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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-033251- -00003-0000

E. _____ S. _____

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Folios: 3

Ref: Expediente No. 06-033.251

Solicitud de patente de invención titulada: "ANTAGONISTAS DE RECEPTORES DE ACETILCOLINA MUSCARINICOS".

Solicitante: GLAXO GROUP LIMITED

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 580

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado sustituto tal como consta en la sustitución adjunta, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto un recibo que de \$404.000 pesos para cubrir la tasa correspondiente, según la Resolución 36155 del año 2006.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$404.000 pesos
Sustitución

57
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SECRETARIA DE INDUSTRIA Y COMERCIO

SECRETARIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SECCION INTERNACIONAL

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 96,119
FECHA : NOVIEMBRE 26 DE 2007

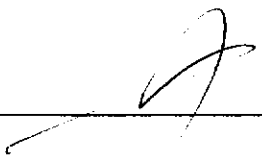
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
CLARTE RAISBEK	CONSIGNACION	BANCO POPULAR	050-00110-6	67993475	26/11/2007	5,090,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	404,000.00
		TOTAL :	\$ 404,000.00

SON: CUATROCIENTOS CUATRO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Expediente No. 06-033.251

Solicitud de patente de invención titulada: "ANTAGONISTAS DE RECEPTORES DE
ACETILCOLINA MUSCARINICOS"

Solicitante: GLAXO GROUP LIMITED

SUSTITUCIÓN DE PODER

J. IAN RAISBECK LLINAS, mayor de edad y vecino de Bogotá D.C., identificado como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad, en el doctor **CARLOS R. OLARTE** mayor de edad, domiciliado en Bogotá D.C., identificado con la Cédula de Ciudadanía No. 79.782.747 de Bogotá y portador de la Tarjeta Profesional No. 74.295 del Consejo Superior de la Judicatura, para que sea él quien en adelante asuma el trámite de la presente acción.

El apoderado sustituto conserva las mismas facultades del principal.

Atentamente,

J. IAN RAISBECK
C.C. No. 79.376.996 de Bogotá
T.P. 135.799 del C. S. de la J.

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DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-33251

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **580** DE

FECHA **28 DE SEPTIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **27 DE DICIEMBRE DE 2007**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO X

United States Patent Office

2,800,481

Patented July 23, 1957

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2,800,481

TERTIARY ALCOHOL DERIVATIVES OF 8-ALKYLNORTROPANES AND THE ACID AND QUATERNARY AMMONIUM SALTS THEREOF

Charles L. Zirkle, Haddon Heights, N. J., assignor to Smith, Kline & French Laboratories, Philadelphia, Pa., a corporation of Pennsylvania

No Drawing. Application July 1, 1955,
Serial No. 519,649

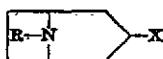
6 Claims. (Cl. 266-292)

This invention relates to certain new physiologically active tertiary alcohol derivatives of 8-alkylnortropanes and the organic and inorganic salts thereof. It also relates to quaternary ammonium salts of these tertiary alcohol derivatives of 8-alkylnortropanes.

The new chemical compounds according to this invention have utility, for example, for treating the parasympathetic nervous system in providing, for example, antispasmodic and anticholinergic action and further have utility as antiemetics and for treating the central nervous system, for example, for treating psychotics and psychoneurotics. The compounds of this invention also have utility as intermediates for use in the preparation of compounds having utility for treating the parasympathetic nervous system in providing, for example, antispasmodic and anticholinergic action and further having utility as antiemetics and for treating the central nervous system, for example, for treating psychotics and psychoneurotics. Where the salts are used for therapeutic purposes, it will be obvious to those skilled in the art to select a non-toxic salt.

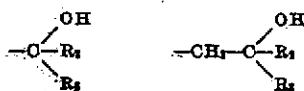
The new compounds according to this invention have the structure shown by the following formula:

FORMULA 1

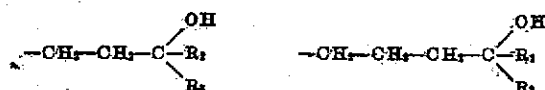


in which: R is a straight or branched chain lower alkyl radical having preferably from 1 to 4 carbon atoms.

X is selected from the group consisting of



which is preferred;



R₂ and R₃ being selected from the group consisting of straight or branched chain lower alkyl groups having preferably from 1 to 6 carbon atoms, cycloalkyl groups having from 5 to 6 carbon atoms, cycloalkyl-alkyl having 6 to 10 carbon atoms, 2-thienyl, 2-pyridyl, phenyl, phenyl substituted with an alkyl group having not in excess of 4 carbon atoms and phenyl substituted with an alkoxy group having not in excess of 4 carbon atoms.

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Where hereinafter the symbols R, R₁ and R₂ and n are mentioned in the description, they will indicate the substituents indicated for them in connection with the above general formulas.

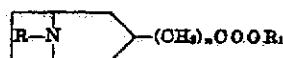
The organic and inorganic salts of the base of the above formulas contemplated by this invention include by way of example salts of the base formed with organic acids such as, for example, tartaric, maleic, camphorsulfonic, citric, acetic, propionic, butyric, succinic, glutaric, adipic, ascorbic, lactic, levulinic, malic, mandelic, cinnamic, gluconic, methanesulfonic, benzene sulfonic, fumaric, citraconic, itaconic, lauric, stearic, myristic, palmitic, linoleic, aspartic and sulfoacetic, and inorganic acids such as, for example, hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, etc. and can readily be produced by reacting the free base with the appropriate acid.

This invention also embraces quaternary ammonium salts formed with organic esters of sulfuric, hydrohalic and aromatic sulfonic acids. Exemplary of such esters are methyl chloride, methyl bromide, methyl iodide, ethyl chloride, propyl bromide, butyl chloride, isobutyl chloride, ethylene bromohydrin, ethylene chlorohydrin, allyl bromide, methallyl bromide, crotyl bromide, benzyl chloride, benzyl bromide, naphthylmethyl chloride, phenethyl bromide, dimethyl sulfate, diethyl sulfate, methyl benzene-sulfonate, ethyl toluene-sulfonate, and the like.

The quaternary ammonium salts will be prepared by treating a solution of the base of the above structural formulas in a suitable solvent such as chloroform, acetone, benzene, toluene or ether with an excess of an organic ester of sulfuric, hydrohalic or aromatic sulfonic acid. This reaction will be carried out most advantageously at a temperature in the range of from about 25° C. to about 115° C.

Compounds having the structure of Formula 2 may be prepared by first producing a compound of the following structure:

FORMULA 3



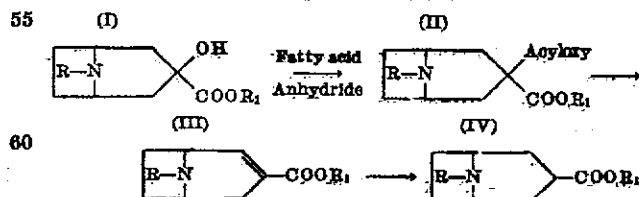
in which: R is a straight or branched chain lower alkyl radical having preferably from 1 to 4 carbon atoms.

R₁ is selected from the group consisting of hydrogen and a straight or branched chain lower alkyl radical having preferably from 1 to 4 carbon atoms and n is from 0 to 3.

The compounds of Formula 3 may be variously produced by Methods A through D.

METHOD A

The compounds of Formula 3 where n is 0 are obtained by the reaction sequence outlined below:

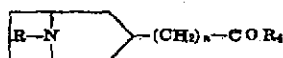


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formed only in low yield. In carrying out this reaction, it is advantageous to use a solvent such as diethyl ether and to employ an excess of the organo-metallic reagent.

The compounds of this invention having the formula (Formula 2) where R_1 and R_2 are the same or different can be prepared by utilizing the compounds of Formula 3 to prepare an intermediate compound having the following structure:

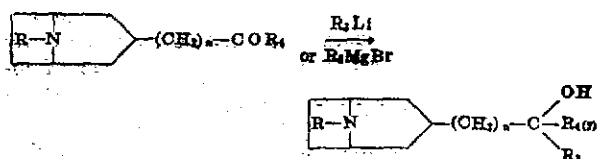
FORMULA 4



in which: R_4 is selected from the group consisting of straight or branched chain lower alkyl groups having preferably 1 to 6 carbon atoms, 2-thienyl, cyclopentyl, cyclohexyl, cycloalkyl-alkyl having 6 to 10 carbon atoms, phenyl, phenyl substituted with an alkyl group containing not in excess of 4 carbon atoms and phenyl substituted with an alkoxy group containing not more than 4 carbon atoms.

The compounds of Formula 4 are readily formed by reacting the Grignard derivative prepared from straight or branched chain lower alkyl bromides having preferably 1 to 6 carbon atoms, phenyl bromide, lower alkyl substituted phenyl bromide, lower alkoxy substituted phenyl bromide, 2-bromothiophene, cyclohexyl bromide, cyclopentyl bromide or cycloalkyl-alkyl bromides having 6 to 10 carbon atoms with one of the esters defined in Formula 3 above. It is desirable to carry out the Grignard reaction in a solvent, such as diethyl ether, using a molar excess of the Grignard reagent. The resulting amino ketones (Formula 4) will be isolated and purified by distillation or by the crystallization of the organic or inorganic acid salts from a suitable solvent. The intermediate amino ketone compounds of Formula 4, except for the cyclohexyl and cyclopentyl compounds, are also readily formed by the reaction of the lithium derivative prepared from lower alkyl bromides, cycloalkyl-alkyl bromides having 6 to 10 carbon atoms, phenyl bromide lower alkyl substituted phenyl bromides, lower alkoxy substituted phenyl bromides, 2-bromothiophene with one of the carboxylic acids defined in Formula 3 above. This reaction is carried out using a solvent such as diethyl ether and preferably employing an excess of the lithium reagent.

The intermediate amino ketone of Formula 4 can be used to produce the compounds of this invention, Formula 2, where R_1 and R_2 are the same or different as illustrated by the following scheme:



The ketone is variously reacted with the lithium or magnesium derivative prepared from lower alkyl bromides, cyclopentyl bromide, cyclohexyl bromide, cycloalkyl-alkyl bromides having 6 to 10 carbon atoms, phenyl bromide, substituted phenyl bromides, 2-bromopyridine and 2-bromothiophene, depending on the end product desired and desirably in a solvent such as diethyl ether and using an excess of the lithium or magnesium reagent.

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ing it with, a mineral acid, such as hydrochloric, sulfuric or phosphoric acid, organic acids such as oxalic or trichloroacetic, a carboxylic acid chloride, such as acetyl chloride, a carboxylic acid anhydride, such as acetic anhydride, or thionyl chloride, neutralizing the reaction mixture and extracting the dehydrated product with a solvent such as ether, benzene or chloroform.

The thus formed unsaturated amines have utility, for example, for treating the parasympathetic nervous system in providing, for example, antispasmodic and anticholinergic action and further having utility as antiemetics and for treating the central nervous system, for example, for treating psychotics and psychoneurotics.

This invention will be further clarified by the following examples:

Example 1.—Di-(2-thienyl)-3-tropanecarbinol

Methyl 3-(3-acetoxytropane)carboxylate (α -ecgonine acetate).—A solution of 10 g. of methyl 3-(3-hydroxytropane)carboxylate (methyl α -ecgonine) (Willstätter, Ber. 29 1575 (1896) in 50 ml. of acetic anhydride is heated at 100° C. for 4 hours. The excess acetic anhydride and acetic acid are removed in vacuo and the residue is poured into ice water. The mixture is saturated with potassium carbonate and the product extracted with ether. After evaporation of ether the crude methyl 3-(3-acetoxytropane)carboxylate is purified by distillation; B. P. 162–165° C. (15 mm.); M. P. 66–67° C. The picrate after recrystallization from alcohol-water mixture melts at 215–217.5° C.

Methyl 3-(2-tropane)carboxylate.—Methyl 3-(3-acetoxytropane)carboxylate (29 g.) is added dropwise over a 7 min. period to a vertical Pyrex tube (25 mm. diameter), packed for a length of 8 in. with 1/4 to 1/2 in. pieces of Pyrex tubing of 7 mm. diameter, and heated at 420° C. During the addition, the apparatus is swept out with nitrogen. The product, collected by means of an efficient condenser at the bottom of the tube, is dissolved in dilute hydrochloric acid and the mixture extracted with three portions of ether. The aqueous acid solution is saturated with potassium carbonate and the product removed by extraction with ether. Distillation of the ether solution gives methyl 3-(2-tropane)carboxylate as a pale yellow liquid, B. P. 131–134° C. (15 mm.); n_D^{25} 1.4998.

Methyl 3-tropanecarboxylate.—Methyl 3-(2-tropane)carboxylate (13 g.) dissolved in 100 ml. of methanol is hydrogenated over 5 g. of Raney nickel catalyst at 50 p. s. i. pressure at room temperature until hydrogen absorption ceases. Distillation of the mixture, after removal of the catalyst by filtration, gives methyl 3-tropanecarboxylate as a colorless liquid, B. P. 128–132° C. (18 mm.); n_D^{25} 1.4819.

Di-(2-thienyl)-3-tropanecarbinol.—A solution of 2-thienyl magnesium bromide in 100 ml. of ether is prepared in the usual way from 16.6 g. of 2-bromothiophene and 2.4 g. of magnesium. To the stirred solution, cooled to 0° C., is slowly added a solution of 6.3 g. of methyl 3-tropanecarboxylate in 20 ml. of ether. After the addition the mixture is stirred for two hours at room temperature. The mixture is cooled to 0° C., and an aqueous solution of 97 g. of the sodium salt of ethylenediamine tetraacetic acid added slowly with stirring. The ether layer is removed and the aqueous mixture is extracted with several portions of ether. Extraction of the

tion of 50 ml. of water. The ether layer is removed, the aqueous layer extracted with ether, and the extracts are dried over sodium sulfate. Passage of hydrogen chloride into the ether solution precipitates the hydrochloride salt of phenyl 3-tropanemethyl ketone. The crude salt, after washing with ether, is reconverted to the base by treatment with ammonium hydroxide and extraction of the product with ether. Distillation of the ether extract under reduced pressure gives phenyl 3-tropanemethyl ketone, B. P. 138–141° C. (0.2 mm.).

1,1-diphenyl-2-(3-tropane)ethanol hydrobromide.—An ether solution of phenyl lithium is prepared in the usual way from 0.7 g. of lithium and 16 g. of bromobenzene. To the stirred solution cooled to 0° C. is slowly added an ether solution of 9 g. of phenyl 3-tropanemethyl ketone. The mixture is stirred several hours at room temperature and then poured into ice water. The resulting mixture is acidified with hydrochloric acid and the white precipitate which forms collected by filtration. Recrystallization of the solid from a mixture of ethanol and ether gives the hydrobromide salt of 1,1-diphenyl-2-(3-tropane)ethanol which melts at 230° C.

Example 6.—1-phenyl-1-(2-thienyl)-2-(3-tropane)ethanol

A solution of phenyl lithium in 100 ml. of ether is prepared in the usual way from 19 g. of bromobenzene and 1.7 g. of lithium. With stirring 10 g. of thiophene dissolved in ether is slowly added and the resulting mixture is stirred and heated at reflux temperature for 2 hours. To the mixture cooled to –20° C. is slowly added a solution of 10 g. of phenyl 3-tropanemethyl ketone, made following the procedure of Example 5, in 90 ml. of ether after which stirring is continued for 2 hours at room temperature. The ether solution is decanted from the solid lithium complex which formed and added with shaking to ice water. The ether layer is removed and the solvent evaporated to give solid crude 1-phenyl-1-(2-thienyl)-2-(3-tropane)ethanol. To the solid lithium complex is added a mixture of equal volumes of ice water and chloroform and the mixture is stirred mechanically until two clear layers result. The chloroform layer is separated and the solvent evaporated to give an additional amount of the amino thienylcarbinol. Recrystallization of the crude product from ethyl acetate solution decolorized by charcoal gives white crystals of 1-phenyl-1-(2-thienyl)-2-(3-tropane)ethanol melting at 137.5–139° C.

1-phenyl-1-(2-thienyl)-2-(3-tropane)ethanol maleate.—Addition of the thus prepared carbinol base to an equimolecular amount of maleic acid in acetone solution gives the maleate salt as white crystals melting at 145–146° C. after recrystallization from ethanol-ether.

1-phenyl-1-(2-thienyl)-2-(3-tropane)ethanol methobromide.—By allowing a mixture of 1-phenyl-1-(2-thienyl)-2-(3-tropane)ethanol and excess methyl bromide in acetone solution to stand for several hours at room temperature, the methobromide salt is obtained. After recrystallization from ethanol the salt melts at 256° C.

Example 7.—1-phenyl-1-(2-pyridyl)-2-(3-tropane)ethanol

A solution of n-butyl lithium in 25 ml. of ether is prepared in the usual way from 3.7 g. of n-butyl chloride and 0.7 g. of lithium. With stirring the solution is cooled to –45° C. and 5.5 g. of 2-bromopyridine dissolved in 10

form and water until two clear layers result. The chloroform layer is removed and combined with the ether solution above. Evaporation of the solvents in vacuo gives a yellow oil which crystallizes when stirred with ether. By recrystallization of the product from ethyl acetate 1-phenyl-1-(2-pyridyl)-2-(3-tropane)ethanol is obtained as white crystals melting at 117–118.5° C.

1-phenyl-1-(2-pyridyl)-2-(3-tropane)ethanol hydroiodide.—To an ethanolic solution of the thus prepared carbinol base is added dropwise 57% hydriodic acid until no more fuming occurs. Addition of a mixture of acetone and ether to the solution, precipitates the hydroiodide salt as a white gummy solid which becomes crystalline when triturated with ether. Analysis of the product, M. P. 194–196° C., shows it to be the monohydroiodide salt of the carbinol base.

1-phenyl-1-(2-pyridyl)-2-(3-tropane)ethanol methobromide.—By allowing a mixture of the carbinol base prepared above and excess methyl bromide in acetone solution to stand for several hours at room temperature a methobromide salt is obtained which melts at 268° C. after recrystallization from ethanol. Analysis of the product shows it to be the monomethobromide salt of the carbinol base.

Example 8.—1-ethyl-1-phenyl-2-(3-tropane)ethanol

A solution of ethyl magnesium bromide in 200 ml. of ether is prepared from 7.3 g. of magnesium and 32.7 g. of ethyl bromide in the usual way. While the solution is stirred and cooled at 0° C., 12.2 g. of phenyl 3-tropanemethyl ketone, prepared following the procedure of Example 5, dissolved in 50 ml. of ether is added slowly. The reaction mixture is stirred 1.5 hours at room temperature and then 1.5 hours at reflux temperature after which time it is decomposed by addition to a mixture of cracked ice and 21 g. of ammonium chloride in 50 ml. of water. The ether layer is removed and the aqueous phase extracted twice with chloroform. Evaporation of solvents from the combined extracts gives an oily residue which yields, when stirred with ether, 1-ethyl-1-phenyl-2-(3-tropane)ethanol as a white powder melting at 119–120° C. From the filtrate from the solid is recovered the starting material, phenyl 3-tropanemethyl ketone.

1-ethyl-1-phenyl-2-(3-tropane)ethanol hydrochloride.—Treatment of 1-ethyl-1-phenyl-2-(3-tropane)ethanol dissolved in ether with ethereal hydrogen chloride solution yields the hydrochloride salt which melts at 237–237.5° C. after recrystallization from ethanol.

Example 9.—1-cyclohexyl-1-phenyl-2-(3-tropane)ethanol

Cyclohexyl 3-tropanemethyl ketone.—A solution of cyclohexyl magnesium bromide in 700 ml. of ether is prepared in the usual way from 11.5 g. of magnesium and 77 g. of cyclohexyl bromide. To the stirred solution cooled to 0° C. is added slowly 25 g. of ethyl 3-tropanoacetate (made following the procedure of Example 3) dissolved in 45 ml. of ether. The mixture is stirred at 0° C. for 0.5 hr. and then heated at the reflux temperature for 5 hours. The mixture is again cooled to 0° C. and a solution of 483 g. of the sodium salt of ethylenediamine-tetraacetic acid in 590 ml. of water is added slowly with stirring. The ether layer is removed and the aqueous mixture is extracted with several portions of ether. Distillation of the ether solution under reduced pressure gives cyclohexyl 3-tropanemethyl ketone boiling

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The acid chloride hydrochloride is suspended in 30 ml. of methylene chloride and the mixture added in portions to a solution of diazomethane, prepared in the usual way from 14.7 g. of N-methyl-N-nitroso-N'-nitroguanidine, in 200 ml. of methylene chloride kept at 0° C. After storage of the mixture at room temperature for two hours, the solvent is evaporated in vacuo to give diazomethyl 3-tropanemethyl ketone as a hygroscopic brown powder.

The diazo ketone is dissolved in 35 ml. of absolute ethanol and the solution maintained at 50-60° C. while a suspension of silver oxide, freshly prepared from 10 ml. of 10% silver nitrate solution, in 30 ml. of dry ethanol is added over a 45 min. period. After the addition the mixture is refluxed for 30 min. and then filtered. By distillation of the filtrate in vacuo, ethyl β -(3-tropane) propionate is obtained.

1,1-diphenyl-3-(3-tropane)propanol.—A solution of phenyl lithium in 500 ml. of ether is prepared in the usual way from 75 g. of bromobenzene and 6.7 g. of lithium. To the stirred solution is slowly added 18 g. of ethyl β -(3-tropane)propionate dissolved in 50 ml. of ether. The mixture is stirred and heated at reflux temperature for 3.5 hours. After cooling 50 ml. of water is added and the mixture stirred vigorously for one hour. The ether layer is removed and the aqueous layer which contains a white solid is shaken vigorously with chloroform. The chloroform layer is separated, combined with the ether solution and the solvents are evaporated in vacuo. In this way, 1,1-diphenyl-3-(3-tropane)propanol is obtained as a white crystalline solid melting at 141-142.5° C.

1,1-diphenyl-3-(3-tropane)propanol hydrochloride.—A portion of the carbinol base dissolved in ether is neutralized with hydrogen chloride to give 1,1-diphenyl-3-(3-tropane)propanol hydrochloride. The salt, after recrystallization from a mixture of methanol and ether, melts at 249-250° C.

1,1-diphenyl-3-(3-tropane)propanol methobromide.—The methobromide salt of 1,1-diphenyl-3-(3-tropane)propanol is prepared as described in Example 6. The quaternary salt melts at 299° C.

Example 13.—1-ethyl-1-(2-pyridyl)-3-(3-tropane)-propanol

Ethyl β -(3-tropane)ethyl ketone.—A solution of ethyl magnesium bromide in 35 ml. of ether is prepared in the usual way from 1.3 g. of magnesium and 6.4 g. of ethyl bromide. To the stirred solution, cooled to 0° C., is slowly added 3 g. of ethyl β -(3-tropane)propionate (prepared following the procedure of Example 12) dissolved in 30 ml. of ether. The mixture is stirred 4 hours, then cooled to 0° C. and a solution of 45 g. of the sodium salt of ethylenediamine tetraacetic acid in 58 ml. of water is slowly added. The ether layer is removed and the aqueous phase is extracted with several portions of ether. Distillation of the ether extracts under reduced pressure gives ethyl β -(3-tropane)ethyl ketone as a colorless liquid; B. P. 105-109° (0.35 mm.); n_D^{25} 1.4870. The picrate of the amino ketone melts at 123-124.5° C. after recrystallization from alcohol.

1-ethyl-1-(2-pyridyl)-3-(3-tropane)propanol.—A solution of n-butyl lithium in 15 ml. of ether is prepared in the usual way from 1.9 g. of n-butyl chloride and 0.35 g. of lithium. With stirring the solution is cooled to -45° C. and 2.8 g. of 2-bromopyridine dissolved in 5 ml.

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crystallizes when stirred with a small volume of cold ether. Recrystallization of the product from ethyl acetate gives 1-ethyl-1-(2-pyridyl)-3-(3-tropane)propanol as a white crystalline solid.

Example 14.—1-(2-pyridyl)-1-p-tolyl-4-(3-tropane)-butanol

3-(3-tropane)propanol.—To a stirred solution of 3 g. of lithium aluminum hydride in 200 ml. of ether is added a solution of 17.8 g. of ethyl β -(3-tropane)propionate (prepared as in Example 12) in 50 ml. of ether at such a rate that steady reflux of ether is maintained. After the mixture is stirred at reflux temperature for three hours, it is cooled at 0° C. and 7.2 ml. of water is added gradually. The resulting mixture is stirred for two hours, filtered and the collected solid is washed with ether. Distillation of the ether solution in vacuo gives 3-(3-tropane)propanol boiling at 128-131° C. (2 mm.).

1-chloro-3-(3-tropane)propane.—To a solution of 7.7 g. of 3-(3-tropane)propanol in 30 ml. of chloroform is slowly added 10 g. of thionyl chloride. The reaction mixture is heated at gentle reflux for 45 minutes and then evaporated to dryness in vacuo. The residue of crude 1-chloro-3-(3-tropane)propane hydrochloride is treated with potassium carbonate solution and the oily base which forms is extracted with ether. Distillation of the ether solution gives 1-chloro-3-(3-tropane)propane boiling at 100-102° C. (1 mm.).

γ -(3-tropane)butyronitrile.—1-chloro-3-(3-tropane)propane (5 g.) and 0.1 g. of sodium iodide is added to a solution of 5 g. of potassium cyanide in a mixture of 18 ml. of alcohol and 8 ml. of water. The resulting solution is heated at reflux temperature for 18 hours and then evaporated in vacuo. Sodium hydroxide solution is added to the residual mixture of oil and solid and the oil is separated by extraction with ether. Distillation of the ether solution under reduced pressure gives γ -(3-tropane)butyronitrile boiling at 132-135° (0.3 mm.).

Ethyl γ -(3-tropane)butyrate.—A solution of 3 g. of γ -(3-tropane)butyronitrile in 15 ml. of 37% hydrochloric acid is heated at reflux temperature for several hours and then evaporated to dryness in vacuo. The solid residue is dissolved in 35 ml. of absolute ethanol, 0.5 ml. of concentrated sulfuric acid is added, and the resulting solution is heated at reflux temperature for 7 hours. The mixture is concentrated in vacuo and the residue is treated with 40% sodium hydroxide solution. The oil which separates is removed by extraction with ether and purified by distillation under reduced pressure. In this way, ethyl γ -(3-tropane)butyrate distilling at 115-119° C. (0.5 mm.) is obtained.

p-Tolyl γ -(3-tropane)propyl ketone.—A solution of p-tolyl magnesium bromide in 40 ml. of ether is prepared in the usual way from 5.1 g. of p-bromotoluene and 0.75 g. of magnesium. To the stirred solution, cooled to 0° C., is slowly added a solution of 2.3 g. of ethyl γ -(3-tropane)butyrate in 10 ml. of ether. After the addition the mixture is stirred at room temperature for one hour and then at reflux temperature for 2 hours. The mixture is cooled to 0° C. and a solution of 27 g. of the sodium salt of ethylenediaminetetraacetic acid in 36 ml. of water is added slowly with stirring. The ether layer is removed and the aqueous layer is extracted with several portions of ether. Distillation of the ether extracts under reduced pressure gives p-tolyl γ -(3-tropane)propyl ketone boiling at 188-192° C. (0.2 mm.).

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clear layers result. By evaporation of the combined ether and chloroform solutions in *vacuo* and stirring the residual oily residue with petroleum ether, 1-cyclopentyl-1-phenyl-4-(3-tropane)butanol is obtained as a white crystalline solid.

Example 18.—Diphenyl 3-tropanecarbinol ethylsulfate

By heating a mixture of one gram of diphenyl 3-tropanecarbinol, made as in Example 2, and excess diethyl sulfate in acetone solution at reflux temperature for 5 hours, the quaternary ammonium salt is obtained as a white solid.

Example 19.—1,1-diphenyl-2-(3-tropane)ethanol metho-p-toluenesulfonate

An acetone solution of one gram of 1,1-diphenyl-2-(3-tropane)ethanol, made as in Example 4, and excess methyl p-toluenesulfonate is heated at reflux temperature for five minutes. By addition of ether to the cooled solution the quaternary ammonium salt of the carbinol base is precipitated as a white crystalline solid melting at 172–174° C.

Example 20.—1,1-diphenyl-2-(3-tropane)ethanol ethylsulfate

By heating a mixture of one gram of 1,1-diphenyl-2-(3-tropane)ethanol, made as in Example 4, and excess diethyl sulfate in acetone solution at reflux temperature for 5 hours the quaternary ammonium salt melting at 234–235° C. is obtained.

Example 21.—1,1-diphenyl-2-(3-tropane)ethanol butyl bromide

By heating a mixture of one gram of 1,1-diphenyl-2-(3-tropane)ethanol, made as in Example 4, and excess butyl bromide in acetone solution at reflux temperature for 20 hours, the quaternary ammonium salt melting at 225–227° C. is obtained.

Example 22.—1,1-diphenyl-2-(3-tropane)ethanol butyl iodide

By heating a mixture of one gram of 1,1-diphenyl-2-(3-tropane)ethanol, made as in Example 4, and excess butyl

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iodide in acetone solution at reflux temperature for 5 hours the quaternary salt melting at 227–229° C. is obtained.

Example 23.—1-cyclohexyl-1-phenyl-2-(3-tropane)ethanol butyl bromide

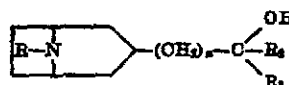
By heating a mixture of one gram of 1-cyclohexyl-1-phenyl-2-(3-tropane)ethanol, made as in Example 9, and excess butyl bromide in acetone solution at reflux temperature for 20 hours the quaternary ammonium salt is obtained as a white solid.

The compounds of Formulas 3 and 4 and the dehydration products of the compounds of this invention are the subject-matter of my copending applications Serial No. 519,647, filed July 1, 1955; Serial No. 519,648, filed July 1, 1955; and Serial No. 519,650, filed July 1, 1955, respectively and reference may be made thereto for further examples of these compounds as well as for methods of their preparation.

It is not desired to be limited except as set forth in the following claims.

What is claimed is:

1. Compounds of the class consisting of a free base and the acid addition and quaternary ammonium salts thereof, the free base having the following formula:



in which R is a lower alkyl radical, n is from 0 to 2, and R₁ and R₂ are selected from the group consisting of lower alkyl, cycloalkyl having from 5 to 6 carbon atoms, cycloalkyl alkyl having 6 to 10 carbon atoms, 2-thienyl, 2-pyridyl, phenyl, phenyl substituted with an alkyl group having 1 to 4 carbon atoms and phenyl substituted with an alkoxy group having 1 to 4 carbon atoms.

2. 1,1-diphenyl-2-(3-tropane) ethanol.
3. Diphenyl-3-tropanecarbinol.
4. 1,1-di-(2-thienyl)-2-(3-tropane)ethanol.
5. 1-phenyl-1-(2-thienyl)-2-(3-tropane)ethanol.
6. 1-cyclohexyl-1-phenyl-2-(3-tropane)ethanol.

No references cited.

98-95

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE

ASUNTO	Radicación	06 033251
	Trámite	002
	Evento	378
	Actuación	430
	Oficio	
	Folios	010

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

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

No. Sol. Internacional PCT/US2004/033638
Fecha de Presentación Internal. 12-10-2004.

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

Descripción: Folios: 36 a 63 (como se radicó inicialmente)

Reivindicaciones: Folios: 64 a 68 (como se radicó inicialmente)

Prioridad: Folio1 , (14-10-2003, US60/511.009).

Objeto de la invención

Título de la solicitud: Antagonistas de receptores de acetilcolina muscarínicos.

El objeto de la presente solicitud de patente de invención consiste en:
Compuestos derivados de 8-azoniabicyclo[3.2.2]octanos.



Reivindicaciones 6-13 : Un Método de tratamiento.

El problema planteado en esta solicitud es la necesidad de compuestos que sean antagonistas de los receptores de la acetilcolina muscarínicos (mAChR).

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos derivados de 8-azoniabicyclo[3.2.2]octanos y composiciones farmacéuticas que los contienen.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la Clasificación Internacional de Patentes (IPC): A61K31/46, C07D451/02; A61P11/00;

De la solicitud de Patente

Título : Se requiere al solicitante ajustar el título de la solicitud a los compuestos que son objeto de la invención.

Reivindicaciones (artículo 30 D 486)

La reivindicación 1, carece de concisión cuando

- se encuentran términos como: arilo y heteroarilo los cuales no se definen el número de átomos de carbono ni miembros que los conforman, tamaños de los anillos y en el caso de "hetero" no se definen ni el número ni el tipo de heteroátomos.

Se le sugiere al solicitante

Definir al final de la reivindicación 1 a :

arilo como fenilo y naftilo.

heteroarilo como pirrol, pirazol, furano, tiofeno, quinolina, isoquinolina, quinazolinilo, piridina, pirimidina, oxazol, tetrazol, tiazol, tiadizol, imidazol o bencimidazol.

El sustento de esto se encuentra en el folio 40.

- Existen múltiples posibilidades de sustitución a nivel de los compuestos de fórmula I o II para los radicales R1, R2, R3, R4, R5, R6 y R7 especificados de acuerdo con los parámetros de sustitución señalados.

Por lo tanto se sugiere al solicitante teniendo en cuenta los ejemplos y haciendo una generalización razonable de estos definir a :

R2 y R3 como : un grupo alquilo inferior de cadena lineal o ramificada (que tiene de 1 a 6 átomos de carbono), cicloalquilo (que tiene de 5 a 6 átomos de carbono), arilo o heteroarilo.

R4 como: arilo, ciano, CONR_7R_8 , $-\text{CO}_2\text{R}_7$, $-\text{CH}_2\text{NR}_8\text{CONHR}_7$, $\text{CH}_2\text{NR}_8\text{CONR}_6$, $\text{CH}_2\text{N}(\text{R}_7)\text{SO}_2\text{R}_5$, $\text{CH}_2\text{N}(\text{R}_8)\text{CO}_2(\text{R}_5)$, $\text{CH}_2\text{N}(\text{R}_8)\text{SO}_2(\text{R}_6)-$.

R5 como : alquilo (C1-6), alquilo (C1-6)-cicloalquilo (C3-12), alquil(C1-6)-aril, alquil(C1-6)-heteroarilo.

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R7 y R8 como : hidrógeno, alquilo (C1-6), cicloalquilo (C3-12), alquilo (C1-6)-cicloalquilo (C3-12), alquil(C1-6)-aril, alquil(C1-6)-heteroarilo.

Excepción a la patentabilidad (artículo 20 D486 literal a)-d))

Se aclara que, de acuerdo al Art 20 literal d) el método de tratamiento de las reivindicaciones 6 a 13, no es patentable.

Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 14-10-2003, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud : de publicación anterior a esta.

Nº	Documento	Título	Fecha de Publicación
D1	US2800481	Tertiary alcohol derivatives of 8-alkylnortropanes and the acid and quaternary ammonium salts thereof	23-07-1957

D1 (Folios 90 a 95) divulga compuestos alcohol terciarios derivados de 8-alquil - tropanos y sus sales de amonio cuaternarios , los cuales poseen una acción antimuscarínica (Ver folio 90, columna 1 línea 15 a columna 2, línea 26)

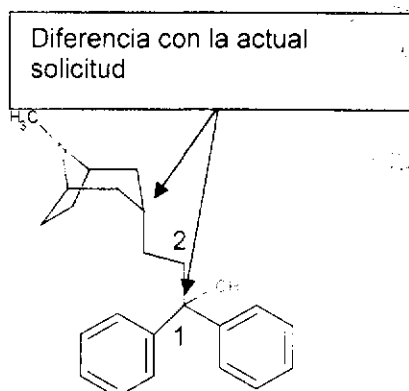
Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo 18 D486)

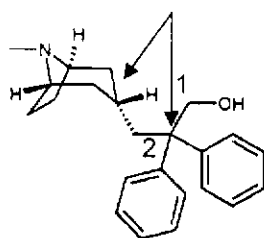
La reivindicación 1 dice "Un compuesto que tiene la estructura I o II que se indican a continuación, excepto el compuesto de fórmula (II) en la que R2 y R3 son 2-tiofeno y R4 es -OC(O)CH₃ .



El documento del estado de la técnica más cercano es D1 (Folios 90 a 95) que divulga compuestos derivados alcohol terciarios derivados de 8-alquil - tropanos y sus sales de amonio cuaternarios. En particular enseña el compuesto 1,1-difenil-3-(3-tropano)propanol y su sal cloruro y metabromuro (Ver folios 93A a 94, columna 12, línea 64, ejemplo 12 a la columna 13 línea 42),



La solicitud (ejemplo 8) se del ejemplo divulgado en D1, en que la cadena del propanol se encuentra disustituida en la posición 2 y en posición endo.



ejemplo 8 de la descripción folio 54.

Sin embargo esta diferencia no parece conceder un efecto técnico inesperado ò una ventaja a las compuestos reclamados en esta solicitud ya que no parecen presentar una mayor acción antimuscarínica en comparación con los compuestos del estado de la técnica más cercano .

El problema técnico objetivo de la solicitud es cómo proporcionar compuestos derivados de 8- alquil-tropanos con acción antimuscarínica alternativos.

El Experto en la Materia, enfrentado al Problema Técnico Objetivo y conociendo el Estado de la Técnica (D1), hubiera sugerido sin mucho esfuerzo de su parte, modificar la estequiometría y la posición de la disustitución sobre la cadena del propanol (de la posición 1 a la posición 2, Ver folio 92A, columnas 7 y 8 ejemplos 3 y 4) para obtener más compuestos con la misma actividad .

De manera que la solución propuesta por esta solicitud en la reivindicación 1 y su dependientes 2 es obvia y no tiene Nivel Inventivo.

La composición farmacéutica de la reivindicación 5 carece de nivel inventivo, ya que el componente que lo caracteriza no es inventivo.

En cuanto a las reivindicaciones 3 y 4, algunos compuestos presentan, la sustitución en la posición 3 del azabicyclo[3.2.1]octano significativamente diferente a los compuestos de D1 . Por ejemplo : cuando R4 se define como : ciano

Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US2800481	1-5	Nivel inventivo

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

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



JOSE LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (E).

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

CONCEPTO TÉCNICO No. 73	EXAMINADOR TÉCNICO Código No. 202075
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