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A B O G A D O S

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 444 RESPUESTAREQUE Folios: 6

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. 02.104.490
Solicitud de patente a nombre de
Ortho-McNeil Pharmaceutical, Inc.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 94-76, Of. 305, obrando como apoderada de la sociedad Ortho-McNeil Pharmaceutical, Inc., domiciliada en Raritan, New Jersey, Estados Unidos de América, solicitante de la patente de la referencia, en respuesta al oficio No. 2014 notificado por fijación en lista el 09 de febrero de 2007, relacionado con el concepto técnico No. 209, me permito acompañar los siguientes documentos solicitados por el examinador:

- 1-CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; POGOSYAN, S. A. ET AL: "Synthesis and biological activity of 3-substituted-1,2,3,4-tetrahydro-.beta.-carboline derivatives" retrieved from STN Database accession no. 107:190347 XP002187735 & KHIM.-FARM. ZH. (1987), 21(6), 678-81.

Espero con esto haber dado cabal cumplimiento a lo solicitado por ese despacho y de conformidad con lo indicado en los artículos 3º, inciso 3, 35 inciso 2 y 59 inciso 2 del CCA, al analizar este memorial, atentamente solicito se traten todas las cuestiones planteadas con motivo del mismo.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de Usaquén
T.P. 68228

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The University
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S.A. Pogorian, A.S. Melik-Ogandzhanian, R.G. Paronikyan,
O.S. Noravian, N.E. Akopian

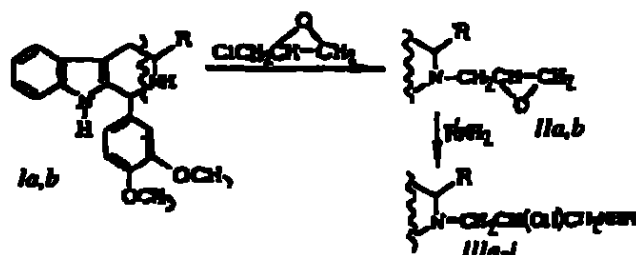
SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3-R-1,2,3,4-TETRAHYDRO- β -CARBOLINE DERIVATIVES

A.L. Mindzhoian Institute of Fine Organic Chemistry of the Academy of Sciences of the Armenian SSR, Erevan

From the literature it is known that substituted tetrahydro- β -carbolines are compounds having a broad spectrum of biological action, including hypotensive [4], analgesic [3], and psychotropic [5, 6].

Earlier [7] we synthesized new tetrahydro- β -carbolines containing an aminoalkyl group in position 2 which have psychotropic and anticonvulsive activity.

To continue these studies and in order to study the influence on pharmacological activity of various substituents in position 2 of the β -carboline ring, we produced new tetrahydro- β -carboline derivatives with an aminopropanol substituent, which is a typical fragment of substances having action on the adrenergic system [1].



R = H (Ia, IIa, IIIa-d); CH₃ (Ib, IIb, IIIe-IIIh); R' = CH₃ (IIIa, IIIe); C₂H₅ (IIIb, IIIf); (CH₃)₂CH (IIIc, IIIg); (CH₃)₃C (IIId, IIIh).

The starting compounds for the synthesis were 1-(3,4-dimethoxyphenyl)-3-R-1,2,3,4-tetrahydro- β -carbolines (I) [7, 9], which were reacted with epichlorohydrin in the presence of sodium hydroxide to produce 2,3-epoxypropyl-substituted β -carbolines (II) in high yield.

The reaction of compounds II with aliphatic amines produced the corresponding aminopropanol derivatives of the β -carboline series (IIIa-IIIh). Most of them are oily, non-distilling substances; they are characterized in the form of dihydrochlorides.

Experimental Chemistry Part

IR spectra were taken using a UR-20 apparatus (GDR) in liquid petrolatum. TLC was conducted on aluminum oxide of activity grade II according to the Brockmann scale: II in the solvent system chloroform-acetone (8:2). III on Silufol UV-254 plates (Czechoslovak Socialist Republic) in the system chloroform-alcohol (9:1). The developer was iodine vapors.

1-(3,4-dimethoxyphenyl)-2-(2,3-epoxypropyl)-1,2,3,4-tetrahydro- β -carbolines (IIa). A solution was prepared of 6.16 g (0.02 mol) of tetrahydro- β -carboline Ia in 50 mL of benzene, and 1.8 g (0.02 mol) of epichlorohydrin was added over 10 minutes under agitation, while maintaining the temperature of the reaction mixture within the limits of 30-35°C. The reaction mixture is agitated at this temperature for 30 minutes, and then heated for 2.5 h at 70-75°C. The reaction mixture is cooled and 2.2 g (0.022 mol) of a 40% aqueous sodium hydroxide solution at a temperature of 20-25°C is added dropwise over 20 minutes. The reaction mixture is agitated at this temperature for 1 h, and at 45-50°C for another 2 h. The reaction mixture is cooled, the benzene solution is washed with water (3 $\times$ 15), and then the solvent is driven off. The remainder is dissolved in absolute ether, concentrated to a volume of 50 mL, passed through a column with aluminum oxide (200 g), and eluted with ether. The remainder after the solvent is driven off is an oily substance. The yield is 5.8 g (80%), *R*_f 0.57. Found (%): C 73.10; H 7.30; N 7.41. C₂₂H₂₄N₂O₃. Calculated (%) C 72.50; H 6.80; N 7.69. IR spectrum ν_{max} (cm⁻¹): 950, 1260

1620 (C-C aromatic), 3360-3380 (NH ind.).

Hydrochloride IIa, m.p. 125-126°C. Found (%): N 7.71; Cl⁻ 9.42. C₂₂H₂₅N₂O₃Cl. Calculated (%): N 6.99; Cl⁻ 8.86.

14240

1-(3,4-dimethoxyphenyl)-2-(2,3-epoxypropyl)-3-methyl-1,2,3,4-tetrahydro- β -carboline IIb is produced in an analogous manner to IIa. Yield 73%. R_f 0.75. Found (%): C 73.20; H 7.28; N 7.38. $C_{23}H_{26}O_3N_2$. Calculated (%): C 73.03; H 6.87; N 7.40. IR spectrum ν_{max} (cm^{-1}): 950, 1260

1620 (C=C aromatic), 3360 (NH ind.). Hydrochloride IIb, m.p. 115-117°C. Found (%): N 6.19; Cl⁻ 9.2. $C_{23}H_{27}ClN_2O_3$. Calculated (%): N 6.75; Cl⁻ 8.56.

1-(3,4-dimethoxyphenyl)-2-(2-hydroxy-3-alkylaminopropyl)-3-substituted-1,2,3,4-tetrahydro- β -carb lines IIIa-IIIh. A solution is prepared of 0.01 mol β -carboline II in 50 mL of absolute alcohol, and 0.025 mol of the corresponding alkylamine in 50 mL of absolute alcohol is added dropwise. The reaction mixture is agitated for 6 h at room temperature and heated for 6 h at 40°C. The solvent is driven off, the precipitate is dissolved in ether, treated with a 10% hydrochloric acid solution, and the aqueous layer is alkalized with a solution of sodium hydroxide and extracted with ether. The ether layer is dried over sodium sulfate, concentrated to a volume of 50 mL, passed through a column with aluminum oxide (200 g) and eluted with ether.

The hydrochlorides are precipitated from ether solutions and recrystallized from an ethanol-ether mixture (1:1). The data are given in Table I.

The mass spectra of these hydrochlorides show a series of characteristic fragments. IIIf: m/z (rel. int.): 335(15), 318(16), 281(9), 208(16), 199(22), 180(44), 157(57), 130(100).

Experimental Pharmacology Part

The anticonvulsive and β -adrenergic blocking activity of 10 derivatives of 1,2,3-substituted β -carboline were studied.

The anticonvulsive activity was studied on white mice weighing 18-22 g. The convulsive models were provided by electroshock and convulsions induced by injecting corazole, nicotine, and arecoline. The investigated compounds were injected intraperitoneally 30 minutes before the convulsive agents and the application of electrical stimulation.

1-(3,4-dimethoxyphenyl)-2-(2-oxy-3-alkylaminopropyl)-3-methyl-1,2,3,4-tetrahydro- β -carboline IIIa-IIIh

Compound	Yield (%)	M.p. of hydrochlorides (°C)	R_f	Found (%)				Empirical Formula	Calculated (%)				IR spectrum ν_{max} (cm^{-1})
				C	H	N	Cl		C	H	N	Cl	
IIIa	64	242-3	0.78	70.32	8.0	10.6	-	$C_{23}H_{26}N_2O_3$	69.85	7.39	10.63	-	1600, 3200-3400
IIIa-2HCl	-	-	-	-	-	8.70	15.20	$C_{23}H_{27}Cl_2N_2O_3$	-	-	8.97	15.14	-
IIIb	55	90-92*	0.48	71.00	7.60	10.50	-	$C_{23}H_{26}N_2O_3$	70.38	7.63	10.26	-	1600, 3200-3400
IIIb-2HCl	-	-	-	-	-	8.90	15.00	$C_{23}H_{27}Cl_2N_2O_3$	-	-	8.71	14.70	-
IIIc	77	108-10	0.8	70.85	7.50	9.35	-	$C_{23}H_{26}N_2O_3$	70.89	7.85	9.92	-	1610
IIIc-2HCl	-	-	-	-	-	8.91	14.28	$C_{23}H_{27}Cl_2N_2O_3$	-	-	8.46	14.20	-
IIId	88	180-82	0.65	72.07	8.80	9.40	-	$C_{23}H_{26}N_2O_3$	71.36	8.06	9.50	-	1600, 3200-3400
IIId-2HCl	-	-	0.65	-	-	8.39	14.00	$C_{23}H_{27}Cl_2N_2O_3$	-	-	8.23	13.89	-
IIIe	62	85*	0.67	70.90	7.19	10.3	-	$C_{23}H_{26}N_2O_3$	70.38	7.63	10.26	-	1600, 3200-3400
IIIe-2HCl	-	-	-	-	-	8.50	14.90	$C_{23}H_{27}Cl_2N_2O_3$	-	-	8.71	14.70	-
IIIf	87	190-92	0.61	70.65	8.00	9.70	-	$C_{23}H_{26}N_2O_3$	70.89	7.85	9.92	-	1600, 3200-3400
IIIf-2HCl	-	-	-	-	-	7.96	14.00	$C_{23}H_{27}Cl_2N_2O_3$	-	-	8.46	14.28	-
IIIg	61	128*	0.66	71.90	8.84	9.70	-	$C_{23}H_{26}N_2O_3$	71.36	8.06	9.50	-	1600, 3200-3400
IIIg-2HCl	-	-	-	-	-	8.21	14.00	$C_{23}H_{27}Cl_2N_2O_3$	-	-	8.23	13.89	-
IIIh	76	75*	0.69	71.47	7.80	8.93	-	$C_{23}H_{26}N_2O_3$	71.80	8.25	9.30	-	1610, 3200-3400
IIIh-2HCl	-	-	-	-	-	7.90	13.80	$C_{23}H_{27}Cl_2N_2O_3$	-	-	8.01	13.52	-

* Melts with decomposition.

143
141

Indicators of Anticonvulsive Activity and Toxicity of Derivatives of β -Carboline and Puphemidum

Compound	Anticonvulsive Activity for Electroshock (ED ₅₀ , mg/kg)	Toxicity (LD ₅₀ , mg/kg)	Protective Index (TI = LD ₅₀ /ED ₅₀)
IIb	126 (106.7-148.7)	220 (173-279)	1.75
IIIe	137 (128-147)	280 (244.5-320.6)	2.04
IIIa	170 (150-192)	235 (188-294)	1.38
Puphemidum	77 (52.7-112.3)	2150 (1930-2390)	27.9

Note. The numbers in parentheses represent the range of variation.

For electrical stimulation, supramaximal current was used. The indicator of anticonvulsive activity was prevention of the phase of tonic extension [12]. To test substances according to the corazole test the method of minimal corazole convulsive attack was used [11].

The effect on the spectral n- and m-cholinergic systems was judged according to the ability of compounds to prevent nicotine convulsions and arecoline tremor [2, 8].

The mean effective doses (ED₅₀) and toxic doses (LD₅₀) were determined according to the method of Litchfield and Wilcoxon [10]. Acute daily toxicity of the compounds was determined in mice with intraperitoneal injection. Puphemidum was used as a control preparation.

The β -adrenergic blocking properties of the compounds were studied in experiments on rats anesthetized by pentobarbital. The β -adrenergic blocking activity was determined according to the magnitude of ED₅₀, the reduction of the positive chronotropic and depressive effects of isoproterenol (0.5 μ g/kg). The investigated compounds were injected intravenously. The known β -adrenergic blocking agent propranolol was used as a control preparation.

The results of the studies showed that all investigated derivatives of 1,2,3-substituted β -carbolines remove the tonic phase of maximum electroshock to some extent. Table 2 shows the results of tests of the most active of them.

As can be seen from Table 2, the most interesting of the investigated compounds are compounds IIb, IIIe, and IIIh, which have, in position 2, 2,3-epoxypropyl, 2-methylaminopropyl, and 3-*tert*-butylaminopropyl groups, respectively. The activity and also breadth of pharmacological action of these compounds are significantly inferior to those of the anticonvulsive preparation puphemidum from the group of succinimides. The compound with an isopropyl group in position 2 (IIIg) in a dose of 100 mg/kg eliminates the tonic phase of maximal electroshock in 60% of animals. A further increase in the dose of the compound causes the death of the animals.

A weak antielectroshock activity is shown by compounds having an ethylaminopropyl group in position 2 (IIIb and IIIf), and also by compounds IIa, IIIa, IIIc, and IIId.

In a dose of 200 mg/kg, none of the investigated compounds influence corazole convulsions, nor do they prevent nicotine convulsions or arecoline tremor.

Compounds IIa and IIIc have weak β_2 -adrenergic blocking activity. Compounds IIb, IIIa, IIIb, and IIId-IIIh do not act on the β_1 - and β_2 -adrenergic blocking receptors.

Thus, the investigated 1,2,3-substituted tetrahydro- β -carbolines showed anticonvulsive activity for antagonism with maximum electroshock. It is interesting to note that the most active compounds (IIb, IIIe, IIIg, IIIh) have a methyl group in position 3. Compounds having 2,3-epoxypropyl (IIa) and isopropylaminopropyl (IIIb) groups in position 2 have a weak β_2 -adrenergic blocking activity.

SUMMARY

Dihydrochlorides of 1-(3,4-dimethoxyphenyl)-2-(hydroxy-3-alkylaminopropyl)-1,2,3,4-tetrahydro- β -carbolines have been synthesized by the reaction of 1-(3,4-dimethoxyphenyl)-2-(2,3-epoxypropyl)-1,2,3,4 tetrahydro- β -carbolines with aliphatic amines.

143/44

The investigated derivatives of 1,2-disubstituted β -carbolines displayed an anticonvulsive activity in the maximum electroshock test. The compounds bearing 2,3-epoxypropyl- and isopropylaminopropyl- groups in the position 2 exhibited a slight β_2 -adrenoblocking action.

REFERENCES

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2. Mikhail'son M.Ia., Savinskii Ia.R. // *Farmakol. i toksikol.* - 1955. - vol. 18. - no. 3. - pp. 28-33.
3. Patent 1055203, 1965, Great Britain.
4. Patent 4291039, 1981, U.S.A.
5. Patent 4336256, 1982, U.S.A.
6. Patent 4336260, 1982, U.S.A.
7. Pogosian, S.A., Matevosian, L.A., Melik-Ogandzhanian A.S. et al. // *Khim.-farm. zhurn.* - 1986. - no. 10 - p. 1191.
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11. Swinyard E. A., Brown W. C., Goodman L. S. // *Ibid.* - 1952. - Vol. 106. - pp. 319-330.
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Received 1/17/86

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, DC, 24 de mayo de 2007

Apoderado: Jimena Escobar Uribe

Oficio: 6924

ASUNTO

Radicación: 02-104490

Trámite 002

Evento 001

Actuación 430

Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

- ◆Capítulo descriptivo, folios 22 a 98;
- ◆Capítulo reivindicatorio, folios 99 a 109;
- ◆Solicitud PCT/US01/14357, fase nacional;
- ◆ Solicitud del examen de patentabilidad, folios 131 y 132.
- ◆Examen de patentabilidad Art-46, folios 136 a 138;
- ◆Respuesta al examen Art-46, folios 140 a 144.

Objeto de la invención:

El título de la invención "DERIVADOS β -CARBOLINA ÚTILES COMO INHIBIDORES DE LA FOSFODIESTEASA".

Tiene como objeto los compuestos derivados de 2-*aril*-2,3,4,9-tetrahidro-1H- β -carbolina; 2-*aril*-1,2,3,4-tetrahidro[1]benzotieno[2,3-*c*]piridina; 2-*aril*-1,2,3,4-tetrahidro[1]benzofuro[2,3-*c*]piridina.

El campo de la invención, según la Clasificación Internacional de Patentes:

10A/H6

A61K31/437; A61K31/4385.

Claridad de la solicitud:

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

-La reivindicación 1 y sus dependientes puesto que definen los sustituyentes con términos como "arilo", "heteroarilo", "heteroarilcarbonilo", "heterocicloalquilo", esos sustituyentes están definidos de manera ambigua y especulativa, porque se definen dichos sustituyentes en términos de denominaciones generales o genéricas de grupos químicos; cuando lo correcto es definir los sustituyentes de manera técnica, o sea, que determine de manera inequívoca estructuras químicas, de acuerdo con lo sustentado en la descripción.

-Las reivindicaciones 7 y 8 son redundantes, reclaman exactamente la misma materia, el mismo principio activo con un vehículo farmacéuticamente aceptable.

-La reivindicación 9 se refiere a un proceso para la preparación de una composición pero no se especifica ninguna característica nueva e inventiva como proceso de obtención de un medicamento.

Excepciones de Patentabilidad:

El artículo 20 de la Decisión 486 de la Comisión de la Comunidad Andina establece en su inciso d) 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"*.

Las reivindicaciones 10 a 14 reclaman un método para tratamiento del cuerpo animal, el cual incluye la administración de una composición farmacéutica que contiene alguno de los derivados de la solicitud, por lo tanto están inmersas bajo el alcance del artículo 20 de la Decisión 486.

117
145

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

Se realizó la búsqueda del estado de la técnica con fecha anterior a la fecha de presentación de la primera solicitud, de la cual se reivindica prioridad, 17 de mayo de 2000, se encontró los siguientes documentos:

No.	Documento No.	Título	*Fecha de Publicación
D1	US4.628.057	Tetrahydro- β -carboline derivatives and treatment of liver diseases	09-dic-1986
D2	Zhurnal Farmatsevticheskii	Síntesis and biological activity of 3-R-1,2,3,4-tetrahydro- β -carboline derivatives	1987

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"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 con este artículo, 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.

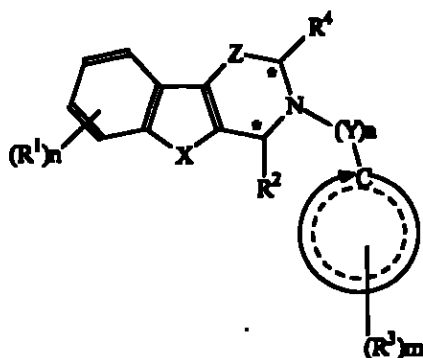
Evaluación de la Novedad:

El art.18 de la Decisión 486 de la Comisión de la Comunidad Andina establece: ***"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica." "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.***

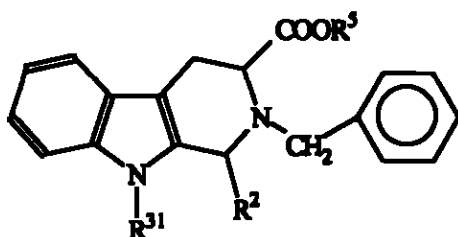
Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

- La solicitud en estudio reclama un compuesto de fórmula Markush:

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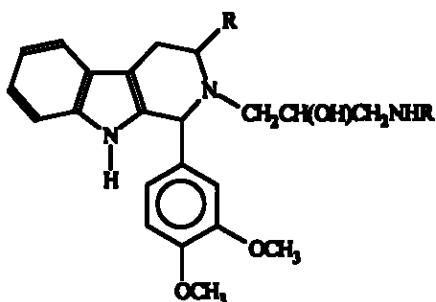


-D1 describe compuestos específicos de β -carbolina especialmente:



Y los compuestos (X), (XI) que se encuentran en los esquemas de reacción, lo que demuestra contundentemente que los compuestos de formula Markush de la solicitud en estudio, son una generalización especulativa de la anterioridad, por lo cual no se observa novedad en la presente solicitud.

-Por su parte el documento D2, es específico para el derivado de carbolina de fórmula:



Esta anterioridad describe derivados de carboline, que caen dentro de la materia reclamada como nueva en la solicitud en estudio, por lo cual solo se considera que la solicitud en estudio es una generalización especulativa de la anterioridad, ya que además se le atribuye a derivados 2-aryl-1,2,3,4-tetrahidro[1]benzotieno[2,3-c]piridina; 2-aryl-1,2,3,4-tetrahidro[1]benzofuro[2,3-c]piridina, la misma actividad que a los derivados carbolina, sin estar sustentado realmente el efecto para todos esos derivados diferentes a carbolina.

120
148

-Por lo tanto cuando se enmiende al capítulo reivindicatorio se debe tener en cuenta la unidad inventiva a posteriori.

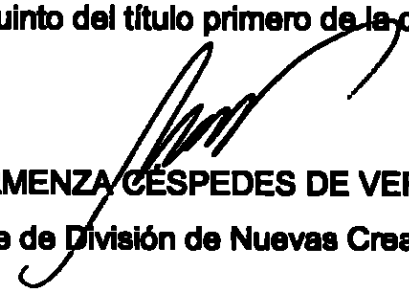
-Cuando una solicitud esta afectada su novedad, obviamente no posee nivel inventivo.

En conclusión los requisitos de Patentabilidad de la presente solicitud están afectadas así:

No.	Documento	Reivindicaciones	Requisito que afecta
	D1	1 a 8	Novedad
	D2	1 a 8	Novedad

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2,literal e), del capítulo quinto del título primero de la circular única No. 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
08 JUN 2007

CONCEPTO TÉCNICO No.	EXAMINADOR TÉCNICO Código No.202012
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United States Patent [19]

Iijima et al.

[11] Patent Number: 4,628,057

[45] Date of Patent: Dec. 9, 1986

[54] **TETRAHYDRO- β -CARBOLINE DERIVATIVES AND TREATMENT OF LIVER DISEASES**

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[30] **Foreign Application Priority Data**

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[51] **Int. Cl.⁴** A61K 31/398; C07D 471/02

[52] **U.S. Cl.** 514/292; 546/85; 546/86; 546/87; 546/63; 544/60

[58] **Field of Search** 546/85, 86, 87, 63; 544/60; 514/292

[56] **References Cited**

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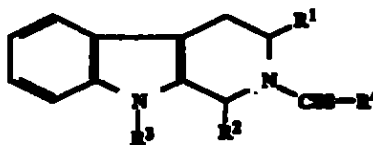
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[57] **ABSTRACT**

Novel tetrahydro- β -carboline derivatives of the formula:



wherein

R¹ is carboxyl, a lower alkoxy-carbonyl, carbamoyl, an N,N-di-lower alkyl-carbamoyl, an N-(phenyl-substituted lower alkylideneamino)-carbamoyl, a [N,N-di(lower alkyl)amino]-lower alkyl, or a nitrogen-containing monocyclic heterocyclic group;

R² is hydrogen atom, a lower alkyl, or a hydroxy-lower alkyl group, or R² is combined with R¹ to form a group: —CO—O—CH₂—;

R³ is hydrogen atom, a lower alkyl, a phenyl-lower alkyl, or a group: —CSS—R⁴;

R⁴ is hydrogen atom, an alkyl, or a group: —(CH₂)_nY¹;

n is 0, 1 or 2,

Y¹ is a lower alkenyl, a phenyl-substituted lower alkenyl, an N,N-di(lower alkyl)amino, a lower alkyl-mercapto, a lower alkoxy-carbonyl, benzoyl, naphthyl, a cycloalkyl, a monocyclic heterocyclic group, or a substituted or unsubstituted phenyl, which have excellent activities for alleviating, curing and preventing hepatic damages and are useful as a therapeutic or prophylactic agent for hepatic diseases,

and processes for the preparation thereof, and a pharmaceutical composition containing the above compound as an active ingredient.

27 Claims, No Drawings

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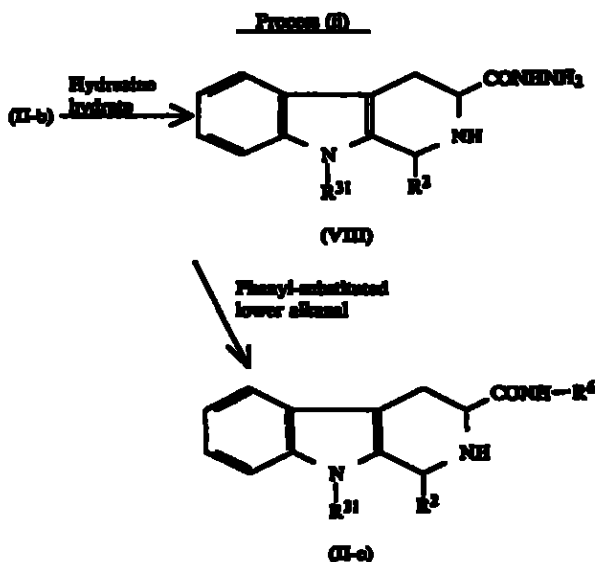
(II) wherein R^1 is carboxyl group and R^2 is hydroxymethyl group. The reaction is readily carried out under the same conditions as Process A.

Among the desired compound (I) thus prepared, the compound of the formula (I) wherein R^1 is carboxyl, an N-(phenyl-substituted lower alkylideneamino)carbamoyl, a [N,N-di(lower alkyl)amino]-lower alkyl, or a nitrogen-containing monocyclic heterocyclic group, and the compound of the formula (I) wherein R^4 is hydrogen atom, or a group of the formula: $-(CH_2)_n Y^1$; n is 0, 1 or 2; and Y^1 is an N,N-di(lower alkyl)amino, a nitrogen-containing monocyclic heterocyclic group, or a phenyl substituted by carboxyl or amino, are optionally converted into a pharmaceutically acceptable salt thereof, which can be obtained by treating the free

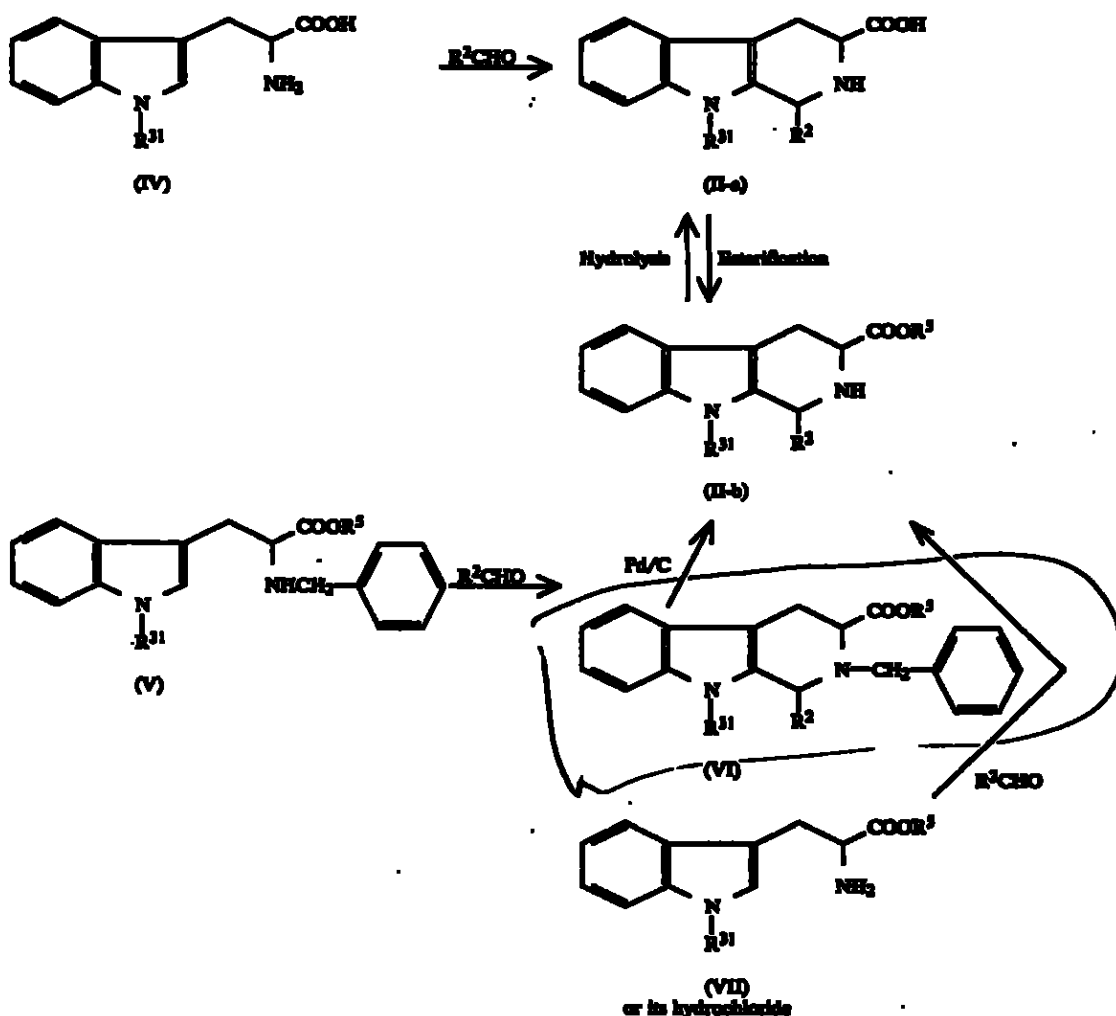
The above reactions can proceed without racemization, and hence, when an optical active compound is used as the starting compound, the desired compounds are also obtained in an optically active form.

The starting compounds (II) can be prepared, for example, by the processes of the following reaction schemes:

8



Process (C)

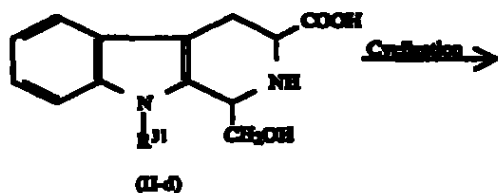


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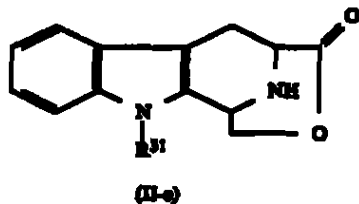
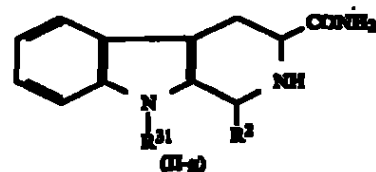
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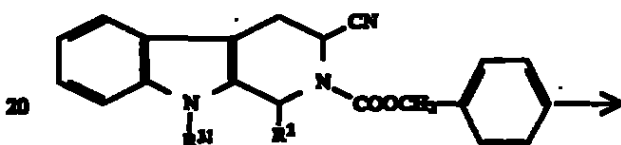
Process (iii)



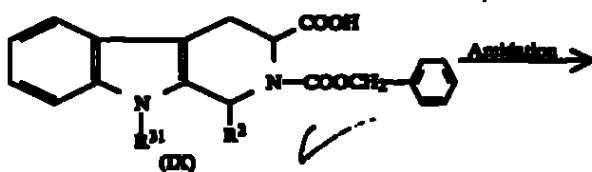
continued
Process (v)



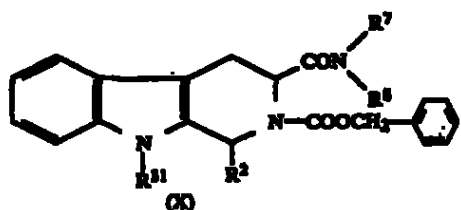
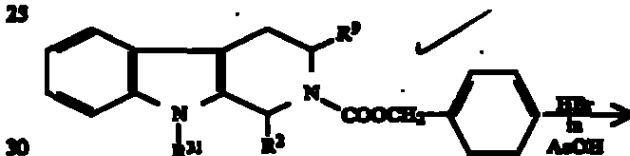
(XI) Dehydration



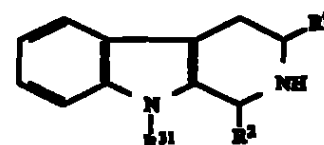
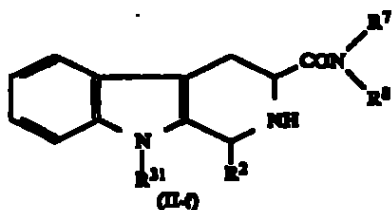
Process (iv)



(XII)



Catalytic
reduction



(II-b)

wherein R⁵ is a lower alkyl, R⁶ is a phenyl-substituted lower alkylidenamino, R⁷ and R⁸ are each a lower alkyl, R⁹ is a nitrogen-containing monocyclic heterocyclic group, and R² and R³¹ are as defined above.

According to Process (i), the starting compounds (II-a) and (II-b), i.e. the compound (II) wherein R¹ is carboxyl or a lower alkoxy-carbonyl group, can be prepared by well known processes, for example, as disclosed in J. Med. Chem., 16, 418 (1973); J. Med. Chem., 16, 560 (1973); J. Med. Chem., 25, 1081 (1982); and J. Am. Chem. Soc., 102, 6976 (1980).

According to Process (ii), the starting compound (II-c), i.e. the compound (II) wherein R¹ is an N-(phenyl-substituted lower alkylidenamino)carbamoyl group, can be prepared by reacting a compound (II-b) with hydrazine hydrate in a solvent (e.g. dimethylformamide, methanol, ethanol, dioxane) at room temperature, and reacting the resulting acid hydrazide compound (VIII) with a phenyl-substituted lower alkylal in a solvent (e.g. dimethylsulfoxide, dimethylformamide) at room temperature. The compound (II-c) thus obtained can be used as it stands, i.e. without isolating from the reaction mixture.

According to Process (iii), the starting compound (II-e), i.e. the compound (II) wherein R¹ and R² are

Process (v)

