



No. 14-196748- -00002-0000

Fecha: 2014-12-30 10:41:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 30

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

- ☒ Patente de invención
☐ Registro de Diseño Industrial
☐ Patente de Modelo de Utilidad
☐ Esquema de Trazado de Circuitos Integrados

Número de expediente: 14-196-748

Solicitante: ZENTIVA, K.S.

Apoderado: JUAN CARLOS URIBE RESTREPO

Título de la Nueva Creación: UN METODO PARA PREPARAR EL ESTER DE ESCOPINA DE DI-92-TIENIL) ÁCIDO GLICÓLICO, UN INTERMEDIO EN LA SÍNTESIS DE BROMURO DE TIOOTROPIO

Gaceta: 707 de 30 septiembre de 2014, No. de publicación 1127

2. Datos del Opositor

☐ Persona Natural

☒ Persona Jurídica

LAFRANCOL S.A.S.

Nombre o denominación /Razón social completa

Documento de identificación: C.C. ☐ C.E. ☐ NIT ☒ Otro ☐ Cuál

Número 890 301 463-8

Dirección Carrera 1 No. 46-84 Ciudad Cali

Teléfono (092) 449.30.51 Fax: E-mail:



Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del representante o apoderado:

REYES VILLAMIZAR JOSE LUIS

79`152.473

44655

Apellidos y Nombre

Documento de identificación

T.P. No.

Dirección del representante

Cra 17 No. 88-23 Of.205

Dirección electrónica

info@reyes-abogados.com

No. Fax

621.25.42

Número telefónico

621.26.31

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación

72

6. Fundamentos de la oposición

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000)

Justificación: VER ANEXO

Prórroga:

SI

☐

NO

☒

7.

Anexos

☒

Comprobante de pago de la tasa para la presentación de la solicitud No. 14 Fecha:

☒

Poder, si fuera el caso con el que se acredita la representación.

☒

Pruebas de los fundamentos de la oposición

☐

Copias para traslado

8. Firma

JOSÉ LUIS REYES VILLAMIZAR



Nombre y apellidos

Firma

79.152.473

44655

C.C.

T.P.

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: EXPEDIENTE 14-196-748

TÍTULO SOLICITADO: “UN MÉTODO PARA PREPARAR EL ESTER DE ESCOPINA DE DI-(2-TIENIL) ÁCIDO GLICÓLICO, UN INTERMEDIO EN LA SÍNTESIS DE BROMURO DE TIOTROPIO”

PUBLICACIÓN: Gaceta 707 de 30 de septiembre de 2014, N° de publicación 1127.

PRIORIDAD: CZ PV 2012-226 30/03/2012

SOLICITANTE: ZENTIVA, K.S.

APODERADO: JUAN CARLOS URIBE RESTREPO

TRÁMITE: PRESENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LAFRANCOL S.A.S.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente **14-196-748**, por no cumplir con lo dispuesto en la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LAFRANCOL S.A.S.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud colombiana en trámite 14-196-748, referida a un nuevo método de preparación de Bromuro de Tiotropio, no cumple los requisitos materiales para otorgársele el privilegio de patente de invención, tal como puede determinarse al valorar los siguientes argumentos:

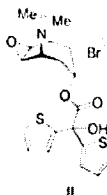
Falta de claridad

El método reclamado es general e incluye muchas rutas sintéticas que no pueden presentar el mismo rendimiento y pureza reclamados:

Este resumen de literatura de patente claramente documenta la necesidad de un método simple, económico y ambientalmente aceptable de síntesis de bromuro de tiotropio, aplicable también en una escala mayor con suficiente control sobre impurezas posiblemente producidas.

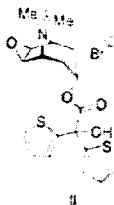
Divulgación de la Invención

La invención suministra un nuevo método eficiente de preparación de ester de escopina II



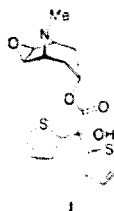
Como se muestra a continuación, la materia reclamada carece de información suficiente para llevar a cabo el método reclamado pues no presenta la totalidad de los reactivos involucrados en esta síntesis y tampoco las condiciones requeridas para tal preparación:

1. Un método para preparar bromuro de tiotropio de fórmula II

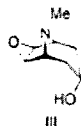
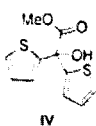


caracterizado porque comprende los siguientes pasos

a) preparación del ester de escopina de fórmula I



mediante transesterificación de metilo di(2benil)glicolato de fórmula IV con escopina de fórmula III

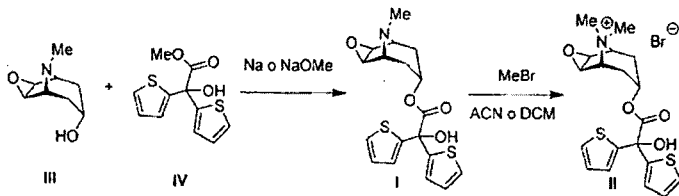


en presencia de una base estéricamente obstruida seleccionada del grupo de sales de álcali de alcóxidos C₃ a C₅ ramificados en un solvente inerte,
b) aislamiento del ester de escopina de fórmula I, y
c) cuaternización del ester de escopina de fórmula I con bromuro de metilo.

Como se observa según la misma descripción de la solicitud en trámite, este intermediario había sido presentado por otros documentos de patente, tal es el caso de EP 0 418 716 y US 6 506 900, veamos:

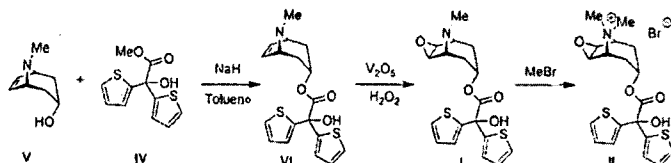
Un proceso de preparación de bromuro de tiotropio se publicó primero en la patente EP 0 418 716 y se ilustra en el Esquema 1.

Esquema 1



Un método alternativo de síntesis de bromuro de tiotropio se describe en la patente
US 6 506 900 B1 y se ilustra en el Esquema 2.

Esquema 2



pero, según la descripción, estas preparaciones no divulgaban sus rendimientos y aquellos que si lo hacen presentan un rendimiento muy bajo, por lo que según la solicitante, la síntesis reclamada ofrece una mejoría en la pureza y el rendimiento.

Sin embargo, se considera que para el técnico versado en la materia no hay cambios sustanciales a la materia reclamada, pues la ruta sintética sigue siendo básicamente la misma y los resultados en cuanto al rendimiento y la pureza no son tales que puedan considerarse sorprendentes o inesperados a la luz de los cambios que la solicitante realizó con elementos como:

- i) la selección de un solvente inerte,
- ii) el aislamiento del éster de escopina y
- iii) la cuaternización del éster con bromuro de metilo

pues finalmente la selección de los solventes es un factor que influye directamente sobre el resultado alcanzado en las síntesis orgánicas.

Se llama la atención de ese Despacho sobre la ausencia de datos que confirmen la existencia de un valor sorprendente para el rendimiento de esta síntesis:

Referencias	Descripción solicitante/anterioridad
EP 0 418 716	con diclorometano. El producto se cristaliza a partir de acetonitrilo. Los rendimientos de la síntesis del éster de escopina I varían en el rango de 45% a 70%. VER EJEMPLOS 1, 2 Y 3

Referencias	Descripción solicitante/anterioridad
US 6 506 900	temperatura de 60-75°C y una presión de 25-30 kPa. El segundo paso es la oxidación del ester de tropenol VI al ester de escopina I con el uso de dióxido de vanadio y peróxido de hidrógeno, y la posterior cuaternización suministra bromuro de tiotropio II en el rendimiento total de 71%. Aunque se prefiere el procedimiento <u>Preparation of the Scopine Ester (IV)</u> 260 l DMF are placed in a suitable reaction apparatus and heated to 50° C. Then 16.2 kg of tropenol ester (VII) are added and the mixture is stirred until a clear solution is obtained. After cooling to 40° C., hydrogen peroxide-urea complex (10.2 kg), water (13 l) and vanadium(V)-oxide (0.7 kg) are added successively and in batches and the contents of the apparatus are heated to about 50° C. After 2-3 h stirring at constant temperature the mixture is cooled to about 20° C. The reaction mixture obtained is adjusted to a pH of about 4.0 with hydrochloric acid (36%). Prepared sodium bisulphite solution (2.4 kg in 24 l of water) is added. At an internal temperature of 35° C. the solvent is partly distilled off in vacuo (about 210 l). The mixture is cooled to about 20° C. again and Clarcel (3.2 kg) is added. The resulting mixture is adjusted to a pH of about 2.0 with dilute hydrochloric acid (36%, 0.8 kg in about 440 l of water). The solution obtained is filtered and extracted with methylene chloride (58 l). The methylene chloride phase is discarded. Methylene chloride (130 l) is again added to the aqueous phase and a pH of about 10.0 is obtained using a prepared soda solution (11.0 kg in 51 l of water). The methylene chloride phase is separated off and the aqueous phase is extracted with methylene chloride (136 l). Methylene chloride (about 175 l) is distilled off from the combined methylene chloride phases in a slight vacuum (600-700 mbar) at 40° C. The contents of the apparatus are cooled to 20° C., acetyl chloride (about 0.5 kg) is added and the mixture is stirred for about 40 minutes at 20° C. The reaction solution is transferred into a second apparatus. The pH is adjusted to 2.0 with a prepared hydrochloric acid solution (4.7 kg of hydrochloric acid, 36% strength in 460 l water) at 20° C. The methylene chloride phase is separated off and discarded. The aqueous phase is washed with methylene chloride (39 l). Then methylene chloride (130 l) is added and a pH of 10.0 is obtained with a prepared soda solution (7.8 kg of soda in 38 l water) at 20° C. After 15 minutes' stirring the organic phase is separated off and the aqueous phase is washed twice with methylene chloride (97 l and 65 l). The methylene chloride phases are combined and some of the methylene chloride (90 l) is distilled off in a slight vacuum at a temperature of 30-40° C. Then dimethylformamide (114 kg) is added and the remaining methylene chloride is distilled off in vacuo at 40° C. The contents of the apparatus are cooled to 20° C. <u>Preparation of the Tiotropium Bromide (I)</u> Methyl bromide (5.1 kg) is added to the scopine ester solution obtained according to the procedure described above at 20° C. The contents of the apparatus are stirred at 30° C. for about 2.5 days. At 50° C., 70 l of DMF are distilled off in vacuo. The solution is transferred into a smaller apparatus. It is rinsed with DMF (10 l). More DMF is distilled off at 50° C. in vacuo until a total of about 100 l of distillate is obtained. It is cooled to 15° C. and stirred for another 2 hours at this temperature. The product is isolated using suction dryers, then washed with cold DMF (10 l) at 15° C. and cold acetone (25 l) at 15° C. It is dried at a maximum temperature of 50° C. for not more than 36 hours in a nitrogen current. Yield: 13.2 kg (88%); melting point: 200-230° C. (depending on the purity of the crude product); (COL 13 Y 14)
US 2006/0047120	derivado protegido X, esto aumenta la complejidad de la síntesis. Los rendimientos de la secuencia ejecutada de esta forma varían en el rango de 34-85% del bromuro de tiotropio resultante II.

Referencias	Descripción solicitante/anterioridad
	SYNTHESIS EXAMPLE 1 5.43 g (50 mmol) chlorotrimethylsilane are added dropwise at 20° C. to a mixture of 13.1 g (50 mmol) sodium dithienylglycolate and 8.1 g (50 mmol) carbonyldiimidazole in 25 ml N-methylpyrrolidone (NMP). After 30 min stirring 9.38 g (37.5 mmol) scopolamine methobromide are added and a solution of 2.59 g (38 mmol) imidazole and 1.52 g (38 mmol) sodium hydride (60%) in 15 ml NMP is added dropwise at 20° C. and the mixture is stirred for 1 h at 20° C. After cooling to 0° C. 50 ml of a 33% solution of hydrogen bromide in glacial acetic acid are added dropwise while the temperature does not exceed 20° C. Then 50 ml methanol are added and the mixture is stirred for 1 h at 20° C. The reaction mixture is extracted twice with 200 ml toluene and, after separation of the toluene phase, crystallised from 150 ml isopropanol at 0° C. The crude product is filtered off, washed with 30 ml cold isopropanol and dried in vacuo. Yield 15.0 g (85%, based on scopolamine methobromide).
WO2008/008376	en acetonitrilo a temperatura ambiente. El rendimiento total del bromuro de tiotropio fue 42-61%. p 8 - 9
WO2009/087419	producto resultante en una pureza inadecuada y bajo rendimiento. El rendimiento total es 41 a 50%. Examples Tiotropium base (3) Scopolamine HCl was taken in DMF (5vol), cooled to 5°C, and NaH (1.7eq) was added slowly maintaining the temperature at 5°C. The reaction was stirred for 1 hour at 10°C and DBU (1eq) and methyl di(2-thienyl)glycolate (1eq) were added. The reaction was heated to 60°C for 1 hour and a second portion of DBU (2eq) was added. The reaction was heated for a further 4 hours at 60°C and monitored by TLC. After completion of the reaction, the mixture was cooled to 5°C and a solution of cone. HCl (2.5vol) in cold water (10vol) at 10°C (pH 2) was added. The mixture was washed with toluene and basified with aqueous sodium carbonate (7.5eq) to pH 10 and extracted with DCM (3 x 10vol). The combined DCM layer was washed with water (3 x 10vol) and DCM was distilled under vacuum (150 mbar) at 30°C. The product was obtained as light brown solid. Molar Yield = 60%; HPLC purity = 98%.

Referencias	Descripción solicitante/anterioridad
Ejemplo 1	de cristales beige del ester de escopina I se obtuvieron en la pureza de 98.75% (analizado por UPLC) y el rendimiento de 50%.
Ejemplo 2	ambiente por 20 horas. 0.26 g del ester de escopina I se obtuvieron en la pureza de 98.71% (analizado con UPLC) y el rendimiento de 21%.
Ejemplo 4	vacio a temperatura ambiente por 20 horas. 0.30 g del ester de escopina I se obtuvieron en la pureza de 98.75% (analizado con UPLC), punto de fusión 149.2-150.3°C, con el rendimiento de 25%.
Ejemplo 5	escopina I se obtuvieron en la pureza de 99.08% (analizado con UPLC), punto de fusión 150.2-150.4°C, con el rendimiento de 19%.

Como se presentó en el cuadro anterior, no hay datos de rendimiento y pureza que demuestren que el método de síntesis reivindicado en la solicitud en trámite realmente supera los problemas relacionados con la preparación del bromuro de Tiotropio y su intermediario.

Tampoco hay datos que cuantifiquen o demuestren que la ruta reclamada puede usarse con expectativa de éxito a grande escala y de una manera más simple, económica y ambientalmente aceptable en comparación con las rutas sintéticas ya mencionadas en el estado del arte.

Por lo tanto, no se puede considerar que el proceso sea nuevo e inventivo a la luz de la materia del estado de la técnica, del conocimiento del técnico versado en la materia y de la carencia de evidencia de la superioridad de tal método.

Rogamos se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tenga como tal, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- EP 0418716 - ESTERS AMINOALCOHOL D'ACIDE THIENYLCARBOXYLIQUES LEURS PRODUITS QUATERNAIRES, LEUR PRÉPARATION ET L'UTILISATION DE CES COMPOSÉS - Fecha de publicación: 6 Abr 1994, portada
- US 6506900 - EPOXIDATION OF THE 2,2-DITHIENYL-2-HYDROXYACETIC ACID ESTER; ESTERIFICATION - Fecha de publicación: 14 Ene 2003, portada p. 8, reivindicaciones
- US 20060047120 - NEW METHOD FOR PREPARING TIOTROPIUM SALTS - Fecha de publicación: 2 Mar 2006, portada p. 4-5, reivindicaciones
- WO2008008376 - SCOPINE SALTS AND THEIR USE IN PROCESSES FOR THE PREPARATION OF N-DEMETHYL-TIOTROPIUM AND TIOTROPIUM BROMIDE - Fecha de publicación: 17 ene 2008, portada p. 8-9, reivindicaciones.
- WO2009087419 - NOVEL PROCESS FOR THE PREPARATION OF SCOPINE ESTERS - Fecha de publicación: 16 jul 2009, portada p. 13, reivindicaciones

VI. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Certificado de existencia y representación legal de LAFRANCOL S.A.S.
2. Constancia de pago de las tasas de tramitación de oposición.
3. El mencionado en el acápite de pruebas.

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Lafrancol S.A. las recibirá en sus oficinas localizadas las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén
T.P.A. 44.655 de C.S.J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -



RECIBO DE CAJA

No. 14 - 138827

Bogotá D.C., Diciembre 26 de 2014 - 14:07:23

RECIBIDO DE : REYES Y REYES ABOGADOS

NI 900.048.328

RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	223295133	26/12/2014	2.319.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	644247741	23/12/2014	2.680.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICACIONES	OPOSICION POR CADA CLASE-MARCAS Y LEAS COMERCIALES	335.000.00	335.000.00
				\$335.000.00

SON: **TRESCIENTOS TREINTA Y CINCO MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



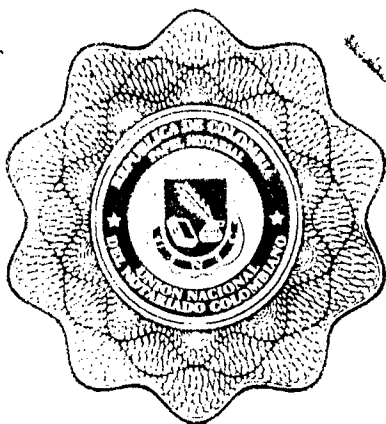
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Act. 400 OPOSIOBSERVTER Folios: 30

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Diciembre 26 de 2014 - 14:07:25



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AA 8567146

REPUBLICA DE COLOMBIA

NOTARIA 33 DE BOGOTA D.C.

ESCRITURA PUBLICA NUMERO: 1 6 5 8

- - MIL SEISCIENTOS CINCUENTA Y OCHO - -

FECHA DE OTORGAMIENTO: CUATRO (4) DE

JULIO - - - - -

DEL AÑO DOS MIL DOS (2002). -----

ACTO: -----

1.- PODER ESPECIAL.-----

OTORGADO POR: LAFRANCOL S.A., con Nit. No. - - -

890.301.463-8 - - - - -

a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.No.

79.152.473 de Usaquén - Bogotá.-----

DIANA BEATRIZ LOPEZ

NOTARIA TREINTA Y TRES (33) DE BOGOTA D.C.

EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL,

DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA,

ANTE MI, DIANA BEATRIZ LOPEZ, - - - - -

NOTARIA TREINTA Y TRES (33) - - - - -

DE ESTE CIRCULO SE OTORGA LA ESCRITURA PUBLICA QUE

SE CONSIGNA EN LOS SIGUIENTES TERMINOS:-----

COMPARECIO: JUAN MARIA RENDON, mayor de edad,

vecino de Bogotá, D.C, identificado con la cédula de

ciudadanía número 17.125.100 - - - - -

Expedida en Bogotá - - - - -

Y manifestó:-----

PRIMERO: Que obra en su carácter de Representante

Legal de en nombre y representación de LAFRANCOL

S.A, sociedad comercial organizada y existente

conforme a las leyes colombianas, con domicilio y

sede principal en Cali - Valle, constituida mediante

escritura pública número

De la Notaría

De fecha

Reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali - Valle.-----

SEGUNDO: Que en tal carácter, por este público instrumento, concede PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE a **JOSE LUIS REYES VILLAMIZAR**, mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 79.152.473 de Usaqué, abogado en ejercicio, portador de la T.P.No. 446 55 del C.S. de la J., domiciliado en Bogotá, D.C, República de Colombia, con dirección en la carrera 17 No. 88-23, Oficina 205, de la misma ciudad, como su representante con poder especial, amplio y suficiente, para obtener la protección los derechos de propiedad industrial y de libre competencia de Lafrancol S.A., a cuyo efecto lo autorizo, par que nos represente ante cualesquiera entidad o persona, ejerza o no jurisdicción, especialmente ante las el orden administrativo, contencioso, administrativo y judicial, en todo lo concerniente a los siguientes asuntos:-----

a.- Obtención, formulación de observaciones y oposición a patentes de invención, modelos y dibujos industriales y el registro de licencias de uso de esos derechos.-----

b.- Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso- administrativos relacionados con estos derechos u otros de diferente naturaleza, acciones y procesos que

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promueva Lafrancol S.A., o se
promuevan contra esta y.-----

c.- Para que en todos los asuntos
arriba determinados, tanto en
los términos señalados por los
artículos 42 y complementarios

de la decisión 486 de la Comunidad Andina como del
artículo 70 del C.P.C. pueda sustituir este
mandato, transigir, conciliar, admitir los hechos del
proceso, desistir, cancelar, recibir, renunciar y
ratificar los actos de agentes oficiosos y ceder a
título gratuito y/o oneroso, licenciar, inscribir
contratos de cesión y de licencia, inscripción de
prendas, levantamiento de prendas, inscribir
derechos de retención y en general todos los asuntos
que se deban tramitar ante la Superintendencia de
Industria y Comercio.-----

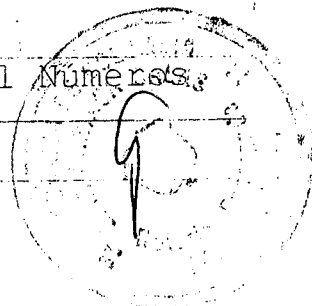
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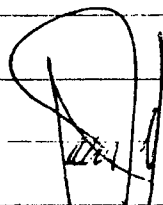
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AA 8567146, 8567152.



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JUAN MARIA RENDON

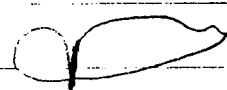
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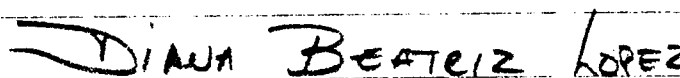
TEL: 622-04-66.

ACEPTO :


JOSE LUIS REYES VILLAMIZAR

C.C. No. 29.152.473

TEL: 621-2631


DIANA BEATRIZ LOPEZ

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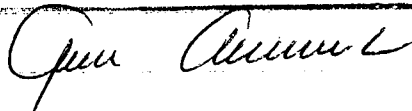
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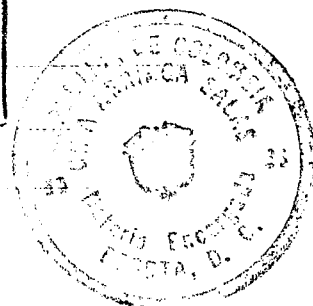
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Veröffentlichungsnummer: **0 418 716 B1**

EUROPÄISCHE PATENTSCHRIFT

- Veröffentlichungstag der Patentschrift: **06.04.94**
- Int. Cl.⁵: **C07D 451/10, C07D 451/14, A61K 31/46, A61K 31/445**
- Anmeldenummer: **90117554.7**
- Anmeldetag: **12.09.90**

Die Akte enthält technische Angaben, die nach dem Eingang der Anmeldung eingereicht wurden und die nicht in dieser Patentschrift enthalten sind.

Neue Thienylcarbonsäureester von Aminoalkoholen, ihre Quaternierungsprodukte sowie die Herstellung und Verwendung dieser Verbindungen.

③① Priorität: 16.09.89 DE 3931041 ④③ Veröffentlichungstag der Anmeldung: 27.03.91 Patentblatt 91/13 ④⑤ Bekanntmachung des Hinweises auf die Patenterteilung: 06.04.94 Patentblatt 94/14 ⑧④ Benannte Vertragsstaaten: AT BE CH DE DK ES FR GB GR IT LI LU NL SE ⑤⑥ Entgegenhaltungen: DE-B- 1 166 787 GB-A- 955 535 US-A- 3 673 195 US-A- 3 808 263 ACTA CHEMICA SCANDINAVICA, Band 24, 1970, Seiten 1590-1596, Copenhagen, DK; K. NYBERG et al.: "Investigation of dithienylglycolic esters" J. Chem. Soc., 1957, S. 3575-3578 ⑦③ Patentinhaber: BOEHRINGER INGELHEIM KG	D-55216 Ingelheim(DE) ⑧④ Benannte Vertragsstaaten: BE CH DE DK ES FR GR IT LI LU NL SE AT ⑦③ Patentinhaber: BOEHRINGER INGELHEIM INTERNATIONAL G.M.B.H. D-55216 Ingelheim(DE) ⑧④ Benannte Vertragsstaaten: GB ⑦② Erfinder: Banholzer, Rolf, Dr. Johann-Calvin-Strasse 11 D-6507 Ingelheim am Rhein(DE) Erfinder: Bauer, Rudolf, Dr. Mainzerstr.58 D-6531 Ockenheim(DE) Erfinder: Reichl, Richard, Dr. Im Hippel 55 D-6535 Gau-Algesheim(DE)
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EP 0 418 716 B1



US006506900B1

16

(12) **United States Patent**
Banholzer et al.

(10) **Patent No.: US 6,506,900 B1**
(45) **Date of Patent: Jan. 14, 2003**

(54) **PROCESS FOR PREPARING A SCOPINE
ESTER INTERMEDIATE**

(75) **Inventors:** Rolf Banholzer, Stuttgart (DE);
Manfred Graulich, Waldalgesheim
(DE); Sven Luettkke, Ockenheim (DE);
Andreas Mathes, Ockenheim (DE);
Helmut Meissner, Ingelheim (DE);
Peter Specht, Ober-Hilbersheim (DE);
Wolfgang Broeder, Heidesheim (DE)

(73) **Assignee:** Boehringer Ingelheim Pharma AG,
Ingelheim (DE)

(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** 10/223,152

(22) **Filed:** Aug. 19, 2002

Related U.S. Application Data

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19, 2001.
(60) Provisional application No. 60/265,443, filed on Jan. 31,
2001.
(51) **Int. Cl.⁷** C07D 45/00; C07D 401/12
(52) **U.S. Cl.** 546/91; 546/125
(58) **Field of Search** 546/91, 125

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Primary Examiner—Joseph K. McKane
Assistant Examiner—Jennifer C. Murphy
(74) *Attorney, Agent, or Firm*—Robert P. Raymond; Philip
I. Datlow; Alan R. Stempel

(57) **ABSTRACT**

The invention relates to a new process for preparing a
scopine ester useful as an intermediate in preparing (1 α ,2 β ,
4 β ,5 α ,7 β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-
dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}] nonane-
bromide.

14 Claims, No Drawings

The Examples which follow serve to illustrate some methods of synthesis carried out by way of example in order to prepare tiotropium bromide. They are intended to be taken as possible methods provided by way of example, without limiting the invention to their content.

Preparation of the Tropenol Ester (VII)

Ammonia (1.8 kg) is added to 10.9 kg of tropenol hydrochloride in toluene (95 l) at 25° C. The suspension obtained is stirred at constant temperature for about 1 h. The ammonium hydrochloride formed is then filtered off and rinsed with toluene (26 l). At an external temperature of about 50° C. some of the toluene (about 60 l) is distilled off in vacuo. After cooling to about 25° C., 15.8 kg of methyl di-(2-thienyl)glycolate is added and the resulting mixture is heated to 50° C. to dissolve it. Toluene (40 l) is placed in another apparatus and sodium hydride (2.7 kg) is added thereto at about 25° C. The solution previously prepared from tropenol and methyl glycolate is added to this solution within 1 hour at 30° C. After it has all been added the mixture is heated to 75° C. at reduced pressure for about 7 hours with stirring. The methanol formed is distilled off. The mixture remaining is cooled and added to a mixture of water (958 l) and 36% hydrochloric acid (13.2 kg). The aqueous phase is then separated off and washed with methylene chloride (56l). After the addition of some more methylene chloride (198 l) the mixture thus obtained is adjusted to pH=9 with prepared soda solution (9.6 kg of soda in 45 l of water). The methylene chloride phase is separated off and the aqueous phase is stirred with methylene chloride (262 L). The methylene chloride phase is evaporated down to the residue at 65° C. The residue is taken up in toluene (166 l) and heated to 95° C. The toluene solution is cooled to 0° C. The crystals obtained are separated off, washed with toluene (33 l) and dried at about 50° C. for a maximum of 24 hours in a nitrogen current.

Yield: 18.6 kg (83%); melting point: about 160° C. (measured by DSC at a heating rate of 10 K/min); Preparation of the Scopine Ester (IV)

260 l DMF are placed in a suitable reaction apparatus and heated to 50° C. Then 16.2 kg of tropenol ester (VII) are added and the mixture is stirred until a clear solution is obtained. After cooling to 40° C., hydrogen peroxide-urea complex (10.2 kg), water (13 l) and vanadium(V)-oxide (0.7 kg) are added successively and in batches and the contents of the apparatus are heated to about 50° C. After 2-3 h stirring at constant temperature the mixture is cooled to about 20° C. The reaction mixture obtained is adjusted to a pH of about 4.0 with hydrochloric acid (36%). Prepared sodium bisulphite solution (2.4 kg in 24 l of water) is added. At an internal temperature of 35° C. the solvent is partly distilled off in vacuo (about 210 l). The mixture is cooled to about 20° C. again and Clarcel (3.2 kg) is added. The resulting mixture is adjusted to a pH of about 2.0 with dilute hydrochloric acid (36%, 0.8 kg in about 440 l of water). The solution obtained is filtered and extracted with methylene chloride (58 l). The methylene chloride phase is discarded. Methylene chloride (130 l) is again added to the aqueous phase and a pH of about 10.0 is obtained using a prepared soda solution (11.0 kg in 51 l of water). The methylene chloride phase is separated off and the aqueous phase is extracted with methylene chloride (136 l). Methylene chloride (about 175 l) is distilled off from the combined methylene chloride phases in a slight vacuum (600-700 mbar) at 40° C. The contents of the apparatus are cooled to 20° C., acetyl chloride (about 0.5 kg) is added and the mixture is stirred for about 40 minutes at 20° C. The reaction solution is transferred into a second apparatus. The pH is adjusted to

2.0 with a prepared hydrochloric acid solution (4.7 kg of hydrochloric acid, 36% strength in 460 l water) at 20° C. The methylene chloride phase is separated off and discarded. The aqueous phase is washed with methylene chloride (39 l). Then methylene chloride (130 l) is added and a pH of 10.0 is obtained with a prepared soda solution (7.8 kg of soda in 38 l water) at 20° C. After 15 minutes' stirring the organic phase is separated off and the aqueous phase is washed twice with methylene chloride (97 l and 65 l). The methylene chloride phases are combined and some of the methylene chloride (90 l) is distilled off in a slight vacuum at a temperature of 30-40° C. Then dimethylformamide (114 kg) is added and the remaining methylene chloride is distilled off in vacuo at 40° C. The contents of the apparatus are cooled to 20° C.

Preparation of the Tiotropium Bromide (I)

Methyl bromide (5.1 kg) is added to the scopine ester solution obtained according to the procedure described above at 20° C. The contents of the apparatus are stirred at 30° C. for about 2.5 days. At 50° C., 70 l of DMF are distilled off in vacuo. The solution is transferred into a smaller apparatus. It is rinsed with DMF (10 l). More DMF is distilled off at 50° C. in vacuo until a total of about 100 l of distillate is obtained. It is cooled to 15° C. and stirred for another 2 hours at this temperature. The product is isolated using suction dryers, then washed with cold DMF (10 l) at 15° C. and cold acetone (25 l) at 15° C. It is dried at a maximum temperature of 50° C. for not more than 36 hours in a nitrogen current.

Yield: 13.2 kg (88%); melting point: 200-230° C. (depending on the purity of the crude product);

The crude product thus obtained (10.3 kg) is added to methanol (66 l). The mixture is refluxed to dissolve it. The solution is cooled to 7° C. and stirred for 1.5 h at this temperature. The product is isolated using suction dryers, washed with cold methanol (11 l) at 7° C. and dried for max. 36 h at about 50° C. in a nitrogen current.

Yield: 9.9 kg (96%); melting point: 228° C. (determined by DSC at a heating rate of 10 K/min).

If desired, the product thus obtained can be converted into the crystalline monohydrate of tiotropium bromide. This can be done as follows.

15.0 kg of tiotropium bromide are added to 25.7 kg of water in a suitable reaction vessel. The mixture is heated to 80-90° C. and stirred at constant temperature until a clear solution is formed. Activated charcoal (0.8 kg), moistened with water, is suspended in 4.4 kg of water, this mixture is added to the solution containing tiotropium bromide and rinsed with 4.3 kg of water. The mixture thus obtained is stirred for at least 15 min at 80-90° C. and then filtered through a heated filter into an apparatus which has been preheated to an outer temperature of 70° C. The filter is rinsed with 8.6 kg of water. The contents of the apparatus are cooled to a temperature of 20-25° C. at a rate of 3-5° C. per 20 minutes. The apparatus is further cooled to 10-15° C. using cold water and the crystallisation is completed by stirring for at least one hour. The crystals are isolated using a suction drier, the isolated crystal slurry is washed with 9 l of cold water (10-15° C.) and cold acetone (10-15° C.). The crystals obtained are dried at about 25° C. over about 2 hours in a nitrogen current.

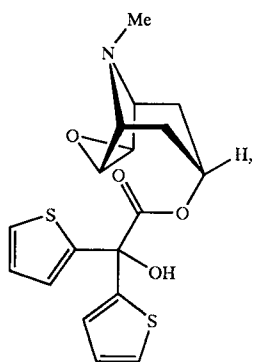
Yield: 13.4 kg of tiotropium bromide monohydrate (86% of theory)

Melting point: 230° C. (determined by DSC at a heating rate of 10 K/min).

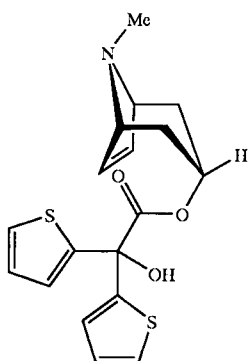
We claim:

1. A process for preparing the scopine ester of formula (IV):

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said process comprising epoxidizing the tropenol ester of formula (VII):

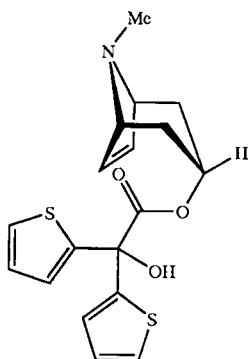


to form the scopine ester of formula (IV).

2. A process according to claim 1, wherein a mixture of vanadium pentoxide with hydrogen peroxide is used as the epoxidising agent for epoxidising (VII) to form (IV).

3. A process according to claim 1, wherein the epoxidation of (VII) to form (IV) is carried out in a solvent which is selected from among water, dimethylformamide, acetonitrile, dimethylacetamide and N-methylpyrrolidinone.

4. A process according to any one of claims 1 to 3, wherein the compound of formula (VII):

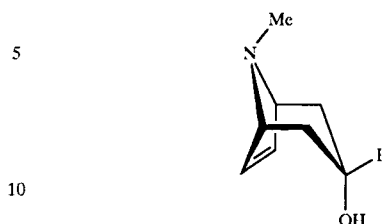


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is obtained by reacting tropenol of formula (V),

(IV)

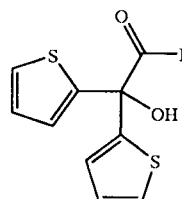
(V)



optionally in the form of an acid addition salt thereof, with an ester of formula (VI)

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(VI)



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(VII)

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wherein R is a group which is selected from among hydroxy, methoxy, ethoxy, O—N-succinimide, O—N-phthalimide, phenyloxy, nitrophenyloxy, fluorophenyloxy, pentafluorophenyloxy, vinyloxy, —S-methyl, —S-ethyl and —S-phenyl.

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5. A process according to claim 4, wherein the tropenol (V) is used in the form of an acid addition salt thereof which is selected from among the hydrochloride, hydrobromide, hydrogen phosphate, hydrogen sulphate, tetrafluoroborate and hexafluorophosphate salts.

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6. A process according to claim 4, wherein the reaction of (V) with (VI) to form (VII) is carried out in a suitable organic solvent.

7. A process according to claim 4, wherein the reaction of (V) with (VI) to form (VII) is carried out in an organic solvent selected from among toluene, benzene, n-butylacetate, dichloromethane, THF, dioxane, dimethylacetamide, DMF and N-methylpyrrolidinone.

8. A process according to claim 4, wherein the reaction of (V) with (VI) to form (VII) is carried out in the presence of an organic or inorganic base.

9. A process according to claim 4, wherein the reaction of (V) with (VI) to form (VII) is carried out in the presence of a base selected from among the organic amines.

10. A process according to claim 4, wherein the reaction of (V) with (VI) to form (VII) is carried out in the presence of diisopropylethylamine, triethylamine, DBU or pyridine.

11. A process according to claim 4, wherein the reaction of (V) with (VI) to form (VII) is carried out in the presence of an inorganic base.

12. A process according to claim 4, wherein the reaction of (V) with (VI) to form (VII) is carried out in the presence of an alkali metal or alkaline earth metal carbonate, alkoxide or hydride of lithium, sodium, potassium or calcium.

13. A process according to claim 4, wherein if R denotes hydroxy in the compound of formula (VI), the reaction of (V) with (VI) to form (VII) is carried out in the presence of coupling reagents.

14. A process according to claim 13, wherein the coupling reagents are selected from among carbonyldiimidazole, carbonyldi-1,2,4-triazole, dicyclohexylcarbodiimide and ethyl-dimethylaminopropylcarbodiimide.

* * * * *



(19) **United States**

(12) **Patent Application Publication**

Lock et al.

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(43) **Pub. Date: Mar. 2, 2006**

(54) **NEW METHOD FOR PREPARING
TIOTROPIUM SALTS**

(75) **Inventors:** **Ralf Lock**, Mainz (DE); **Werner
Belzer**, St. Goar (DE); **Rainer Hamm**,
Ingelheim (DE); **Monika Hofmann**,
Mainz (DE)

Correspondence Address:

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM CORPORATION
900 RIDGEBURY ROAD
P. O. BOX 368
RIDGEFIELD, CT 06877-0368 (US)

(73) **Assignee:** **Boehringer Ingelheim Pharma GmbH
& Co., KG**, Ingelheim (DE)

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Publication Classification

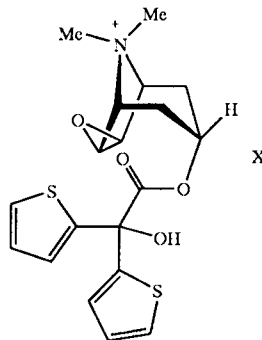
(51) **Int. Cl.**
C07D 491/08 (2006.01)

(52) **U.S. Cl. 546/91**

(57) **ABSTRACT**

The invention relates to a new process for preparing tiotropium salts of general formula 1

1



wherein X⁻ may have the meanings given in the claims and in the specification.

optionally in the presence of a base such as for example pyridine, imidazole or N-alkylamine, or first of all placed together with dithienylglycolic acid or the dithienylglycolic acid salt in the above-mentioned solvent, optionally in the presence of a base such as, for example, pyridine, imidazole or N-alkylamine, and then combined with the above-mentioned coupling reagent.

[0029] Preferably the three components mentioned above for forming the compound of formula 3 are added in stoichiometric amounts, but if desired the reaction may also be carried out with one of the three components present in excess (for example 1.1 to 1.5 equivalents). Preferably between 0.2 and 1.5 L, particularly preferably between 0.3 and 1 L of the specified solvent are used at this point per mol of the compound of formula 3 generated in situ.

[0030] After all three components have been added, the resulting solution is mixed at the temperature indicated above for about 5 minutes to 2 hours, preferably 10 minutes to 1 hour, particularly preferably for 20-40 minutes, for example by stirring, in order to form the compound of general formula 3.

[0031] The compound of formula 2 is then added to the solution thus obtained. This may be done either by the addition of a solution or suspension of the compound of formula 2 in one or more of the above-mentioned solvents or by, preferably batchwise, addition of the actual compound of formula 2. If the compound of formula 2 is added after being dissolved or suspended in one or more solvents, it is convenient to use the same solvent which is used for the preparation in situ of the compound of formula 3.

[0032] The amount in which the compound of formula 2 is added is determined by the amount of compound of formula 3 generated in situ. If the three components dithienylglycolic acid or dithienylglycolic acid salt, coupling reagent and compound of formula 5 are used in stoichiometric quantities to form the compound of formula 3, the compound of formula 3 is present in the molar amount which was selected for the three components dithienylglycolic acid or dithienylglycolic acid salt, coupling reagent and compound of formula 5. If the three components dithienylglycolic acid or dithienylglycolic acid salt, coupling reagent and compound of formula 5 are not used in stoichiometric amounts to form the compound of formula 3, the compound of formula 3 is present in the molar amount of the particular one of the three starting compounds dithienylglycolic acid or dithienylglycolic acid salt, coupling reagent and compound of formula 5 which is present in the smallest quantity.

[0033] The molar ratio of compound of formula 2 to compound of formula 3 generated in situ is preferably maintained within the range from 2:1 to 1:5, preferably 1.5:1 to 1:3, particularly preferably 1:1 to 1:2, while a ratio of 1:1 to 1:1.5 according to the invention is of particular importance.

[0034] After the addition of the compound of formula 3 the reaction mixture obtained is combined with a base taken up in a suitable solvent. Suitable solvents according to the invention are those mentioned hereinbefore. Preferably the solvent used here is the one which is also used to form the compound of formula 3. The bases used may be organic or inorganic bases. Organic bases used are preferably alkali

metal imidazolides which may be generated in situ for example from the alkali metals and imidazole or the alkali metal hydrides and imidazole. Preferred alkali metal imidazolides include imidazolides of lithium, sodium or potassium, sodium or lithium imidazolidine being preferred according to the invention. Particularly preferred are alkali metal alkoxides of sterically hindered alcohols (e.g. potassium *tert*-butoxide). Other preferred bases according to the invention are selected from among lithium diisopropylamide (LDA), lithium or sodium hexamethyldisilazane (LiHMDS or NaHMDS). Suitable inorganic bases preferably include hydrides of lithium, sodium or potassium. Sodium hydride is particularly preferably used as the inorganic base.

[0035] 0.5-2 mol, particularly preferably 1-1.5 mol, of base are preferably added per mol of the compound of formula 2 used. Within the scope of the process according to the invention, however, it is generally sufficient if only 1-1.1 mol of base are added per mol of compound of formula 2 used.

[0036] To prepare the solution or suspension of base, between 0.2 and 1.5 L, particularly preferably between 0.3 and 1 L of the specified solvent are preferably used per mol of base.

[0037] The base is preferably added at a temperature of -20-60° C., preferably 0-45° C., particularly preferably 0-25° C. After the addition of the base the resulting mixture is stirred for about 10 minutes to 6 hours, preferably 30 minutes to 3 hours, particularly preferably 45 minutes to 1.5 hours at constant temperature in order to form the compound of formula 4.

[0038] In order to liberate the compound of formula 1 from the compound of formula 4 generated in situ, a suitable acid H—X is preferably added at a temperature below 10° C., particularly preferably at about 0° C. Preferably the choice of the acid depends on the anion X⁻ in the desired end product of general formula 1. If desired, within the scope of the present invention, in addition to the acid H—X, a suitable desilylating reagent may also be added which is preferably selected from among the ammonium fluorides, particularly preferably tetrabutylammonium fluoride, tetraethylammonium fluoride, benzyltrimethylammonium fluoride, tetrahexylammonium fluoride, tetraoctylammonium fluoride or hydrogen fluoride, either free or complexed, such as e.g. pyridinium fluoride or triethylamine-HF complex.

[0039] As an alternative to using one of the above-mentioned acids the compound of formula 1 may also be liberated exclusively using the de-silylating reagents mentioned above.

[0040] Inasmuch as compounds of general formula 1 wherein X⁻ denotes bromide are preferably synthesised within the scope of the present invention, the following procedure for preparing the tiotropium bromide which is preferred according to the invention is described. It is evident to the skilled man that, by a suitable choice of reagent H—X or Y—F [where Y may denote a cation such as a proton or a metal cation or ammonium, alkylammonium, tetraalkylammonium or pyridinium or a complex such as e.g. aluminium trifluoride-HF or some other fluoride

donor such as e.g. diethylaminosulphur trifluoride (DAST)], a corresponding procedure can also be used analogously to prepare compounds wherein X^- does not represent bromide.

[0041] In order to prepare compounds of formula 1 wherein X^- =bromide (=tropylium bromide), preferably 0.2 to 20 mol, preferably 0.5 to 15 mol, particularly preferably 1 to 14 mol of hydrogen bromide, based on the compound of formula 2 used, are added at constant temperature. The hydrogen bromide used may be added either in gaseous form or in the form of preferably saturated solutions. Preferably, according to the invention, the hydrogen bromide is added after being dissolved in glacial acetic acid or water. Particularly preferably, a 33% hydrogen bromide solution in glacial acetic acid is used or particularly preferably it is used as an aqueous 62% hydrobromic acid. The acid is preferably added slowly enough that the temperature of the reaction mixture does not exceed 20° C. After the addition has ended the mixture is stirred at constant temperature, optionally also while cooling with ice (between 0.5 and 6 hours).

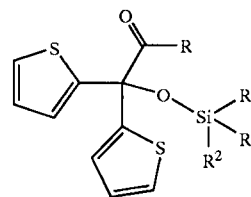
[0042] Working up may be carried out particularly as specified in the Examples, using methods known per se. For example, the reaction mixture is combined with a protic solvent, preferably with an alcohol, particularly preferably with methanol or ethanol or isopropanol. According to the invention, preferably 0.5 to 20 L, particularly preferably 0.7 to 13 L alcohol are added per mol of the compound of formula 2 used and the resulting mixture is stirred at a temperature of 0-60° C., preferably 10-45° C., particularly preferably 15-25° C. for a period of about 0.5-6 hours, preferably 0.5-5 hours, particularly preferably 0.5-4 hours.

[0043] Finally, the solution obtained is combined with a more non-polar organic solvent, preferably with a solvent selected from among a ketone (such as for example acetone or methyl ethyl ketone), an alcohol (such as for example methanol, ethanol, propanol, isopropanol, butanol or amyl alcohol), toluene, ethyl acetate, n-butyl acetate, dichloromethane, diethyl ether, methyl-tert.-butyl-ether, tetrahydrofuran and dioxane, particularly preferably isopropanol, toluene or acetone.

[0044] After thorough mixing the product that crystallises out is separated off and washed with the above-mentioned solvent. In order to separate off any water-soluble impurities, the crude product may be treated with water or aqueous bromide solutions, e.g. sodium or potassium bromide solution.

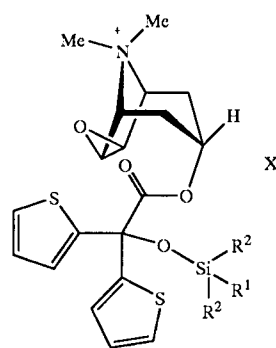
[0045] A more extensive purification of the compounds of formula 1 thus obtained may be carried out, if necessary, by chromatography on silica gel or by recrystallisation from suitable solvents such as e.g. lower alcohols, for example methanol, ethanol or isopropanol, optionally with prior treatment with activated charcoal.

[0046] In view of its central importance as an intermediate in the process according to the invention for preparing the compounds of formula 1 the present invention further relates to the compound of formula 3



wherein R, R^1 and R^2 may have the meanings given above, per se.

[0047] In view of its central importance as an intermediate in the process according to the invention for preparing the compounds of formula 1 the present invention further relates to the compound of formula 4



wherein X^- , R^1 and R^2 may have the meanings given above, per se.

[0048] The present invention also relates to the use of the above-mentioned compounds of formula 3 for preparing compounds of formula 1.

[0049] The present invention also relates to the use of the above-mentioned compounds of formula 4 for preparing compounds of formula 1.

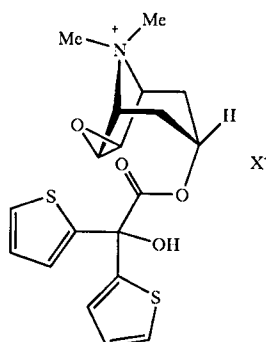
[0050] The Examples that follow serve to illustrate some methods of synthesis carried out by way of example. They are to be construed only as possible methods described by way of example without restricting the invention to their contents.

SYNTHESIS EXAMPLE 1

[0051] 5.43 g (50 mmol) chlorotrimethylsilane are added dropwise at 20° C. to a mixture of 13.1 g (50 mmol) sodium dithienylglycolate and 8.1 g (50 mmol) carbonyldiimidazole in 25 ml N-methylpyrrolidone (NMP).

[0052] After 30 min stirring 9.38 g (37.5 mmol) scopine methobromide are added and a solution of 2.59 g (38 mmol)

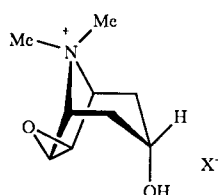
1) A process for preparing tiotropium salts of formula 1



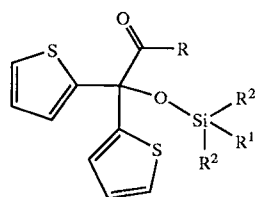
wherein

X^- may represent an anion with a single negative charge, preferably an anion selected from among chloride, bromide, iodide, methanesulphonate or trifluoromethanesulphonate,

wherein a compound of formula 2



wherein X^- may have the meanings given above, is reacted in one step with a compound of formula 3



generated in situ

wherein

R is a group selected from N-imidazolyl, N-triazolyl, $-O-C(=NR')-NHR''$, $-O-SO_2$ -phenyl, $-O-SO_2$ -phenyl-methyl, $-O-SO_2-R'-O-CO-C(methyl)_3$, $-O-CO$ -phenyl- NO_2 , chlorine, bromine, $-N_3$ and $-O-(P=O)R'''$, where

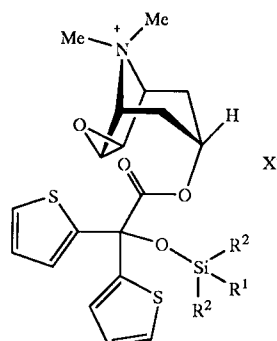
R' denotes C_1 - C_4 -alkyl or C_3 - C_6 -cycloalkyl;

R'' denotes C_1 - C_4 -alkyl, C_3 - C_6 -cycloalkyl, C_1 - C_4 -alkylene- $N(C_1$ - C_4 -alkyl) $_2$;

R''' denotes C_1 - C_4 -alkyl, $-O-C_1$ - C_4 -alkyl, phenyl or $-O$ -phenyl;

R¹ and R², which may be identical or different, represent methyl, ethyl, propyl, butyl or phenyl, wherein phenyl may optionally be substituted by one or more C_1 - C_4 -alkyl groups,

in a suitable solvent with the addition of a suitable base to yield a compound of formula 4



wherein the groups X^- , R¹ and R² may have the meanings as given above, and without being isolated the compound of formula 4 is converted into the compound of formula 1 by reaction with a suitable acid or a suitable desilylating reagent while cleaving the silyl group.

2) The process for preparing tiotropium salts of formula 1 according to claim 1, wherein

X^- represents an anion with a single negative charge selected from chloride, bromide, iodide, methanesulphonate or trifluoromethanesulphonate.

3) The process for preparing tiotropium salts of formula 1 according to claim 1, wherein the reaction is carried out with a compound of formula 3 generated in situ, wherein

R is a group selected from among N-imidazolyl, N-triazolyl, $-O-C(=NR')-NHR''$, $-O-SO_2$ -phenyl-methyl, $-O-CO-C(methyl)_3$, and chlorine, where

R' denotes methyl, ethyl or cyclohexyl;

R'' denotes methyl, ethyl, cyclohexyl, C_1 - C_3 -alkylene- $N(methyl)_2$ or C_2 - C_3 -alkylene- $N(ethyl)_2$, and

R¹ and R², which may be identical or different, denote methyl, ethyl, propyl or butyl.

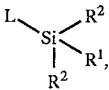
4) The process for preparing tiotropium salts of formula 1 according to claim 1, wherein the reaction is carried out with a compound of formula 3 generated in situ, wherein

R is a group selected from among N-imidazolyl, N-triazolyl, $-O-C(=N-cyclohexyl)-NHcyclohexyl$, $-O-C(=N-ethyl)-NH-CH_2-CH_2-CH_2-NMe_2$ and $-O-CO-C(methyl)_3$, preferably N-imidazolyl or N-triazolyl, particularly preferably N-imidazolyl and

R¹ and R², which may be identical or different, denote methyl, ethyl, propyl or butyl, preferably methyl or ethyl, particularly preferably methyl;

R² denotes methyl or ethyl, preferably methyl.

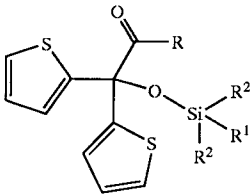
5) The process for preparing tiotropium salts of formula 1 according to claim 1, wherein the compound of formula 3 is generated in situ in a suitable solvent by reacting dithienylglycolic acid or alkali metal salts of dithienylglycolic acid with a coupling reagent selected from among carbonyldiimidazole, carbonyldi-1,2,4-triazole, dicyclohexylcarbodiimide, ethyl-dimethylaminopropylcarbodiimide, toluenesulphonyl chloride, pivaloyl chloride, nitrobenzoic acid anhydride, oxalyl chloride, phosgene, sulphonyl chloride and phosphorus chlorides, and subsequently adding a silyl compound of formula 5



wherein the groups R¹ and R² may have the meanings given above and L denotes a leaving group which is selected from among the halide, methanesulphonate, trifluoromethanesulphonate and para-toluenesulphonate.

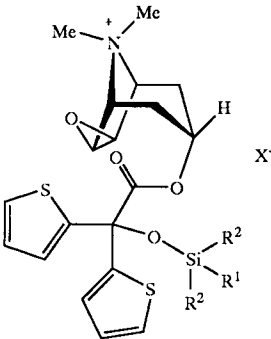
6) The process for preparing tiotropium salts of formula 1 according to claim 5, wherein the solvent is selected from acetonitrile, nitromethane, formamide, dimethylformamide, N-methylpyrrolidinone, dimethylsulphoxide, dimethylacetamide, tetrahydrofuran, dioxane and sulfolane.

7) A compound of formula 3



wherein R, R¹ and R² may have the meanings given in claim 1.

8) A compound of formula 4



wherein X⁻, R¹ and R² may have the meanings given in claim 1.

* * * * *

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GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).(71) Applicant (*for all designated States except US*): **SICOR
INC.** [US/US]; 19 Hughes, Irvine, CA 92618 (US).

(71) Applicant and

(72) Inventor: **SCARPITTA, Francesca** [IT/IT]; Via S. Per-
tini N. 8, I-10015 Ivrea (TO) (IT).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BUSOLLI,
Jonathan** [IT/IT]; Via Buronzo N. 65, I-13040 Carisio
(vc) (IT). **DIULGHEROFF, Nicola** [IT/IT]; C. So Tas-
soni, 34, Torino (IT). **VOLONTÈ Roberta** [IT/IT]; Via de
Amicis N. 4, I-22069 Rovellasca (co) (IT). **PONTIROLI,
Alessandro** [IT/IT]; Via Begoglio 40, S. Maria Della
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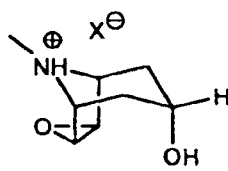
(54) Title: PROCESS FOR THE PREPARATION OF TIOTROPIUM BROMIDE

(57) Abstract: The invention is directed to improved processes for preparing Tiotropium bromide.

WO 2008/008376 A2

SUMMARY OF THE INVENTION

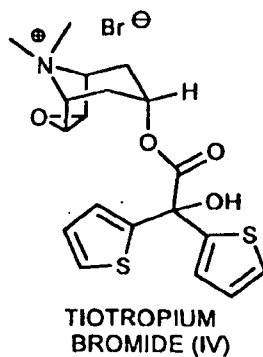
[0012] In one embodiment, the present invention encompasses scopine salt of formula II-s :



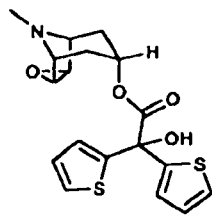
II-s

containing about 0.5% to about 40% by weight of salts; wherein X is Br, Cl, SO₄, MeCOO, PO₄, MeSO₃, tartrate, fumarate, citrate, maleate, succinate, p-toluene sulphonate or amidosulphonate.

[0013] In another embodiment, the present invention encompasses a process to convert scopine salt of formula II-s containing about 0.5% to about 40% by weight of salts to Tiotropium bromide of formula IV.

TIOTROPIUM
BROMIDE (IV)

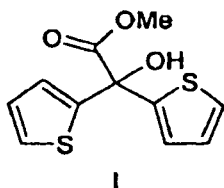
[0014] In yet another embodiment, the present invention encompasses the preparation of N-demethyl-tiotropium of formula III,



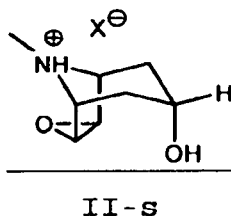
III

comprising combining methyl-di-(2-thienyl)-glycolate of

formula I,

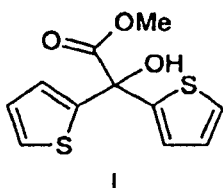


a weak inorganic base, a polar organic solvent and scopolamine salt of formula II-s



containing about 0.5% to about 40% by weight of salts to obtain a mixture, and heating the mixture.

[0015] In one embodiment, the present invention encompasses a process for the preparation of Tiotropium bromide comprising a) combining methyl-di-(2-thienyl)-glycolate of formula I,



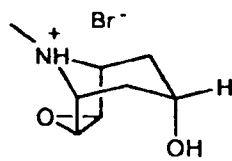
a weak base, a polar organic solvent, and scopolamine salt of formula II-s containing about 0.5% to about 40% by weight of salt to obtain a mixture; b) heating the mixture providing N-demethyl-tiotropium of formula III; c) recovering the N-demethyl-tiotropium of formula III; d) combining N-demethyl-tiotropium of formula III with methylbromide (MeBr) and an organic solvent to yield Tiotropium bromide.

[0016] In another embodiment, the present invention encompasses a process to prepare Tiotropium bromide, by preparing N-demethyl-tiotropium of formula III by the process of the present invention, and further converting it to Tiotropium bromide.

DETAILED DESCRIPTION OF THE INVENTION

[0017] As used herein, the term "room temperature" refers to a temperature ranging from about 20°C to about 26°C.

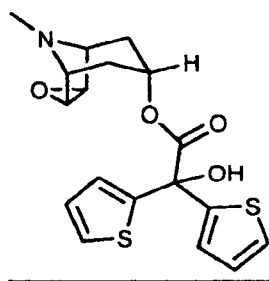
[0018] The present application discloses a novel approach to the synthesis of Tiotropium bromide, in particular from a Scopine hydrohalide of formula II-s, and even more specifically, from scopine HBr of the formula



that contains a low level of salts, as compared to the process disclosed in GB '781, where the obtained scopine HCl contained a high level of more than 60% by weight of inorganic salts. These salts are insoluble in water, and thus cannot be removed by a simple washing operation.

[0019] Typically, scopine hydrohalide containing low level of salts refers to scopine salt with less than 40% by weight of salts. Typically, the measurement of the salts content is done by sulfuric ashes, as exemplified in example 1.

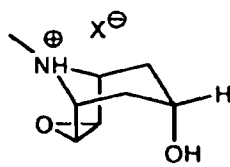
[0020] Moreover, the inventors of this application have found that the purity of the scopine salt affects the purity and the yield of N-demethyl-tiotropium of formula III, a key intermediate in the synthesis of Tiotropium bromide.



III

For example, without restricting the invention, using pure scopine salt leads to higher yield and purity, as will be further demonstrated.

[0021] The present invention encompasses scopine salt of formula II-s



II-s

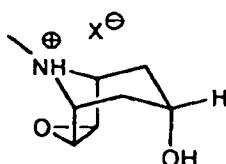
containing about 0.5% to about 40% by weight of salts; wherein X is Br, Cl, SO₄, MeCOO, PO₄, MeSO₃, tartrate, fumarate, citrate, maleate, succinate, p-toluene sulphonate or amidosulphonate.

[0022] Preferably, scopine salt of formula II-s contains about 0.5% to about 20% by weight of salts, more preferably of about 0.5% to about 15% by weight, even more preferably of about 0.5% to about 5% by weight, and most preferably of about 0.5% to about 1% by weight. As mentioned before, the content of the salts can be determined by sulfuric ashes.

[0023] Preferably, the scopine salt is selected from a group consisting of HBr, HCl, H₂SO₄, CH₃COOH, H₃PO₄, MeSO₃H, tartrate, fumarate, citrate, maleate, succinate, malate, p-toluenesulphonate, and amidosulphonate. More, preferably, the salt is HBr.

What is claimed is:

1. A scopine salt of formula II-s



Formula II-s

comprising about 0.5% to about 40% by weight of salts; wherein X is selected from the group consisting of Br, Cl, SO₄, MeCOO, PO₄, MeSO₃, tartrate, fumarate, citrate, maleate, succinate, p-toluene sulphonate and amidosulphonate.

2. The scopine salt of claim 1, wherein X is Br.
3. The scopine salt of claim 1 or claim 2, wherein said salt content is about 0.5% to about 20% by weight.
4. The scopine salt of any of the preceding claims, wherein said scopine salt is selected from the group consisting of an HBr, HCl, H₂SO₄, CH₃COOH, H₃PO₄, MeSO₃H, tartrate, fumarate, citrate, maleate, succinate, maleate, p-toluenesulphonate, borate and amidosulphonate scopine salt.
5. A process of preparing said scopine salt of any of the preceding claims, comprising:
 - a. filtering a reaction mixture containing said scopine salt to produce a filtrate,
 - b. adding water to said filtrate to precipitate insoluble salts;
 - c. filtering said insoluble salts from said filtrate;
 - d. adding an acid to said filtrate to precipitate said scopine salt; and
 - e. collecting said precipitated scopine salt.
6. The process of claim 5, wherein said acid is HBr.

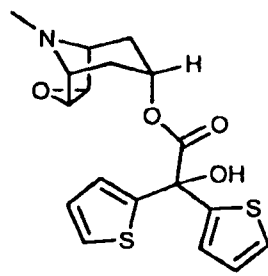
7. The process of claim 5 or claim 6, further comprising washing said precipitated scoline salts with a polar organic solvent.

8. The process of any of claims 5 to 7, wherein said polar organic solvent is selected from the group consisting of a C₁₋₆ alcohol, a C₄₋₈ ether, a C₃₋₁₀ ketone, a C₂₋₄ nitrile, and mixtures thereof.

9. The process of claim 8, wherein said polar organic solvent is selected from the group consisting of methanol, ethanol, isopropanol, 1,4-dioxane, acetone, acetonitrile, and mixtures thereof.

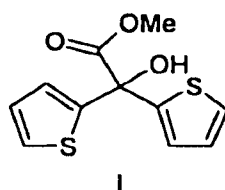
10. A process for preparing Tiotropium bromide comprising preparing scoline salt of formula II-s containing about 0.5% to about 40% by weight of salts by the process of claim 5, and converting it to Tiotropium bromide.

11. A process for the preparation of N-demethyl-tiotropium of formula III,



III

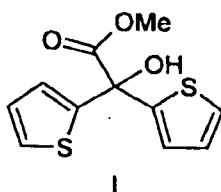
comprising reacting methyl-di-(2-thienyl)-glycolate of formula I,



I

with a scoline salt as defined in any of claims 1 to 4.

12. A process according to claim 11, wherein the process comprises combining methyl-di-(2-thienyl)-glycolate of formula I,



a weak inorganic base, a polar organic solvent, and a scopine salt of formula II-s containing about 0.5% to about 40% by weight of salts to obtain a mixture, and heating said mixture.

13. The process of any of claims 11 or 12, wherein said scopine salt is suspended in a polar organic solvent prior to said combination.

14. The process of claim 13, wherein said weak inorganic base is added to said suspension providing a new suspension.

15. The process of claim 14, wherein said weak inorganic base is anhydrous.

16. The process of any of claims 13 to 15, wherein said weak inorganic base has a pKa of about 8 to about 12.

17. The process of claim 14, wherein said weak inorganic base is selected from the group consisting of K_2CO_3 , $NaHCO_3$, Li_2CO_3 , Cs_2CO_3 , t-ButOK, and t-ButOLi.

18. The process of claim 17, wherein said weak inorganic base is K_2CO_3 .

19. The process of any of claims 12 to 18, wherein after said addition of said weak inorganic base, a mixture of said Methyl-di-(2-thienyl)-glycolate and

another portion of said weak inorganic base are added to said new suspension to provide a mixture.

20. The process of any of claims 12 to 19, wherein said Methyl-di-(2-thienyl)-glycolate is added in solution in a polar organic solvent.

21. The process of any of claims 12 to 20, wherein said polar organic solvent is selected from a group consisting of C₁-C₄ amides, C₂-C₄ sulfoxides, C₂-C₄ sulfones, C₇-C₈ aromatic hydrocarbons, and C₂-C₄ nitriles.

22. The process of claim 21, wherein said polar organic solvent is dimethylformamide.

23. The process of any of claims 12 to 22, wherein an amount of said weak inorganic base is about 0.45 to about 2.5 moles per mole equivalent of said scopine salt.

24. The process of any of claims 14 to 23, wherein said addition of said weak inorganic base is performed at a temperature of about 25°C to about 65°C.

25. The process of claim 24, wherein said mixture is heated to a temperature of below about 70°C.

26. The process of any of claims 11 to 25, further comprising recovering said N-demethyl-tiotropium.

27. The process of any of the claims 11 or 12, wherein a scopine base is used instead of said scopine salt.

28. The process of claim 11, wherein a scopine base is used and about 1 to 1.5 mole equivalents of said weak inorganic base is used per mole equivalent of said scopine base.

29. A process for the preparation of Tiotropium bromide comprising the steps of:

- a. preparing N-demethyl-tiotropium by a process as defined in any of claims 11 to 28; and

b. reacting said N-demethyl-tiotropium with methylbromide in an organic solvent to form Tiotropium bromide.

30. The process of claim 29, wherein said organic solvent is selected from the group consisting of a C₂₋₄ nitrile, a C₄₋₈ linear or cyclic ether, a mixture of a C₂₋₄ nitrile and a C₄₋₈ linear or cyclic ether, a mixture of a C₇₋₈ aromatic hydrocarbon and a C₂₋₄ nitrile, and a mixture of a C₂₋₄ nitrile and a C₃₋₁₀ ketone.

31. The process of claim 30, wherein said organic solvent is selected from the group consisting of acetonitrile, tetrahydrofuran, a mixture of acetonitrile and tetrahydrofuran, a mixture of toluene and acetonitrile, and a mixture of acetone and acetonitrile.

32. The process of claim 31, wherein said organic solvent is acetonitrile.

33. Use of a scoline salt as defined in any of claims 1 to 5 in a process for the manufacture of N-demethyl tiotropium of Formula III or Tiotropium bromide.

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Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad, Maharashtra 410208 (IN).

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(74) Agents: ELEND, Almut et al.; Venner Shipley LLP, Byron House, Cambridge Business Park, Cowley Road, Cambridge Cambridgeshire CB4 0WZ (GB).

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(71) Applicants (for all designated States except US):
GENERIC [UK] LIMITED [GB/GB]; Albany Gate, Darkes Lane, Potters Bar Hertfordshire EN6 1AG (GB).
MYLAN DEVELOPMENT CENTRE PRIVATE LIMITED [IN/IN]; Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad, Maharashtra 410208 (IN).

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(72) Inventors; and

(75) Inventors/Applicants (for US only): GAITONDE, Abhay [IN/IN]; Mylan Development Centre Private Limited, Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad, Maharashtra 410208 (IN). MANOJKUMAR, Bindu [IN/IN]; Mylan Development Centre Private Limited, Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad, Maharashtra 410208 (IN). SHINDE, Dattatraya [IN/IN]; Mylan Development Centre Private Limited, Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad, Maharashtra 410208 (IN). TANK, Sinderpal [IN/IN]; Mylan Development Centre Private Limited,

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(54) Title: NOVEL PROCESS FOR THE PREPARATION OF SCOPINE ESTERS

(57) Abstract: The present invention relates to novel processes for the preparation of scopine esters and their quaternary salts. In particular, the present invention relates to a process for the preparation of tiotropium bromide, pharmaceutical compositions comprising tiotropium bromide and the use of such compositions in the treatment of respiratory disorders.

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pharmaceutical composition is suitable for use in a dry powder inhaler (DPI), an aqueous nebulizer, or a pressurized metered dosage inhaler (pMDI).

The DPI compositions of the present invention preferably contain, in addition to the active
5 substance, one or more of the following physiologically acceptable excipients: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, sucrose, maltose), oligo- and polysaccharides (e.g. dextrane), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is
10 preferred, particularly in the form of their hydrates. For the purposes of the present invention, lactose is a particularly preferred excipient, while lactose monohydrate is most particularly preferred.

Preferably the pMDI uses HFA 134a, HFA 227 or mixtures thereof as propellant gas.
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The pharmaceutical composition according to the fifth aspect of the present invention can also be a solution, suspension or a solid oral dosage form if so desired. Preferred oral dosage forms in accordance with the invention include tablets, capsules and the like which, optionally, may be coated if desired. Tablets can be prepared by conventional techniques,
20 including direct compression, wet granulation and dry granulation. Capsules are generally formed from a gelatine material and can include a conventionally prepared granulate of excipients in accordance with the invention.

The pharmaceutical composition according to the present invention typically comprises
25 one or more conventional pharmaceutically acceptable excipient(s) selected from the group comprising a filler, a binder, a disintegrant, a lubricant and optionally further comprises at least one excipient selected from colouring agents, adsorbents, surfactants, film formers and plasticizers.

30 If the solid pharmaceutical formulation is in the form of coated tablets, the coating may be prepared from at least one film-former such as hydroxypropyl methyl cellulose, hydroxypropyl cellulose or methacrylate polymers which optionally may contain at least one plasticizer such as polyethylene glycols, dibutyl sebacate, triethyl citrate, and other

pharmaceutical auxiliary substances conventional for film coatings, such as pigments, fillers and others.

The pharmaceutical compositions of the present invention preferably contain about 0.001 to 20% tiotropium bromide in admixture with a physiologically acceptable excipient. Preferred compositions contain 0.01 to 10% of tiotropium bromide, more preferred are compositions which contain 0.01 to 2% of tiotropium bromide, and most preferred are compositions which contain 0.04 to 0.8% of tiotropium bromide.

The following examples are provided to illustrate the present invention and should not be construed as limiting thereof.

Examples

Tiotropium base (3)

Scopine HCl was taken in DMF (5vol), cooled to 5°C, and NaH (1.7eq) was added slowly maintaining the temperature at 5°C. The reaction was stirred for 1 hour at 10°C and DBU (1eq) and methyl di(2-thienyl)glycolate (1eq) were added. The reaction was heated to 60°C for 1 hour and a second portion of DBU (2eq) was added. The reaction was heated for a further 4 hours at 60°C and monitored by TLC. After completion of the reaction, the mixture was cooled to 5°C and a solution of conc. HCl (2.5vol) in cold water (10vol) at 10°C (pH 2) was added. The mixture was washed with toluene and basified with aqueous sodium carbonate (7.5eq) to pH 10 and extracted with DCM (3 x 10vol). The combined DCM layer was washed with water (3 x 10vol) and DCM was distilled under vacuum (150 mbar) at 30°C. The product was obtained as light brown solid. Molar Yield = 60%; HPLC purity = 98%.

The crude base (3) was recrystallized from acetonitrile (5vol). Yield of crystallization = 86%; HPLC purity > 99.8%.

Tiotropium bromide (1)

The purified tiotropium base (3) was dissolved in DCM (10vol) and acetonitrile (3vol) and purged with methyl bromide gas at a pressure of 10 kg/cm² for 20 minutes. The solution
5 was kept at 25-30°C for 30 hours. The precipitated solid was filtered and washed with DCM (20vol). Drying of the solid at 25-30°C under vacuum gave the product as a white solid. Molar Yield = 97.76%; HPLC purity = 99.83%.

¹H-NMR (300 MHz, CD₃OD): 7.45 (2H dd), 7.23 (2H dd), 7.00 (2H dd), 5.27 (1H t), 4.60
10 (1H br s OH), 3.35 (8H m), 3.10 (2H s), 2.85 (2H dt), 2.10 (2H d).

MS: 392.3 (M+1)

Alternative process for the preparation of tiotropium bromide (1) without isolation of tiotropium base (3)

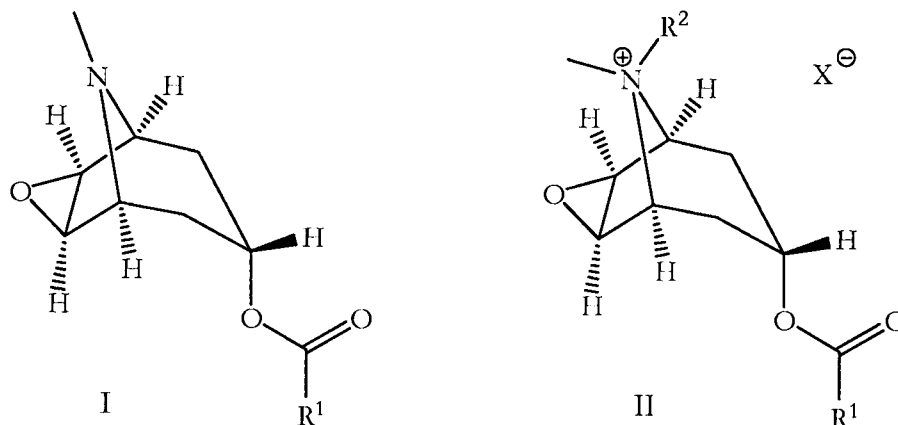
15

Scopine HCl was taken in DMF (5vol), cooled to 5°C, and NaH (1.7eq) was added slowly maintaining the temperature at 5°C. The reaction mixture was stirred for 1 hour at 10°C and DBU (1eq) and methyl di(2-thienyl)glycolate (1eq) were added. The reaction was heated to 60°C for 1 hour and a second lot of DBU (2eq) was added. The reaction mixture
20 was heated for a further 4 hours at 60°C and monitored by TLC. After completion of the reaction, the mixture was cooled to 5°C and a solution of conc. HCl (2.5vol) in cold water (10vol) at 10°C (pH 2) was added. The mixture was washed with toluene (1vol) and the aqueous layer was basified with saturated sodium carbonate (7.5eq) solution to pH 10 and extracted with DCM (3 x 10vol). The combined DCM layer was washed with water (3 x
25 10vol) and dried over anhydrous sodium sulfate.

To the DCM solution, acetonitrile was added and the mixture was purged with methyl bromide gas at a pressure of 3 kg/cm² for 30 minutes. The solution was kept at 25-30°C for 30 hours. The precipitated solid was filtered and washed with DCM (20vol). Drying of
30 the solid at 25-30°C under vacuum gave the product as a white solid. Molar yield = 41%; HPLC purity = 98.66%.

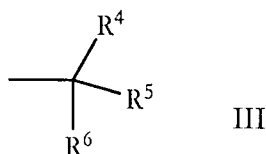
Claims

1. A process for the preparation of scopine ester I or its quaternary salt II:



- 5 comprising transesterification of scopine, or a salt thereof, with a suitable carboxylic ester represented by formula $R^1CO_2R^3$; wherein R^1 and R^2 independently represent hydrogen, alkyl, alkenyl, alkynyl, optionally substituted aryl, or optionally substituted arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl; R^3 represents alkyl, alkenyl, alkynyl, optionally substituted aryl, or optionally substituted arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl; and X represents a pharmaceutically acceptable anion.

2. A process according to claim 1, wherein R^1 is represented by formula III:



- 15 wherein R^4 , R^5 and R^6 independently represent hydrogen, hydroxy, halo, alkoxy, alkyl, hydroxyalkyl, alkenyl, alkynyl, optionally substituted aryl, or optionally substituted arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl.

3. A process according to claim 2, wherein R^4 and/or R^5 represent aryl.

4. A process according to claim 3, wherein the aryl group is selected from phenyl, naphthyl, thienyl and furyl, which may optionally be mono- or disubstituted by one or two groups selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, halo or haloalkyl.
- 5 5. A process according to claim 4, wherein the aryl group is 2-thienyl.
6. A process according to any one of claims 2 to 5, wherein R⁶ represents hydroxy, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxyalkyl, halo or haloalkyl.
- 10 7. A process according to any one of claims 2 to 6, wherein R⁴ is 2-thienyl, R⁵ is 2-thienyl and R⁶ is hydroxyl.
8. A process according to any one of the preceding claims, wherein R² represents hydrogen or C₁-C₄ alkyl.
- 15 9. A process according to any one of the preceding claims, wherein R³ represents C₁-C₄ alkyl.
10. A process according to claim 9, wherein R³ represents methyl.
- 20 11. A process according to any one of the preceding claims, wherein X represents a halo, a methanesulfonate, a toluenesulfonate or a trifluoromethanesulfonate group.
12. A process according to claim 11, wherein X represents a bromo group.
- 25 13. A process according to any one of the preceding claims, wherein R² is methyl and X is bromo.
14. A process according to any one of the preceding claims, wherein the scopine is
30 used in the form of its hydrochloride salt.
15. A process according to any one of the preceding claims, wherein the transesterification reaction is performed in the presence of a base.

16. A process according to claim 15, wherein the base is an organic base.
17. A process according to claim 16, wherein the organic base is an organic amine base.
- 5 18. A process according to claim 17, wherein the organic amine base is a trialkylamine or a heterocyclic amine.
19. A process according to claim 18, wherein the organic amine base is selected from
10 triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (Dabco), pyridine or 4-(dimethylamino)pyridine (DMAP).
20. A process according to claim 19, wherein the organic amine base is DBU.
- 15 21. A process according to any one of claims 15 to 20, wherein a further base is used.
22. A process according to claim 21, wherein the further base is an inorganic base.
- 20 23. A process according to claim 22, wherein the inorganic base is a hydride.
24. A process according to claim 23, wherein the hydride is NaH, KH or CaH₂.
25. A process according to claim 24, wherein the hydride is NaH.
- 25 26. A process according to any one of claims 21 to 25, wherein the scopolamine is used in the form of a salt.
27. A process according to claim 26, wherein the further base is used to liberate
30 scopolamine free base in situ.
28. A process according to any one of the preceding claims, wherein formation of the quaternary salt II is carried out without purification and/or isolation of ester I.

29. A process according to any one of the preceding claims, wherein the transesterification reaction is carried out in dimethylformamide.
- 5 30. A process according to any one of the preceding claims, wherein the scopine ester I or its quaternary salt II are obtained in an HPLC purity of greater than 95%.
31. A process according to any one of the preceding claims, wherein the scopine ester I or its quaternary salt II are obtained in a yield of greater than 50%.
- 10 32. Substantially pure tiotropium base (3).
33. Substantially pure tiotropium bromide (1).
- 15 34. Tiotropium base (3) or tiotropium bromide (1) prepared by a process according to any one of claims 1 to 31.
35. Tiotropium base (3) or tiotropium bromide (1) according to claim 34, which is substantially pure.
- 20 36. Tiotropium bromide (1) according to any one of claims 33 to 35, for use in medicine.
37. Tiotropium bromide (1) according to claim 36, for treating or preventing a
25 respiratory disorder.
38. Tiotropium bromide (1) according to claim 37, wherein the respiratory disorder comprises asthma or COPD.
- 30 39. Tiotropium bromide (1) according to claim 38, wherein the COPD is chronic bronchitis or emphysema.

40. A pharmaceutical composition comprising tiotropium bromide (1) according to any one of claims 33 to 39.

41. The pharmaceutical composition according to claim 40, which is suitable for use in
5 a dry powder inhaler (DPI), an aqueous nebulizer, or a pressurized metered dosage inhaler (pMDI).

42. Use of tiotropium bromide (1) according to any one of claims 33 to 39, or use of the composition according to claim 40 or 41, for the manufacture of a medicament for the
10 treatment or prevention of a respiratory disorder.

43. The use according to claim 42, wherein the respiratory disorder comprises asthma or COPD.

15 44. The use according to claim 43, wherein the COPD is chronic bronchitis or emphysema.

45. A method of treating or preventing a respiratory disorder, comprising administering to a patient in need thereof a therapeutically or prophylactically effective amount of
20 tiotropium bromide (1) according to any one of claims 33 to 39, or a therapeutically or prophylactically effective amount of the composition according to claim 40 or 41.

46. The method according to claim 45, wherein the respiratory disorder comprises asthma or COPD.

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47. The method according to claim 46, wherein the COPD is chronic bronchitis or emphysema.

48. The method according to any one of claims 45 to 47, wherein the patient is a
30 mammal.

49. The method according to claim 48, wherein the patient is a human.