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1545 FF

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite :002 Evento :001 Actuación:538

Referencia : **Expediente No. 00.093.237**

Solicitante : **PHARMACIA CORPORATION**

Asunto : Solicitud de patente para **"FORMA CRISTALINA DE EPLERENONA"**

Fecha de solicitud : 06 de diciembre de 2000

Publicada en : **la Gaceta No. 528 del 30 de mayo de 2003**

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo No. 03-80,509 por valor de $335.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 41687 del 24 de diciembre de 2002.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo, para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Bogotá, 24 NOV. 2003
Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

COLO 12482-801-001-5
MRE/DLM/ID-000070/WPC12482

1546

SUPERINTENDENCIA Y COMERCIO
Radicacion : 00092837 00000006 Folios: 2
Fecha (AMD): 2003-11-24 16:50:45
Tramite : 002 PATENTES D 1 REGISTRO/ SIN PETICION
Dependencia: 0020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 80,509
FECHA : NOVIEMBRE 5 DE 2003

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	15534424	05/11/2003	27,780,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85	EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
			TOTAL : $	335,000.00

SON: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Folio 12482-801-001-5

Industria y Comercio
SUPERINTENDENCIA

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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **00- 93237**

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **528**, DE

FECHA **30** DE **MAYO** DE **2003**, EL TERMINO HABIL SEÑALADO POR LA LEY

EXPIRA EL **29** DE **AGOSTO** DE **2003**.

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ____x_____

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1548 1760

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Emilio Ferrero
Apoderado

Oficio Nº 13157

REFERENCIA	**Radicación**	**00 93237**
	Trámite	**002**
	Evento	**001**
	Actuación	**430**
	Folios	**010**

Como resultado del examen de patentabilidad de la solicitud de patente de invención Nº 00 93237, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

. Descripción: folios 3-122
. Ejemplos: folios 123-169
. Capítulo reivindicatorio estudiado: folios 170-174
. Se reivindica prioridad presentada en Estados Unidos, el 08.12.99, bajo los números 60/169707, 60/169608, 60/169556, 60/169683, 60/169807 y 60/169639

Objeto de la invención

Según las reivindicaciones 1 a 18 de la presente solicitud, se refiere a eplerenona de forma cristalina L que tiene un sistema de cristal monoclínico y un patrón definido de difracción de rayos X, también se relaciona con el procedimiento de preparación de la misma.

Clasificación internacional de patentes A 61 K 31/566

Excepciones a la patentabilidad

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*"

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El contenido de la reivindicación 12, que trata de "El uso de la eplerenona...", no es patentable, debido a que la legislación actual contempla que los productos y procedimientos son los únicos objetos de patente.

El artículo 20d de la decisión 486 contempla que *"No serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

Teniendo en cuenta lo anterior, el contenido de la reivindicación 11, que trata de "Un método para tratar o impedir una condición...", no es patentable.

Claridad de la solicitud

El art. 30 de la decisión 486 contempla que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*

Los términos "cerca de" y "alrededor de" de las reivindicaciones 2-5 y 7 no delimitan de manera correcta la materia técnica que se protege, haciendo de dichas reivindicaciones faltas de claridad.

La expresión "cantidad detectable" que se encuentra en la reivindicación 6 no permite saber la cantidad de materia que se pretende proteger.

EL término "disolvente farmacéuticamente aceptable" de la reivindicación 13 es muy general y puede abarcar disolventes que no se encuentran revelados en la descripción.

Favor hacer las aclaraciones y correcciones del caso.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 08.12.99-, relacionados con la materia de la presente solicitud:

N°	Documento	Título	Fecha de publicación
1	WO 9825948	"Proceso para la preparación de 9,11-epoxi esteroides y sus intermediarios útiles"	18.06.98

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*"

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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60/049,388 11 June 1997 (11.06.97) US

(71) Applicant (*for all designated States except US*): G.D. SEARLE & CO. [US/US]; P.O. Box 5110, Chicago, IL 60680-9899 (US).

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(74) Agents: ROHDE, John, K., Jr. et al.; Senniger, Powers, Leavitt & Roedel, 16th floor, One Metropolitan Square, St. Louis, MO 63102 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

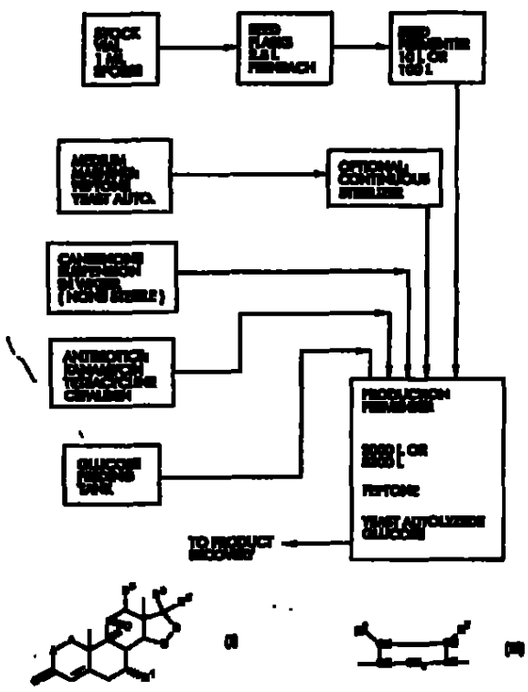
Published

Without international search report and to be republished upon receipt of that report.

(54) Title: PROCESSES FOR PREPARATION OF 9,11-EPOXY STEROIDS AND INTERMEDIATES USEFUL THEREIN

(57) Abstract

Multiple novel reaction schemes, novel process steps and novel intermediates are provided for the synthesis of epoxymexrenone and other compounds of formula (I) wherein: -A-A- represents the group $-CHR^4-CHR^5-$ or $-CR^4=CR^5-$, R^3, R^4 and R^5 are independently selected from the group consisting of hydrogen, halo, hydroxy, lower alkyl, lower alkoxy, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, cyano, aryloxy; R^1 represents an alpha-oriented lower alkoxycarbonyl or hydroxyalkyl radical; -B-B- represents the group $-CHR^6-CHR^7-$ or an alpha- or beta-oriented group (III), where R^6 and R^7 are independently selected from the group consisting of hydrogen, halo, lower alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy; and R^8 and R^9 are independently selected from the group consisting of hydrogen, hydroxy, halo, lower alkoxy, acyl, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkyl, alkoxycarbonyl, acyloxyalkyl, cyano and aryloxy, or R^8 and R^9 together comprise a carbocyclic or heterocyclic ring structure, or R^8 or R^9 together with R^6 or R^7 comprise a carbocyclic or heterocyclic ring structure fused to the pentacyclic D ring.



Example 45

Scheme 1: Step 3D: Method E: Synthesis of Methyl Hydrogen 9,11α-Epoxy-17α-hydroxy-3-oxopregn-4-ene-7α,21-dicarboxylate, γ-Lactone.

The enester of Formula IIA was converted to epoxymexrenone in the manner generally described in Example 43. In the reaction of this Example, enester charge was 5.4 g (assaying 74.4% enester), the trichloroacetamide charge was 4.9 g, hydrogen peroxide charge was 25 g, dipotassium hydrogen phosphate charge was 3.5 g. The reaction was run at 20°C for 18 hrs. The residual enester was less than 2%. After work up, 5.71 g of epoxymexrenone resulted.

Example 46

Scheme 1: Step 3D: Method F: Synthesis of Methyl Hydrogen 9,11α-Epoxy-17α-hydroxy-3-oxopregn-4-ene-7α,21-dicarboxylate, γ-Lactone.

Enester of Formula IIA was converted to epoxymexrenone in the manner described in Example 43 except that the reaction temperature in this Example was 28°C. The materials charged in the reactor included enester (2.7 g), trichloroacetamide (2.5 g), dipotassium hydrogen phosphate (1.7 g), hydrogen peroxide (17.0 g) and methylene chloride (50 mL). After 4 hrs. reaction, unreacted enester was only 2% based on the enester charge. After work up as described in Example 43, 3.0 g of epoxymexrenone was obtained.

Example 47-1

Scheme 1: Step 3D: Method G: Synthesis of Methyl Hydrogen 9,11α-Epoxy-17α-hydroxy-3-oxopregn-4-ene-7α,21-dicarboxylate, γ-Lactone.

Enester of Formula IIA (40.0 g, assaying 68.4% enester) was charged into a 1000 mL, jacketed reactor and dissolved in 175 mL of methylene chloride. The solution was stirred as trichloroacetamide (22.3 g) and dipotassium hydrogen phosphate (6.0 g) were added as solids. The mixture was stirred at 400 RPM and the temperature adjusted to 27°C with a constant temperature bath to control the liquid circulating through the reactor jacket. Hydrogen peroxide (72.8 mL at 30% assay) was added over a 3 to 5 minute period. Following the hydrogen peroxide addition, the mixture was stirred at 400 RPM and 27°C. HPLC assay indicated that the reaction was 99% complete within 5 hours. At the end of six hours, 72.8 mL of water was added. The aqueous hydrogen peroxide was separated and back extracted one time with 50 mL of methylene chloride. The combined methylene chloride was washed with 6% sodium sulfite (62.3 mL) to destroy any contained peroxide. The methylene chloride removal was started with atmospheric distillation and concluded under vacuum. A yellowish residue (48.7 g, 55.4% assay) was obtained. This correlated with a 94.8% assay adjusted molar yield.

A portion (47.8 g) of the residue was combined with 498 mL of ethanol 3A (95% ethanol denatured with 5% methanol). The mixture was heated to reflux and 249 mL of distillate removed at atmospheric pressure. The mixture was cooled to 25°C and filtered. An ethanol 3A rinse (53 mL) was used to assist the transfer. The dried solid weighed 27.6 g (87.0% assay) which correlated with a 91% recovery. A portion of the solid (27.0 g) was dissolved in 292 mL of methyl ethyl ketone at reflux. The hot solution was filtered through a pad of solka floc (powdered cellulose) with another 48.6 mL of methyl ethyl ketone used to assist the transfer. A 146 mL portion of the methyl ethyl ketone was removed via atmospheric distillation. The solution was cooled to 50°C and

stirred for one hour as the product crystallized. After one hour the mixture was cooled to 25°C. Stirring was continued for one hour and the solid filtered with 48.6 mL of methyl ethyl ketone used as a rinse. The solid was dried to a constant weight of 20.5 g which represented an 87.2% recrystallization recovery. The reaction yield and ethanol, methyl ethyl ketone recoveries combined for a 75% overall yield.

The methyl ethyl ketone mother liquor was suitable for recycling with an incoming methylene chloride solution from a subsequent reaction. The combined methylene chloride and methyl ethyl ketone mixture was evaporated to dryness with atmospheric and vacuum distillation. The residue was combined with 19 volumes of ethanol 3A based on epoxymexrenone content. One half of the solvent was removed under atmospheric distillation. After cooling to 25°C the solid was filtered and dried. The dry solid was dissolved in 12 volumes of methyl ethyl ketone at reflux. The hot solution was filtered through a solka floc pad with 2 volumes of methyl ethyl ketone added as a rinse. The filtrate was concentrated with the atmospheric distillation of 6 volumes of methyl ethyl ketone. The solution was cooled to 50°C and stirred for one hour as the product crystallized. After one hour the mixture was cooled to 25°C. Stirring was continued for one hour and the solid filtered with 2 volumes of methyl ethyl ketone used as a rinse. The solid was dried to a constant weight. The incorporation of the methyl ethyl ketone mother liquor raised the overall yield to 80-85%.

This method appears particularly suited for scaleup since it maximizes throughput and minimizes washing volumes and waste.

Example 47A

Scheme 1: Step 3D: Method H: Synthesis of Methyl Hydrogen 9,11α-Epoxy-17α-hydroxy-3-oxopregn-4-ene-7α,21-dicarboxylate, γ-Lactone.

Enester of Formula IIA (17 g, assaying 72% enester) was dissolved in methylene chloride (150 mL) after which trichloroacetamide (14.9 g) was added under slow agitation. The temperature of the mixture was adjusted to 25°C and a solution of dipotassium hydrogen phosphate (10.6 g) in water (10.6 mL) was stirred into the enester substrate solution under 400 rpm agitation. Hydrogen peroxide (30% by weight solution; 69.4 mL) was added to the substrate/phosphate/ trichloroacetamide mixture over a 3-5 min. period. No exotherm or oxygen evolution was observed. The reaction mixture thus prepared was stirred at 400 rpm and 25°C for 18.5 hrs. No oxygen evolution was observed throughout the course of the reaction, but analysis of the hydrogen peroxide consumption indicated that some oxygen was formed during the reaction. The reaction mixture was diluted with water (69.4 mL) and the mixture stirred at about 250 rpm for 15 min. No temperature control was necessary for this operation and it was conducted essentially at room temperature (any temperature in the range of 5-25°C being acceptable). The aqueous and organic layers were allowed to separate and the lower methylene chloride layer was removed.

The aqueous layer was back extracted with methylene chloride (69.4 mL) for 15 min. under agitation of 250 rpm. The layers were allowed to separate and the lower methylene chloride layer was removed. The aqueous layer (177 g; pH = 7) was submitted for hydrogen peroxide determination. The result (12.2%) indicated that 0.0434 mol of hydrogen peroxide were consumed in the reaction of 0.0307 mol of olefin. The excess hydrogen peroxide consumption was a measure of oxygen generation in the

reaction. Back extraction with a small amount of methylene chloride volume was sufficient to insure no loss of epoxymexrenone in the aqueous layer. This result was confirmed with the application of a second large methylene chloride extraction in which only trichloroacetamide was recovered.

The combined methylene chloride solutions from the above described extractions were combined and washed with 3% by weight sodium sulfite solution (122 mL) for at least 15 min. at about 250 rpm. A negative starch iodide test (KI paper; no color observed; in a positive test a purple coloration indicates the presence of peroxide) was observed at the end of the stir period.

The aqueous and organic layers were allowed to separate and the lower methylene chloride layer removed. The aqueous layer (pH = 6) was discarded. Note that addition of sodium sulfite solution can cause a slight exotherm so that such addition should be carried out under temperature control.

The methylene chloride phase was washed with 0.5 N sodium hydroxide (61 mL) for 45 min. at about 250 rpm and a temperature in the range of 15-25°C (pH = 12-13). Impurities derived from trichloroacetamide were removed in this process. Acidification of the alkaline aqueous fraction followed by extraction of the methylene chloride confirmed that very little epoxymexrenone was lost in this operation.

The methylene chloride phase was washed once with 0.1 N hydrochloric acid (61 mL) for 15 min. under 250 rpm agitation at a temperature in the range 15-25°C. The layers were then allowed to separate and the lower methylene chloride layer removed and washed again with 10% by weight aqueous sodium chloride (61 mL) for 15 min at 250 rpm at a temperature in the range of 15-25°C. Again the layers were allowed to separate and the organic layer removed. The organic layer was filtered through a