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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

Referencia : Expediente No. **00.025.244**

Solicitante : **AKZO NOBEL N.V.**

Asunto : Solicitud de patente para: **"NUEVOS ANDROGENOS ORALMENTE ACTIVOS DERIVADOS DE 7α-METIL-19-NORTESTOSTERONA"**

Fecha de solicitud : 6 de abril de 2000

TRAMITE 002 EVENTO 001 ACTUACION 009

1. Yo, Emilio FERRERO, obrando como apoderado de la solicitud en referencia, atentamente, presento con este escrito la copia certificada de la solicitud de patente europea No. 99201070.2 del 6 de abril de 1999, junto con la traducción de sus reivindicaciones y certificaciones de la cual se reclama prioridad en esta solicitud de patente.

2. Ruego a la Señora Jefe se sirva aceptar este escrito con sus anexos, y se continúe con el trámite de la solicitud.

Bogotá, - 6 JUL. 2000
Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

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Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

99201070.2

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.: 99201070.2
Demande n°:

Anmeldetag:
Date of filing: 06/04/99
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Anmelder:
Applicant(s):
Demandeur(s):
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Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Orally active 7.alpha.-alkyl androgens

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

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The original title of the application reads as follows: Orally active androgens.

ORALLY ACTIVE ANDROGENS

The invention is in the field of androgenic hormones, more specifically derivatives of 19-nortestosterone.

Testosterone derivatives are known. As a medicine testosterone itself, the natural male hormone, has many known drawbacks as far as methods of administration are concerned. It has a short-lasting activity, is insoluble in the usual pharmaceutically acceptable media, and is not very potent. The more potent dihydrotestosterone (5α-reduced form of testosterone) is considered a health-risk, notably for the prostate.

A more potent androgen is 7α-methyl-19-nortestosterone (MENT) disclosed in FR 4,521 M and US 5,342,834. An important drawback of MENT, however, is its unfavourable kinetics which limits its use as an orally active androgen.

In the field of pharmaceutical preparations in general it is a common desire for a medicinal agent to be orally active. Oral dosage forms, *e.g.* solid dosage forms such as tablets and capsules, are among the most widely accepted forms of administration. In the field of androgens, a particular desire exists for the oral administration in connection with a utility such as male contraception. Since in the area of female contraception the word "pill" has almost become a synonym for reliable birth-control, it is evident that also in the case of male contraception oral activity is desired, so as to enable providing a male "pill."

Several, mostly very old publications can be mentioned which form the background-art relating to groups of steroid compounds which include 19-nortestosterone derivatives. None of these references teaches orally active androgens.

Thus, in FR 1,432,561, published in 1966, 19-nortestosterones like MENT having an alkyl substituent at C-7 are employed as a starting material for hormonal agents having a double bond between carbon atoms 5 and 6. Alkyl groups other than methyl are not disclosed.

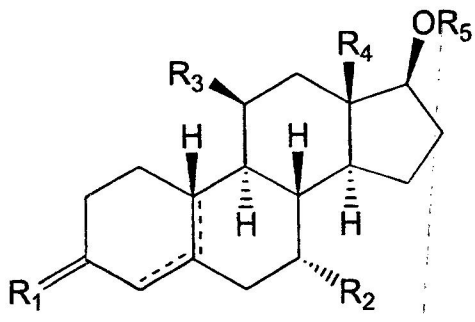
BE 861 224 concerns all possible esters of a wide variety of 17-hydroxysteroids. The disclosure, which dates from 1976, specifically teaches that certain esters are desired for prolonged activity of the steroids. Among the large group of steroids disclosed are oestrogens, anti-oestrogens, androgens and anabolics. A great many possible substituents at various positions is given, among which are methyl and ethyl at C-7.

Chemical Abstracts 110: 95601y (1989) refers to a 17-hydroxy acetate of 7-allyl-19-nortestosterone as an intermediate in the synthesis of 7-allyloestradiol.

EP 159 739 teaches immunomodulating agents of the oestrane series, including particularly Δ^4- and $\Delta^{5(10)}$-oestrene derivatives having an alkyl substituent in position 6 or 7. Said alkyl substituent typically is methyl.

DE 20 43 404 concerns 7β-steroids which have anti-hormonal activities. The alkyl substituent mostly is methyl, but ethyl and propyl are disclosed as well. In the synthesis of 7β-ethyl-19-nortestosterone, which is a compound according to the teaching of DE 20 43 404, the 7α-isomer is formed as well. It is not taught to use this isomer for anything, and the teaching of this document does not distinguish the ethyl or propyl substituents from the methyl moiety.

It is an object of the invention to provide orally active androgens. A further object of the invention is to provide androgens which in general have a desirable high potency. According to the invention, these and other objectives are achieved by compounds satisfying the general formula I given below.



Formula I

wherein

R_1 is O, (H,H), (H,OR), NOR, with R being hydrogen, (C_{1-6}) alkyl, or (C_{1-6}) acyl;

R_2 is (C_{2-3}) alkyl, isopropyl, (C_{2-3}) 1-alkenyl, isopropenyl, 1,2-propadienyl, or (C_{2-3}) 1-alkynyl, each optionally substituted by halogen; or R_2 is cyclopropyl, or cyclopropenyl, each optionally substituted by (C_{1-2}) alkyl or halogen;

R_3 is hydrogen, (C_{1-2}) alkyl, or ethenyl;

R_4 is (C_{1-2}) alkyl;

R_5 is hydrogen, or (C_{1-15}) acyl;

and the dotted lines indicate optional bonds;

with the proviso that the compound is not (7α)-7-ethyl-17-hydroxyestr-4-en-3-one (7α-ethyl-19-nortestosterone) or a carboxylic ester thereof.

The term (C_{1-6}) alkyl as used in the definition of formula I means a branched or unbranched alkyl group having 1-6 carbon atoms, like methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, and hexyl. Likewise, the term (C_{1-2}) alkyl means an alkyl group having 1-2 carbon atoms and the term (C_{2-3}) alkyl an alkyl group having 2-3 carbon atoms.

The term (C_{2-3}) alkenyl means an alkenyl group having 2-3 carbon atoms. Preferred is ethenyl.

The term (C_{2-3}) alkynyl means an alkynyl group having 2-3 carbon atoms. Preferred is ethynyl.

The term (C_{1-6}) acyl means an acyl group derived from a carboxylic acid having from 1-6 carbon atoms, like formyl, acetyl, propanoyl, butyryl, 2-methylpropanoyl, pentanoyl, pivaloyl, and hexanoyl. Likewise, the term (C_{1-15}) acyl means an acyl group derived from a carboxylic acid having from 1-15 carbon atoms. Also included within the definition of (C_{1-15}) acyl are

[(C_{3-6}) cycloalkyl]carbonyl,

[(C_{5-6}) cycloalkenyl]carbonyl,

benzoyl,
[[(C_{1-12}) alkyl](C_{3-6}) cycloalkyl]carbonyl,
[[(C_{2-12}) alkenyl](C_{3-6}) cycloalkyl]carbonyl],
[[(C_{2-12}) alkynyl](C_{3-6}) cycloalkyl]carbonyl],
[[(C_{1-10}) alkyl](C_{5-6}) cycloalkenyl]carbonyl],
[[(C_{2-10}) alkenyl](C_{5-6}) cycloalkenyl]carbonyl],
[[(C_{2-10}) alkynyl](C_{5-6}) cycloalkenyl]carbonyl],
(C_{1-9}) alkylbenzoyl,
(C_{2-9}) alkenylbenzoyl,
(C_{2-9}) alkynylbenzoyl.

Also included within the definition of (C_{1-6}) acyl or (C_{1-15}) acyl are acyl groups derived from dicarboxylic acids, like hemi-maloyl, hemi-succinoyl, hemi-glutaroyl, and so on. Preferred is hemi-succinoyl.

The term halogen means fluorine, chlorine, bromine, or iodine. When halogen is a substituent at an alkyl group, Cl and F are preferred, F being most preferred.

It is understood that the 7α-substituted nandrolone derivatives of the invention have the natural configurations 5α, 8β, 9α, 10β, 13β, 14α, 17β.

The 7α-substituted nandrolone derivatives of this invention have the natural configurations 5α, 8β, 9α, 10β, 13β, 14α and 17β, and possess also one or more additional chiral carbon atoms. The compounds may therefore be obtained as a pure diastereomer, or as a mixture of diastereomers. Methods for obtaining the pure diastereomers are well known in the art, *e.g.* crystallization or chromatography.

Unlike the known compound (MENT), which possesses a 7α-methyl substituent, the compounds of formula I, which can be referred to as 7α-substituted nandrolones, surprisingly have sufficient androgenic potency upon oral administration. None of the above, mostly very old references teaches orally active androgens, let alone that they provide the person skilled in the art with a clue to distinguish any other substituent at C-7 from the widely used methyl moiety.

The compounds according to the above formula are novel, with the exception of the aforementioned 7α-ethyl-19-nortestosterone, which is incidentally known as a by-product in synthesis. The compound is novel as a medicine in general, as an androgen, and more particularly as an orally active androgen.

Preferred compounds of the invention have R_2 selected from the group consisting of ethyl, ethenyl, ethynyl, propyl, 1-propenyl, 1-propynyl, 1,2-propadienyl, and cyclopropyl.
Even more preferred are compounds in which R_1 is oxo, R_3 is hydrogen, R_4 is methyl, and the dotted lines indicate a Δ^4 double bond.
Most preferred are those compounds in which R_2 is C_2, with the highest preference being ethyl or ethenyl.

The invention also pertains to the compounds described hereinbefore as a medicine. The 7α-substituted nandrolones of the present invention being potent androgens, they can be used in, int.al., male contraception and male or female hormone replacement therapy. Thus the invention also pertains to a method of treatment of androgen insufficiency, by administering to a human male or female an effective amount of any of the above compounds. The invention also is in the use of any of the above compounds for the preparation of a medicine for treating androgen insufficiency. In the context of the invention, the term "androgen insufficiency" is to be understood to pertain to all kinds of diseases, disorders, and symptoms in which a male or a female suffers from too low a testosterone level, such as in hypogonadal men. In particular, the androgen insufficiency to be treated by the compound of the invention is the reduction of the testosterone level which a human male incurs as a result of age (the compound of the invention is then used for male hormone replacement therapy), or when he is subject to male contraception. In the context of male contraception, the compound of the invention especially serves to neutralise the effect of regimens of male hormone contraception in which a sterilitant such as a progestagen or LHRH (luteinizing hormone releasing hormone) is administered regularly, *e.g.* daily, or it is used as the sole male contraceptive substance.

The androgens can be administered principally via any suitable route available to the skilled person. As indicated above, oral administration is preferred, most preferably in the form of a solid dosage unit such as a tablet or a capsule. The invention also relates to pharmaceutical formulations comprising a compound as described hereinbefore and a pharmaceutically acceptable carrier. Thus the carrier may be in a solid form or liquid form, and the formulation may be an oral dosage unit such as a tablet or an oral solution, *e.g.* in a capsule. Methods and compositions for making such dosage units are well-known to those skilled in the art. For example, conventional techniques for making tablets and pills, containing active ingredients, are described in the standard reference, Gennaro *et al*, Remington 's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture). The compound can also be administered via an implant, a patch, or any other suitable device for the sustained release of an androgen composition.

The dose of and regimen of administration of the compounds of the invention, or a pharmaceutical composition thereof, to be administered will obviously depend on the therapeutic effect to be achieved and will vary with the route of administration, and the age and condition of the individual subject to whom the medicament is to be administered, and/or or the particular contraceptive or HRT regimen in which it is used. Typical dosage amounts are 0.001-5 mg per kg body weight.

The compounds of the invention may be produced by various methods known in the art of organic chemistry in general, and especially in the art of the chemistry of steroids (see, for example: Fried, J. *et al*, *Organic Reactions in Steroid Chemistry*, Volumes I and II, Van Nostrand Reinhold Company, New York, 1972).

Essential is the introduction of a saturated or unsaturated 7α-substituent, optionally substituted by halogen, onto the steroid nucleus.

For 7α-substitution, several methodologies are known in the art, among others:

1) - Conjugate addition (1,6-addition) of organocopper reagents to suitably substituted (17β)-17-hydroxyestra-4,6-dien-3-one derivatives, in which the 17-hydroxy group is protected as an ester, *e.g.* an acetate ester or a benzoate ester, or as an alkoxyalkyl ether, *e.g.* an ethoxyethyl ether or a tetrahydropyranyl ether, or as a silyl ether, *e.g.* a trimethylsilyl ether or

a *t*-butyldimethylsilyl ether [for conjugate additions of organocopper reagents, see Lipshutz, B.H. *et al* in Org. Reactions 41, p. 135, Wiley, New York, 1992].

2) - Transition metal-mediated ($TiCl_4$, $AlCl_3$, $ZrCl_4$, etc.) reaction of an organosilicon compound with a (17β)-17-hydroxyestra-4,6-dien-3-one derivative as described above [again formal 1,6-addition; see *e.g.* Nickisch, K. *et al*, Tetrahedron Lett. 29, 1533 (1988)].

3) - Base-catalyzed conjugate addition (1,6-addition) of a dialkyl malonate or alkyl cyanoacetate to a (17β)-17-hydroxyestra-4,6-dien-3-one derivative as described above [see *e.g.* Cruz, R. *et al*, Austr. J. Chem. 35, 451 (1982)].

4) - Lewis acid-catalyzed reaction of an estra-1,3,5(10),7-tetraene derivative with an aldehyde (Prins reaction), resulting in an estra-1,3,5(10),8-tetraene-7-alkanol derivative [see: Kuenzer, H. *et al*, Tetrahedron Lett. 32, 743 (1991)].

5) - Alkylation at C-7 of an estra-1,3,5(10)-trien-6-one derivative [see: *e.g.* Tedesco, R. *et al*, Tetrahedron Lett. 38, 7997 (1997)].

6) - Conjugate addition (1,4-addition) of a suitable nucleophilic reagent (*e.g.* an organocopper reagent) to a 6-[alkyl(or aryl)sulfonyl]estra-1,3,5(10),6-tetraen derivative [Schering AG, DE 42 18 743 A 1].

Using these methodologies, the compounds of the invention can further be prepared using standard methods known in the art.

The invention will be further explained hereinafter with reference to the following Examples.

Example 1

(7α,17β)-7-Ethyl-17-hydroxyestr-4-en-3-one.

i) - A mixture of lithium (0.647 g) and dry diethyl ether (26 ml) was cooled to -30 °C. Bromoethane (3.45 ml) was added dropwise while maintaining the temperature below -25 °C. After 30 min. stirring at -30 °C the solution of ethyllithium was added dropwise to a suspension of copper(I) iodide (4.0 g) in dry tetrahydrofuran (40 ml), cooled to -40 °C. The resulting cuprate solution was stirred at -30 °C for 30 min. and a solution of (17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]estra-4,6-diene-3-one [Nickisch, K. *et al*, Tetrahedron Lett. 29, 1533 (1988); 2.5 g] in dry tetrahydrofuran (20 ml) was added dropwise. Stirring was

continued at -30 °C for 30 min., chlorotrimethylsilane (2.58 ml) was added and stirring was continued for another 30 min. The reaction mixture was poured into a mixture of a saturated aqueous solution of ammonium chloride and concentrated ammonia (9:1). The product was extracted into ethyl acetate; the combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate, water, and brine, dried over magnesium sulfate and concentrated under reduced pressure, to give (7α,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-ethyl-3-[(trimethylsilyl)oxy]estra-3,5-diene (2.81 g). The product was used in the following step without further purification.

ii) - A solution of the diene obtained in the previous step (2.81 g) in acetone (60 ml) was treated with hydrochloric acid (6 M, 6.0 ml). After 1 h stirring at room temperature, the reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogencarbonate. The product was extracted into ethyl acetate; the combined organic phases were washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography and crystallization afforded (7α,17β)-7-ethyl-17-hydroxyestr-4-en-3-one (0.556 g), m.p. 142.5-143.5 °C.

Example 2

(7α,17β)-17-Hydroxy-7-propylestr-4-en-3-one.

(7α,17β)-17-Hydroxy-7-propylestr-4-en-3-one was prepared in a manner analogous to that described under Example 1. $[\alpha]_D^{20} = +38.4°$ (c = 0.505, dioxane).

Example 3

(7α,17β)-7-(3-Fluoropropyl)-17-hydroxyestr-4-en-3-one.

i) - A mixture of lithium (2.65 g) and dry diethyl ether (150 ml) was cooled to 0 °C. 1-Bromo-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propane (one tenth of 47.6 g) was added and the reaction was allowed to start. After cooling to -10 °C the remainder of the bromide was added dropwise. The reaction mixture was stirred at 0 °C for 1.5 h and then added dropwise to a suspension of copper(I) iodide (18.0 g) in dry tetrahydrofuran (100 ml), cooled to -20 °C. After 45 min. stirring at that temperature, a solution of (17β)-17-(acetyloxy)estra-4,6-diene-3-one [Syntex, DE 1143199 (1963); 15.0 g] in dry tetrahydrofuran (87 ml) was

added dropwise. The reaction mixture was stirred for 2 h while the temperature was allowed to rise to 0 °C. After cooling to -10 °C, chlorotrimethylsilane (10 ml) was added and stirring was continued for 15 min. A mixture of water (400 ml) and hydrochloric acid (4 M, 20 ml) was added and the reaction mixture was stirred overnight. Then it was poured into a saturated aqueous solution of ammonium chloride and the product extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate, and concentrated under reduced pressure. Column chromatography afforded (7α,17β)-17-(acetyloxy)-7-(3-hydroxypropyl)estr-4-en-3-one (14.8 g).

ii) - (Diethylamino)sulfur trifluoride (1.05 ml) was added to a solution of the product obtained in the previous step (1.5 g) in dry dichloromethane (30 ml). After 24 h stirring at room temperature, a saturated aqueous solution of sodium hydrogencarbonate was added and the product extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Column chromatography afforded (7α,17β)-17-(acetyloxy)-7-(3-fluoropropyl)estr-4-en-3-one (1.03 g).

iii) - A solution of the product obtained in the previous step (1.03 g) and sodium hydroxide (0.202 g) in methanol (20 ml) was stirred at room temperature for 1 h and then at 35 °C for another 1 h. The reaction mixture was poured into water and the product extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate, and concentrated under reduced pressure. Column chromatography and crystallization afforded (7α,17β)-7-(3-fluoropropyl)-17-hydroxyestr-4-en-3-one (0.74 g), m.p. °C.

Example 4

(7α,17β)-7-Ethenyl-17-hydroxyestr-4-en-3-one.

i) - Vinylmagnesium chloride in tetrahydrofuran (2 M, 9.55 ml) was added dropwise to a mixture of (17β)-17-(acetyloxy)estra-4,6-diene-3-one (Example 3, step **i**; 3.0 g), copper(I) bromide-dimethyl sulfide complex (0.191 g), lithium bromide (0.083 g), and lithium thiophenoxide (0.96 ml of a 1 M solution in tetrahydrofuran), in dry tetrahydrofuran (10 ml), cooled to -15 °C. After 25 min. stirring a saturated aqueous solution of ammonium chloride

was added and the product extracted into ethyl acetate. The combined organic phases were concentrated under reduced pressure whereafter the residu was dissolved in acetone (100 ml) and treated with hydrochloric acid (4 M, 10 ml). After 30 min. stirring at room temperature, a saturated aqueous solution of sodium hydrogencarbonate was added. The product was extracted into ethyl acetate; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure, to give (7α,17β)-17-(acetyloxy)-7-ethenylestr-4-en-3-one (3.76 g). The product was used in the following step without further purification.

ii) - Potassium hydroxide (1.6 g) was added to a solution of the product obtained in the previous step (3.76 g) in a mixture of tetrahydrofuran (50 ml), methanol (44.3 ml), and water (14.3 ml). The reaction mixture was stirred at room temperature for 45 min. and then poured into water. The product was extracted into ethyl acetate; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography followed by crystallization afforded (7α,17β)-7-ethenyl-17-hydroxyestr-4-en-3-one (0.407 g), m.p. 130.5-133.5 °C.

Example 5

[7α(E),17β]-7-(2-Chloroethenyl)-17-hydroxyestr-4-en-3-one (a) and [7α(Z),17β]-7-(2-chloroethenyl)-17-hydroxyestr-4-en-3-one (b).

i) - A solution of (7α,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methoxyestra-1,3,5(10),8-tetraene-7-methanol [Kuenzer, H. *et al*, Tetrahedron Lett. 32, 743 (1991); 7.3 g] in dry tetrahydrofuran (100 ml) was added to liquid ammonia (400 ml), cooled at -40 °C. Lithium granulate (3.58 g) was added and the reaction mixture was stirred at reflux temperature for 1 h. Ethanol (22.1 ml) was added carefully and the mixture was stirred for 30 min. Solid ammonium chloride was added and the ammonia was allowed to evaporate. Water was added and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure, to give (7α,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methoxyestra-2,5(10)-diene-7-methanol (7.22 g). The product was used in the following step without further purification.

ii) - A solution of the product obtained in the previous step (7.22 g) in a mixture of pyridine (40 ml) and acetic anhydride (4.7 ml) was stirred at room temperature for 2 h. After cooling to 0 °C, water was added and stirring was continued for another 1 h. The product was extracted into ethyl acetate; the combined organic phases were washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure, to give (7α,17β)-7-[(acetyloxy)methyl]-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methoxyestra-2,5(10)-diene (7.80 g). The product was used in the following step without further purification.

iii) - Following a procedure analogous to that described under **ii** of Example 1, the diene described above (15.9 g) was converted to (7α,17β)-7-[(acetyloxy)methyl]-17-hydroxyestr-4-en-3-one (4.10 g).

iv) - Boron trifluoride diethyl etherate (1.34 ml) was added to a mixture of the ketone obtained in the previous step (3.52 g), 1,2-ethanedithiol (2.82 ml), and dry methanol (32 ml), cooled to 0 °C. After 2 h stirring the reaction mixture was filtered; the residu was washed with water and dissolved in dichloromethane. The dichloromethane solution was washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure, to give (7α,17β)-7-[(acetyloxy)methyl]-17-hydroxyestr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal (4.21 g). The product was used in the following step without further purification.

v) - A solution of the product obtained in the previous step (4.21 g) and imidazole (4.75 g) in dry dimethylformamide (80 ml) was cooled to 0 °C and treated with *t*-butyldimethylsilyl chloride (6.01 g). After 2 h stirring the reaction mixture was poured into water. The product was extracted into ethyl acetate; the combined organic phases were washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography afforded (7α,17β)-7-[(acetyloxy)methyl]-17-[[(1,1-dimethylethyl)dimethyl silyl]oxy] estr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal (6.0 g).

vi) - A solution of the product obtained in the previous step (5.9 g) in dry tetrahydrofuran (70 ml) was added dropwise to an ice-cooled suspension of lithium aluminium hydride (1.25 g) in tetrahydrofuran (140 ml). After stirring of the mixture for 45 min., the reaction was quenched by addition of a saturated aqueous solution of sodium sulfate. Ethyl acetate was added, and the mixture was filtered over dicalite. The filtrate was concentrated under reduced pressure to give (7α,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-(hydroxymethyl)estr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal (4.66 g). The product was used in the following step without further purification.

vii) - Tetrapropylammonium perruthenate (0.200 g) was added to a solution of the product obtained in the previous step (4.66 g) and 4-methylmorpholine *N*-oxide (3.31 g) in acetone (70 ml). After 4 h stirring at room temperature additional portions of 4-methylmorpholine *N*-oxide (0.65 g) and tetrapropylammonium perruthenate (0.010 g) were added and stirring was continued for another 2 h. The reaction mixture was filtered over dicalite and silica. The filtrate was concentrated under reduced pressure, to give (7α,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-formylestr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal (4.50 g) which was used in the following step without further purification.

viii) - A suspension of (chloromethyl)triphenylphosphonium chloride (3.52 g) in dry tetrahydrofuran (100 ml) was cooled to 0 °C. Sodium *t*-butoxide (0.917 g) was added and the mixture was stirred for 30 min. A solution of the aldehyde obtained in the previous step (1.0 g) in dry tetrahydrofuran (15 ml) was added and the reaction mixture was stirred at room temperature for 2 h. Then it was poured into water and the product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate, water and brine, dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography afforded a mixture of [7α(E),17β]-7-(2-chloroethenyl)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]estr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal and [7α(Z),17β]-7-(2-chloroethenyl)-17-[[(1,1-dimethylethyl)dimethylsilyl] oxy]estr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal (0.60 g, 3:1).

ix) - A solution of periodic acid (0.011 g) in a mixture of methanol and water (1:1, 0.60 ml) was added to a solution of the product obtained in the previous step (0.10 g) in dichloromethane (1 ml). After 1 h stirring at room temperature the reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate. The product was extracted into dichloromethane; the combined organic phases were washed with a saturated aqueous solution of sodium thiosulfate, water, and brine, dried over magnesium sulfate and concentrated under reduced pressure, to give a mixture of [7α(E),17β]-7-(2-chloroethenyl)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]estr-4-en-3-one and [7α(Z),17β]-7-(2-chloroethenyl)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]estr-4-en-3-one (0.080 g). The product was used in the following step without further purification.

x) - Following a procedure analogous to that described under **ii** of Example 1, the product obtained in the previous step (0.070 g) was desilylated, to produce a mixture of [7α(E),17β]-

7-(2-chloroethenyl)-17-hydroxyestr-4-en-3-one and [7α(Z),17β]-7-(2-chloroethenyl)-17-hydroxyestr-4-en-3-one (0.025 g). A part of this mixture (0.01 g) was separated by preparative HPLC to afford [7α(E),17β]-7-(2-chloroethenyl)-17-hydroxyestr-4-en-3-one (7.0 mg) and [7α(Z),17β]-7-(2-chloroethenyl)-17-hydroxyestr-4-en-3-one (2.5 mg).

Example 6

[7α(E),17β]-17-Hydroxy-7-(1-propenyl)estr-4-en-3-one (a) and [7α(Z),17β]-17-hydroxy-7-(1-propenyl)estr-4-en-3-one (b).

i) - Potassium *t*-butoxide (0.346 g) was added to a suspension of ethyltriphenylphosphonium bromide (1.21 g) in dry tetrahydrofuran (10 ml) and the mixture was stirred for 1 h at 50 °C. A solution of (7α,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-formylestr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal (Example 5, step **vii**; 0.40 g) in dry tetrahydrofuran (2 ml) was added and stirring was continued for another 1 h. Then it was poured into water and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography afforded a mixture of [7α(E),17β]-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-(1-propenyl)estr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal and [7α(Z),17β]-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-(1-propenyl)estr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal (0.317 g, 1:3).

ii) - Following a procedure analogous to that described under **ii** of Example 1, the product obtained in the previous step (0.317 g) was desilylated, to produce a mixture of [7α(E),17β]-17-hydroxy-7-(1-propenyl)estr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal and [7α(Z),17β)]-17-hydroxy-7-(1-propenyl)estr-4-en-3-one cyclic 1,2-ethanediyl dithioacetal (0.32 g).

iii) - Following a procedure analogous to that described under **ix** of Example 5, the product obtained in the previous step (0.32 g) was converted to the 3-oxo compound, to produce a mixture of [7α(E),17β]-17-hydroxy-7-(1-propenyl)estr-4-en-3-one and [7α(Z),17β]-17-hydroxy-7-(1-propenyl)estr-4-en-3-one (0.083 g). A part of this mixture (0.025 g) was separated by preparative HPLC to afford [7α(E),17β]-17-hydroxy-7-(1-propenyl)estr-4-en-3-one (3.5 mg) and [7α(Z),17β]-17-hydroxy-7-(1-propenyl)estr-4-en-3-one (14.0 mg).

Example 7

(7α,17β)-7-Ethynyl-17-hydroxyestr-4-en-3-one.

i) - A solution of (7α,17β)-7-[(acetyloxy)methyl]-17-[[(1,1-dimethylethyl) dimethylsilyl] oxy]-3-methoxyestra-2,5(10)-diene (Example 5, step **ii**; 4.88 g) in a mixture of tetrahydrofuran (22 ml) and methanol (31 ml) was treated with a solution of oxalic acid (1.1 g) in water (18.5 ml). After 1 h stirring at 40 °C, the reaction mixture was poured into water and the product extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate, water, and brine, dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography afforded (7α,17β)-7-[(acetyloxy)methyl]-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]estr-5(10)-en-3-one (1.91 g).

ii) - *p*-Toluenesulfonic acid (0.020 g) was added to a solution of the ketone obtained in the previous step (1.91 g) in methanol (40 ml) and trimethyl orthoformate (2.3 ml). After 10 min. stirring at room temperature the reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure, to give (7α,17β)-7-[(acetyloxy)methyl]-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]estr-5(10)-en-3-one dimethyl acetal (1.77 g). The product was used in the following step without further purification.

iii) - Following a procedure analogous to that described under **vi** of Example 5, the product obtained in the previous step (1.77 g) was converted to (7α,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-(hydroxymethyl)estr-5(10)-en-3-one dimethyl acetal (1.58 g).

iv) - Following a procedure analogous to that described under **vii** of Example 5, the product obtained in the previous step (1.58 g) was converted to (7α,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-formylestr-5(10)-en-3-one dimethyl acetal (2.0 g).

v) - Following a procedure analogous to that described under **viii** of Example 5, the product obtained in the previous step (2.0 g) was converted to a mixture of [7α(E),17β]-7-(2-chloroethenyl)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]estr-5(10)-en-3-one dimethyl acetal and [7α(Z),17β]-7-(2-chloroethenyl)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]estr-5(10)-en-3-one dimethyl acetal (0.90 g, 3:1).

vi) - A solution of the product obtained in the previous step (0.90 g) in dry tetrahydrofuran (30 ml) was cooled to -15 °C and then treated with *n*-BuLi in hexanes (1.6 M, 1.5 ml). After 10 min. stirring at -15 °C and 20 min. at room temperature another portion of *n*-BuLi in hexanes (1.6 M, 1.0 ml) was added and after 15 min. a third portion of *n*-BuLi in hexanes (1.6 M, 0.5 ml) was added. Stirring was continued for 1.25 h. The reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography afforded (7α,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-ethynylestr-5(10)-en-3-one dimethyl acetal (0.40 g).

vii) - Following a procedure analogous to that described under **ii** of Example 1, the product obtained in the previous step (0.24 g) was converted to (7α,17β)-7-ethynyl-17-hydroxyestr-4-en-3-one (0.117 g), $[\alpha]_D^{20} = +38.0°$ (c = 0.395, dioxane).

Example 8

(7α,17β)-17-Hydroxy-7-(1-propynyl)estr-4-en-3-one.

i) - A solution of (7α,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-ethynylestr-5(10)-en-3-one dimethyl acetal (Example 7, step **vi**; 0.12 g) in dry tetrahydrofuran (2.5 ml) was cooled to -20 °C and then treated with *n*-BuLi in hexanes (1.6 M, 0.41 ml). After 30 min. stirring at -20 °C, iodomethane (0.066 ml) was added and stirring was continued for 15 min. Another portion of iodomethane (0.066 ml) was added and stirring was continued for 1 h at 0 °C. The reaction mixture was poured into water and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography afforded (7α,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-(1-propynyl)estr-5(10)-en-3-one dimethyl acetal (0.051 g). The product was used in the following step without further purification.

ii) - Following a procedure analogous to that described under **ii** of Example 1, the product obtained in the previous step (0.051 g) was converted to (7α,17β)-17-hydroxy-7-(1-propynyl)estr-4-en-3-one (0.03 g), $[\alpha]_D^{20} = +29.4°$ (c = 0.35, dioxane).

Example 9

(7α,17β)-7-Cyclopropyl-17-hydroxyestr-4-en-3-one.

i) - Chlorotrimethylsilane (19 ml) was added in 5 min. to a suspension of (17α)-17-hydroxy-19-norpregna-4,6-dien-20-yn-3-one [Syntex S.A., GB 935116 (1958); 18.0 g] in a mixture of dichloromethane (300 ml) and pyridine (25 ml), cooled to 0 °C. After 2 h stirring at 0 °C the reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate. The product was extracted into dichloromethane; the combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure, to afford (17α)-17-[(trimethylsilyl)oxy]-19-norpregna-4,6-dien-20-yn-3-one (22.3 g). The product was used in the following step without further purification.

ii) - A mixture of the product described above (60.7 g), diethyl malonate (126 ml), sodium methoxide (9 g), and dry ethanol (165 ml) was stirred at room temperature for 24 h. Part of the ethanol was removed (80 ml) and stirring was continued for another 24 h. Again part of the ethanol was removed (25 ml) and the reaction mixture was stirred for an additional 24 h. The mixture was poured into a saturated aqueous solution of ammonium chloride and the product was extracted into ethyl acetate. The combined organic phases were concentrated under reduced pressure and dissolved in acetone (400 ml). Hydrochloric acid was added (6 M, 20 ml) and the reaction mixture was stirred at room temperature for 2 h. A saturated aqueous solution of sodium hydrogencarbonate was added and the acetone was removed under reduced pressure. The product was extracted into ethyl acetate; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated. Column chromatography afforded diethyl 2-[(7α,17α)-17-hydroxy-3-oxo-19-norpregn-4-en-20-yn-7-yl]propanedioate (33.8 g).

iii) - A mixture of the product obtained in the previous step (14.4 g), copper(II) bromide (14.3 g), and lithium bromide (2.84 g) in acetonitrile (288 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into a mixture of a saturated aqueous solution of ammonium chloride and a saturated aqueous solution of ammonia (9:1) and the product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded diethyl

2-[(7α,17α)-3,17-dihydroxy-19-norpregna-1,3,5(10)-trien-20-yn-7-yl]propanedioate (13.6 g).

iv) - Following a procedure analogous to that described under **v** of Example 5, the product obtained in the previous step (12.5 g) was converted to diethyl 2-[(7α,17α)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-17-hydroxy-19-norpregna-1,3,5(10)-trien-20-yn-7-yl]propanedioate (15.3 g).

v) - A mixture of the product obtained in the previous step (7.50 g) and copper(II) carbonate on dicalite (16.5 g) in toluene (112 ml) was heated at reflux temperature for 2.5 h under removal of water by use of a Dean-Stark trap. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure, to give diethyl 2-[(7α)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-17-oxoestra-1,3,5(10)-trien-7-yl]propanedioate (7.07 g). The product was used in the following step without further purification.

vi) - *p*-Toluenesulfonic acid (0.36 g) was added to a solution of the ketone obtained in the previous step (7.07 g) in ethylene glycol (12 ml) and triethyl orthoformate (21 ml). After 1.5 h stirring at room temperature water (200 ml) was added and stirring was continued for 1 h. The product was extracted into ethyl acetate; the combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate and concentrated under reduced pressure, to give diethyl 2-[(7α)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-17,17-[1,2-ethanediylbis(oxy)]estra-1,3,5(10)-trien-7-yl]propanedioate (8.48 g). The product was used in the following step without further purification.

vii) - Following a procedure analogous to that described under **vi** of Example 5, the product obtained in the previous step (8.48 g) was converted to (7α)-7-(1,3-dihydroxyprop-2-yl)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]estra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal (3.0 g).

viii) - Methanesulfonyl chloride (4.60 ml) was added to a solution of the diol obtained in the previous step (3.0 g) in dry pyridine (116 ml), cooled to 0 °C. After 35 min. stirring the reaction mixture was poured into water and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure, to give (7α)-7-[1,3-bis[(methylsulfonyl)oxy]prop-2-yl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]estra-1,3,5(10)-trien-17-one cyclic 1,2-

ethanediyl acetal (4.08 g). The product was used in the following step without further purification.

ix) - A mixture of the product obtained in the previous step (2.0 g), sodium iodide (3.45 g), zink powder (3.14 g), water (4.1 ml), and dimethoxyethane (41 ml) was heated under reflux for 3.25 h. After cooling, the reaction mixture was filtered. The filtrate washed with a saturated aqueous solution of sodium thiosulfate and brine, dried over sodium sulfate and concentrated under reduced pressure, to afford (7α)-7-cyclopropyl-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]estra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal (1.47 g). The product was used in the following step without further purification.

x) - Following a procedure analogous to that described under **ii** of Example 1, the product obtained in the previous step (1.47 g) was converted to (7α)-7-cyclopropyl-3-hydroxyestra-1,3,5(10)-trien-17-one (0.63 g).

xi) - Sodium borohydride (0.45 g) was added to a solution of the compound obtained in the previous step (0.63 g) in a mixture of tetrahydrofuran (8.3 ml), ethanol (8.3 ml), water (1.4 ml), and pyridine (0.05 ml). The reaction mixture was stirred at room temperature for 1.25 h and then poured into water. The product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate and concentrated, to give (7α,17β)-7-cyclopropylestra-1,3,5(10)-triene-3,17-diol (0.710 g). The product was used in the following step without further purification.

xii) - A mixture of the product obtained in the previous step (0.29 g), dry potassium carbonate (0.77 g), iodomethane (0.35 ml), and dry dimethylformamide (0.87 ml) was stirred at room temperature overnight. The mixture was poured into a saturated aqueous solution of ammonium chloride and the product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (7α,17β)-7-cyclopropyl-3-methoxyestra-1,3,5(10)-trien-17-ol (0.096 g).

xiii) - Following a procedure analogous to that described under **i** of Example 5, the product described above (0.167 g) was converted to (7α,17β)-7-cyclopropyl-3-methoxyestra-2,5(10)-dien-17-ol (0.24 g).

xiv) - Following a procedure analogous to that described under **ii** of Example 1, the product obtained in the previous step (0.24 g) was converted to (7α,17β)-7-cyclopropyl-17-hydroxyestr-4-en-3-one (0.081 g), m.p. 154-158 °C.

Example 10

(7α,17β)-17-Hydroxy-7-(1-methylcyclopropyl)estr-4-en-3-one.

i) - A solution of diethyl 2-[(7α)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-17,17-[1,2-ethanediylbis(oxy)]estra-1,3,5(10)-trien-7-yl]propanedioate (Example 9, step **vi**; 2.0 g) in dry dimethylformamide (10 ml) was added dropwise to a suspension of sodium hydride (0.481 g) in the same solvent (5 ml). After 30 min. stirring, iodomethane (0.94 ml) was added and stirring was continued for 1 h. The reaction mixture was poured into a saturated aqueous solution of ammonium chloride and the product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate, and concentrated under reduced pressure, to give diethyl 2-[(7α)-17,17-[1,2-ethanediylbis(oxy)]-3-methoxyestra-1,3,5(10)-trien-7-yl]-2-methylpropanedioate (2.19 g). The product was used in the following step without further purification.

ii) - Following procedures analogous to those described under **vii** - **xi**, **xiii**, and **xiv** of Example 9, the product obtained in the previous step was converted to (7α,17β)-17-hydroxy-7-(1-methylcyclopropyl)estr-4-en-3-one, $[\alpha]_D^{20} = -13.6°$ (dioxane).

Test Example

The in vivo potency of the different androgens was determined in a mature male castrated rat model. In this model serum LH is high (50x fold higher than intact rats, due to the absence of the negative feedback of testicular testosterone). These rats are treated for 4 days daily with a suspension fluid containing the androgens per orally, at the afternoon of day 4 serum is obtained by orbita punction and serum LH is determined. Potency of the different androgens are expressed as concentration of serum LH as a % of controle treated rats (which are castrated and placebo treated). A lower percentage thus is indicative of a higher potency.

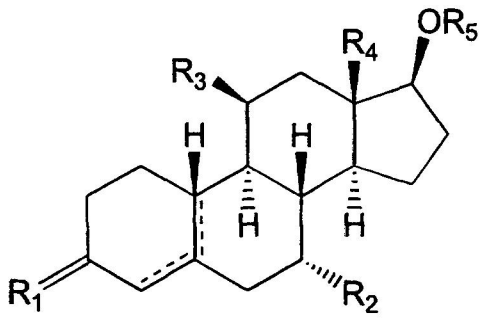
Compared were the compounds of Examples 1 and 4, and the prior art compound MENT. Even though, in a regular receptor binding assay using the cytoplasmic androgen receptor from human breast tumor cells (MCF-7 cell line), the compounds of the invention have an androgenic potency of the same order of magnitude as MENT (Example 1) or lower (Example 4), oral activity is much higher. The aforementioned percentage in the case of MENT is 64%. The compounds of the invention both lead to a percentage of 21%.

The rat LH Time-Resolved Immuno Fluorometricassay (TR-IFMA) has been developed in house using home made reagents, a monoclonal catching antibody directed against the ß-subunit of human chorion gonadotrophin (hCG, which cross react with rat ß-subunit) and a biotin labelled detecting antibody (rabbit polyclonal antibody directed against the alfa-subunit of recombinant rat LH). Recombinant rat LH was prepared according to the methods described by Hakola et al. 1997. In this two-site-IFMA, only intact rat LH is determined by a final incubation with streptavidin-europium. The detection in the IFMA is based on fluorescence of the lanthanide europium during a relative long exitation period. The concentration range of rat LH standard is 0.001- 10 ng/ml, for optimal accuracy measuremnts of serum LH serum samples were diluted 8-times with assay buffer.

1. Hakola, K., Boogaart, P.V., Mulders, J., de Leeuw, R., Schoonen, W., Heyst, J.V., Swolfs, A., Casteren, J.V., Huhtaniemi, I., and Kloosterboer, H. Recombinant rat luteinizing hormone; production by Chinese hamster ovary cells, purification and functional characterization. *Molecular.&.Cellular.Endocrinology* 128(1-2):47-56, 1997.

Claims:

1. A compound of the structural formula:



Formula I

wherein

R_1 is O, (H,H), (H,OR), NOR, with R being hydrogen, (C_{1-6}) alkyl, or (C_{1-6}) acyl;

R_2 is (C_{2-3}) alkyl, isopropyl, (C_{2-3}) 1-alkenyl, isopropenyl, 1,2-propadienyl, or (C_{2-3}) 1-alkynyl, each optionally substituted by halogen; or R_2 is cyclopropyl, or cyclopropenyl, each optionally substituted by (C_{1-2}) alkyl or halogen;

R_3 is hydrogen, (C_{1-2}) alkyl, or ethenyl;

R_4 is (C_{1-2}) alkyl;

R_5 is hydrogen, or (C_{1-15}) acyl;

and the dotted lines indicate optional bonds;

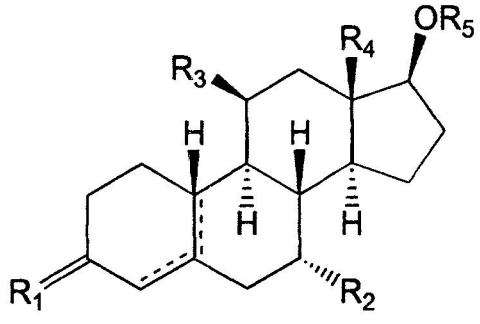
with the proviso that the compound is not (7α)-7-ethyl-17-hydroxyestr-4-en-3-one (7α-ethyl-19-nortestosterone) or a carboxylic ester thereof.

2. A compound according to claim 1, characterised in that R_2 is selected from the group consisting of ethyl, ethenyl, ethynyl, propyl, 1-propenyl, 1-propynyl, 1,2-propadienyl, and cyclopropyl.

3. A compound according to claim 2, characterised in that R_2 is C_2.

4. The compound 7α-ethyl-19-nortestosterone as a medicine.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and comprising, as a medicinally active agent, a steroid compound satisfying the general formula I



Formula I

wherein

R_1 is O, (H,H), (H,OR), NOR, with R being hydrogen, (C_{1-6}) alkyl, or (C_{1-6}) acyl;

R_2 is (C_{2-3}) alkyl, isopropyl, (C_{2-3}) 1-alkenyl, isopropenyl, 1,2-propadienyl, or (C_{2-3}) 1-alkynyl, each optionally substituted by halogen; or R_2 is cyclopropyl, or cyclopropenyl, each optionally substituted by (C_{1-2}) alkyl or halogen;

R_3 is hydrogen, (C_{1-2}) alkyl, or ethenyl;

R_4 is (C_{1-2}) alkyl;

R_5 is hydrogen, or (C_{1-15}) acyl;

and the dotted lines indicate optional bonds.

6. A pharmaceutical formulation according to claim 5, characterised in that in the steroid compound R_2 is selected from the group consisting of ethyl, ethenyl, ethynyl, propyl, 1-propenyl, 1-propynyl, 1,2-propadienyl, and cyclopropyl.

7. A pharmaceutical formulation according to claim 5, characterised in that the steroid compound is (7α)-7-ethyl-17-hydroxyestr-4-en-3-one and (7α)-7-ethenyl-17-hydroxyestr-4-en-3-one.

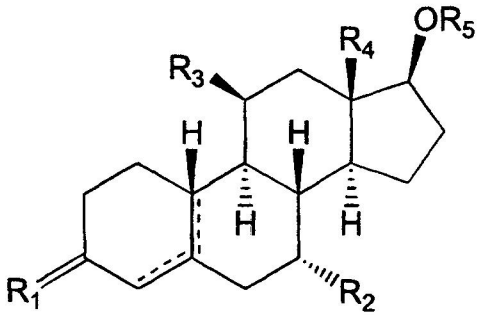
8. A pharmaceutical formulation according to claim 6 or 7, characterised in that it is suitable for oral administration.

9. The use of a compound satisfying formula I for the preparation of a medicine for treating androgen insufficiency.

10. A kit for male contraception comprising means for the administration of a progestagen and means for the administration of an androgen, characterised in that the latter means is a pharmaceutical formulation according to any one of claims 6-8.

ABSTRACT

Novel, orally active androgens are derivatives of 7α-methyl-19-nortestosterone. The compounds satisfy the general formula



Formula I

wherein

R_1 is O, (H,H), (H,OR), NOR, with R being hydrogen, (C_{1-6}) alkyl, or (C_{1-6}) acyl;

R_2 is selected from the group consisting of (C_{2-3}) alkyl, isopropyl, (C_{2-3}) 1-alkenyl, isopropenyl, 1,2-propadienyl, or (C_{2-3}) 1-alkynyl, each optionally substituted by halogen; or

R_2 is cyclopropyl, or cyclopropenyl, each optionally substituted by (C_{1-2}) alkyl, or halogen;

R_3 is hydrogen, (C_{1-2}) alkyl, or ethenyl;

R_4 is (C_{1-2}) alkyl;

R_5 is hydrogen, or (C_{1-15}) acyl;

and the dotted lines indicate optional bonds.

TRADUCCION: Se traduce la carátula y las reivindicaciones anexas a una copia de la solicitud de patente europea Nº 99201070.2, escrita en inglés para el invento denominado:
ANDROGENOS ORALMENTE ACTIVOS.

A N E X O S

OFICINA DE PATENTES EUROPEA

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Los documentos adjuntos son copias exactas de la solicitud de patente europea descrita en la siguiente página, como fue presentada originalmente.

Solicitud de patente Nº. 99201070.2

Por el Presidente de la Oficina de Patentes Europea
(Firmado Ilegible)
I.L.C. HATTEN-HECKMAN

La Haya, 11/04/00

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Solicitud Nº 99201070.2 Fecha de presentación 06/04/99

Solicitante(s)

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Título del invento: **ANDROGENOS 7-ALFA-ALQUILO ORALMENTE ACTIVOS**

Prioridades reivindicadas

País	Fecha	Archivo Nº

Clasificación Internacional de Patente:

C07J1/00, A61K31/565

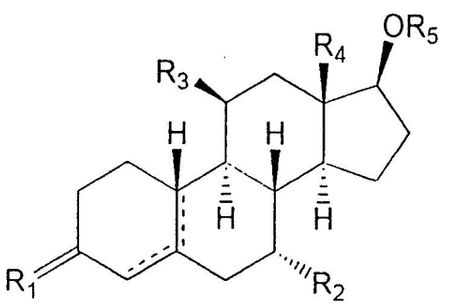
Países contratantes designados en la fecha de presentación:

AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE

Observaciones: **El titulo original de la solicitud es como sigue: ANDROGENOS ORALMENTE ACTIVOS**

REIVINDICACIONES

1. Un compuesto de la fórmula estructural:



Fórmula I

donde R_1 es O, (H,H), (H,OR), NOR, siendo R hidrógeno, (C_{1-6})alquilo o (C_{1-6})acilo;

R_2 es (C_{2-3})alquilo, isopropilo, (C_{2-3})1-alquenilo, isopropenilo, 1,2-propadienilo o (C_{2-3})1-alquinilo, cada uno opcionalmente sustituido por halógeno; o R_2 es ciclopropilo o ciclopropenilo, cada uno opcionalmente sustituido por (C_{1-2})alquilo o halógeno;

R_3 es hidrógeno, (C_{1-2})alquilo o etenilo;

R_4 es (C_{1-2})alquilo;

R_5 es hidrógeno o (C_{1-15})acilo;

y las líneas de puntos indican enlaces opcionales;

con la salvedad de que el compuesto no es (7α)-7-etil-17-hidroxiestr-4-en-3-ona (7α-etil-19-nortestosterona) ni un éster carboxílico de la misma.

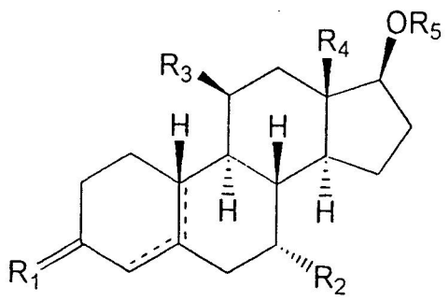
2. Un compuesto de acuerdo con la reivindicación 1, caracterizado porque R_2 se selecciona del grupo consistente

en etilo, etenilo, etinilo, propilo, 1-propenilo, 1-propinilo, 1,2-propadienilo y ciclopropilo.

3. Un compuesto de acuerdo con la reivindicación 2, caracterizado porque R_2 es C_2.

4. El compuesto 7α-etil-19-nortestosterona como un medicamento.

5. Una composición farmacéutica que comprende un vehículo farmacéuticamente aceptable y comprende, como un agente medicinal activo, un compuesto esteroide que satisface la Fórmula general I:



Fórmula I

donde R_1 es O, (H,H), (H,OR), NOR, siendo R hidrógeno, (C_{1-6})alquilo o (C_{1-6})acilo;

R_2 es (C_{2-3})alquilo, isopropilo, (C_{2-3})1-alquenilo, isopropenilo, 1,2-propadienilo o (C_{2-3})1-alquinilo, cada uno opcionalmente sustituido por halógeno; o R_2 es ciclopropilo o ciclopropenilo, cada uno opcionalmente sustituido por (C_{1-2})alquilo o halógeno;

R_3 es hidrógeno, (C_{1-2})alquilo o etenilo;

R_4 es (C_{1-2})alquilo;

R_5 es hidrógeno o (C_{1-15})acilo;

y las líneas de puntos indican enlaces opcionales.

6. Una formulación farmacéutica de acuerdo con la reivindicación 5, caracterizada porque en el compuesto esteroide, R_2 se selecciona del grupo consistente en etilo, etenilo, etinilo, propilo, 1-propenilo, 1-propinilo, 1,2-propadienilo y ciclopropilo.

7. Una formulación farmacéutica de acuerdo con la reivindicación 5, caracterizada porque el compuesto esteroide es (7α)-7-etil-17-hidroxiestr-4-en-3-ona y (7α)-7-etenil-17-hidroxiestr-4-en-3-ona.

8. Una formulación farmacéutica de acuerdo con la reivindicación 6 ó 7, caracterizada porque es adecuada para administración oral.

9. El uso de un compuesto que satisface la Fórmula I para la preparación de un medicamento para tratar la insuficiencia androgénica.

10. Un kit para la anticoncepción masculina que comprende un medio para la administración de un progestágeno y un medio para la administración de un andrógeno, caracterizado porque este último medio es una formulación farmacéutica de acuerdo con cualquiera de las reivindicaciones 6-8.