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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 03-018359- -00018-0000

Fecha: 2009-12-02 16:40:25 Dep. 2020 DIR.NUEVASCR
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Act. 444 RESPUESTAREQUE Folios: 38

NO ESTÁ INTERE

Re: Expediente No. 03.018.359

Solicitud de patente de invención titulada: "17-METILEN ESTEROIDES 4-HALOGENADOS, MÉTODO PARA SU PREPARACIÓN Y COMPOSICIONES FARMACÉUTICAS QUE CONTIENEN ESTOS COMPUESTOS."

Solicitante: SCHERING AKTIENGESELLSCHAFT.

N. Ref.: P2003/000185

RESPUESTA AL OFICIO No. 221 NOTIFICADO POR FIJACIÓN EN LISTA No. 24,

DE FECHA 24 DE JULIO DE 2009

(TERCER EXAMEN DE FONDO)

J. IAN RAISBECK, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 45 de la Decisión 486:

1. En primer lugar y con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un Capítulo Reivindicatorio Modificado, que reemplaza en su totalidad al Capítulo Reivindicatorio Modificado presentado en respuesta al primer examen de fondo.

Así entonces, el Capítulo Reivindicatorio Modificado contiene los siguientes cambios:

- Se eliminó el significado R20a = H de la Reivindicación 7. De esta manera, la nueva Reivindicación 7 no se superpone con lo definido en la Reivindicación 6.

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Valga anotar que las modificaciones efectuadas al Capítulo Reivindicatorio cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial.

2. a- El Examinador señala que las Reivindicaciones 6 y 7 tienen el mismo alcance.

b- Con el ánimo de superar la anterior objeción se eliminó el significado R20a = H de la Reivindicación 7 y de esta manera la nueva Reivindicación 7 no se superpone con lo definido en la Reivindicación 6.

3. a- El Examinador señala que los documentos J-Prakt. Chem., 27 (1-2), págs. 18-33 (D4); y (Chem. Rev., 1996, 96, págs. 3147-3176) (D5) afectan el nivel inventivo de las Reivindicaciones 1-5. Adicionalmente, el Examinador argumenta que las patentes US3,146,239 (D2) y US3,661,940 (D3) afectan el nivel inventivo del proceso reclamado en las Reivindicaciones 6-7.

Específicamente, el Examinador opina que el problema técnico objetivo de la solicitud presentada (es decir, obtener compuestos 17-metilesteroides que sean inhibidores de la 5 α -reductasa y que al mismo tiempo actúen como gestágenos) podría ser solucionado fácilmente por el experto en la materia a partir del compuesto divulgado en el documento D4, sustituyendo en el grupo metileno uno de los dos hidrógenos por un halógeno, alquilo o hidroxialquilo conforme a lo divulgado en el documento D5.

Adicionalmente, el Examinador objeta las Reivindicaciones 6 y 7 por carecer de nivel inventivo, pues considera que describen un procedimiento que aplica principios de síntesis química ya establecidos para compuestos esteroides en las anterioridades D2 (US 3,146,239) y D3 (US 3,661,940).

b- i) En cuanto a la falta de nivel inventivo de las Reivindicaciones 1-5, cabe destacar que ni el documento D5 ni el documento D4 apuntan al problema que pretende resolver el presente invento, es decir, el problema de proporcionar 17-metilenesteroides con un perfil de tipo híbrido (que actúan como inhibidores de la 5 α -reductasa y al mismo tiempo como gestágenos). De hecho, el documento D4 ni siquiera menciona la actividad farmacológica de los compuestos allí obtenidos. Por otro lado, el documento D5 no se refiere en ningún momento al reemplazo de un átomo de hidrógeno por un átomo de halógeno o un grupo alquilo en un compuesto esteroide, ni tampoco investiga la correlación entre tal reemplazo y un efecto

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específico sobre la actividad biológica. Por consiguiente, el experto en la materia que pretende encontrar un compuesto esteroide que actúe como inhibidor de la 5 α -reductasa y al mismo tiempo como gestágeno no tomaría como información relevante alguna a partir de lo divulgado en los documentos D4 y D5, ya sea en forma individual o combinada. Con base en estos argumentos, cabe concluir que el objeto de las Reivindicaciones 1 a 5 no se desprende en forma evidente a partir de los documentos D4 y D5.

ii) En cuanto a las Reivindicaciones 6-7, cabe destacar que un procedimiento se define tanto por sus etapas como por las condiciones a las cuales éstas se llevan a cabo, por lo que un procedimiento general no necesariamente precluye la novedad o el nivel inventivo de un procedimiento específico. En este sentido, las divulgaciones efectuadas por D2 y D3 no permiten establecer los pasos y condiciones específicas descritas en las Reivindicaciones 6 y 7 para la síntesis de compuestos de Formula I. No sería dable explicar que basado en las divulgaciones hechas por D2 y D3, una persona medianamente versada en la materia tendría certeza sobre la obtención de los productos de Formula I. Es decir, con base en D2 y D3, no se podría establecer que los procesos descritos en las Reivindicaciones 6 o 7 efectivamente conducirían a la síntesis de los compuestos de Formula I. Es por esto que conforme a la práctica general de patentes, cuando existe un producto que es novedoso e inventivo, no es necesario investigar la novedad y la actividad inventiva de cualquier reivindicación de procedimiento cuyo resultado inevitable es la manufacturación de dicho producto. En otras palabras, un proceso es considerado novedoso e inventivo en la medida en que proporcione como resultado un producto novedoso e inventivo, puesto que las condiciones específicas para producir un compuesto novedoso e inventivo no serían predecibles. En atención a ello, las Reivindicaciones de procedimiento No. 6 y 7 son novedosas e inventivas pues divulgan la manufactura de los 17-metilesteroides de las Reivindicaciones 1 a 5, los cuales son novedosos e inventivos frente al arte previo citado.

Por lo tanto, considero que con los argumentos aquí expuestos ha quedado demostrado el nivel inventivo de la presente invención por sobre las enseñanzas del arte previo citado.

3. A fin de aportar datos adicionales que demuestren la patentabilidad del presente invento cabe mencionar que la presente solicitud de patente ya fue concedida en los siguientes países: HK, AU, BY, CA, EE, IL, KR, MX, NO, NZ, RU, SK, UA, US y EP. Al presente escrito se adjuntan las correspondientes carátulas y pliegos reivindicatorios de algunas de estas patentes concedidas.

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4. Por todo lo anterior, considero que las objeciones presentadas por el Examinador en su examen de fondo No. 1723 han sido resueltas y por consiguiente solicito respetuosamente que el Despacho tengan por cumplidos los requisitos de patentabilidad, en tanto no se logró desvirtuar ninguno de ellos por parte del Despacho, y se proceda con la concesión de la patente. En el evento que el Despacho considere que persisten objeciones frente a algunas reivindicaciones, solicito respetuosamente emita un nuevo examen de fondo a fin de poder atenderlas.

Atentamente,



J. IAN RAISBECK

C.C. 79'376.996 de Bogotá D.C.

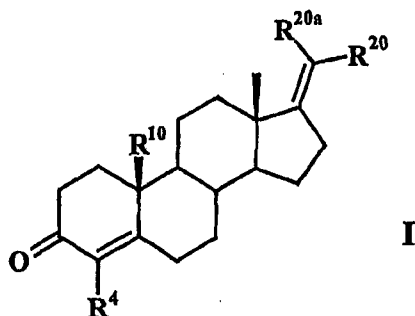
T.P. 135.799 del C. S. de la J.

- Capítulo Reivindicatorio Modificado.
- Carátulas y Reivindicaciones de algunas de las patentes concedidas en otros países.

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CAPITULO REIVINDICATORIO MODIFICADO
(Tercer Examen de Fondo)

1. 17-metilenesteroides caracterizado porque es de la fórmula general I



donde

R⁴ es un átomo de halógeno o un pseudohalógeno seleccionado del grupo que consiste de cianato, rodanuro, ciano o azido;

R¹⁰ es un átomo de hidrógeno o un grupo alquilo C₁₋₄ de cadena lineal o ramificada;

R²⁰ y R^{20a} son, independientemente entre sí, un átomo de hidrógeno, un grupo alquilo C₁₋₄ o hidroxialquilo C₁₋₄ de cadena lineal o ramificada; o

uno de los radicales R²⁰ y R^{20a} significan un átomo de hidrógeno, un grupo alquilo C₁₋₄ o hidroxialquilo C₁₋₄ de cadena lineal o ramificada y el otro radical es un átomo de halógeno o un pseudohalógeno seleccionado del grupo que consiste de cianato, rodanuro, ciano o azido, con la excepción de los siguientes compuestos: 4-cloro-17-metilen-4-androsten-3-ona y 4-cloro-20-fluoro-21-hidroxipregna-4,17(20)-dien-3-ona.

2. 17-metilenesteroides de acuerdo con la Reivindicación 1, caracterizado porque R⁴ es un átomo de cloro- o bromo o un grupo ciano.

3. 17-metilenesteroides de acuerdo con la Reivindicación 1 o 2, caracterizado porque uno de los radicales R²⁰ y R^{20a} es un átomo de hidrógeno o un grupo metilo y el otro radical es un átomo de flúor, cloro o bromo, un grupo azido, ciano o tiocianato o hidroximetilo.

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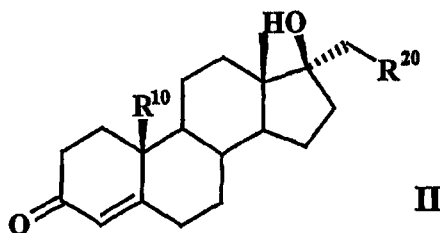
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4. 17-metilenesteroides de acuerdo con la Reivindicación 1, 2 o 3 caracterizado porque R^{10} es un átomo de hidrógeno o un grupo metilo.

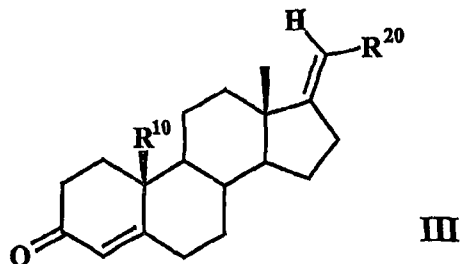
5. 17-metilenesteroides de acuerdo con la Reivindicación 1, caracterizado porque son:

- 1). E-17-clorometilen-4-cloroestr-4-en-3-ona;
- 2). E-17-cianometilen-4-cloroestr-4-en-3-ona;
- 3). Z-17-cianometilen-4-cloroestr-4-en-3-ona;
- 4). Z-17-(1')-cianoetiliden-4-cloroestr-4-en-3-ona;
- 5). Z-17-etiliden-4-cloroestr-4-en-3-ona;
- 6). E-17-etiliden-4-cloroestr-4-en-3-ona;
- 7). E-17-bromometilen-4-cloroestr-4-en-3-ona;
- 8). Z-17-cloretiliden-4-cloroestr-4-en-3-ona;
- 9). Z-17-brometiliden-4-cloro-estr-4-en-3-ona;
- 10). E-17-clorometilen-4-cianoandrost-4-en-3-ona;
- 11). E-17-clorometilen-4-cloroandrost-4-en-3-ona;
- 12). E-17-(2')-hidroxietiliden-4-cloroestr-4-en-3-ona; y
- 13). Z-17-(2')-hidroxietiliden-4-cloroestr-4-en-3-ona.

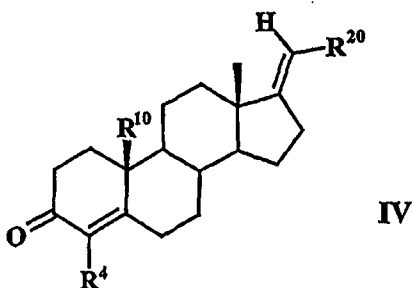
6. Método para preparar 17-metilenesteroides de acuerdo con la Reivindicación 1, donde R^{20a} es un átomo de hidrógeno, caracterizado porque, un compuesto de la fórmula general II,



se hace reaccionar con un cloruro ácido, en un solvente aprótico para obtener un 17-metilenesteroide de la fórmula general III,

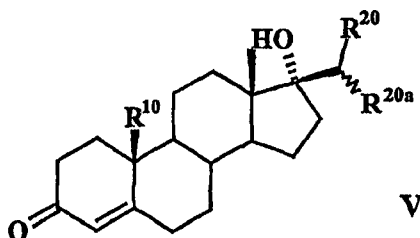


se genera el 4,5-epóxido con $\text{H}_2\text{O}_2/\text{NaOH}$, se abre este con un reactivo nucleófilo que se deriva de un átomo de halógeno o pseudohalógeno seleccionado del grupo que consiste de cianato, rodanuro, ciano o azido, en un solvente aprótico dipolar para obtener una hidrina halógena o pseudohalógena y, si fuera necesario se hace reaccionar con un ácido mineral, ácido carboxílico o ácido sulfónico en un solvente prótico o aprótico con deshidratación, para obtener un compuesto de la fórmula general IV,



donde R^4 es un átomo de halógeno o pseudohalógeno seleccionado del grupo que consiste de cianato, rodanuro, ciano o azido, donde R^{10} tiene el significado mencionado en la Reivindicación 1 y R^{20} significa un grupo alquilo C_{1-4} o hidroxialquilo C_{1-4} , un átomo de halógeno o un pseudohalógeno seleccionado del grupo que consiste de cianato, rodanuro, ciano o azido.

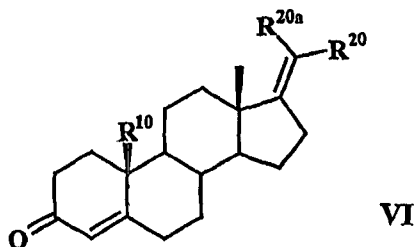
7. Método para preparar 17-metilenesteroides de acuerdo con la Reivindicación 1, caracterizado porque un compuesto de la fórmula general V,



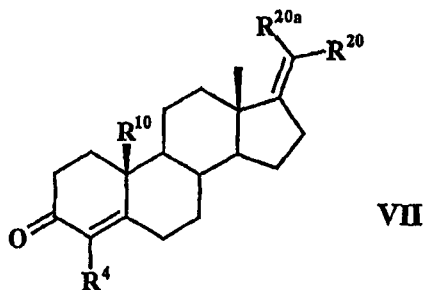
se hace reaccionar con un cloruro ácido, en un solvente aprótico para obtener un

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metilenesteroide de la fórmula general VI,



se genera el 4,5-epóxido con H₂O₂ / NaOH, se abre este con un reactivo nucleófilo que se deriva de un átomo de halógeno o pseudohalógeno seleccionado del grupo que consiste de cianato, rodanuro, ciano o azido, en un solvente aprótico dipolar para obtener una hidrina halógena o pseudohalógena y, si fuera necesario se hace reaccionar con un ácido mineral, ácido carboxílico o ácido sulfónico en un solvente prótico o aprótico con deshidratación para obtener un compuesto de la fórmula general VII,



donde R⁴ es un átomo de halógeno o pseudohalógeno seleccionado del grupo que consiste de cianato, rodanuro, ciano o azido, donde R¹⁰ tiene el significado mencionado en la Reivindicación 1 y R²⁰ significa un grupo alquilo-C₁₋₄ o hidroxi-alquilo-C₁₋₄ y R^{20a} significa un átomo de halógeno o un pseudohalógeno seleccionado del grupo que consiste de cianato, rodanuro, ciano o azido.

8. Composiciones farmacéuticas caracterizadas porque contienen por lo menos un 17-metilenesteroide de acuerdo con las Reivindicaciones 1, 2, 3, 4 o 5, en caso necesario junto con sustancias auxiliares y vehículos farmacéuticamente aceptables.



US006855836B2

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(12) **United States Patent**
Menzenbach et al.

(10) **Patent No.:** **US 6,855,836 B2**
(45) **Date of Patent:** **Feb. 15, 2005**

a

(54) **17-METHYLENE STEROIDS, PROCESS FOR THEIR PRODUCTION AND PHARMACEUTICAL COMPOSITIONS THAT CONTAIN THESE COMPOUNDS**

2,789,989 A * 4/1957 Julian et al. 260/397.47
2,802,015 A * 8/1957 Colton 260/397.45
5,194,602 A * 3/1993 Batisi et al. 540/29

OTHER PUBLICATIONS

(75) **Inventors:** **Bernd Menzenbach**, Jena (DE); **Peter Droscher**, Weimar (DE); **Walter Elger**, Berlin (DE); **Alexander Hillisch**, Jena (DE); **Gunter Kaufmann**, Jena (DE); **Hans-Udo Schweikert**, Bonn (DE); **Gerd Muller**, Jena (DE)

Barnikol-Oettler et al. (AN CA62:11871e, CAOLD, DN 62:66733, HCAPLUS, abstract of J. Prakt. Chem. (1965), 27(1-2), 18-23).*

AN CA51:18017b, CAOLD, DN 62:66733, HCAPLUS, abstract of US Patent 2802015.*

(73) **Assignee:** **Jenapharm GmbH & Co. KG**, Jena (DE)

AN CA51:12161f, CAOLD, abstract of US 2789989.*

.AN CA51:8821c, CAOLD, abstract of US Patent 2769823.*

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 73 days.

* cited by examiner

(21) **Appl. No.:** **09/963,680**

Primary Examiner—Sabiha N. Qazi

(22) **Filed:** **Sep. 27, 2001**

(74) *Attorney, Agent, or Firm*—Millen, White, Zelano & Branigan, P.C.

(65) **Prior Publication Data**

US 2002/0091112 A1 Jul. 11, 2002

(57) ABSTRACT

The invention relates to 17-methylene steroids, process for their production and pharmaceutical compositions that contain these compounds.

Related U.S. Application Data

(60) Provisional application No. 60/243,281, filed on Oct. 26, 2000.

(51) **Int. Cl.⁷** **C07J 13/00**; A61K 31/56

(52) **U.S. Cl.** **552/526**; 552/527; 552/530; 514/169; 514/171; 514/177

(58) **Field of Search** 552/526, 527, 552/530, 531, 532; 514/169, 171, 177

The compounds according to the invention have a hybrid-type profile of action in the sense that they act as inhibitors of 5 α -reductase and simultaneously as gestagens. They are therefore suitable for treating diseases that are the result of elevated androgen levels in certain organs and tissues in men and women. Together with other hormonal substances, such as an estrogen, testosterone or a strong androgen, the compounds according to the invention are suitable as contraceptive agents for women and for men.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,769,823 A * 11/1956 Schneider et al. 260/397.45

25 Claims, No Drawings

17-METHYLENE STEROIDS, PROCESS FOR THEIR PRODUCTION AND PHARMACEUTICAL COMPOSITIONS THAT CONTAIN THESE COMPOUNDS

This application claims the benefit of the filing date of U.S. Provisional Application Ser. No. 60/243,281 filed Oct. 26, 2000.

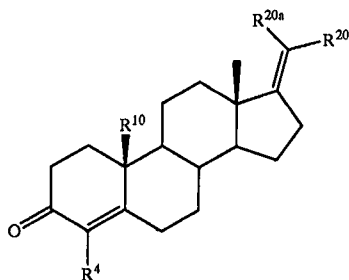
The invention relates to 17-methylene steroids, process for their production and pharmaceutical compositions that contain these compounds.

The compounds according to the invention have a hybrid-type profile of action in the sense that they act as inhibitors of 5 α -reductase and simultaneously as gestagens. They are therefore suitable for treating diseases that are the result of elevated androgen levels in certain organs and tissues in men and women. Together with other hormonal substances, such as an estrogen, testosterone or a strong androgen, the compounds according to the invention are suitable as contraceptive agents for women and for men.

In women, elevated levels of 5 α -dihydroprogesterone can contribute to serious feelings of ill-health during the premenstrual syndrome. These disruptions can also be advantageously affected by inhibition of 5 α -reductase. The simultaneous presence of a gestagenic action results in an inhibition of gonadal function in males and females. This effect is then desired if an antifertile action or else an inhibition of the hormone secretion of the gonads is to be achieved with the treatment. Since the inhibition of 5 α -reductase can irreversibly disrupt the sexual development of the fetus in the case of a woman pregnant with a male fetus, an elimination of fertility accompanied by an antiandrogenic therapy is very desirable. Possible indications are prostate diseases, alopecia of the male type, acne, and hirsutism. The symptoms during the premenstrual syndrome can be alleviated in correspondingly disposed women.

It was found, surprisingly enough, that 17-methylene steroids of general formula I act both as inhibitors of 5 α -reductase and as gestagens.

This invention consequently relates to 17-methylene steroids of general formula I



in which

R⁴ stands for a halogen atom or a pseudohalogen,

R¹⁰ stands for a hydrogen atom or a straight-chain or branched C₁₋₄ alkyl group,

R²⁰ and R^{20a}, independently of one another, represent a hydrogen atom, a straight-chain or branched C₁₋₄ alkyl or hydroxy-C₁₋₄ alkyl group, or

one of radicals R²⁰ and R^{20a} means a hydrogen atom, a straight-chain or branched C₁₋₄ alkyl or hydroxy-C₁₋₄ alkyl group, and the other radical means a halogen atom or a pseudohalogen.

R⁴ can mean a halogen atom, such as a fluorine, chlorine, bromine or iodine atom, or a pseudohalogen, such as a

cyanate, rhodanid, cyano or azide group, whereby a bromine atom or a cyano group is preferred, and a chlorine atom is especially preferred.

R¹⁰ can stand for a hydrogen atom or a straight-chain or branched C₁₋₄ alkyl group, whereby examples of straight-chain or branched C₁₋₄ alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert-butyl. R¹⁰ preferably means a hydrogen atom or a methyl group.

On the one hand, R²⁰ and R^{20a}, independently of one another, can represent a hydrogen atom, a straight-chain or branched C₁₋₄ alkyl or hydroxy-C₁₋₄ alkyl group. In this case, R²⁰ and R^{20a}, independently of one another, preferably mean a hydrogen atom, a methyl group or a group —CH₂OH.

In addition, one of radicals R²⁰ and R^{20a} can mean a hydrogen atom, a straight-chain or branched C₁₋₄ alkyl or hydroxy-C₁₋₄ alkyl group, and the other radical can mean a halogen atom, such as a fluorine, chlorine, bromine or iodine atom, or a pseudohalogen, such as a cyanate, rhodanid, cyano or azide group. Examples of straight-chain or branched C₁₋₄ alkyl groups are the groups cited for R¹⁰. Straight-chain or branched hydroxy-C₁₋₄ alkyl groups are derived from the above-mentioned straight-chain or branched C₁₋₄ alkyl groups, whereby one or more hydrogen atoms are replaced by hydroxy groups.

In this case, one of radicals R²⁰ and R^{20a} preferably means a hydrogen atom or a methyl group, and the other radical means a halogen atom, preferably a fluorine atom, especially preferably a chlorine or bromine atom, or a pseudohalogen, preferably an azido or rhodano group, especially preferably a cyano group.

In the case of R²⁰ and R^{20a}, examples of straight-chain or branched C₁₋₄ alkyl groups are the groups that are cited for R¹⁰. Straight-chain or branched hydroxy-C₁₋₄ alkyl groups are derived from these C₁₋₄ alkyl groups, whereby one or more hydrogen atoms are replaced by hydroxy groups, such as especially a group —(CH₂)_n—OH with n=1 to 4.

Especially preferred are the following compounds:

- 1) E-17-Chloromethylene-4-chloro-estr-4-en-3-one,
- 2) E-17-Cyanomethylene-4-chloro-estr-4-en-3-one,
- 3) Z-17-Cyanomethylene-4-chloro-estr-4-en-3-one,
- 4) Z-17-(1')-Cyanoethylidene-4-chloro-estr-4-en-3-one,
- 5) Z-17-Ethylidene-4-chloro-estr-4-en-3-one,
- 6) E-17-Ethylidene-4-chloro-estr-4-en-3-one,
- 7) E-17-Bromomethylene-4-chloro-estr-4-en-3-one,
- 8) Z-17-Chloroethylidene-4-chloro-estr-4-en-3-one,
- 9) Z-17-Bromoethylidene-4-chloro-estr-4-en-3-one,
- 10) E-17-Chloromethylene-4-cyano-androst-4-en-3-one,
- 11) E-17-Chloromethylene-4-chloro-androst-4-en-3-one,
- 12) E-17-(2')-Hydroxyethylidene-4-chloro-estr-4-en-3-one and
- 13) Z-17-(2')-Hydroxyethylidene-4-chloro-estr-4-en-3-one.

Subjects of this invention are also pharmaceutical compositions that contain at least one 17-methylene steroid of general formula I as active ingredient, whereby these compositions also contain suitable adjuvants and vehicles, and the use of these compounds for the production of pharmaceutical agents, especially for the indications below.

The compounds according to the invention are suitable for the production of pharmaceutical compositions and preparations. The pharmaceutical compositions or pharmaceutical agents contain as active ingredient one or more of the compounds according to the invention, optionally mixed with other pharmacologically or pharmaceutically active substances. The production of the pharmaceutical agents is carried out in a known way, whereby the known and

commonly used pharmaceutical adjuvants and other commonly used vehicles and diluents can be used.

As such vehicles and adjuvants, for example, those are suitable that are recommended or indicated in the following bibliographic references as adjuvants for pharmaceuticals, cosmetics and related fields: Ullmans Encyklopädie der technischen Chemie [Ullman's Encyclopedia of Technical Chemistry], Volume 4 (1953), pages 1 to 39; Journal of Pharmaceutical Sciences, Volume 52 (1963), page 918 ff., H. V. Czetsch-Lindenwald, Hilfsstoffe für Pharmazie und angrenzende Gebiete [Adjuvants for Pharmaceutics and Related Fields], Pharm. Ind., No. 2, 1961, pages 72 and ff.; Dr. H. P. Fiedler, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete [Dictionary of Adjuvants for Pharmaceutics, Cosmetics and Related Fields], Cantor KG, Aulendorf in Württemberg 1971.

The compounds can be administered orally or parenterally, for example intraperitoneally, intramuscularly, subcutaneously or percutaneously. The compounds can also be implanted in the tissue.

For oral administration, capsules, pills, tablets, coated tablets, etc. are suitable. In addition to the active ingredient, the dosage units can contain a pharmaceutically compatible vehicle, such as, for example, starch, sugar, sorbitol, gelatin, lubricant, silicic acid, talc, etc.

For parenteral administration, the active ingredients can be dissolved or suspended in a physiologically compatible diluent. As diluents, very frequently oils with or without the addition of a solubilizer, a surfactant, a suspending agent or emulsifier can be used. Examples of oils that are used are olive oil, peanut oil, cottonseed oil, soybean oil, castor oil and sesame oil.

The compounds can also be used in the form of a depot injection or an implant preparation that can be formulated in such a way that a delayed release of active ingredient is made possible.

Implants can contain as inert materials, for example, biodegradable polymers or synthetic silicones such as, for example, silicone gum. In addition, the active ingredients can be added to a patch for percutaneous administration, for example.

For the production of intravaginal systems (e.g., vaginal rings) or intrauterine systems (e.g., pessaries, coils, IUDs, Mirena[®]) that are charged with active compounds of general formula I for local administration, various polymers, such as, for example, silicone polymers, ethylenevinyl acetate, polyethylene or polypropylene, are suitable.

To achieve a better bio-availability of the active ingredient, the compounds can also be formulated as cyclodextrin clathrates. In this connection, the compounds are reacted with α -, β - or γ -cyclodextrin or derivatives of the latter (PCT/EP95/02656).

According to the invention, the compounds of general formula I can also be encapsulated with liposomes.

The compounds according to the invention have a hybrid-type profile of action. They are inhibitors of 5α -reductase and, moreover, also act as gestagens. They are therefore suitable for treating diseases that are the result of elevated androgen levels in certain organs and tissues in men and women. In women, elevated levels of 5α -dihydroprogesterone can contribute to serious feelings of ill-health during the premenstrual syndrome. This can be advantageously influenced by inhibition of the 5α -reductase.

The simultaneous presence of a gestagenic action in compounds according to the invention results in an inhibition of gonadal function in males and females. This effect is

desirable if an antifertile action or else an inhibition of the hormone secretion of the gonads is to be achieved with the treatment. This is frequently the case in diseases of the prostate (benign prostate hyperplasia). In addition to prostate diseases, possible indications are contraception in both sexes, alopecia of the male type, acne and hirsutism. Together with other hormonal substances, such as an estrogen, testosterone or a strong androgen, the compounds according to the invention are suitable as contraceptive agents for women or for men. In the latter case, the action of testosterone in the prostate by inhibition of the 5α -reductase is reduced, while the gestagenic activity enhances the action in the male gonads, i.e., the inhibition of spermatogenesis.

If the compounds according to the invention are used for female contraception, they can be used by themselves or together with an estrogen. As estrogens, basically all estrogen-active compounds are suitable: estrogens that can be used are, for example, ethinylestradiol, 17β -estradiol as well as its esters, such as estradiol-3-benzoate, estradiol-17-valerate, -cypionate, -undecylate, -enanthate and/or other estradiol esters (U.S. Pat. Nos. 2,611,773, 2,990,414, 2,054,271, 2,225,419 and 2,156,599) and conjugated estrogens.

Estradiol, ethinylestradiol- and estrone-3-sulfamates, for example estrone-N,N-dimethylsulfamate, estrone-N,N-diethylsulfamate, ethinylestradiol-3-N,N-dimethylsulfamate, ethinylestradiol-3-N,N-diethylsulfamate, ethinylestradiol-3-N,N-tetramethylenesulfamate, estrone sulfamate, estradiol-3-sulfamate, estradiol-3-N,N-dimethylsulfamate, estradiol-3-N,N-diethylsulfamate, and ethinylestradiol-3-sulfamate, which produce all prodrugs of the corresponding 3-hydroxy compounds (W. Elger et al., in J. Steroid Biochem. Molec. Biol., Vol. 55, No. 3/4, 395-403, 1995, DE 44 29 398 A1 and DE 44 29 397 A1), can also be used according to the invention.

If the compounds according to the invention are used for male contraception, they can be used by themselves or together with an androgen, such as, for example, testosterone and testosterone esters.

Data for 5α -reductase-type 2-activity in genital dermal homogenates and in vivo data for gestagenic activity are presented by way of example in Tables 1 and 2 below.

TABLE 1

5α -Reductase-Type 2-Activity in Genital Dermal Homogenates under Optimized Conditions at pH 5.5 (IC_{50} (nM)) Progesterone-receptor binding to uterus-cytosol, rabbits, primed Tracer: $3H$ -ORG 2058/incubation conditions 0-4° C.; 18 hours Reference substance: progesterone = 100%		
Compound	IC_{50} (nM)	PR Progesterone = 100%
(1) E-17-Chloromethylene-4-chloro-estr-4-en-3-one	250	60

TABLE 2

In-vivo Data for Gestagenic Activity <u>Mouse pregnancy maintenance test after s.c. administration</u>		
Compound	Dosage mg/animal/day s.c.	Pregnancy rate achieved
(1) E-17-Chloromethylene-4-chloro-estr-4-en-3-one	1.0 0.1	5/5 0/5

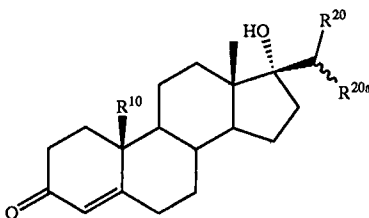
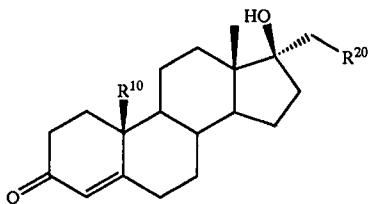
The data presented in Tables 1 and 2 confirm the hybrid-type profile of action of the compounds according to the

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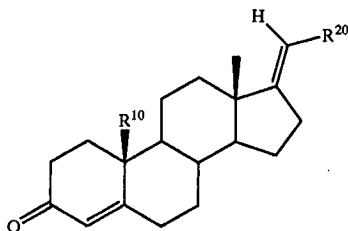
invention that act as inhibitors of 5 α -reductase and as gestagens.

The 17-methylene steroids of general formula I according to the invention are available from compounds of general formula II (K. Ponsold et al., Pharmazie [Pharmaceutics] 33, 792 (1978)) and general formula V.

The compounds of general formula V are obtained from the corresponding 17 α -epoxy compounds (G. Drefahl et al., Ber. 98, 604 (1965)) by reaction with a halide, such as, for example, hydrogen chloride or hydrogen bromide, or pseudohalide, such as, for example, hydrogen thiocyanate or hydrogen nitride, in a dipolar aprotic solvent, preferably DMSO or DMPU.

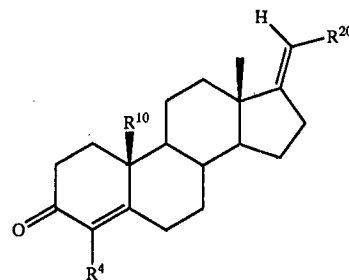


The compounds of Formula I are obtained by a compound of general formula II being reacted in an aprotic solvent, preferably in pyridine or triethylamine, with an acid chloride, preferably thionyl chloride or phosphoroxo chloride, to a compound of general formula III,



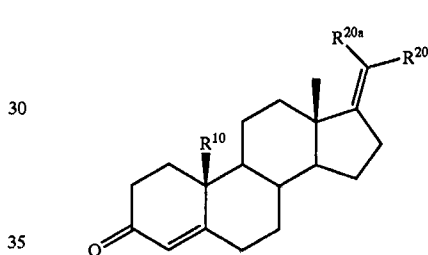
the latter being subjected in a way that is known in the art to an epoxidation with H₂O₂/NaOH in an alcohol, preferably methanol or ethanol, the resulting 4,5-epoxide being opened with nucleophiles, such as halide, such as for example, hydrogen chloride or hydrogen bromide or pseudohalide, such as, for example, hydrogen thiocyanate or hydrogen nitride, in a dipolar aprotic solvent, preferably DMSO or DMPU, dioxane or acetone, to halogen- or pseudohalogen hydrins, and the latter being dehydrated with catalytic mediation by mineral acid, carboxylic acid or sulfonic acid, such as hydrochloric acid, oxalic acid or p-toluenesulfonic acid, in a protic or aprotic solvent, such as methanol or acetone, to a compound of general formula IV

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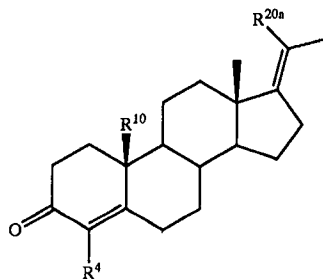


in which R⁴ stands for a halogen atom or pseudohalogen, whereby R¹⁰ has the above-indicated meaning, and R²⁰ means a C₁₋₄ alkyl or hydroxy-C₁₋₄ alkyl group, a halogen atom or a pseudohalogen.

In addition, 17-methylene steroids of general formula I are obtained by a compound of general formula V being reacted in an aprotic solvent, preferably in pyridine or triethylamine, with an acid chloride, preferably thionyl chloride or phosphoroxo chloride, to a compound of general formula VI

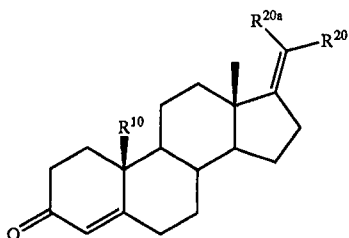
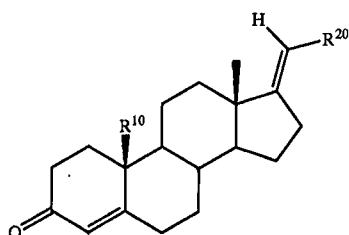


the latter being subjected in a way that is known in the art to an epoxidation with H₂O₂/NaOH in an alcohol, preferably methanol or ethanol, the resulting 4,5-epoxide being opened with a nucleophile, such as a halide, such as, for example, hydrogen chloride or hydrogen bromide or pseudohalide, such as, for example, hydrogen thiocyanate or hydrogen nitride, in a dipolar aprotic solvent, preferably DMSO or DMPU, dioxane or acetone to a halogen- or pseudohalogen hydrin, and the latter then being dehydrated with catalytic mediation by mineral acid, carboxylic acid or sulfonic acid, such as hydrochloric acid, oxalic acid or p-toluenesulfonic acid, in a protic or aprotic solvent, such as methanol or acetone, to a compound of general formula VII.

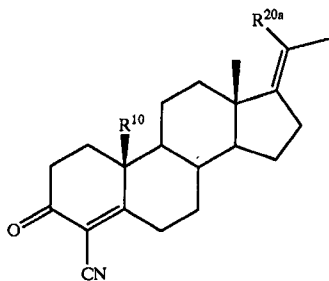
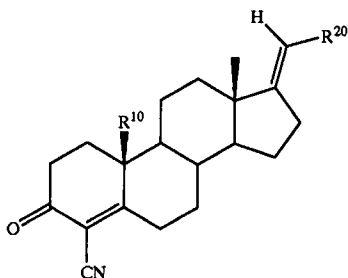


Finally, other 17-methylene steroids of general formula I can be obtained by compounds of general formulas III and VI

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being reacted in a way that is known in the art (M. Haase-Held, M. Mattis and J. Mann, J. Chem. Soc. Perkin Trans. 1, 2999, 1992) with $\text{NaO}_4/\text{KMnO}_4$ in alcohols, preferably in $t\text{-BuOH}$ to the 3,5-seco-keto acids, the latter being converted with $\text{Ac}_2\text{O}/\text{AcCl}$ into unsaturated lactones and the latter being reacted with $n\text{-BuLi}/\text{CH}_3\text{CN}$ in a dipolar aprotic solvent, such as tetrahydrofuran (THF), into compounds of general formulas VIII and IX.



E-17-Chloromethylen-estr-4-en-3-one can also be produced by WITTIG reaction with chloromethyltriphenylphosphonium chloride (S. Miyano et al., J. C. S. Chem. Comm., 446 (1978)). The isomeric 17-cyanomethylen-estr-4-en-3-ones can also be obtained by carbonyl olefination according to HORNER with cyanomethylene diethyl phosphonate or by PETERSON olefination with trimethylsilylacetonitrile (EP-A-0 077 040 or I. Ojima et al., Tetrahedron Lett. 46 (1974) 4005-4008).

Z-20-Cyano-19-norpregna-4,17(20)-dien-3-one is synthesized by PO-activated carbonyl activation with 2-diethylphosphono-propionitrile (R. W. Freerksen et al., Journal American Chemical Society (1977) 1536).

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The invention is explained in more detail by the examples below.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and, all parts and percentages are by weight, unless otherwise indicated.

The entire disclosures of all applications, patents and publications, cited, and of corresponding U.S. Provisional Application Ser. No. 60/248,281, filed Oct. 26, 200, is hereby incorporated by reference.

EXAMPLE 1

Z-17-(1'-Chloroethylidene-4-chloro-estr-4-en-3-one
A) Z-17-(1'-Chloroethyliden-estr-4-en-3-one

9.74 mmol (3.28 g) of 17 β -(1'-chloroethyl-17-hydroxy-estr-4-en-3-one (see compounds of general formula V) is dissolved in 34 ml of pyridine. While being cooled slightly, 12.66 mmol (0.92 ml) of thionyl chloride is added in drops while being stirred. It is stirred for about 1 hour under a cover gas (argon), and the reaction solution is then added to ice-cooled, dilute hydrochloric acid with a pH=3-4. The sticky precipitation product is extracted with methylene chloride, the combined, neutral-washed extracts are dried with sodium sulfate and concentrated by evaporation. The accumulating solid product is purified by chromatography on silica gel (eluant: toluene/ethyl acetate=95/5) and optionally recrystallization from methanol. 0.6 g of a solid product is obtained.

Flash point=138-141° C.; $[\alpha]_D^{20}=+104^\circ$ (CHCl_3)

B) Z-17-(1'-Chloroethylidene-4 ξ ,5 ξ -epoxy-estr-4-en-3-one

2.80 mmol (894 mg) of Z-17-(1'-chloroethyliden-estr-4-en-3-one is dissolved in a mixture of 9 ml of methanol and 7.3 ml of methylene chloride and cooled to 0° C. 6.31 mmol (0.63 ml) of hydrogen peroxide (30%) and 1.26 mmol (0.3 ml) of sodium hydroxide solution (c=4 mol/l) are added in drops in succession to the cooled solution while being stirred and under a cover gas (argon). After dropwise addition is completed, the temperature is slowly increased to room temperature. After about 1.5 hours of reaction time, the mixture is added to ice water and then extracted with methylene chloride. The combined extracts are dried with sodium sulfate and concentrated by evaporation. 926 mg of a light yellow solid is obtained.

$^1\text{H-NMR}/\delta$ (CDCl_3/ppm) 0.94(18-H), 1.99(21-H), 3.04(4-H)

C) Z-17-(1'-Chloroethylidene-4-chloro-estr-4-en-3-one

2.71 mmol (896 mg) of Z-17-(1'-chloroethyliden-4 ξ ,5 ξ -epoxy-estr-4-en-3-one is dissolved in 25 ml of 1,3-dimethyltetrahydro-2(1H)-pyrimidinone (DMPU), and 26.54 mmol (2.2 ml) of hydrochloric acid (37%) is slowly added in drops. After 1 hour of stirring under a cover gas (argon), the reaction solution is added to ice-cooled, aqueous sodium bicarbonate solution, the precipitation is suctioned off, and it is finally dried in a desiccator with potassium hydroxide. By flash-chromatography on silica gel (eluant: toluene/ethyl acetate=99/1) and subsequent recrystallization from methanol/acetone, 353 mg of solid product is obtained.

Flash point=182-185° C.; $[\alpha]_D^{20}=+137^\circ$ (CHCl_3)

EXAMPLE 2

Z-17-(1'-Bromoethylidene-4-chloro-estr-4-en-3-one

Starting from 17 β -(1'-bromoethyl-17-hydroxy-estr-4-en-3-one (see compounds of general formula V), Z-17-(1'-

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bromoethylidene-4-chloro-estr-4-en-3-one is obtained analogously to 17 β -(1')-chloroethyl-estr-4-en-3-one.

Flash point=164–173° C.; [α]_D²⁰=+138° (CHCl₃)

EXAMPLE 3

E-17-Chloromethylene-4-chloro-estr-4-en-3-one

A) E-17-Chloromethylen-estr-4-en-3-one

18.27 mmol (5.9 g) of 17 α -chloromethyl-17-hydroxy-estr-4-en-3-one is dissolved in 60 ml of pyridine. While being cooled slightly, 21.9 mmol (1.56 ml) of thionyl chloride is added in drops while being stirred. It is stirred under a cover gas (argon) for about 1 hour, and the reaction solution is then added to ice-cooled, dilute hydrochloric acid with a pH=3–4. The sticky precipitation product is extracted with methylene chloride, the combined, neutral-washed extracts are dried on sodium sulfate and concentrated by evaporation. The accumulating solid product is purified by chromatography on silica gel (eluant: n-hexane/ethyl acetate=85/15). After recrystallization from acetone, 1.6 g of product is obtained.

Flash point=143–146° C.; [α]_D²⁰=+20° (CHCl₃)

B) E-17-Chloromethylene-4 ξ ,5 ξ -epoxy-estr-4-en-3-one

3.93 mmol (1.2 g) of E-17-chloromethylen-estr-4-en-3-one is dissolved in a mixture of 12 ml of methanol and 10 ml of methylene chloride under a cover gas (argon) and cooled to 0° C. 9.2 mmol (0.94 ml) of hydrogen peroxide (30%) and 1.65 mmol (0.4 ml) of sodium hydroxide solution (c=4 mol/l) are added in drops in succession to the cooled solution while being stirred. After dropwise addition is completed, the temperature is slowly increased to room temperature. After about 1.5 hours of reaction time, the mixture is added to ice water and extracted with methylene chloride. The combined extracts are dried on sodium sulfate and concentrated by evaporation. 1.1 g of a white, sticky foam is obtained.

¹H-NMR/ δ (CDCl₃/ppm) 0.87(18-H), 3.04(4-H), 5.70(20-H)

C) E-17-Chloromethylene-4-chloro-estr-4-en-3-one

3.42 mmol (1.1 g) of E-17-chloromethylene-4 ξ ,5 ξ -epoxy-estr-4-en-3-one is dissolved in 26 ml of DMPU, and 33 mmol (2.74 ml) of hydrochloric acid (37%) is slowly added in drops. After 1 hour, the reaction solution is added to ice-cooled, aqueous sodium bicarbonate solution, the precipitation is suctioned off and dried in a desiccator on potassium hydroxide. After recrystallization from acetone, 760 mg of white crystals is obtained.

Flash point=182–194° C.; [α]_D²⁰=+63° (CHCl₃)

EXAMPLE 4

E-17-Bromomethylene-4-chloro-estr-4-en-3-one

Starting from E-17-bromomethyl-17 β -hydroxy-estr-4-en-3-one (see compounds of general formula II), E-17-bromomethylene-4-chloro-estr-4-en-3-one is obtained analogously to 17 α -chloromethyl-17-hydroxy-estr-4-en-3-one.

Flash point=169–176° C.; [α]_D²⁰=+45° (CHCl₃)

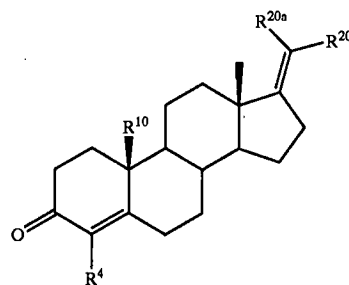
The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

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What is claimed is:

1. A 17-Methylene steroid of formula I



in which

R⁴ is a halogen atom or a pseudohalogen,

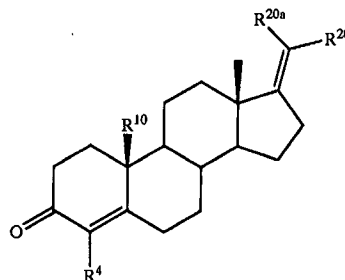
R¹⁰ is a hydrogen atom or a straight-chain or branched C₁–C₄ alkyl group,

R²⁰ and R^{20a} are, independently of one another, a straight-chain or branched C₁₋₄ alkyl or hydroxy-C₁₋₄ alkyl group, or

one of radicals R²⁰ and R^{20a} is a hydrogen atom, a straight-chain or branched C₁₋₄ alkyl or hydroxy-C₁₋₄ alkyl group, and the other radical is a halogen atom or a pseudohalogen.

2. A 17-Methylene steroids according to claim 1, wherein R⁴ is a chlorine or bromine atom or a cyano group.

3. A 17-Methylene steroid of formula I



in which

R⁴ is a halogen atom or a pseudohalogen,

R¹⁰ is a hydrogen atom or a straight-chain or branched C₁–C₄ alkyl group,

one of radicals R²⁰ and R^{20a} is a hydrogen atom or a methyl group, and the other radical is a fluorine, chlorine or bromine atom, an azido, cyano or rhodano group or hydroxymethyl.

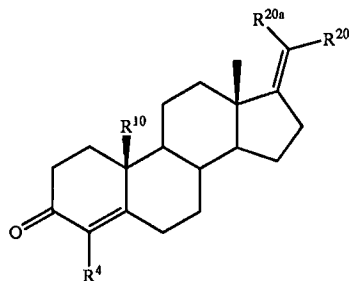
4. A 17-Methylene steroids according to claim 1, wherein R¹⁰ is a hydrogen atom or a methyl group.

5. A 17-Methylene steroid selected from the group consisting of

- 1) E-17-Chloromethylene-4-chloro-estr-4-en-3-one,
- 2) E-17-Cyanomethylene-4-chloro-estr-4-en-3-one,
- 3) Z-17-Cyanomethylene-4-chloro-estr-4-en-3-one,
- 4) Z-17-(1')-Cyanoethylidene-4-chloro-estr-4-en-3-one,
- 5) Z-17-Ethylidene-4-chloro-estr-4-en-3-one,
- 6) E-17-Ethylidene-4-chloro-estr-4-en-3-one,
- 7) E-17-Bromomethylene-4-chloro-estr-4-en-3-one,
- 8) Z-17-Chloroethylidene-4-chloro-estr-4-en-3-one,
- 9) Z-17-Bromoethylidene-4-chloro-estr-4-en-3-one,

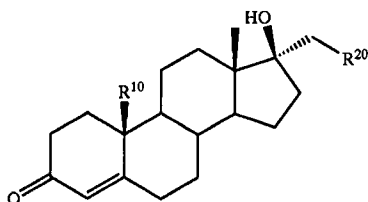
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- 10) E-17-Chloromethylene-4-cyano-androst-4-en-3-one,
 11) E-17-Chloromethylene-4-chloro-androst-4-en-3-one,
 12) E-17-(2')-Hydroxyethylidene-4-chloro-estr-4-en-3-one, and
 13) Z-17-(2')-Hydroxyethylidene-4-chloro-estr-4-en-3-one.
 6. A process for preparing a 17-methylene steroid of formula I

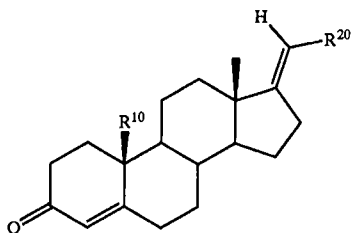


in which

- R^4 is a halogen atom or a pseudohalogen,
 R^{10} is a hydrogen atom or a straight-chain or branched C_1 - C_4 alkyl group,
 R^{20} is a hydrogen atom, a straight-chain or branched C_1 - C_4 alkyl or hydroxy- C_1 - C_4 alkyl group, or a halogen atom or a pseudohalogen, and
 R^{20a} is a hydrogen atom, comprising reacting a compound of formula II,

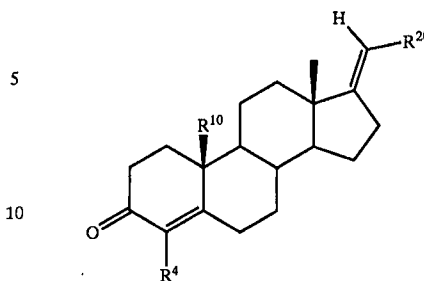


in an aprotic solvent with an acid chloride to form a 17-methylene steroid of formula III,



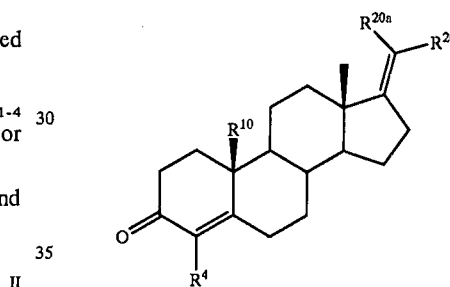
the 4,5-epoxide is generated with $H_2O_2/NaOH$, the 4,5-epoxide is then opened with a nucleophilic reagent, which is derived from a halogen atom or pseudohalogen, in a dipolar aprotic solvent to a halogen- or pseudohalogen hydrin, and optionally reacted with mineral acid, carboxylic acid or sulfonic acid in a protic or aprotic solvent with dehydration to a compound of formula IV,

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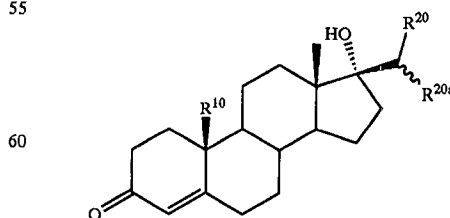
- wherein R^4 is a halogen atom or pseudohalogen, R^{10} is a hydrogen atom or a straight-chain or branched C_1 - C_4 alkyl group,
 and R^{20} is a C_1 - C_4 alkyl or hydroxy- C_1 - C_4 alkyl group, a halogen atom or a pseudohalogen.

7. A process for preparing a 17-methylene steroid of formula I



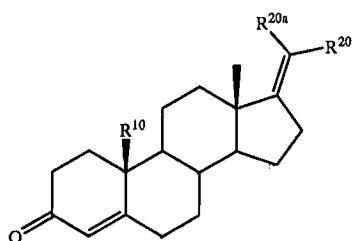
in which

- R^4 is a halogen atom or a pseudohalogen,
 R^{10} is a hydrogen atom or a straight-chain or branched C_1 - C_4 alkyl group,
 R^{20} and R^{20a} are, independently of one another, a hydrogen atom, a straight-chain or branched C_1 - C_4 alkyl or hydroxy- C_1 - C_4 alkyl group, or
 one of radicals R^{20} and R^{20a} is a hydrogen atom, a straight-chain or branched C_1 - C_4 alkyl or hydroxy- C_1 - C_4 alkyl group, and the other radical is a halogen atom or a pseudohalogen, comprising reacting a compound of formula V,

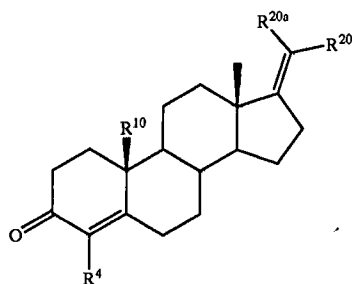


with an acid chloride in an aprotic solvent to form a methylene steroid of formula VI,

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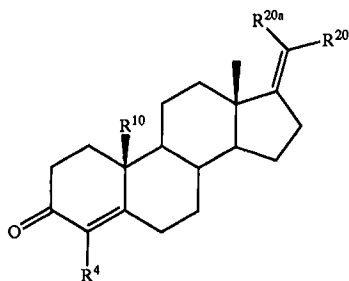
the 4,5-epoxide is generated with $\text{H}_2\text{O}_2/\text{NaOH}$, the 4,5-epoxide is then opened with a nucleophilic reagent, which is derived from a halogen atom or pseudohalogen, in a dipolar aprotic solvent to a halogen- or pseudohalogen hydrin, and optionally reacted with mineral acid, carboxylic acid or sulfonic acid in a protic or aprotic solvent with dehydration to a compound of formula VII,



in which R^4 is a halogen atom or pseudohalogen, R^{10} is a hydrogen atom or a straight-chain or branched $\text{C}_1\text{--C}_4$ alkyl group,

and R^{20} is a C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, and R^{20a} is a hydrogen atom, a halogen atom or a pseudohalogen.

8. A 17-methylene steroid of formula I



in which

R^4 is a halogen atom or a pseudohalogen,

R^{10} is a hydrogen atom or an ethyl, propyl, isopropyl, butyl, isobutyl, or tert-butyl group,

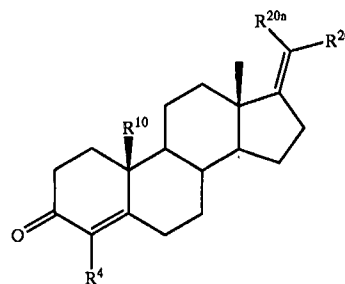
R^{20} and R^{20a} are, independently of one another, a hydrogen atom, a straight-chain or branched C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, or

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one of radicals R^{20} and R^{20a} is a hydrogen atom, a straight-chain or branched C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, and the other radical is a halogen atom or a pseudohalogen,

and a pharmaceutically compatible adjuvant or vehicle.

9. A 17-Methylene steroid of formula I



VII in which

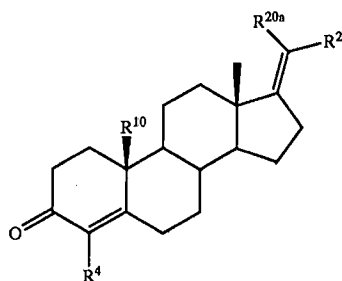
R^4 is a fluorine, bromine, or iodine atom or a pseudohalogen,

R^{10} is a hydrogen atom or a straight-chain or branched $\text{C}_1\text{--C}_4$ alkyl group,

R^{20} and R^{20a} are, independently of one another, a hydrogen atom, a straight-chain or branched C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, or

one of radicals R^{20} and R^{20a} is a hydrogen atom, a straight-chain or branched C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, and the other radical is a halogen atom or a pseudohalogen.

10. A 17-Methylene steroid of formula I



in which

R^4 is a halogen atom or a pseudohalogen,

R^{10} is a hydrogen atom or a straight-chain or branched $\text{C}_1\text{--C}_4$ alkyl group,

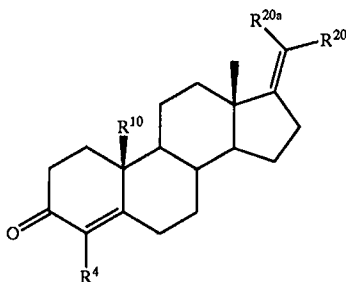
R^{20} is a hydrogen atom, a straight-chain or branched C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group,

R^{20a} is a straight-chain or branched C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, or

one of radicals R^{20} and R^{20a} is a hydrogen atom, a straight-chain or branched C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, and the other radical is a halogen atom or a pseudohalogen.

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11. A 17-Methylene steroid of formula I

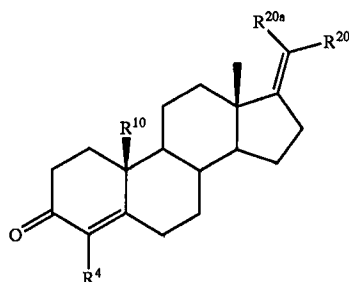


in which

 R^4 is a pseudohalogen, R^{10} is a hydrogen atom or a straight-chain or branched C_1 - C_4 alkyl group, R^{20} and R^{20a} are, independently of one another, a hydrogen atom, a straight-chain or branched C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, orone of radicals R^{20} and R^{20a} is a hydrogen atom, a straight-chain or branched C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, and the other radical is a halogen atom or a pseudohalogen.

12. A pharmaceutical composition comprising at least one 17-methylene steroid according to claim 8 and a pharmaceutically compatible adjuvant or vehicle.

13. A 17-Methylene steroid of formula I



in which

 R^4 is an azido, rhodano or cyano group, R^{10} is a hydrogen atom or a straight-chain or branched C_1 - C_4 alkyl group, R^{20} and R^{20a} are, independently of one another, a hydrogen atom, a straight-chain or branched C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, orone of radicals R^{20} and R^{20a} is a hydrogen atom, a straight-chain or branched C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, and the other radical is a halogen atom or a pseudohalogen.

14. A pharmaceutical composition comprising at least one 17-methylene steroid according to claim 1 and a pharmaceutically compatible adjuvant or vehicle.

15. A pharmaceutical composition comprising at least one 17-methylene steroid according to claim 9 and a pharmaceutically compatible adjuvant or vehicle.

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16. A pharmaceutical composition comprising at least one 17-methylene steroid according to claim 10 and a pharmaceutically compatible adjuvant or vehicle.

17. A pharmaceutical composition comprising at least one 17-methylene steroid according to claim 11 and a pharmaceutically compatible adjuvant or vehicle.

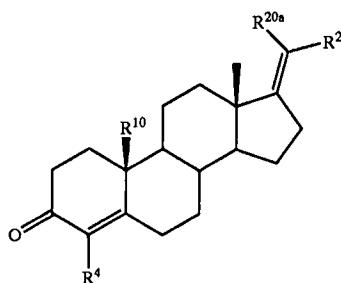
18. A pharmaceutical composition comprising at least one 17-methylene steroid according to claim 5 and a pharmaceutically compatible adjuvant or vehicle.

19. A method of treating a prostate disease comprising administering to a patient in need thereof an effective amount of a compound according to claim 5 or a pharmaceutical composition comprising said effective amount of said compound and a pharmaceutical compatible adjuvant or vehicle.

20. A method of effecting contraception in a man or in a woman comprising administering to a patient in need thereof an effective amount of a compound according to claim 5 or a pharmaceutical composition comprising said effective amount of said compound and a pharmaceutical compatible adjuvant or vehicle.

21. A method inhibiting 5 α -reductase comprising administering to a patient in need thereof an effective amount of a compound according to claim 5.22. A 17-Methylene steroid according to claim 1, wherein R^4 is a halogen atom.23. A 17-Methylene steroid according to claim 1, wherein R^4 is an azido, rhodano or cyano group.24. A 17-Methylene steroid according to claim 1, wherein R^4 is a cyano group.

25. A 17-Methylene steroid of formula I



in which

 R^4 is a halogen atom or a pseudohalogen, R^{10} is a hydrogen atom or a straight-chain or branched C_1 - C_4 alkyl group,one of R^{20} or R^{20a} is a hydrogen atom, a straight-chain or branched C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, and the other of R^{20} or R^{20a} is a straight-chain or branched C_{1-4} alkyl, a hydroxy- C_{1-4} alkyl group, a halogen atom or a pseudohalogen.

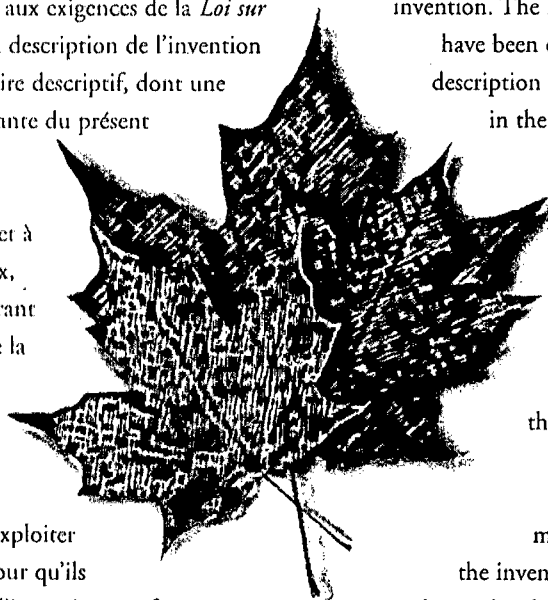
* * * * *

18 301

Brevet canadien / Canadian Patent

✳ Le commissaire aux brevets a reçu une demande de délivrance de brevet visant une invention. Ladite requête satisfait aux exigences de la *Loi sur les brevets*. Le titre et la description de l'invention figurent dans le mémoire descriptif, dont une copie fait partie intégrante du présent document.

Le présent brevet confère à son titulaire et à ses représentants légaux, pour une période expirant vingt ans à compter de la date du dépôt de la demande au Canada, le droit, la faculté et le privilège exclusif de fabriquer, construire, exploiter et vendre à d'autres, pour qu'ils l'exploitent, l'objet de l'invention, sauf jugement en l'espèce rendu par un tribunal compétent, et sous réserve du paiement des taxes périodiques.



✳ The Commissioner of Patents has received a petition for the grant of a patent for an invention. The requirements of the *Patent Act* have been complied with. The title and a description of the invention are contained in the specification, a copy of which forms an integral part of this document.

The present patent grants to its owner and to the legal representatives of its owner, for a term which expires twenty years from the filing date of the application in Canada, the exclusive right, privilege and liberty of making, constructing and using the invention and selling it to others to be used, subject to adjudication before any court of competent jurisdiction, and subject to the payment of maintenance fees.

B R E V E T C A N A D I E N

2,421,302

C A N A D I A N P A T E N T

Date à laquelle le brevet a été
accordé et délivré

2007/08/14

Date on which the patent
was granted and issued

Date du dépôt de la demande

2001/08/29

Filing date of the application

Date à laquelle la demande est
devenue accessible au public
pour consultation

2003/03/03

Date on which the application
was made available for
public inspection

Commissaire aux brevets / Commissioner of Patents

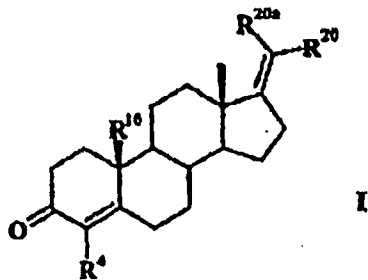
Canada

3256 (CIPO 91) 07-06

OPIC  CIPO

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A 17-methylenesteroid of the general formula I:



wherein:

R^4 is a halogen atom or a pseudohalogen;

R^{10} is a hydrogen atom or a straight-chain or branched C_{1-4} -alkyl group;

R^{20} and R^{20a} are, independently of one another, a hydrogen atom, a straight-chain or branched C_{1-4} -alkyl or hydroxy- C_{1-4} -alkyl group; or

one of the radicals R^{20} and R^{20a} is a hydrogen atom, a straight-chain or branched C_{1-4} -alkyl or hydroxy- C_{1-4} -alkyl group, and the other radical is a halogen atom or a pseudohalogen;

with the exception of the following compounds:

4-chloro-17-methylene-4-androsten-3-one and
4-chloro-20 ξ -fluoro-21-hydroxypregna-4,17(20)-dien-3-one.

2. A 17-methylenesteroid according to claim 1, wherein R^4 is a chlorine or bromine atom or a cyano group.

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3. A 17-methylenesteroid according to claim 1 or 2, wherein one of the radicals R^{20} and R^{20a} is a hydrogen atom or a methyl group, and the other radical is a fluorine, chlorine or bromine atom, an azido, cyano or thiocyanato group or hydroxymethyl.

4. A 17-methylenesteroid according to claim 1, 2 or 3, wherein R^{10} is a hydrogen atom or a methyl group.

5. A 17-methylenesteroid according to claim 1, which is:

E-17-chloromethylene-4-chloroestr-4-en-3-one;

E-17-cyanomethylene-4-chloroestr-4-en-3-one;

Z-17-cyanomethylene-4-chloroestr-4-en-3-one;

Z-17-(1')-cyanoethylidene-4-chloroestr-4-en-3-one;

Z-17-ethylidene-4-chloroestr-4-en-3-one;

E-17-ethylidene-4-chloroestr-4-en-3-one;

E-17-bromomethylene-4-chloroestr-4-en-3-one;

Z-17-chloroethylidene-4-chloroestr-4-en-3-one;

Z-17-bromoethylidene-4-chloroestr-4-en-3-one;

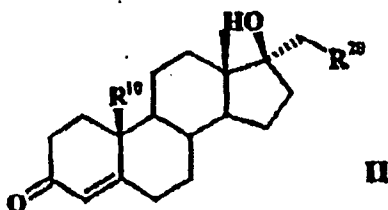
E-17-chloromethylene-4-cyanoandrost-4-en-3-one ;

E-17-chloromethylene-4-chloroandrost-4-en-3-one;

E-17-(2')-hydroxyethylidene-4-chloroestr-4-en-3-one; or

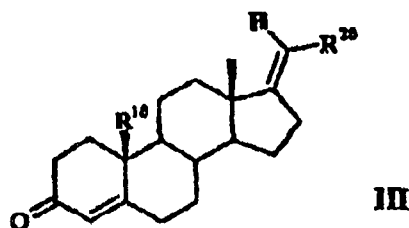
Z-17-(2')-hydroxyethylidene-4-chloroestr-4-en-3-one.

6. A process for preparing a 17-methylenesteroid as defined in claim 1, in which R^{20a} is a hydrogen atom, wherein a compound of the general formula II:

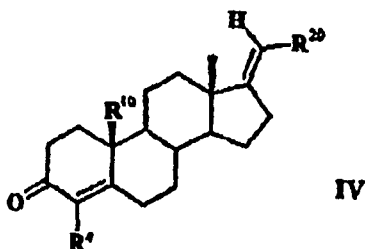


21 304

is reacted in an aprotic solvent with an acid chloride to give a 17-methylenesteroid of the general formula III:



the 4,5-epoxide is generated with $\text{H}_2\text{O}_2/\text{NaOH}$, the latter is then opened with a nucleophilic reagent which is derived from a halogen atom or pseudohalogen, in a dipolar aprotic solvent, to give a halo- or pseudohalohydrin and, where appropriate, reacted with mineral acid, carboxylic acid or sulphonic acid in a protic or aprotic solvent with dehydration to give a compound of the general formula IV:



wherein, in each case:

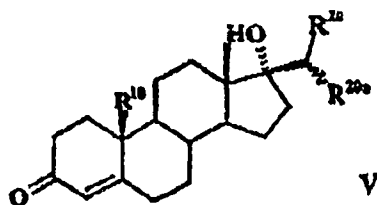
R^4 is a halogen atom or pseudohalogen;

R^{10} is defined in claim 1; and

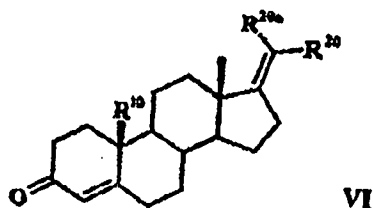
R^{20} is a C_{1-4} -alkyl or hydroxy- C_{1-4} -alkyl group, a halogen atom or a pseudohalogen.

7. A process for preparing a 17-methylenesteroid as defined in claim 1, wherein a compound of the general formula V:

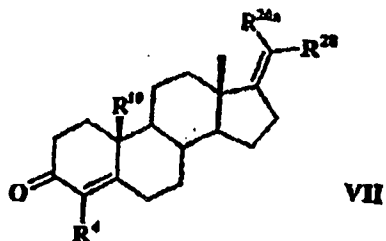
W 305



is reacted with an acid chloride in an aprotic solvent to give a methylenesteroid of the general formula VI:



the 4,5-epoxide is generated with $\text{H}_2\text{O}_2/\text{NaOH}$, the latter is then opened with a nucleophilic reagent which is derived from a halogen atom or pseudohalogen, in a dipolar aprotic solvent, to give a halo- or pseudohalohydrin and, where appropriate, reacted with mineral acid, carboxylic acid or sulphonic acid in a protic or aprotic solvent with dehydration to give a compound of the general formula VII:



wherein, in each case:

R^4 is a halogen atom or pseudohalogen;

R^{10} is defined in claim 1;

R^{20} is a C_{1-4} -alkyl or hydroxy- C_{1-4} -alkyl group; and

R^{20a} is a hydrogen atom, a halogen atom or a pseudohalogen.

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8. A pharmaceutical composition comprising at least one 17-methylenesteroid as defined in any one of claims 1 to 5, together with a pharmaceutically acceptable excipient or carrier.

9. A 17-methylenesteroid as defined in any one of claims 1 to 5 for use as a therapeutic active ingredient.

10. Use of a compound as defined in any one of claims 1 to 5 in the manufacture of a medicament for the treatment of a prostate disorder, male-type alopecia, acne, or hirsutism, for contraception in men or women, or for inhibition of 5 α -reductase.

LETTERS PATENT

Number 524485

ELIZABETH THE SECOND, by the Grace of God Queen of New Zealand and Her Other Realms and Territories, Head of the Commonwealth, Defender of the Faith; To all to whom these presents shall come, Greeting:

WHEREAS pursuant to the Patents Act 1953 an application has been made for a patent of an invention for

4-halogenated 17-methylene steroids, method for the production thereof and pharmaceutical compositions containing these compounds

(more particularly described in the complete specification relating to the application)

AND WHEREAS

SCHERING AKTIENGESELLSCHAFT, Mullerstrasse 178, 13353 Berlin, Germany

(hereinafter together with his or their successors and assigns or any of them called "the patentee") is entitled to be registered as the proprietor of the patent hereinafter granted:

Address for service: HENRY HUGHES, Patent Attorneys, 119-125 Willis Street, Wellington, New Zealand

NOW, THEREFORE, We by these letters patent give and grant to the patentee our special licence, full power, sole privilege, and authority, that the patentee by himself, his agents, or licensees and no others, may subject to the provisions of any statute or regulation for the time being in force make, use, exercise and vend the said invention within New Zealand and its dependencies during a term of twenty years from 29 August 2001 and that the patentee shall have and enjoy the whole profit and advantage from time to time accruing by reason of the said invention during the said term:

AND WE strictly command all our subjects whomsoever within New Zealand and its dependencies that they do not at any time during said term either directly or indirectly make use of or put into practice the said invention, nor in any way imitate the said invention without the consent, licence, or agreement of the patentee in writing under his hand, on pain of incurring such penalties as are prescribed by law and of being answerable to the patentee according to law for his damages thereby occasioned:

PROVIDED ALWAYS:

- (1) That these letters patent shall determine and become void if the patentee does not from time to time pay the renewal fees prescribed by law in respect of the patent:
- (2) That these letters patent are revocable on any of the grounds prescribed by the Patents Act 1953 as grounds for revoking letters patent:
- (3) That nothing in these letters patent shall prevent the granting of licences in the manner in which and for the considerations on which they may by law be granted:
- (4) That these letters patent shall be construed in the most beneficial sense for the advantage of the patentee.

IN WITNESS whereof We have caused these letters patent to be signed and sealed on 9 March 2006 with effect from 29 August 2001.



Neville Harris

Neville Harris
Commissioner of Patents, Trade Marks and Designs



TÍTULO DE PATENTE NO. 248776

Titular(es): SCHERING AG

Domicilio(s): Müllerstrasse 178, D-13353, Berlín, ALEMANIA

Denominación: 17-METILENESTEROIDES 4-HALOGENADOS, METODO PARA SU PRODUCCION Y COMPOSICIONES FARMACEUTICAS QUE CONTIENEN ESTOS COMPUESTOS.

Clasificación: Int.Cl.8: A61K31/56; A61K31/57; A61P5/28; A61P5/34; C07J13/00

Inventor(es): BERND MENZENBACH; WALTER ELGER; PETER DROESCHER; ALEXANDER HILLISCH; GÜNTER KAUFMANN; HANS-UDO SCHWEIKERT; GERD MÜLLER.

SOLICITUD

Número:

PA/a/2003/001912

Fecha de presentación Internacional:

29 de Agosto de 2001

PRIORIDAD

País:

DE

Fecha:

4 de septiembre de 2000

Número:

100 43 846.6

ESTA PATENTE CONCEDE A SU TITULAR EL DERECHO EXCLUSIVO DE EXPLOTACIÓN DEL INVENTO RECLAMADO EN EL CAPÍTULO REIVINDICATORIO Y TIENE UNA VIGENCIA IMPRORROGABLE DE VEINTE AÑOS CONTADOS A PARTIR DE LA FECHA DE PRESENTACIÓN INTERNACIONAL DE LA SOLICITUD.

Fecha de expedición: 7 de septiembre de 2007

EL DIRECTOR DIVISIONAL DE PATENTES

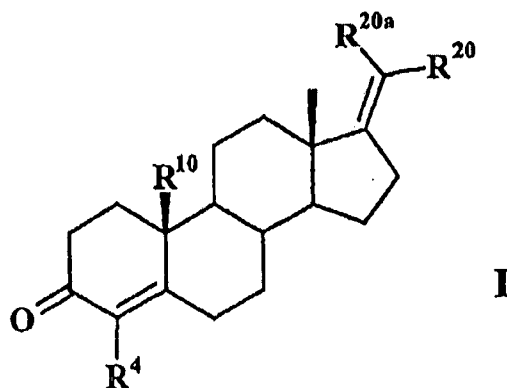
QUÍMICO FABIAN R. SALAZAR GARCÍA



MX/2008/5054

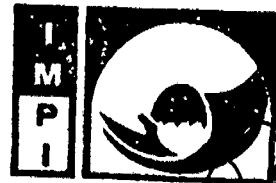
REIVINDICACIONES

1. 17-metilenesteroides de la fórmula general



en la que, R^4 representa un átomo de halógeno o un pseudo-halógeno, R^{10} representa un átomo de hidrógeno o un grupo alquilo- C_{1-4} de cadena recta o ramificada, R^{20} y R^{20a} representan independientes uno de otro un átomo de hidrógeno, un grupo alquilo- C_{1-4} ó hidroxialquilo- C_{1-4} de cadena recta o ramificada, o uno de los radicales R^{20} y R^{20a} significa un átomo de hidrógeno un grupo alquilo- C_{1-4} ó hidroxialquilo- C_{1-4} de cadena recta o ramificada y el otro radical un átomo de halógeno o un pseudo-halógeno, con la excepción de los siguientes compuestos: 4-cloro-17-metilen-4-androsten-3-ona y 4-cloro-20ξ-flúor-21-hidroxipregna-4,17(20)-dien-3-ona.

2. 17-metilenesteroides según la reivindicación 1, caracterizados porque R^4 representa un átomo de cloro o



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bromo o un grupo ciano.

3. 17-metilenesteroides según la reivindicación 1 ó 2, caracterizados porque uno de los radicales R^{20} y R^{21} significa un átomo de hidrógeno o un grupo metilo, y el otro radical un átomo de flúor, cloro o bromo, un grupo azido, ciano o tiocianato, o hidroximetilo.

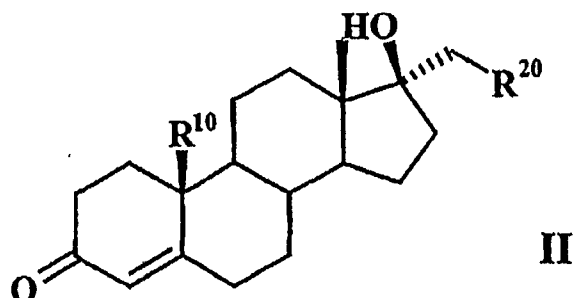
4. 17-metilenesteroides según la reivindicación 1, 2 ó 3, caracterizados porque R^{10} representa un átomo de hidrógeno o un grupo metilo.

5. 17-metilenesteroides según la reivindicación 1, específicamente

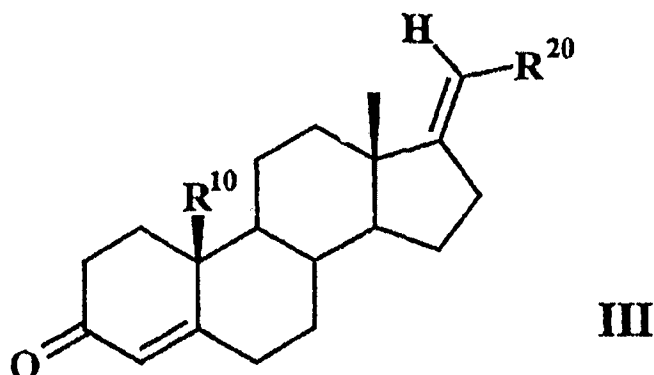
- 1) E-17-clormetilen-4-clor-estr-4-en-3-ona,
- 2) E-17-cianometilen-4-clor-estr-4-en-3-ona,
- 3) Z-17-cianometilen-4-clor-estr-4-en-3-ona,
- 4) Z-17-(1')-cianoetiliden-4-clor-estr-4-en-3-ona,
- 5) Z-17-etiliden-4-clor-estr-4-en-3-ona,
- 6) E-17-etiliden-4-clor-estr-4-en-3-ona,
- 7) E-17-bromometilen-4-clor-estr-4-en-3-ona,
- 8) Z-17-cloretiliden-4-clor-estr-4-en-3-ona,
- 9) Z-17-bromoetiliden-4-clor-estr-4-en-3-ona,
- 10) E-17-clormetilen-4-ciano-androst-4-en-3-ona,
- 11) E-17-clormetilen-4-clor-androst-4-en-3-ona,
- 12) E-17-(2')-hidroxietiliden-4-clor-estr-4-en-3-ona, y
- 13) Z-17-(2')-hidroxietiliden-4-clor-estr-4-en-3-ona.

6. Proceso para la elaboración de 17-

metilenesteroides según la reivindicación 1, en donde R^{20} significa un átomo de hidrógeno, caracterizado porque se hace reaccionar un compuesto de fórmula general II



10 en un disolvente aprótico con un cloruro de ácido, para obtener un 17-metilenesteroide de fórmula general III,

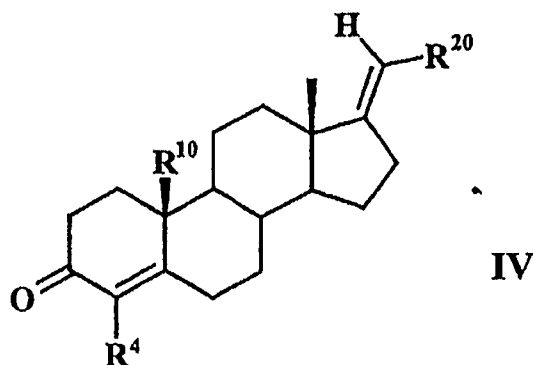


se genera el 4,5-epóxido con $H_2O_2/NaOH$, este se desdobla
 20 entonces en un disolvente dipolar aprótico con un reactivo nucleófilo que se deriva de un átomo de halógeno o respectivamente un pseudohalógeno para obtener una hidrina de halógeno o de pseudohalógeno, y opcionalmente se hace reaccionar con ácido mineral, ácido carbónico o ácido
 25 sulfónico en un disolvente prótico o aprótico con



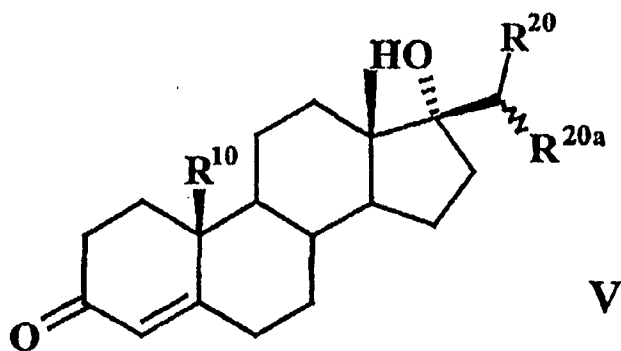
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Industrial

deshidrogenación para obtener un compuesto de fórmula general IV



en la que R^4 representa un átomo de halógeno o un pseudohalógeno, siendo que R^{10} tiene el significado indicado en la reivindicación 1 y R^{20} significa un grupo alquilo- C_{1-4} ó hidroxialquilo- C_{1-4} , un átomo de halógeno o un pseudohalógeno.

7. Proceso para la elaboración de 17-metilenesteroides según la reivindicación 1, caracterizado porque se hace reaccionar un compuesto de fórmula general V

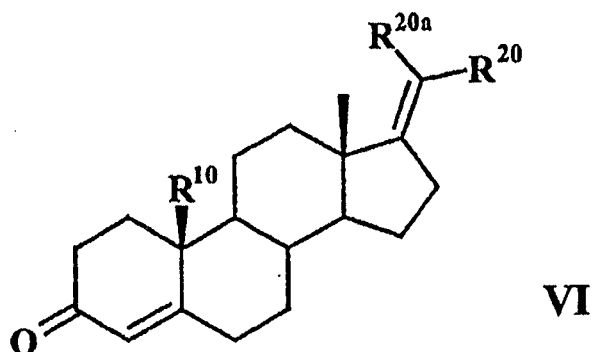


en un disolvente aprótico con un cloruro de ácido, para

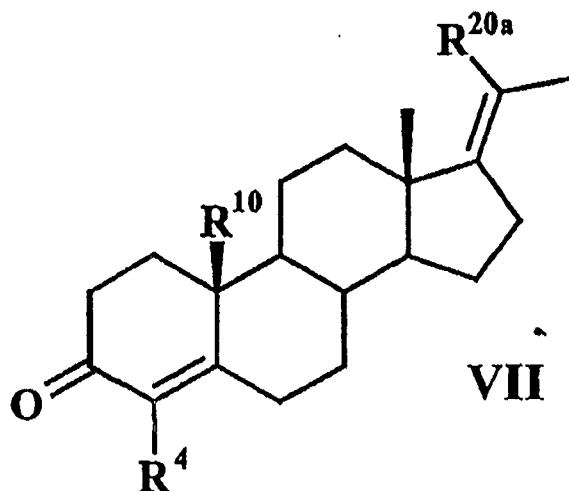


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obtener un metilenesteroide de fórmula general VI



se genera el 4,5-epóxido con $\text{H}_2\text{O}_2/\text{NaOH}$, este se desdobra
 10 entonces en un disolvente dipolar aprótico con un reactivo
 nucleófilo que se deriva de un átomo de halógeno o
 respectivamente un pseudohalógeno para obtener una hidrina de
 halógeno o de pseudohalógeno, y opcionalmente se hace
 reaccionar con ácido mineral, ácido carbónico o ácido
 15 sulfónico en un disolvente prótico o aprótico con
 deshidrogenación para obtener un compuesto de fórmula
 general VII





en la que R^4 representa un átomo de halógeno o un pseudohalógeno, siendo que R^{10} tiene el significado indicado en la reivindicación 1 y R^{20} significa un grupo alquilo-ó hidroxialquilo- C_{1-4} , y R^{20a} significa un átomo de hidrógeno, un átomo de halógeno o un pseudohalógeno.

8. Composiciones farmacéuticas que contienen al menos un 17-metilenesteroide según la reivindicación 1, 2, 3, 4 ó 5, opcionalmente en combinación con coadyuvantes y vehículos farmacéuticamente compatibles.

10 9. 17-metilenesteroides según una de las reivindicaciones 1 a 5 para su uso como principios activos terapéuticos.

15 10. Uso de los compuestos según una de las reivindicaciones 1 a 5 para la elaboración de un medicamento para el tratamiento de enfermedades de la próstata, alopecia del tipo masculino, acné e hirsutismo, para la anticoncepción en el hombre y la mujer y/o para la inhibición de la 5α -reductasa.



Australian Government

IP Australia

LETTERS PATENT

STANDARD PATENT

315
27

2002210470

I, Fatima Beattie, the Commissioner of Patents, grant a Standard Patent with the following particulars:

Name and Address of Patentee(s):

Schering AG
Mullerstrasse 178, Berlin, 13353, Germany

Name of Actual Inventor(s):

Droescher, Peter; Schweikert, Hans-Udo; Menzenbach, Bernd; Hillisch, Alexander; Elger, Walter;
Muller, Gerd and Kaufmann, Gunter.

Title of Invention:

4-halogenated 17-methylene steroids, method for the production thereof and pharmaceutical compositions containing these compounds

Term of Letters Patent:

Twenty years from 29 August 2001

Priority Details :

Number

100 43 846.6

Date

4 September 2000

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DE



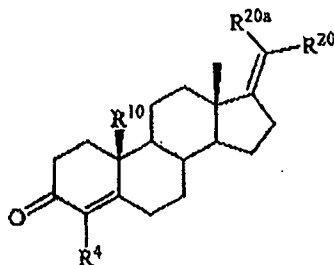
Dated this 2nd day of November 2006

PATENTS ACT 1990

Fatima Beattie
Commissioner of Patents

The claims defining the invention are as follows:

1. 17-Methylene steroids of the general formula I



in which

R^4 is a halogen atom or a pseudohalogen,

R^{10} is a hydrogen atom or a straight-chain or branched C_{1-4} -alkyl group,

R^{20} and R^{20a} are, independently of one another, a hydrogen atom, a straight-chain or branched C_{1-4} -alkyl or hydroxy- C_{1-4} -alkyl group or

one of the radicals R^{20} and R^{20a} is a hydrogen atom, a straight-chain or branched C_{1-4} -alkyl or hydroxy- C_{1-4} -alkyl group, and the other radical is a halogen atom or a pseudohalogen with the

proviso that the following compounds:

4-chloro-17-methylene-4-androsten-3-one and 4-

chloro-20 β -fluoro-21-hydroxypregna-4,17(20)-dien-3-one

are specifically disclaimed.

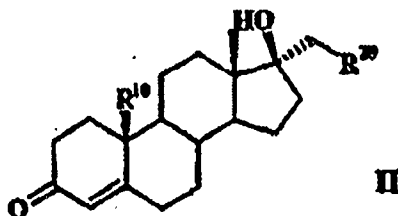
2. 17-Methylene steroids as claimed in claim 1, characterized in that R^4 is a chlorine or bromine atom or a cyano group.
3. 17-Methylene steroids as claimed in claim 1 or 2, characterized in that one of the radicals R^{20} and R^{20a} is a hydrogen atom or a methyl group, and the other radical is a fluorine, chlorine or bromine atom, an azido, cyano or thiocyanato group or hydroxymethyl.
4. 17-Methylene steroids as claimed in claim 1, 2 or 3, characterized in that R^{10} is a hydrogen atom or a methyl group.

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5. 17-Methylene steroids as claimed in claim 1, namely

- 5 15) E-17-chloromethylene-4-chloroestr-4-en-3-one,
16) E-17-cyanomethylene-4-chloroestr-4-en-3-one,
17) Z-17-cyanomethylene-4-chloroestr-4-en-3-one,
18) Z-17-(1')-cyanoethylidene-4-chloroestr-4-en-3-one,
10 19) Z-17-ethylidene-4-chloroestr-4-en-3-one,
20) E-17-ethylidene-4-chloroestr-4-en-3-one,
21) E-17-bromomethylene-4-chloroestr-4-en-3-one,
22) Z-17-chloroethylidene-4-chloroestr-4-en-3-one,
15 23) Z-17-bromoethylidene-4-chloroestr-4-en-3-one,
24) E-17-chloromethylene-4-cyanoandrost-4-en-3-one,
25) E-17-chloromethylene-4-chloroandrost-4-en-3-one,
20 26) E-17-(2')-hydroxyethylidene-4-chloroestr-4-en-3-one and
27) Z-17-(2')-hydroxyethylidene-4-chloroestr-4-en-3-one.

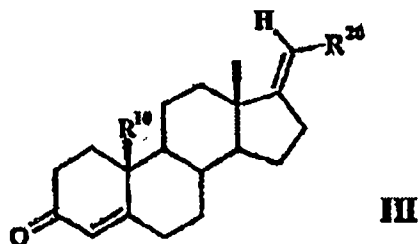
25 6. A process for preparing 17-methylene steroids as claimed in claim 1, in which R^{20a} is a hydrogen atom, characterized in that a compound of the general formula II



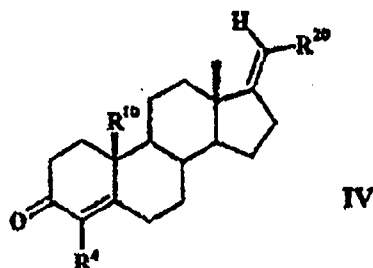
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is reacted in an aprotic solvent with an acid chloride to give a 17-methylene steroid of the general formula III,

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5 the 4,5-epoxide is generated with $H_2O_2/NaOH$, the
latter is then opened with a nucleophilic reagent
which is derived from a halogen atom or pseudo-
halogen, in a dipolar aprotic solvent, to give a
halo- or pseudohalohydrin and, where appropriate,
10 reacted with mineral acid, carboxylic acid or
sulfonic acid in a protic or aprotic solvent with
dehydration to give a compound of the general
formula IV, in which



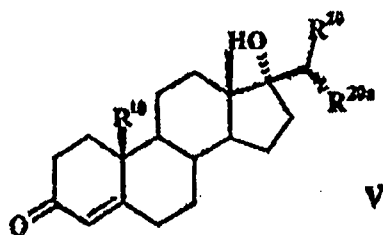
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R^4 is a halogen atom or pseudohalogen, where R^{10}
has the meaning given in claim 1, and R^{20} is a C_{1-4} -
alkyl or hydroxy- C_{1-4} -alkyl group, a halogen atom
or a pseudohalogen.

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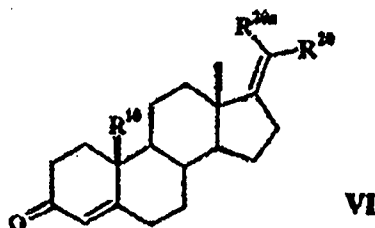
7. A process for preparing 17-methylene steroids as
claimed in claim 1, characterized in that a
compound of the general formula V

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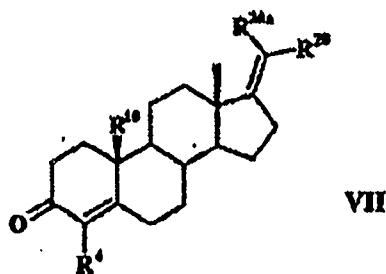
is reacted with an acid chloride in an aprotic solvent to give a methylene steroid of the general formula VI,



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the 4,5-epoxide is generated with H₂O₂/NaOH, the latter is then opened with a nucleophilic reagent which is derived from a halogen atom or pseudo-halogen, in a dipolar aprotic solvent, to give a halo- or pseudohalohydrin and, where appropriate, reacted with mineral acid, carboxylic acid or sulfonic acid in a protic or aprotic solvent with dehydration to give a compound of the general formula VII

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in which R⁴ is a halogen atom or pseudohalogen, where R¹⁰ has the meaning given in claim 1, and R²⁰ is a C₁₋₄-alkyl or hydroxy-C₁₋₄-alkyl group, and R^{20a}

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is a hydrogen atom, a halogen atom or a pseudohalogen.

8. Pharmaceutical compositions comprising at least one 17-methylene steroid as claimed in claim 1, 2, 3, 4 or 5, where appropriate together with pharmaceutically acceptable excipients and carriers.
9. 17-Methylene steroids as claimed in any one of claims 1 to 5 for use as therapeutic active ingredients.
10. The use of the compounds as claimed in any one of claims 1 to 5 for the treatment of prostate disorders, male-type alopecia, acne and hirsutism, for contraception in men and women and/or for inhibition of 5 α -reductase.

DATED this 29th day of June 2006

SCHERING AG

By its Patent Attorneys

DAVIES COLLISON CAVE

U

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets

(11)

EP 1 423 407 B1

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EUROPÄISCHE PATENTSCHRIFT

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(54) **4-HALOGENIERTE 17-METHYLENSTEROIDE, VERFAHREN ZU DEREN HERSTELLUNG UND
DIESE VERBINDUNGEN ENTHALTENDE PHARMAZEUTISCHE ZUSAMMENSETZUNGEN**

4-HALOGENATED 17-METHYLENE STEROIDS, METHOD FOR THE PRODUCTION THEREOF
AND PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS

4-HALOGENES STEROIDES DE 17-METHYLENE, PROCEDE PERMETTANT DE LES PRODUIRE
ET COMPOSITIONS PHARMACEUTIQUES CONTENANT CES COMPOSES

(84) Benannte Vertragsstaaten:

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MC NL PT SE TR

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(30) Priorität: 04.09.2000 DE 10043846

(43) Veröffentlichungstag der Anmeldung:

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(56) Entgegenhaltungen:

EP-A- 0 077 040

WO-A-02/00681

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US-A- 3 146 239

US-A- 3 232 960

US-A- 3 661 940

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- CHEMICAL ABSTRACTS, vol. 62, no. 10, 10. Mai 1965 (1965-05-10) Columbus, Ohio, US; abstract no. 11871e, K. BARNIKOL-OETTLER ET AL: "Wittig reaction of steroid ketones" XP002187567 & J. PRAKT CHEM., Bd. 27, Nr. 1-2, 1965, Seiten 18-33,
- DATABASE CA[Online]CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; JARMAN, MICHAEL ET AL: "Evaluation of some 4-fluoro- and 4-cyano derivatives of DELTA.4, 3-ketosteroids as inhibitors of testosterone 5.alpha.-reductase" retrieved from STN Database accession no. 122:1349 XP002187568 & J. ENZYME INHIB. (1994), 8(1), 17-23 ,
- M. CABEZA ET AL: "Synthesis and Pharmacological Evaluation of 4-Halo Progesterone Derivatives as Antlandrogen" CHEMICAL AND PHARMACEUTICAL BULLETIN, Bd. 47, Nr. 9, September 1999 (1999-09), Seiten 1232-1236, XP002187564 TOKYO JP

Anmerkung: Innerhalb von neun Monaten nach der Bekanntmachung des Hinweises auf die Erteilung des europäischen Patents kann jedermann beim Europäischen Patentamt gegen das erteilte europäische Patent Einspruch einlegen. Der Einspruch ist schriftlich einzureichen und zu begründen. Er gilt erst als eingelegt, wenn die Einspruchsgebühr entrichtet worden ist. (Art. 99(1) Europäisches Patentübereinkommen).

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

Radicación No. 03-018359

**Clasificación Internacional (IPC): A61K31/569; A61K31/57; C07J13/00;
C07J17/00**

Concepto Técnico No: 0282

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

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

No. Sol. Internacional PCT/EP01/09943

Fecha de Presentación Internal. 29 de Agosto de 2001

Como resultado del examen de fondo, realizado con fundamento en el artículo 48 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios: 32 a 86 y 93 como se radicó inicialmente

Reivindicaciones: Folios 87 a 92 como se radicó inicialmente
Folios 202 a 207 modificadas
Folios 231 a 235 modificadas
Folios 288 a 291 modificadas

Prioridad: Folios: 133 a 157
04 de Septiembre de 2000, DE, 10043846.6

Respuesta del solicitante: Folios: 227 a 230; Folios 255 a 260; Folios 284 a 287

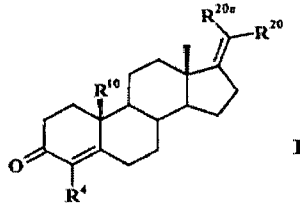
2. Análisis de la Prioridad

La fecha de prioridad del 04 de Septiembre de 2000 y su correspondiente documento, son aceptados para el estudio de patentabilidad.

3. Objeto de la invención

Título de la solicitud: **"17-METILEN ESTEROIDES 4 HALOGENADOS, MÉTODO PARA SU PREPARACIÓN Y COMPOSICIONES FARMACÉUTICAS QUE CONTIENEN ESTOS COMPUESTOS"** Folio 1.

El objeto de la presente solicitud de patente de invención consiste en compuestos de fórmula I:



El problema planteado en esta solicitud es obtener compuestos inhibidores de la 5 α -reductasa que actúan al mismo tiempo como gestágeno; y que en combinación con otras sustancias hormonales tales como estrógeno, testosterona o un andrógeno fuerte son útiles como contraceptivos femeninos y masculinos.

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos 17-metilen esteroides de fórmula I

Clasificación Internacional de Patentes (IPC): A61K31/569; A61K31/57; C07J13/00; C07J17/00

4. De la solicitud de Patente

Descripción (artículo 28 D. 486)

La descripción cumple con el requisito de claridad o comprensión de acuerdo al art. 28 de la Decisión 486.

Reivindicaciones (artículo 30 D 486)

Realizadas las modificaciones por el solicitante al capítulo reivindicatorio, se encuentra que es claro y conciso y está lo suficientemente sustentado por la descripción, cumpliendo con el requisito de claridad, concisión y sustento en la descripción de acuerdo al art. 30 de la Decisión 486.

5. Unidad de invención (artículo 25 D 486)

La solicitud presentada cumple con el requisito de unidad de invención.

6. No es una invención (artículo 15 D 486 literal a)-f))

El capítulo reivindicatorio presentado por el solicitante corresponde a una invención.

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

El capítulo reivindicatorio presentado por el solicitante, es patentable.

8. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

El capítulo reivindicatorio presentado por el solicitante, es patentable.

9. Análisis de la(s) Oposición(es): (artículo 43 D. 486):

No se presentaron oposiciones durante el estudio de patentabilidad de la solicitud presentada

10. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

- Fecha de presentación de la solicitud prioritaria: 04 de Septiembre de 2000

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 04/09/2000, no se encontraron documentos que divulguen los compuestos de la solicitud presentada

11. Análisis de patentabilidad (artículo 14 D486)

Novedad (artículo 16 D486)

Los compuestos presentados en la solicitud se consideran novedosos de acuerdo con las enseñanzas del estado de la técnica.

Nivel Inventivo (Art18 D486)

No se encontró dentro del estado de la técnica, tal como lo estipulado en el numeral 10, documento alguno que afecte el nivel inventivo.

La solicitud presentada posee nivel inventivo pues el solicitante resuelve el problema de obtener compuestos inhibidores de la 5 α -reductasa que actúan al mismo tiempo como gestágeno; reemplazando un átomo de hidrógeno por un átomo de halógeno o por un grupo alquilo en un compuesto con el anillo esteroide, siendo estas sustituciones no obvias para el experto en la materia.

El problema técnico planteado en esta solicitud como es “**obtener compuestos inhibidores de la 5 α -reductasa que actúan al mismo tiempo como gestágeno**” no sería solucionado fácilmente por el Experto en la Materia y queda plenamente resuelto en la solicitud presentada, demostrando que posee nivel inventivo de acuerdo con el artículo 18 de la Decisión 486.

12. Conclusión:

En consecuencia y por todo lo expuesto anteriormente, se recomienda **Conceder** la reivindicación: 1 a 8 (folios: 288-291).

Bogotá, D.C.,

CONCEPTO TÉCNICO No. 0282	EXAMINADOR TÉCNICO Código No. 202070
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