CICLOHEXANO, PARA
LA TERAPIA DE SINTOMATOLOGÍA DEPRESIVA, DOLOR E INCONTINENCIA.**

La invención se relaciona con compuestos de la [2-(3-metoxifenil)-ciclohexil-metil]-
5 dimetilamina como bases libres y/o en forma de sales fisiológicamente admisibles,
medicamentos que las contienen, así como el empleo de la [2-(3-metoxifenil)-
ciclohexil-metil]-dimetilamina y sus compuestos para preparar un medicamento para
el tratamiento de depresiones y procedimientos para el tratamiento de depresiones.

10 La depresión es una perturbación de la afectividad, en la que se presenta ante todo
un síndrome depresivo, en el que lo depresivo está relacionado con el mal humor o
con la tristeza. Los antidepresivos que se usan en la terapia también son eficaces
coadyuvantes en la terapia del dolor (R. van Schayk et al. 1998, MMP, 10, 304-313;
Jung et al. 1887, J.Gen.Intern.Med.12, 384-389; Onghena y Van Houdenhove 1992,
15 Pain, 49, 205-219; Feuerstein 1997, Diagnostik un Therapie, 3, 213-225; Rowbotham
1997, The Pain Medicine Journal Club Journal, 3, 119-122), en especial en
condiciones de dolor crónico, porque el dolor duradero puede conducir a un mal
humor depresivo del paciente. Este es especialmente el caso en los pacientes de
dolor por cáncer (Berard 1996, Int.Med.J., 3, 257-259). Ya que hasta ahora no existe
20 un medicamento para el dolor que tenga componentes antidepresivos clínicamente
importantes, se deben usar los antidepresivos como medicamento sustituto en dosis
antianalgésicas. Ya que los pacientes del dolor crónico necesitan con frecuencia
diversas cantidades de varios medicamentos, la dosis adecuada del antidepresivo
causa mayor carga en el organismo. Con esta base, y para mejorar el apego al
25 tratamiento, había necesidad especial de contar con una sustancia analgésica que
contuviera ya componentes con eficacia antidepresiva.

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La base del efecto antidepresivo es la supresión de la reabsorción de noradrenalina y serotonina. Los opioides con supresión masiva de absorción, como el Tramadol, se conocen desde hace mucho, y se usan como analgésicos terapéuticos potentes, con un bajo potencial de alteración y adicción (Raffa et al. 1992, Journal of Pharmacology and experimental Therapeutics, 260, 275-285; Raffa y Friedrichs 1996, Pain Review, 3, 249-271). Sin embargo, el componente supresor de absorción no es suficientemente enérgico para presentar un efecto antidepresivo clínicamente relevante.

Junto con el verdadero efecto antidepresivo, la supresión de la reabsorción de noradrenalina y serotonina también causan un efecto analgésico independiente, en el que las vías de supresión del dolor se activan en el plano de la espina dorsal. En combinación con los opiáceos, que asimismo suprimen la conducción del dolor en el plano de la espina dorsal, causa una potenciación recíproca de los mecanismos de supresión del dolor, y con ella una analgesia especialmente efectiva.

Sería especialmente valioso, entonces, en esta indicación, en especial en el tratamiento de depresiones y también en combinación con la terapia del dolor, que una sustancia opioide con un componente relativamente enérgico supresor de la absorción de la NA y/o de la 5HT, tuviera un efecto antidepresivo (por ejemplo, determinado en un modelo de comportamiento experimental animal adecuado).

Por consiguiente, la tarea de la presente invención es encontrar sustancias, en especial sustancias opioides, que sean adecuadas para el tratamiento de las depresiones, y en especial aquellas que combinen este efecto con un efecto analgésico.

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En forma sorprendente se encontró que la 2-(3-metoxifenil)-ciclohexil-metil-dimetilamina, así como sus compuestos y entre ellos en especial el 3-(2-dimetilamino-metil-ciclohexil)-fenol, tienen un componente de relevante efecto terapéutico antidepresivo.

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De acuerdo con lo anterior, el objeto de la invención es el empleo de

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- 3-(2-dimetilaminometil-ciclohexil)-fenol,
- (1R,2R)-3-(-dimetilaminometil-ciclohexil)—fenol,
- [2-(3-metoxifenil)-ciclohexil-metil]-dimetilamina,
- (1R,2R)-[2-(3-metoxifenil)-ciclohexil-metil]-dimetilamina
- Éster mono-[3-(2-dimetilamino-metil-ciclohexil)-fenílico] del ácido sulfúrico,
- Éster mono-(1R,2R)-[3-(2-dimetilamino-metil-ciclohexil)-fenílico] del ácido sulfúrico,

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- 3-(2-metilaminometil-ciclohexil)-fenol,
- (1R,2R)-3-(2-metilaminometil-ciclohexil)-fenol,
- 3-(2-dimetilaminometil-ciclohexil)-fenol-N-oxida,
- (1R,2R)-3-(2-dimetilaminometil-ciclohexil)-fenol-N-oxida,
- Ácido 6-[3-(2-dimetilamino-metil-ciclohexil)-fenoxi]-3,4,5-trihidroxi-tetrahidropirano-2-carboxílico,
- Ácido 6-[(1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenoxi]-3,4,5-trihidroxi-tetrahidropirano-2-carboxílico,

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- 4-(2-dimetilaminometil-ciclohexil)-catecol,
- (1R,2R)-4-(2-dimetilaminometil-ciclohexil)-catecol,
- 3-(2-aminometil-ciclohexil)-fenol,
- (1R,2R)-3-(2-aminometil-ciclohexil)-fenol,
- 4-(2-dimetilamino-metil-ciclohexil)-bencen-1,2-diol,

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- (1R,2R)-4-(2-dimetilamino-metil-ciclohexil)-bencen-1,2-diol,
- C-[2-(3-metoxi-fenil)-ciclohexil]-metilamina,
- (1R,2R)-C-[2-(3-metoxi-fenil)-ciclohexil]-metilamina,
- [2-(3-metoxi-fenil)-ciclohexil-metil]-metil-amina,
- 5 ▪ (1R,2R)-[2-(3-metoxi-fenil-ciclohexil-metil)-metil-amina,
- [2-(3-metoxi-fenil)-ciclohexil-metil]-dimetil-amina; N-oxida o
- (1R,2R)-[2-(3-metoxi-fenil)-ciclohexil-metil]-dimetil-amina; N-oxida;

según el caso en forma de sus racematos, sus estereoisómeros puros, en especial enantiómeros o diastereómeros, o en forma de mezclas de los estereoisómeros, en especial de los enantiómeros o diastereómeros, en cualquier relación de mezcla, en forma pura o en forma de sus ácidos o de sus bases, o en forma de sus sales, en especial de sales fisiológicamente admisibles, o en forma de sus solvatos, en especial de los hidratos;

para preparar un medicamento para el tratamiento de las depresiones.

Se prefiere en especial que los compuestos empleados se encuentren en forma de los estereoisómeros R, R, y de preferencia 1R,2R.

Bajo el término sal se debe entender aquella forma de las sustancias activas de acuerdo con esta invención en los que esas sustancias tienen una forma iónica, o están cargadas, y se encuentran acopladas con un ion contrario (un catión o un anión), o se encuentran en solución. Para ello, también se deben entender los complejos de las sustancias activas con otras moléculas e iones, en especial complejos que estén acomplejados a través de intercambio iónico. En especial, se entiende por sales fisiológicamente admisibles (y eso también es una forma de

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presentación de esta invención), en especial las sales fisiológicamente admisibles con cationes o bases, y sales fisiológicamente admisibles con aniones o ácidos, o también con un ácido fisiológicamente admisible o una sal preparada con un catión fisiológicamente admisible.

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La sal preferida de los compuestos empleados es el clorhidrato.

Por fisiológicamente admisible se debe entender que la sustancia, en especial la sal como tal, puede ser admitida por el hombre o los mamíferos, y que también no tiene efectos fisiológicos negativos (por ejemplo, que no sea tóxica).

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Por el término sales fisiológicamente admisibles con aniones o ácidos se entiende, en el sentido de esta invención, sales de al menos uno de los compuestos de acuerdo con la invención – principalmente, por ejemplo, protonadas en el nitrógeno - como catión, con al menos un anión que sea admisible en especial en su uso en el hombre y/o los mamíferos. En especial, se entiende la sal preparada con un ácido fisiológicamente admisible, o sea sales de las sustancias activas con ácidos inorgánicos u orgánicos, que sean fisiológicamente admisibles, en especial en su empleo en hombres y/o mamíferos. Como ejemplos de sales fisiológicamente admisibles de algunos ácidos están las sales del ácido: clorhídrico, bromhídrico, sulfúrico, metano sulfónico, fórmico, acético, oxálico, butírico, málico, acético, mandélico, fumárico, láctico, cítrico, glutámico, 1,1-dioxo-1,2-dihidro1b6-benzo[d]isotiazol-3-ona (ácido sacárico), monometil sebácico, 5-oxo-prolina, hexano-1-sulfónico, nicotínico, 2, 3 o 4-aminobenzoico, 2,4,6-trimetilbenzoico, adipico, acetilglicina, salicílico, hipúrico y/o aspártico. Se prefiere en especial la sal clorhidrato.

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Bajo el término de sal preparada con un ácido fisiológicamente admisible se entiende, en el sentido de esta invención, sales de las presentes sustancias activas con ácidos inorgánicos u orgánicos que sean fisiológicamente admisibles, en especial para su uso en hombres y/o mamíferos. Se prefiere en especial el clorhidrato. Como ejemplos de ácidos fisiológicamente admisibles están los ácidos: clorhídrico, bromhídrico, sulfúrico, metano sulfónico, fórmico, acético, oxálico, butírico, acético, mandélico, fumárico, láctico, cítrico, glutámico, 1,1-dioxo-1,2-dihidro1 λ ⁶-benzo[d]isotiazol-3-ona (ácido sacárico), monometil sebácico, 5-oxo-prolina, hexano-1-sulfónico, nicotínico, 2-, 3- o 4-aminobenzoico, 2,4,6-trimetilbenzoico, a-adípico, acetilglicina, acetilsalicílico, hipúrico y/o aspártico.

Bajo el término de sal fisiológicamente admisible con cationes o base se entiende, en el sentido de esta invención, sales de al menos uno de los compuestos de acuerdo con la invención – principalmente un ácido (desprotonado) como anión con al menos un catión, de preferencia inorgánico – que sea fisiológicamente admisible en especial para emplearlo en hombres y/o mamíferos. Se prefieren en especial las sales de los metales alcalinos y alcalinotérreos, y también con NH_4^+ , en especial las sales de mono- o di-sodio, mono- o di-potasio, magnesio o calcio.

Bajo el término de sal preparada con un catión fisiológicamente admisible se entiende, en el sentido de esta invención, sales de al menos uno de los presentes compuestos como anión con al menos un catión inorgánico, que sea fisiológicamente admisible, en especial para usarse en hombres y/o mamíferos. Se prefieren en especial las sales de los metales alcalinos y alcalinotérreos, y también del NH_4^+ , en especial de mono- o di-sodio, mono- o di-potasio, magnesio o calcio.

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De acuerdo con las investigaciones hechas, las sustancias empleadas, y en especial el (1R,2R)- 3-(2-dimetilamino-metil-ciclohexil)-fenol, son potentes analgésicos y antidepresivos, y adicionalmente poseen un componente activo antidepresivo y clínicamente relevante. En especial el (1R,2R)- 3-(2-dimetilamino-metil-ciclohexil)-fenol puede administrarse en dolores agudos de regulares a fuertes, y en dolores crónicos, y permite el tratamiento de la sintomática de depresión acompañante a los estados de dolor crónico. En ellos conduce a una distinta mejoría del tratamiento del dolor crónico, ya que los antidepresivos actuales deben administrarse como medicamentos adicionales a los de la terapia del dolor. El (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol y las demás sustancias usadas de acuerdo con la invención también se pueden usar como genuinos antidepresivos, independientemente de su efecto analgésico.

Un objetivo más de la invención son los compuestos, en especial de la [2-(3-metoxifenil)-ciclohexil-metil]-dimetilamina o del 3-(2-dimetilamino-metil-ciclohexil)-fenol seleccionados entre

- Éster mono-[3-(2-dimetilamino-metil-ciclohexil)-fenil] del ácido sulfúrico,
- Éster mono-(1R,2R)-[3-(2-dimetilamino-metil-ciclohexil)-fenil] del ácido sulfúrico,
- 3-(2-metilamino-metil-ciclohexil)-fenol,
- (1R,2R)-3-(2-metilamino-metil-ciclohexil)-fenol,
- 3-(2-dimetilamino-metil-ciclohexil)-fenol-N-oxida,
- (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol-N-oxida,
- Ácido 6-[3-(2-dimetilamino-metil-ciclohexil)-fenoxi]-3,4,5-trihidroxi-tetrahidropirano-2-carboxílico,

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- Ácido 6-[(1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenoxi]-3,4,5-trihidroxi-tetrahidropirano-2-carboxílico,
- 4-(2-dimetilaminometil-ciclohexil)-catecol,
- (1R,2R)-4-(2-dimetilamino-metil-ciclohexil)-catecol,
- 5 ▪ 3-(2-aminometil-ciclohexil)-fenol,
- (1R,2R)-3-(2-aminometil-ciclohexil)-fenol,
- 4-(2-dimetilamino-metil-ciclohexil)-bencen-1,2-diol,
- (1R,2R)-4-(2-dimetilamino-metil-ciclohexil)-bencen-1,2-diol,
- C-[2-(3-metoxi-fenil)-ciclohexil]-metilamina,
- 10 ▪ (1R,2R)-C-[2-(3-metoxi-fenil)ciclohexil-metil]-metil-amina,
- [2-(3-metoxi-fenil)-ciclohexil-metil]-metil amina,
- (1R,2R)-[2-(3-metoxi-fenil)-ciclohexil-metil]-metil amina
- [2-(3-metoxi-fenil)-ciclohexil-metil]-dimetil amina ; N-oxida, o bien
- (1R,2R)-[2-(3-metoxi-fenil)ciclohexil-metil]-dimetil-amina; N-oxida;

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según el caso en forma de sus racematos, sus estereoisómeros puros, en especial enantiómeros o diastereómeros, o en forma de mezclas de los estereoisómeros, en especial de enantiómeros o diastereómeros, en cualquier relación de mezcla, en forma aislada o en forma de sus ácidos o de sus bases, 20 o en forma de sus sales, en especial de sales fisiológicamente admisibles, o en forma de sus solvatos, en especial del hidrato.

Se prefieren en especial los compuestos de acuerdo con esta invención, que se encuentren como estereoisómeros R,R, y en especial 1R, 2R.

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Los compuestos de acuerdo con la presente invención son fisiológicamente inocuos. En consecuencia, un objetivo más de la invención es un medicamento que

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contenga como sustancia activa al menos uno de los compuestos de acuerdo con la invención, y también, según el caso, sustancias suplementarias y/o coadyuvantes. En especial un objetivo de la invención es un medicamento que contenga como sustancia activa al menos un compuesto seleccionado entre

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- Éster mono-[3-(2-dimetilamino-metil-ciclohexil)-fenil] del ácido sulfúrico,
- Éster mono-(1R,2R)-[3-(2-dimetilamino-metil-ciclohexil)-fenil] del ácido sulfúrico,

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- 3-(2-metilamino-metil-ciclohexil)-fenol,
- (1R,2R)-3-(2-metilamino-metil-ciclohexil)-fenol,
- 3-(2-dimetilamino-metil-ciclohexil)-fenol-N-oxida,
- (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol-N-oxida,
- Ácido 6-[3-(2-dimetilamino-metil-ciclohexil)-fenoxi]-3,4,5-trihidroxi-tetrahidropirano-2-carboxílico,

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- Ácido 6-[(1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenoxi]-3,4,5-trihidroxi-tetrahidropirano-2-carboxílico,
- 4-(2-dimetilaminometil-ciclohexil)-catecol,
- (1R,2R)-4-(2-dimetilamino-metil-ciclohexil)-catecol,
- 3-(2-aminometil-ciclohexil)-fenol,

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- (1R,2R)-3-(2-aminometil-ciclohexil)-fenol,
- 4-(2-dimetilamino-metil-ciclohexil)-bencen-1,2-diol,
- (1R,2R)-4-(2-dimetilamino-metil-ciclohexil)-bencen-1,2-diol,
- C-[2-(3-metoxi-fenil)-ciclohexil]-metilamina,
- (1R,2R)-C-[2-(3-metoxi-fenil)-ciclohexil-metil]-metil-amina,

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- [2-(3-metoxi-fenil)-ciclohexil-metil]-metil amina,
- (1R,2R)-[2-(3-metoxi-fenil)-ciclohexil-metil]-metil amina
- [2-(3-metoxi-fenil)-ciclohexil-metil]-dimetil amina ; N-oxida, o bien

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- (1R,2R)-[2-(3-metoxi-fenil)ciclohexil-metil]-dimetil-amina; N-oxida;

según el caso en forma de sus racematos, sus estereoisómeros puros, en especial enantiómeros o diastereómeros, o en forma de mezclas de los estereoisómeros, en especial de enantiómeros o diastereómeros, en cualquier relación de mezcla, en forma aislada o en forma de sus ácidos o de sus bases, o en forma de sus sales, en especial de sales fisiológicamente admisibles, o en forma de sus solvatos, en especial del hidrato;

así como de acuerdo con el caso, sustancias adicionales y/o coadyuvantes.

Se prefiere en especial que los compuestos contenidos sean estereoisómeros R, R, y de preferencia sean 1R,2R.

Las sustancias aditivas y/o coadyuvantes adecuadas, en el sentido de esta invención, todas las sustancias conocidas por el especialista, de acuerdo con el estado de la técnica, para obtener formulaciones galénicas. La evaluación de esas sustancias aditivas así como las cantidades por adicional dependen de si el medicamento se administrará por vía oral, intravenosa, intraperitoneal, intradérmica, intramuscular, intranasal, bucal o local. Para la aplicación oral son adecuadas las preparaciones en forma de tabletas, comprimidos, grageas, cápsulas, granulados, gotas, zumos o jarabes; para la aplicación parenteral, tópica e inhalativa son adecuadas soluciones, suspensiones, preparaciones secas fácilmente reconstituibles y también las nebulizaciones. Una posibilidad más son los supositorios, para uso rectal. El empleo en un depósito, en forma disuelta, en un vehículo o en un emplasto, según el caso agregando medios dosificadores de la penetración cutánea, son ejemplos de formas de aplicación percutánea adecuadas. Como ejemplos de

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sustancias aditivas y coadyuvantes para las formas de aplicación oral están los activadores, lubricantes, aglomerantes, cargas, desmoldeadores, de acuerdo con el caso solventes, saborizantes, azúcar, en especial vehículos, adelgazadores, colorantes, antioxidantes, etc. Para los supositorios se pueden usar, entre otros, jabón o éster de ácido graso, y para la aplicación parenteral, vehículos, conservadores, emulsionantes, etc. Las cantidades de sustancia activa por administrar a los pacientes varían de acuerdo con el peso del paciente, de la forma de aplicación y de la gravedad de la enfermedad. Como formas de preparación de uso oral, rectal o percutáneo se pueden administrar los compuestos de acuerdo con la invención en estado puro. En la indicación de acuerdo con la invención, se prefieren en especial las correspondientes formulaciones retardantes, en especial en forma de un preparado de "una diaria," que sólo se deben tomar una vez al día.

También se prefieren los medicamentos que contengan cuando menos de 0.05 al 90.0%, en especial las dosis activas menores, para evitar efectos secundarios o analgésicos. En el caso normal se pueden aplicar dosis de 0.1 a 5000 mg/kg, en especial de 1 a 500 mg/kg, y de preferencia de 2 a 250 mg/kg de peso corporal, de al menos uno de los compuestos de acuerdo con la invención. También se prefiere, y es la aplicación normal, de 0.01 a 5 mg/kg, de preferencia de 0.03 a 2 mg/kg, en especial de 0.05 a 1 mg/kg de peso corporal.

Las sustancias aditivas pueden ser, por ejemplo: agua, etanol, 2-propanol, glicerina, etilenglicol, propilenglicol, polietilenglicol, polipropilenglicol, glucosa, fructosa, lactosa, sacarosa, dextrosa, melaza, almidón, almidón modificado, gelatina, sorbitol, inositol, manitol, celulosa microcristalina, metilcelulosa, carboximetilcelulosa, acetato de celulosa, goma laca, alcohol cetílico, polivinil pirrolidona, parafina, cera, gomas naturales y sintéticas, goma de acacia, alginato, dextrana, ácidos grasos saturados y

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no saturados, ácido esteárico, estearato de magnesio, estearato de zinc, estearato de glicerilo, sulfato de sodio y laurilo, aceites comestibles, aceite de ricino, aceite de coco, aceite de nuez, aceite de semilla de soya, lecitina, lactato de sodio, éster de ácido graso de polioxietileno y polioxipropileno, éster de ácido sórbico, ácido benzoico, ácido cítrico, ácido ascórbico, ácido tánico, cloruro de sodio, cloruro de potasio, cloruro de magnesio, cloruro de calcio, óxido de magnesio, óxido de zinc, dióxido de silicio, óxido de titanio, sulfato de magnesio, sulfato de zinc, sulfato de calcio, carbonato de potasio, fosfato de calcio, fosfato de dicalcio, bromuro de potasio, yoduro de potasio, talco, caolín, pectina, Crospovidón, agar y bentonita.

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La preparación de los medicamentos de acuerdo con la invención, y las formulaciones farmacéuticas se hace con ayuda de los medios, dispositivos, métodos y procedimientos conocidos en la formulación farmacéutica de acuerdo con el estado de la técnica, como por ejemplo se describen en "Remington's Pharmaceutical Sciences," A.R. Gennaro Ed., 17ª Ed., Mack Publishing Company, Easton, Pa. (1985), en especial en la parte 8, capítulos 76 a 93.

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Así se puede preparar una formulación sólida, como una tableta, con la sustancia activa del medicamento, es decir, un compuesto que tenga la estructura general I o una de sus sales farmacéuticamente admisibles, y con un vehículo farmacéutico, por ejemplo con las sustancias adecuadas para las tabletas como almidón de maíz, lactosa, sacarosa, sorbitol, talco, estearato de magnesio, fosfato dicálcico o gomas farmacéuticamente aceptables, y también adelgazantes farmacéuticos como agua, se granulan para preparar un compuesto sólido, que contenga un compuesto de acuerdo con la invención o una de sus sales farmacéuticamente admisibles, en dispersión homogénea. Por dispersión homogénea se entiende aquí que la sustancia activa está repartida por igual en toda la preparación, para que si más se pueda

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elaborar en formas con iguales dosis activas, como tabletas, píldoras o cápsulas. La preparación sólida terminará repartida en formas de dosis unitarias. Las tabletas o píldoras del medicamento de acuerdo con la invención, o las preparaciones de acuerdo con la invención, también pueden componerse en otras formas, para preparar una forma de dosificación con liberación retardada. Los medios cubrientes adecuados son, entre otros, ácidos poliméricos y mezclas de ácidos poliméricos con materiales como goma laca, alcohol cetílico y /o acetato de celulosa.

También cuando los medicamentos de acuerdo con la invención presentan efectos secundarios muy pequeños, se pueden usar con buen efecto, siempre que sea totalmente necesario, por ejemplo para aliviar ciertas formas de dependencia, junto con los compuestos mencionados, antagonistas de morfina, en especial Naloxon, Naltrexon y/o Levallorphan.

Como los compuestos de acuerdo con esta invención tienen acción analgésica - como se mencionó arriba- un objetivo más de la invención es el empleo de un compuesto de acuerdo con la invención, o un compuesto de acuerdo con la invención, para preparar un medicamento para el tratamiento del dolor, en especial del dolor agudo, visceral, crónico o neuropático, y el dolor del cáncer.

Como también los compuestos de acuerdo con la invención también muestran efecto contra la incontinencia urinaria, un objetivo más de la invención es el empleo de uno de los compuestos de acuerdo con la invención, o uno de los compuestos de acuerdo con la invención, para preparar un medicamento para el tratamiento del deseo grande de orinar, o incontinencia urinaria.

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Además, la invención también se relaciona con un procedimiento para tratar la depresión, en el que se pueden emplear los compuestos de acuerdo con la invención.

5 También, la invención se relaciona con un procedimiento para el tratamiento del dolor, en especial del dolor agudo, visceral, crónico o neuropático, o el dolor por cáncer, en el que se usen los compuestos o los compuestos de acuerdo con la invención.

10 Asimismo, la invención se relaciona con un procedimiento para el tratamiento del impulso grande de orinar o incontinencia urinaria, en el que se usen los compuestos o los compuestos de acuerdo con la invención.

La 2-(3-metoxifenil)-ciclohexil-metil-dimetilamina y la (1R,2R)-[2-(3-metoxifenil)-
15 ciclohexil-metil)-dimetilamina] y su preparación se describen en la patente DE 195 25 137 A1 ejemplo 8, o en US 5,733,936 ejemplo 8, en las cuales se describe la estereoquímica absoluta del compuesto (-6) de acuerdo con el ejemplo 8, en forma correcta como (1R,2R) y no (1R,2S). También, el (2-dimetilaminometil-ciclohexil)-
fenol y su preparación se conocen por la patente DE 195 25 137 A1 ejemplo 10, o la
20 US 5,733,936 ejemplo 10, donde se muestra la estereoquímica absoluta del compuesto (-7) de acuerdo con el ejemplo 10, en la forma correcta (1R,2R), y no es (1R,2S).

Los compuestos y su preparación todavía no se conocían en la patente DE 195 25
25 137 A1 o la US 5,733,936, se prepararon de acuerdo con los ejemplos.

Los ejemplos siguientes deben aclarar la invención, sin limitar los objetivos de la misma.

Ejemplos

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En general, la purificación y la separación de enantiómeros, se hacen en todos los procedimientos descritos como ejemplo, en diversos pasos, mediante cromatografía en columna y principalmente por HPLC (cromatografía líquida de alto rendimiento).

10 **Ejemplo 1: Preparación del clorhidrato de (1R,2R)-[2-(3-metoxifenil)-ciclohexil-metil]-metilamina**

La [2-(3-metoxifenil)-ciclohexil-metil]-metilamina, o la (1R,2R)-[2-(3-metoxifenil)-ciclohexil-metil]-metilamina, en especial su sal clorhidrato, se preparan como sigue:

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5.67 g (22.9 mmol) de (1R,2R)-[2-(3-metoxifenil)-ciclohexil-metil]-dimetilamina como base libre se calentaron en 389.64 mL de tolueno, con 3.16 mL (25.2 mmol) de cloroformato de fenilo, durante 3 h. Después de enfriar y lavar, se evaporó el residuo orgánico y se agitó con calentamiento ocasional a 110 °C y enfriamiento, durante 8.5 h en total, con 192.53 mL de etilenglicol y en total 45.84 mL de NaOH 5N. Se obtuvo: (1R,2R)-[2-(3-metoxifenil)-ciclohexilmetil]-metilamina. Se extrajo y se precipitó con TMCS como clorhidrato.

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25 **Ejemplo 2: Preparación del clorhidrato de (1R,2R)-3-(2-metilamino-metil-ciclohexil)-fenol**

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3.55 g (15.2 mmol) de clorhidrato del (1R,2R)-[2-(3-metoxi-fenil)-ciclohexil-metil]-metilamina de acuerdo con el ejemplo 1 se agitaron en 4.59 mL de HBr acuoso (47-48%) durante 7.5 h a reflujo, y se enfrió durante la noche. Se obtuvo (1R,2R)-3-(2-metilamino-metil-ciclohexil)-fenol. Este se extrajo y se precipitó como clorhidrato con
5 TMCS.

Ejemplo 3: Preparación del éster mono-(1R,2R)-[3-(2-dimetilamino-metil-ciclohexil)-fenilo del ácido sulfúrico

10 Se prepararon éster mono-[3-(2-dimetilamino-metil-ciclohexil)-fenílico] del ácido sulfúrico, o éster mono-(1R,2R)-[3-(2-dimetilamino-metil-ciclohexil)-fenil] del ácido sulfúrico como sigue:

Se trató clorhidrato de (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol con
15 diciclohexil carbo-diimida (DCC) en H₂SO₄. Se obtuvo éster mono-(1R,2R)-[3-(2-dimetilamino-metil-ciclohexil)-fenilo del ácido sulfúrico.

Ejemplo 4: Preparación del ácido 6-[(1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenoxi]-3,4,5-trihidroxi-tetrahidropiran-2-carboxílico

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Se preparó ácido 6-[3-(2-dimetilamino-metil-ciclohexil)-fenoxi]-3,4,5-trihidroxi-tetrahidropiran-2-carboxílico o ácido 6-[(1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenoxi]-3,4,5-trihidroxi-tetrahidropiran-2-carboxílico como sigue:

25 Se trató clorhidrato del éster metílico del ácido (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol con 3,4,5-tri-O-acetil-1-a-bromo-D-glucurónico con 1) LiOH y 2) HOAc. Se obtuvo ácido 6-[(1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenoxi]-3,4,5-

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trihidroxi-tetrahidropiran-2-carboxílico. La purificación se uso en columna RP128 de LObar-Lichoprep, con sistema MeOH:H₂O y finalmente con separación en HPLC.

Ejemplo 5: Preparación de la [2-(3-metoxi-fenil)-ciclohexil-metil]-dimetil-amina;

5 **N-oxida**

Se preparó [2-(3-metoxi-fenil)-ciclohexil-metil]-dimetil-amina; N-oxida o (1R,2R)-[2-(3-metoxi-fenil)-ciclohexil-metil—dimetil-amina; N-oxida, como sigue:

Se disolvió clorhidrato de [2-(3-metoxi-fenil)-ciclohexil-metil]-dimetil-amina y se trató
10 con H₂O₂ a temperatura ambiente. Se obtuvo [2-(3-metoxi-fenil)-ciclohexil-metil]-
dimetil-amina; N-oxida.

Ejemplo 6: Preparación de (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol-N-oxida

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Se preparó 3-(2-dimetilamino-metil-ciclohexil)-fenol-N-oxida o (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol-N-oxida como sigue:

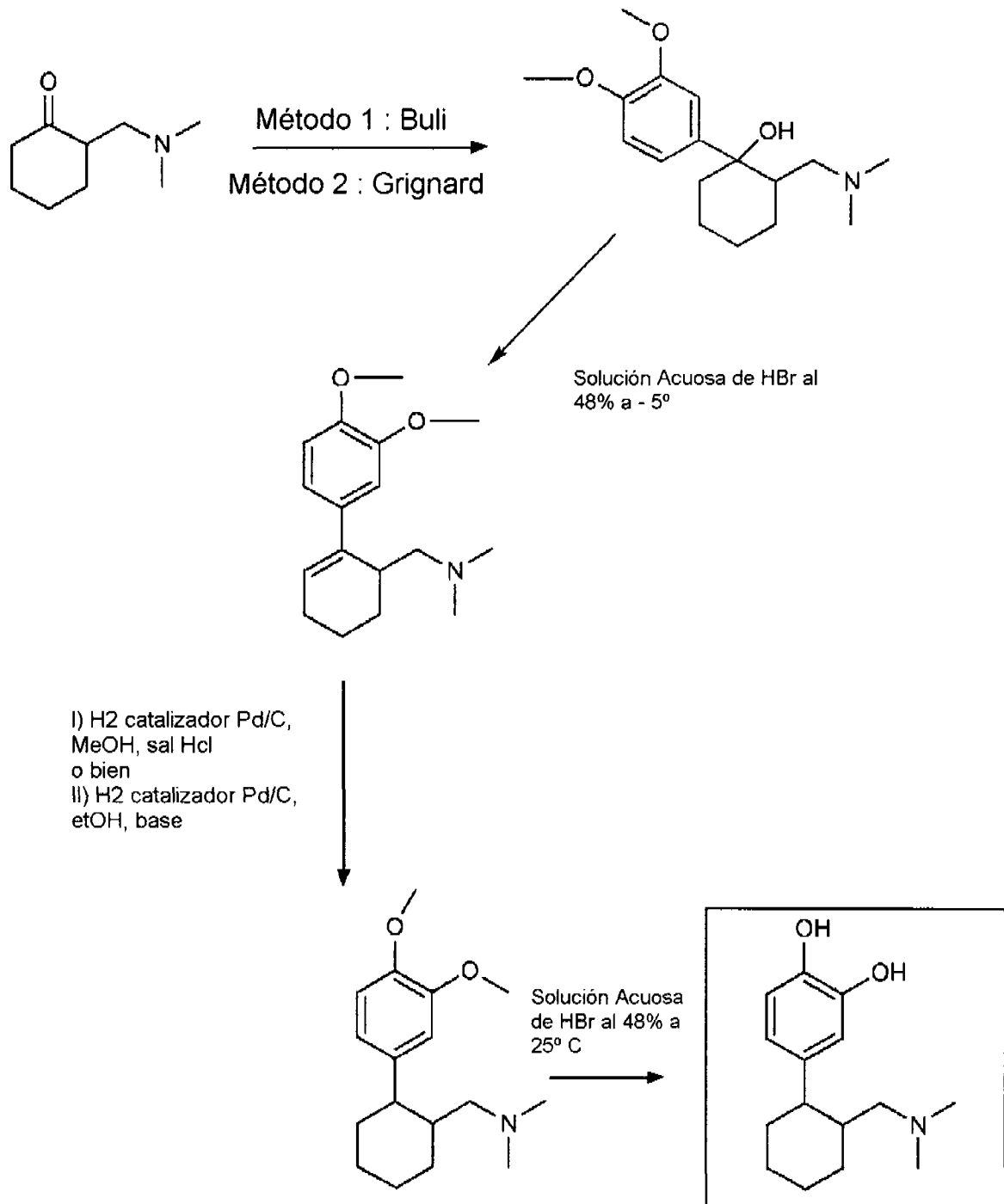
Se disolvió clorhidrato de (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol y se trató
20 con H₂O₂ a temperatura ambiente. Se obtuvo (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol-N-oxida

Ejemplo 7: Preparación de 4-(2-dimetilamino-metil-ciclohexil)-catecol, o del 4-(2-dimetilamino-metil-ciclohexil)bencen-1,2-diol.

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La preparación del 4-(2-dimetilamino-metil-ciclohexil)-catecol, o del 4-(2-dimetilamino-metil-ciclohexil)bencen-1,2-diol se hizo de acuerdo con el siguiente esquema de reacciones:

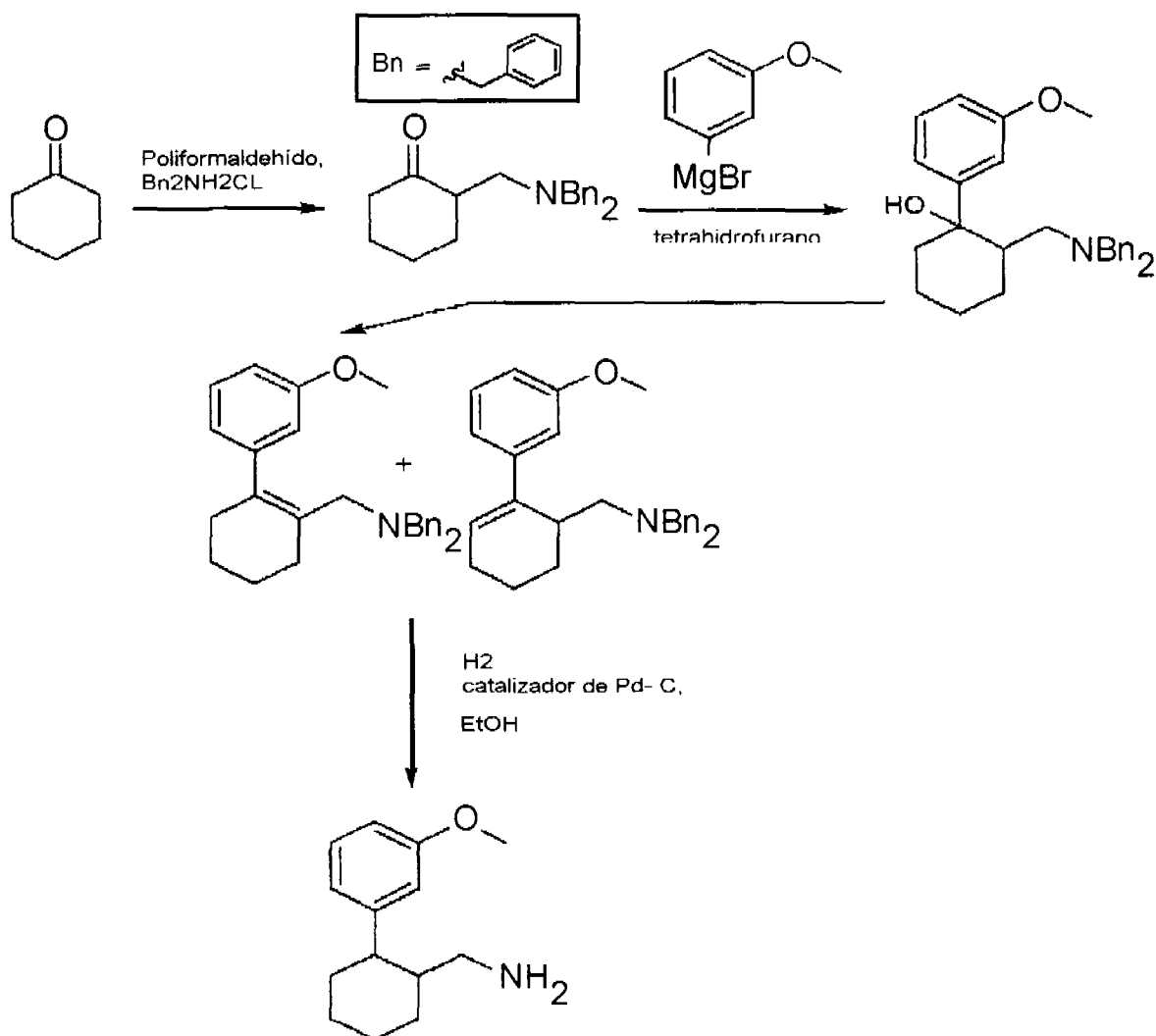


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Además se hace notar que el método 1 BuLi, es una síntesis muy conocida por el especialista, sobre reactivo de BuLi (butil litio), y que el método 2 Grignard es una síntesis muy conocida por el especialista, sobre reactivo de Mg.

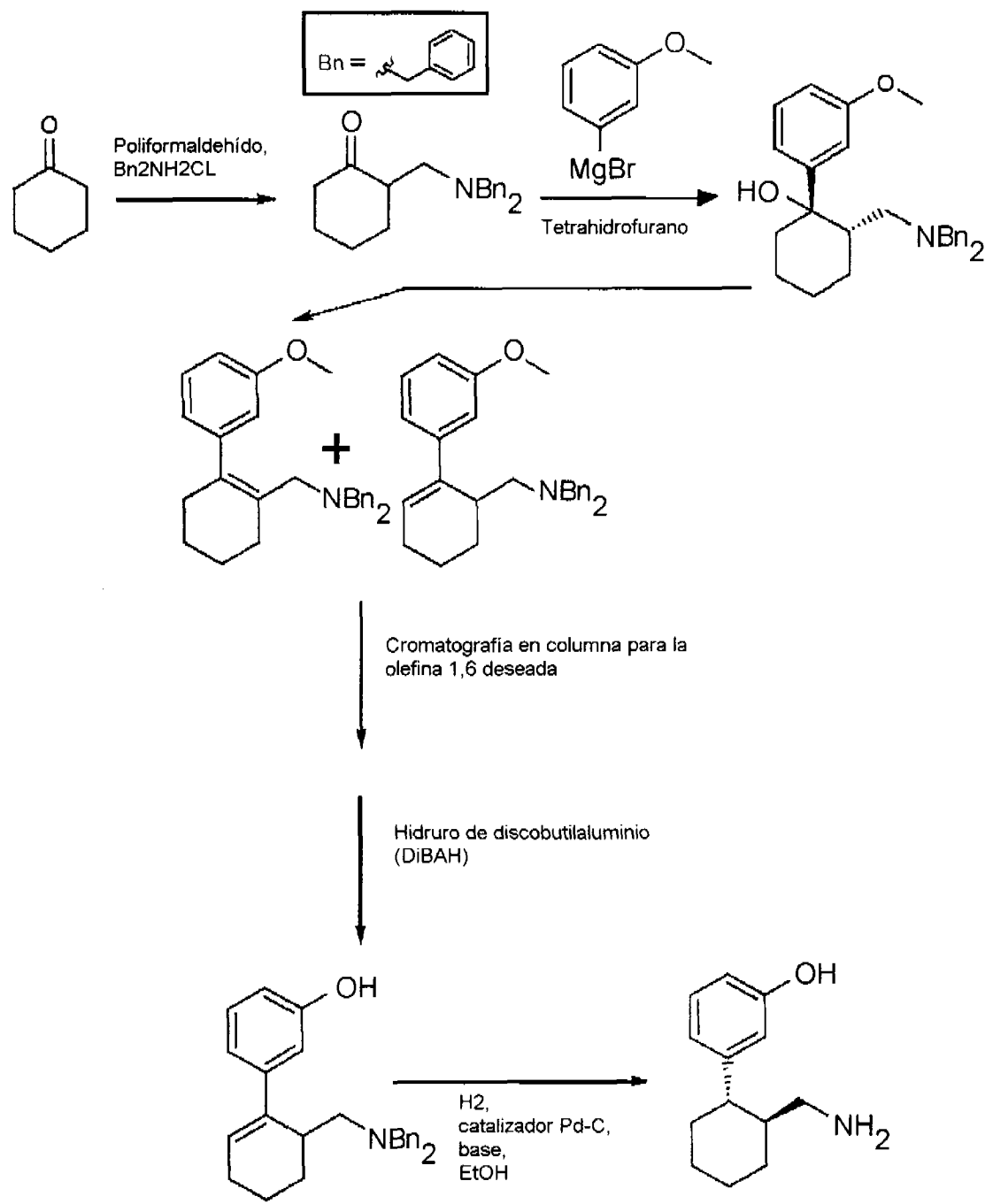
182
172**Ejemplo 8: Preparación de C-[2-(3-metoxi-fenil)-ciclohexil]-metilamina**

La preparación de la C-[2-(3-metoxi-fenil)-ciclohexil]-metilamina se efectuó con el siguiente esquema de reacciones:

**Ejemplo 9: Preparación del (1R,2R)-3-(2-aminometil-ciclohexil)-fenol.**

La preparación del 3-(2-aminometil-ciclohexil)-fenol o del (1R,2R)-3-(2-aminometil-ciclohexil)-fenol se hizo con el siguiente esquema de reacciones:

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5 Ejemplo 10: Aislamiento de los compuestos in vitro:

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Se disolvieron clorhidrato de [2-(3-metoxifenil)-ciclohexil-metil]-dimetilamina, y en otro ejemplo, clorhidrato de (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol, en solución reguladora TRIS/HCl a pH 7.4. Se agregaron MgCl, así como, de acuerdo con el caso, los demás cofactores necesarios, conocidos en las publicaciones, para
 5 citocromo P450 (CytP450) y se incubaron con CytP450 3A4 (desmetilación N) y/o CytP450 2D6 (desmetilación O) a 37 °C. Por último se separó la mezcla en HPLC, se identificaron los compuestos en las fracciones con resonancia magnética nuclear, y se aislaron de las fracciones.

10 **Ejemplo 11: Aislamiento de los compuestos in vivo:**

Algunos mamíferos se inyectaron con clorhidrato de [2-(3-metoxifenil)-ciclohexil-metil]-dimetilamina, y en otro ejemplo con clorhidrato de (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol; se tomó sangre del mamífero y después de separar la parte
 15 corpuscular se separó en HPLC, se identificaron los compuestos en las fracciones, con NMR, y se aislaron entonces de las fracciones.

Ejemplo 12 Afinidad al receptor de opioide μ y componentes de supresión de absorción de NA y de 5HT:

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Junto con el decisivo enlace a las sustancias opioides en el receptor de opioide μ , también se investigaron los componentes supresores de la absorción de NA y de 5HT en dos antidepresivos clínicamente usados, Fluoxetin y Desipramin. Los resultados de las investigaciones, que se hicieron de acuerdo con las pruebas
 25 estándar publicadas, ya conocidas en la especialidad, se resumen en la tabla 1:

Tabla 1: Supresión de absorción y enlazamiento con receptor de opioides

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	Clorhidrato de (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol	Clorhidrato de (1R,2R)-3-(2-metilamino-metil-ciclohexil)-fenol	Fluoxetina	Desipramina
	Valores K_i (μ M)			
Receptor de opioide μ	0.038 (rata)	0.91 (humano)	No valor.	No valor.
Supresión de absorción de NA	0.16	0.56	0.53	0.0011
Supresión de absorción de 5HT	0.05	9.41	0.026	1.44

La supresión de reabsorción de 5HT directamente por (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol tiene el mismo orden de magnitud que el enlazamiento con opioide μ de la sustancia. Por tanto, la sustancia posee una relación exactamente balanceada de componente de opioide μ y supresión de absorción, y con ello también posee un potencial para una supresión del dolor especialmente efectiva. La supresión de absorción tiene el orden de magnitud de los antidepresivos de uso clínico, y con ello conduce a un componente activo independiente en el que la sustancia posee una acción supresora relativamente enérgica de reabsorción de noradrenalina y, en especial, de serotonina.

Ejemplo 13 “prueba de suspensión de cola”

La “prueba de suspensión de cola” detecta la actividad antidepresiva y ansiolítica, y se apeg a el método de Porsolt et al. (Porsolt R.D., Bertin A., Jalfre M., Behavioural despair in mice: a primary screening test for antidepressants. Arch. Int. Pharmacodyn. Ther., **229**, 327-336, **1977**) y Stéru et al. (Stéru L., Chermat R., Thierry B., Simon P. The Tail Suspension Test: a new method for screening antidepressants in mice. Psychopharmacology, **85**, 367-370, **1985**). Roedores, que se cuelgan de la cola, se

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inmovilizan con rapidez. Los antidepresivos reducen la duración de la inmovilidad, mientras que los tranquilizantes la alargan. Se observó el comportamiento de los animales durante 6 minutos, de preferencia con un aparato computarizado (Itemac-TST), desarrollado por Stéru et al (1985) (ver arriba). Se investigaron varios ratones en paralelo y se determinó la duración de la inmovilidad. Esos parámetros es análogo al usado en la prueba de "intranquilidad conductual" (Stéru L., Chermat R., Thierry B., Mico J.A., Lenègre A., Stéru M., Simon P., Porsolt R. D., The Automated Tail Suspension Test: A computerized device which differentiates psychotropic drugs. Prog. Neuropsychopharmacol. Exp. Psychiatry, **11**, 659-671, **1987**). Se investigaron de 10 a 20 ratones por grupo. Se administraron morfina, clorhidrato de (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol y Desipramina 30 minutos antes de la prueba, por vía intraperitoneal, y Naloxon intravenoso.

Este modelo de comportamiento es para mostrar el efecto antidepresivo de los componentes supresores de absorción en presencia simultánea de un efecto opioide. En este y en otros modelos de comportamiento los antidepresivos causan un acortamiento de la fase de inmovilidad, mientras que los opioides como la morfina alargan la fase de inmovilidad. En la presencia de ambos componentes activos se causan los mismos efectos, por lo que sólo resulta un menor cambio en la movilidad. Esta se aumentó gracias a que el componente de opiato se desbloqueó con administración previa de Naloxon. Después del tratamiento con Naloxon se presentó claramente el efecto estimulante de (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol, que cuando no había tratamiento previo, sólo fue bajo. Por consiguiente, la sustancia es muy adecuada en especial en combinación con una terapia de dolor. Los resultados de estas investigaciones, junto con las sustancias de referencia, se resumen en la tabla 2.

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Tabla 2: Efecto del (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol, Imipramina y morfina en la prueba de “suspensión de cola” en ratones (10-20 animales por grupo)

Sustancia	Dosis (mg/kg i.p.)	Duración de la inmovilidad % de cambio respecto a los controles con solvente
Clorhidrato de (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol	4.64	+6%
	10.0	+12%
	21.5	+9%
	31.6	-13%
Clorhidrato de (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol + 1.0 mg/kg Naloxon i.v.	21.5	-90%
	31.6	-85%
Naloxon, 1.0 mg/kg, i.v.	-	-15%
Morfina	4.64	+90%
	10.0	+145%
	21.5	+169%
Imipramina	31.6	-61%

5 La tabla 2 muestra que el clorhidrato de (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol causa una fuerte disminución de la duración de la inmovilidad, después del tratamiento previo con Naloxon, como también se encontró con la Imipramina. Los opioides causan, como muestra la morfina, un alargamiento de la duración de la inmovilidad. Esto explica por qué el (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol sin tratamiento previo con Naloxon sólo causa un efecto neto de supresión de absorción y efecto del opioide, sólo un cambio menor de la duración de la inmovilidad, en comparación con los controles con solvente.

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De acuerdo con las determinaciones anteriores, se vio que, en forma sorprendente, el (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol es el primer analgésico opioide que posee efecto antidepresivo relevante y evidente, clínicamente útil.

5 Ejemplo 14: Forma de aplicación parenteral

Se disuelve 1 g de (1R,2R)-3-(2-dimetilamino-metil-ciclohexil)-fenol en 1 L de agua inyectable, a temperatura ambiente, y se ajustó a condiciones isotónicas por adición de NaCl.

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182**Resumen:**

La invención se relaciona con compuestos de la [2-(3-metoxifenil)-ciclohexil-metil]-
dimetilamina como bases libres y/o en forma de sales fisiológicamente aceptables,
5 los medicamentos correspondientes, el uso de la [2-(3-metoxifenil)-ciclohexil-metil]-
dimetilamina y sus compuestos para producir un medicamento para el tratamiento de
depresiones, y métodos para tratar depresiones.

REIVINDICACIONES

1. Compuestos del 3-(2-dimetilaminometil-ciclohexil)-fenol, CARACTERIZADO porque se seleccionan entre:

- 5
- éster sulfúrico del mono-[3-(2-dimetilaminometil-ciclohexil)-fenilo],
 - éster sulfúrico del mono-(1R,2R)-[3-(2-dimetilaminometil-ciclohexil)-fenilo],
 - 3-(2-metilaminometil-ciclohexil)-fenol, (r)
 - (1R,2R)-3-(2-metilaminometil-ciclohexil)-fenol, (r) — — — — — (1R,2R)

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 - N-óxido de 3-(2-dimetilaminometil-ciclohexil)-fenol,
 - N-óxido de (1R,2R)-3-(2-dimetilaminometil-ciclohexil)-fenol,
 - ácido-6-[3-(2-dimetilaminometil-ciclohexil)-fenoxi]-3,4,5-trihidroxitetrahidropiran-2-carboxílico,
 - ácido 6-[(1R,2R)-3-(2-dimetilaminometil-ciclohexil)-fenoxi]-3,4,5-

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 - trihidroxitetrahidropiran-2-carboxílico,
 - 4-(2-dimetilaminometil-ciclohexil)-catecol,
 - (1R,2R)-4-(2-dimetilaminometil-ciclohexil)-catecol,
 - 3-(2-aminometil-ciclohexil)-fenol,
 - (1R,2R)-3-(2-aminometil-ciclohexil)-fenol,

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 - 4-(2-dimetilaminometil-ciclohexil)-bencen-1,2-diol,
 - (1R,2R)-4-(2-dimetilaminometil-ciclohexil)-bencen-1,2-diol,
 - C-[2-(3-metoxi-fenil)-ciclohexil]-metilamina,
 - (1R,2R)-C-[2-(3-metoxi-fenil)-ciclohexil]-metilamina,
 - [2-(3-metoxi-fenil)-ciclohexilmetil]-metil-amina,

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 - (1R,2R)-[2-(3-metoxi-fenil)-ciclohexilmetil]-metil-amina,
 - N-óxido de [2-(3-metoxi-fenil)-ciclohexilmetil]-dimetil-amina,
 - o
 - N-óxido de (1R,2R)-[2-(3-metoxi-fenil)-ciclohexilmetil]-dimetil-amina,

según el caso en forma de sus racematos, sus estereoisómeros puros, en

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especial los enantiómeros o diastereómeros, o en forma de mezclas de enantiómeros o diastereómeros, en cualquier relación de mezcla; en forma aislada o en forma de sus ácidos o de sus bases, o en forma de sus sales, en especial de sales fisiológicamente admisibles, o en forma de sus solvatos, en especial de los hidratos.

2. Compuestos de acuerdo con la reivindicación 1, CARACTERIZADO porque los compuestos se encuentran como estereoisómeros R,R, y de preferencia 1R,2R.

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3. Composición farmacéutica CARACTERIZADO porque contiene como sustancia activa al menos un compuesto de acuerdo con las reivindicaciones anteriores, así como, según el caso, materiales aditivos y/o coadyuvantes.



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183**United States Patent** [19]**Buschmann et al.**[11] **Patent Number:** **5,733,936**[45] **Date of Patent:** **Mar. 31, 1998****[54] 6-DIMETHYLAMINOMETHYL-1-PHENYL-CYCLOHEXANE COMPOUNDS AS PHARMACEUTICAL ACTIVE INGREDIENTS**

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[21] **Appl. No.:** **679,756**

[22] **Filed:** **Jul. 10, 1996**

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A61K 31/16; **A61K 31/44**; **A61K 31/425**;
A61K 31/38; **C07C 211/35**; **C07D 211/72**

[52] **U.S. Cl.** **514/646**; **514/506**; **514/620**;
514/349; **514/369**; **514/445**; **564/305**; **560/39**;
558/70; **546/300**; **548/189**; **549/65**

[58] **Field of Search** **514/646**, **506**,
514/546, **620**, **349**, **369**, **445**; **564/305**,
165; **560/39**; **558/70**; **546/300**; **548/189**;
549/65

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Primary Examiner—Deborah Lambkin
Attorney, Agent, or Firm—Evenson, McKeown, Edwards & Lenahan P.L.L.C.

[57] ABSTRACT

6-dimethylaminomethyl-1-phenyl-cyclohexane compounds, methods of preparing them and the use of these compounds in drugs are described.

5 Claims, No Drawings

6-DIMETHYLAMINOMETHYL-1-PHENYL-CYCLOHEXANE COMPOUNDS AS PHARMACEUTICAL ACTIVE INGREDIENTS

BACKGROUND OF THE INVENTION

6-dimethylaminomethyl-1-phenyl-cyclohexane compounds as pharmaceutical active ingredients

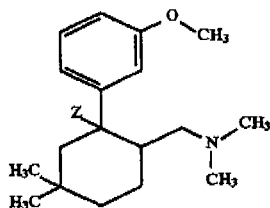
This invention relates to 6-dimethylaminomethyl-1-phenyl-cyclohexane compounds, to methods of preparing them and to the use of these compounds in drugs.

The treatment of chronic and non-chronic pain conditions is of great importance in medicine. There is currently a world-wide need for additional pain therapy which is not exclusively opioid but which exhibits good efficacy. The pressing requirement for a target-oriented treatment of chronic and non-chronic pain conditions which is right for the patient, which is to be understood as the successful and satisfactory treatment of pain for the patients, is documented in the large number of scientific works which have recently appeared in the field of applied analgesics or on basic research on nociception.

Opioids have been used for many years for the treatment of pain, even though they give rise to a series of side effects, for example dependency, respiratory depression, gastrointestinal inhibition effects and obstipation. They can therefore only be given over an extended period of time or in high dosages subject to special precautions, for example special prescription regulations (Goodman, Gilman "The Pharmaceutical Basis of Therapeutics" Pergamon Press, New York, 1990).

Tramadol hydrochloride—(1RS,2RS)-2[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride—assumes a special position amongst centrally acting analgesics, since this active ingredient acts as a strong inhibitor of pain without the side effects which are known for opioids (J. Pharmacol. Exp. Ther. 267, 331 (1993)). Tramadol is a racemate and consists of equal amounts of (+) and (−) enantiomers. In vivo, this active ingredient forms the metabolite O-desmethyl-tramadol, which likewise exists as a mixture of enantiomers. Investigations have shown that both the enantiomers of tramadol and the enantiomers of the tramadol metabolite have a part in the analgesic effect (J. Pharmacol. Exp. Ther. 260, 275 (1992)).

Compounds of formula



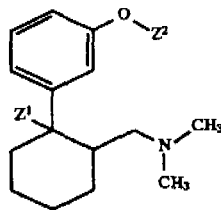
are known from Chem. Pharm. Bull. 32, 2279 (1984) in which Z represents H or OH. These substances have an analgesic effect which is considerably weaker than that of tramadol.

SUMMARY OF THE INVENTION

The underlying object of the present invention was to develop substances with an analgesic effect which are suitable for the treatment of severe pain without giving rise to

the side effects which are known for opioids. The object was also that the substances to be developed should not exhibit the side effects which occur in some cases of treatment with tramadol for example nausea and vomiting.

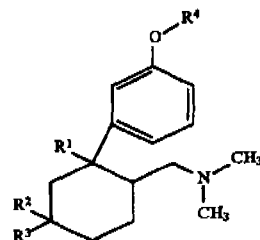
It has now been found that the requirements imposed on the substances to be developed are fulfilled by certain 6-dimethylaminomethyl-1-phenyl-cyclohexane compounds. These compounds are distinguished by a pronounced analgesic effect, which is significantly more intense compared with tramadol and with the compounds of formula



which are known from Arzneim.-Forsch./Drug Res. 28 (IA) 107 (1978), where Z¹ is H, OH or Cl and Z² is CH₃, or Z¹ is OH and Z² is H.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Accordingly, the present invention relates to 6-dimethylaminomethyl-1-phenylcyclohexane compounds of formula I



in which

R¹ is H, OH, Cl or F,

R² and R³ are the same or different, and represent H, C₁₋₄ alkyl, benzyl, CF₃, OH, OCH₂-C₆H₅, O-C₁₋₄-alkyl, Cl or F, with the proviso that at least one of the radicals R² or R³ represents H,

R⁴ represents H, CH₃, PO(OC₁₋₄-alkyl)₂, CO(OC₁₋₈ alkyl), CO-NH-C₆H₄-C₁₋₃-alkyl, CO-C₆H₄-R⁵, CO-C₁₋₅-alkyl, CO-CHR⁶-NHR⁷ or an unsubstituted or substituted pyridyl, thienyl, thiazoyl or phenyl group,

R⁵ represents OC(O)C₁₋₃-alkyl in the ortho position or CH₂-N(R⁸)₂ in the meta or para position, wherein R⁸ represents C₁₋₄ alkyl or both radicals R⁸ together with N constitute the 4-morpholino radical, and

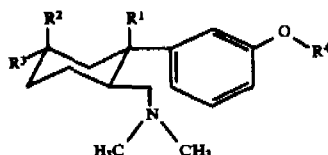
R⁶ and R⁷ are the same or different and represent H or C₁₋₆ alkyl,

with the proviso that if both radicals R² and R³ represent H, R⁴ is not CH₃ if R¹ represents H, OH or Cl, or R⁴ is not H if R¹ represents OH, in the form of their bases or salts of physiologically compatible acids.

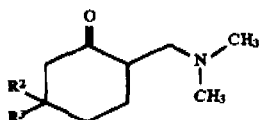
Preferred 6-dimethylaminomethyl-1-phenyl-cyclohexane compounds correspond to formula I where R¹ represents H, OH or F. Particularly preferred 6-dimethylaminomethyl-1-phenyl-cyclohexane compounds are in the form of their

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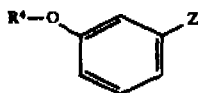
diastereoisomers with the configuration of formula Ia, in which the phenyl ring and the dimethylaminomethyl group are situated trans in relation to each other:



The present invention also relates to a method of preparing 6-dimethylaminomethyl-1-phenyl-cyclohexane compounds of formula I, in which R¹ represents OH and R² and R³ are the same or different and represent H, C₁-C₄ alkyl, benzyl, CF₃, Cl or F, with the proviso that at least one of the radicals R² or R³ is H and R⁴ represents H, CH₃ or an unsubstituted or substituted pyridyl, thienyl, thiazoyl or phenyl group, with the proviso that R⁴ is neither CH₃ nor H if both radicals R² and R³ represent H. The method being characterised in that a β-dimethylaminoketone of formula II



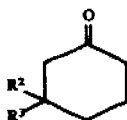
is reacted with an organometallic compound of formula III



in which Z represents MgCl, MgBr, MgI or Li, to form a compound of formula I.

The reaction of a β-dimethylaminoketone with a Grignard compound of formula III or with an organolithium compound of formula III can be conducted in an aliphatic ether, for example diethyl ether and/or tetrahydrofuran, at a temperature between -70° C. and +60° C. Organolithium compounds of formula III can be obtained by the reaction of a compound of formula III, in which Z represents Cl, Br or I, with an n-butyllithium/hexane solution, for example, by halogen/lithium exchange. On the reaction of a β-dimethylaminoketone of formula II with an organometallic compound, 6-dimethylaminomethyl-1-phenyl-cyclohexane compounds are obtained with the preferred relative configuration of formula Ia.

β-dimethylaminoketones of formula II are obtainable from ketones of formula IV

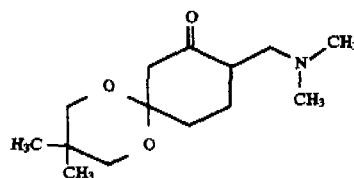


by reaction with dimethylaminohydrochloride and formaldehyde in glacial acetic acid or in a C₁-C₄ alkyl alcohol, or by reaction with dimethylammonium methylene chloride in acetonitrile catalysed by acetyl chloride (Synthesis 1973, 703; Tietze, Eicher in "Reaktionen und Synthesen im Organisch-Chemischen Praktikum" ["Reactions and Synthesis in the Practice of Organic Chemistry"], Thieme-Verlag,

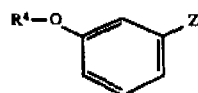
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Stuttgart 1991, page 189). The diastereoisomeric β-dimethylaminoketones produced by the aminomethylation reaction can be obtained as pure diastereoisomers, either by separating them by column chromatography or by the fractional crystallisation of their hydrochlorides from an organic solvent, for example 2-butanone and/or acetone.

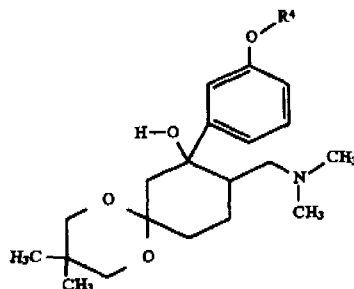
The present invention further relates to a method of preparing 6-dimethylaminomethyl-1-phenyl-cyclohexane compounds of formula I, in which R¹ is OH, one of the radicals R² or R³ represents H and the other represents OH, O-C₁-C₄-alkyl or OCH₂C₆H₅, and R⁴ represents H, CH₃ or an unsubstituted or substituted pyridyl, thienyl, thiazoyl or phenyl group, which is characterised in that a β-dimethylaminoketone with a spirocyclic acetal structure of formula V



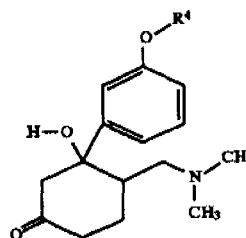
is reacted with an organometallic compound of formula III



in which Z represents MgCl, MgBr, MgI or Li, to form a compound of formula VI



the compound of formula VI which is obtained is converted into the corresponding ketone derivative of formula VIII

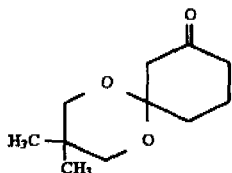


by proton-catalysed deacetylation and the ketone derivative obtained is subsequently reduced with a complex alkali metal hydride to form a compound of formula I in which one of the radicals R² or R³ represents OH, and if desired the compound of formula I which is obtained by reduction is

converted, after conversion into an alkali salt with a C_1 - C_4 alkyl or benzyl halide, into a compound of formula I in which one of the radicals R^2 or R^3 represents $O-C_1-C_4$ -alkyl or $OCH_2C_6H_5$.

The reduction of a compound of formula VIII is preferably carried out with sodium borohydride or lithium aluminium hydride in an organic solvent, for example tetrahydrofuran, diethyl ether and/or a C_2 - C_4 alkyl alcohol. If a compound in which R^2 or R^3 represents OC_1-C_4 -alkyl or OCH_2Ph is to be obtained by the method according to the invention, the compound obtained by reduction is converted with an alkali hydride, for example sodium and/or potassium hydride, in a solvent such as dimethylformamide into the corresponding alkali salt compound and is subsequently reacted with a C_1 - C_4 alkyl or benzyl halide.

β -dimethylaminoketones with a spirocyclic acetal structure of formula V are obtainable from 9-dimethylaminomethyl-3,3-dimethyl-1,5-dioxaspiro[5,5]undecan-8-one of formula VII



which is accessible by the targeted monoacetylation of cyclohexane-1,3-dione, by reaction with dimethylammonium ethylene chloride in acetonitrile catalysed by acetyl chloride (Synthesis 1973, 703; Tietze, Either in "Reaktionen und Synthesen im Organisch-Chemischen Praktikum", Thieme-Verlag, Stuttgart 1991, page 189).

The present invention also relates to a method of preparing 6-dimethylaminomethyl-1-phenyl-cyclohexane compounds of formula I, in which R^1 is H, and R^2 and R^3 are the same or different and represent H, C_1 - C_4 alkyl, benzyl, CF_3 , $OCH_2C_6H_5$ or F, with the proviso that at least one of the radicals R^2 or R^3 is H, and R^4 represents H, CH_3 or an unsubstituted or substituted pyridyl, thienyl, thiazoyl or phenyl group, which is characterised in that a compound of formula I in which R^1 is Cl is reacted with zinc borohydride, zinc cyanoborohydride or tin cyanoborohydride in an ether, or a compound of formula I in which R^1 is OH is reacted with Raney nickel in a C_2 - C_4 alkyl alcohol.

The reaction of a compound of formula I, in which R^1 is Cl, with a borohydride, is preferably conducted in diethyl ether and/or tetrahydrofuran at a temperature between 0° and 30° C. The reaction of a compound of formula I, in which R^1 is OH, with Raney nickel is preferably conducted in a C_2 - C_4 alkyl alcohol at a temperature between 70° and 100° C. (J. Org. Chem. 59, 6895 (1994); and Angew. Chem. 95, 568 (1983)).

Cyclohexane compounds of formula I, in which R^1 is H, one of the radicals R^2 or R^3 represents H and the other represents Cl, and R^4 represents H, CH_3 or an unsubstituted or substituted pyridyl, thienyl, thiazoyl or phenyl group, are obtainable from the corresponding cyclohexane compounds of formula I, in which one of the radicals R^2 or R^3 is H and the other is OH and R^1 and R^4 have one of the meanings given above, by reaction with thionyl chloride or hydrochloric acid/zinc chloride in the known manner (J. Chem. Soc. 1943, 636; J. Org. Chem. 17, 1116 (1952)).

The present invention also relates to a method of preparing 6-dimethylaminomethyl-1-phenyl-cyclohexane compounds of formula I, in which R^1 is H, R^2 and R^3 are the

same or different and represent H, C_1 - C_4 alkyl, benzyl, CF_3 or F, with the proviso that at least one of the radicals R^2 or R^3 is H and R^4 represents CH_3 , which is characterised in that a compound of formula I where R^1 is Cl is hydrogenated in the presence of a palladium catalyst in a C_1 - C_4 alkyl alcohol. The hydrogenation is preferably conducted at a pressure between 1 and 100 bar and at a temperature between 20° and 80° C.

Compounds of formula I, in which R^1 is H, R^2 and R^3 are the same or different and represent H, a C_1 - C_4 alkyl, benzyl, CF_3 or F, and R^4 is H, can be obtained from the corresponding methoxyphenyl compounds by heating for several hours with concentrated hydrobromic acid (Chem. Rev. 54, 615 (1954); J. Am. Chem. Soc. 74, 1316 (1952)).

Cyclohexane compounds of formula I, in which R^1 is Cl and none of the radicals R^2 and R^3 represents OH, are obtainable by the reaction of a compound of formula I, in which R^1 is OH, in the form of the free base or as the hydrochloride with thionyl chloride in the absence of a solvent at a temperature between 0° and 20° C. In this method, chlorine exchange proceeds with the configuration being maintained. Cyclohexane compounds of formula I where R^1 is Cl and R^2 or R^3 are OH are obtainable in the manner known in the art from the corresponding compounds in which R^1 is Cl and R^2 or R^3 is $OCH_2C_6H_5$.

The present invention also relates to a method of preparing 6-dimethylaminomethyl-1-phenyl-cyclohexane compounds of formula I, in which R^1 is F, R^2 and R^3 are the same or different and represent H, a C_1 - C_4 alkyl, benzyl, CF_3 , $OCH_2C_6H_5$, Cl or F, with the proviso that at least one of the radicals R^2 or R^3 is H and R^4 represents CH_3 or an unsubstituted or substituted pyridyl, thienyl, thiazoyl or phenyl group, which is characterised in that a compound of formula I in which R^1 is OH is reacted with dimethylammonium sulphur trifluoride. The reaction is preferably conducted in an organic solvent, for example dichloromethane, 1,1,2-trichloroethane and/or toluene, at a temperature between -50° and $+30^\circ$ C. (Org. React. 35, 513 (1988)).

Compounds of formula I, in which R^1 is F, R^2 and R^3 are the same or different and represent H, a C_1 - C_4 alkyl, benzyl, CF_3 , $OCH_2C_6H_5$, Cl or F, with the proviso that at least one of the radicals R^2 or R^3 is H and R^4 represents H, can be obtained by the reaction of compounds of formula I, in which R^1 represents OH and R^4 represents a trialkylsilyl group, with dimethylammonium sulphur trifluoride and subsequent cleavage of the silyl ether with aqueous mineral acids. The dimethyl-tert-butylsilyl group is a preferred trialkylsilyl group.

A further possible way of obtaining 6-dimethylaminomethyl-1-phenyl-cyclohexane compounds of formula I, in which R^1 represents OH or H, R^4 represents H and neither of the two radicals R^2 and R^3 represents Cl, F or CH_3 , consists of the selective ether cleavage, with diisobutylaluminium hydride, of a 6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane compound, which is preferably conducted in an aromatic hydrocarbon, for example toluene, at a temperature between 60° and 130° C. (Synthesis, 1975, 617).

Furthermore, 6-dimethylaminomethyl-1-phenyl-cyclohexane compounds of formula I, in which R^1 represents OH, H or F and R^4 represents H, and R^2 and R^3 are the same or different and represent H, C_1 - C_4 alkyl, benzyl, CF_3 , F, Cl, OH or $O-C_1-C_4$ -alkyl, can be obtained from the corresponding 6-dimethylaminomethyl-1-(3-benzyloxyphenyl)-cyclohexane compounds by reductive debenzylation. Debenzylation is preferably conducted in the presence of platinum or palladium on a support material in the presence of hydrogen in a solvent, for example acetic acid

and/or a C₁-C₄ alkyl alcohol, at a pressure between 1 and 100 bar and at a temperature between 20° and 100° C.

6-dimethylaminomethyl-1-phenyl-cyclohexane compounds of formula I, in which OR⁴ represents a phosphate, carbonate, carbamate, carboxylate, aryloxy or heteroaryloxy group, can be obtained by the reaction of the corresponding 6-dimethylaminomethyl-1-(3-hydroxyphenyl)-cyclohexane compounds in the form of their alkali salts with an alkali salt of a dialkylchlorophosphate, with an alkyl chloroformate, with an aryl or heteroaryl isocyanate, with a carboxylic acid chloride or with an aryl or heteroaryl halide. The reactions are usually conducted in a solvent, for example toluene, dichloromethane, diethyl ether and/or tetrahydrofuran, at temperatures between -15° C. and +110° C. (Drugs of the Future 16, 443 (1991); J. Med. Chem. 30, 2008 (1989) and 32, 2503 (1989); J. Org. Chem. 43, 4797 (1978); Tetrahedron Lett. 1977, 1571; J. Pharm. Sci. 57, 774 (1968)). The reactions with an aryl or heteroaryl halide are conducted in the presence of copper powder and/or a copper(I) halide as a catalyst.

6-dimethylaminomethyl-1-phenyl-cyclohexane compounds of formula I, in which OR⁴ is an α-amino acid group, can be obtained by the reaction of the corresponding 6-dimethylaminomethyl-1-(3-hydroxyphenyl)-cyclohexane compound with the corresponding 2-t-butoxycarbonylamino-carboxylic acid using triethylamine and coupling reagents, for example benzotriazol-1-yl-oxy-tripyrrolidinophosphonium hexafluorophosphate, in a solvent, for example dichloromethane.

The compounds according to the invention can be converted with physiologically compatible acids, for example hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid and/or aspartic acid, into the salts thereof in the manner known in the art. Salt formation is preferably conducted in a solvent, for example diethyl ether, an acetic acid alkyl ester, acetone and/or 2-butanone. Trimethylchlorosilane in the presence of water in one of the aforementioned solvents is also suitable for the preparation of the hydrochlorides.

The compounds according to the invention have a pronounced analgesic effect and are toxicologically harmless. They are therefore suitable as pharmaceutical active ingredients. Accordingly, the present invention also relates to the use of a 6-dimethylaminomethyl-1-phenyl-cyclohexane compound of formula I as an active ingredient in drugs, preferably as an active ingredient in pain-killing drugs.

In addition to at least one 6-dimethylaminomethyl-1-phenyl-cyclohexane compound, drugs according to the invention contain support materials, fillers, solvents, diluents, colorants and/or binders. The selection of the auxiliary materials and of the amounts to be used depends upon whether the drug is to be applied orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally or locally, for example for infections of the skin, of the mucous membranes and of the eyes. Preparations in the form of tablets, dragees, capsules, granules, drops, juices and syrups are suitable for oral application. Solutions, suspensions, readily reconstitutable dry preparations and sprays are suitable for parenteral application. Compounds according to the invention as a deposit in a dissolved form or in a patch, optionally with the addition of agents which promote dermal penetration, are examples of suitable percutaneous forms of application. The compounds according to the invention can be released in a delayed manner from forms of preparations which can be applied orally or percutaneously.

The amount of active ingredient to be administered to the patient varies depending on the weight of the patient, on the type of application, on the indication and on the severity of the illness. 10 to 500 mg of at least one 6-dimethylaminomethyl-1-phenyl-cyclohexane compound of formula I are usually applied per kg.

EXAMPLES

Petroleum ether with a boiling range of 50°-70° C. was used unless indicated otherwise. The term "ether" denotes diethyl ether.

Silica gel 60 (0.040-0.063 mm) supplied by E. Merck, Darmstadt, was used as the stationary phase for column chromatography.

Thin-layer chromatography investigations were performed using ready-for-use HPTLC plates of silica gel 60 F 254, supplied by E. Merck, Darmstadt.

Racemate separations were performed on a Chiracel OD column.

The mixture ratios of the mobile phases for all the chromatographic investigations are always given in volume/volume.

RT denotes room temperature; m.p. denotes melting point.

Example 1

(-)-(1S,2S)-3-(2-dimethylaminomethyl-1-fluorocyclohexyl)-phenol hydrochloride (-1)

1st Step

(-)-(1S,2S)-1-(3-benzoyloxy-phenyl)-2-dimethylaminomethyl-cyclohexanol hydrochloride (-2)

The base was released from (-)-(1S,2S)-3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl hydrochloride with aqueous sodium hydrogen carbonate solution/dichloromethane, and the dichloromethane was removed by distillation after drying the solution. 135 g (545 mmole) base were dissolved in 675 ml of dry dimethylformamide and mixed in several portions with 29.1 g of 50% sodium hydride. After adding 69 ml (594 mmole) benzoyl chloride the mixture was heated at 70° C. for three hours. The reaction mixture was then cooled to room temperature and poured on to ice water. It was extracted three times with 150 ml ethyl acetate each time. After drying the organic phases over magnesium sulphate, the solvent was distilled off. The residue (204 g) was taken up in 1000 ml 2-butanone and mixed with 76 ml (600 mmole) trimethylchlorosilane and 10.9 ml water. 190 g of hydrochloride (-2) (93% theoretical) with a melting point of 207°-210° C. crystallised out at room temperature.

$[\alpha]_D^{25} = -27.0^\circ$ (c=1.02; methanol)

2nd Step

(-)-(1S,2S)-[2-(3-benzoyloxy-phenyl)-2-fluoro-cyclohexylmethyl]-dimethylamine (-3)

147.7 g (435 mmole) (-2), dissolved in 1500 ml of dry dichloromethane, were added drop-wise at -40° C. to a solution of 80.6 g (500 mmole) diethylamino-sulphur trifluoride in 450 ml of dry dichloromethane. After the addition was complete, the mixture was stirred for 120 minutes at this temperature and subsequently heated to room temperature. After stirring for a further one hour at room temperature the mixture was cooled to 0°-5° C. and hydrolysed with 500 ml water. The aqueous phase was extracted twice with 200 ml dichloromethane. After drying the organic phases the solvent was removed by distillation. The crude mixture obtained (185 g) was divided into four portions. Each portion was introduced on to an 8x50 cm column packed

with silica gel and eluted with 1:1 ethyl acetate/methanol. In total, 103 g (69% theoretical) of base (-3) were obtained as a light yellow, viscous oil.

3rd Step

(-)-(1S,2S)-3-(2-dimethylaminomethyl-1-fluorocyclohexyl)-phenol hydrochloride (-1)

7.75 g (22.7 mmole) of (-3) were dissolved in 40 ml of dry methanol and introduced into a hydrogenation apparatus with 2.0 g palladium on activated carbon (10% Pd). 430 ml hydrogen were consumed after stirring for 35 minutes at room temperature. The catalyst was removed by filtration, and the methanol was removed by distillation. 6.3 g of base were obtained, from which 4.9 g (75% theoretical) of hydrochloride (-1) were obtained with trimethylchlorosilane/water in 2-butanone/acetone (1/1).

m.p.: 188°-190° C. $[\alpha]^{RT}_D = -29.6^\circ$ (c=1.02; methanol)

Example 2

(+)-(1R,2R)-3-(2-dimethylaminomethyl-1-fluorocyclohexyl)-phenol hydrochloride (+1)

Enantiomer (+1) was obtained in a yield of 48% theoretical from (+)-(1R,2R)-3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenol hydrochloride, under the conditions given in Example 1.

m.p.: 188°-190° C. $[\alpha]^{RT}_D = +28.3^\circ$ (c=1.00; methanol)

Example 3

(+)-(1R,2R)-[2-chloro-2-(3-methoxy-phenyl)-cyclohexylomethyl]-dimethylamine hydrochloride (+4)

10 g (33.4 mmole) (+)-(1R,2R)-2-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexanol hydrochloride were mixed with 10 ml thionyl chloride at room temperature. Nitrogen was subsequently passed for two hours over the reaction mixture to remove excess thionyl chloride. After adding a further 10 ml thionyl chloride, the reaction mixture was allowed to stand for 12 hours before excess thionyl chloride was removed again over 2.5 hours with the aid of a stream of nitrogen. After drying, the residue was dissolved in 50 ml of ice-cold 2-butanone and mixed with 50 ml diisopropyl ether with stirring, whereupon the hydrochloride crystallised out. For completion, the suspension was stirred for another two hours with ice bath cooling. 5.9 g (55% theoretical) of (+4) were obtained.

m.p.: 120°-121° C. (decomposition) $[\alpha]^{RT}_D = +4.7^\circ$ (c=0.91; methanol)

Example 4

(-)-(1S,2S)-[2-chloro-2-(3-methoxy-phenyl)-cyclohexylomethyl]-dimethylamine hydrochloride (-4)

Enantiomer (-4) was obtained in a yield of 55% theoretical from (-)-(1S,2S)-2-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexanol hydrochloride under the conditions given in Example 3.

m.p.: 120°-122° C. $[\alpha]^{RT}_D = -5.2^\circ$ (c=0.93; methanol)

Example 5

(+)-(1R,2R)-3-(1-chloro-2-dimethylaminomethyl-cyclohexyl)-phenol hydrochloride (+5)

3.6 g (12.6 mmole) (+)-(1S,2S)-3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenol hydrochloride were mixed at room temperature with 3 ml thionyl chloride. The mixture was then stirred for one hour at room temperature. Nitrogen was then passed for two hours over the reaction mixture to remove excess thionyl chloride. After adding a further 4 ml thionyl chloride, the reaction mixture was stirred for two hours at room temperature before excess thionyl chloride was removed over two hours with the aid of a stream of nitrogen. The residue was

dissolved in 70 ml 2-butanone and mixed with 50 ml diisopropyl ether with stirring. The hydrochloride which crystallised out was washed three times by decantation with 25 ml 2-butanone. 1.8 g (46% theoretical) of (+5) were obtained after drying.

m.p.: 145°-146° C. (decomposition) $[\alpha]^{RT}_D = +5.2^\circ$ (c=0.93; methanol)

Example 6

(-)-(1S,2S)-3-(1-chloro-2-dimethylaminomethyl-cyclohexyl)-phenol hydrochloride (-5)

Enantiomer (-5) was obtained in a yield of 48% theoretical from (-)-(1S,2S)-3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenol hydrochloride under the conditions given in Example 5.

m.p.: 146°-147° C. (decomposition) $[\alpha]^{RT}_D = -7.8^\circ$ (c=1.01; methanol)

Example 7

(+)-(1S,2R)-[2-(3-methoxy-phenyl)-cyclohexylmethyl]-dimethylamine hydrochloride (+6)

46 g of dried zinc chloride were dissolved in 580 ml of dry ether and subsequently added drop-wise to a slurry of 31 g sodium borohydride in 1800 ml ether. After stirring for 12 hours 500 ml were decanted off from the zinc borohydride/sodium chloride suspension obtained and were added drop-wise to 10.2 g (32 mmole) of (+4) in 200 ml of dry ether. The reaction mixture was stirred for 48 hours at room temperature and was then added drop-wise with ice-bath cooling to 40 ml of a saturated ammonium chloride solution. After phase separation, the ether phase was washed twice with saturated common salt solution and the solvent was removed by distillation under vacuum after drying over sodium sulphate. 9.6 g of an amine-borane complex were obtained, which was dissolved in 100 ml of dry methanol to isolate the free base. After adding 7.5 g triphenylphosphine, the mixture was heated for 18 hours under reflux. After removing the solvent by distillation, the residue was mixed with 100 ml of 5% hydrochloric acid, and the hydrochloric acid phase was then washed twice with 50 ml ether. Thereafter the hydrochloric acid phase was made alkaline with concentrated sodium hydroxide solution whilst being cooled in an ice bath and was shaken twice with 50 ml dichloromethane. After drying the combined organic phases over sodium sulphate the solvent was distilled off under vacuum and the remaining residue (7.8 g) was taken up in 2-butanone. After adding trimethylchlorosilane/water, 6.9 g (76% theoretical) of hydrochloride (+6) crystallised out.

m.p.: 203°-204° C. (decomposition) $[\alpha]^{RT}_D = +68.0^\circ$ (c=1.00; methanol)

Example 8

(-)-(1R,2S)-[2-(3-methoxy-phenyl)-cyclohexylmethyl]-dimethylamine hydrochloride (-6)

Enantiomer (-6) was obtained in a yield of 75% theoretical from 10.2 g (32 mmole) (-4) under the conditions given in Example 7.

m.p.: 201°-203° C. (decomposition) $[\alpha]^{RT}_D = -67.1^\circ$ (c=1.0; methanol)

Example 9

(+)-(1S,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol hydrochloride (+7)

4.3 g (15 mmole) (+6), obtained according to Example 7, were mixed with 100 ml of concentrated hydrobromic acid. The mixture was then heated for two hours under reflux. After cooling to room temperature, the reaction mixture was concentrated under the vacuum from a water pump. The

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residue was treated with concentrated sodium hydrogen carbonate solution until an alkaline reaction was obtained. After extracting twice with 50 ml dichloromethane each time, the combined organic phases were dried over sodium sulphate. Dichloromethane was then removed by distillation under vacuum and the residue (4 g) was taken up in 2-butanone. After adding trimethylchlorosilane/water, 3.96 g (98% theoretical) of hydrochloride (+7) crystallised out. m.p.: 177°-178° C. (decomposition) $[\alpha]_D^{25} = +67.5^\circ$ (c=1.0; water)

Example 10

(-)-(1R,2S)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol hydrochloride (-7)

Enantiomer (-7) was obtained in 95% yield, under the conditions given in Example 9, from (-6), which was prepared according to Example 8.

m.p.: 174°-176° C. (decomposition) $[\alpha]_D^{25} = -66.1^\circ$ (c=0.96; methanol)

Example 11

(-)-(1R,2S)-2,2-dimethylpropionic acid-3-(2-dimethylaminomethyl-cyclohexyl)-phenyl ester hydrochloride (-8)

The base was released with dichloromethane/aqueous sodium hydrogen carbonate solution from enantiomer (-7), which was obtained according to Example 10, and the dichloromethane was removed by distillation after drying the solution. 1.7 g (7.3 mmole) of the base obtained were dissolved in 10 ml of dry dimethylformamide and added drop-wise to a suspension of 400 mg sodium hydride (50%) in 5 ml of dry dimethylformamide. The mixture was then stirred for a further 30 minutes at 50° C. After cooling to room temperature, 1.03 ml (8.4 mmole) 2,2-dimethylpropionyl chloride were added drop-wise and the reaction mixture was stirred for a further two hours at room temperature before it was poured on to ice/water. The aqueous phase was extracted three times with 50 ml ether. The combined organic phases were dried over sodium sulphate. After removing the solvent by distillation, 2.3 g of crude mixture were obtained and were introduced on to a 4x30 cm column packed with silica gel. Elution with 7/1 diisopropyl ether/methanol gave 1.75 g base, from which 1.75 g (70% theoretical) of hydrochloride (-8) with a melting point of 218°-219° C. was obtained with trimethylchlorosilane/water in 2-butanone/diisopropyl ether.

$[\alpha]_D^{25} = -3.7^\circ$ (c=1.07; methanol)

Example 12

(-)-(1R,2S)-{2-[3-(p-isopropyl-phenyl-carbamoyl)-oxy-phenyl]-cyclohexyl-methyl}-dimethylamine hydrochloride (-9)

The base was released with dichloromethane/aqueous sodium hydrogen carbonate solution from enantiomer (-7), which was obtained according to Example 10, and the dichloromethane was removed by distillation after drying the solution. 2.1 g (9.0 mmole) of the base obtained were dissolved in 20 ml of dry toluene and mixed with 1.62 g (10 mmole) 4-isopropylphenyl isocyanate. After stirring for 20 hours at room temperature, the toluene was removed by distillation. The residue (2.5 g) was introduced on to a 5.5x15 cm column packed with silica gel and eluted with 1/1 methanol/ethyl acetate. 1.94 g base were obtained, from which 1.8 g (46% theoretical) of hydrochloride (-9) were obtained with trimethylchlorosilane/water in n-propyl acetate.

m.p.: 156° C. $[\alpha]_D^{25} = -16.3^\circ$ (c=1.09; methanol)

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Example 13

(-)-(1R,2S)-2-acetoxy-benzoic acid-3-(2-dimethylaminomethyl-cyclohexyl)-phenyl ester hydrochloride (-10)

The base was released with dichloromethane/aqueous sodium hydrogen carbonate solution from enantiomer (-7), which was obtained according to Example 10, and the dichloromethane was removed by distillation after drying the solution. 0.7 g (3.0 mmole) of the base obtained were dissolved in 7 ml of dry dichloromethane and mixed at room temperature with 0.6 g (3.24 mmole) 2-acetyl-benzoyl chloride dissolved in 3 ml of dry dichloromethane. After stirring for 20 hours at room temperature, the reaction mixture was mixed with 20 ml sodium hydrogen carbonate solution and the aqueous phase was extracted twice with 10 ml dichloromethane. The organic phases were combined and dried over sodium sulphate. After removing the solvent by distillation, 1.1 g of crude mixture was obtained, and was introduced on to a 3x8 cm column packed with silica gel. Elution with ether gave 0.77 g base, from which 0.77 g (54% theoretical) of hydrochloride (-10) were obtained with trimethylchlorosilane/water in ether.

m.p.: 171°-174° C. $[\alpha]_D^{25} = -27.6^\circ$ (c=1.15; methanol)

Example 14

(-)-(1R,2S)-carbonic acid-[3-(2-dimethylaminomethyl-cyclohexyl)-phenyl]-ester-isobutyl ester hydrochloride (-11)

The base was released with dichloromethane/aqueous sodium hydrogen carbonate solution from enantiomer (-7), which was prepared according to Example 10, and the dichloromethane was removed by distillation after drying the solution. 2.34 g (10 mmole) of the base obtained were dissolved in 11 ml of dry dimethylformamide and added drop-wise to a suspension of 0.54 g sodium hydride (50%) in 5 ml of dry dimethylformamide. The mixture was then stirred for 30 minutes at room temperature. Thereafter, 1.44 ml (11 mmole) isobutyl chloroformate were added drop-wise and the reaction mixture was stirred for a further two hours at room temperature before it was mixed with 40 ml water. The aqueous phase was extracted three times with 50 ml ether. The combined organic phases were dried over sodium sulphate. After removing the solvent by distillation, 3.8 g of crude mixture were obtained and were introduced on to a 3x15 cm column packed with silica gel. Elution with ether gave 2.17 g base, from which 1.5 g (41% theoretical) of hydrochloride (-11) was obtained as a colourless syrup. $[\alpha]_D^{25} = -33.7^\circ$ (c=1.16; methanol)

Example 15

(-)-(1R,2S)-4-morpholin-4-yl-methyl-benzoic acid-3-(2-dimethylaminomethyl-cyclohexyl)-phenyl ester dihydrochloride (-12)

The base was released with dichloromethane/aqueous sodium hydrogen carbonate solution from enantiomer (-7), which was prepared according to Example 10, and the dichloromethane was removed by distillation after drying the solution. 1.9 g (8.1 mmole) of the base obtained were dissolved in 20 ml of dry dichloromethane and mixed at room temperature with 2.2 g (9.2 mmole) 4-morpholin-4-yl-methyl-benzoyl chloride hydrochloride (prepared according to U.S. Pat. No. 4,623,486). After stirring for 20 hours at room temperature, the reaction mixture was mixed with 50 ml sodium hydrogen carbonate solution and the aqueous phase was extracted three times with 10 ml dichloromethane. The organic phases were combined and dried over sodium sulphate. After removing the solvent by distillation, 2.9 g of crude mixture was obtained, and was

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introduced on to a 4x20 cm column packed with silica gel. Elution with 2/1 diisopropyl ether/methanol gave 0.77 g base, from which 0.41 g (10% theoretical) of dihydrochloride (-12) were obtained with trimethylchlorosilane/water in ether.

m.p.: 234°-236° C. $[\alpha]_D^{25} = -26.8^\circ$ (c=1.00; methanol)

Example 16

(+)-(2S,3S)-2-amino-3-methyl-pentanoic acid-(1R,2S)-3-(2-dimethylaminomethyl-cyclohexyl)-phenyl ester dihydrochloride (+13)

1st Step

(-)-(2S,3S)-2-tert.-butoxycarbonylamino-3-methyl-pentanoic acid-(1R,2S)-3-(2-dimethylaminomethyl-cyclohexyl)-phenyl ester (-14)

The base was released with dichloromethane/aqueous sodium hydrogen carbonate solution from enantiomer (-7), which was prepared according to Example 10, and the dichloromethane was removed by distillation after drying the solution. 2.1 g (9.8 mmole) of the base obtained were dissolved in 140 ml of dry dichloromethane and mixed in succession at room temperature with 2.19 g (9.5 mmole) (-)-(2S,3S)-2-tert.-butoxycarbonyl-amino-3-methyl-pentanoic acid monohydrate, 2.63 ml (19 mmole) triethylamine and 4.94 g (9.5 mmole) benzotriazol-1-yl-oxy-tripyrrolidino-phosphonium hexafluorophosphate. After stirring for 2 hours at room temperature, the solvent was distilled off and the residue (10.1 g) was introduced on to a 7x40 cm column packed with silica gel. Elution with 1/1 ethyl acetate/methanol gave 2.66 g of base (-14).

2nd Step

(+)-(2S,3S)-2-amino-3-methyl-pentanoic acid-(1R,2S)-3-(2-dimethylaminomethyl-cyclohexyl)-phenyl-ester hydrochloride (+13)

2.66 g (5.7 mmole) of (-14) were dissolved in 60 ml of dry dichloromethane and mixed with 0.23 ml water (13 mmole) and 2.52 ml (19.5 mmole) trimethylchlorosilane. The mixture was then stirred for 20 hours at room temperature. After adding 100 ml ether, 2.1 g (56% theoretical) of hydrochloride (+13) crystallised out.

m.p.: 154° C. (decomposition) $[\alpha]_D^{25} = +16.6^\circ$ (c=1.05; methanol)

Example 17

(-)-(1R,2S)-dimethyl-[2-[3-(6-methyl-pyridin-2-yloxy)-phenyl]-cyclohexyl-methyl]-amine dihydrochloride (-15)

The base was released with dichloromethane/aqueous sodium hydrogen carbonate solution from enantiomer (-7), which was prepared according to Example 10, and the dichloromethane was removed by distillation after drying the solution. 2.1 g (9.0 mmole) of the base obtained were dissolved in 10 ml of dry dimethylformamide and added drop-wise to a suspension of 475 mg sodium hydride (50%) in 5 ml of dry dimethylformamide. The mixture was then stirred for 10 minutes at 60° C. 1.5 ml (13.7 mmole) 2-chloro-6-methylpyridine were added drop-wise at this temperature. After adding 30 mg copper powder and 30 mg copper(I) chloride, the reaction mixture was stirred for 7 hours at 140° C. before cooling to room temperature. The reaction mixture was mixed with 50 ml water and the aqueous phase was extracted three times with 50 ml ether. The organic phases were combined, washed with 10 ml sodium hydroxide solution and then with 10 ml water and dried over sodium sulphate. After removing the solvent by distillation, 3.2 g of crude mixture were obtained and were introduced on to a 5x20 cm column packed with silica gel. Elution with 99.5/0.5 ether/concentrated ammonia solution gave 1.0 g base, from which 1.89 g (53% theoretical) of

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dihydrochloride (~15) was obtained with trimethylchlorosilane/water in 2-butanone/ethyl acetate.

m.p.: 60° C. (sintering) $[\alpha]_D^{25} = -44.6^\circ$ (c=1.0; methanol)

Example 18

(1RS,3SR,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol hydrochloride (16) and (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol hydrochloride (17)

1st Step

9-dimethylaminomethyl-3,3-dimethyl-1,5-dioxaspiro[5.5]undec-8-one hydrochloride (18)

125 g (630 mmole) 3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-8-one, which was obtained by the azeotropic acetylation of cyclohexane-1,3-dione with 2,2-dimethylpropane-1,3-diol in toluene as a solvent using p-toluenesulphonic acid as a catalyst, and 59 g (630 mmole) dimethylammonium methylene chloride were stirred at room temperature in 400 ml of dry acetonitrile. After adding 1 ml acetyl chloride the mixture was stirred for a further 3 hours at room temperature, whereupon a clear colourless solution was obtained. 800 ml of dry ether were then added drop-wise to the reaction mixture, whereupon the hydrochloride crystallised out. 158 g of (18) were obtained (98% theoretical).

2nd Step

(8RS,9RS)-9-dimethylaminomethyl-8-(3-methoxy-phenyl)-3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-8-ol (19)

20 ml (158 mmole) 1-bromo-3-methoxybenzene, dissolved in 100 ml of dry tetrahydrofuran, were added drop-wise to 3.88 g (160 mmole) magnesium turnings in 10 ml of dry tetrahydrofuran so that the reaction mixture boiled gently. After the addition of 1-bromo-3-methoxybenzene was complete, the mixture was heated for one hour under reflux and was thereafter cooled to 5°-10° C. The base was, released from hydrochloride (18) from step 1 with dichloromethane/sodium hydroxide solution and the dichloromethane was removed by distillation after drying the solution. 32.7 g (150 mmole) of the base obtained were dissolved in 50 ml of dry tetrahydrofuran and added to the Grignard solution. The reaction mixture was allowed to stand overnight and was then cooled to 5°-10° C. again. The Grignard solution was decomposed by the addition of 140 ml of 20% ammonium chloride solution. The reaction mixture was diluted with 200 ml of 1/1 ether/tetrahydrofuran, and the organic phase was separated off and extracted twice with 100 ml ether. The combined organic phases were dried over sodium sulphate. After removing the solvent by distillation, the residue (43.6 g) was introduced on to an 8x50 cm column packed with silica gel and extracted with 1/1 ethyl acetate/methanol. The base obtained was again introduced on to a 5x13 cm column packed with silica gel and eluted with 1/1 diisopropyl ether/methanol. 22.1 g base (42% theoretical) were obtained as a light yellow, viscous oil.

3rd Step

(3RS,4RS)-4-dimethylaminomethyl-3-hydroxy-3-(3-methoxy-phenyl)-cyclohexanone (20)

61.8 g (176 mmole) of base (19) from step 2 were dissolved in 800 ml tetrahydrofuran and cooled to 0°-5° C. 800 ml of aqueous hydrochloric acid (conc. hydrochloric acid/water=1/5) were added over 30 minutes at this temperature. The mixture was then stirred for a further one hour at room temperature before it was cooled again to 0°-5° C. 200 ml concentrated sodium hydroxide solution were added at this temperature. The reaction mixture was then extracted three times with 250 ml ether. The combined organic phases were dried over sodium sulphate. After removing the solvent by distillation, the residue (55 g) was introduced on to an

8x50 cm column packed with silica gel and eluted with 7/1 diisopropyl ether/methanol and then with 4/1 ethyl acetate/methanol. The base obtained (24.7 g) was taken up in 1000 ml 2-butanone and mixed with trimethylchlorosilane/water. 16.5 g of hydrochloride (20) (24% theoretical) with a melting point of 161°–163° C. crystallised out.

4th Step

(1RS,3SR,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol hydrochloride (16) and (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol hydrochloride (17)

The base was released with dichloromethane/sodium hydroxide solution from hydrochloride (20), which was prepared according to step 3, and the dichloromethane was removed by distillation after drying the solution. 27 g (97 mmole) of the base obtained were dissolved in 300 ml isopropanol and mixed in portions at room temperature with 1.8 g (47.5 mmole) sodium borohydride. The mixture was stirred for one hour at room temperature before it was cooled to 0°–5° C. 68 ml of diluted hydrochloric acid (conc. hydrochloric acid/water=1/3) were added at this temperature. Immediately after the addition, the reaction mixture was made alkaline with concentrated sodium hydroxide solution. After removing the solvent by distillation, the residue (40 g) was taken up in 200 ml water and extracted three times with 50 ml dichloromethane. The combined organic phases were dried over sodium sulphate and the solvent was removed by distillation. The residue (29.6 g) was introduced on to a 7x45 cm column packed with silica gel and eluted firstly with methanol and then with 99.5/0.5 methanol/concentrated ammonia solution. It was possible to obtain 11.3 g of the base of compound (16) and 13.5 g of the base of compound (17) in this manner. The bases obtained were taken up in 2-butanone and mixed with trimethylchlorosilane/water, whereupon the hydrochlorides crystallised out.

(16): yield: 9.9 g (32% theoretical) m.p.: 263°–264° C.

(17): yield: 13.7 g (45% theoretical) m.p.: 197°–198° C.

Example 19

Enantiomers of (17)

(+)-(1R,3R,6R)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol hydrochloride (+17) and (–)-(1S,3S,6S)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol hydrochloride (–17)

The base was released from (17) with dichloromethane/sodium hydroxide solution. The dichloromethane was removed by distillation under vacuum after drying the solution. The racemate was then separated on the chiral HPLC column. The hydrochlorides, which had a melting point of 232°–233° C., were prepared from the enantiomers obtained by reaction with trimethylchlorosilane/water in 2-butanone.

(+17): yield: 42% theoretical $[\alpha]_D^{25} = +14.0^\circ$ ($c=1.12$; methanol)

(–17): yield: 44% theoretical $[\alpha]_D^{25} = -13.5^\circ$ ($c=0.99$; methanol)

Example 20

(1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-hydroxyphenyl)-cyclohexane-1,3-diol hydrochloride (21)

The base was released with dichloromethane/sodium hydroxide solution from compound (17), which was obtained according to Example 18. The dichloromethane was removed by distillation after drying the solution. 8.06 g (28.8 mmole) base were dissolved in 70 ml of dry toluene and slowly added drop-wise to 120 ml (144 mmole) of a 1.2 molar solution of diisobutylaluminium hydride in toluene.

After the addition was complete, the mixture was heated for 8 hours under reflux and then cooled to room temperature. The reaction mixture was diluted with 50 ml toluene, 13 ml ethanol and then 13 ml water were added drop-wise whilst cooling in an ice bath. After stirring for one hour whilst cooling in the ice bath, the reaction mixture was freed from aluminium salts by filtration, and the residue was washed three times with 50 ml ethyl acetate each time. Thereafter, the combined organic phases were dried and the solvent was removed by distillation. 7.3 g of the base (84% theoretical), which had a melting point of 226°–228° C. were obtained with aqueous hydrochloric acid solution in acetone.

Example 21

Enantiomers of (21)

(+)-(1R,3R,6R)-6-dimethylaminomethyl-1-(3-hydroxyphenyl)-cyclohexane-1,3-diol hydrochloride (+21) and (–)-(1S,3S,6S)-6-dimethylaminomethyl-1-(3-hydroxyphenyl)-cyclohexane-1,3-diol hydrochloride (–21)

The base was released from (21) with dichloromethane/ aqueous sodium hydrogen carbonate solution. The dichloromethane was removed by distillation under vacuum after drying the solution. The racemate was then separated on the chiral HPLC column. The hydrochlorides, which had a melting point of 217°–219° C., were prepared from the enantiomers obtained with aqueous hydrochloric acid in acetone.

(+21): yield: 40% theoretical $[\alpha]_D^{25} = +11.3^\circ$ ($c=1.04$; methanol)

(–21): yield: 40% theoretical $[\alpha]_D^{25} = -11.1^\circ$ ($c=1.02$; methanol)

Example 22

(1RS,2RS,5RS)-5-benzyloxy-2-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexanol hydrochloride (22)

The base was released with dichloromethane/sodium hydroxide solution from hydrochloride (17), which was prepared according to Example 18, and the dichloromethane was removed by distillation after drying the solution. 4.0 g (14.3 mmole) of the base obtained were dissolved in 30 ml of dry dimethylformamide and added drop-wise to a suspension of 690 mg sodium hydride (50%) in 5 ml of dry dimethylformamide. The mixture was then stirred for two hours at room temperature. After heating to 50° C., 1.81 ml (14.3 mmole) benzyl chloride were added drop-wise, and the reaction mixture was stirred for a further two hours at 65° C. and for 15 hours at room temperature. The reaction mixture was then poured on to ice water. The aqueous phase was extracted three times with 50 ml ether. The organic phases were combined and dried over sodium sulphate. After removing the solvent by distillation, 4.6 g of crude mixture were obtained and were introduced on to a 4x30 cm column packed with silica gel. Elution with 4/1 ethyl acetate/methanol gave 1.5 g base, from which 1.38 g (24% theoretical) of hydrochloride (22), which had a melting point of 138°–139° C., were obtained with trimethylchlorosilane/water in 2-butanone/diisopropyl ether.

Example 23

(1RS,2RS,5SR)-2-dimethylaminomethyl-1-(3-methoxyphenyl)-5-methyl-cyclohexanol hydrochloride (23)

95 ml (750 mmole) 1-bromo-3-methoxybenzene were dissolved in 425 ml of dry tetrahydrofuran and cooled to –75° C. After adding 469 ml (750 mmole) of 1.6 molar n-butyllithium solution in hexane, the mixture was stirred for one hour at –75° C. 82 g (484 mmole) (2RS,5SR)-dimethylaminomethyl-5-methyl-cyclohexanone, prepared from 3-methyl-cyclohexanone, dimethylamine hydrochloride

ride and paraformaldehyde in glacial acetic acid and dissolved in 120 ml of dry tetrahydrofuran, were then added drop-wise. The reaction mixture was heated to room temperature over 2.5 hours.

For the work-up, 200 ml water were added whilst cooling in an ice bath so that the internal temperature did not exceed 15° C. After phase separation, the aqueous phase was extracted three times with 50 ml ethyl acetate. The combined organic phases were dried over sodium sulphate. After removing the solvent by distillation, the residue (148.3 g) was dissolved in 700 ml acetone and mixed with trimethylchlorosilane/water. 67 g (48% theoretical) of hydrochloride (23), which had a melting point of 173°–175° C., crystallised out at 4°–5° C.

Example 24

Enantiomers of (23)

(+)-(1R,2R,5S)-2-dimethylaminomethyl-1-(3-methoxyphenyl)-5-methyl-cyclohexanol hydrochloride (+23) and (–)-(1S,2S,5S)-2-dimethylaminomethyl-1-(3-methoxyphenyl)-5-methyl-cyclohexanol hydrochloride (–23)

Enantiomers (+23) and (–23) were prepared under the conditions given in Example 19.

(+23): yield: 43% theoretical m.p.: 151°–152° C. $[\alpha]_D^{25} = +36.4^\circ$ (c=1.01; methanol)

(–23): yield: 44% theoretical m.p.: 151°–153° C. $[\alpha]_D^{25} = -37.7^\circ$ (c=1.01; methanol)

Example 25

(+)-(1R,2R,5S)-3-(2-dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol hydrochloride (+24)

Enantiomer (+24) was prepared under the conditions given in Example 20 from the methoxy compound (+23) obtained according to Example 24.

yield: 87% theoretical m.p.: 221°–223° C. $[\alpha]_D^{25} = +31.0^\circ$ (c=1.09; methanol)

Example 26

(–)-(1S,2S,5R)-3-(2-dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol hydrochloride (–24)

Enantiomer (–24) was prepared under the conditions given in Example 20 from the methoxy compound (–23) obtained according to Example 24.

yield: 87% theoretical m.p.: 220°–222° C. $[\alpha]_D^{25} = +30.1^\circ$ (c=1.00; methanol)

Example 27

(1R,2RS,5SR)-3-(2-dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol hydrochloride (25)

1st Step

(1RS,2RS,5SR)-1-(3-benzyloxy-phenyl)-2-dimethylaminomethyl-5-trifluoromethyl-cyclohexanol (26)

43.9 g (167 mmole) 3-benzyloxy-1-bromobenzene, dissolved in 200 ml of dry tetrahydrofuran, were added drop-wise to 4.06 g (167 mmole) magnesium turnings in 40 ml of dry tetrahydrofuran so that the reaction mixture boiled gently. After the addition of 3-benzyloxy-1-bromobenzene was complete, the mixture was heated for one hour under reflux and was thereafter cooled to 5°–10° C. 30.8 g (139 mmole) (2RS,5SR)-2-dimethylaminomethyl-5-trifluoromethyl-cyclohexanone, prepared from 3-trifluoromethyl-cyclohexanone and dimethylaminomethylene chloride in acetonitrile, dissolved in 80 ml of dry tetrahydrofuran, were added at this temperature. The reaction mixture was allowed to stand overnight and was then cooled to 5°–10° C. again. The Grignard solution was decomposed by the addition of 150 ml of 20% ammonium chloride solution. The reaction mixture was diluted with 200

ml of ether, the organic phase was separated off and the aqueous phase was extracted twice with 100 ml ether. The combined organic phases were dried over sodium sulphate. After removing the solvent by distillation, the residue (60.6 g) was introduced on to an 8×50 cm column packed with silica gel and extracted with ethyl acetate/methanol. 27.8 g (50% theoretical) of base (26) were obtained.

2nd Step

(1RS,2RS,5SR)-3-(2-dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol hydrochloride (25)

(25) was obtained, under the conditions given in Example 1 (step 3), from (26) from step 1, in a yield of 64% and with a melting point of 228°–230° C.

Example 28

(1RS,2RS,5SR)-3-(2-dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol hydrochloride (27)

The 5-epimer (27) of compound (25) was prepared, under the conditions given in Example 27, from (2RS,5RS)-2-dimethylaminomethyl-5-trifluoromethyl-cyclohexanone, prepared from 3-trifluoromethyl-cyclohexanone and dimethylaminomethylene chloride in acetonitrile. (27) was obtained in a yield of 27% theoretical and had a melting point of 221°–223° C.

Example 29

(1RS,2RS,5SR)-3-(2-dimethylaminomethyl-1-fluoro-5-trifluoromethyl-cyclohexyl)-phenol hydrochloride (28)

Hydrochloride (28) was obtained in a yield of 24% theoretical and with a melting point of 204°–205° C., under the conditions given in Example 1, steps 2 and 3, from the base (26) obtained according to Example 27 (step 1).

Example 30

(1RS,2RS,5SR)-3-(2-dimethylaminomethyl-1-fluoro-5-trifluoromethyl-cyclohexyl)-phenol hydrochloride (29)

Hydrochloride (29) was obtained in a yield of 22% theoretical and with a melting point of 204° C. under the conditions given in Example 29, from the base (1RS,2RS,5SR)-1-(3-benzyloxy-phenyl)-2-dimethylaminomethyl-5-trifluoromethyl-cyclohexanol obtained according to Example 27 (step 1).

Pharmacological investigations

Testing for analgesia using the tail flick test on mice

The analgesic effectiveness of the compounds according to the invention was investigated in the thermal radiation (tail flick) test on mice using the method of D'Amour and Smith (J. Pharm. Exp. Ther. 72, 74–79 (1941)). NMRI mice with a weight between 20 and 24 g were used for this purpose. The animals were placed in a special test cage and the bases of their tails were exposed to the focused thermal radiation from an electric lamp (Rhema Analgesimeter Type 3010). The lamp intensity was adjusted so that the time from switching on the lamp until the sudden twitching away of the tail (latency of pain) was 3–5 seconds for untreated animals. Before the administration of a compound according to the invention, the animals were pre-tested twice within five minutes and the average value of these measurements was calculated as the pre-test average. The pain measurement was made 20, 40 and 60 minutes after intravenous administration. When the latency of pain increased, the maximum time of exposure was restricted to 12 seconds and an increase in the latent period to >150% of the pre-test average value was assessed as an analgesic effect. In order to determine the dosage-dependency, the respective compound according to the invention was applied in doses increasing logarithmically by a factor of 3–5, which included the threshold and the maximum effective dose each

time. The ED_{50} values were determined from the number of analgesic animals by the method of Litchfield and Wilcoxon (J. Pharm. Exp. Ther. 96, 99-113, (1949)). Calculation of the ED_{50} was made at the effective maximum 20 minutes after intravenous administration of the substance.

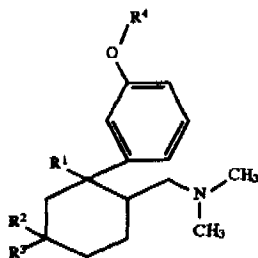
All the compounds according to the invention which were used exhibited a pronounced analgesic effect. The results are summarised in the following Table.

TABLE

Testing of analgesia using the tail flick test on mice		
Example	Compound according to the invention	ED_{50} (mg/kg intravenously)
1	(-1)	2.28
2	(+1)	0.64
5	(+5)	2.78
7	(+6)	10.70
9	(+7)	1.13
10	(-7)	5.90
11	(-8)	4.61
13	(-10)	8.71
14	(-11)	5.01
18	(17)	5.54
19	(+17)	3.93
21	(+21)	7.34
Tramadol	—	13.60

We claim:

1. A 6-dimethylaminomethyl-1-phenyl-cyclohexane compound corresponding to formula I:



wherein

R^1 represents H, OH, Cl or F;

R^2 represents benzyl, CF_3 , OH, $OCH_2-C_6H_5$, $O-C_{1-4}$ -alkyl, Cl or F,

R^3 represents H,

R^4 represents H, CH_3 , $PO(OC_{1-4}$ -alkyl) $_2$, $CO(OC_{1-5}$ -alkyl), $CO-NH-C_6H_4-C_{1-3}$ -alkyl, $CO-C_6H_4-R^5$, $CO-C_{1-5}$ -alkyl, $CO-CH(R^6)-NHR^7$ or an unsubstituted or substituted pyridyl, thienyl, thiazoyl or phenyl group;

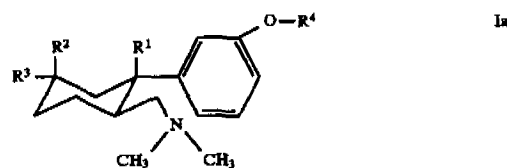
R^5 represents $OC(O)C_{1-3}$ -alkyl in the ortho position or $CH_2-N(R^8)_2$ in the meta or para position, wherein R^8 represents C_{1-4} alkyl or both groups R^8 together with N constitute a 4-morpholino radical, and

R^6 and R^7 are each independently selected from H and C_{1-6} alkyl,

or a pharmaceutically acceptable acid addition salt thereof.

2. A 6-dimethylaminomethyl-1-phenyl-cyclohexane compound according to claim 1, wherein R^1 is H, OH or F.

3. A 6-dimethylaminomethyl-1-phenyl-cyclohexane compound according to claim 1, wherein the compound has the configuration of formula Ia:



4. A pharmaceutical composition comprising a 6-dimethylaminomethyl-1-phenyl-cyclohexane compound according to claim 1, and at least one pharmaceutical carrier or diluent.

5. A method of relieving pain in a mammal comprising administering to said mammal an effective pain relieving amount of a 6-dimethylaminomethyl-1-phenyl-cyclohexane compound according to claim 1.

* * * * *



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⑤④ 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen als pharmazeutische Wirkstoffe

⑤⑦ Es werden 6-Dimethylaminomethyl-1-phenyl-cyclohexan-
verbindungen, Verfahren zu deren Herstellung sowie die
Verwendung dieser Verbindungen in Arzneimitteln beschrie-
ben.

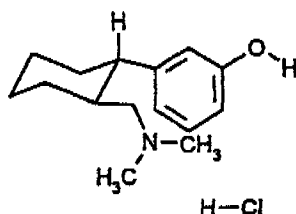
DE 195 25 137 A 1

(-)-(1R,2S)-[2-3-Methoxy-phenyl]-cyclohexylmethyl]-dimethylamin, Hydrochlorid (-6)

Ausgehend von 10,2 g (32 mmol) (-4) wurde unter den in Beispiel 7 angegebenen Bedingungen das Enantiomere (-6) in einer Ausbeute von 75% der Theorie erhalten.

Schmp: 201–203°C (Zersetzung)
 $[\alpha]_D^{25} = -67,1^\circ$ (c = 1,0; Methanol)

Beispiel 9

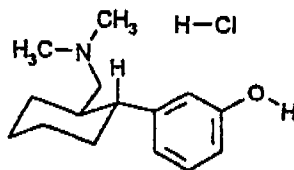


(+)-(1S,2R)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol, Hydrochlorid (+7)

4,3 g (15 mmol) (+6), erhalten gemäß Beispiel 7, wurden mit 100 ml konzentrierter Bromwasserstoffsäure versetzt. Anschließend wurde zwei Stunden unter Rückfluß erhitzt. Nach dem Abkühlen auf Raumtemperatur wurde das Reaktionsgemisch im Wasserstrahlvakuum eingedunstet. Der Rückstand wurde bis zur alkalischen Reaktion mit konzentrierter Natriumhydrogencarbonatlösung versetzt. Nach zweimaliger Extraktion mit je 50 ml Dichlormethan wurden die vereinigten organischen Phasen über Natriumsulfat getrocknet. Anschließend wurde Dichlormethan im Vakuum abdestilliert und der Rückstand (4 g) in 2-Butanon aufgenommen. Nach der Zugabe von Trimethylchlorsilan/Wasser kristallisierten 3,96 g (98% der Theorie) Hydrochlorid (+7) aus.

Schmp: 177–178°C (Zersetzung)
 $[\alpha]_D^{25} = +67,5^\circ$ (c = 1,0; Wasser)

Beispiel 10

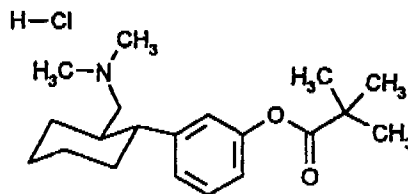


(-)-(1R,2S)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol, Hydrochlorid (-7)

Ausgehend von (-6), hergestellt nach Beispiel 8, wurde das Enantiomere (-7) unter den in Beispiel 9 angegebenen Bedingungen in 95%iger Ausbeute erhalten.

Schmp: 174–176°C (Zersetzung)
 $[\alpha]_D^{25} = -66,1^\circ$ (c = 0,96; Methanol)

Beispiel 11

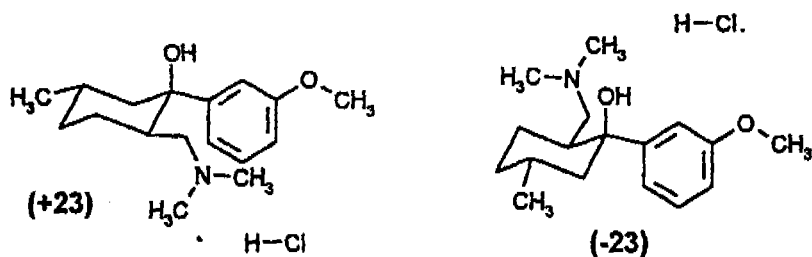


(-)-(1R,2S)-2,2-Dimethyl-propionsäure-3-(2-dimethylaminomethyl-cyclohexyl)-phenylester, Hydrochlorid (-8)

Aus dem Enantiomeren (-7), hergestellt nach Beispiel 10, wurde mit Dichlormethan/wäßriger Natriumhydrogencarbonat-Lösung die Base freigesetzt und nach dem Trocknen der Lösung Dichlormethan destillativ entfernt. 1,7 g (7,3 mmol) der erhaltenen Base wurden in 10 ml trockenem Dimethylformamid gelöst und zu einer Suspension von 400 mg Natriumhydrid (50%ig) in 5 ml trockenem Dimethylformamid getropft. Anschließend wurde noch 30 Minuten bei 50°C gerührt. Nach Abkühlen auf Raumtemperatur wurden 1,03 ml (8,4 mmol)

versetzt. Bei 4–5°C kristallisierten 67 g (48% der Theorie) Hydrochlorid (23) mit einem Schmelzpunkt von 173–175°C aus.

Beispiel 24



Enantiomere von (23)

(+)-(1R,2R,5S)-2-Dimethylaminomethyl-1-(3-methoxy-phenyl)-5-methyl-cyclohexanol, Hydrochlorid (+ 23)

und

(-)-(1S,2S,5R)-2-Dimethylaminomethyl-1-(3-methoxy-phenyl)-5-methyl-cyclohexanol, Hydrochlorid (- 23)

Die Enantiomere (+ 23) und (- 23) wurden unter den in Beispiel 19 angegebenen Bedingungen hergestellt.

(+ 23): Ausbeute: 43% der Theorie

Schmp.: 151–152°C

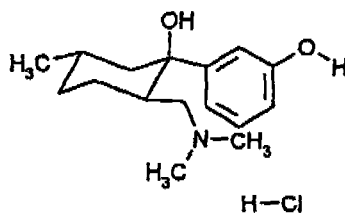
$[\alpha]_D^{25} = +36,4^\circ$ (c = 1,01; Methanol)

(- 23): Ausbeute: 44% der Theorie

Schmp.: 151–153°C

$[\alpha]_D^{25} = -37,7^\circ$ (c = 1,01 Methanol)

Beispiel 25



(+)-(1R,2R,5S)-3-(2-Dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol, Hydrochlorid (+ 24)

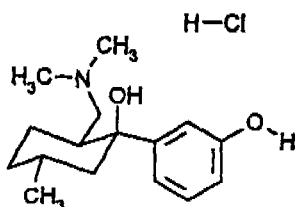
Unter den in Beispiel 20 angegebenen Bedingungen wurde das Enantiomere (+ 24) aus der nach Beispiel 24 erhaltenen Methoxyverbindung (+ 23) hergestellt.

Ausbeute: 87% der Theorie

Schmp.: 221–223°C

$[\alpha]_D^{25} = +31,0^\circ$ (c = 1,09; Methanol)

Beispiel 26



Nomenclature of Carbohydrates (Recommendations 1996)

2-Carb-24

Continued from 2-Carb-23

Contents

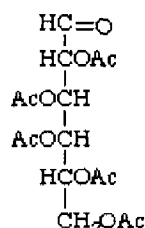
- 2-Carb-24. O-Substitution
 - 24.1. Acyl (alkyl) names
 - 24.2. Phosphorus esters
 - 24.2.1. Phosphates
 - 24.2.2. Phosphonates
 - 24.2.3. Phosphinates
 - 24.3. Sulfates
- References for this section

2-Carb-24. O-Substitution

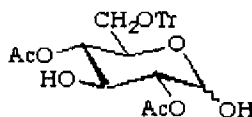
2-Carb-24.1. Acyl (alkyl) names

Substituents replacing the hydrogen atom of an alcoholic hydroxy group of a saccharide or saccharide derivative are denoted as *O*-substituents. The '*O*-' locant is not repeated for multiple replacements by the same atom or group. Number locants are used as necessary to specify the positions of substituents; they are not required for compounds fully substituted by identical groups. Alternative periphrase names for esters, ethers, etc. may be useful for indexing purposes. For cyclic acetals see 2-Carb-28.

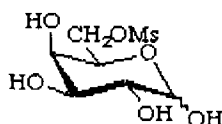
Examples:



Penta-*O*-acetyl-*aldehydo*-D-glucose
or *aldehydo*-D-glucose pentaacetate

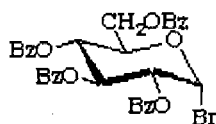


2,4-Di-*O*-acetyl-6-*O*-trityl-D-glucopyranose

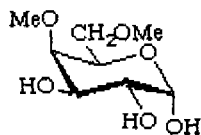


6-*O*-Methanesulfonyl-D-galactopyranose

or D-galactopyranose 6-methanesulfonate



Tetra-*O*-benzoyl- α -D-glucopyranosyl bromide



4,6-Di-*O*-methyl- α -D-galactopyranose

Note. Acyl substituents on anomeric OH are designated (as above) by *O*-acyl prefixes. However, anomeric *O*-alkyl derivatives are named as glycosides (see 2-Carb-33).

2-Carb-24.2. Phosphorus oxoacid esters

2-Carb-24.2.1. Phosphates

Of special biochemical importance are the esters of monosaccharides with phosphoric acid. They are generally termed phosphates (e.g. glucose 6-phosphate). In biochemical use, the term 'phosphate' indicates the phosphate residue regardless of the state of ionization or the counter ions.

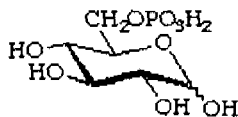
The prefix terms used for phosphate esters in organic nomenclature ([14], p.65) are '*O*-phosphono-' and '*O*-phosphonato-' for the groups $(\text{HO})_2\text{P}(\text{O})-$ and $(\text{O}^-)_2\text{P}(\text{O})-$ respectively, bonded to oxygen.

The term 'phospho-' is used for $(\text{HO})_2\text{P}(\text{O})-$ or ionized forms in a biochemical context (see recommendations for the nomenclature of phosphorus-containing compounds [24]).

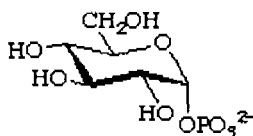
If a sugar is esterified with two or more phosphate groups, the compound is termed bisphosphate, trisphosphate etc. (e.g. fructofuranose 1,6-bisphosphate). The term diphosphate denotes an ester with diphosphoric acid, e.g. adenosine 5'-diphosphate.

Note. In abbreviations, a capital *P* is used to indicate a terminal $-\text{PO}_3\text{H}_2$ group or a non-terminal $-\text{PO}_2\text{H}-$ group (or dehydronated forms).

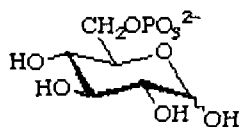
Examples:



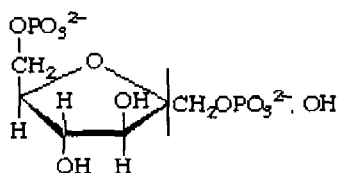
D-Glucopyranose 6-(dihydrogen phosphate)
or 6-*O*-phosphono-D-glucopyranose



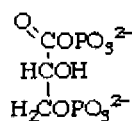
α -D-Glucopyranosyl phosphate
(biochemical usage: glucose 1-phosphate) (Glc1P)



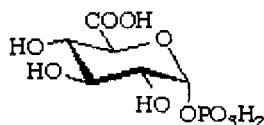
D-Glucopyranose 6-phosphate (often shortened to glucose 6-phosphate)
or 6-O-phosphonato-D-glucopyranose
or 6-phospho-D-glucose (Glc6P) (in a biochemical context)



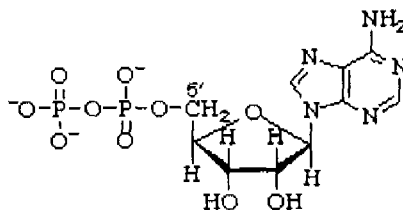
D-Fructofuranose 1,6-bisphosphate
(often shortened to fructose 1,6-bisphosphate)
or 1,6-di-O-phosphonato-D-fructofuranose
or 1,6-bisphospho-D-fructofuranose



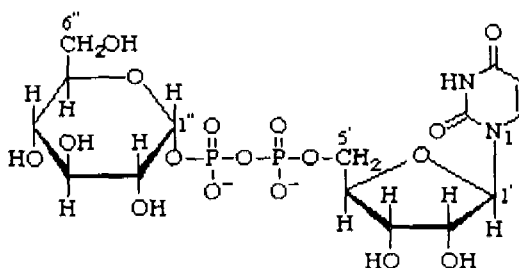
3-O-Phosphonato-D-glyceroyl phosphate
or 3-phospho-D-glyceroyl phosphate
or 1,3-bisphospho-D-glycerate (for biochemical usage)



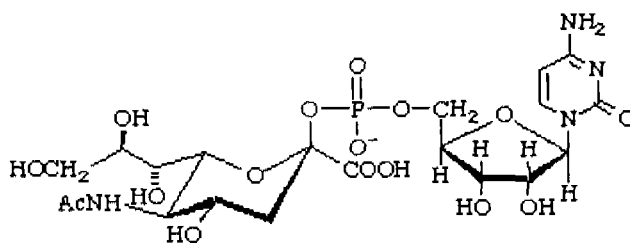
α -D-Glucopyranuronic acid
1-(dihydrogen phosphate)
(biochemical usage: glucuronate 1-phosphate) (GlcA1P)



Adenosine 5'-diphosphate (ADP) or 5'-diphosphoadenosine



Uridine 5'-(α -D-glucopyranosyl diphosphate)
(trivial name uridinediphosphoglucose) (UDP-Glc)

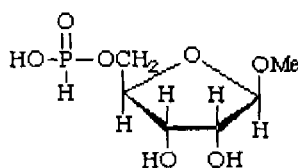


Cytidine 5'-(5-acetamido-3,5-dideoxy-D-glycero- β -D-galacto-non-2-ulopyranosylonic acid monophosphate) (CMP- β -Neu5Ac)

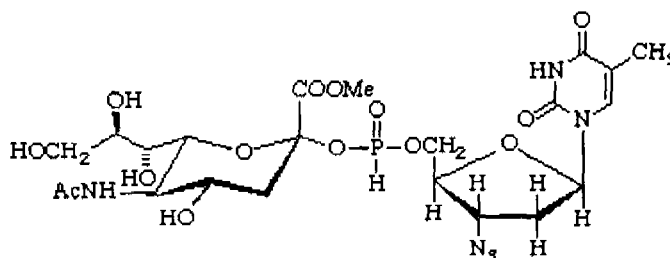
2-Carb-24.2.2. Phosphonates

The following examples illustrate the use of phosphonate terminology for esters of phosphonic acid, HP (O)(OH)₂. For formation of the alternative (substitutive) names, see 2-Carb-31.2.

Examples:



Methyl β -D-ribofuranoside 5-(hydrogen phosphonate)
or methyl 5-deoxy- β -D-ribofuranosid-5-yl hydrogen phosphonate

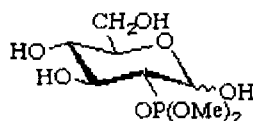


3'-Azido-3'-deoxythymidine 5'-[(methyl 5-acetamido-3,5-dideoxy-L-glycero- α -D-galacto-on-2-ulopyranosylonate) phosphonate]

Derivatives substituted on phosphorus are named by standard procedures [13, 14]; e.g. *P*-methyl derivatives are named as methylphosphonates.

Compounds with a phosphonate group linked by a P-C bond to a carbohydrate residue may be named as glycos-*n*-ylphosphonates (cf. 2-Carb-31.2) or as C-substituted carbohydrates (cf. amino sugars, 2-Carb-14).

Example:



2-Deoxy-2-dimethoxyphosphoryl-D-glucopyranose
(this usage of 'phosphoryl' is given in [13], Section D, Rule 5.68, and [14], p. 65)
or dimethyl 2-deoxy-D-glucopyranos-2-ylphosphonate

150
203

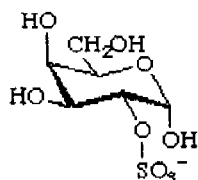
2-Carb-24.2.3. Phosphinates

Esters of phosphinic acid, $\text{H}_2\text{P}(\text{O})(\text{OH})$, are named by the same methods as used for phosphonates. For examples with two P-C bonds see 2-Carb-31.3.

2-Carb-24.3. Sulfates

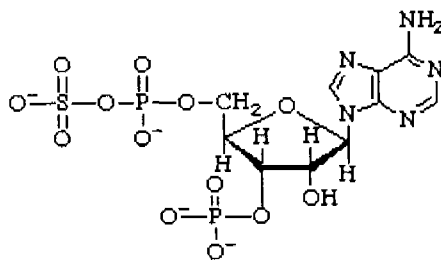
The prefix terms used for sulfuric esters are 'O-sulfo-' and 'O-sulfonato-', for the groups $(\text{HO})\text{S}(\text{O})_2$ - and $(\text{O}^-)\text{S}(\text{O})_2$ - respectively, bonded to oxygen. Sulfates may also be named by citing the word 'sulfate', preceded by the appropriate locant, after the carbohydrate name.

Example:



α -D-Galactopyranose 2-sulfate
or 2-O-sulfonato- α -D-galactopyranose

The mixed sulfuric phosphoric anhydride (PAdoPS or PAPS) of 3'-phospho-5'-adenylic acid is named as an acyl sulfate:



3'-Phospho-5'-adenylyl sulfate (PAPS) 

References

13. IUPAC Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F and H, 1979 Edition, Pergamon Press, Oxford, U.K. Sections E and F are reprinted in ref. 2, pp. 1-18 and 19-26, respectively.

14. Guide to IUPAC Nomenclature of Organic Compounds, Recommendations 1993, Blackwell Scientific Publications, Oxford (1993).

24. IUPAC-IUB Commission on Biochemical Nomenclature (CBN), Nomenclature of phosphorus-containing compounds of biochemical importance (Recommendations 1976), *Hoppe-Seyler's Z. Physiol. Chem.*, **358**, 599-616 (1977); *Eur. J. Biochem.*, **79**, 1-9 (1977); *Proc. Natl. Acad. Sci. USA*, **74**, 2222-

2230 (1977); *Biochem. J.*, **171**, 1-19 (1978); ref. 2. pp. 256-265.

Continue to the next section with 2-Carb-25 and 2-Carb-26 of Nomenclature of Carbohydrates.

Return to Carbohydrates home page.

Revised Nomenclature for Radicals, Ions, Radical Ions and Related Species
(IUPAC Recommendations 1993)

RC-81 Radicals

Continued from RC-80 General Principles

Contents of this section

- **RC-81. Radicals**
 - **RC-81.0.** Introduction
 - **RC-81.1.** Radical centers in parent hydrides
 - **RC-81.1.1.** Monovalent radical centers in saturated acyclic and monocyclic hydrocarbons, and the mononuclear EH_4 parent hydrides of the carbon family.
 - **RC-81.1.2.** Monovalent radical centers in parent hydrides other than those described by RC-81.1.1
 - **RC-81.1.3.** Divalent and trivalent radical centers
 - **RC-81.1.3.1.** Carbenes, carbynes, nitrenes, and silylenes
 - **RC-81.1.3.2.** Divalent and trivalent radical centers other than those described by RC-81.1.3.1
 - **RC-81.1.3.3.** The λ -convention
 - **RC-81.1.4.** Nondetachable hydro prefixes vs. added (indicated) hydrogen
 - **RC-81.1.5.** A number of trivial and abbreviated names

RC-81. Radicals [replaces C-81 (ref 1)]

RC-81.0. Introduction. For the purposes of organic nomenclature, a parent radical is a molecular compound formally derived by the removal of one or more hydrogen atoms from one or more atoms of a parent hydride, a parent compound, or a hydro derivative of either. An atom at which the resulting (nonbonding) electron(s) is(are) considered to reside is called a radical center. An atom with one free (nonbonding) electron is a monovalent radical center; an atom with two (or three) free (nonbonding) electrons, which may be paired, i.e., having antiparallel spins (singlet), or unpaired, i.e., having parallel spins (triplet), but which cannot be nonbonding electron pairs ("lone pairs") of that atom in the parent structure is called a divalent (or trivalent) radical center. A parent radical with two or more monovalent radical centers is called a diradical, triradical, etc.

RC-81.1. Radical centers in parent hydrides

RC-81.1.1. Monovalent radical centers in saturated acyclic and monocyclic hydrocarbons, and the mononuclear EH_4 parent hydrides of the carbon family. A monovalent radical center derived formally by removal of one hydrogen atom from a terminal atom of a saturated, unbranched acyclic hydrocarbon; from an atom of a saturated monocyclic hydrocarbon; or from any of the mononuclear parent hydrides methane (CH_4), silane (SiH_4), germane (GeH_4), stannane (SnH_4), or plumbane (PbH_4) is named by replacing the "-ane" ending of the name of the parent hydride by "-yl" (ref 4f, 10i).

Examples:



methyl

$\text{H}_3\text{Ge}^\bullet$ germyl

$\text{CH}_3-\text{CH}_2-\text{CH}_2^\bullet$
3 2 1 propyl

$\square\text{CH}^\bullet$ cyclobutyl

$\text{CH}_3-\text{CH}^\bullet-\text{CH}_3$ 1-methylethyl propan-2-yl (see RC-81.1.2 and RC-80.8)
isopropyl (traditional name; see item 1, Appendix, List A)

RC-81.1.2. Monovalent radical centers in parent hydrides other than those described by RC-81.1.1. A radical center formally derived by the removal of one hydrogen atom from any position of a parent hydride, except as provided by RC-81.1.1 above, is named by adding the operational suffix "-yl" to the name of the parent hydride, eliding the final "e" of the name of the parent hydride, if present. The trivial name phenyl (ref 10j), and the abbreviated (or contracted) names naphthyl, anthryl, phenanthryl (ref 10k); furyl, pyridyl, piperidyl, quinolyl, isoquinolyl, thienyl (ref 3f); and hydrazyl (ref 2r) are retained. Locants describing the position of the radical center for these abbreviated names are placed in front of the names (see RC-80.1).

Note 1. This recommendation is consistent with the generalized principles for naming and numbering acyclic substituent prefixes as given in Section D of the 1979 IUPAC Organic Rules (ref 4c, 10f) rather than the principles of Section A (ref 10g) and the ACS silicon rules (ref 12a), where the principal chain must terminate at the free valence position (see also RC-80.8).

Note 2. The systematic names phosphane and arsane (ref 4g, 6b) must be used for naming the radicals derived from the mononuclear parent hydrides PH_3 and AsH_3 , according to this recommendation, because use of the traditional names phosphine and arsine (ref 4g, 6b) will generate the names phosphinyl (ref 12b) and arsinyl (ref 13b), which are traditional prefix names for the oxo phosphoric and arsenic acid groups $\text{H}_2\text{P}(\text{O})^-$ and $\text{H}_2\text{As}(\text{O})^-$, respectively, as substituents. Even though the names phosphinoyl and arsinoyl are recommended in the 1979 IUPAC Organic Rules for these groups (ref 4h), ambiguity would still exist.

Note 3. The traditional names phosphino, arsino, stibino, and bismuthino (ref 4i) are less acceptable alternative names for the radicals $\text{H}_2\text{P}^\bullet$, $\text{H}_2\text{As}^\bullet$, $\text{H}_2\text{Sb}^\bullet$, and $\text{H}_2\text{Bi}^\bullet$.

Note 4. The name "aminyl" for the parent radical $\text{H}_2\text{N}^\bullet$ used in the 1979 IUPAC Organic Rules (ref 2r) is continued in these recommendations as an alternative to "azanyl", derived from the parent hydride name azane (ref 6b, 14), even though "amine" is not used as a parent hydride name for NH_3 herein (see also footnote to Table 2 in RC-80.9.1).

Note 5. Although the name "amine" would be quite consistent with parent hydride names, such as phosphine and arsine, and is used as such by Beilstein, it is not used as a parent hydride name in these recommendations because it has also been added to the name of a radical to form the name of a parent compound (ref 15), for example butylamine. In these recommendations, the term "amine" is used only as a suffix to denote the attachment of the $-\text{NH}_2$ group to a parent hydride, for example, pyridin-2-amine.

Note 6. The names of the radicals $\text{HO}^\bullet$, and $\text{HO-O}^\bullet$ are hydroxyl (ref 6c) and

hydroperoxyl (ref 2s), respectively, but, in keeping with tradition, are not used as parent radical names in these recommendations. For names of such "substituted" radicals, see RC-81.2.4.

Examples:



sulfanyl [trivial name: mercapto (ref 2k)]

Note. The name mercapto is not used as a parent radical name in these recommendations. For names of such "substituted" radicals, see RC-81.2.5.

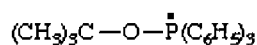


azanyl
aminyl
(traditional name: amino)

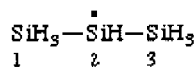
Note. The trivial name amidogen is used for $\text{H}_2\text{N}^\bullet$ in CAS index nomenclature (ref 13c)



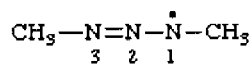
boranyl (previously (ref 4j) and in inorganic nomenclature recommendations (ref 6d), boryl)



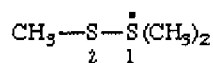
[(2-methylpropan-2-yl)oxyltriphenyl- λ^5 -phosphanyl
(ref 16) (see RC-80.8)
tert-butoxytriphenylphosphoranyl (ref 4k) (see RC-80.8)



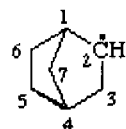
trisilan-2-yl



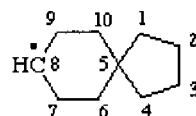
1,3-dimethyltriaz-2-en-1-yl



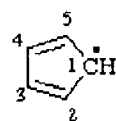
1,1,2-trimethyl-1 λ^4 -disulfan-1-yl (ref 16)



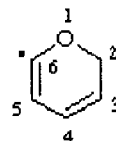
bicyclo[2.2.1]heptan-2-yl
[previously (ref 10m), bicyclo[2.2.1]hept-2-yl]



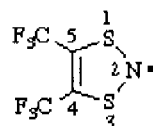
spiro[4.5]decan-8-yl
[previously (ref 10n), spiro[4.5]dec-8-yl]



cyclopenta-2,4-dien-1-yl

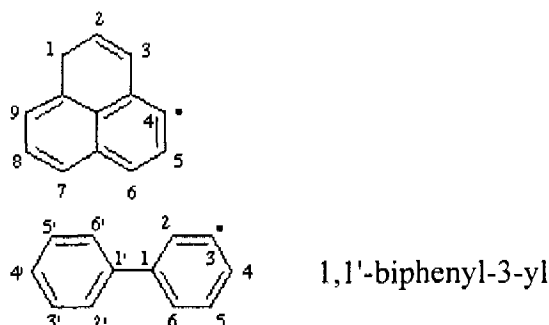


2H-pyran-6-yl



4,5-bis(trifluoromethyl)-1,3,2-dithiazol-2-yl

1H-phenalen-4-yl



RC-81.1.3. Divalent and trivalent radical centers in a neutral parent hydride are derived formally by the removal of two or three hydrogen atoms from the same skeletal atom of a parent hydride, a parent compound, or a hydro derivative of either.

Nomenclature methods for describing divalent and trivalent radical centers are complicated by current definitions of the term "radical" (ref 7, 17). According to these definitions and many experts in the field, the free (nonbonding) electrons of a radical must be unpaired and therefore a divalent radical center in which the free (nonbonding) electrons are paired (singlet state) is not considered to be a radical. Hence, there is objection to the use of "radical suffixes", such as "-diyl" and "-ylidene", to describe such divalent radical centers. However, in these recommendations, the radical suffixes "-ylidene" and "-ylidyne" are used to describe divalent and trivalent radical centers regardless of the electronic state of the free (nonbonding) electrons. Alternative suffixes, such as "-ylidene" and "-diyl", should not be used to differentiate between a singlet and a triplet state. If necessary, such a distinction should be made by adding the separate word "singlet" or "triplet" to the name of the divalent radical.

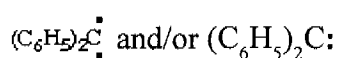
RC-81.1.3.1. Carbenes, carbynes, nitrenes, and silylenes. Divalent radical centers derived formally by the removal of two hydrogen atoms from the mononuclear parent hydrides CH_4 , NH_3 , and SiH_4 , i.e., $\text{H}_2\dot{\text{C}}$ and/or $\text{H}_2\text{C}\cdot$; $\text{H}\dot{\text{N}}$ and/or $\text{HN}\cdot$; and $\text{H}_2\dot{\text{Si}}$ and/or $\text{H}_2\text{Si}\cdot$, respectively, may be named carbene (or methylene) (ref 2t), nitrene [or aminylene (ref 2r)], and silylene, respectively. The mononuclear parent hydride derived formally by removal of three hydrogen atoms from CH_4 , i.e., $\text{H}\dot{\text{C}}$ and/or $\text{HC}\cdot$, may be named carbyne. Derivatives of these parent hydrides are named according to the usual principles of substitutive nomenclature.

Note 1. The name nitrene is widely used in the literature; the name imino also has been used. The trivial name imidogen is used in CAS index nomenclature (ref 13c).

Note 2. Because the compound $\text{CH}_2=\text{SiH}_2$ is quite well known in the literature as silene (ref 18), this name cannot be used for the mononuclear parent radical $\text{H}_2\dot{\text{Si}}$ and/or $\text{H}_2\text{Si}\cdot$. The name "silylene" (ref 12a) is widely used in the literature and in CAS index nomenclature (ref 13c).

Note 3. A generally accepted principle of substitutive nomenclature does not allow a structure containing a carbene carbon atom in a carbon chain or ring to be named as a derivative of carbene or methylene; therefore, such structures should be named according to RC-81.1.3.2 or RC-81.1.3.3, below. However, such radicals are included in the general class known as carbenes.

Examples:



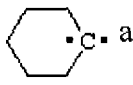
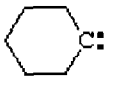
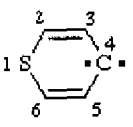
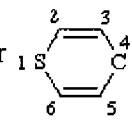
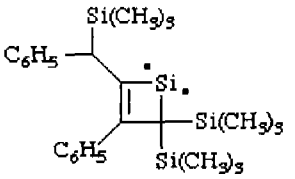
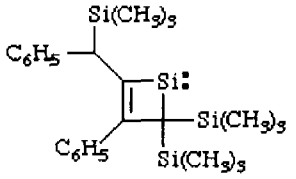
diphenylcarbene
diphenylmethylene

$(\text{CH}_3\text{-O-CO})_2\dot{\text{C}}$ and/or $(\text{CH}_3\text{-O-CO})_2\text{C}:$	bis(methoxycarbonyl)carbene bis(methoxycarbonyl)methylene
$\text{CH}_3\text{-}\dot{\text{N}}$ and/or $\text{CH}_3\text{-N}:$	methylnitrene methyaminylene
$\text{C}_6\text{H}_5\text{-CH}_2\text{-}\dot{\text{Si}}\text{H}$ and/or $\text{C}_6\text{H}_5\text{-CH}_2\text{-}\ddot{\text{Si}}\text{H}$	benzylsilylene
$\text{C}_6\text{H}_5\text{-}\dot{\text{C}}$ and/or $\text{C}_6\text{H}_5\text{-C}:$	phenylcarbyne

RC-81.1.3.2. Divalent and trivalent radical centers other than those described by RC-81.1.3.1 derived formally by the removal of two or three hydrogen atoms from the same skeletal atom of a parent hydride or a hydro derivative may be described by using an operational suffix "-ylidene" or "-ylidyne" in the same way as prescribed for the suffix "-yl" in RC-81.1.1 and RC-81.1.2.

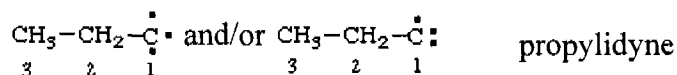
Note. Although the traditional names methylene (ref 2t), aminylene (ref 2r), and silylene (ref 12a), are used in RC-81.1.3.1 above, the suffix "-ylene" for describing other divalent radical centers is no longer recommended (see RC-80.5).

Examples:

$\text{HP}\dot{\text{P}}$ and/or $\text{HP}:$	phosphanylidene [the traditional name is phosphinidene (ref 12b), but phosphinediyl according to the 1979 IUPAC Organic Rules (ref 4m)]
$\text{H}_2\text{N}-\dot{\text{N}}$ and/or $\text{H}_2\text{N}-\text{N}:$ _{2 1 2 1}	diazanylidene hydrazinylidene (traditional parent hydride name (ref 14)) (trivial name: hydrazono (ref 2u)) (not aminonitrene)
$\text{H}_2\text{P}-\dot{\text{P}}$ and/or $\text{H}_2\text{P}-\text{P}:$ _{2 1 2 1}	diphosphanylidene
$\text{CH}_2=\text{CH}-\dot{\text{C}}\text{H}$ and/or $\text{CH}_2=\text{CH}-\ddot{\text{C}}\text{H}$ _{3 2 1 3 2 1}	prop-2-en-1-ylidene
$\text{C}_6\text{H}_5\text{-CH}_2\text{-}\dot{\text{C}}\text{-Cl}$ and/or $\text{C}_6\text{H}_5\text{-CH}_2\text{-}\ddot{\text{C}}\text{-Cl}$ _{2 1 2 1}	1-chloro-2-phenylethylidene (not benzylchlorocarbene)
$\text{CF}_3\text{-CO}-\dot{\text{C}}\text{-CF}_3$ and/or $\text{CF}_3\text{-CO}-\ddot{\text{C}}\text{-CF}_3$	1,1,1,4,4,4-hexafluoro-3-oxobutan-2-ylidene (see RC-80.8) [3,3,3-trifluoro-2-oxo-1-(trifluoromethyl)propylidene (see RC-80.8)]
 and/or 	cyclohexylidene
 and/or 	4H-thiopyran-4-ylidene
 and/or 	3-phenyl-2-[phenyl(trimethylsilyl)methyl]-4,4-bis(trimethylsilyl)-1-silacyclobut-2-en-1-ylidene [replacement name (ref 3g)]

3-phenyl-4-[phenyl(trimethylsilyl)methyl]-2,2-bis(trimethylsilyl)-1,2-dihydrosilet-1-ylidene
(Hantzsch-Widman name (ref 3e, 11))

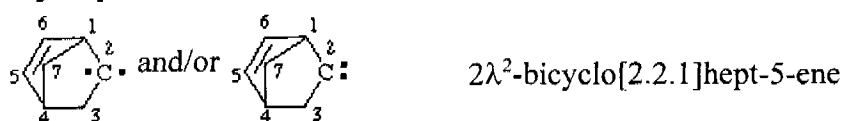
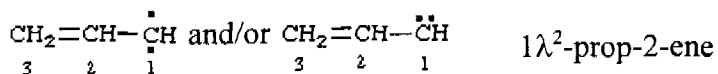
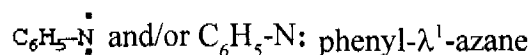
Note. The trivial name "benzyl" is not used as a substituent prefix when α -substituted (see footnote to item 17 in the Appendix, List A).



RC-81.1.3.3. The λ -convention (ref 16) (alternative to RC-81.1.3.1 and RC-81.1.3.2). Divalent and trivalent radical centers in a parent hydride formally derived by the removal of two or three hydrogen atoms from the same skeletal atom in a standard valence state may be described by the λ -convention (ref 16). Locants for the radical centers are followed by the symbol λ^n , where n is the bonding number of the skeletal atom, i.e., the sum of the total number of valence bonds to adjacent skeletal atoms, if any, and the number of attached hydrogen atoms.

Note. Use of the λ -convention (ref 16) to describe a radical center derived by the loss of two hydrogen atoms from a skeletal atom that is in a valence state higher than the standard one is ambiguous because it would not be clear whether the name was describing a standard valence state or a divalent radical center derived from the higher valence state. However, the use of the λ -convention to describe a radical center that is in a lower valence state than the standard one may be useful for naming radical ions (see RC-85.2). 

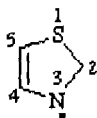
Examples:



RC-81.1.4. Nondetachable hydro prefixes vs. added (indicated) hydrogen. A radical center at a position in a cyclic parent hydride having the maximum number of noncumulative double bonds where there is an insufficient number of hydrogen atoms to apply directly the recommendations for the use of "-yl" or "-ylidene" given above is derived formally from a dihydro derivative of the cyclic parent hydride. Such a radical center may be described by using nondetachable hydro prefixes (ref 2f) (see also RC-80.2) or by applying the principle of indicated (added) hydrogen (ref 2g) (see RC-80.3). In the latter method, the "hydro" derivative is described by specifying the hydrogen atom of a dihydro pair that remains after the radical center is created by citing an italic capital H (*H*) and the locant of the skeletal atom at which the hydrogen atom resides, both enclosed in a set of parentheses and inserted into the name of the corresponding unsaturated parent hydride immediately after the locant for the radical center.

Note. This procedure is exactly analogous to the use of "indicated hydrogen" to describe saturated ring positions that remain after the introduction of suffixes for principal characteristic groups, such as "-one", into the name of a parent ring or ring system that otherwise expresses the maximum number of noncumulative double bonds (ref 2g).

Example:



2,3-dihydrothiazol-3-yl
thiazol-3(2H)-yl

RC-81.1.5. A number of trivial and abbreviated names, other than those given in RC-81.1.2, above, have a long and well-established usage for expressing substituent groups as prefixes and for naming radicals; therefore they are recognized throughout the 1979 IUPAC organic Rules (ref 1). Although each of these groups can be named easily by the systematic methods given above, their trivial or abbreviated names are acceptable as names for radicals and are given in the Appendix.

References for this section

1. International Union of Pure and Applied Chemistry. Organic Chemistry Division. Commission on Nomenclature of Organic Chemistry, *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F and H*, 1979 ed., Pergamon Press, Oxford, 1979, 559 p.

2. Reference 1, Section C, pp. 79-322: [a] Subsection C-0.8, pp. 133-43; [f] Rule C-16.1, p. 108; [g] Rule C-315.1, p. 172; [k] Rule C-502, pp. 210-1; [r] Rule C-81.2, p. 134; [s] Rules C-218.1, p. 161; and C-81.1, pp. 133-4; [t] Rule C-81.1, pp. 133-4; [u] Rule C-922.1, p. 288.

3. Reference 1, Section B, pp. 53-76: [e] Rule B1.1, pp. 53-5; [f] Rule B-5.11, p. 70; [g] Rule B-4, p. 68-70.

4. Reference 1, Section D, pp. 323-471: [c] Rule D-4.14, p. 374-5, esp. footnote, p. 374; and Rule D-6.12, pp. 409-10, Note. p. 410; [g] Rule D-5.11, p. 384, footnote; [h] Rule D-5.66, pp. 403-4; [i] Rule D-5.12, pp. 385-6; [j] Rule D-7.3, pp. 433-4; [k] Rule D-5.74, P. 407; [m] Rule D-5.14, p. 387.

6. International Union of Pure and Applied Chemistry. Inorganic Chemistry Division. Commission on Nomenclature of Inorganic Chemistry, *Nomenclature of Inorganic Chemistry, Recommendations 1990*, G. J. Leigh, ed., Blackwell Scientific Publications, Oxford, England, 1990, 289 p. [b] Section I-7.2.2.1, pp. 83-5, Table 17.2; [c] Section I-8.4.2.2, p. 113; [d] Section I-8.4.2.3, pp. 114-5.

7. International Union of Pure and Applied Chemistry, *Compendium of Chemical Terminology (IUPAC Recommendations)*, V. Gold, K. L. Loening, A. D. McNaught, P. Sehmi, compilers, Blackwell Scientific Publications, Oxford, 1987, 456 p.

10. Reference 1, Section A, pp. 5-52: [f] Rule A-4, p. 14, ** footnote; [g] Rules A-1.2, p. 5; A-2.25, pp. 6-7; A-3.5, p. 13; A-4.1, p. 14; and A-4.4, p. 15; [i] Rules A-1.2, p. 5; and A-11.2, p. 16; [j] Rule A-11.4, p. 17; [k] Rule A-24.2, p. 29-30, Exceptions, p. 30; [m] Rule A-31.4, p. 32; [n] Rule A-43, pp. 41-2.

11. International Union of Pure and Applied Chemistry. Organic Chemistry Division. Commission on Nomenclature of Organic Chemistry, *Revision of the Extended Hantzsch-Widman System of Nomenclature for Heteromonocycles*, Recommendations 1982, *Pure Appl. Chem.* **55**, 409-16, 1983; [a] *ibid.* Recommendation RB-1.5; [b] *ibid.* Recommendation RB-1.2.

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17. International Union of Pure and Applied Chemistry. Organic Chemistry Division, (a) Commission on Physical Organic Chemistry, Glossary of Terms Used in Physical Organic Chemistry, Recommendations 1982, *Pure Appl. Chem.* **55**, 1281-371 (1983); (b) Commission on Photochemistry, "Glossary of Terms Used in Photochemistry, Recommendations 1988", *Pure Appl. Chem.* **60**, 1055-106 (1988).

18. See, for example, G. Raabe and J. Michl, *Chem. Rev.* **85**, 419-509 (1985), Part III, pp. 442-84.

Continue with RC-81.2.Radical centers on characteristic groups

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⑫ Offenlegungsschrift
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㉖ 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen als pharmazeutische Wirkstoffe

㉗ Es werden 6-Dimethylaminomethyl-1-phenyl-cyclohexan-
verbindungen, Verfahren zu deren Herstellung sowie die
Verwendung dieser Verbindungen in Arzneimitteln beschrie-
ben.

DE 195 25 137 A 1

Beschreibung

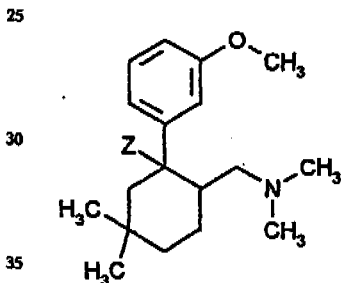
Die Erfindung betrifft 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen, Verfahren zu deren Herstellung sowie die Verwendung dieser Verbindungen in Arzneimitteln.

Die Behandlung chronischer und nicht chronischer Schmerzzustände hat in der Medizin eine große Bedeutung. Zur Zeit besteht ein weltweiter Bedarf an zusätzlicher, nicht ausschließlich opioider, aber gut wirksamer Schmerztherapie. Der dringende Handlungsbedarf für eine patientengerechte und zielorientierte Behandlung chronischer und nicht chronischer Schmerzzustände, wobei hierunter die erfolgreiche und zufriedenstellende Schmerzbehandlung für die Patienten zu verstehen ist, dokumentiert sich in der großen Anzahl von wissenschaftlichen Arbeiten, die auf dem Gebiet der angewandten Analgetik bzw. der Grundlagenforschung zur Nociception in letzter Zeit erschienen sind.

Opiode werden seit vielen Jahren zur Schmerzbehandlung eingesetzt, obwohl sie eine Reihe von Nebenwirkungen, beispielsweise Abhängigkeit, Atemdepression, gastrointestinale Hemmwirkung und Obstipation, hervorrufen. Sie können daher nur unter besonderen Vorsichtsmaßnahmen, beispielsweise speziellen Verordnungsvorschriften über einen längeren Zeitraum oder in höheren Dosierungen gegeben werden (Goodman, Gilman "The Pharmacological Basis of Therapeutics" Pergamon Press, New York, 1990).

Tramadolhydrochlorid — (1RS,2RS)-2[(Dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol, Hydrochlorid — nimmt unter den zentral wirksamen Analgetika eine Sonderstellung ein, da dieser Wirkstoff eine starke Schmerzhemmung ohne die für Opiode bekannten Nebenwirkungen hervorruft (J. Pharmacol. Exp. Ther. 267, 33 (1993)). Tramadol ist ein Racemat und besteht aus gleichen Mengen an (+)- und (-)-Enantiomer. In vivo bildet der Wirkstoff den Metaboliten O-Desmethyl-tramadol, der ebenfalls als Enantiomerenmisch vorliegt. Untersuchungen haben ergeben, daß sowohl die Enantiomeren von Tramadol als auch die Enantiomeren der Tramadolmetabolite an der analgetischen Wirkung beteiligt sind (J. Pharmacol. Exp. Ther. 260, 275 (1992)).

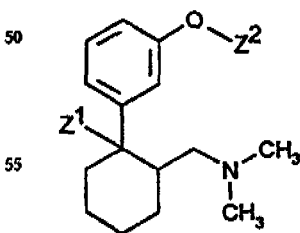
Aus Chem. Pharm. Bull. 32, 2279 (1984) sind Verbindungen der Formel



bekannt, in der Z H oder OH bedeutet. Diese Substanzen besitzen eine analgetische Wirkung, die im Vergleich zu Tramadol deutlich schwächer ist.

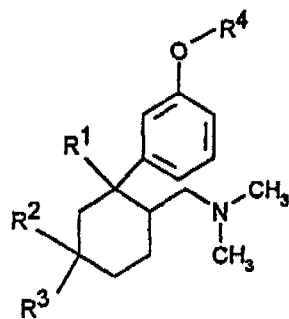
Die der Erfindung zugrundeliegende Aufgabe bestand in der Entwicklung von analgetisch wirksamen Substanzen, die sich zur Behandlung starker Schmerzen eignen, ohne die für Opiode typischen Nebenwirkungen hervorzurufen. Darüber hinaus sollten die zu entwickelnden Substanzen nicht die während der Behandlung mit Tramadol in manchen Fällen auftretenden Nebenwirkungen, beispielsweise Übelkeit und Erbrechen, besitzen.

Es wurde nun gefunden, daß die an die zu entwickelnden Substanzen gestellten Anforderungen von bestimmten 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen erfüllt werden. Diese Verbindungen zeichnen sich durch eine ausgeprägte analgetische Wirkung aus, die im Vergleich zu Tramadol und zu den aus Arzneim.-Forsch./Drug Res. 28 (IA) 107 (1978) bekannten Verbindungen der Formel



mit Z¹ H, OH oder Cl und Z² CH₃ oder Z¹ OH und Z² H deutlich verstärkt ist.

Gegenstand der Erfindung sind dementsprechend 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen der Formel I



in der

R^1 H, OH, Cl oder F ist,

R^2 und R^3 gleich oder verschieden sind und H, C_1-4 -Alkyl, Benzyl, CF_3 , OH, $OCH_2-C_6H_5$, $O-C_1-4$ -Alkyl, Cl oder F bedeuten mit der Maßgabe, daß wenigstens einer der Reste R^2 oder R^3 H bedeutet,

R^4 H, CH_3 , $PO(C_1-4-Alkyl)_2$, $CO(OC_1-5-Alkyl)$, $CO-NH-C_6H_4-C_1-3-Alkyl$, $CO-C_6H_4-R^5$, $CO-C_1-5-Alkyl$, $CO-CHR^6-NHR^7$ oder eine unsubstituierte oder substituierte Pyridyl-, Thienyl-, Thiazoyl- oder Phenylgruppe bedeutet,

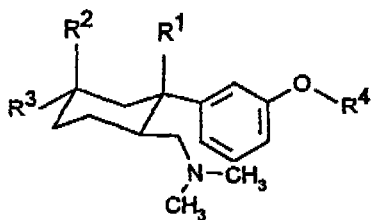
R^5 $OC(O)C_1-3-Alkyl$ in ortho-Stellung oder $CH_2-N(R^8)_2$ in meta- oder para-Stellung, wobei R^8 C_1-4 -Alkyl oder beide Reste R^8 zusammen mit N den 4-Morpholino-Rest darstellen, bedeutet, und

R^6 und R^7 gleich oder verschieden sind und H oder C_1-6 -Alkyl bedeuten,

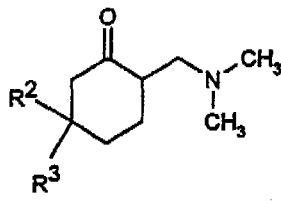
mit der Maßgabe, daß wenn beide Reste R^2 und R^3 H bedeuten, R^4 nicht CH_3 ist, wenn R^1 H, OH oder Cl bedeutet oder R^4 nicht H ist, wenn R^1 OH bedeutet,

in Form ihrer Basen oder Salze von physiologisch verträglichen Säuren.

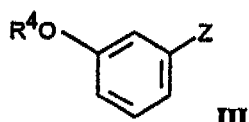
Bevorzugte 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen entsprechen der Formel I mit R^1 H, OH oder F. Besonders bevorzugt werden 6-Dimethylaminomethyl-1-phenylcyclohexanverbindungen in Form ihrer Diastereomeren mit der Konfiguration der Formel Ia, in der der Phenylring und die Dimethylaminomethyl-Gruppe trans zueinander stehen:



Weiterer Erfindungsgegenstand ist ein Verfahren zur Herstellung von 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen der Formel I, in der R^1 OH bedeutet und R^2 und R^3 gleich oder verschieden sind und H, C_1-4 -Alkyl, Benzyl, CF_3 , Cl oder F bedeuten mit der Maßgabe, daß mindestens einer der Reste R^2 oder R^3 H ist und R^4 H, CH_3 oder eine unsubstituierte oder substituierte Pyridyl-, Thienyl-, Thiazoyl- oder Phenylgruppe bedeutet, mit der Maßgabe, daß R^4 weder CH_3 noch H ist, wenn beide Reste R^2 und R^3 H bedeuten, wobei das Verfahren dadurch gekennzeichnet ist, daß ein β -Dimethylaminoketon der Formel II



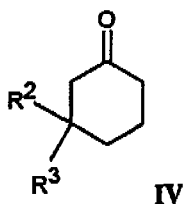
mit einer metallorganischen Verbindung der Formel III



in der Z MgCl, MgBr, MgI oder Li bedeutet, zu einer Verbindung der Formel I umgesetzt wird.

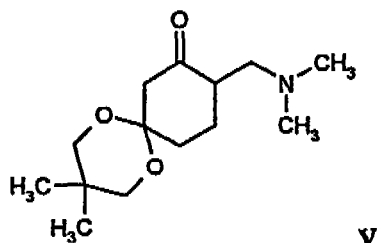
Die Reaktion eines β -Dimethylaminoketons mit einer Grignard-Verbindung der Formel III oder mit einer lithiumorganischen Verbindung der Formel III kann in einem aliphatischen Ether, beispielsweise Diethylether und/oder Tetrahydrofuran, bei einer Temperatur zwischen -70°C und $+60^{\circ}\text{C}$ durchgeführt werden. Lithiumorganische Verbindungen der Formel III lassen sich durch Umsetzung einer Verbindung der Formel III, in der Z Cl Br oder I bedeutet, mit beispielsweise einer n-Butyllithium/Hexan-Lösung durch Halogen/Lithiumaustausch erhalten. Bei der Umsetzung eines β -Dimethylaminoketons der Formel II mit einer metallorganischen Verbindung werden 6-Dimethylaminomethyl-1-phenylcyclohexanverbindungen mit der bevorzugten relativen Konfiguration der Formel Ia erhalten.

β -Dimethylaminoketone der Formel II sind aus Ketonen der Formel IV

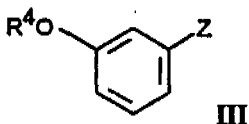


durch Umsetzung mit Dimethylaminohydrochlorid und Formaldehyd in Eisessig oder in einem C_1 -4-Alkylalkohol oder durch Umsetzung mit Dimethylammoniummethylenchlorid in Acetonitril unter Acetylchloridkatalyse erhältlich (Synthesis 1973, 703; Tietze, Eicher in "Reaktionen und Synthesen im Organisch-Chemischen Praktikum", Thieme-Verlag, Stuttgart 1991, Seite 189). Die bei der Aminomethylierungsreaktion entstehenden diastereomeren β -Dimethylaminoketone können entweder durch säulenchromatographische Trennung oder durch fraktionierte Kristallisation ihrer Hydrochloride aus einem organischen Lösungsmittel, beispielsweise 2-Butanon und/oder Aceton, diastereomerenrein erhalten werden.

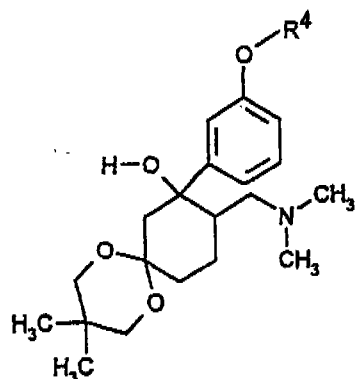
Ferner ist Erfindungsgegenstand ein Verfahren zur Herstellung von 6-Dimethylaminomethyl-1-phenylcyclohexanverbindungen der Formel I, in der R^1 OH ist, einer der Reste R^2 oder R^3 H und der andere OH, $\text{O}-\text{C}_1$ -4-Alkyl oder $\text{OCH}_2\text{C}_6\text{H}_5$ bedeuten und R^4 H, CH_3 oder eine unsubstituierte oder substituierte Pyridyl-, Thienyl-, Thiazoyl- oder Phenylgruppe bedeutet, welches dadurch gekennzeichnet ist, daß man ein β -Dimethylaminoketon mit spirocyclischer Acetalstruktur der Formel V



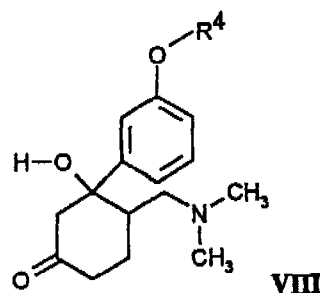
mit einer metallorganischen Verbindung der Formel III



in der Z MgCl, MgBr, MgI oder Li bedeutet, zu einer Verbindung der Formel VI



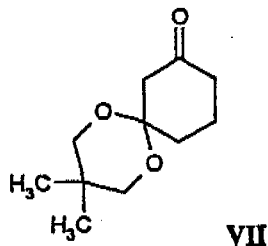
umsetzt, die erhaltene Verbindung der Formel VI durch protonen-katalysierte Deacetalisierung in das entsprechende Ketonderivat der Formel VIII



überführt und das erhaltene Ketonderivat anschließend mit einem komplexen Alkalimetallhydrid zu einer Verbindung der Formel I, in der einer der Reste R² oder R³ OH bedeutet, reduziert und gewünschtenfalls die durch Reduktion erhaltene Verbindung der Formel I nach Überführung in ein Alkalisalz mit einem C₁₋₄-Alkyl- oder Benzylhalogenid in eine Verbindung der Formel I, in der einer der Reste R² oder R³ O-C₁₋₄-Alkyl oder OCH₂C₆H₅ bedeutet, überführt.

Die Reduktion einer Verbindung der Formel VIII wird vorzugsweise mit Natriumborhydrid oder Lithiumaluminiumhydrid in einem organischen Lösungsmittel, beispielsweise Tetrahydrofuran, Diethylether und/oder einem C₂₋₄-Alkylalkohol durchgeführt. Sofern nach dem erfindungsgemäßen Verfahren eine Verbindung mit R² oder R³ OC₁₋₄-Alkyl oder OCH₂Ph erhalten werden soll, wird die durch Reduktion erhaltene Verbindung mit einem Alkalihydrid, beispielsweise Natrium- und/oder Kaliumhydrid, in einem Lösungsmittel, wie Dimethylformamid in die entsprechende Alkalisalzverbindung überführt und anschließend mit einem C₁₋₄-Alkyl- oder Benzylhalogenid umgesetzt.

β-Dimethylaminoketone mit spirocyclischer Acetalstruktur der Formel V sind aus 9-Dimethylaminomethyl-3,3-dimethyl-1,5-dioxa-spiro[5.5]undecan-8-on der Formel VII



welches durch gezielte Monoacetalisierung von Cyclohexan-1,3-dion zugänglich ist, durch Umsetzung mit Dimethylammoniummethylenchlorid in Acetonitril unter Acetylchlorid-Katalyse erhältlich (Synthesis 1973, 703; Tietze, Eicher in "Reaktionen und Synthesen im Organisch-Chemischen Praktikum", Thieme-Verlag, Stuttgart 1991, Seite 189).

Weiterer Erfindungsgegenstand ist ein Verfahren zur Herstellung von 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen der Formel I, in der R¹ H ist und R² und R³ gleich oder verschieden sind und H.



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Pharmacology letter Accelerated communication**Tramadol induces antidepressant-type effects in mice**

M. O. Rojas-Corrales*, J. Gibert-Rahola and J. A. Micó

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Received 26 January 1997; revised 1 July 1997; accepted 17 April 1998. ; Available online 16 November 1998.

Abstract

Tramadol is a clinically-effective, centrally-acting analgesic. This drug is a racemic mixture of two enantiomers, each one displaying different

mechanisms: (+)tramadol displays opioid agonist properties and inhibits serotonin reuptake while (-) tramadol inhibit preferentially noradrenaline reuptake. The action of tramadol on the monoaminergic reuptake is similar to that of antidepressant drugs. Therefore, we have examined the effects of ($\pm$) tramadol, (+)tramadol and (-)tramadol in a test predictive of antidepressant activity, the forced swimming test in mice. Both ($\pm$)tramadol and its (-) enantiomer displayed a dose-dependent reduction on immobility; while the effect induced by the (+) enantiomer was not significant. Inhibition of noradrenaline synthesis, but not of serotonin synthesis, was capable of blocking the effect of ($\pm$) tramadol. The alpha-adrenoceptor antagonist phentolamine, as well as the alpha₂-adrenergic antagonist yohimbine, and the beta-adrenoceptor blocker propranolol, countered the immobility-reducing action of ($\pm$)tramadol. Moreover, neither the serotonergic blocker methysergide nor the opioid antagonist naloxone antagonized the effect of ($\pm$) tramadol. Our results show that ($\pm$)tramadol and (-) tramadol have antidepressant-like effect in mice, probably mediated by the noradrenergic system rather than the serotonergic or opioidergic ones.

Author Keywords: tramadol; antidepressant; serotonin; noradrenaline; opioids

Article Outline

• References

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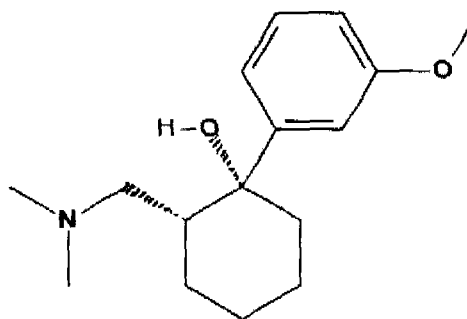
Tramadol - Compound Summary

(CID 33741)

A narcotic analgesic proposed for severe pain.
It may be habituating.

Table of Contents

- Drug and Chemical Information
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 - Literature Links
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- Compound Information
- Substance Information
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- Exports

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Compound ID	33741	?
Molecular Weight	263.3752 [g/mol]	?
Molecular Formula	C ₁₆ H ₂₅ NO ₂	?
XLogP3	2.6	?
H-Bond Donor	1	?
H-Bond Acceptor	3	?

Drug and Chemical Information:

(Total:1) [?](#)

Tramadol

Medication Information [?](#)

[tramadol hydrochloride \[Labopharm Inc.\]](#)

RYZOLT (tramadol hydrochloride extended-release tablets) is a centrally acting analgesic composed of a dual-matrix delivery system with both immediate-release and extended-release characteristics. The chemical name for tramadol [more...](#)

Description	Clinical	Indication & Pharmacology Usage
-------------	----------	---------------------------------

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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. | <u>Descripción:</u> | Folios: 6 a 32 | | | | | | | | | | | | | | |
| 1.2. | <u>Reivindicaciones:</u> | Folios: 33 a 36
Folios: 122 a 124 Memorial de 30/01/2009
Folios: 160 y 161 Memorial de 13/05/2009 | | | | | | | | | | | | | | |
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| Capítulo II | | | | | | | | | | | | | | | | |
| Fecha Sol. Internacional: | 16/07/2003 | | | | | | | | | | | | | | | |
| Publicación. Internacional: | WO04/009067 | | | | | | | | | | | | | | | |
| Fecha Pub. Internacional: | 29/01/2004 | | | | | | | | | | | | | | | |
| Fecha Inicio Fase Nacional: | 19/02/2005 | | | | | | | | | | | | | | | |
| Fecha Sol. Nacional: | 18/01/2005 | | | | | | | | | | | | | | | |
| 1.4. | <u>Prioridad:</u> | DE10233048.4 de 19/07/2002 | | | | | | | | | | | | | | |
| 1.5. | <u>Respuesta del solicitante:</u> | Folios: 119 a 124 Memorial de 30/01/2009
Folios: 131 a 161 Memorial de 13/05/2009 | | | | | | | | | | | | | | |

2. Objeto de la invención

Título de la solicitud

Compuestos del 1-fenil-2-dimetilamino-metil-ciclohexano para la terapia de sintomatología depresiva, dolor e incontinencia

Reivindicaciones

Reivindicación 1: Se reivindican compuestos del 3-(2-dimetilaminometil-ciclohexil)-fenol caracterizados porque se eligen de la siguiente lista:

Éster sulfúrico del mono-[3-(2-dimetilaminometil-ciclohexil)-fenilo]
 Éster sulfúrico del mono-(1R,2R)-[3-(2-dimetilaminometil-ciclohexil)-fenilo]
 3-(2-metilaminometil-ciclohexil)-fenol
 (1R,2R)-3-(2-metilaminometil-ciclohexil)-fenol
 N-óxido de 3-(2-metilaminometil-ciclohexil)-fenol
 N-óxido de (1R,2R)-3-(2-dimetilaminometil-ciclohexil)-fenol
 Ácido 6-[3-(2-dimetilaminometil-ciclohexil)-fenoxi]-3,4,5-trihidroxi.tetrahidropiran-2-carboxílico
 4-(2-dimetilaminometil-ciclohexil)-catecol
 3-(2-aminometil-ciclohexil)-fenol
 (1R,2R)-3-(2-aminometil-ciclohexil)-fenol
 4-(2-dimetilaminometil-ciclohexil)-bencen-1,2-diol
 (1R,2R)-4-(2-dimetilaminometil-ciclohexil)-bencen-1,2-diol
 C-[2-(3-metoxi-fenil)-ciclohexil]-metilamina
 (1R,2R)-C[2-(3-metoxi-fenil)-ciclohexil]-metilamina
 [2-(3-metoxi-fenil)-ciclohexilmetil]-metil-amina
 (1R,2R)-[2-(3-metoxi-fenil)-ciclohexilmetil]-metil-amina
 N-óxido de [2-(3-metoxi-fenil)ciclohexilmetil]-dimetil-amina
 N-óxido de (1R,2R)-[2-(3-metoxi-fenil)-ciclohexilmetil]-dimetil-amina

Reivindicación 2: Se reivindican composiciones farmacéuticas que contienen los compuestos.

Sustento Descriptivo

El objeto de la invención se relaciona con metabolitos de la [2-(3-metoxifenil)-ciclohexil-metil]-dimetilamina como bases libres u/o en forma de sales fisiológicamente admisibles, medicamentos que las contienen, así como el empleo de la [2-(3-metoxifenil)-ciclohexil-metil]-dimetilamina y sus metabolitos para preparar un medicamento para el tratamiento de depresiones y procedimientos para el tratamiento de depresiones.

La base del efecto antidepresivo es la supresión de la reabsorción de noradrenalina y serotonina, por tal motivo, el objetivo de la presente invención es encontrar sustancias, en especial sustancias opioides que sean adecuadas para el tratamiento de las depresiones y en especial aquellas que combinen este efecto con un efecto analgésico.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹/I₁₃₅// A 61 P²⁵/I₀₄** de la **Clasificación Internacional de Patentes**.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D. 486)

Los compuestos:

Éster sulfúrico del mono-[3-(2-dimetilaminometil-ciclohexil)-fenilo]
Éster sulfúrico del mono-(1R,2R)-[3-(2-dimetilaminometil-ciclohexil)-fenilo]

No cumplen con las reglas IUPAC para la denominación de sustancias que presentan grupos funcionales tipo $(HO)S(O)_2$ y $(O^-)S(O)_2$, ya que según recomendaciones formuladas en 1996 por esta institución internacional¹, cuando se utilizan como prefijo se deben denominar en la forma de O-sulfo o bien O-sulfonatos y acto seguido se denomina la especie orgánica.

Por otra parte, el término fenilo corresponde a la denominación señalada para el benceno cuando se encuentra en forma de radical $(Ph)^2$. Así las cosas, el solicitante no puede denominar todo el compuesto en la forma de radicales aislados sin seleccionar una estructura básica en torno al cual se delimiten las sustituciones.

Ejemplo: O-sulfonato de [3-(2-dimetilaminometil-ciclohexil)-benceno]

De otra parte, se requiere al señor solicitante en los términos del presente examen técnico para que indique el significado técnico de la letra C antecediendo la denominación IUPAC del compuesto:

C-[2-(3-metoxi-fenil)-ciclohexil]-metilamina

Lo anterior, con el ánimo de dar cumplimiento a las disposiciones normativas del artículo 30 sobre definición clara y precisa de la materia reivindicada.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 19/07/2002, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

Nº	Documento	Título	Fecha de Publicación
D1	US5733936	"6-dimethylaminomethyl-1-phenyl-cyclohexane compounds as pharmaceutical active ingredients"	31/03/1998
D2	DE19525137	"6-dimethylaminomethyl-1-phenyl-cyclohexanverbindungen als pharmazeytische wirkstoffe"	16/01/1997
D3	Artículo*	"Tramadol induces antidepressant-type effects in mice"	16/11/1998

Anterioridades D1 y D2 en los folios 162 a 175, anterioridad D3 en los folios 195 a 198

Artículo. Rojas M. O., Gibert-Rahola J., Micó J.A. "Tramadol induces antidepressant-type effects in mice". Pharmacology letter. Department of Neuroscience, Neuropsychopharmacology Unit, Spain. 16/11/1998. Elsevier Science Inc.

¹ Ver recomendaciones para la denominación de carbohidratos 2-Carb-24 folios 176 a 181

² Ver regla IUPAC RC-81 para radicales folios 182 a 189

5. Análisis de patentabilidad (artículo 14 D. 486)

5.1 Nivel inventivo (artículo 18 D. 486)

El nivel inventivo del objeto reclamado se evaluó por comparación entre las características esenciales de los compuestos definidas en el pliego reivindicatorio y las anticipaciones más cercanas reveladas por el estado del arte.

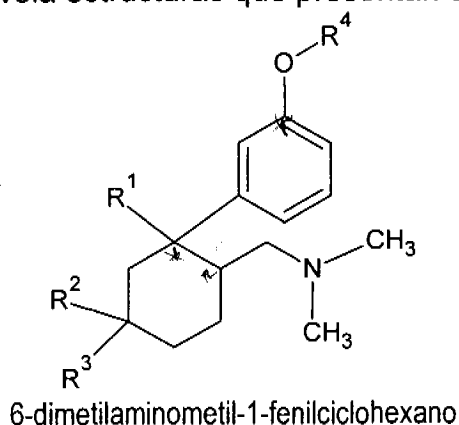
Se reivindican compuestos del **3-(2-dimetilaminometil-ciclohexil)-fenol** caracterizados porque se eligen de la siguiente lista:

- 1) Éster sulfúrico del mono-[3-(2-dimetilaminometil-ciclohexil)-fenilo]
- 2) Éster sulfúrico del mono-(1R,2R)-[3-(2-dimetilaminometil-ciclohexil)-fenilo]
- 3) 3-(2-metilaminometil-ciclohexil)-fenol
- 4) (1R,2R)-3-(2-metilaminometil-ciclohexil)-fenol
- 5) N-óxido de 3-(2-metilaminometil-ciclohexil)-fenol
- 6) N-óxido de (1R,2R)-3-(2-dimetilaminometil-ciclohexil)-fenol
- 7) Ácido 6-[3-(2-dimetilaminometil-ciclohexil)-fenoxi]-3,4,5-trihidroxi-tetrahidropiran-2-carboxílico
- 8) 4-(2-dimetilaminometil-ciclohexil)-catecol
- 9) 3-(2-aminometil-ciclohexil)-fenol
- 10) (1R,2R)-3-(2-aminometil-ciclohexil)-fenol
- 11) 4-(2-dimetilaminometil-ciclohexil)-bencen-1,2-diol
- 12) (1R,2R)-4-(2-dimetilaminometil-ciclohexil)-bencen-1,2-diol
- 13) C-[2-(3-metoxi-fenil)-ciclohexil]-metilamina
- 14) (1R,2R)-C[2-(3-metoxi-fenil)-ciclohexil]-metilamina
- 15) [2-(3-metoxi-fenil)-ciclohexilmetil]-metil-amina
- 16) (1R,2R)-[2-(3-metoxi-fenil)-ciclohexilmetil]-metil-amina
- 17) N-óxido de [2-(3-metoxi-fenil)ciclohexilmetil]-dimetil-amina
- 18) N-óxido de (1R,2R)-[2-(3-metoxi-fenil)-ciclohexilmetil]-dimetil-amina

- El estado del arte previo a la invención presenta los siguientes documentos:

Anterioridad D1:

La publicación **D1** revela estructuras que presentan el núcleo:



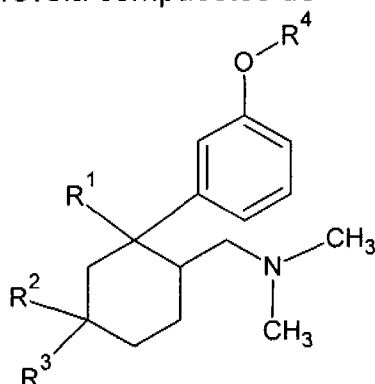
Dentro de las especies más representativas el documento **D1** señala las siguientes:

- a) (+)-(1R,2R)-[2-cloro-2-(3-metoxi-fenil)-ciclohexilmetil]-dimetil-amina clorhidrato (ejemplo 3)
- b) (-)-(1R,2S)-3-(2-dimetilaminometil-ciclohexil)-fenol clorhidrato (ejemplo 10)

c) (+)-(1R,2R,5S)-3-(2-dimetilaminometil-1-hidroxi-5-metil-ciclohexil)-fenol clorhidrato (ejemplo 25)

Anterioridad D2:

La publicación D2 revela compuestos derivados del núcleo:



Y entre otros los siguientes compuestos:

a) (+)-(1S,2R)-3-(2-dimetilaminometil-ciclohexil)-fenol clorhidrato (ejemplo 9)

b) (+)-(1R,2R,5S)-2-dimetilaminometil-1-(3-metoxifenil)-5-metil-ciclohexanol (ejemplo 24)

Identificación de las diferencias técnicas

De esta manera, al evaluar los elementos característicos de la materia reivindicada, en especial, los grupos químicos funcionales y la estructura de los compuestos es posible concluir que entre ellos las diferencias estriban en la clase de sal que se forma y en algunos casos en las sustituciones tipo halógeno (Cl-) que de manera adicional se reportan en el documento D1 para sustancias estructuralmente similares.

Tabla 1.

No.	Compuestos Reivindicados	Compuestos revelados en D1 y D2
16	(1R,2R)-[2-(3-metoxi-fenil)-ciclohexilmetil]-metil-amina	(+)-(1R,2R)-[2-cloro-2-(3-metoxi-fenil)-ciclohexilmetil]-dimetil-amina clorhidrato (ejemplo 3 publicación D1)
17	N-óxido de [2-(3-metoxi-fenil)ciclohexilmetil]-dimetil-amina	
4	(1R,2R)-3-(2-metilaminometil-ciclohexil)-fenol	(-)-(1R,2S)-3-(2-dimetilaminometil-ciclohexil)-fenol clorhidrato (ejemplo 10 publicación D1)
5	N-óxido de 3-(2-metilaminometil-ciclohexil)-fenol	
2	Éster sulfúrico del mono-(1R,2R)-[3-(2-dimetilaminometil-ciclohexil)-fenilo]	(+)-(1R,2R,5S)-3-(2-dimetilaminometil-1-hidroxi-5-metil-ciclohexil)-fenol clorhidrato (ejemplo 25 publicación D1)
10	(1R,2R)-3-(2-aminometil-ciclohexil)-fenol	(+)-(1S,2R)-3-(2-dimetilaminometil-ciclohexil)-fenol clorhidrato (ejemplo 9 publicación D2)
12	(1R,2R)-4-(2-dimetilaminometil-ciclohexil)-bencen-1,2-diol	(+)-(1R,2R,5S)-2-dimetilaminometil-1-(3-metoxifenil)-5-metil-ciclohexanol (ejemplo 24 publicación D2)

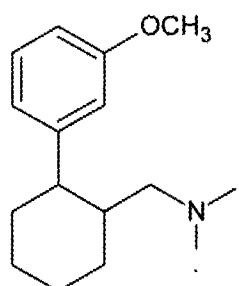
Con respecto al documento D2 la diferencia estriba en la información adicional sobre la estereoisomería de las estructuras y a la incorporación de grupos dimetilo sobre la estructura anular de los ciclohexil-fenoles.

Sin embargo, dichas diferencias no parecen conferir un efecto técnico inesperado, por cuanto, en los documentos se reporta la actividad analgésica y nociceptiva de las estructuras derivadas del núcleo de fórmula: dimetilaminometil-1-fenil-ciclohexano, tal y como se indica en la publicación D1.

El documento **D2** por su parte, señala la actividad analgésica de las estructuras, pero con efectos secundarios disminuidos respecto de otros analgésicos como los opioides (ver folio 191 correspondiente al documento **D2**).

Del problema técnico y la solución

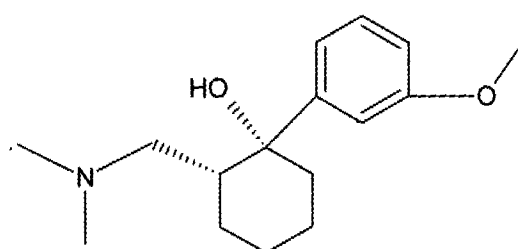
La materia reivindicada en los folios 160 y 161 versa sobre compuestos de la 2-(3-metoxifenil)-ciclohexil]-metil-dimetil-amina, es decir, sobre el núcleo:



Y sus compuestos derivados, los que son útiles por su actividad farmacológica dual como antidepresivos y analgésicos. Lo anterior, gracias a su capacidad de modular la actividad del receptor 5HT.

El problema técnico planteado estriba en la necesidad de diseñar estructuras que presenten actividad dual como antidepresivos y analgésicos, especialmente porque para el tratamiento de la depresión generalmente se administran combinaciones de antidepresores con analgésicos opioides con el fin de conseguir una disminución efectiva en la absorción de noradrenalina y 5-hidroxi-triptamina. Precisamente para solventar esa necesidad se diseñaron compuestos que presentaran actividad dual.

Al respecto es preciso señalar que en el estado del arte existe evidencia clara de la actividad dual de compuestos como Tramadol, cuyo núcleo básico es similar al de los compuestos reivindicados por el señor solicitante, para ello se remite al señor solicitante al contenido de la publicación **D3**, en el que se publica un estudio realizado en ratones para comprobar la actividad antidepresora del compuesto, cuyos elementos químicos y funcionales característicos son:



Estructura molecular de Tramadol

Así las cosas, el estado del arte se aproximó a la actividad dual de estructuras como las reivindicadas por el señor solicitante desde la década del 90, motivo por el cual esta Dependencia considera que al combinar las enseñanzas que en conjunto revelan los documentos **D1** y **D3** o **D2** y **D3** es posible derivar los elementos característicos de los compuestos reivindicados por el solicitante, toda vez que los compuestos revelados por el estado del arte cumplen a cabalidad la premisa de ser derivados de 2-(3-metoxifenil)-ciclohexil]-metil-dimetil-amina y de presentar actividad dual como analgésicos y antidepresores, es decir, el efecto técnico perseguido mediante el diseño de estructuras análogas al Tramadol.



Y dado que el estado del arte presenta anticipaciones cercanas a la materia reivindicada y no existe un efecto técnico que permita evidenciar el salto cualitativo en la regla técnica, esta dependencia considera que una persona versada en la materia habría podido diseñar moléculas como las reivindicadas por el señor solicitante, toda vez que existe amplia evidencia en documentos y publicaciones científicas tanto del grupo farmacofórico de los compuestos como de la actividad dual de análogos del Tramadol.

Por las razones expuestas esta Dependencia considera que la materia objeto de estudio carece de altura inventiva, motivo por el cual incumple con las disposiciones normativas del artículo 18 de la Decisión 486.

6. Conclusión:

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

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	US5733936	1 y 2	Nivel Inventivo
D2	DE19525137	1 y 2	Nivel Inventivo
D3	Artículo	1 y 2	Nivel Inventivo

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

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

CONCEPTO TÉCNICO No. 1779	EXAMINADOR TÉCNICO Código No. 202044
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