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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.

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DESCRIPCION

Esta invención se refiere a antagonistas de prostaglandinas útiles para el tratamiento de diversas condiciones tales como asma alérgico donde se produce una actividad contráctil excesiva de las prostaglandinas y de los intermedios biosintéticos de las prostaglandinas.

Estos compuestos antagonizan las acciones de las prostaglandinas contráctiles, tales como $\text{PGF}_{2\alpha}$, PGG_2 , PGH_2 , PGD_2 y TXA_2 . El uso de agentes que actúan como antagonistas de las prostaglandinas ofrece nuevas soluciones a la terapia en numerosos estados patológicos. Por ejemplo, ciertas prostaglandinas, tales como $\text{PGF}_{2\alpha}$, PGD_2 , PGG_2 , y PGH_2 , son potentes agentes broncoespásticos. De hecho, se ha demostrado que las personas asmáticas son especialmente sensibles a la acción constrictora bronquial de la $\text{PGF}_{2\alpha}$.

Los compuestos de esta invención también son agentes antitrombóticos. Por lo tanto, son útiles en el tratamiento y/o prevención de las enfermedades tromboembólicas tales como trombosis arterial y las que implican la deposición de plaquetas, v.g. protesis.

Además de la implicación de las prostaglandinas contráctiles en el asma, se sabe que las prostaglandinas desempeñan un papel en otras condiciones alérgicas así como en la diarrea, hipertensión, angina de pecho, agregación de plaquetas, espasmos cerebrales, isquemia cerebral, arritmia, shock circulatorio, muerte súbita, aterosclerosis, isquemia de miocardio, parto prematuro, aborto espontáneo, dismenorrea, nefritis glomerular y lupus eritematoso sistémico. Por consiguiente, los compuestos de esta invención aliviarán las enfermedades mencionadas.

Además de las acciones antagonistas de las prostaglandinas, los compuestos de esta invención son inhibidores de la biosíntesis de la 5 - lipoxigenasa, de los metabolitos del ácido araquidónico tales como 5 - HPETE, 5 - HETE y los leucotrienos. Se sabe que los leucotrienos B_4 , C_4 , D_4 y E_4 contribuyen a diversas enfermedades tales como asma, psoriasis, dolores, úlceras y anafilaxis sistémica. Por lo tanto, la inhibición de la síntesis de estos compuestos aliviará estas y otras enfermedades relacionadas con los leucotrienos.

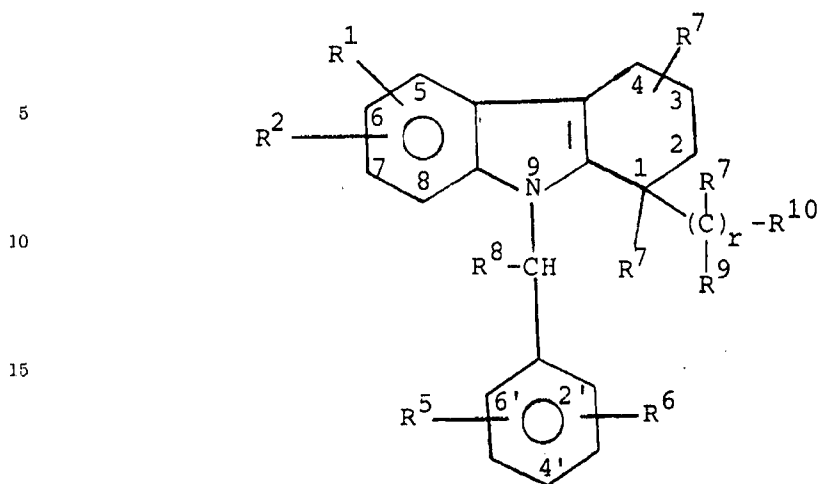
Los compuestos de esta invención pueden ser utilizados para tratar o evitar enfermedades de los mamíferos (especialmente de los seres humanos) tales como gastritis erosiva, esofagitis erosiva, erosiones hemorrágicas inducidas por el etanol, isquemia hepática, lesiones o necrosis inducidas por agentes nocivos en los tejidos hepáticos, pancreático, renal o miocárdico, lesiones parenquimatosas del hígado causadas por agentes hepatotóxicos tales como tetracloruro de carbono y D - galactosamina, insuficiencia renal isquémica, lesiones hepáticas inducidas por enfermedad, lesiones pancreáticas o gástricas inducidas por sales biliares, lesiones celulares inducidas por traumas o tensiones e insuficiencia renal inducida por glicerol.

Se sabe que ciertos ácidos 9 - bencil - 1,2,3,4 - tetrahidrocarbazol - acético o sus ésteres son intermedios químicos en la preparación de carbazoles, conocidos como agentes anti - inflamatorios, analgésicos y anti - reumáticos (véase la Patente Estadounidense 3.896.145 y la Patente Británica 1.385.620). Se conocen ciertos ácidos 9 - bencil - 1,2,3,4 - tetrahidrocarbazol - carboxílicos como agentes anti - inflamatorios, analgésicos y anti - reumáticos (véanse las Patentes Estadounidenses 3.868.387, 4.009.181, 3.905.998 y 3.758.496) y los ácidos 9 - bencil - carbazol - carboxílicos (Patentes Estadounidenses 3.956.295 y 4.057.640) y los ácidos 9 - bencilcarbazol - acéticos y sus ésteres (Patente Estadounidense 3.896.145 y Patente Británica 1.385.620) son conocidos como agentes anti - inflamatorios, analgésicos y anti - reumáticos. Sin embargo, no se ha demostrado que ninguno de estos compuestos sean antagonistas de las prostaglandinas o del tromboxano o inhibidores de la biosíntesis de leucotrienos.

Descripción de la invención

Esta invención se refiere a nuevos compuestos de Fórmula I:

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donde

25 R^1, R^2, R^5 y R^6 están seleccionados cada uno de ellos independientemente entre:

(1) hidrógeno;

30 (2) alquilo lineal de 1 a 6 átomos de carbono;

(3) M, donde M es

35 (a) OR^{13} ,

(b) halógeno,

40 (c) CF_3 ,

(d) SR^{13} ,

(e) fenilo,

45 (f) $COOR^{14}$,

50 (g) $\begin{array}{c} O \\ || \\ -C - R^{15} \end{array}$,

(h) tetrazol,

55 (i) $\begin{array}{c} O \\ || \\ -NH - C - R^{16} \end{array}$ donde R^{16} es alquilo C_{1-6} lineal,

(j) $-NR^{14}R^{14}$,

60 (k) $-NH SO_2 R^{17}$ donde R^{17} es alquilo C_{1-6} lineal o CF_3 ,

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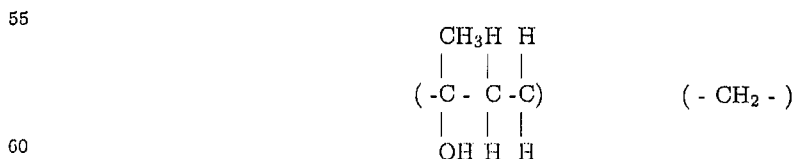
(l) - SOR^{13} ,(m) - $\text{CONR}^{14}\text{R}^{14}$,5 (n) - $\text{SO}_2\text{R}^{14}\text{R}^{14}$,(o) - SO_2R^{13} ,10 (p) NO_2 ,(q) CN ,15 (r) N_3 ; R^7 es H o alquilo lineal de 1 a 6 átomos de carbono;20 R^8 es H o alquilo lineal de 1 a 6 átomos de carbono; R^9 es cada uno de ellos independientemente H, OH, O - alquilo C_{1-4} lineal o alquilo lineal de 1 a 4 átomos de carbono;25 R^{10} es COOH , CH_2OH , CHO , tetrazol, $\text{CONHSO}_2\text{R}^{11}$, CN , $\text{CON}(\text{R}^9)_2$ o $\text{NHSO}_2\text{R}^{11}$, donde R^{11} es OH, alquilo lineal o alcoxi lineal de 1 a 6 átomos de carbono, perhaloalquilo lineal de 1 a 6 átomos de carbono, fenilo o fenilo sustituido con grupos alquilo lineal o alcoxi lineal de 1 a 3 átomos de carbono, halógeno, hidroxil, COOH , CN , formilo o acilo de 1 a 6 átomos de carbono;

30 r es 1 a 6;

 R^{13} es cada uno de ellos independientemente H o alquilo C_{1-6} lineal, R^{14} es cada uno de ellos independientemente H o alquilo C_{1-6} lineal y35 R^{15} es cada uno de ellos independientemente H, alquilo C_{1-6} lineal o CF_3 ;

o sales farmacéuticamente aceptables de los mismos.

40 En el sentido utilizado aquí, las expresiones "cada uno de ellos independientemente" o sus equivalentes se emplean para describir un número de posibles isómeros de posición y/o de variación estructurales. Por ejemplo, como se ha señalado antes, la siguiente unidad está enlazada a la posición 1 del anillo de tetrahydrocarbazol:

50 La letra r representa las posibles cadenas alcánicas de 1 a 6 átomos de carbono, conteniendo cada una de ellas los grupos sustituyentes R^7 y R^9 . Sobre cada átomo de carbono de la cadena alcánica, los sustituyentes R^7 y/o R^9 pueden ser diferentes. Por lo tanto, la descripción anterior contempla estructuras tales como las siguientes para el fragmento $-(\text{CR}^7\text{R}^9)_r-$:

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CERTAIN TETRAHYDRO CARBOLINE
DERIVATIVES

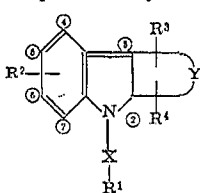
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Int. Cl. C07d 31/44

U.S. Cl. 260—295

5 Claims

ABSTRACT OF THE DISCLOSURE

Indole derivatives represented by the formula,

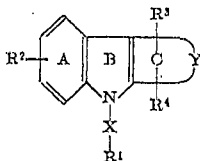


wherein R¹ is a non-substituted or lower alkyl- having 1 to 3 carbons, alkoxy- having 1 to 3 carbons, alkylthio- having 1 to 3 carbons or halogen-substituted aromatic ring, a non-substituted or halogen- or alkyl- having 1 to 3 carbons substituted 5- or 6-membered heterocyclic ring containing a nitrogen, oxygen or sulfur, or a non-substituted or halogen-, phenyl-, phenoxy- or alkoxy- having 1 to 2 carbons substituted alkyl having 1 to 10 carbons or alkenyl having 1 to 10 carbons; R² is a lower alkyl having 1 to 3 carbons, alkoxy having 1 to 3 carbons, alkylthio having 1 to 3 carbons, halogen or hydrogen; R³ and R⁴ are hydrogen or halogen or hydroxycarbonyl, alkoxycarbonyl (the alkoxy having 1 to 3 carbons), alkyl having 1 to 3 carbons, alkenyl having 1 to 3 carbons or alkoxy having 1 to 3 carbons; X is carbonyl or sulfonyl; and



is a 5- or 6-membered ring or a nitrogen-containing 5- or 6-membered heterocyclic ring, which are useful as anti-inflammatory drug.

This invention relates to novel indole derivatives and a process for preparing the same. More particularly, the invention pertains to novel indole derivatives represented by the general formula:



wherein R¹ is a non-substituted or lower alkyl- having 1 to 3 carbons, alkoxy- having 1 to 3 carbons, alkylthio- having 1 to 3 carbons or halogen-substituted aromatic ring, a non-substituted or halogen- or alkyl- having 1 to 3 carbons substituted 5- or 6-membered heterocyclic ring containing a nitrogen, oxygen or sulfur, or a non-substituted or halogen-, phenyl-, phenoxy- or alkoxy- having 1 to 2 carbons substituted alkyl having 1 to 10 carbons or alkenyl having 1 to 10 carbons; R² is a lower alkyl having 1 to 3 carbons, alkoxy having 1 to 3 carbons, alkylthio having 1 to 3 carbons, halogen or hydrogen; R³ and R⁴ are hydrogen or halogen or hydroxycarbonyl, alkoxycarbonyl

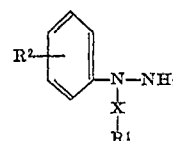
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(the alkoxy having 1 to 3 carbons), alkyl having 1 to 3 carbons, alkenyl having 1 to 3 carbons or alkoxy having 1 to 3 carbons; X is carbonyl or sulfonyl; and



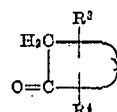
is a 5- or 6-membered ring or a nitrogen-containing 5- or 6-membered heterocyclic ring, and a process for preparing the same.

The novel indole derivatives represented by the general Formula I are obtained in high yields by reacting at an elevated temperature a hydrazine derivative, or a salt thereof, represented by the general formula:



(II)

wherein R¹, R² and X are the same as in the case of the general Formula I, with a compound represented by the general formula:



(III)

wherein R³, R⁴ and



are the same as in the case of the general Formula I.

The above reaction progresses smoothly even in the absence of solvent, but the use of suitable solvents is preferable. As the solvents, there are used organic acids such as acetic, formic, propionic, lactic and butyric acids, non-polar organic solvents such as cyclohexane, n-hexane, benzene and toluene, and general organic solvents such as dioxane and dimethylformamide and, in some cases, alcohols such as methyl, ethyl and i-propyl alcohols.

The reaction progresses at a temperature within the range of 40°–200° C., but a temperature range of 60°–100° C. is most preferable. The use of condensing agents is not always necessary but there are used inorganic acids such as hydrochloric, sulfuric and phosphoric acids, heavy metal halides such as zinc chloride and copper chloride, boron fluorides, polyphosphoric acids and cation exchange resins.

The process of the present invention is quite novel, and not only the reaction is entirely unknown but also the hydrazine derivatives and salts thereof, which are the starting materials to be used, are novel compounds not disclosed in the literature.

The synthesis of N-acyl-indole compounds has heretofore been effected according to a method in which an indole compound is first synthesized and is then subjected to acylation. In the above synthesis method, there have frequently been adopted such complex and disadvantageous procedures that a metal salt of indole is initially prepared by use of NaH, NaNH₂, etc. and is then reacted with an acyl halide.

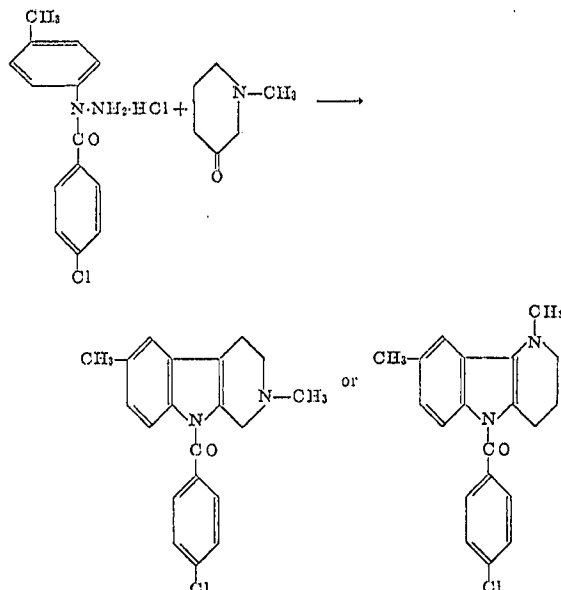
In accordance with the present process, the product is obtained in extremely high yields, and the after-treatments thereof are markedly simple as compared with the conventional method. That is, in most cases, the desired product is directly obtained as a precipitate after completion of the reaction. Even in the case where no precipitate is formed, the reaction liquid is concentrated or is added to a suitable liquid such as, for example, water or

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acetic acid water, whereby the desired product is obtained in the form of beautiful crystals.

Depending on the kind of starting materials, there are some cases where two isomers are obtained as products, as shown by, for example, the following reaction equation:



All the N-acyl-indole derivatives obtained in accordance with the present process are not only novel compounds but are useful compounds having prominent antiphlogistic, analgesic, antifebric and calmative actions.

According to the present process, compounds of the substituents enumerated below are obtained in high yields, in general.

R¹-X—: acetyl, chloroacetyl, propionyl, isobutyryl, 4'-chlorocrotonyl, n-pentanoyl, n-hexanoyl, 2,4-hexadienoyl, n-decanoyl, n-octanoyl, n-heptanoyl, cinnamoyl, cinnamylacryloyl, acryloyl, benzoyl, p-chlorobenzoyl, p-methylbenzoyl, p-methoxybenzoyl, p-methylthiobenzoyl, m,p-dimethoxybenzoyl, p-bromobenzoyl, benzenesulfonyl, p-toluenesulfonyl, α-naphthoyl, β-naphthoyl, nicotinoyl, isonicotinoyl, 2-chloroisonicotinoyl, 2-furoyl, 3-furoyl, 2-thenoyl, 3-thenoyl, 5-chloro-2-thenoyl, N-methyl-hexahydronicotinoyl, phenylacetyl, phenoxyacetyl, phenoxyacryloyl, 2-phenylcinnamoyl, p-chlorocinnamoyl, p-methoxycinnamoyl, 3-methoxypropionyl and 4-methoxycrotonoyl groups.

R²—: methyl, ethyl, isopropyl, methoxy, ethoxy, methylthio, ethylthio, chloro, bromo and hydrogen groups.

R³ and R⁴: hydrogen, hydroxycarbonyl, methoxycarbonyl, ethoxycarbonyl, methyl, ethyl, methylene, ethylidene, methoxy, ethoxy, chloro and bromo groups.

Y-containing ring C: pyrrolidine, piperidine, cyclohexene and cyclopentene rings.

In accordance with the present process, the following compounds were easily obtained in high yields:

- 6-methoxy-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydrocarbazole.
- 1-(p-methylbenzoyl)-5-methyl-2,3-cyclopenteno-indole.
- 1-(p-methoxybenzoyl)-5-methylthio-2,3-cyclopenteno-indole.
- 1-(p-chlorobenzoyl)-5-chloro-2,3-(1'-methoxycarbonyl-cyclopenteno)-indole.
- 1-(p-chlorobenzoyl)-5-chloro-2,3-(2'-methoxycarbonyl-cyclopenteno)-indole.
- 3-methyl-6-methoxy-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydrocarbazole.
- 3-methyl-6-methoxy-9-(p-methylthiobenzoyl)-1,2,3,4-tetrahydrocarbazole.
- 3-methyl-6-methoxy-9-(2',4'-hexadienoyl)-1,2,3,4-tetrahydrocarbazole.

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- 6-methoxy-9-chloroacetyl-1,2,3,4-tetrahydrocarbazole.
- 3-methyl-6-methoxy-9-nicotinoyl-1,2,3,4-tetrahydrocarbazole.
- 3-methyl-6-methoxy-9-(5'-chloro-2'-thenoyl)-1,2,3,4-tetrahydrocarbazole.
- 3-methyl-6-methoxy-9-(2'-furoyl)-1,2,3,4-tetrahydrocarbazole.
- 3-methyl-6-methoxy-9-(N'-methyl hexahydro-nicotinoyl)-1,2,3,4-tetrahydrocarbazole.
- 3-methyl-6-methoxy-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydro-γ-carboline.
- 2-methyl-6-methoxy-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydro-β-carboline.
- 3,5-dimethyl-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydrocarbazole.
- 3,7-dimethyl-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydrocarbazole.
- 4-methyl-5-methoxy-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydrocarbazole.
- 4-methyl-7-methoxy-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydrocarbazole.
- 3-methyl-6-methylthio-9-(N'-methylhexahydronicotinoyl)-1,2,3,4-tetrahydrocarbazole.

As mentioned before, these compounds contain compounds having prominent antiphlogistic and the like actions and are extremely useful in practice.

For example, the present inventors have obtained the following test results:

Compound	Effectiveness		
	ID ₅₀ * (per os, mg./kg.)	LD ₅₀ † (per os, mg./kg.)	Therapeutic ratio, LD ₅₀ /ID ₅₀
35 3-methyl-6-methoxy-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydrocarbazole	250	>1,500	>6
2-methyl-6-methoxy-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydrocarbazole	250	>1,500	>6
1-(p-chlorobenzoyl)-5-methoxy-2,3-(1'-methoxycarbonyl-cyclopenteno)-indole	135	>1,500	>11
3-methyl-6-methoxy-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydro-γ-carboline hydrochloride	150	>1,500	>10
40 Phenylbutazone	145	680	4.7

*50% inhibition dose of earageen hind paw edema of rat.
†50% lethal dose of mouse in 1 week.

The following examples illustrate the present process, but the examples are merely illustrative and it is not intended to limit the invention only to these examples.

EXAMPLE 1

7.5 g. of N₁-(p-chlorobenzoyl)-p-methoxyphenylhydrazine hydrochloride was added to 15 ml. of cyclohexanone, and the mixture was heated at 90° C. for 5 minutes. After allowing the mixture to cool, the produced precipitate was filtered, and the filtrate was charged with 80 ml. of a 40% aqueous acetic acid solution to give a large amount of crystals. The crystals were filtrated and dried to give 8.1 g. of crude crystals of 6-methoxy-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydrocarbazole, M.P. 94°–97° C. The crude crystals were recrystallized from a solution of 420 ml. of ethanol and 200 ml. of water to obtain 7.1 g. of a pure product, M.P. 104°–105° C.

EXAMPLE 2

7 g. of N₁-(p-chlorobenzoyl)-p-methoxyphenylhydrazine hydrochloride, 10 ml. of 4-methylcyclohexanone and 26 ml. of cyclohexane were heated with stirring at 80° C. for 15 minutes. Thereafter, the precipitate was filtered and washed with 5 ml. of cyclohexane. The collected filtrate was concentrated to about half volume and was then charged with 120 ml. of a 50% aqueous acetic acid solution to give a large amount of solids. After cooling the reaction liquid with ice, the solids were filtered, washed with 20 ml. of cold water and dried to give 7.7 g. of pale yellow crude crystals of 3-methyl-6-methoxy-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydrocarbazole. The crude crystals were recrystallized from 400 ml. of ethanol to give 6.9 g. of a pure product, M.P. 142°–143° C.