

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

235

Re: P1.-GLAXO GROUP LIMITED.-Expediente número
01-063.014.-

1. Me refiero al memorial de sustitución de poder presentado a ese Despacho el 31 de Agosto de 2004.

2. Por medio del presente, atentamente me permito manifestar a ese Despacho, que hubo un cambio de Representante Legal para todos los asuntos de la Propiedad Industrial en Bogotá de **GLAXO GROUP LIMITED**, una sociedad organizada y existente de conformidad con las leyes de Inglaterra y Gales, domiciliada en Greenford, Middlesex, Inglaterra.

3. En consecuencia, atentamente solicito a ese Despacho reconocerme personería, en este asunto, de conformidad con el documento de Representación Legal para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **GLAXO GROUP LIMITED**, otorgado a favor del **SUSCRITO (GUSTAVO TAMAYO)** y/o a la doctora ALICIA LLOREDA y/o al doctor IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ de acuerdo con la copia debidamente autenticada ante Notario Público que adjunto al presente expediente (Artículos 26 y 39 de la Decisión 486 de la Comunidad Andina de Naciones).

4. Anexo al presente acompaño fotocopia, de:

- (a) Documento que acredita al SUSCRITO y/o a la doctora ALICIA LLOREDA y/o al doctor IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ en los términos del párrafo 1º. del Artículo 543 del Decreto-Ley 410 de 1971, como Representantes Legales en Bogotá para todos los asuntos relacionados con la propiedad industrial de la sociedad **GLAXO GROUP LIMITED**, una sociedad organizada y existente de conformidad con las leyes de Inglaterra y Gales, domiciliada en Greenford, Middlesex, Inglaterra.

(b) Certificación Notarial expedida el 26 de Agosto de 2004; y

(c) Traducción Oficial No. 2004-09-02-440 correspondiente a las partes pertinentes del documento anterior, también debidamente legalizada hasta por el Ministerio de Relaciones Exteriores bajo el número 258650 de 3 de Septiembre de 2004.

5. Finalmente, llamo la atención de ese Despacho al hecho de que la copia auténtica del documento que me acredita para actuar como Representante Legal de la sociedad peticionaria, reposa en el Expediente número **98-032.525**.

6. Ruego a usted tomar atenta nota de lo anterior y continuar con el trámite correspondiente.

Señor Superintendente,


GUSTAVO TAMAYO
T.P. 37.172
Código 231

237

Yo, el infrascrito, **Martin Emil BUCHNER**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

CERTIFICO:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **Peter John GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada "**GLAXO GROUP LIMITED**", Sociedad legalmente constituida y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número 305979, con domicilio social en Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra;

QUE el citado Señor Don **Peter John GIDDINGS** está debida y suficientemente autorizado para firmar documentos de esta clase, en virtud del Poder otorgado en su favor por la referida Sociedad fechado el 30 de enero de 2003, una copia del cual he tenido a la vista;

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy veintiseis de agosto del año dos mil cuatro.

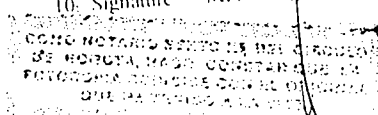

Martin Emil BUCHNER
Notario Publico de Londres, Inglaterra

SCRIVENER
NOTARIES

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord
This public document / Le présent acte public
2. Has been signed by Martin E. Buchner
a été signé par
3. Acting in the capacity of Notary Public
agissant en qualité de
4. Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de
5. at London/à Londres
6. Certified/Attesté
the/le 26 August 2004
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.
8. Number/sous No G499865
9. Stamp
timbre:
10. Signature M. Monaghan



03 SET 2004

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

Los abajo firmados, **GLAXO GROUP LIMITED**, una sociedad organizada y existente de conformidad con las leyes de Inglaterra y Gales..

con domicilio en **Glaxo Wellcome House
Berkeley Avenue
Greenford Middlesex UB6 0NN
Inglaterra**

nombramos por el presente a **ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ**, domiciliados en Bogotá, Colombia, con oficinas en dicha ciudad, Calle 72 No. 5-83, piso 6o., nuestros representantes legales y verdaderos en Bogotá, con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales, con el fin de dar cumplimiento al parágrafo 1o. del artículo 543 del decreto 410 de 1971.

Los doctores **ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ**, o los apoderados que cualquiera de ellos designe, quedan especialmente facultados para representarnos ante las autoridades colombianas, administrativas, judiciales o de policía, en todos los trámites relativos a la propiedad industrial, a cuyo efecto les facultamos para dar ante dichas autoridades todos los pasos necesarios al objeto indicado; elevar solicitudes, declaraciones, reclamos, recursos y presentar desistimientos; formular descripciones, enmiendas, limitar el alcance de las solicitudes, presentar oposiciones y apelaciones; instaurar cancelaciones, renunciar total o parcialmente a los registros, abonar todos los impuestos y cuotas y efectuar todo otro pago determinado por la ley; recibir todos los documentos y valores, dando el descargo respectivo; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses; y en caso de producirse oposición, pasando los antecedentes a los tribunales, quedan facultados para tomar intervención como demandantes o demandados ante los jueces que sean competentes, pudiendo transar, someter a árbitros, desistir, percibir y apelar, con todas las demás facultades que resulten necesarias, y por el presente declaramos desde ahora válido y bueno cuanto dichos representantes y/o los apoderados que cualquiera de ellos nombre hicieren en nuestro beneficio.

Asimismo, facultamos a los doctores **ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ**, para solicitar en la Oficina de Propiedad Industrial la protocolización de este documento y de cualquier poder que cualquiera de ellos otorgue a nombre nuestro.

Dado y firmado

The undersigned, **GLAXO GROUP LIMITED**, a corporation organized and existing under the laws of England and Wales.

domiciled at **Glaxo Wellcome House
Berkeley Avenue
Greenford Middlesex UB6 0NN
Great Britain**

hereby appoint, **ALICIA LLOREDA and/or GUSTAVO TAMAYO and/or IGNACIO SANTAMARIA and/or ENRIQUE ALVAREZ**, of Bogota, Colombia, with offices in said town, Calle 72 No. 5-83, Sixth Floor, our true and legal representatives in Bogotá, with power to receive notifications and to appoint judicial or extrajudicial agents, so as to comply with paragraph 1o. of article 543 of decree 410 of 1971.

Doctors **ALICIA LLOREDA and/or GUSTAVO TAMAYO and/or IGNACIO SANTAMARIA and/or ENRIQUE ALVAREZ**, or the agents by any one of them appointed, are especially empowered to represent us before the administrative, judicial or police authorities of Colombia, in all proceedings pertaining to industrial property, for which purpose we authorize them to take before the said authorities all the necessary steps for the said end; to file petitions, declarations, claims, recourses and withdrawals, to draw up specifications; to file amendments, to limit the scope of applications, file oppositions; file cancellations total or partially waive registrations, to pay all installments and effect all other payments prescribed by law; to receive proper receipts, to comply with all other requirements and, in short, to take all those measures which they may deem fit for the protection of our interests; and in case of opposition, where the proceedings be passed over to the courts, we authorize said agents to act on our behalf, as complainants as well as defendants, before the competent judges, with full powers to make arrangements, to submit to arbitrators, to desist, to collect, to appeal and, in short, with all such further powers as may be required, and we hereby declare from now on as valid and good all that said representatives and/or the agents by any one of them appointed may do for our benefit.

We also authorize doctors **ALICIA LLOREDA and/or GUSTAVO TAMAYO and/or IGNACIO SANTAMARIA and/or ENRIQUE ALVAREZ**, to apply for protocolization of this document and of any power of attorney by any one of them conferred in our name, before the Office of Industrial Property.

Given and signed this

23 AUG 2004

Peter John GIDDINGS as Attorney and
Authorised Official

NOTARY SHOULD EXECUTE OTHER SIDE

TRADUCCION OFICIAL No. 2004-09-02-440
DE LAS PARTES PERTINENTES DE UN DOCUMENTO
PRESENTADO EN INGLES

PODER

Legalización de un Poder de Representación Legal, Documento escrito en inglés y en español.

Notarización del documento es español.

Hay un sello rojo sobre una cinta verde.

APOSTILLA

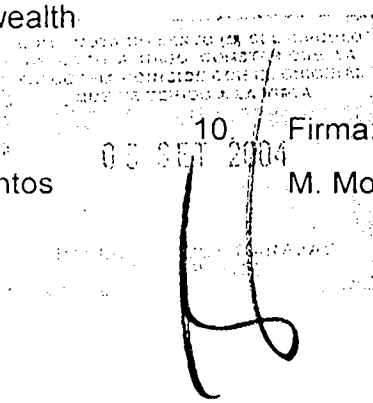
(Convención de La Haya del 5 de octubre de 1961)

Reino Unido de la Gran Bretaña e Irlanda del Norte

1. País: Reino Unido de la Gran Bretaña e Irlanda del Norte
Este documento público
2. ha sido firmado por Martin E Buchner
3. actuando como Notario Público
4. lleva el sello/estampilla de dicho Notario Público

CERTIFICADO

5. en Londres
6. el 26 de agosto de 2004.
7. por el Secretario de Estado Principal de Su Majestad para Asuntos Exteriores y del Commonwealth.
8. Número G499865
9. Sello/Estampilla
10. Firma: (ilegible)
M. Monaghan
- Sello de la Oficina de Asuntos



TRADUCTOR OFICIAL
RESOLUCION 2177

ANITA ESCOBAR DE TAMAYO

MINISTERIO DE
RELACIONES EXTERIORES

258650

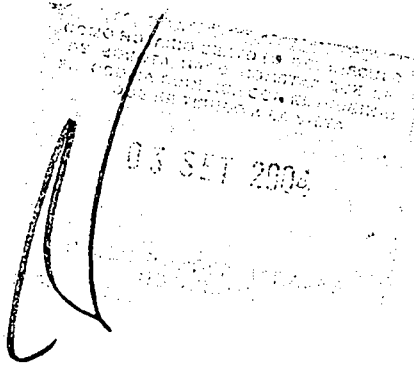
Anita Escobar
CUYA FIRMA APOZEE EN EL
DOCUMENTO DESEMPENA
LAS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2004 SET -3 P 12: 12

ues

JEFE DE LEGALIZACIONES
BOGOTÁ D.C.



Exteriores y del Commonwealth

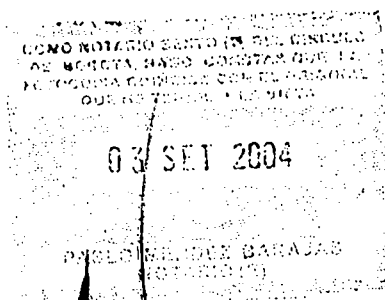
Por el Secretario de Estado

Si este documento se va a usar en un país que no es parte de la Convención de La Haya del 5 de octubre de 1961, debe presentarse en la sección consular de la misión que representa a ese país. Una apostilla o certificado de legalización únicamente confirma que la firma, sello o estampilla sobre el documento es autentica. No significa que los contenidos del documento sean correctos o que la Oficina de Asuntos Exteriores y del Commonwealth apruebe los contenidos.

Traducido a mi mejor saber y entender, este día 2 de septiembre de 2004, en la ciudad de Bogotá, D.C., por Anita Escobar de Tamayo, Traductora Oficial, Res. 2177 de 1989, Ministerio de Justicia, República de Colombia.

TRADUCTOR OFICIAL
RESOLUCION 2177

Anita Escobar de Tamayo
ANITA ESCOBAR DE TAMAYO



DIVISION DE NUEVAS CREACIONES

241

RADICACIÓN EXPEDIENTE No. 01-63014

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 531, DE
FECHA 29 DE AGOSTO DE 2003, EL TERMINO HABIL SEÑALADO POR LA
LEY EXPIRA EL 26 DE NOVIEMBRE 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 ☒ ☐

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Gustavo Tamayo
Apoderado
GLAXO GROUP LIMITED

Oficio N° 11903

REFERENCIA	Radicación	01 63014
	Trámite	002
	Evento	001
	Actuación	430
	Folios	002

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 01 63014, realizado según el artículo 46 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

SOLICITUD DE SUMINISTRO DE INFORMACIÓN

El art. 46 de la Decisión 486 establece que "La Oficina Nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial. De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más documentos relativos a una o más solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina: ...b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera...Si el solicitante no presentara los documentos requeridos dentro del plazo señalado en el presente artículo la oficina nacional competente denegará la patente"

Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente solicitud, se determinó que existen en el estado de la técnica los siguientes documentos que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- ISOGAI, MITSUTAKA ET AL: "Binding affinities of mometasone furoate and related compounds including its metabolites for the glucocorticoid receptor of rat skin tissue". J. STEROID BIOCHEM. MOL. BIOL. (1993), 44(2), 141-5, XP002182261.
- PHILLIPPS G H ET AL: "Synthesis and structure-activity relationships in a series of anti-inflammatory corticosteroid analogues, halomethyl androstane-17beta-carbothioates and 17-beta-carboselenoates". Journal of Medicinal

chemistry, American Chemical Society. Washington. US. Vol. 37, no. 22, 1 October 1994, pages 3717-3729, XP002025925. ISSN: 0022-2623.

- POPPER T L ET AL: "Structure-activity relationship of a series of novel topical corticosteroids". Journal of Steroid biochemistry, Pergamon Press PLC, GB, Vol 27, no. 4-6, 1987, pages 837-843, XP000972215. ISSN: 0022-4731. PAGE 840-841, examples 21-24, 29-32.
- SHAPIRO E L ET AL: "17 Heteroaroyl esters of corticosteroids 2. 11-beta hydroxy series" Journal of Medicinal chemistry, American Chemical Society. Washington, US, vol. 30, no. 9, 1987, pages 1581-1588, XP...2153839. ISSN: 0022-2623. Page 1582; examples 1H-IK; table I; page 1583; examples 2C-2E, 2G; table II.

Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud WO 0212266, equivalente a la solicitud colombiana aquí estudiada, y no siendo viable la consecución de dichos artículos por este despacho, se requiere que el solicitante, en virtud de lo establecido en el art. 46 de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione la publicación completa, con lo que podrá realizarse un análisis absoluto de la patentabilidad de la invención correspondiente a la presente solicitud

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001.


Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

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

19 OCT. 2006

CONCEPTO TÉCNICO Número 01623	EXAMINADOR TÉCNICO Código 202044
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[54] ANTI-INFLAMMATORY STEROIDS OF THE ANDROSTANE SERIES HAVING A HALO-SUBSTITUTED C₁-C₂ ALKOXY CARBONYL GROUP AT THE 17 β POSITION

[75] Inventors: Gordon Hanley Phillipps, Wembley; Peter John May, North Harrow; Brian McDonald, Chalfont St. Peter; Edward Arthur Woollett, Fulmer, all of England

[73] Assignee: Glaxo Laboratories Limited, Middlesex, England

[22] Filed: July 16, 1973

[21] Appl. No.: 379,471

[30] Foreign Application Priority Data

July 19, 1972 Great Britain 33834/72

[52] U.S. Cl. 260/397.1, 424/243

[51] Int. Cl. C07c 169/24

[58] Field of Search 260/397.1;
/Machine Searched Steroids

[56] References Cited

FOREIGN PATENTS OR APPLICATIONS

778,285 7/1972 Belgium

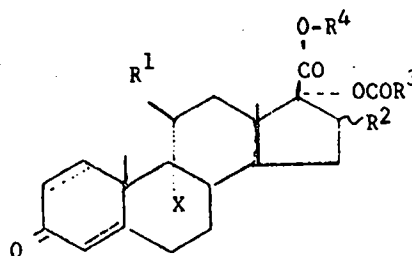
Primary Examiner—Henry A. French

Attorney, Agent, or Firm—Bacon & Thomas

[57] ABSTRACT

The Specification describes compounds of the general

formula



I

wherein X represents a hydrogen, chlorine or fluorine atom;

R¹ represents a β -hydroxy group, an oxo group or (when X is a chlorine atom) a β -chlorine atom;

R² represents a hydrogen atom, a methylene group or an α - or β -methyl group;

R³ represents a hydrogen atom or C₁₋₄alkyl or phenyl group;

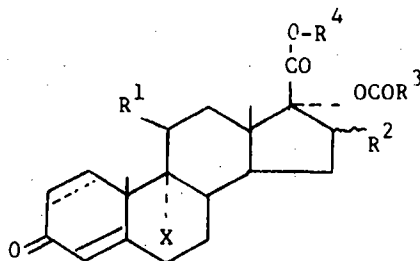
R⁴ represents a methyl group substituted by at least one halogen atom; an ethyl group substituted by at least one fluorine and/or iodine atom; or a propyl group substituted by at least one halogen atom; and == represents a single or double bond. The Specification also describes processes for the preparation of compounds of formula I as well as pharmaceutical compositions containing such compounds. The compounds of formula I have good anti-inflammatory activity, particularly on topical application.

19 Claims, No Drawings

**ANTI-INFLAMMATORY STEROIDS OF THE
ANDROSTANE SERIES HAVING A
HALO-SUBSTITUTED C₁-C₂ALKOXY CARBONYL
GROUP AT THE 17 β POSITION**

The present invention relates to novel anti-inflammatory steroids of the androstane series.

Our Belgian Patent No. 778,285 describes and claims a novel class of androstane steroids having anti-inflammatory activity, these steroids containing an esterified carboxyl group in the 17 β -position and an esterified hydroxy group in the 17 α -position. Such steroids may broadly be represented by the general formula



where X represents a hydrogen, chlorine or fluorine atom;

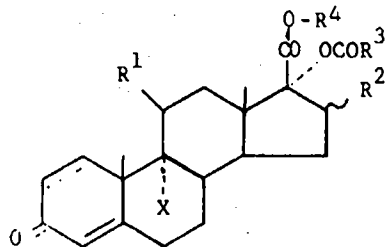
R¹ represents a β -hydroxy group, a β -chlorine atom or an oxo group;

R² represents a hydrogen atom, a methylene group or an α - or β -methyl group;

R³ represents a hydrogen atom or an alkyl group, preferably containing 1-3 carbon atoms or a phenyl group; R⁴ represents a lower alkyl group, which may be substituted by at least one halogen atom or by a lower acyloxy group or a lower alkoxycarbonyl group; and $\equiv$ represents a single or double bond. In our above Belgian Patent, certain exclusions were made from this general class.

We have now discovered that among this class of androstane steroids those in which R⁴ is a haloalkyl group have particularly advantageous anti-inflammatory activity, especially on topical application.

According to one feature of the present invention we provide compounds of the general formula



wherein X represents a hydrogen, chlorine or fluorine atom; R¹ represents a β -hydroxy group, an oxo group or (when X is a chlorine atom) a β -chlorine atom; R² represents a hydrogen atom, a methylene group or an α - or β -methyl group; R³ represents a hydrogen atom or a C₁₋₄ alkyl or phenyl group; R⁴ represents a methyl group substituted by at least one halogen atom; an ethyl group substituted by at least one fluorine and/or iodine atom; or a propyl group substituted by at least one hal-

ogen atom; and $\equiv$ represents a single or double bond.

The only 17 β -haloalkoxycarbonyl steroids specifically described in our above Patent are 2'-chloroethyl and 2'-bromoethyl 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate; the 17 β -haloalkoxycarbonyl steroids which we have subsequently tested and which are the subject of the present application have generally shown markedly superior anti-inflammatory properties as compared with these two compounds.

In formula I above, R⁴ preferably represents a halogen-substituted methyl or ethyl group. Fluorine or chlorine are preferred substituents on the specified alkyl groups. For example, R⁴ may represent a halo-methyl group, e.g., a fluoro-, chloro-, bromo- or iodo-methyl group; or a fluoro alkyl group such as a 2-fluoro-ethyl or 3-fluoro-propyl group.

In general, those groups R⁴ which are lighter than the chloroethyl and bromoethyl groups are preferred i.e., the fluoro and chloromethyl groups and fluoroethyl group.

Those compounds of formula I wherein R₃ represents an alkyl group containing 1 to 3 carbon atoms are generally preferred, and it is particularly preferred, in general, that R¹ represents a β -hydroxy group.

In general, compounds in which $\equiv$ represents a double bond have been found to have good topical anti-inflammatory activity. X is also preferably fluorine or hydrogen. R² is preferably a methyl group, advantageously in the β -configuration, or a methylene group.

Preferred compounds of formula I above on account of their high topical anti-inflammatory activity are those wherein R³ represents an ethyl group and R¹ represents a β -hydroxy group, R² advantageously representing a methyl group in the β -configuration.

A further preferred class of compounds of formula I are those wherein X represents a fluorine atom, R¹ represents a β -hydroxy group, R² represents a methylene group and $\equiv$ represents a double bond.

Compounds of formula I in which R¹ represents a β -hydroxy group, R² represents hydrogen, X represents hydrogen and $\equiv$ represents a single bond are also of particular interest.

A particularly preferred class of compounds of formula I having especially favourable topical anti-inflammatory activity are those wherein R⁴ represents a methyl group substituted by a fluorine or chlorine atom e.g. a chloromethyl group or a fluoroethyl group.

Particularly preferred compounds of formula I according to the present invention include those set out in the following Table ($\equiv$ representing a double bond)

X	R ₁	R ₂	R ₃	R ₄
F	β -OH	β -CH ₃	C ₂ H ₅	CH ₂ CH ₂ F
do.	do.	do.	do.	CH ₂ Cl
H	do.	do.	do.	do.
F	do.	do.	do.	CH ₂ F
Cl	do.	do.	do.	CH ₂ F
F	do.	α -CH ₃	do.	do.
do.	do.	$\equiv$ CH ₂	do.	CH ₂ Cl
do.	do.	do.	do.	CH ₂ F
H	do.	β -CH ₃	do.	CH ₂ F

A further interesting compound according to the invention is 3'-fluoropropyl 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate.

cyclohexane in the presence of a palladium catalyst in a solvent e.g. ethanol, preferably under reflux. This reduction may be carried out on a haloalkyl ester where this is sufficiently stable in such a reaction or may be effected at an earlier stage.

As is well known to those skilled in the art it may frequently be convenient to elaborate the desired substituents in the 17 α - and 17 β -positions at an intermediate stage of the preparation of the desired final compound, one or more other substituents (or unsaturation) being introduced at a later stage. For example, it is possible for the preparation of 11-oxo compounds first to prepare an 11-hydroxy compound having the desired 17 α -acyloxy group and the desired 17 β -carboxylate ester group and then oxidise the 11 β -hydroxy group. Other instances where the desired substituents may be introduced before final elaboration of the remainder of the desired androstane molecule include for example preparing $\Delta^{9(11)}$ or Ring A saturated compounds having the desired 17 α -acyloxy and 17 β -carboxylate ester groups, completion of the elaboration of Rings A, B and C then being completed in conventional manner.

There are also provided pharmaceutical compositions for use in anti-inflammatory therapy, comprising at least one compound according to the invention together with one or more pharmaceutical carriers or excipients. Such compositions may be in forms adapted for topical or internal administration.

The active androstane compound may be formulated into a preparation suitable for topical administration with the aid of a topical vehicle therefor. Examples of various types of preparation for topical administration, include ointments, lotions, creams, powders, drops, (e.g. eye or ear drops), sprays, (e.g. for the nose or throat), suppositories, retention enemas, chewable or suckable tablets or pellets (e.g. for the treatment of aphthous ulcers) and aerosols. Ointments and creams may for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or glycols. Such base may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a glycolic solvent such as propylene glycol or 1,3-butane-diol. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, woolfat, hydrogenated lanolin and beeswax and/or glyceryl monostearate and/or non-ionic emulsifying agents.

The solubility of the steroid in the ointment or cream may be enhanced by incorporation of an aromatic alcohol such as benzyl alcohol, phenylethyl alcohol or phenoxyethyl alcohol.

Lotions may be formulated with an aqueous or oily base and will in general also include one or more of the following namely, emulsifying agents, dispersing agents, suspending agents, thickening agents, solvents, colouring agents and perfumes.

Powders may be formed with the aid of any suitable powder base e.g. talc, lactose or starch. Drops may be formulated with an aqueous base also comprising one or more dispersing agents, suspending agents or solubilising agents etc.

Spray compositions may for example be formulated as aerosols with the use of a suitable propellant, e.g. dichloro-difluoromethane or trichlorofluoromethane.

The proportion of active androstane compound in the topical compositions according to the invention depends on the precise type of formulations to be prepared but will generally be within the range of from 0.0001 to 5.0 percent by weight. Generally however for most types of preparations advantageously the proportion used will be within the range of from 0.001 to 0.5 percent and preferably 0.01 to 0.25 percent.

Topical preparations may be administered by one or more applications per day to the affected area; over skin areas occlusive dressings may often be used with advantage.

For internal administration the new compounds according to the invention may, for example, be formulated for oral, parenteral or aectal administration. For oral administration, syrups, elixirs, powders and granules may be used which may be formulated in conventional manner. Dosage unit forms are however preferred as described below.

For parenteral administration the compounds may be presented in sterile aqueous or oily vehicles, suitable oily vehicles including arachis oil, olive oil etc.

Preferred forms of preparation for internal administration are dosage unit forms i.e. presentations in unitary form in which each unit contains a desired dose of the active steroid. Such dosage unit forms contain from 0.05 to 2.0mg, preferably from 0.25 to 1.0 mg of the active steroid. For oral administration suitable dosage unit forms include tablets, coated tablets and capsules. For parenteral administration dosage unit forms include sealed ampoules or vials each containing a desired dose of the steroid. Suppositories, which may be prepared for example with conventional commercial suppository bases, provide a dosage unit form for rectal administration. Sterile tablet or pellet implants may also be used, e.g. where slow systemic absorption is desired.

The compounds according to the invention may in general be given by internal administration in cases where systemic adreno-cortical therapy is indicated.

In general terms preparations for internal administration may contain from 0.01 to 5.0 % of active ingredient dependent upon the type of preparation involved. The daily dose may vary from 0.05 to 10.0 mg. dependent on the condition being treated and the duration of treatment desired.

The compositions according to the invention may also include one or more preservatives or bacteriostatic agents e.g. methyl hydroxy benzoate, propyl hydroxy benzoate, chlorocresol or benzalkonium chlorides. The compositions according to the invention may also contain other active ingredients such as antimicrobial agents, particularly antibiotics, such as neomycin.

The following Examples and Preparations illustrate the present invention.

PREPARATION I

9 α -Fluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -propionyloxyandrost-1,4-diene-17 β -carboxylic acid

A mixture of 9 α -fluoro-11 β ,17 α -dihydroxy-16-methylene-3-oxoandrost-1,4-diene-17 β -carboxylic acid (648 mg.) and redistilled triethylamine (0.80 ml.) in dry methylene chloride (16 ml.) was stirred at 0° and treated dropwise during 15 minutes with propionyl chloride (0.538 ml.). After being stirred at 0° for 30 minutes the mixture was diluted with methylene chloride and washed successively with 3 percent sodium bicarbonate solution, N-hydrochloric acid and water.

13

EXAMPLE 17

Chloromethyl

9 α -fluoro-11 β -hydroxy-17 α -isobutyryloxy-16-methylene-3-oxoandrosta-1,4-diene-17 β -carboxylate

A suspension of sodium 9 α -fluoro-11 β -hydroxy-17 α -isobutyryloxy-16-methylene-3-oxoandrosta-1,4-diene-17 β -carboxylate (1.6 g) in hexamethylphosphoramide (4.1 ml) was stirred with chloromethyl iodide (1.28 ml.) for approx. 4 hours. The reaction mixture was diluted with ethyl acetate and ether, and washed successively with water, 5% sodium bicarbonate solution, sodium thiosulphate solution and water then dried (MgSO₄) and evaporated under reduced pressure to a white crystalline solid (1.51 g). Recrystallization from ether containing a little acetone gave colourless crystals (977 mg), a portion (400 mg) of which was recrystallized further to give the title chloromethyl ester as an ether solvate (264 mg), m.p. 142–147° (softening > 100°), $[\alpha]_D^{25}$ -60.3° (c 0.97, dioxan) λ_{max} 237 nm (ϵ 15,600).

Example 18

Fluoromethyl

9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate

A solution of chloromethyl 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carboxylate [containing a little (< 5%) of the corresponding bis-(androsta-17 β -carbonyloxy methane) (121 mg) in dry acetonitrile (1.4 ml) was stirred and treated with silver difluoride (182 mg). Stirring was continued for 2 days and the mixture was then diluted with ethyl acetate, filtered through kieselguhr, and the filtrate was washed with water. The organic phase was dried (MgSO₄) and evaporated to a white foam (122 mg) which was subjected to preparative layer chromatography on silica in chloroform-acetone (10:1) to give a colourless crystalline solid, the title fluoromethyl ester (100 mg), m.p. 192–195°, softening at 183°, $[\alpha]_D^{25}$ +35.5° (c 1.02 dioxan).

Example 19

Dichloromethyl

9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carboxylate

A mixture of 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carboxylic acid (500mg, solvated with 0.75 mole ethyl acetate) and phenyl(bromodichloromethyl)mercury (440 mg) in the benzene (20 ml) was stirred under oxygen-free nitrogen and heated under reflux for 5 hours. The mixture was allowed to cool and ethyl acetate (50 ml) was added; some crystalline solid (246 mg) was removed by filtration and washed with a little ethyl acetate. The filtrate and washings were washed with saturated sodium bicarbonate solution, then with water, then with water, dried (MgSO₄) and concentrated to a small volume. A further quantity, (49 mg) of crystalline solid was removed and the mother liquors were evaporated in vacuo to a semi-crystalline gum (503 mg). Preparative layer chromatography on silica developing with chloroform twice, then with chloroform-acetone (10:1) gave the major product as a very pale yellow foam (216 mg). Crystallization from ether containing traces of acetone gave colourless crystals (76 mg), of

14

the title compound, m.p. 156–160° decomp, $[\alpha]_D^{25}$ × 33.8° (c 0.36, dioxan), λ_{max} 237 nm (ϵ 15,210).

Preparation 5

17 α -Benzoyloxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylic acid

A solution of 11 β ,17 α -dihydroxy-9 α -fluoro-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (5.027g) and triethylamine (4.65 ml, 3.38 g., 2.5 equiv.) in dry methylene chloride (60 ml.) at below 5° was treated with a cooled solution of benzoylchloride (3.9 ml., 4.67g, 2.5 equiv.) in methylene chloride (60 ml) during 45 minutes. The solution was stirred for a further 45 minutes at below 5°, diluted with methylene chloride (100 ml.), then washed with 3.5% sodium bicarbonate solution, water, 2N-hydrochloric acid, and water, dried (MgSO₄), filtered and evaporated to give a white foam (9.04 g).

The foam was dissolved in acetone (120 ml) and stirred with diethylamine (4.8 ml., 3.4 g., 3.5 equiv.) at 22° [a solid crystallised after 2 minutes, and the reaction was substantially complete after 4 hours] for 18 hours. The mixture was concentrated and filtered and the solid was washed with acetone and dried at 23°/0.5 mm, for 1 hour to give the diethylamine salt of the title compound (7.4 g., 100% but possibly solvated).

The salt was dissolved in water (120 ml.) and the pH was adjusted to 2.0 to give a solid which was washed with water and dried over phosphorus pentoxide at 22°/0.5 mm. to give the 17 α -benzoyloxy acid (5.666 g.) which was used in Preparation 17 without purification. A sample (845 mg.) was crystallised from ethylacetate, and dried at 50°/0.5mm for 18 hours to give the 17 α -benzoyloxy acid solvated with ethyl acetate (0.25 mole) as white prisms (720 mg.), m.p. 187–190°, $[\alpha]_D^{25}$ +0.2° (c 1.01, dioxan), $[\alpha]_D^{25}$ +3.3° (c 1.202, Me₂SO), λ_{max} 230.5 nm. (ϵ 25,800).

PREPARATION 6

Sodium

17 α -Benzoyloxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate

A suspension of 17 α -benzoyloxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (from example 21, 4.406 g) was reacted with sodium hydroxide as described in Preparation 16 to give the title sodium salt (4.284 g.).

EXAMPLE 20

Chloromethyl 17 α -benzoyloxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate

The sodium salt (from preparation 17, 4.223 g.) was added during 20 minutes to a solution of chloriodomethane (3.05 ml., 7.38 g., 5 equiv.) in hexamethylphosphoramide (11 ml.) at 22°. The orange mixture was stirred at 22° for approx. 4 hours. (when almost all the salt had dissolved), diluted with ethyl acetate, washed with water, 3.5% sodium bicarbonate solution, dilute sodium thiosulphate solution, water, dried (MgSO₄) and evaporated to give a pale yellow foam (4.288g.). The foam (1.895g) was crystallised from methanol, chromatographed on a column of silica and recrystallized from methanol:acetone to give the title chloromethyl ester (1.045 g.) as colourless prisms, m.p. 209–216°, $[\alpha]_D^{25}$ +18.5° (c 1.019, dioxan), λ_{max} 233nm. (ϵ 27,000).

15

EXAMPLE 21

Fluoromethyl

17 α -benzoyloxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate

A mixture of chloromethyl 17 α -benzoyloxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate (1.26 g.) and finely ground silver fluoride (2.125 g., 7 equiv.) was stirred in dry acetonitrile (20 ml.) at 22° in the dark for 5 days. The mixture was filtered through Kieselguhr and diluted with ethyl acetate, washed with water, dried, and evaporated to give a colourless foam (1.272 g.). Preparative layer chromatography on silica gave a foam (1.044 g) which was crystallised from acetone:petrol (b.p 60 to 80°) to give title fluoromethyl ester (0.69 g.) as colourless prisms, m.p. 233–245°, $[\alpha]_D^{22} + 12.2^\circ$ (c 1.021, dioxan), λ_{max} 232 nm (ϵ 26,750).

EXAMPLE 22

Fluoromethyl

11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carboxylate

A mixture of chloromethyl 11 β -hydroxy-16 β -methyl-3-oxo-17 β -propionyloxyandrosta-1,4-diene-17 β -carboxylate (196 mg) and silver monofluoride (373 mg) in dry acetonitrile (4 ml) was stirred at room temperature for 5 days. The mixture was then diluted with ethyl acetate and filtered through kieselguhr; the filtrate was washed with water then dried (MgSO₄) and evaporated under reduced pressure. The residue (185 mg) was recrystallised from acetone-petrol (bp. 60–80°) to give the title fluoromethyl 17 β -carboxylate, mp. 209–212° (Kofler), $[\alpha]_D + 38^\circ$ (c 0.665, dioxan), (EtOH) 242 nm (ϵ 15,100).

Example 23

Fluoromethyl

11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carboxylate

A mixture of chloromethyl 11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carboxylate (223 mg) and silver monofluoride (397 mg) in dry acetonitrile (4 ml) was stirred at room temperature for 5 days. More silver fluoride (297 mg) was added and stirring was continued for 7 days. The mixture was diluted with ethyl acetate, filtered through kieselguhr and the filtrate was washed with water and dried (Mg SO₄) removal of solvent gave the product which was shown by t.l.c. to contain a considerable amount of starting material. The mixture was retracted with silver monofluoride (500 mg) and acetonitrile (4 ml) at room temperature for 12 days, the product was reisolated as above and recrystallised five times from methanol to give the title fluoromethyl ester (103 mg), mp.223–225°, $[\alpha]_D + 15^\circ$ (c 1.0, dioxan), λ_{max} (EtOH) 242 non (ϵ 14,800).

EXAMPLE 24

Fluoromethyl

11 β -hydroxy-3-oxo-17 α -propionyloxyandrost-4-ene-17 β -carboxylate

A mixture of chloromethyl 11 β -hydroxy-3-oxo-17 α -propionyloxyandrost-4-ene-17 β -carboxylate (500 mg) and silver monofluoride (980 mg) in dry acetonitrile

16

(8.3 ml) was stirred at room temperature for 7 days and the product (487 mg) was isolated as described in Example 22. Two crystallisations from acetone gave the title fluoromethyl ester as colourless crystals (243 mg), mp 188–191° (Kofler) $[\alpha]_D + 58^\circ$ (c 0.94 dioxan), λ_{max} (EtOH) 240 nm (ϵ 15,770).

EXAMPLE 25

2',2',2'-Frifluoromethyl

9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carboxylate

A stirred mixture of sodium 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carboxylate (457 mg) and hexamethylphosphoramide (1.2 ml) was treated with 2,2,2-trifluoroethyl iodide (0.53 ml); stirring was continued at room temperature for 4 days. More trifluoroethyl iodide (0.53 ml) was added and reaction was continued for a further 13 days at room temperature then for 8½ hours at 50°. A further quantity of trifluoroethyl iodide (0.53 ml) was added and heated and stirring was continued at 50° for 45 hours. The mixture was diluted with ethyl acetate, washed with 5% aqueous sodium bicarbonate solution, and then with water, dried (Mg SO₄) and evaporated under reduced pressure to a semicrystalline foam (238 mg). The title trifluoroethyl 17 β -carboxylate crystallised from acetone to give colourless crystals, mp.224–228° with softening at 213°, $[\alpha]_D + 36^\circ$ (c 0.19, dioxan) λ_{max} (EtOH) 237 nm (ϵ 15,550).

EXAMPLE 26

2',2',3',3'-Tetrafluoropropyl

9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo

17 α -propionyloxyandrosta-1,4-diene-17 β -carboxylate

A mixture of sodium 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carboxylate (457 mg) and 1-iodo-2,2,3,3-tetrafluoropropane (940 mg) in hexamethylphosphoramide (1.2 ml) was stirred at room temperature for 3 days. A further addition of the iodide (327 mg) was made, stirring was continued for 3 more days and the product was isolated; the mixture was diluted with ethyl acetate and ether and washed with 5% aqueous sodium bicarbonate (twice) then with water, dried (MgSO₄) and evaporated under reduced pressure to a foam (349 mg). The product was subjected to preparative layer chromatography on silica in chloroformacetone (10:1) and eluted with ethyl acetate to give the major component (226 mg) which was recrystallised twice from acetone-petrol (bp 60–80°) to give colourless crystals of the title tetrafluoropropyl 17 β -carboxylate, (130 mg), mp.210–212°(Kofler), λ_{max} (ethanol) 238.5 nm (ϵ 15,500). (Found: C,59.3; H,6.1, C₂₇H₃₃F₅O₆ requires C,59.1, H,6.1%).

EXAMPLE 27

Fluoromethyl

9 α -fluoro-11 β -hydroxy-17 α -isobutyryloxy-16-methylene-3-oxoandrosta-1,4-diene-17 β -carboxylate

A mixture of chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -isobutyryloxy-16-methylene-3-oxoandrosta-1,4-diene-17 β -carboxylate (545 mg) and silver difluoride (802 mg) in acetonitrile (6.2 ml) was stirred at room temperature for 6 days. The mixture was diluted with ethyl acetate and solid material was removed by filtration through kieselguhr; the filtrate was washed with water, dried (MgSO₄) and evaporated to a foam (516

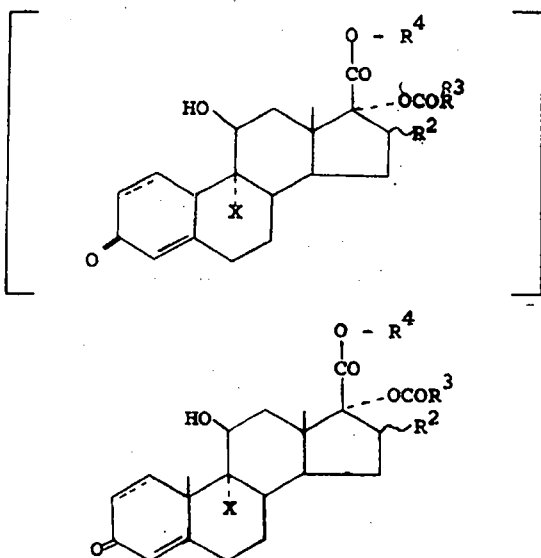
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EXAMPLE (i)

Ointment
2'-Fluoroethyl-9 α -fluoro-11 β -hydroxy- 0.25% w/w
16 β -methyl-3-oxo-17 α -
propionyloxyandrosta-1,4-diene-17 β -
carboxylate
Benzyl Alcohol 1.0% w/w
White soft paraffin to produce 100 parts by weights

Dissolve the steroid in the benzyl alcohol. Add this solution to the melted white soft paraffin at 50°C. Stir until cold to give a homogenous ointment.

We claim:

1. A compound of the formula



wherein

X represents a hydrogen, chlorine or fluorine atom;
R² represents a hydrogen atom, a methylene group or an α - or β -methyl group;
R³ represents a hydrogen atom or C₁₋₄ alkyl group;
R⁴ represents a fluoro-, chloro- or bromomethyl group or a fluoroethyl group and == represents a single or double bond.

2. A compound according to claim 1 wherein R⁴ represents a methyl group substituted by a fluorine or chlorine atom; or a fluoroethyl group.

3. A compound according to claim 1 wherein R³ represents an alkyl group containing 1 to 3 carbon atoms.

4. A compound according to claim 1 wherein R³ represents an ethyl group.

22

5. A compound according to claim 1 wherein R² represents a methyl group or a methylene group.

6. A compound according to claim 1 wherein == represents a double bond.

7. A compound according to claim 1 wherein X represents a fluorine or hydrogen atom.

8. A compound according to claim 1 wherein R² represents a hydrogen atom, X represents a hydrogen atom and == represents a single bond.

9. A compound according to claim 1 wherein X represents a fluorine atom, R² represents a methylene group and == represents a double bond.

10. A compound according to claim 1, said compound being 2'-fluoroethyl 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate.

11. A compound according to claim 1, said compound being chloromethyl 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate.

12. A compound according to claim 1, said compound being chloromethyl 11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate.

13. A compound according to claim 1, said compound being fluoromethyl 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate.

14. A compound according to claim 1, said compound being fluoromethyl 9 α -chloro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate.

15. A compound according to claim 1, said compound being fluoromethyl 9 α -fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate.

16. A compound according to claim 1, said compound being chloromethyl 9 α -fluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate.

17. A compound according to claim 1, said compound being fluoromethyl 9 α -fluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate.

18. A compound according to claim 1, said compound being fluoromethyl 11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate.

19. Fluoromethyl 9 α -fluoro-16 β -methyl-3,11-dioxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carboxylate.

* * * * *

United States Patent [19]

Phillipps et al.

[11] 4,335,121

[45] Jun. 15, 1982

[54] ANDROSTANE CARBOTHIOATES

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[58] Field of Search /Steroids MS File; 260/397.1; 424/241

[56] References Cited

U.S. PATENT DOCUMENTS

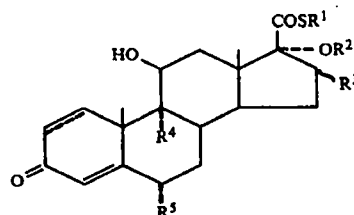
3,636,010	1/1972	Basel et al.	260/397.1
3,828,080	8/1974	Phillipps et al.	260/397.1
4,093,721	6/1978	Phillipps et al.	260/397.1
4,188,385	2/1980	Edwards	260/397.1

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[57] ABSTRACT

Compounds of the formula



wherein R¹ represents a fluoro-, chloro- or bromo-methyl group or a 2'-fluoroethyl group, R² represents a group COR⁶ where R⁶ is a C₁₋₃ alkyl group or OR² and R³ together form a 16 α ,17 α -isopropylidenedioxy group; R³ represents a hydrogen atom, a methyl group (which may be in either the α - or β -configuration) or a methylene group; R⁴ represents a hydrogen, chlorine or fluorine atom; R⁵ represents a hydrogen or fluorine atom and symbol $\cdots\cdots$ represents a single or double bond have good anti-inflammatory activity, particularly on topical applications.

The compounds of formula I are prepared by esterification, halogenation, reduction, deprotection and reaction at a 9,11-double bond to form a 9 α -halo-11 β -hydroxy grouping.

Pharmaceutical compositions containing the compounds of formula I and methods for the use of the compounds are described and claimed.

25 Claims, No Drawings

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4,335,121

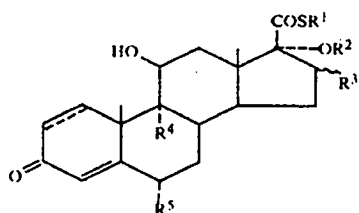
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ANDROSTANE CARBOTHIOATES

The present invention relates to anti-inflammatory steroids of the androstane series.

Anti-inflammatory steroids are most typically of the corticoid type, i.e. are pregnane derivatives. Our United Kingdom Pat. Nos. 1,384,372, 1,438,940 and 1,514,476 describe esters of certain androstane 17 α -carboxylic acids having anti-inflammatory activity. European Patent Application No. 79300500.0 (Publication No. 0004741) describes esters of androstane 17 β -carbothioic acids also possessing anti-inflammatory activity. We have now discovered that certain androstane compounds containing a haloalkyl carbothioate grouping in the 17 β -position have particularly advantageous anti-inflammatory properties as discussed in greater detail below.

The new androstane compounds may be represented by the formula



wherein R¹ represents a fluoro-, chloro- or bromomethyl group or a 2'-fluorocethyl group; R² represents a group COR⁶ where R⁶ is a C₁₋₃ alkyl group or OR² and R³ together form a 16 α ,17 α -isopropylidenedioxy group; R⁴ represents a hydrogen atom, a methyl group (which may be in either the α - or β - configuration) or a methylene group; R⁵ represents a hydrogen, chlorine or fluorine atom; and symbol represents a single or double bond.

The new compounds of formula (I) have good anti-inflammatory activity, particularly on topical application, as judged by the McKenzie patch test in man and as measured by the reduction of croton oil induced oedema when the compounds are applied topically to the skin of mice and rats.

Certain of the compounds show good topical anti-inflammatory activity in the croton oil ear test coupled with minimal hypothalamus-pituitary-adrenal-suppressive activity after topical application in the same animal species. These results indicate that such compounds may be of value in the local treatment of inflammation in man and animals with minimal liability to cause undesired systemic side effects.

Compounds of formula (I) which are preferred for their good anti-inflammatory activity include the following categories namely (a) those in which R¹ is chloro- or fluoromethyl (b) those in which R² is acetyl or propionyl, preferably propionyl, (c) those in which R⁴ is fluorine (d) those in which R⁵ is fluorine (e) the 1,4-dienes, and (f) those 1,4-dienes in which R⁴ is fluorine and R³ is hydrogen, α - and β -methyl or methylene.

Compounds of formula (I) which have good anti-inflammatory activity coupled with minimal hypothalamus-pituitary-adrenal-suppressive activity when applied topically include 1,4-dienes in which R¹ is chloro-

2

ro- or fluoro-methyl, R⁴ and R⁵ are fluorine and in particular those in which R³ is α -methyl.

Especially preferred compounds according to the invention in view of their good topical anti-inflammatory activity and favourable ratio of topical anti-inflammatory activity to undesired systemic activity include:

S-chloromethyl 9 α -fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate;

S-chloromethyl 9 α -fluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate;

S-fluoromethyl 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carbothioate;

S-fluoromethyl 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate;

S-chloromethyl 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate. The last compound is especially preferred in view of its particularly favourable ratio and in addition minimal skin atrophy.

The compounds of formula (I) may be prepared by a variety of different processes.

One such process comprises esterifying an androstane compound corresponding to formula (I) but containing either a free 17 β -carbothioic acid group (or functionally equivalent group) or a free 17 α -hydroxy group (R³ being a hydrogen atom or a methyl or methylene group), any other reactive groups present in the molecule being suitably protected as desired.

For example, a salt of the parent 17 β -carbothioic acid such as an alkali metal, e.g. lithium, sodium or potassium, salt or an alkylammonium, e.g. triethylammonium or tetrabutylammonium, salt may be reacted with an appropriate alkylating agent, preferably in a polar solvent such as a ketone, e.g. acetone or an amide such as dimethylformamide, dimethylacetamide or hexamethylphosphoramide, conveniently at a temperature of 15° to 100° C. The alkylating agent may comprise an appropriate dihalo compound i.e. one containing a further halogen atom (preferably a bromine or iodine atom) in addition to the halogen atom of the desired R¹ group. This process is particularly applicable to the preparation of compounds in which R¹ is a chloromethyl group, the alkylating agent advantageously being bromochloromethane.

Alternatively, the parent 16-hydrogen, methyl or methylene-17 α -hydroxy-17 β -carbothioates corresponding to compounds of formula I may be subjected to esterification of the 17 α -hydroxyl group. This may be effected by conventional techniques, e.g. by reacting the parent 17 α -hydroxy compound with a mixed anhydride of the required carboxylic acid, which may, for example, be generated in situ by reacting the carboxylic acid with an appropriate anhydride such as trifluoroacetic anhydride, preferably in the presence of an acid catalyst, e.g. p-toluenesulphonic acid or sulphosalicylic acid. Alternatively, the mixed anhydride may be generated in situ by reaction of a symmetrical anhydride of the required acid with an appropriate further acid, e.g. trifluoroacetic acid.

The reaction is advantageously effected in an organic solvent medium such as benzene, methylene chloride or an excess of the carboxylic acid employed, the reaction

23

washed with water and back extracted with 5% sodium carbonate solution: the alkaline extracts were acidified with hydrochloric acid and extracted with ethyl acetate (3×). After being washed with water and brine the organic extracts were dried and concentrated to low volume: the title thioacid separated as cream crystals (101 mg), whose sole major component was identified by comparison with an authentic specimen by ^1H nmr and by t.l.c. (silica, chloroform-acetone 4:1).

Method B

A solution of 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carboxylic acid (701 mg, 0.75 mol ethyl acetate solvate) and N,N'-carbonyldiimidazole (473 mg) in dry dimethylformamide (26 mg) was stirred under nitrogen at ca 22° C. for 19.5 h., then treated with a solution (10 ml) of sodium hydride (60% dispersion in oil, 233 mg) in dimethylformamide (10 ml) saturated with hydrogen sulphide. The resulting mixture was then stirred at ambient temperature for 5.5 h. The reaction mixture was diluted with ethyl acetate (100 ml) and washed with 2 N-hydrochloric acid, water and brine, then dried and evaporated to a froth (186 mg). The title thioacid was shown to be the major component in the produced by ^1H nmr and by t.l.c. (silica, chloroform-acetone [4:1], and chloroform-acetone-acetic acid [30:8:1]) comparison with an authentic specimen.

Method C

In an almost identical reaction to that described in Method A the carboxylic acid was treated with 1,1'-carbonyldibenzotriazole (1.587 g) instead of N,N'-carbonyldi(1,2,4-triazole), at room temperature for 6 h. After the addition of the solution obtained from hydrogen sulphide and sodium hydride in dimethylformamide, reaction was continued for 41.5 h. The crude product was obtained as a foam; t.l.c. (silica, chloroform-acetone, 4:1, and chloroform-acetone-acetic acid 30:8:1) showed the title thioacid was present as a major component by comparison with an authentic specimen.

PREPARATION LXII

S-Chloromethyl

6 α ,9 α -difluoro-16 α -methyl-3-oxo-17 α -propionyloxy-11 β -trifluoroacetoxyandrosta-1,4-diene-17 β -carbothioate (LXII)

A solution of the compound of Example 5 (hereinafter disclosed) (100 mg) in dry tetrahydrofuran (2 ml) and pyridine (0.1 ml) was treated with trifluoroacetic anhydride (0.05 ml) and the mixture was kept at room temperature for 0.5 h. The reaction mixture was poured into water and the product was extracted with ethyl acetate (3×). The organic extracts were washed with water, dried and evaporated to give the homogenous title trifluoroacetate (116 mg) according to ^1H nmr spectroscopy (singlet at 8.59 τ , 19-protons, in deuteriochloroform) and t.l.c. on silica (acetone-petrol, b.p. 40°-60° C., 1:3). An analytical sample from ether-pentane had m.p. 158°-162°, $[\alpha]_D + 56^\circ$ (c 0.23).

24

EXAMPLE 1

S-Chloromethyl

9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

Method A

A solution of I (2.115 g) in dimethylacetamide (7 ml) was treated with sodium hydrogen carbonate (592 mg) and bromochloromethane (0.46 ml) and the mixture was stirred at room temperature. After 2 h, the reaction mixture was diluted with ethyl acetate (500 ml) and washed with 5% sodium hydrogen carbonate solution and water, dried and evaporated to give an orange foam (1.560 g). P.l.c. in chloroform-acetone (19:1) gave an off-white foam (803 mg) which was crystallised twice from methanol to give off-white needles of the title S-chloromethyl ester (668 mg), m.p. 212°-214° C., $[\alpha]_D + 44^\circ$ (c 1.06).

Method B

The title compound was similarly prepared using chloriodomethane instead of bromochloromethane.

Method C

Sodium borohydride (19 mg) was added to a solution of II (230 mg) in ethanol (3.5 ml) and the solution was stirred at room temperature. After 20 min acetone (1 ml) was added and the solution was concentrated to ca. $\frac{1}{4}$ volume. Ethyl acetate (30 ml) was then added and the solution was washed with N-hydrochloric acid and water, dried and evaporated to give a white foam (239 mg). P.l.c. in chloroform-acetone (19:1) gave a white foam (188 mg) which was crystallised twice from methanol to give white needles of the title S-chloromethyl ester (158 mg) m.p. 210°-212°, $[\alpha]_D + 44^\circ$ (c 1.07).

EXAMPLE 2

S-Chloromethyl

9 α -fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

A solution of IV (0.927 g) in dimethylacetamide (4 ml) was treated with sodium hydrogen carbonate (0.256 g) and bromochloromethane (0.20 ml) and the mixture was stirred at 22° C. for 2 h. The reaction mixture was partitioned between ethyl acetate (100 ml) and 2 N-hydrochloric acid (20 ml) and the aqueous layer extracted further with ethyl acetate. The combined extracts were washed successively with 2 N-hydrochloric acid, water, 3% sodium hydrogen carbonate, water and saturated brine. After being dried the solvent was removed and the crude product (757 mg) was crystallised twice from acetone to give the title chloromethyl thiolester (0.367 g), m.p. 247°-250°, $[\alpha]_D + 50.5^\circ$ (c 0.63).

EXAMPLE 3

S-Chloromethyl

11 β -hydroxy-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

A solution of crude XV (2.366 g) in dimethylacetamide (10 ml) was treated with sodium hydrogen carbonate (756 mg) and bromochloromethane (0.59 ml) at 22° C. for 16 h. It was partitioned between ethyl acetate and 2 N-hydrochloric acid and the aqueous layer was extracted further with ethyl acetate. The combined organic phases were washed successively with 2 N-hydrochloric acid, water, sodium hydrogen carbonate, water,

4,335,121

25

saturated brine then dried and the solvent was removed to give a yellow froth. The neutral product was purified by preparative h.p.l.c. on silica (15 μ) in 7% acetone in chloroform and the major product crystallised from acetone to give the title chloromethyl thiolester (0.511 g), m.p. 117°–120°, [α]_D+56° (c 1.3).

EXAMPLE 4

S-Chloromethyl

6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carbothioate

A stirred solution of IX (1.360 g) in N,N-dimethylacetamide (10 ml) was treated with sodium hydrogen carbonate (0.377 g) and bromochloromethane (0.3 ml) and stirring was continued for 1.5 h. Ethyl acetate (100 ml) was added and the resulting solution was successively washed with 2N-hydrochloric acid, water, sodium metabisulphite solution, water, sodium bicarbonate solution, water and saturated sodium chloride solution, then dried and the solution was concentrated, whereupon crystallisation occurred. The crystallised product (0.765 g) was purified by p.l.c. on silica gel, developed with chloroform:acetone (9:1). The main band was eluted with ethyl acetate and was crystallised from ethyl acetate to give the title S-chloromethyl thiolester (0.475 g) as white prisms, m.p. 271°–278°, [α]_D+116°, (c 0.96, dimethylsulphoxide).

EXAMPLE 5

S-Chloromethyl

6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

A solution of XIX (0.546 g) in dimethylacetamide (3 ml) was treated with sodium hydrogen carbonate (202 mg) and bromochloromethane (0.16 ml) at 22° for 3 h. The mixture was treated with 2 N hydrochloric acid (50 ml) and the product was extracted with ethyl acetate. The extracts were combined and washed successively with 2 N hydrochloric acid, water, saturated brine, dried and the solvent was removed. Two crystallisa-

26

tions from ethyl acetate gave the title chloromethyl thiolester (0.404 g), m.p. 272°–275°, [α]_D+49° (c 0.35).

EXAMPLE 6–15

Following the same general procedure as Example 1 (Method A) but using as starting material the 17 β -carbothioic acid corresponding to the desired 17 β -carbothioate (process details being summarised in Table III below), the following compounds were prepared:

6. S-Chloromethyl 11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate, m.p. 192°–193°, [α]_D+65° (c 1.05).
7. S-Chloromethyl 9 α -fluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate, m.p. 212°–221°, [α]_D–56° (c 0.99).
8. S-Chloromethyl 17 α -acetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, m.p. 220°–223°, [α]_D+39.5° (c 1.06).
9. S-Chloromethyl 17 α -butyryloxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, m.p. 172°–175°, [α]_D+46° (c 1.10).
10. S-Chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -isobutyryloxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, m.p. 234°–239°, [α]_D+43° (c 1.00).
11. S-Chloromethyl 9 α -fluoro-11 β -hydroxy-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate, m.p. 196°–199°, [α]_D+38° (c 0.97).
12. S-Chloromethyl 6 α -fluoro-11 β -hydroxy-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate, m.p. 188°–191°, [α]_D+48° (c 0.91).
13. S-Chloromethyl 17 α -acetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, m.p. 280°–283°, [α]_D+45° (c 0.80).
14. S-Chloromethyl 17 α -butyryloxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, m.p. 235°–238°, [α]_D+49° (c 0.65).
15. S-Chloromethyl 9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carbothioate, m.p. 276°–280° (dec), [α]_D+127° (c 0.51, dimethylsulphoxide).

TABLE III

Ex. No.	REAGENT (ml)	NaHCO ₃ (mg)	STERIOD INPUT (mg)	REACTION			CRYSTAL- LISATION SOLVENT	PRODUCT (mg)
				SOL- VENT (DMA) (ml)	TIME (h) at room tempera- ture	PLC (Silica) CHCl ₃ — Me ₂ CO		
6	BrCH ₂ Cl (0.25)	300	981	5	3	—	EA	826
7	BrCH ₂ Cl (0.58)	749	2000	11	1.5	19:1	EA	201
8	BrCH ₂ Cl (0.44)	565	1955	7	2.0	—	EA	307*
9	BrCH ₂ Cl (0.32)	421	1501	10	1.8	14:1	EA	871
10	BrCH ₂ Cl (0.084)	121	385	3	2.75	—	EA	255
11	BrCH ₂ Cl (0.90)	1100	2750	20	1.25	—	M	1600
12	BrCH ₂ Cl (0.86)	1080	2740	20	2	—	EA-P	2460
13	BrCH ₂ Cl (2.00)	2500	6600	40	1.75	—	A	5410
14	BrCH ₂ Cl (1.40)	1600	4600	46	2	—	A	2140
15	BrCH ₂ Cl	615	1600	12	1.5	4:1	A	244**

TABLE III-continued

Ex. No.	REAGENT (ml)	NaHCO ₃ (mg)	STERIOD INPUT (mg)	SOL-VENT (DMA) (ml)	REACTION TIME (h) at room temperature	PLC (Silica) CHCl ₃ -Me ₂ CO	CRYSTAL-LISATION SOLVENT	PRODUCT (mg)
(0.48)								

Notes:

EA = ethyl acetate

A = acetone

M = methanol

P = petrol h.p. 60-80°

*Obtained from a portion (400 mg) of the crude product (2.35 g).

**Obtained from a portion (300 mg) of the crude product (1.72 g).

EXAMPLE 16

S-Chloromethyl

9 α -chloro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate and

S-Chloromethyl

9 β ,11 β -epoxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

A solution of the mixture XXIV (1.032 g) in dimethylacetamide (5 ml) was treated with sodium bicarbonate (0.203 g) followed by bromochloromethane (0.2 ml) and the reaction was stirred at 22° C. for 1.5 h, when it was partitioned between ethyl acetate (50 ml) and 2 N-hydrochloric acid (35 ml). The aqueous phase was extracted with further ethyl acetate (2 $\times$ 30 ml) and the combined extracts were washed with 2 N-hydrochloric acid, water, saturated sodium bicarbonate solution, water, saturated sodium chloride solution and dried and the solvent removed in vacuo to give a cream froth (0.856 g) containing a mixture of the title S-chloromethyl esters.

These were separated by p.l.c. on silica, developed with chloroform:acetone (19:1). The more polar component (0.306 g) was crystallised twice from ethyl acetate to give S-chloromethyl 9 α -chloro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate (0.232 g) as white plates, m.p. 222°-229°, [α]_D+70° (c 1.23).

The less polar component (0.210 g) was crystallised from acetone-petrol to give S-chloromethyl 9 β ,11 β -epoxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate (0.065 g), m.p. 169°-173°, [α]_D+49° (c 0.60).

EXAMPLE 17

S-Fluoromethyl

9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

XXV (660 mg) was stirred with a suspension of silver fluoride (1.421 g) in acetonitrile (8.5 ml) in the dark at room temperature. After 72 h the reaction mixture was diluted with ethyl acetate (200 ml) and filtered through a pad of kieselguhr. The filtrate was washed with water, dried and evaporated to give a white foam (517 mg). P.l.c. in chloroform-cyclohexane (19:1) and chloroform gave an off-white foam (270 mg) which was crystallised from methanol, then methanol-diethyl ether to give the title S-fluoromethyl ester (176 mg), m.p. 241°-242° C., [α]_D+97.5° (c 0.98).

EXAMPLE 18

S-Fluoromethyl 9 α -fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

20 A solution of XXX (0.640 g) in acetonitrile (8 ml) was treated with dry silver fluoride (1.511 g) and stirred in the dark at 22° C. for 46.5 h. The mixture was diluted with ethyl acetate (200 ml) and filtered through kieselguhr. The solution was washed with 2 N-hydrochloric acid, water and saturated sodium chloride solution and the solvent removed in vacuo to give a pale yellow froth (0.504 g). This was chromatographed (p.l.c.) on silica gel, developed with 5% acetone in chloroform. The major band was eluted with ethyl acetate and crystallised twice from acetone to give the title fluoromethyl thioester (0.244 g), m.p. 242°-243° (dec), [α]_D+37° (c 0.75).

EXAMPLE 19

S-Fluoromethyl

6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -propionyloxy-3-oxoandrosta-1,4-diene-17 β -carbothioate

35 A solution of XXXI (310 mg) in acetonitrile (10 ml) was stirred with silver fluoride (947 mg) for 3 days at room temperature in the dark. Ethyl acetate (100 ml) was added and the mixture was filtered through kieselguhr. The filtrate was washed successively with 2 N-hydrochloric acid, water, saturated brine, then dried. The solvent was removed and the residue was subjected to p.l.c. in chloroform then chloroform-acetone (19:1). The product was eluted with ethyl acetate and crystallised on concentration of the solution to give the title fluoromethyl thioester (0.075 g) m.p. 272°-273° (dec), [α]_D+30° (c 0.35).

EXAMPLE 20

S-Fluoromethyl

9 α -fluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 β -carbothioate

55 A suspension of XXXVII (1.290 g) in acetonitrile (20 ml) was stirred with silver(I) fluoride (2.842 g) at room temperature in the dark. After 11 days (no starting iodide remained, t.l.c. (chloroform, six runs)) the reaction mixture was diluted with ethyl acetate (400 ml) and filtered through kieselguhr. The filtrate was evaporated to a pale yellow crystalline solid (726 mg) and the kieselguhr was extracted continuously with ethyl acetate in a Soxhlet apparatus to give a yellow solid (197 mg). The solid from the filtrate was suspended in chloroform-methanol (10:1) and the insoluble fraction (203 mg) was collected. This was combined with the solid from the Soxhlet extraction in ethyl acetate (300 ml)

and filtered through a column of silica (Merck Kieselgel 60) (50 g). The eluates containing the product (t.l.c.) were combined, washed with water, dried with simultaneous treatment with charcoal and concentrated to a low volume. The resulting white solid (276 mg) was collected and recrystallised from ethyl acetate to give colourless crystals of the title S-fluoromethyl ester (231 mg), m.p. 320°–322° C. (dec.), $[\alpha]_D + 132^\circ$ (c 0.22, dimethylsulphoxide).

EXAMPLE 21

S-Fluoromethyl

6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -isopropylidene-dioxy-3-oxoandrosta-1,4-diene-17 β -carbothioate

A solution of XXXVIII (0.804 g) in acetonitrile (60 ml) was treated with silver fluoride (1.821 g) and the

26. S-Fluoromethyl 9 α -fluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate, m.p. 205°–215°, $[\alpha]_D - 58^\circ$ (c 1.00).
 27. S-Fluoromethyl 9 α -fluoro-11 β -hydroxy-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate, m.p. 207°–211°, $[\alpha]_D + 70^\circ$ (c 0.88).
 28. S-Fluoromethyl 6 α -fluoro-11 β -hydroxy-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate, m.p. 224°–255°, $[\alpha]_D + 70^\circ$ (c 0.79).
 29. S-Fluoromethyl 17 α -acetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, m.p. 308°–310° $[\alpha]_D + 29^\circ$ (c 0.80).
 30. S-Fluoromethyl 17 α -butyryloxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, m.p. 249°–252°, $[\alpha]_D + 32^\circ$ (c 1.05).

S-Fluoromethyl 17 α -acyloxyandrosta-17 β -carbothioates
via halogen exchange

Ex. No.	Ag F (mg)	STARTING STEROID HALIDE	INPUT mg	SOLVENT (MeCN) (ml)	REACTION TIME (h) at room temperature	PLC (Silica) CHCl ₃ –Me ₂ CO	CRYSTALLISATION SOLVENT	PRODUCT (mg)
22	3745	I	1702	22	20	24:1	A	477
23	2071	I	1034	10	26	19:1	EA	585*
24	1945	I	850	6	26	19:1	EA	166
25	1161	I	550	8	23.5	19:1	M	106
26	3574	I	1658	26	24	19:1	A	300
27	700	I	1000	50	3	—	M	470
28	462	I	700	35	2	—	EA-P	350
29	2600	I	4000	200	0.75	—	EA	2280
30	780	I	1200	60	1	—	EA	755

EA = ethyl acetate

A = acetone

M = methanol

P = petrol b.p. 60–80°

*Purity ca. 95%

reaction was stirred in the dark for 18 h. The reaction was diluted with ethyl acetate and filtered through kieselguhr. The filtrate was washed with water and saturated sodium chloride solution then dried and the solvent removed in vacuo to give a pale cream solid (0.636 g). This was purified by p.l.c. on silica gel developed twice with chloroform:acetone (14:1). The major band was eluted with ethyl acetate and crystallised five times from ethyl acetate to give the title S-fluoromethyl thioester (0.118 g) as white prisms, m.p. 305°–311° C., $[\alpha]_D + 125^\circ$ (c 0.73, dimethylsulphoxide).

EXAMPLES 22–30

Following the same general procedure as Example 17 but using as starting material the S-iodomethyl 17 β -carbothioate corresponding to the desired product (process details being summarised in Table IV below), the following compounds were prepared:

22. S-Fluoromethyl 17 α -acetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, m.p. 248°–249°, $[\alpha]_D + 101^\circ$ (c 1.08).
 23. S-Fluoromethyl 11 β -hydroxy-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate, m.p. 112–117°, $[\alpha]_D + 67^\circ$ (c 0.76).
 24. S-Fluoromethyl 11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate, m.p. 223°–225°, $[\alpha]_D + 103^\circ$ (c 0.38).
 25. S-Fluoromethyl 9 α -chloro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate, m.p. 182°–193°, $[\alpha]_D + 116^\circ$ (c 0.75).

EXAMPLE 31

S-Bromomethyl

9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

A solution of XXV (660 mg) in acetone (20 ml) was stirred with lithium bromide (972 mg) at room temperature for 5 days. The reaction mixture was diluted with ethyl acetate (150 ml) and then washed successively with 10% sodium thiosulphate solution, water and brine, dried and evaporate to an off-white foam (624 mg). This was crystallised twice from acetone-petroleum ether (m.p. 40°–60°) to give colourless crystals of the title S-bromomethyl ester (499 mg) m.p. 186.5°–187° C., $[\alpha]_D + 2^\circ$ (c 0.99).

EXAMPLE 32

S-Bromomethyl

6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

A solution of XXXI (850 mg) in acetone (25 ml) was stirred with lithium bromide (1.21 g) at ca 22° C. for 5 days. The product was isolated as described for Example 31 and recrystallised twice from ethyl acetate to give colourless crystals (690 mg). These were retreated under the same reaction conditions for a further 4 days to give the pure title S-bromomethyl ester (600 mg), colourless crystals from ethyl acetate, m.p. 255°–257°, $[\alpha]_D + 62^\circ$ (c 0.82).

EXAMPLE 33

S-2'-Fluoroethyl

9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

A solution of XXXIX (910 mg) in acetonitrile (20 ml) was stirred with silver(I) fluoride (2.071 g) at room temperature in the dark. After 6 days the reaction mixture was diluted with ethyl acetate (150 ml) and filtered through kieselguhr. The filtrate was diluted with more ethyl acetate (150 ml) and washed with water, dried and evaporated to a white foam (704 mg) P.l.c. in chloroform-acetone (9:1) gave the less polar product, as a yellow foam (431 mg), which was crystallised twice from methanol to give the title S-2'-fluoroethyl ester (253 mg), m.p. 133°-134° C., $[\alpha]_D + 104.5^\circ$ (c 0.98).

EXAMPLE 34

S-Chloromethyl

9 α -fluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

A suspension of XLII (227 mg) in propionic acid (2.2 ml) and trifluoroacetic anhydride (0.7 ml) was treated with a dry chloroform solution of toluene-p-sulphonic acid (0.044 ml, c ca 80 mg/ml) and then stirred at room temperature for 6 h, and then stirred at 3° C. for 16.5 h. The reaction mixture was diluted with 5% sodium hydrogen carbonate solution (75 ml) and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried and evaporated to a brown gum (254 mg). The gum was subjected to p.l.c. in chloroform-acetone (19:1) (three runs). The major band (152 mg) was crystallised twice from ethanol to give white crystals (30 mg) of the title S-chloromethyl ester 17 α -propionate contaminated with S-chloromethyl 9 α -fluoro-17 α -hydroxy-16-methylene-3-oxo-11 β -propionyloxyandrosta-1,4-diene-17 β -carbothioate as shown by ¹Hnmr spectroscopy.

EXAMPLE 35

S-Chloromethyl

11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-4-ene-17 β -carbothioate

Catalytic reduction of the compound of Example 6 (0.517 g) in the presence of tris(triphenylphosphine)-chlororhodium(I) (497 mg) in benzene (50 ml) for 22 h afforded, after chromatography (p.l.c.) on silica in chloroform (four runs), elution with ethyl acetate, and crystallisation twice from ethyl acetate, the title Δ^4 -3-ketone (0.130 g), m.p. 176°-177°, $[\alpha]_D + 78^\circ$ (c 0.80).

EXAMPLE 36

S-Chloromethyl

9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-4-ene-17 β -carbothioate

Catalytic reduction of the compound of Example 1 (0.646 g) with tris(triphenylphosphine)chlororhodium(I) (800 mg) in benzene (100 ml) for 21.5 h afforded, after chromatography on silica in chloroform-acetone (9:1) and two crystallisations from acetone, the title chloromethyl thiolester (0.142 g) as white needles, m.p. 217°-225°, $[\alpha]_D + 54^\circ$ (c 0.83).

EXAMPLE 37

S-Fluoromethyl

11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-4-ene-17 β -carbothioate

Catalytic reduction of the compound of Example 24 (0.413 g) in the presence of tris(triphenylphosphine)-chlororhodium(I) (432 mg) in benzene (60 ml) at 22° C. for 24 h afforded, after multiple chromatography on silica in chloroform-acetone mixtures and crystallisation from acetone, the title Δ^4 -3-ketone (0.106 g) m.p. 174°-177° C., $[\alpha]_D + 123^\circ$ (c 0.55).

EXAMPLE 38

S-Chloromethyl

9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

S-Chloromethyl 9 β ,11 β -epoxy-16 β -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate (ca 0.9 mg) from Example 16 was treated with hydrogen fluoride-urea complex (ca 1 ml) and stirred for a total of 24 h at room temperature. The mixture was treated with sodium hydrogen carbonate and the product was extracted twice with ethyl acetate: the extracts were washed twice with water, dried, and evaporated. The resulting product was shown by t.l.c. on silica in three different solvent systems (acetone-petrol, b.p. 40°-60° C., 1:2; chloroform-acetone, 9:1; ethyl acetate-petrol, b.p. 40°-60° C., 1:2, two runs) to contain the title fluorohydrin by comparison with an authentic specimen.

EXAMPLE 39

S-Chloromethyl

6 α ,9 α -fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

A solution of LXII (29 mg) in methanol (2 ml) was kept at room temperature for 3 h. The mixture was evaporated to dryness to give the title 11 β -alcohol (25 mg) identified by comparison of its ¹Hnmr spectrum (in deuteriodimethylsulphoxide) and t.l.c. properties (silica, acetone-petrol b.p. 40°-60° C., 1:3) with those of an authentic specimen.

There are also provided pharmaceutical compositions for use in anti-inflammatory therapy, comprising at least one androstane compound of formula (I) (as defined above), together with one or more pharmaceutical carriers or excipients. Such compositions may be in forms adapted for topical or internal administration.

The active androstane compounds may advantageously be formulated in conventional manner into preparations suitable for topical administration with the aid of a topical vehicle therefor. By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include ointments, lotions, creams, powders, drops, (e.g. eye or ear drops), sprays, (e.g. for the nose, throat, lung or skin), suppositories, retention enemas, chewable or suckable tablets or pellets (e.g. for the treatment of aphthous ulcers), capsules or cartridges for use in an inhaler or insufflator, and aerosols, (e.g. for the nose, throat or lung).

Ointments and creams, may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or sol-

vents. Such base may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a solvent such as a polyethylene glycol having an average molecular weight in the range 200-600. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols having an average molecular weight in the range 4,000-6,000, woolfat and beeswax and/or glyceryl monostearate and/or non-ionic emulsifying agents.

Spray compositions may for example be formulated as aqueous solutions or suspensions or as aerosols with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas.

Capsules and cartridges for use in an inhaler or insufflator, of e.g. gelatin, may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch. Each capsule or cartridge may generally contain between 20 μ g-10 mg of the active androstane compound.

The proportion of the active androstane compound in the topical compositions according to the invention depends on the precise type of formulation to be prepared but will generally be within the range of from 0.001 to 5.0% weight. Generally, however for most types of preparations advantageously the proportion used will be within the range of from 0.005 to 0.5% and preferably 0.01 to 0.25%. However with powders for inhalation or insufflation the proportion used will be within the range of from 0.1-2%.

The foregoing formulations for topical application to the skin may be used for the treatment of inflammatory dermatoses of humans and animals, for example eczema, which are normally responsive to corticosteroid therapy, and also of less responsive conditions such as psoriasis in humans.

The formulations for administration by inhalation or insufflation are intended for administration on a prophylactic basis to humans suffering from allergic and/or inflammatory conditions of the nose, throat or lungs such as asthma and rhinitis, including hay fever. Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains 20 μ g-1000 μ g, preferably about 50 μ g-100 μ g of a compound of the invention. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example 1, 2 or 3 doses each time. The overall daily dose with an aerosol will be within the range 100 μ g-10 mg preferably, 200 μ g-1000 μ g. The overall daily dose and the metered dose delivered by capsules and cartridges in an inhaler or insufflator will generally be double those with aerosol formulations.

Topical preparations may be administered by one or more applications per day to the affected area; over skin areas occlusive dressings may often be used with advantage.

For internal administration the new compounds according to the invention may, for example, be formulated in conventional manner for oral, parenteral or rectal administration. For oral administration, syrups, elixirs, powders and granules may be used which may be formulated in conventional manner. Dosage unit forms are however preferred as described below.

Preferred forms of preparation for internal administration are dosage unit forms i.e. tablets and capsules.

Such dosage unit forms contain from 0.1 mg to 20 mg preferably from 2.5 to 10 mg of the active steroid.

The compounds according to the invention may in general be given by internal administration in cases where systemic adreno-cortical therapy is indicated.

In general terms preparations for internal administration may contain from 0.05 to 10% of the active ingredient dependent upon the type of preparation involved. The daily dose may vary from 0.1 mg to 60 mg, e.g. 5-30 mg, dependent on the condition being treated, and the duration of treatment desired.

EXAMPLE (A)

Ointment	
Active Ingredient	0.1% w/w
Liquid Paraffin B.P.	10% w/w
White soft paraffin to produce	100 parts by weight

Ball-mill the active ingredient with a little of the liquid paraffin until the particle size is reduced to 95% by number below 5 μ . Dilute the paste and rinse out the mill with the remaining liquid paraffin, mix and add the suspension to the melted white soft paraffin at 50° C. Stir until cold to give a homogenous ointment.

EXAMPLE (B)

Cream	
	% w/w
Active ingredient	0.1
Cetostearyl alcohol	10.0
Cetamacrogol 1,000	2.5
White soft paraffin	10.0
Liquid paraffin	10.0
Chlorocresol	0.1
Sodium acid phosphate	0.5
Purified water	to 100.0

Method of Preparation

The chlorocresol and sodium acid phosphate are dissolved in water at about 70°-75° C. The waxes are melted together at about 65°-70° C. and added with stirring to the aqueous phase when this has cooled to 65°-70° C. The steroid is micronised (particle size as defined in BPC 1973 pg. 911 for Ultra-Fine powder) and dispersed in a portion of the liquid paraffin. The steroid suspension and the remainder of the liquid paraffin are added to the base with stirring at 60° to 65° C. The preparation is cooled with stirring to ambient temperature.

EXAMPLE (C)

Metered dose aerosol formulation		
	per dose	% w/w
Active ingredient	0.05 mg	0.059
Fluorotrichloromethane	25.5 mg	30.0
Dichlorodifluoromethane	to 85.0 mg to	100.0

The active ingredient is micronised (particle size as defined in BPC 1973 pg. 911 for Ultra-Fine powder) and dispersed in the fluorotrichloromethane. This suspension is filled into aluminium aerosol containers, the headspace purged with gaseous dichlorodifluoromethane to exclude air, and a metered aerosol valve crimped

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258

1

3,828,080
**ANDROSTANE - 17 β - CARBOXYLIC ACIDS AND
PROCESSES FOR THE PREPARATION THEREOF**
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tories Limited, Greenford, Middlesex, England
No Drawing. Filed Jan. 20, 1972, Ser. No. 219,574
Int. Cl. C07c 169/52
U.S. Cl. 260-397.1 23 Claims

ABSTRACT OF THE DISCLOSURE

The specification describes new androstane compounds having anti-inflammatory activity. The new androstanes described in the specification have an esterified 17 β -carboxylic acid grouping wherein the alcohol residue comprises a lower alkyl group; a lower alkyl group substituted by either at least one halogen atom or a lower alkoxy-carbonyl group; or a (C₂₋₄) lower alkyl group substituted by a lower acyloxy group. The 17 α -grouping of these androstanes is an esterified hydroxy group comprising a formyl, C₂₋₄ alkanoyl or benzoyl group.

This invention is concerned with steroid compounds having anti-inflammatory properties.

Since the discovery of cortisone, a wide variety of compounds of analogous structure have been prepared having anti-inflammatory properties, such compounds being generally members of the pregnane series.

Anti-inflammatory steroids have found wide use in medicine and in latter years considerable attention has been directed to compounds having high anti-inflammatory action on topical administration.

Anti-inflammatory steroids of the pregnane series so far described, being generally analogous to cortisone, tend to a greater or lesser extent to exert the physiological action of the natural hormone and thus possess, in addition to anti-inflammatory action other actions similar to cortisone-like compounds. The physiological effects of the pregnane-type anti-inflammatory steroids may be broadly classified as glucocorticoid and mineralocorticoid effects, anti-inflammatory action at least until recently having been regarded as a glucocorticoid action. Glucocorticoid effects also include general disturbance of the body metabolism and may be very undesirable. Mineralocorticoid effects involve disturbance of the salt and water balance within the body and compounds having marked mineralocorticoid action are thus likely to produce undesirable effects on administration.

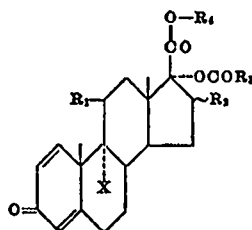
Even in the topical application of anti-inflammatory steroids, there is a risk that the steroid may be absorbed into the system through the skin, with subsequent development of undesired side effects.

There is thus a general desire to have available an anti-inflammatory steroid with high anti-inflammatory action but with which the undesired effects, either mineralocorticoid or glucocorticoid in nature, are reduced.

We have now found that certain new steroids of the androstane series, possess marked anti-inflammatory action. Moreover our researches indicate that generally the ratio of anti-inflammatory action to undesired cortisone-like action in our new compounds is generally good.

The steroid compounds with which the invention is concerned are compounds of the general formula

2



wherein

- (a) X represents a hydrogen, chlorine or fluorine atom; R₁ represents a hydroxy group in the β -configuration or (when X represents a chlorine atom) R₁ may also represent a chlorine atom in the β -configuration; R₂ represents a hydrogen atom, a methylene group or a methyl group (in either the α - or β -configuration); R₃ represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or a phenyl group; R₄ represents a lower alkyl group; a lower alkyl group substituted by either at least one halogen atom or a lower alkoxy carbonyl group; or a (C₂₋₄) lower alkyl group substituted by a lower acyloxy group; and = represents a single or double bond; or
- (b) X represents a chlorine or fluorine atom; R₁ represents an oxo group; R₂ represents a hydrogen atom, a methylene group or a methyl group (in either the α - or β -configuration); R₃ represents a methyl or ethyl group; R₄ represents a lower alkyl group; a lower alkyl group substituted by either at least one halogen atom or a lower alkoxy carbonyl group; or a (C₂₋₄) lower alkyl group substituted by a lower acyloxy group; and = represents a single or double bond.

The new androstane compounds have anti-inflammatory action on topical and internal administration, the anti-inflammatory activity of the compounds on topical administration being generally high.

In general, the group R₃ in formula I is preferably an alkyl group containing up to 3 carbon atoms, i.e. a methyl, ethyl, n-propyl or iso-propyl group. In compounds wherein R₃ represents a hydrogen atom R₄ preferably represents a methyl group.

The group R₄ in formula I is preferably an alkyl group containing 1 to 4 carbon atoms, advantageously a methyl, ethyl or propyl group.

In regard to the possible substituents of the lower alkyl group, the halogen atom is preferably a fluorine, chlorine or bromine atom, the lower (e.g. C₂₋₆) acyloxy group is preferably an acetoxy group and the alkoxy carbonyl group (wherein the alkoxy group advantageously contains 1 to 4 carbon atoms) is advantageously a methoxycarbonyl group.

Generally compounds of formula I in which R₁ represents a β -hydroxy group are preferred. Also in general terms, compounds of formula I in which R₂ represents a methyl group in the β -configuration are preferred on account of their high topical anti-inflammatory activity.

A preferred class of compounds of formula I having particularly good topical anti-inflammatory activity with a favourable ratio of topical anti-inflammatory activity to glucocorticoid activity are those compound wherein X represents a chlorine or fluorine atom preferably a fluorine atom), R₁ represents a β -hydroxy group, R₂ represents

23

(b) Production of injectable preparation:

Composition:	Percent w./v.
Fine particle ingredient prepared as in (a) -----	0.50
Hydroxyethyl cellulose -----	0.40
Benzyl alcohol -----	1.00
Sodium citrate -----	0.30
Sodium salt of EDTA ¹ -----	0.01
Sodium chloride -----	0.44
Citric acid, q.s.	
Water for injection to 100.0	
pH value 4.80 to 5.50.	

¹ EDTA is ethylene diamine tetracetic acid.

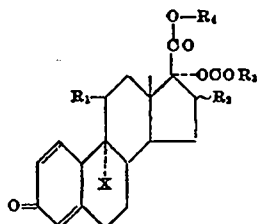
(1) Vehicle.—The hydroxyethyl cellulose was dissolved in 17.5 litres of water for injection using a high speed vortex stirrer. The benzyl alcohol was added with stirring. The sodium chloride, sodium citrate salt of EDTA were dissolved in 1 litre of water and added to the bulk vehicle with stirring. The pH value of the bulk vehicle was adjusted to 4.80 to 5.50 with a solution of citric acid. The volume was then adjusted to 19.3 litres and the vehicle clarified by filtration through nylon. The vehicle was finally sterilised by autoclaving.

(2) Sterile wet-cake of small particle active ingredient prepared as in (a) containing 100 g. of the active ingredient was added with stirring and under aseptic conditions to 19 litres of the vehicle, and the volume made up to 20 litres.

The resulting suspension was passed through a sterile 100 mesh British Standard sieve and stored in a sealed container. Dosage units for injection were prepared by aseptically filling neutral glass ampoules or vials closed by a pure latex plug.

What is claimed is:

1. A compound of the formula



wherein

- (a) X represents a hydrogen, chlorine or fluorine atom; R₁ represents β -hydroxy or when X represents a chlorine atom, β -chloro; R₂ represents a hydrogen atom, methylene or methyl; R₃ represents alkyl of 1 to 3 carbon atoms or phenyl, or when R₂ is methylene or methyl, a hydrogen atom; R₄ represents lower alkyl; lower alkyl substituted by at least one halogen atom or lower alkoxy; or (C₂₋₄) alkyl substituted by lower acyloxy; and = represents a single or double bond; or
- (b) X represents a chlorine or fluorine atom; R₁ represents oxo; R₂ represents a hydrogen atom, methylene or methyl; R₃ represents methyl or ethyl; R₄ represents lower alkyl; lower alkyl substituted by at least one halogen atom or lower alkoxy; or (C₂₋₄) alkyl substituted by lower acyloxy; and = represent a single or double bond.
2. A compound as claimed in claim 1 wherein R₃ represents methyl, ethyl, n-propyl or iso-propyl and R₄ represents methyl, ethyl or propyl.
3. A compound as claimed in claim 1 wherein R₃ represents a hydrogen atom and R₄ represents methyl.
4. A compound as claimed in claim 1 wherein R₄ represents alkyl of 1 to 4 carbon atoms.
5. A compound as claimed in claim 1 wherein R₂ represents β methyl.

24

6. A compound as claimed in claim 1 wherein X represents a chlorine or fluorine atom, R₁ represents β -hydroxy, R₂ represents methyl, R₃ represents methyl, ethyl or n-propyl, R₄ represents methyl and = represents a double bond.

7. A compound as claimed in claim 6 wherein X represents a fluorine atom and R₂ represents β methyl.

8. A compound as claimed in claim 1 wherein X represents a fluorine atom, R₁ represents oxo, R₂ represents β methyl, R₃ represents methyl or ethyl, R₄ represents methyl and = represents a double bond.

9. A compound as claimed in claim 1 wherein X represents a fluorine or chlorine atom, R₁ represents β -hydroxy, R₂ represents methylene, R₃ represents methyl, ethyl, n-propyl or iso-propyl and R₄ represents methyl or ethyl.

10. A compound as claimed in claim 9 wherein X represents a fluorine atom and R₄ represents methyl and = represents a double bond.

11. Compounds as claimed in claim 1 wherein = represents a single bond, X represents a fluorine or chlorine atom, R₁ represents β -hydroxy, R₂ represents methyl, R₃ represents methyl, ethyl or n-propyl and R₄ represents methyl or ethyl.

12. A compound as claimed in claim 11 wherein X represents a fluorine atom, R₂ represents β methyl and R₄ represents methyl.

13. A compound as claimed in claim 1 wherein X represents a hydrogen atom, R₁ represents β -hydroxy and R₂ represents a hydrogen atom or methyl.

14. A compound as claimed in claim 13 wherein R₂ represents β methyl.

15. A compound as claimed in claim 13 wherein R₃ represents alkyl of 1 to 3 carbon atoms.

16. A compound as claimed in claim 13 wherein R₄ represents methyl.

17. A compound as claimed in claim 1 wherein X and R₁ represent chlorine atoms, R₂ represents methyl, R₃ represents methyl or ethyl, R₄ represents methyl or ethyl and = represents a double bond.

18. A compound as claimed in claim 1 selected from the group consisting of

- methyl 17 α -acetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate;
 methyl 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate;
 methyl 17 α -butyryloxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate;
 methyl 17 α -acetoxy-9 α -fluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carboxylate;
 methyl 9 α -fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate;
 methyl 17 α -butyryloxy-9 α -fluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carboxylate;
 methyl 9 α -fluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate;
 methyl 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androst-4-ene-17 β -carboxylate;
 methyl 17 α -acetoxy-9 α -fluoro-16 β -methyl-3,11-dioxo-androsta-1,4-diene-17 β -carboxylate;
 methyl 9 α -chloro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate;
 ethyl 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy androsta-1,4-diene-17 β -carboxylate;
 methyl 17 α -acetoxy-9 α ,11 β -dichloro-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carboxylate;
 methyl 9 α -fluoro-11 β -hydroxy-17 α -isobutyryloxy-16-methylene-3-oxo-androsta-1,4-diene-17 β -carboxylate;
 ethyl 9 α -fluoro-11 β -hydroxy-17 α -isobutyryloxy-16-methylene-3-oxo-androsta-1,4-diene-17 β -carboxylate;
 methyl 11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate; and
 methyl 11 β -hydroxy-3-oxo-17 α -propionyloxy-androst-4-ene-17 β -carboxylate.

3,828,080

25

19. The compound of claim 18 which is methyl 17 α -acetoxo - 9 α - fluoro-11 β -hydroxy - 16 β - methyl-3-oxo-androsta-1,4-diene-17 β -carboxylate.

20. The compound of claim 18, which is methyl 9 α -fluoro-11 β -hydroxy - 16 β - methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate.

21. The compound of claim 18, which is methyl 17 α -butyryloxy - 9 α - fluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carboxylate.

22. The compound of claim 18, which is methyl 11 β -hydroxy - 16 β - methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carboxylate.

23. The compound of claim 18, which is methyl 11 β -

26

hydroxy-3-oxo - 17 α - propionyloxy-androst-4-ene-17 β -carboxylate.

References Cited

UNITED STATES PATENTS

3,579,551	5/1971	Craddock et al.	260—413
3,636,010	1/1972	Anner et al.	260—397.1
3,560,558	2/1971	Hayakawa et al.	260—514

ELBERT L. ROBERTS, Primary Examiner

U.S. Cl. X.R.

260—397.45; 424—242

12

EUROPEAN PATENT APPLICATION

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71 Applicant: **SCHERING CORPORATION, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US)**

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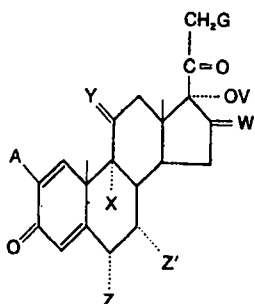
72 Inventor: **Shapiro, Elliot L., 24 Brookshire Drive, Cedar Grove New Jersey 07009 (US)**

84 Designated Contracting States: **AT BE CH DE FR GB IT LI NL SE**

74 Representative: **Antony, Fritz, Dr. et al, P.O. Box 601 Winkelriedstrasse 35, CH-6002 Lucerne (CH)**

54 **Aromatic heterocyclic esters of steroids, their preparation and pharmaceutical compositions containing them.**

57 Disclosed herein are novel 3,20-dioxo-1,4-pregnadiene-17-01-17-aromatic heterocyclic carboxylates (and the 6-dehydro and 1,2-dihydro derivatives thereof) of general formula I:



(I).

wherein:

A is hydrogen or, provided that Y is (H,βOH), A may also be chloro, fluoro or methyl;

X is hydrogen or a halogen atom having an atomic weight less than 100;

Y is oxygen, (H,βOH) or, provided that X is hydrogen, Y may also be (H,H) or, provided X is chloro or bromo, Y may also be (H,β-halogen), the β-halogen having an atomic weight less than 100 and being at least as electronegative as X;

Z is hydrogen, methyl, chloro or fluoro;

Z' is hydrogen or, provided that Z is hydrogen, may also be halogen having an atomic weight of less than 100;

V is an acyl radical of a thiophenecarboxylic acid, pyrrolecarboxylic acid or furancarboxylic acid or the methyl- or halogen-substituted derivatives thereof;

W is (H,H), (H, lower alkyl) or (H, αOV,) where V₁ is hydrogen or specified acyl radicals, or W is a methylene or substituted methylene group; and

G is hydrogen, a halogen atom having an atomic weight of less than 100 or is -QV₂ where Q is oxygen or sulfur and V₂ is specified acyl radicals.

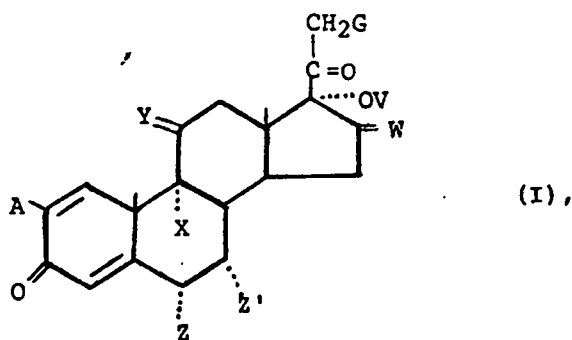
The novel compounds exhibit anti-inflammatory activity and their use for this purpose is disclosed. Also disclosed are methods for the preparation of the novel compounds.

AROMATIC HETEROCYCLIC ESTERS OF STEROIDS, THEIR PREPARATION
AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM.

This invention relates to novel aromatic hetero-
cyclic esters of steroids, to their preparation and to
5 pharmaceutical compositions containing them.

More specifically, this invention relates to novel
3,20-dioxo-1,4-pregnadiene-17 α -ol 17-aromatic heterocyclic
carboxylates, and the 1,2 -dihydro and 6-dehydro derivatives
thereof, useful in the treatment of inflammatory conditions.

10 The novel 17-aromatic heterocyclic carboxylates
of this invention are 3,20-dioxo-1,4-pregnadienes of the
following formula I:



wherein A is hydrogen or, provided Y is (H, β OH), A may also
15 be chloro, fluoro or methyl;

X is hydrogen or a halogen atom having an atomic
weight less than 100;

Y is oxygen, (H, β OH) or, provided that X is hydrogen,
Y may also be (H,H) or, provided that X is chloro or bromo,

- 4 -

lower alkylidenes, i.e. hydrocarbon radicals having preferably up to four carbon atoms including radicals such as methylene, ethylidene, n-propylidene, isopropylidene, n-butylidene, and sec.-butylidene and the like.

- 5 The 3,20-dioxo-1,4-pregnadiene-17 α -ol 17-aromatic heterocyclic carboxylates of formula I are usually white to off-white crystalline solids, which are insoluble in water (with the exception of alkali metal salts of esters such as the hemisuccinate and phosphate esters thereof)
- 10 and soluble in most organic solvents, particularly in acetone, dioxan, dimethylformamide, and dimethylsulfoxide, although of limited solubility in non-polar solvents such as dialkyl ethers and alkylhydrocarbons.

- 15 In general, the 3,20-dioxo-1,4-pregnadiene-17 α -ol 17-aromatic heterocyclic carboxylates of formula I, particularly those wherein G is QV₂ where V₂ is hydrogen or an acyl group as previously defined, exhibit corticosteroid activity. Those that have halogens at both C-9 and C-11 or an oxygen or β -hydroxyl function at C-11 and a halogen or hydrogen at C-9 possess glucocorticoid activity and are particularly valuable as anti-inflammatory agents.
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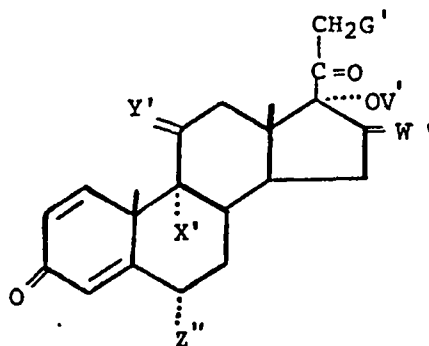
- Particularly useful topical anti-inflammatory agents are the 17-furoyl and 17-thenoyl esters of formula I wherein G is halogeno or QV₂, and C-2 and C-7 are unsubstituted, especially those compounds substituted at C-16 by a lower alkyl group (particularly a 16-methyl group, e.g. 16 α -methyl) which generally exhibit topical anti-inflammatory activity superior to the topical anti-inflammatory activity of the 17-non-heterocyclic-carboxylate derivatives corresponding to formula I.
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The 17-acyloxy-21-desoxy-derivatives of formula I, while exhibiting anti-inflammatory activity, are generally more valuable as progestational agents.

- 54 -

- W is (H,H) , (H, loweralkyl) or (H, αOV_1) where V_1 is hydrogen or an acyl radical of retinoic acid or a carboxylic acid having up to 12 carbon atoms or W is $=\text{CHT}$ where T is hydrogen, lower alkyl, fluoro or chloro and
- 5 G is hydrogen, a halogen atom having an atomic weight less than 100 or $-\text{QV}_2$ where Q is an oxygen or sulfur atom and V_2 is as defined for V or V_1 or is an acyl radical of phosphoric acid which may be in the form of a mono- or
- 10 di-alkali metal or an alkaline earth metal salt thereof; and the 6-dehydro and 1,2-dihydro derivatives of the foregoing.

2. A compound as claimed in claim 1, characterised by being a 3,20-dioxo-1,4-pregnadiene.
- 15 3. A compound as claimed in claim 1 or claim 2, characterised in that V is furan-carbonyl or thiophenecarbonyl.
4. A compound as claimed in any one of claims 1 to 3, characterised by being of the general formula II:



(II),

where X' is fluoro or chloro;

Y' is (H, β OH) or, provided that X' is chloro, Y' may also be (H, β -halogen) the β -halogen having an atomic weight of less than 100 and being at least as electronegative as X';

Z" is hydrogen or fluoro;

W' is (H,H) or (H,CH₃);

V' is furan-carbonyl or thiophene-carbonyl; and

G' is chloro or fluoro or -QV₂', where Q is an oxygen

or sulfur atom (preferably oxygen) and V₂' is hydrogen or an acyl radical of retinoic acid, of a carboxylic acid having up to 12 (preferably up to 8) carbon atoms or of phosphoric acid which may be in the form of a mono- or di-alkali metal or alkaline earth metal salt.

5. A compound as claimed in claim 4, characterized in that G' is chloro, lower alkanoyloxy or lower alkoxy lower alkanoyloxy (preferably acetoxy or methoxyacetoxy), X' is chloro and Y' is (H, β -Cl) or X' is chloro or fluoro and Y' is (H, β OH) and W' is (H,H) or (H, CH₃), preferably (H, α -CH₃).

6. A compound as claimed in claim 1, said compound being selected from:

9 α , 11 β , 21-trichloro-16 α -methyl-1,4-pregnadiene-17 α -ol-3,20-dione 17-(2'-furoate);

9 α , 11 β , 21-trichloro-16 α -methyl-1,4-pregnadiene-17 α -ol-3,20-dione 17-(2'-thenoate);

6 α -fluoro-9 α , 11 β , 21-trichloro-16 α -methyl-1,4-pregnadiene-17 α -ol-3,20-dione 17-(2'-furoate);

9 α -fluoro-16 α -methyl-1,4-pregnadiene-11 β , 17 α , 21-triol-3,20-dione 17-(2'-furoate) 21-acetate;

9 α -fluoro-16 α -methyl-1,4-pregnadiene-11 β , 17 α , 21-triol-3,20-dione 17-(2'-furoate) 21-methoxy-acetate;

9 α -fluoro-16 α -methyl-1,4-pregnadiene-11 β , 17 α , 21-triol-

0057401

- 56 -

- 3,20-dione 17-(2'-thenoate) 21-acetate;
9 α -fluoro-16 α -methyl-1,4-pregnadiene-11 β ,17 α ,21-triol-
3,20-dione 17-(3'-furoate) 21-acetate;
9 α -fluoro-21-chloro-16 α -methyl-1,4-pregnadiene-11 β ,17 α -
5 diol-3,20-dione 17-(2'-furoate);
9 α -fluoro-21-chloro-16 α -methyl-1,4-pregnadiene-11 β ,17 α -
diol-3,20-dione 17-(2'-thenoate);
9 α ,21-dichloro-16 α -methyl-1,4-pregnadiene-11 β ,17 α -diol-
3,20-dione 17(2'-furoate);
10 9 α ,21-dichloro-16 α -methyl-1,4-pregnadiene-11 β ,17 α -diol-
3,20-dione 17-(2'-thenoate);
9 α -chloro-16 α -methyl-1,4-pregnadiene-11 β ,17 α ,21-triol-
3,20-dione 17-(2'-furoate) 21-acetate;
9 α -chloro-16 α -methyl-1,4-pregnadiene-11 β ,17 α ,21-triol-
15 3,20-dione 17-(2'-furoate) 21-methoxyacetate;
9 α -fluoro-21-fluoro-16 α -methyl-1,4-pregnadiene-11 β ,17 α -diol-
-3,20-dione 17-(2'-furoate); and
9 α -chloro-16 α -methyl-1,4-pregnadiene-11 β ,17 α -diol-21-thiol-
-3,20-dione 17-(2'-furoate) 21-pivalate.
- 20 7. A process for the preparation of a 17 α -aromatic he-
terocyclic carboxylate claimed in claim 1, said process being
characterised in that an appropriate 3,20-dioxo-1,4-pregnadiene
starting material, or a 6-dehydro- or 1,2-dihydro derivative
thereof, is subjected to:
- 25 A: introduction of the desired ester group at the 16 α ,17 α
and/or 21 positions, or
B: hydrolysis of an ester group present at one or more
of positions 11 β ,16 α and 21 or of a 16 α ,17 α -or 17 α ,21-ortho
ester group, or
30 C: halogenation at one or more of positions 9 α ,11 β and
21, or
D: reduction of an 11-oxo group to an 11 β -hydroxy group.
8. A process as claimed in claim 7 process A, charac-
terised by esterifying a 3,20-dioxo-1,4-pregnadiene-17 α ,21-

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Gustavo Tamayo
Apoderado
GLAXO GROUP LIMITED

Oficio N° 11902

REFERENCIA	Radicación	01 63014
	Trámite	002
	Evento	001
	Actuación	430
	Folios	008

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 01 63014, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

1. DOCUMENTOS ESTUDIADOS:

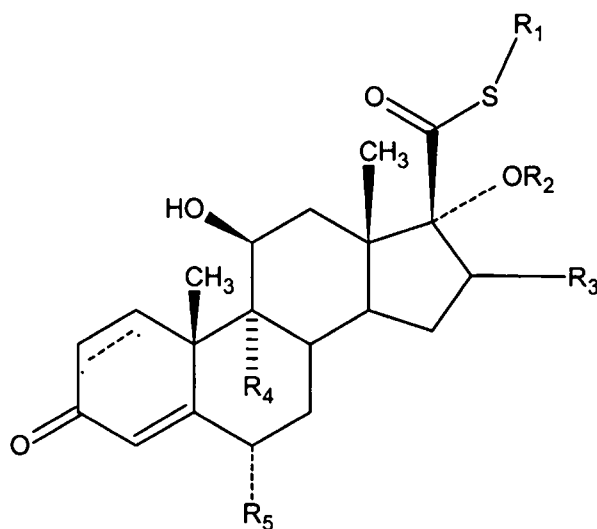
- El resumen y el capítulo descriptivo de la solicitud en los folios 8 a 9 y 10 a 59 respectivamente.
- Los ejemplos que ilustran la invención en los folios 60 a 88.
- Las cláusulas 1 a 32 relacionadas en el capítulo reivindicatorio de la solicitud que se encuentran en los folios 89 a 101.
- El primer examen de forma realizado a la solicitud de oficio No. 8712, que se encuentra en el folio 107.
- Las copias de las solicitudes originales mediante las cuales se reivindica prioridad del Reino Unido GB0108800.4 de 07/04/2001 en los folios 156 a 172 y GB0019172.6 de 05/08/2000 en los folios 205 a 216, junto con sus traducciones correspondientes en los folios 111 a 155 y 173 a 204 respectivamente; allegadas mediante memorial de fecha 25/09/2001.
- La respuesta al primer examen de forma, allegada mediante memorial de fecha 02/04/2002 que se encuentra en los folios 217 a 228, mediante el cual se excluye del alcance del capítulo reivindicatorio la cláusula 30.
- La solicitud de examen de patentabilidad junto con el pago de la tasa correspondiente, allegada mediante memorial de fecha 29/01/2004, que se encuentra en los folios 231 a 232.
- El memorial de fecha 31/08/2004 mediante el cual se manifiesta el cambio de apoderado de la sociedad solicitante en los folios 233 y 234.
- El memorial de fecha 08/09/2004 mediante el cual se informa el cambio de Representante legal para los asuntos de propiedad industrial de la sociedad GLAXO GROUP LIMITED, que se encuentra en los folios 235 a 240.

2. OBJETO DE LA INVENCIÓN:

La solicitud hace referencia a ***“Nuevos derivados de androstano anti-inflamatorios”***

- **Reivindicaciones 1 a 24 y 32:**

Se reivindica un compuesto de la fórmula (I):



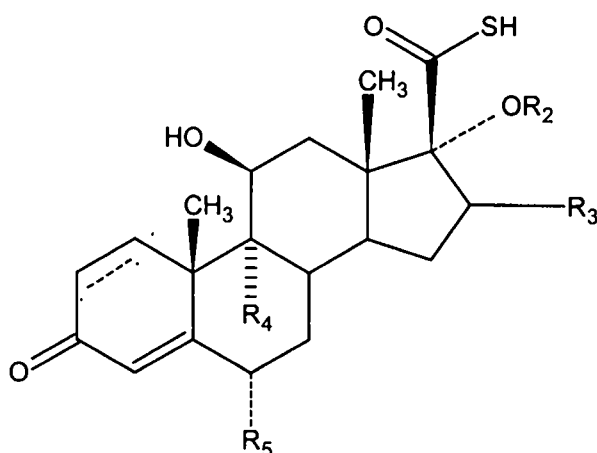
En particular se reivindican los compuestos:

Éster S-fluorometílico del ácido 6 α ,9 α -difluoro-17 α -[(2-furanilcarbonil)oxi]-11 β -hidroxi-16 α -metil-3-oxo-androsta-1,4-dien-17 β -carbotioico

Éster S-fluorometílico del ácido 6 α ,9 α -difluoro-11 β -hidroxi-16 α -metil-3-oxo-17 α -[(2-tienilcarbonil)oxi]-androsta-1,4-dien-17 β -carbotioico

Entre otros...

Además se reivindican los compuestos que responden a la fórmula estructural (II):



- **Reivindicación 25, 27, 28 y 29:**

Se reivindica una composición farmacéutica caracterizada porque comprende un compuesto de fórmula (I) o una sal o solvato fisiológicamente aceptable del mismo, en combinación de con uno o más diluyentes o portadores fisiológicamente aceptables.

Además se reivindican las composiciones en las que se combina un agente activo que responde a las características descritas para la fórmula (I), que se asocia junto a otro agente farmacológicamente activo como un agonista del β_2 -adrenorreceptor o un inhibidor de PDE4.

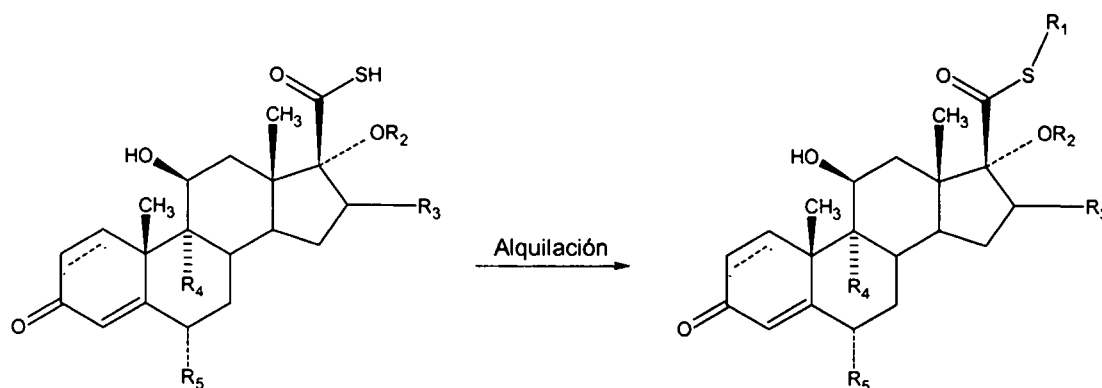
- **Reivindicación 26:**

Se reivindica una formulación farmacéutica en aerosol caracterizada porque comprende un compuesto de fórmula (I) o una sal o solvato fisiológicamente aceptable del mismo, y un fluorocarburo o clorofluorocarburo que contiene hidrógeno como propelente en asociación opcionalmente con un surfactante y/o un cosolvente.

- **Reivindicaciones 30, 31 y 32:**

Se reivindica un proceso para la preparación de un compuesto de la fórmula (I) de conformidad con la reivindicación 1, caracterizado porque comprende la alquilación de un compuesto de fórmula (II).

En particular se reivindica el proceso en el que la alquilación procede al hacer reaccionar el compuesto de fórmula (II) con un haluro de alquilo o de haloalquilo apropiado.



Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹/40** de la **Clasificación Internacional de Patentes**.

3. CLARIDAD DE LA SOLICITUD:

El artículo 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”*

Teniendo en cuenta el alcance del capítulo reivindicatorio y en particular las connotaciones que toma el radical R_2 : $-C(=O)$ -heteroarilo, que se ilustran en la cláusula 5 y siguientes, esta Dependencia se permite señalar el carácter amplio e inespecífico de algunos de los términos que se emplean en el capítulo alegado, por cuanto al mencionar un radical heteroarilo se está haciendo uso de un sinnúmero de sustituyentes comprendidos todos en un gran capítulo de la química heterocíclica.

Ahora bien, no obstante se especifique que se trata de un anillo aromático heterocíclico de 5 miembros, que contiene 1 a 3 heteroátomos seleccionados entre oxígeno, nitrógeno y azufre, anillo que opcionalmente puede estar sustituido por un grupo alquilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6

átomos o halógeno y que particularmente se selecciona entre furanilo, pirrolilo, tiofenilo, tiazolilo, isotiazolilo, pirazolilo, imidazolilo y tiadiazolilo, esta Dependencia objeta el carácter inespecífico del término anillo aromático heterocíclico utilizado en la cláusula 5 y recomienda al interesado precisar el alcance del radical en mención tal y como se realiza en las cláusulas 7 y siguientes.

4. 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 presentación de la solicitud en estudio - 05/08/2000- y relacionados con la materia técnica reivindicada:

Nº	Documento	Título	Fecha de Publicación
D1	US3856828	"Anti-inflammatory steroids of the androstane series having a halo-substituted C ₁ -C ₂ alkoxy carbonyl group at the 17 β position"	24/12/1974
D2	US4335121	"Androstane carbothioates"	15/06/1982
D3	US3828080	"Androstane -17 β -carboxylic acids and processes for the preparation thereof"	06/08/1974
D4	EP0057401	"Aromatic heterocyclic esters of steroids, their preparation and pharmaceutical compositions containing them"	11/08/1982

5. 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"*

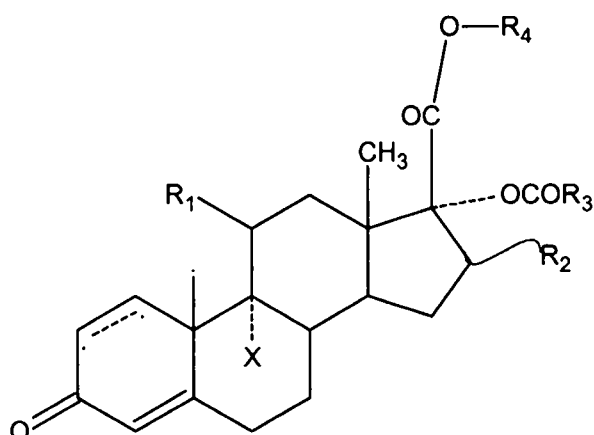
En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

5.1 Evaluación del NIVEL INVENTIVO:

El artículo 18 de la decisión 486 dispone *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la Materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*.

Una vez efectuado el análisis de la afectación ejercida por los documentos contemplados en el estado de la técnica, esta Dependencia se permite emitir el siguiente concepto:

- La anterioridad D1 comprende compuestos que responde a la fórmula estructural (I):



Formula que se sustituye con los siguientes radicales:

X que puede ser un átomo de hidrógeno, cloro o flúor.

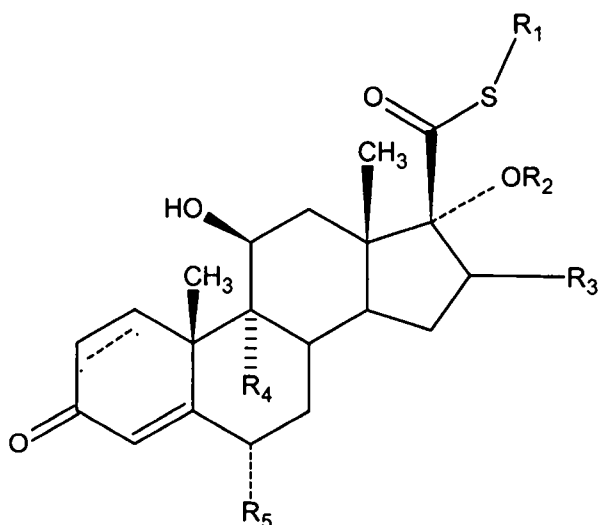
R₁ representa un grupo β-hidroxi, un grupo oxo o (cuando X es un átomo de cloro) **R₁** representa un radical tipo β-cloruro

R₂ representa un átomo de hidrógeno, un grupo metilen o un grupo α ó β metilo
R₃ representa un átomo de hidrógeno o un grupo alquilo C₁ a C₆ o un grupo fenilo

R₄ representa un grupo metilo sustituido por un halógeno, un grupo etilo sustituido por un halógeno (flúor o yodo), un grupo propilo sustituido por un halógeno.

— representa un enlace simple o doble.

Fórmula que al compararse con la reclamada por la solicitud resulta análoga dadas las connotaciones que toman los diferentes radicales del núcleo estructural evaluado:



R₄ y **R₅** son los mismos o diferentes y cada uno representa hidrógeno o halógeno

R₃ representa hidrógeno, metilo (el cual puede estar en la configuración α ó β) o metileno.

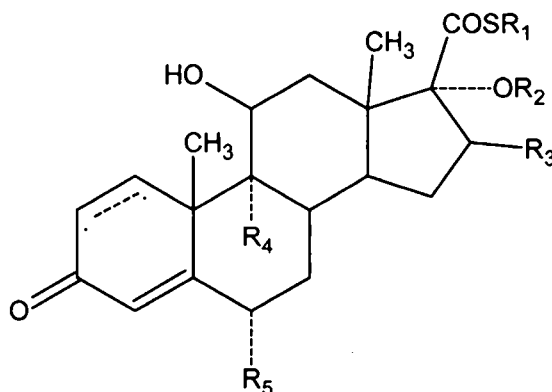
R₂ representa -C(=O)-arilo o -C(=O)-heteroarilo

R₁ representa alquilo de 1 a 6 átomos de carbono o haloalquilo de 1 a 6 átomos de carbono

— representa un enlace simple o doble.

Así las cosas, siendo que las diferencias estructurales y funcionales son mínimas respecto de la fórmula que en su momento publicó la anterioridad **D1**, esta Dependencia objeta la altura inventiva de la presente solicitud por considerarla una derivación evidente del estado de la técnica.

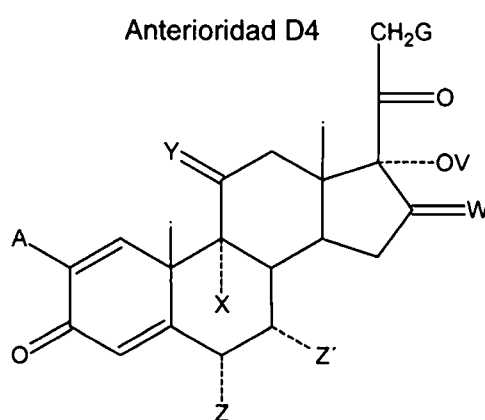
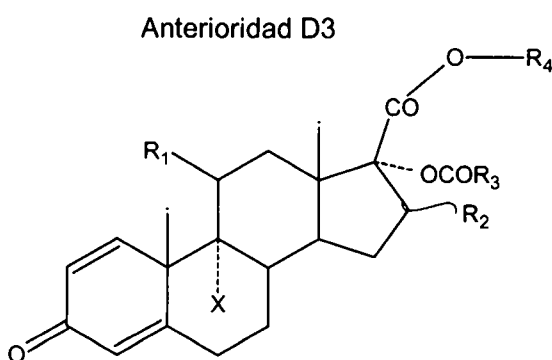
- La anterioridad **D2** por su parte comprende compuestos de la siguiente clase:



Los cuales al efectuar las correspondientes sustituciones también generan análogos estructurales de la materia que se reivindica a lo largo de las cláusulas 1 a 26, porque al efectuar las sustituciones con los radicales R₄, R₅, R₃ y R₁ se encuentran connotaciones homólogas en el caso de R₄ y R₅ que pueden ser hidrógeno o halógeno como en el caso de la solicitud en estudio, homólogas en el caso de R₃ que representa un átomo de hidrógeno o un grupo metilo o metilen como en la solicitud en estudio y homólogas en el caso de R₁ que pueden ser como en el caso de la solicitud un grupo alquilo sustituido por un átomo de flúor, cloro, o bromo tal y como se publica en la anterioridad **D2**.

Así las cosas, dado que la diferencia estructural consiste en las connotaciones que toma el radical R₂, diferencia que se subsana cuando se combinan las enseñanzas que presentan los documentos **D1** y **D2**, es claro que la afectación por la falta de altura inventiva de la materia reclamada se hace más palpable.

- De otro lado, anterioridades como **D3** y **D4** presentan núcleos estructurales con características similares a las que presenta el núcleo reclamado por la solicitud en estudio, analogías que se evidencia en el siguiente orden:



La anterioridad **D3** cuenta con radicales como X que representan un átomo de hidrógeno o un átomo de halógeno: cloro o flúor, un radical R₁ el cual representa un grupo hidroxilo, un radical R₂ que representa un átomo de hidrógeno, un grupo metilen o un grupo metilo, un radical R₃ que representa un

átomo de hidrógeno, un grupo alquilo o un grupo fenilo y un radical R₄ que representa un grupo alquilo de cadena carbonada inferior que puede a su vez sustituirse por un radical halogenado. Así las cosas la única diferencia aparente tiene que ver con el grupo carbonilo y su átomo adyacente, que para el caso de la anterioridad **D3** tiene que ver con un átomo de oxígeno y en el de la solicitud tiene que ver con un átomo de azúfre.

Por su parte la anterioridad **D4** cuenta con sustituciones análogas a las que reclama la solicitud en atención a los grupos A, Z, Z', X, W, V y G de esta manera:

- A representa un átomo de hidrógeno
- Z representa un átomo de hidrógeno, un grupo metilo, cloro o flúor
- Z' representa un átomo de hidrógeno o un halógeno
- X representa un átomo de hidrógeno o un halógeno
- W representa un grupo alquilo inferior o (H, H) o (H, alquilo inferior)
- V representa un radical acilo o un ácido tiofencarboxílico, o un ácido pirrolicarboxílico, o un ácido furancarboxílico o sus derivados metil o halógeno sustituidos.
- G representa un átomo de hidrógeno o un halógeno o puede ser -QV₂ en donde Q representa un átomo de azúfre o de oxígeno V₂ corresponde a un radical acilo.

Así las cosas, resulta evidente que el documento **D4** se acerca aún más a las características que reclama la solicitud, generando de esta manera una afectación directa sobre la verdadera actividad inventiva desplegada entorno al diseño de compuestos con estructura básica de ciclopentanoperhidrofenantreno y sustituciones heterocíclicas en la posición 17 α . Igual sucede con la publicación D3 que homologa un gran porcentaje de la estructura reivindicada y que por tanto de manera independiente constituye en sí mismo evidencia suficiente de que la materia objeto del presente estudio fue posible derivarla del estado del estado de la técnica.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US3856828	1 a 26	Nivel Inventivo
D2	US4335121	1 a 26	Nivel Inventivo
D3	US3828080	1 a 26	Nivel Inventivo
D4	EP0057401	1 a 26	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 la 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 5 del título primero de la Circular Única N° 10 de 2001.

Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 19 Oct. 2006

CONCEPTO TÉCNICO Número 01619	EXAMINADOR TÉCNICO Código 202044
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