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

Referencia : Expediente No. **00.016.933**

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

Asunto : Solicitud de patente para: **"ANDROGENOS NOVEDOSOS"**

Fecha de solicitud : 8 de marzo 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 99200665.0 del 08 de marzo 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, 24 MAY 2000
Señora Jefe,

**EMILIO FERRERO**
T.P.A. No. 31.929

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ATM-ID-71

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| Europäisches Patentamt | European Patent Office | Office européen des brevets |
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# Bescheinigung Certificate Attestation

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| 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° |
|---|---|---|
| | 99200665.0 | |

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

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# Blatt 2 der Bescheinigung
# Sheet 2 of the certificate
# Page 2 de l'attestation

Anmeldung Nr.:
Application no.: 99200665.0
Demande n°:

Anmeldetag:
Date of filing: 08/03/99
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Anmelder:
Applicant(s):
Demandeur(s):
Akzo Nobel N.V.
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NETHERLANDS

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
14.beta.,17.alpha.-Hydroxymethyl Steroid Androgens

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

| Staat: State: Pays: | Tag: Date: Date: | Aktenzeichen: File no. Numéro de dépôt: |
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Internationale Patentklassifikation:
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Bemerkungen:
Remarks: **The original title of the application reads as follows : Novel androgens**
Remarques:

# NOVEL ANDROGENS

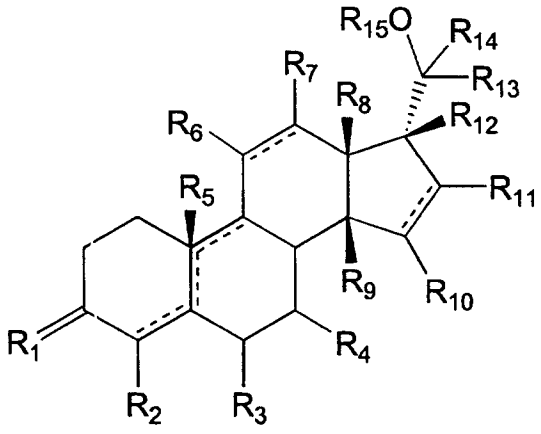
The invention is in the field of steroid hormones. This is a relatively old field, in which a great many possible substitutions on a common steroid skeleton are known to lead to many different hormonal activities and medical utilities, and in which the basic structure-activity relations seemed to be known. Surprisingly, in this well-investigated field, a completely new discovery led to the present invention, according to which novel androgens are provided.

Natural steroid hormones, such as testosterone and estradiol, have the configuration 14α and 17β. The invention now resides in the unexpected finding of novel steroids which are characterised by the opposite configuration, viz. 14β,17α. These steroids according to the invention are (14β,17α)-17-(hydroxymethyl) steroids, and they are found to have in common an androgenic activity.

Except for this requirement, and except for the fact that the 17α-substituent should be a hydroxymethyl moiety, the compounds of the invention are well characterised with reference to the requirement that the configuration be 14β and 17α. In other words, the exact nature of any optional substituents at any carbon atom of the steroid skeleton, or at any subsituent group, is not particularly critical to the invention. The person of ordinary skill in the art of steroid chemistry is well aware of which substituents are practically applicable.

It should be noted that in the past steroids having the abnormal 14β,17α configuration received some attention in the art of organic chemistry. See *e.g.* the more than thirty years old publication of Crabbé, P. *et al*, Can. J. Chem. 46, 349 (1967). This document incidentally mentions one (14β,17α)-17-(hydroxymethyl) steroid, viz. 2-hydroxy-14β,17α-19-norpregn-4-en-3-on as a chemical intermediate. Similarly, other (14β,17α)-17-(hydroxymethyl) steroids known as chemical compounds *per se*, are (3β,5α,14β,17α)-pregna-3,20-diol and (3β,14β,17α)-pregna-5,9(11)-dien-3,20-diol, see Shoppee CW et al, Helv. Chim. Acta, 27, 246 (1944) and J. Chem. Soc., 3610 (1962), and (14β,17α)-20-hydroxy-19-norpregn-4-en-3-one, see Crabbe P et al, Can. J. Chem., 46, 349 (1968). To the extent that the invention pertains to chemical compounds, these known compounds are disclaimed here.

The invention particularly pertains to steroids which satisfy structural formula I given below, or pharmaceutically acceptable salts or esters, prodrugs and precursors thereof.




Formula I

wherein

$R_1$ is O, (H,H), (H,OR), NOR, with R being hydrogen, $(C_{1-6})$ alkyl, $(C_{1-15})$ acyl;

$R_2$ is hydrogen, $(C_{1-6})$ alkyl, or halogen;

$R_3$ is hydrogen, $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl, or $(C_{2-6})$ alkynyl;

$R_4$ is hydrogen, halogen, or cyano; or $R_4$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl or $(C_{2-6})$ alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_5$ is hydrogen, or $(C_{1-6})$ alkyl;

$R_6$ is hydrogen, $(C_{1-6})$ alkoxy, or halogen; or $R_6$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl, $(C_{2-6})$ alkynyl, a $(C_{1-6})$ alkylidene group, or a $(C_{2-6})$ alkenylidene group, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_7$ is hydrogen, or $(C_{1-6})$ alkyl;

$R_8$ is $(C_{1-6})$ alkyl;

$R_9$ is hydrogen, halogen or cyano; or $R_9$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl, or $(C_{2-6})$ alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_{10}$ is hydrogen, $(C_{1-6})$ alkoxy, halogen, or cyano; or $R_{10}$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl or $(C_{2-6})$ alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_{11}$ is hydrogen, $(C_{1-6})$ alkoxy, halogen, or cyano; or $R_{11}$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl or $(C_{2-6})$alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$alkoxy, oxo, halogen, or cyano;

$R_{12}$ is hydrogen, halogen, or cyano; or $R_{12}$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl, $(C_{2-6})$ alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_{13}$ and $R_{14}$ are independently hydrogen, cyano, or phenyl, the latter optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, $(C_{1-4})$ alkyl or halogen; or $R_{13}$ and $R_{14}$ are independently $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl, $(C_{3-6})$ cycloalkyl, $(C_{5-6})$ cycloalkenyl or $(C_{2-6})$ alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, phenyl, oxo, halogen, or cyano; or $R_{13}$ and $R_{14}$ together with the carbon atom at which they are placed form a $(C_{3-6})$ cycloalkane ring or a $(C_{5-6})$ cycloalkene ring;

$R_{15}$ is hydrogen, $SO_3H$, $(C_{1-6})$ alkyl, $(C_{1-15})$ acyl; and

the dotted lines indicate optional bonds.

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 $(C_{1-4})$ alkyl means an alkyl group having 1-4 carbon atoms. Preferred alkyl groups have 1-4 carbon atoms, and most preferred alkyl groups are methyl and ethyl.

The term $(C_{2-6})$ alkenyl means a branched or unbranched alkenyl group having at least one double bond and 2-6-carbon atoms. Preferred alkenyl groups have 2-4 carbon atoms, such as vinyl and propenyl.

The term $(C_{2-6})$ alkynyl means a branched or unbranched alkynyl group having at least one triple bond and 2-6 carbon atoms. Preferred alkynyl groups have 2-4 carbon atoms, such as ethynyl and propynyl.

The term $(C_{1-6})$ alkylidene means a branched or unbranched alkylidene group having 1-6 carbon atoms. Preferred alkylidene groups have 1-4 carbon atoms, and most preferred is methylene.

The term $(C_{2-6})$ alkenylidene means a branched or unbranched alkenylidene group having 2-6 carbon atoms. Preferred alkenylidene groups have 2-4 carbon atoms, such as ethenylidene.

The term ($C_{3-6}$) cycloalkyl or ($C_{3-6}$) cycloalkane ring means a cycloalkane ring having 3-6 carbon atoms, like cyclopropane, cyclobutane, cyclopentane and cyclohexane.

The term ($C_{5-6}$) cycloalkenyl or ($C_{5-6}$) cycloalkene ring means a cycloalkene ring having at least one double bond and 5 or 6 carbon atoms.

The term ($C_{1-6}$) alkoxy means a branched or unbranched alkyloxy group having 1-6 carbon atoms, like methyloxy, ethyloxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, tertiary butyloxy, pentyloxy, and hexyloxy. Likewise, the term ($C_{1-4}$) alkoxy means a branched or unbranched alkyloxy group having 1-4 carbon atoms. Preferred alkyloxy groups have 1-4 carbon atoms, and most preferred is methyloxy.

The term ($C_{1-15}$) acyl means an acyl group derived from a carboxylic acid having from 1-15 carbon atoms, like formyl, acetyl, propanoyl, butyryl, 2-methylpropanoyl, pentanoyl, pivaloyl, hexanoyl, and so on. 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 ($C_{1-15}$) 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, like in the definition $R_2$, $R_4$, $R_6$, $R_{9-14}$, Cl and F are preferred, F being most preferred.

It is understood that the (14β,17α)-17-(hydroxymethyl) steroid derivatives of the invention have the natural configurations 5α, 8β, 9α, 10β, 13β.

The (14β,17α)-17-(hydroxymethyl) steroid derivatives of this invention have the natural configurations 5α, 8β, 9α, 10β, 13β, 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.

For therapeutic use, salts of the compounds of formula I are those wherein the counterion is pharmaceutically acceptable. However, salts of the acids according to formula I [*i.e.* compounds wherein $R_1$ is ($H,OSO_3H$) or wherein $R_{15}$ is $SO_3H$] may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not, are included within the ambit of the present invention. Examples of salts of acids according to the invention are mineral salts such as sodium salt, potassium salt, and salts derived from organic bases like ammonia, imidazole, ethylenediamine, triethylamine and the like.

The compounds of the invention as described hereinbefore in general possess an unexpected androgenic activity. Androgenic activity can be measured in various ways. Thus, the potency of androgens can be determined *in vitro* using the cytoplasmic androgen receptor from human breast tumor cells (MCF-7 cell line); see Bergink, E.W. *et al*, *Comparison of the receptor binding properties of nandrolone and testosterone under in vitro and in vivo conditions*, J. Steroid Biochem. 22, 831-836 (1985). It is also possible to use Chinese hamster ovary (CHO) cells transfected with the human androgen receptor (incubation time 16 h, temperature 4 °C) and compared with the affinity of 5α-dihydrotestosterone [according to the procedure described by Bergink, E.W. *et al*, J. Steroid Biochem. 19, 1563-1570 (1983)]. The

transactivative androgen activity of the compounds of the invention can be measured, *e.g.* in Chinese hamster ovary cells (CHO) transfected with the human androgen receptor (hAR), in combination with a mouse mammary tumor virus (MMTV), and luciferase receptor gene (incubation time 15 h, temperature 37 °C) and compared with the activity of 5α-dihydrotestosterone [according to the procedure described by Schoonen, W.G.E.J. *et al*, Analyt. Biochem. 261, 222-224 (1998)]. For the *in vivo* potency determination of androgens the classical Hershberger test can be used. In this test the androgenic (increase in prostate weight) and anabolic activities [increase of the musculus levator ani (MLA)] of a compound are tested in immature castrated rats after daily administration for 7 days; see Hershberger, L.G. *et al, Myotrophic activity of 19-Nortestosterone and other steroids determined by modified levator ani muscle method*, Proceedings of the society for experimental biology and medicine 83, 175-180 (1953). Additionally, the effect of an androgenic compound on LH suppression can be tested in mature castrated rats according to Kumar, N. *et al, The biological activity of 7alpha-methyl-19-nortestosterone is not amplified in male reproductive tract as is that of testosterone*, Endocrinology 130, 3677-3683 (1992).

The preference goes to those compounds according to the invention which exhibit a relatively high androgenic activity. Thus, the preferred compounds of the invention are those satisfying the above structural formula I, wherein:

$R_1$ is O;

$R_2$, $R_3$, $R_5$, $R_6$, $R_7$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, and $R_{14}$ all are hydrogen;

$R_4$ is H or methyl;

$R_8$ is methyl;

$R_{13}$ is hydrogen, or $C_{1-2}$ (alkyl) with the configuration at carbon atom no. 20 being S;

$R_{15}$ is H or ($C_{1-15}$) acyl;

and wherein a double bond is present between carbon atoms nos. 4 and 5, and optionally also between carbon atoms nos. 9 and 10.

As androgenic hormones the (14β,17α)-17-(hydroxymethyl) steroids of the present invention can be used in, int.al., male contraception and male HRT (hormone replacement therapy). Thus, *e.g.* male contraception may comprise a regimen of administration of hormones in which a progestagen serves to achieve a contraceptive effect and an androgen serves to supplement

the resulting decreased testosterone level. Another option is that male contraception is performed with an androgenic hormone alone. The androgens can also be used for androgen supplementation in the partially androgen deficient ageing male. Next to the use in the male, the androgens of the invention also can be used in the female, *e.g.* as androgen replacement therapy in postmenopausal women.

The present invention also relates to a pharmaceutical composition comprising a steroid compound according to the invention mixed with a pharmaceutically acceptable auxiliary, such as described in the standard reference, Gennaro *et al*, *Remmington's Pharmaceutical Sciences*, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture). The mixture of the steroid compounds according to the invention and the pharmaceutically acceptable auxiliary may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, *e.g.* nasal spray. For making dosage units, *e.g.* tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. The steroid compounds of the invention may also be included in an implant, a vaginal ring, a patch, a gel, and any other preparation for sustained release.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof used in suitable amounts.

Furthermore, the invention relates to the use of the steroid compound according to the invention for the manufacture of a medicament in the treatment of androgen-deficiency, such as in male or female HRT (hormone replacement therapy). Accordingly, the invention also includes a method of treatment in the field of male or female HRT, comprising the administration to a male or female patient suffering from an androgen-deficiency, of a compound as described hereinbefore (in a suitable pharmaceutical dosage form).

Further, the invention relates to the use of a steroid compound according to the invention for the manufacture of a medicamenthaving contraceptive activity (for which in the art the term "contraceptive agent" is also used). Thus the invention also pertains to the medical indication of contraception, *i.e.* a method of contraception comprising the administration to a subject, being a male, preferably a human male, of a compound as described hereinbefore (in a suitable pharmaceutical dosage form), in combined therapy with a progestagen or not.

The androgens according to the invention can also be used in a kit for male contraception. Although this kit can comprise one or more androgens only, it is preferred that it comprises means for the administration of a progestagen and means for the administration of an androgen. The latter means is a pharmaceutical formulation comprising compound according to the invention as described hereinbefore, and a pharmaceutically acceptable carrier.

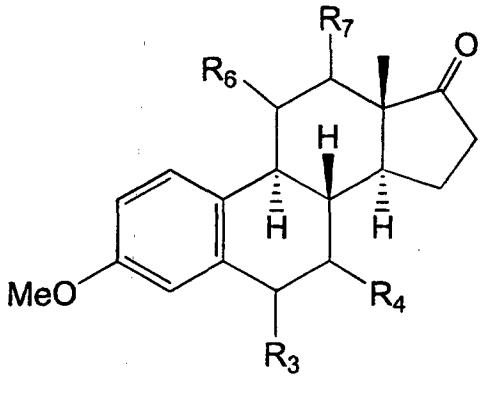
The invention also pertains to a method of treatment comprising administering to a (notably human) male or female in need of androgen-supplementation a therapeutically effective amount of a (14β,17α)-17-(hydroxymethyl) steroid as described hereinbefore. This is irrespective of whether or not the need for androgen-supplementation has arisen as a result of male contraception involving the administration of a sterilitant, such as a progestagen.

Further, the invention pertains to a method of contraception, comprising administering to a fertile male, notably human, a (14β,17α)-17-(hydroxymethyl) steroid as described hereinbefore in a dosage amount and regimen which is sufficient for said compound to be contraceptively effective *per se*. Alternatively, the method of contraception provided by the present invention comprises administering to a fertile male, notably human, a contraceptively effective combination of a sterilitant, such as a progestagen, and a (14β,17α)-17-(hydroxymethyl) steroid as described hereinbefore.

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).

Crucial is the synthesis of steroids of inverted stereochemistry at C-14 (14β-configuration) and possessing a (substituted) 17α-hydroxymethyl group.

A convenient starting material for the preparation of compounds of formula I wherein $R_1$ is oxo; $R_2$ $R_5$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$ and $R_{15}$ are hydrogen; $R_3$, $R_4$, $R_6$ and $R_7$ are hydrogen or ($C_{1-6}$) alkyl; $R_8$ is methyl; $R_{13}$ and $R_{14}$ have the previously given meaning; and the dotted lines indicate a $\Delta^4$ double bond, is for instance a compound of general formula II, wherein $R_3$, $R_4$, $R_6$ and $R_7$ are hydrogen or ($C_{1-6}$) alkyl, whose synthesis is known in literature, or which can be prepared using standard methods.




Formula II

A possible synthesis route is as follows. A 3-methoxyestra-1,3,5(10)-trien-17-one derivative of formula II can be converted to the the corresponding cyclic 1,2-ethanediyl acetal which can then be brominated to afford a (16α)-16-bromo-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal derivative. Bromination can be accomplished using pyridinium tribromide, phenyltrimethylammonium tribromide or other brominating agents known in the art [Rasmusson, G.H. *et al*, Steroids 22, 107 (1973)]. The 16α-bromo compound is dehydrobrominated by reaction with a base, *e.g.* potassium *tert*-butoxide in xylene or dimethyl sulfoxide, to give the $\Delta^{15}$ compound [Johnson, W.S. *et al*, J. Am. Chem. Soc. 79, 2005 (1957); Poirier, D. *et al*, Tetrahedron 47, 7751 (1991)]. Mild hydrolysis of the ethylene ketal, for instance by treatment with *p*-toluenesulfonic acid in a mixture of acetone and water [Johnson, *supra*], results in a 3-methoxyestra-1,3,5(10),15-tetraen-17-one derivative which is then converted to a 3-methoxyestra-1,3,5(10),14,16-pentaen-17-ol acetate by acid-catalyzed reaction with acetic anhydride, isopropenyl acetate or other acetylating agents [Rasmusson, *supra*; Bull, J.R. *et al*, J. Chem. Soc., Perkin Trans. I, 241 (1990)]. The acetate is treated with sodium

borohydride or other reducing agents [Rasmusson, *supra*] to result in the formation of a (17β)-3-methoxyestra-1,3,5(10),14-tetraen-17-ol derivative. The $\Delta^{14}$ double bond is hydrogenated, for instance by using palladium on activated carbon [Schubert, G. *et al*, Z. Chem. 23, 410 (1983)], whereafter oxidation of the resulting (14β,17β)-3-methoxyestra-1,3,5(10)-trien-17-ol derivative results in the formation of a (14β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative. The oxidation can be carried out by using methods known in the art, *e.g.* by the use of an Oppenauer oxidation, a Swern oxidation, a Moffatt oxidation, a Dess-Martin oxidation, or by the use of chromium(VI) reagents like Jones reagent, pyridinium dichromate, pyridinium chlorochromate and similar reagents known in the art, 4-methylmorpholine *N*-oxide/tetrapropylammonium perruthenate and others [Hudlicky, M., *Oxidations in Organic Chemistry*, ACS Monograph 186, Washington, DC, 1990].

A (14β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative can also be optained as follows: a 3-methoxyestra-1,3,5(10)-trien-17-one derivative is brominated directly, for instance by reaction with copper(II) bromide in benzene/methanol [Segaloff, A. *et al*, Steroids 22, 99 (1973)], or by reaction of the corresponding enol acetate with bromine [Johnson, *supra*], to produce a 16α-bromoketone derivative. Dehydrobromination, *e.g.* by reaction with $LiBr/Li_2CO_3$/DMF [Bull, *supra*], usually results in a mixture of (14β)-3-methoxyestra-1,3,5(10),15-tetraen-17-one and 3-methoxyestra-1,3,5(10),14-tetraen-17-one derivatives which can then be hydrogenated as described above to a (14β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative. Alternatively, a 16α-bromoketone can be converted to the ethylene ketal prior to dehydrobromination [Johnson].

A (14β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative can be converted, by Wittig reaction, to a (14β)-3-methoxy-17-methyleneestra-1,3,5(10)-triene derivative [Maercker, A. in Org. Reactions 14, p. 270, Wiley, New York, 1965]. Alternatively, Peterson reactions can be used [Ager, D.J. in Org. Reactions 38, p. 1, Wiley, New York, 1990].

Hydroboration, for instance by use of 9-BBN [Zweifel, G. *et al*, in Org. Reactions 13, p. 1, Wiley, New York, 1963], results in the formation of a (14β,17α)-3-methoxyestra-1,3,5(10)-triene-17-methanol derivative. Birch reduction [Caine, D. in Org. Reactions 23, p. 1, Wiley, New York, 1976] and hydrolysis of the resulting (14β,17α)-3-methoxyestra-2,5(10)-diene-17-methanol derivative then provides a (14β,17α)-17-(hydroxymethyl)estr-4-en-3-one derivative of the invention.

Optionally, a (14β,17α)-3-methoxyestra-1,3,5(10)-trien-17-methanol derivative can be oxidized as described above to the corresponding 17-carboxaldehyde. The aldehyde can be reacted with an (organometallic) compound of formula $R_{13}M$ in which $R_{13}$ has the previously given meaning except for hydrogen, any functional groups present in $R_{13}$ being suitably protected, and M is Li, Na, K, MgX, ZnX, $CeX_2$, $SiR_3$ or $SnR_3$, to produce a (14β,17α)-3-methoxy-17-($CHR_{13}OH$)estra-1,3,5(10)-triene which is usually a mixture of C-20 epimers. The latter can be separated whereafter Birch reduction and hydrolysis as described above and removal of any protecting groups still present provides the (14β,17α)-17-($CHR_{13}OH$)estr-4-en-3-one derivatives of the invention in which $R_{13}$ has the previously given meaning except for hydrogen.

Optionally, a (14β,17α)-3-methoxy-17-($CHR_{13}OH$)estra-1,3,5(10)-triene can be oxidized as described above to obtain a 20-ketone which can then be reacted with an (organometallic) compound of formula $R_{14}M$, $R_{14}$ having the previously given meaning except for hydrogen, any functional groups present in $R_{14}$ being suitably protected, and M having the previously given meaning. In that case Birch reduction, hydrolysis and removal of any protecting groups still present will provide (14β,17α)-17-($CR_{13}R_{14}OH$)estr-4-en-3-one derivatives of the invention wherein $R_{13}$ and $R_{14}$ have the previously given meaning except for hydrogen. This procedure can also be used for the preparation of compounds of the invention in which $R_{13}$ and $R_{14}$ together with the carbon atom at which they are placed form a ($C_{3-6}$)cycloalkyl ring or a ($C_{5-6}$)cycloalkenyl ring.

Optionally, the 20-ketone can be reduced by reaction with $LiAlH_4$, $NaBH_4$ or other reducing agents. In that case, (14β,17α)-17-($CHR_{13}OH$)estr-4-en-3-one derivatives are obtained of inverted stereochemistry at C-20.

Optionally, a (14β,17α)-3-methoxyestra-2,5(10)-diene-17-methanol derivative, *i.e.* the product obtained after the Birch reduction, can be oxidized as described above to the corresponding 17-carboxaldehyde. Reaction with a compound of formula $R_{13}M$ as described above and hydrolysis affords the (14β,17α)-17-($CHR_{13}OH$)estr-4-en-3-one derivatives of the invention as already described above. This reaction sequence allows the introduction of substituents $R_{13}$, and analogously, $R_{14}$, which would not survive a Birch reduction. Optionally, the (14β,17α)-3-methoxyestra-2,5(10)-diene-17-methanol derivative might also be converted to a more stable

system, *e.g.* a (14β,17α)-3,3-dimethoxyestr-5(10)-ene-17-methanol derivative, prior to oxidation and reaction with $R_{13}M$, and so on.

Wittig reaction of a (14β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative with *e.g.* ethyltriphenylphosphonium bromide leads prominantly to the (17Z)-ethylidene derivative which on hydroboration gives the (14β,17α,20R)-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ol derivative. Birch reduction and hydrolysis then results in (14β,17α,20R)-20-hydroxy-19-norpregn-4-en-3-one derivatives of the invention ($R_{13}$ = $CH_3$). On the other hand, Wittig-Horner reaction with *e.g.* triethyl phosphonoacetate results in a ethyl (14β,17E)-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-oate, which can be converted, by methods known in the art, to a (14β,17E)-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene, which on hydroboration results in the (14β,17α,20S)-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ol derivative. Optionally, the ethyl (14β,17E)-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-oate can be subjected to homologation, by using methods known in the art, prior to hydroboration to the 20-hydroxy compound, which provides an additional method to obtain a (14β,17α,20S)-17-($CHR_{13}OH$)estr-4-en-3-one derivative of the invention in which $R_{13}$ has the previously given meaning except for hydrogen. Techniques for homologation are known in the art [Mathieu, J. *et al*: *Formation of C-C Bonds*, Vol. I-III, Georg Thieme Publishers, Stuttgart, 1973].

Compounds of formula I with substituents at C-3, C-4, C-6, C-7, C-10, C-11, C-13, C-14, C-15, C-16 and C-17 other than those described under the definition of formula II, or compounds without double bonds in the steroid nucleus or with double bonds other than a $\Delta^4$ double bond, can be prepared as follows.

Compounds of the invention in which $R_1$ is (H,H), (H,OR), NOR, and R is H, ($C_{1-6}$) alkyl, or ($C_{1-6}$) acyl can be prepared, using standard methods, from compounds of formula I in which $R_1$ is oxo.

Compounds in which $R_2$ is ($C_{1-6}$) alkyl or halogen are obtained, using standard methods, from compounds of formula I in which $R_2$ is hydrogen.

Compounds in which $R_3$ is ($C_{2-6}$) alkenyl or ($C_{2-6}$) alkynyl are obtained, using standard methods, from compounds of formula I in which $R_3$ is hydrogen.

Compounds in which $R_4$ has the meaning described above except for hydrogen or ($C_{1-6}$) alkyl can be prepared from *e.g.* (7α,17β)-17-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methoxyestra-1,3,5(10)-triene-7-methanol [Kuenzer, H. *et al*, Tetrahedron Lett. 32, 743

(1991)]. Inversion of the stereochemistry at C-14 and construction of the side-chain at C-17 are carried out as described above. Construction of the functionalized and/or unsaturated side-chain at C-7 is performed using methods known in the art. It is clear that these processes cannot be executed independently. The precise sequence of reaction steps needed for the inversion at C-14 and for the construction of the two side-chains, including the Birch reduction and the hydrolysis of the resulting estra-2,5(10)-diene is dictated by methods common in synthetic strategy.

Compounds in which $R_5$ is methyl are obtained from *e.g.* (3β)-3-(acetyloxy)androsta-5,14-dien-17-one [Andre, A.F.St. *et al*, J. Am. Chem. Soc. 74, 5506 (1952)] by a sequence of reaction steps analogous to that described above.

Compounds in which $R_6$ has the previously given meaning except for hydrogen or ($C_{1-6}$) alkyl can be obtained from *e.g.* (11α)-11-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal [Collins, D.J. *et al*, Aust. J. Chem. 36, 339 (1983)], (11β)-11-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal [Choe, Y.S. *et al*, J. Med. Chem. 38, 816 (1995)], (11β)-11-(hydroxymethyl)-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal [van den Broek, A.J. *et al*, Steroids 30, 481 (1977)], or 3-methoxyestra-1,3,5(10)-triene-11,17-dione cyclic 17-(1,2-ethanediyl acetal) [van den Broek, A.J. *et al*, Recl. Trav. Chim. Pays-Bas 94, 35 (1975)]. Construction of functionalized and/or unsaturated side-chains at C-11 can be accomplished using methods known in the art. However, these operations are subject to the same limitations described for the introduction of functionalized and/or unsaturated side-chains at C-7.

Compounds in which $R_8$ is ethyl can be prepared from *e.g.* 13-ethylgon-4-ene-3,17-dione [Brito, M. *et al*, Synth. Comm. 26, 623 (1996)].

14β-Substituted compounds can be obtained as follows. A 3-methoxyestra-1,3,5(10),14-tetraen-17-ol derivative, in which the hydroxy group is protected as an ether, *e.g.* as an alkoxyalkyl ether or a silyl ether, or as an ester, *e.g.* an acetate or benzoate ester, is converted, by hydroboration of the $\Delta^{14}$ double bond [Hosoda, H. *et al*, Chem. Pharm. Bull. 23, 3141 (1975)] and subsequent oxidation of the 15-hydroxy compound produced, to a (17β)-3-methoxy-17-OR-estra-1,3,5(10)-trien-15-one derivative. The latter is alkylated, *e.g.* by methyl, a reaction which is accompanied by elimination of the protected hydroxy group at C-17 [Pettit, G.R. *et al*, J. Chem. Soc. (C) 2024 (1967)], to afford *e.g.* a (14β)-3-methoxy-14-methylestra-1,3,5(10),16-tetraen-15-one derivative. Conjugated addition of *e.g.* potassium cyanide and

reduction of the carbonyl group to methylene gives a (14β,17β)-3-methoxy-14-methylestra-1,3,5(10)-trien-17-carbonitrile compound which after epimerization at C-17 by reaction with a base, *e.g.* LDA, followed by protonation, can be reduced to a (14β,17α)-3-methoxy-14-methylestra-1,3,5(10)-trien-17-carboxaldehyde. Reduction of the latter with $LiAlH_4$ or $NaBH_4$, Birch reduction and hydrolysis then results in a (14β,17α)-17-(hydroxymethyl)-14-methylestr-4-en-3-one derivative of the invention.

15-Substituted compounds can be obtained as follows. Conjugated addition of an (organometallic) compound of formula $R_{10}M$ wherein $R_{10}$ has the previously given meaning, any functional groups present in $R_{10}$ being suitably protected, and M having the previously given meaning, to a (14β)-3-methoxyestra-1,3,5(10),15-tetraen-17-one derivative provides a (14β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative, substituted at C-15, which can then be converted as described above to a (14β,17α)-17-(hydroxymethyl)estr-4-en-3-one derivative of the invention, substituted at C-15.

16-Substituted compounds can be obtained from a (14β)-3-methoxyestra-1,3,5(10)-trien-17-one derivative by alkylation at C-16, or, alternatively, from a (14β)-3-methoxyestra-1,3,5(10),15-tetraen-17-one derivative by alkylation and hydrogenation of the 16-substituted $\Delta^{14}$ compound produced. Optionally, the stereochemistry at C-16 can be inverted as described above. The 16-substituted 17-keto derivatives produced can be converted to the compounds of the invention as described above.

17β-Substituted compounds of formula I can be obtained as follows. A (14β,17α)-3-methoxyestra-1,3,5(10)-triene-17-carboxaldehyde derivative can be alkylated using standard methods, or via metalloimine or silyl enol ether chemistry. Alternatively, it can be converted to the corresponding enol silyl ether which is then transformed by cyclopropanation into a protected (14β,17α,21α)-3-methoxy-20-hydroxy-17,21-cyclo-19-norpregna-1,3,5(10)-triene [Orr, J.C. *et al*, J. Chem. Soc., Perkin Trans. I, 2667 (1994); Simmons, H.E. *et al*, in Org. Reactions 20, p. 1, Wiley, New York, 1973]. Hydrolysis results in a (14β,17α)-3-methoxy-17-methylestra-1,3,5(10)-triene-17-carboxaldehyde [Wenkert, E., Acc. Chem. Res. 13, 27 (1980)]. Likewise, cyclopropanation with ethyl diazoacetate [Dave, V. *et al*, in Org. Reactions 18, p. 218, Wiley, New York, 1970], and hydrolysis will produce a ethyl (14β)-3-methoxy-17-formyl-19-norpregna-1,3,5(10)-trien-21-oate, which can then serve as starting material for other 17β-substituted compounds of the invention.

Compounds of the invention in which $R_{15}$ is $SO_3H$, $(C_{1-6})$ alkyl, $(C_{1-15})$ acyl are obtained, by using methods known in the art, from compounds of formula I in which $R_{15}$ is hydrogen.

Compounds of the invention without unsaturations in the steroid nucleus are produced from $\Delta^4$ compounds wherein $R_1$ is oxo.

Compounds of the invention having $\Delta^{5(10)}$ double bond, or a $\Delta^{4,9}$ diene system are produced from the $\Delta^{2,5(10)}$ dienes obtained after the Birch reduction.

Compounds having a $\Delta^{11}$ double bond can be prepared from *e.g.* (11β)-11-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal [Choe, Y.S. *et al*, J. Med. Chem. 38, 816 (1995)].

Compounds of the invention having a $\Delta^{15}$ double bond can be prepared from a (14β)-3-methoxyestra-1,3,5(10),15-tetraen-17-one derivative via a Wittig condensation with $(Ph)_3P$=CHOMe and hydrolysis of the intermediate enol ether. The resulting (14β,17α)-3-methoxyestra-1,3,5(10),15-tetraene-17-carboxaldehyde can then be transformed into a (14β,17α)-17-(hydroxymethyl)estra-4,15-dien-3-one compound of the invention.

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

**Example 1**

(14β,17α)-17-(Hydroxymethyl)estr-4-en-3-one.

**i)** - Lithium amide (6.6 g) was added to a suspension of methyltriphenylphosphonium bromide (113 g) in dry toluene (300 ml) and dry dimethyl sulfoxide (24 ml). The reaction mixture was heated to 65 °C for 30 min. After cooling to 35-40 °C, a solution of (14β)-3-methoxyestra-1,3,5(10)-trien-17-one [Johnson, W.S. *et al*, J. Am. Chem. Soc. 79, 2005 (1957); 30 g] in dry toluene (225 ml) was added and the mixture was heated at 60 °C for 22 h. Then it was cooled and poured into water. The product was extracted into ethyl acetate; the combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. In order to achieve complete conversion of starting material, the procedure was repeated. The triphenylphosphine oxide was removed by addition of diethyl ether and filtration. Column

chromatography of the crude product afforded (14β)-3-methoxy-17-methyleneestra-1,3,5(10)-triene (26 g).

**ii)** - A solution of borane-dimethyl sulfide complex (26.6 ml) in dry tetrahydrofuran (105 ml) was cooled to 0 °C. A solution of 1,5-cyclooctadiene (33 ml) in dry tetrahydrofuran (32 ml) was added dropwise in 45 min. while maintaining the temperature below 10 °C. The mixture was heated under reflux for 1 h and then cooled to 13 °C. A solution of the product obtained in the previous step (25 g) in dry tetrahydrofuran (100 ml) was added in 10 min. and the reaction mixture was heated under reflux for 2.5 h and then stirred at room temperature overnight. An aqueous solution of sodium hydroxide (3 M, 120 ml) was added in 30 min., followed by an aqueous solution of hydrogen peroxide (30 %, 120 ml) in 1 h (T ≤ 50 °C). After 2 h stirring the reaction mixture was poured into an aqueous solution of sodium sulfite (10 %, 1.75 l) and the product was extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Trituration (ethanol/water 1:1) afforded (14β,17α)-3-methoxyestra-1,3,5(10)-triene-17-methanol (23.6 g).

**iii)** - The alcohol obtained in the previous step (2.0 g) in dry tetrahydrofuran (35 ml) was added to a solution of lithium (0.86 g) in liquid ammonia (52 ml), cooled between -50 °C and -60 °C. After 1 h stirring at -50 °C and 1 h at -40 °C, dry ethanol 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 sodium sulfate and concentrated under reduced pressure, to give (14β,17α)-3-methoxyestra-2,5(10)-diene-17-methanol (2.13 g). The product was used in the following step without further purification.

**iv)** - A solution of the diene obtained in the previous step (0.30 g) in acetone (12 ml) was treated with hydrochloric acid (2-6 M, 0.6 ml). After 0.1-2 h stirring at room temperature, the reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogencarbonate, or with an aqueous solution of sodium hydroxide (1 M) followed by addition of a saturated aqueous solution of sodium hydrogencarbonate. Optionally the acetone was evaporated under reduced pressure. The product was extracted into ethyl acetate; the combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate and with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography and crystallization afforded (14β,17α)-17-(hydroxymethyl)estr-4-en-3-one (0.21 g), m.p. 115-118 °C.

**Example 2**

(14β,17α,20S)-20-Hydroxy-19-norpregn-4-en-3-one (a) and (14β,17α,20R)-20-hydroxy-19-norpregn-4-en-3-one (b).

**i)** - A solution of sulfur trioxide pyridine complex (50.0 g) in dimethyl sulfoxide (250 ml) was added in 15 min. to a solution of (14β,17α)-3-methoxyestra-1,3,5(10)-triene-17-methanol (Example 1, step **ii**; 23.6 g) in a mixture of dimethyl sulfoxide (425 ml) and triethylamine (70 ml). After 20 min. stirring, 2-propanol (88 ml) was added and stirring was continued for 15 min. The reaction mixture was poured into water (1300 ml) and the product was extracted into dichloromethane. The combined organic phases were washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. Trituration (water/ethanol, first 3:2, then 1:1) afforded (14β,17α)-3-methoxyestra-1,3,5(10)-triene-17-carboxaldehyde (18.8 g).

**ii)** - A solution of iodomethane (5.11 ml) in dry diethyl ether (24 ml) was added dropwise to a suspension of magnesium (1.82 g) in the same solvent (16 ml) while keeping the temperature below 30 °C. After 30 min. stirring the Grignard reagent was cooled to 0 °C and a solution of the aldehyde obtained in the previous step (3.5 g) in dry tetrahydrofuran (17.5 ml) was added dropwise. The reaction mixture was stirred for 30 min. Then it was poured into an aqueous solution of ammonium chloride (10 %) 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. Column chromatography afforded (14β,17α,20S)-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ol (1.78 g) and (14β,17α,20R)-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ol (1.16 g).

**iiia)** - Following a procedure analogous to that described under **iii** of Example 1, (14β,17α,20S)-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ol (1.5 g) was converted to (14β,17α,20S)-3-methoxy-19-norpregna-2,5(10)-dien-20-ol (1.59 g).

**iiib)** - Following a procedure analogous to that described above, (14β,17α,20R)-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ol (1.0 g) was converted to (14β,17α,20R)-3-methoxy-19-norpregna-2,5(10)-dien-20-ol (1.13 g).

**iva)** - Following a procedure analogous to that described under **iv** of Example 1, (14β,17α,20S)-3-methoxy-19-norpregna-2,5(10)-dien-20-ol (1.42 g) was converted to (14β,17α,20S)-20-hydroxy-19-norpregn-4-en-3-one (0.84 g), m.p. 152-153 °C.

**ivb)** - Following a procedure analogous to that described above, (14β,17α,20R)-3-methoxy-19-norpregna-2,5(10)-dien-20-ol (1.13 g) was converted to (14β,17α,20R)-20-hydroxy-19-norpregn-4-en-3-one (0.72 g), m.p. 108-109.5 °C.

**Example 3**

In a manner analogous to the procedures described in Example 2, and using (14β,17α)-3-methoxyestra-1,3,5(10)-triene-17-carboxaldehyde (Example 2, step **i)** as starting material, the following products were prepared:

a) - [14β,17α(S)]-17-(1-Hydroxypropyl)estr-4-en-3-one. M.p. 122-123 °C.

b) - [14β,17α(R)]-17-(1-Hydroxypropyl)estr-4-en-3-one. M.p. 120-121 °C.

c) - (14β,17α,20S)-20-Hydroxy-19,21-dinorchol-4-en-3-one. M.p. 102-102.5 °C.

d) - (14β,17α,20R)-20-Hydroxy-19,21-dinorchol-4-en-3-one.

**Example 4**

(7α,14β,17α)-17-(Hydroxymethyl)-7-methylestr-4-en-3-one.

**i)** - A mixture of (7α,17β)-3-methoxy-7-methylestra-1,3,5(10),14-tetraen-17-ol [Segaloff, A. *et al*, Steroids 22, 99 (1973); 86.2 g] and palladium on activated carbon (5 %; 34.5 g) in ethanol (578 ml) and dichloromethane (414 ml) was stirred under hydrogen (3 bar) at room temperature for 24 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure, to give (7α,14β,17β)-3-methoxy-7-methylestra-1,3,5(10)-trien-17-ol (83.0 g). The product was used in the following step without further purification.

**ii)** - A solution of the product obtained in the previous step (37.4 g) in acetone (1880 ml) was cooled to 0 °C. Jones reagent (8 M, 37.4 ml) was added dropwise while keeping the temperature below 10 °C. The reaction mixture was stirred for 30 min. 2-Propanol (21 ml) was added and after 10 min. stirring the mixture was filtered over dicalite. The filtrate was partially concentrated under reduced pressure and the product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium thiosulfate, a saturated aqueous solution of sodium hydrogensulfate and brine, dried over sodium sulfate and concentrated under reduced pressure, to give (7α,14β)-3-methoxy-7-methylestra-1,3,5(10)-trien-17-one (35.85 g). The product was used in the following step without further purification.

**iii)** - A mixture of methyltriphenylphosphonium bromide (21.8 g), potassium *tert*-butoxide (5.7 g) and dry toluene (218 ml) was heated under reflux for 1 h. A solution of the ketone obtained in the previous step (6.07 g) in dry toluene (50 ml) was added dropwise and heating was continued for another 1 h. After cooling, 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 sodium sulfate and concentrated under reduced pressure. Column chromatography of the crude product afforded (7α,14β)-3-methoxy-7-methyl-17-methyleneestra-1,3,5(10)-triene (5.85 g).

**iv)** - A solution of borane-dimethyl sulfide complex (5.94 ml) in dry tetrahydrofuran (27 ml) was cooled to 0 °C. A solution of 1,5-cyclooctadiene (7.36 ml) in dry tetrahydrofuran (7 ml) was added dropwise while maintaining the temperature below 10 °C. The mixture was heated under reflux for 1 h and then cooled to room temperature. A solution of the product obtained in the previous step (5.85 g) in dry tetrahydrofuran (70 ml) was added dropwise and the reaction mixture was stirred at room temperature for 1 h. The mixture was cooled to 0 °C, and an aqueous solution of sodium hydroxide (2 M, 14.75 ml) was added carefully (T ≤ 15 °C), followed by an aqueous solution of hydrogen peroxide (30 %, 11.8 ml). After 2 h stirring the reaction mixture was poured into water and the product was extracted into ethyl acetate. The combined organic phases were washed with an aqueous solution of sodium thiosulfate and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (7α,14β,17α)-3-methoxy-7-methylestra-1,3,5(10)-triene-17-methanol (1.60 g).

**v)** - The alcohol obtained in the previous step (1.06 g) in dry tetrahydrofuran (15 ml) was added to a refluxing solution of lithium (1.35 g) in liquid ammonia (64 ml). After 4 h stirring, *tert*-butanol was added followed by ethanol and the ammonia was allowed to evaporate. The 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,14β,17α)-3-methoxy-7-methylestra-2,5(10)-diene-17-methanol (0.79 g). The product was used in the following step without further purification.

**vi)** - Following a procedure analogous to that described under **iv** of Example 1, the diene obtained in the previous step (0.79 g) was converted to (7α,14β,17α)-17-(hydroxymethyl)-7-methylestr-4-en-3-one (0.36 g), m.p. 157-159 °C.

**Example 5**

(7α,14β,17α,20S)-20-Hydroxy-7-methyl-19-norpregn-4-en-3-one (a) and (7α,14β,17α,20R)-20-hydroxy-7-methyl-19-norpregn-4-en-3-one (b).

**i)** - Pyridinium chlorochromate (10.1 g) was added to a solution of (7α,14β,17α)-3-methoxy-7-methylestra-1,3,5(10)-triene-17-methanol (Example 4, step **iv**; 5.90 g) in dichloromethane (295 ml) containing sodium acetate (8.85 g) and silica (17.7 g). After 3 h stirring at room temperature the reaction mixture was filtered over dicalite and the filtrate was concentrated under reduced pressure. Column chromatography afforded (7α,14β,17α)-3-methoxy-7-methylestra-1,3,5(10)-triene-17-carboxaldehyde (4.16 g).

**ii)** - Following a procedure analogous to that described under **ii** of Example 2, the aldehyde obtained in the previous step (1.40 g) was converted to (7α,14β,17α,20S)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-ol (0.53 g) and (7α,14β,17α,20R)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-ol (0.40 g).

**iiia)** - A solution of (7α,14β,17α,20S)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-ol (0.53 g) in dry tetrahydrofuran (10 ml) was added to liquid ammonia (25 ml), cooled to -40 °C. Lithium granulate (0.334 g) was added in portions and the reaction mixture was stirred for 30 min. Dry ethanol (2.9 ml) was added and stirring was continued for 20 min. Solid ammonium chloride (1 g) was added and the reaction mixture was stirred until decolourization. The ammonia was allowed to evaporate and the reaction mixture was poured into water. The product was extracted into ethyl acetate; the combined organic phases were washed with a saturated aqueous solution of ammonium chloride and brine, dried over sodium sulfate, and concentrated under reduced pressure, to afford (7α,14β,17α,20S)-3-methoxy-7-methyl-19-norpregna-2,5(10)-dien-20-ol (0.50 g). The product was used in the following step without further purification.

**iiib)** - Following a procedure analogous to that described above, (7α,14β,17α,20R)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-ol (0.40 g) was converted to (7α,14β,17α,20R)-3-methoxy-7-methyl-19-norpregna-2,5(10)-dien-20-ol (0.39 g).

**iva)** - Following a procedure analogous to that described under **iv** of Example 1, (7α,14β,17α,20S)-3-methoxy-7-methyl-19-norpregna-2,5(10)-dien-20-ol (0.50 g) was

converted to (7α,14β,17α,20S)-20-hydroxy-7-methyl-19-norpregn-4-en-3-one (0.22 g), m.p. 157-160 °C.

**ivb)** - Following a procedure analogous to that described under **iv** of Example 1, (7α,14β,17α,20R)-3-methoxy-7-methyl-19-norpregna-2,5(10)-dien-20-ol (0.39 g) was converted to (7α,14β,17α,20R)-20-hydroxy-7-methyl-19-norpregn-4-en-3-one (0.22 g), $[\alpha]_D^{20}$ = +75 ° (c = 0.5, dioxane).

**Example 6**

[7α,14β,17α(R)]-17-(1-Hydroxy-2-methylpropyl)-7-methylestr-4-en-3-one.

In a manner analogous to the procedures described under **ii** - **iv** of Example 5 [7α,14β,17α(R)]-17-(1-hydroxy-2-methylpropyl)-7-methylestr-4-en-3-one was prepared from (7α,14β,17α)-3-methoxy-7-methylestra-1,3,5(10)-triene-17-carboxaldehyde (Example 5, step **i**). M.p. 142-144 °C.

**Example 7**

(7α,14β,17α)-20-Hydroxy-7,20-dimethyl-19-norpregn-4-en-3-one.

**i)** - Following a procedure analogous to that described under **ii** of Example 4, a mixture (1:1) of (7α,14β,17α,20S)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-ol and (7α,14β,17α,20R)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-ol (Example 5, step **ii**; 1.04 g) was converted to (7α,14β,17α)-3-methoxy-7-methyl-19-norpregna-1,3,5(10)-trien-20-one (0.85 g).

**ii)** - Following a procedure analogous to that described under **ii** of Example 2, the ketone obtained in the previous step (0.85 g) was converted to (7α,14β,17α)-3-methoxy-7,20-dimethyl-19-norpregna-1,3,5(10)-trien-20-ol (0.90 g).

**iii)** - Following a procedure analogous to that described under **v** of Example 4, the product obtained in the previous step (0.90 g) was converted to (7α,14β,17α)-3-methoxy-7,20-dimethyl-19-norpregna-2,5(10)-dien-20-ol (0.90 g).

**iv)** - A solution of the diene obtained in the previous step (0.90 g) in a mixture of acetone (40 ml), tetrahydrofuran (10 ml) and methanol (3 ml) was treated with hydrochloric acid (2 M, 2.5 ml). After 3 h stirring at room temperature, the reaction mixture was neutralized with an

aqueous solution of sodium hydroxide (1 M). 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 and crystallization afforded (7α,14β,17α)-20-hydroxy-7,20-dimethyl-19-norpregn-4-en-3-one (0.45 g). M.p. 179-181 °C.

**Example 8**

(7α,14β,17α)-17-Fluoro-17-(hydroxymethyl)-7-methylestr-4-en-3-one.

**i)** - *m*-Chloroperbenzoic acid (70-75 %, 2.71 g) was added to a solution of (7α,14β)-3-methoxy-7-methyl-17-methyleneestra-1,3,5(10)-triene (Example 4, step **iii**; 2.96 g) in dichloromethane (120 ml). The reaction mixture was stirred at room temperature for 24 h whereafter the reaction was quenched with an aqueous solution of sodium thiosulfate (10 %). The product was extracted into dichloromethane; the combined organic phases were washed with an aqueous solution of sodium thiosulfate (10 %), a saturated aqueous solution of sodium hydrogencarbonate and with brine, and dried over sodium sulfate. The resulting solution was concentrated under reduced pressure, to give (7α,14β,17α)-3-methoxy-7-methylestra-1,3,5(10)-triene[17,2']oxirane (2.94 g). The product was used in the following step without further purification.

**ii)** - A solution of the epoxide obtained in the previous step (0.31 g) in dry dichloromethane (10 ml) was cooled to 0 °C. Hydrogen fluoride-pyridine (70 % HF, 0.1 ml) was added and the reaction mixture was stirred for 3 h. Another portion of hydrogen fluoride-pyridine (0.1 ml) was added and the reaction mixture was stirred for another 3 h. The 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 hydrogencarbonate and brine, dried over sodium sulfate, and concentrated under reduced pressure. Column chromatography afforded (7α,14β,17α)-17-fluoro-7-methylestra-1,3,5(10)-triene-17-methanol, contaminated with (7α,14β)-7-methylestra-1,3,5(10),16-tetraene-17-methanol (0.12 g).

**iii)** - A solution of the mixture obtained in the previous step (0.12 g), dry pyridine (0.50 ml) and acetic anhydride (0.30 ml) in dry tetrahydrofuran (5 ml) was stirred at room temperature for 72 h. The reaction mixture was poured into ice-water, and after 1 h stirring, 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,14β,17α)-17-[(acetyloxy)methyl]-17-fluoro-7-methylestra-1,3,5(10)-triene (0.090 g).

**iv)** - Following procedures analogous to those described under **iii** of Example 5 and **iv** of Example 7 the product obtained in the previous step was converted to (7α,14β,17α)-17-fluoro-17-(hydroxymethyl)-7-methylestr-4-en-3-one (0.026 g). M.p. 145-146 °C.

**Example 9**

(7α,14β,17α)-17-[(Acetyloxy)methyl]-7-methylestr-4-en-3-one.

A solution of (7α,14β,17α)-17-(hydroxymethyl)-7-methylestr-4-en-3-one (Example 4; 0.30 g) in a mixture of pyridine (2 ml) and acetic anhydride (1 ml) was stirred at room temperature for 2 h. 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 brine, dried over sodium sulfate, and concentrated under reduced pressure. Column chromatography afforded (7α,14β,17α)-17-[(acetyloxy)methyl]-7-methylestr-4-en-3-one (0.20 g). M.p. 65-68 °C.

**Example 10**

In a manner analogous to that described in Example 9, and using (7α,14β,17α)-17-(hydroxymethyl)-7-methylestr-4-en-3-one (Example 4) as starting material, the following products were prepared:

a) - (7α,14β,17α)-7-Methyl-17-[[(1-oxoundecyl)oxy]methyl]-estr-4-en-3-one. M.p. 45.5-48.5 °C.

b) - (7α,14β,17α)-17-[[[(*trans*-4-Butylcyclohexyl)carbonyl]oxy]methyl]-7-methylestr-4-en-3-one. $[\alpha]_D^{20}$ = +63.1 ° (c = 0.635, dioxane).

**Example 11**

Following procedures analogous to those described in Example 4 and 2, respectively, and using (17β)-13-ethyl-3-methoxygona-1,3,5(10),14-tetraen-17-ol [US 3577410 (1968)] as starting material, the following products were prepared:

a) - (14β,17α,20S)-13-Ethyl-20-hydroxy-18,19-dinorpregn-4-en-3-one.

$[\alpha]_D^{20}$ = +78.3 ° (c = 0.36, dioxane).

b) - (14β,17α,20R)-13-Ethyl-20-hydroxy-18,19-dinorpregn-4-en-3-one.

M.p. 110.5-111.5 °C.

c) - [14β,17α(S)]-13-Ethyl-17-(1-hydroxypropyl)gon-4-en-3-one.

$[\alpha]_D^{20}$ = +64.1 ° (c = 0.34, dioxane).

d) - [14β,17α(R)]-13-Ethyl-17-(1-hydroxypropyl)gon-4-en-3-one.

M.p. 89.5-90.5 °C.

e) - [14β,17α(S)]-13-Ethyl-17-(1-hydroxy-2-propenyl)gon-4-en-3-one.

f) - [14β,17α(R)]-13-Ethyl-17-(1-hydroxy-2-propenyl)gon-4-en-3-one.

M.p. 128.5-129.5 °C.

**Example 12**

(11β,14β,17α,20S)-11-Ethyl-20-hydroxy-19-norpregn-5(10)-en-3-one (a), and

(11β,14β,17α,20R)-11-ethyl-20-hydroxy-19-norpregn-5(10)-en-3-one (b).

**i)** - A solution of (11β)-11-ethyl-3-methoxyestra-1,3,5(10)-trien-17-one [Pomper, M.G. *et al*, J. Med. Chem. 33, 3143 (1990); 15 g] and *p*-toluenesulfonic acid (0.25 g) in a mixture of tetrahydrofuran (50 ml), ethylene glycol (30 ml) and triethyl orthoformate (30 ml) was stirred at room temperature overnight. Sodium hydrogencarbonate (1 g) was added and after stirring for 10 min. excess solvent was evaporated and the mixture was poured into an aqueous solution of sodium hydrogencarbonate (5 %, 200 ml). The product was extracted into ethyl acetate and the combined organic phases were washed with brine and dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (11β)-11-ethyl-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal (16.2 g).

**ii)** - Phenyltrimethylammonium tribromide (19 g) was added in small portions and in 10 min. to a solution of the product obtained in the previous step (16 g) in tetrahydrofuran (70 ml). After stirring for an additional 30 min. sodium acetate (10 g) was added and the mixture was poured into an aqueous solution of sodium acetate (10 %, 300 ml). The product was extracted into ethyl acetate; the combined organic phases were washed with an aqueous solution of sodium hydrogensulfite (10 %) and water, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography provided (11β,16α)-16-bromo-11-ethyl-3-methoxyestra-1,3,5(10)-trien-17-one cyclic 1,2-ethanediyl acetal (18.5 g).

**iii)** - A solution of the bromide obtained in the previous step (18 g) and potassium *tert*-butoxide (18 g) in dimethyl sulfoxide (140 ml) was heated at 45 °C for 2 h. The 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. Column chromatography provided (11β)-11-ethyl-3-methoxyestra-1,3,5(10),15-tetraen-17-one cyclic 1,2-ethanediyl acetal (13.0 g).

**iv)** - A solution of the product obtained in the previous step (13.0 g) and *p*-toluenesulfonic acid (1 g) in a mixture of acetone (180 ml) and water (20 ml) was stirred at room temperature for 1.5 h. A saturated aqueous solution of sodium hydrogencarbonate (20 ml) was added and the acetone was removed under reduced pressure. The product was extracted into ethyl acetate; the combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Crystallization afforded provided (11β)-11-ethyl-3-methoxyestra-1,3,5(10),15-tetraen-17-one (7.6 g).

**v)** - A solution of the ketone obtained in the previous step (8.5 g) and *p*-toluenesulfonic acid (0.20 g) in isopropenyl acetate (75 ml) was heated under reflux for 30 min. The reaction medium was partially (25 ml) distilled off and replaced by fresh isopropenyl acetate (25 ml). Heating was continued for another 30 min., an aqueous solution of sodium hydrogencarbonate (10 %) was added, and the mixture was concentrated. The product was extracted into diethyl ether; the combined organic phases were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was taken up in a mixture of tetrahydrofuran (75 ml), ethanol (75 ml) and water (10 ml). Sodium borohydride (2 g) was added and the mixture was stirred at room temperature for 1 h. Excess sodium borohydride was destroyed by careful addition of acetone (25 ml). The mixture was concentrated, water was added and the product was extracted into ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated. Column chromatography provided (11β,17β)-11-ethyl-3-methoxyestra-1,3,5(10),14-tetraen-17-ol (8.0 g).

**vi)** - Following procedures analogous to those described under **i** - **v** of Example 4, the alcohol obtained in the previous step was converted to (11β,14β,17α)-11-ethyl-3-methoxyestra-2,5(10)-diene-17-methanol.

**vii)** - A solution of (11β,14β,17α)-11-ethyl-3-methoxyestra-2,5(10)-diene-17-methanol (3.3 g) in tetrahydrofuran (30 ml) was treated with hydrochloric acid (2 M, 10 ml). The reaction mixture was stirred at room temperature for 30 min. and then neutralized with a saturated

aqueous solution of sodium hydrogencarbonate. Water was added 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 (11β,14β,17α)-11-ethyl-17-(hydroxymethyl)estr-5(10)-en-3-one (3.3 g). The product was used in the following step without further purification.

**viii)** - A solution of the ketone obtained in the previous step (3.3 g) and *p*-toluenesulfonic acid (0.1 g) in methanol (30 ml) and trimethyl orthoformate (6 ml) was stirred at room temperature for 15 min. Solid sodium hydrogencarbonate (1 g) was added and stirring was continued for another 15 min. The reaction mixture was partially concentrated, an aqueous solution of sodium hydrogencarbonate (5 %) was added 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. Column chromatography provided (11β,14β,17α)-11-ethyl-3,3-dimethoxyestr-5(10)-ene-17-methanol (3.0 g).

**ix)** - A solution of oxalyl chloride (1 ml) in dichloromethane (60 ml) was cooled to -60 °C. Dimethyl sulfoxide (1.64 ml) was added and the mixture was stirred for 5 min. A solution of the compound obtained in the previous step (2.6 g) in dichloromethane (5 ml) was added and stirring was continued for 20 min. Triethylamine (5 ml) was added and the temperature was allowed to rise to 0 °C in 20 min. Water (50 ml) was added and the product was extracted into diethyl ether. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (11β,14β,17α)-11-ethyl-3,3-dimethoxyestr-5(10)-ene-17-carboxaldehyde (2.4 g).

**x)** - Following a procedure analogous to that described under **ii** of Example 2, the product obtained in the previous step (2.4 g) was converted to (11β,14β,17α,20S)-11-ethyl-3,3-dimethoxy-19-norpregn-5(10)-en-20-ol (1.25 g) and (11β,14β,17α,20R)-11-ethyl-3,3-dimethoxy-19-norpregn-5(10)-en-20-ol (0.90 g).

**xia)** - A solution of (11β,14β,17α,20S)-11-ethyl-3,3-dimethoxy-19-norpregn-5(10)-en-20-ol (1.25 g) in tetrahydrofuran (12 ml) was treated with hydrochloric acid (0.6 M, 2 ml). The reaction mixture was stirred at room temperature for 30 min. and then neutralized with a saturated aqueous solution of sodium hydrogencarbonate. Water was added 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. Crystallization gave

(11β,14β,17α,20S)-11-ethyl-20-hydroxy-19-norpregn-5(10)-en-3-one (0.85 g), m.p. 177-178 °C.

**xib)** - Following a procedure analogous to that described under **xia**, (11β,14β,17α,20R)-11-ethyl-3,3-dimethoxy-19-norpregn-5(10)-en-20-ol (0.90 g) was converted to (11β,14β,17α,20R)-11-ethyl-20-hydroxy-19-norpregn-5(10)-en-3-one (0.68 g).

**Example 13**

In a manner analogous to the procedure described under **iv** of Example 1, the following products were prepared:

a) - (11β,14β,17α,20S)-11-Ethyl-20-hydroxy-19-norpregn-4-en-3-one from (11β,14β,17α,20S)-11-ethyl-20-hydroxy-19-norpregn-5(10)-en-3-one (Example 12a). $[\alpha]_D^{20} = +82.4°$ (c = 0.71, dioxane).

b) - (11β,14β,17α,20R)-11-Ethyl-20-hydroxy-19-norpregn-4-en-3-one from (11β,14β,17α,20R)-11-ethyl-20-hydroxy-19-norpregn-5(10)-en-3-one (Example 12b). M.p. 185-186 °C.

**Example 14**

(14β,17α)-17-(Hydroxymethyl)estr-5(10)-en-3-one.

A solution of (14β,17α)-17-(hydroxymethyl)estra-2,5(10)-dien-3-one (Example 1, step **iii**; 0.30 g) in a mixture of methanol (3 ml) and tetrahydrofuran (2.1 ml) was treated with a solution of oxalic acid (0.105 g) in water (1.8 ml). After 1.5 h stirring at room temperature, the reaction mixture 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 and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (14β,17α)-17-(hydroxymethyl)estr-5(10)-en-3-one (0.20 g).

**Example 15**

(14β,17α)-17-(Hydroxymethyl)estra-4,9-dien-3-one.

Phenyltrimethylammonium tribromide (2.28 g) was added in small portions and in 10 min. to a solution of (14β,17α)-17-(hydroxymethyl)estr-5(10)-en-3-one (Example 14; 1.75 g) in dry

pyridine (47 ml). After 1.5 h stirring at room temperature the mixture was poured into ice-water and the product was extracted into ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of sodium thiosulfate, water, a saturated aqueous solution of sodium hydrogencarbonate and brine, dried over sodium sulfate, and concentrated under reduced pressure. Column chromatography provided (14β,17α)-17-(hydroxymethyl)estra-4,9-dien-3-one (0.36 g), $[\alpha]_D^{20}$ = -241 ° (c = 1, dioxane).

**Example 16**

(14β,17α,20S)-20-Hydroxy-19-norpregna-4,9-dien-3-one (a) and (14β,17α,20R)-20-hydroxy-19-norpregna-4,9-dien-3-one (b).

**i)** - Following a procedure analogous to that described for Example 14, a mixture of (14β,17α,20S)-3-methoxy-19-norpregna-2,5(10)-dien-20-ol and (14β,17α,20R)-3-methoxy-19-norpregna-2,5(10)-dien-20-ol (Example 2, step **iiia** and **iiib**, respectively; ratio 1:1; 7.87 g) was converted to a mixture of (14β,17α,20S)-20-hydroxy-19-norpregn-5(10)-en-3-one and (14β,17α,20R)-20-hydroxy-19-norpregn-5(10)-en-3-one (ratio 1:1, 7.5 g).

**ii)** - Phenyltrimethylammonium tribromide (9.7 g) was added in small portions and in 30 min. to a solution of the mixture obtained above (7.5 g) in dry pyridine (150 ml). After 5 h stirring at room temperature the mixture was poured into ice-water (1500 ml) and the product was extracted into ethyl acetate. The combined organic phases were washed with ice-cold hydrochloric acid (2 M), water and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography provided (14β,17α,20S)-20-hydroxy-19-norpregna-4,9-dien-3-one (2.4 g), m.p. 147-148 °C, and (14β,17α,20R)-20-hydroxy-19-norpregna-4,9-dien-3-one (1.95 g), m.p. 118-119 °C.

**Example 17**

(11β,14β,17α,20S)-11-Ethenyl-20-hydroxy-19-norpregna-4,9-dien-3-one.

**i)** - Following a procedure analogous to that described under **i** of Example 12, (14β,17α,20S)-20-hydroxy-19-norpregna-4,9-dien-3-one (Example 16a; 2.5 g) was converted to (14β,17α,20S)-20-hydroxy-19-norpregna-5(10),9(11)-dien-3-one cyclic 1,2-ethanediyl acetal (1.5 g).

**ii)** - A solution of the product obtained in the previous step (1.5 g) in dry dichloromethane (15 ml), containing sodium hydrogencarbonate (3 g), was cooled to -15 °C. *m*-Chloroperbenzoic acid (60 %, 1.42 g) in dry dichloromethane (12.5 ml) was added in 10 min. and the reaction mixture was stirred at -10 °C for 1.25 h. Then it was poured into a mixture of a saturated aqueous solution of sodium hydrogencarbonate (53 ml) and an aqueous solution of sodium hydrogensulfite (5 %, 12.5 ml) and the product was extracted into dichloromethane. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate, water and brine, dried over sodium sulfate and concentrated under reduced pressure, to give (5α,10α,14β,17α,20S)-5,10-epoxy-20-hydroxy-19-norpregn-9(11)-en-3-one cyclic 1,2-ethanediyl acetal (1.6 g).

**iii)** - A solution of the epoxide obtained in the previous step (1.6 g) in dry tetrahydrofuran (15 ml), containing copper(I) chloride (0.20 g), was cooled to 0 °C and treated with a solution of vinylmagnesium bromide in tetrahydrofuran (15 %, 12.7 ml). After 1 h stirring at 0 °C the reaction mixture was poured into an aqueous solution of ammonium chloride (10 %). 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. Column chromatography afforded (5α,11β,14β,17α,20S)-11-ethenyl-5,20-dihydroxy-19-norpregn-9-en-3-one cyclic 1,2-ethanediyl acetal (0.65 g).

**iv)** - Following a procedure analogous to that descibed under **iv** of Example 1, the product obtained in the previous step (0.60 g) was converted to (11β,14β,17α,20S)-11-ethenyl-20-hydroxy-19-norpregna-4,9-dien-3-one (0.28 g), m.p. 144.5-146.1 °C.

**Example 18**

(11β,14β,17α,20R)-11-Ethenyl-20-hydroxy -19-norpregna-4,9-dien-3-one.

In a manner analogous to the procedures described in Example 17, (14β,17α,20R)-20-hydroxy-19-norpregna-4,9-dien-3-one (Example 16b) was converted to (11β,14β,17α,20R)-11-ethenyl-20-hydroxy-19-norpregna-4,9-dien-3-one. M.p. 96.3-97.2 °C.

**Example 19**

(14β,17α)-17-[(Acetyloxy)methyl]androst-4-en-3-one.

**i)** - A solution of (3β)-3-(acetyloxy)androsta-5,14-dien-17-one [Andre, A.F.St. *et al*, J. Am. Chem. Soc. 74, 5506 (1952); 42.9 g] in dry ethanol (429 ml) was cooled to -10 °C. Sodium borohydride (1.51 g) in dry ethanol (33.5 ml) was added and the mixture was stirred at -10 °C for 7.5 h. Excess sodium borohydride was destroyed by careful addition of an aqueous solution of acetic acid (50 %). The product was extracted into ethyl acetate; the combined organic phases were washed with brine, dried over sodium sulfate and concentrated. Column chromatography provided (3β,17β)-androsta-5,14-diene-3,17-diol 3-acetate (19.5 g).

**ii)** - Following a procedure analogous to that described under **i** of Example 4, the product obtained in the previous step (20.0 g) was hydrogenated to give (3β,14β,17β)-androst-5-ene-3,17-diol 3-acetate (10.0 g).

**iii)** - A solution of the product obtained in the previous step (1.50 g) in acetone (37 ml) was treated with 4-methylmorpholine *N*-oxide (1.58 g) followed by tetrapropylammonium perruthenate (0.095 g). After 2 h stirring at room temperature the mixture was filtered over silica and dicalite and the filtrate concentrated under reduced pressure, to give (3β,14β)-3-(acetyloxy)androst-5-en-17-one (1.08 g). The product was used in the next step without further purification.

**iv)** - A solution of the ketone obtained in the previous step (1.08 g) in tetrahydrofuran (11.6 ml) and methanol (10.4 ml) was treated wit a solution of potassium hydroxide (0.589 g) in water (3.51 ml). The reaction mixture was stirred overnight and then poured into brine. 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 (3β,14β)-3-hydroxyandrost-5-en-17-one (1.06 g). The product was used in the next step without further purification.

**v)** - A solution of the alcohol obtained in the previous step (1.06 g) and imidazole (2.49 g) in dry dichloromethane (7.4 ml) was treated with *t*-butyldimethylsilyl chloride (1.11 g). After 45 min. stirring the reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate. 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 (3β,14β)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]androst-5-en-17-one (1.70 g). The product was used in the next step without further purification.

**vi)** - Following a procedure analogous to the procedure described under **iii** of Example 4, the ketone obtained in the previous step (1.70 g) was converted to (3β,14β)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-17-methyleneandrost-5-ene (1.41 g).

**vii)** - Following a procedure analogous to the procedure described under **iv** of Example 4, the product obtained in the previous step (1.41 g) was converted to (3β,14β)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]androst-5-ene-17-methanol (2.28 g).

**viii)** - Following a procedure analogous to that described in Example 9, the alcohol obtained in the previous step (2.28 g) was converted to (3β,14β)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-17-[(acetyloxy)methyl]androst-5-ene (1.43 g).

**ix)** - Following a procedure analogous to the procedure described under **iv** of Example 1, the product obtained in the previous step (1.43 g) was converted to (3β,14β)-17-[(acetyloxy)methyl]androst-5-en-3-ol (0.78 g).

**x)** - A mixture of the product obtained in the previous step (0.774 g) and aluminium isopropoxide (0.64 g) in dry toluene (9.2 ml) and 2-butanone (5.6 ml) was heated under reflux for 1 h. After cooling, a solution of potassium sodium tartrate tetrahydrate (4.4 g) in water (6 ml) was added and the mixture was stirred at room temperature for 30 min. The product was extracted into ethyl acetate; the combined organic phases were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography afforded (14β,17α)-17-[(acetyloxy)methyl]androst-4-en-3-one (0.44 g), m.p.141-142 °C.

**Example 20**

(14β,17α)-17-(Hydroxymethyl)androst-4-en-3-one.

Following a procedure analogous to that described under **iv** of Example 19, (14β,17α)-17-(acetyloxymethyl)androst-4-en-3-one (Example 19; 0.32 g) was converted to (14β,17α)-17-(hydroxymethyl)androst-4-en-3-one (0.10 g), m.p. 125.1-127.6 °C.

**Results**

A plurality of compounds according to the inventionwere tested for androgenic activity (the procedures for which have been described above) and rated according to the following scheme:

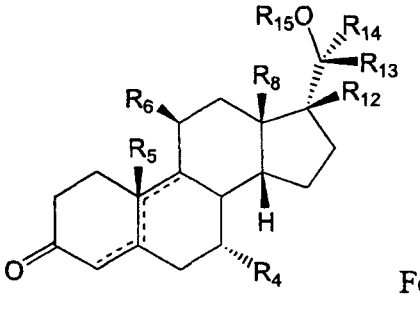
(+) androgenic activity found;

(++) high androgenic activity;

(+++) excellent androgenic activity;

(n.d.) no data available

The results are depicted in the following tables, in which the tested compounds are entered with reference to formula III below.



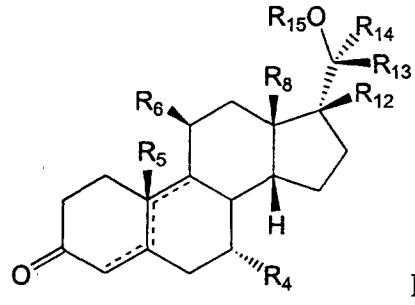

Formula III

**Unsubstituted steroid nucleus**

| Ex. | $R_4$ | $R_5$ | $R_6$ | $R_8$ | $R_{12}$ | $R_{13}$ | $R_{14}$ | $R_{15}$ | Conf. (20) | Unsat | Rating |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | H | Me | H | H | H | H | - | $\Delta^4$ | ++ |
| 2a | H | H | H | Me | H | Me | H | H | S | $\Delta^4$ | ++ |
| 2b | H | H | H | Me | H | H | Me | H | R | $\Delta^4$ | + |
| 3a | H | H | H | Me | H | Et | H | H | S | $\Delta^4$ | ++ |
| 3b | H | H | H | Me | H | H | Et | H | R | $\Delta^4$ | + |
| 3c | H | H | H | Me | H | Pr | H | H | S | $\Delta^4$ | + |
| 3d | H | H | H | Me | H | H | Pr | H | R | $\Delta^4$ | nd |

**7α-Methyl compounds**

| Ex. | $R_4$ | $R_5$ | $R_6$ | $R_8$ | $R_{12}$ | $R_{13}$ | $R_{14}$ | $R_{15}$ | Conf. (20) | Unsat | Rating |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | Me | H | H | Me | H | H | H | H | - | $\Delta^4$ | +++ |
| 8 | Me | H | H | Me | F | H | H | H | - | $\Delta^4$ | ++ |
| 5a | Me | H | H | Me | H | Me | H | H | S | $\Delta^4$ | +++ |
| 5b | Me | H | H | Me | H | H | Me | H | R | $\Delta^4$ | + |
| 6 | Me | H | H | Me | H | H | *i*-Pr | H | R | $\Delta^4$ | + |
| 7 | Me | H | H | Me | H | Me | Me | H | - | $\Delta^4$ | ++ |
| 9 | Me | H | H | Me | H | H | H | Ac | - | $\Delta^4$ | ++ |
| 10a | Me | H | H | Me | H | H | H | Un | - | $\Delta^4$ | + |
| 10b | Me | H | H | Me | H | H | H | Bu | - | $\Delta^4$ | + |




Formula III

**18-Methyl compounds**

| Ex. | $R_4$ | $R_5$ | $R_6$ | $R_8$ | $R_{12}$ | $R_{13}$ | $R_{14}$ | $R_{15}$ | Conf. (20) | Unsat | Rating |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 11a | H | H | H | Et | H | Me | H | H | S | $\Delta^4$ | + |
| 11b | H | H | H | Et | H | H | Me | H | R | $\Delta^4$ | + |
| 11c | H | H | H | Et | H | Et | H | H | S | $\Delta^4$ | + |
| 11d | H | H | H | Et | H | H | Et | H | R | $\Delta^4$ | nd |
| 11e | H | H | H | Et | H | vinyl | H | H | S | $\Delta^4$ | nd |
| 11f | H | H | H | Et | H | H | vinyl | H | R | $\Delta^4$ | nd |

**11β-Ethyl compounds**

| Ex. | $R_4$ | $R_5$ | $R_6$ | $R_8$ | $R_{12}$ | $R_{13}$ | $R_{14}$ | $R_{15}$ | Conf. (20) | Unsat | Rating |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 13a | H | H | Et | Me | H | Me | H | H | S | $\Delta^4$ | ++ |
| 13b | H | H | Et | Me | H | H | Me | H | R | $\Delta^4$ | + |

**$\Delta^{5(10)}$ Compounds**

| Ex. | $R_4$ | $R_5$ | $R_6$ | $R_8$ | $R_{12}$ | $R_{13}$ | $R_{14}$ | $R_{15}$ | Conf. (20) | Unsat | Rating |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 14 | H | H | H | Me | H | H | H | H | - | $\Delta^{5(10)}$ | + |
| 12a | H | H | Et | Me | H | Me | H | H | S | $\Delta^{5(10)}$ | + |
| 12b | H | H | Et | Me | H | H | Me | H | R | $\Delta^{5(10)}$ | nd |

**$\Delta^{4,9}$ Diene derivatives**

| Ex. | $R_4$ | $R_5$ | $R_6$ | $R_8$ | $R_{12}$ | $R_{13}$ | $R_{14}$ | $R_{15}$ | Conf. (20) | Unsat | Rating |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 | H | H | H | Me | H | H | H | H | - | $\Delta^{4,9}$ | ++ |
| 16a | H | H | H | Me | H | Me | H | H | S | $\Delta^{4,9}$ | ++ |
| 16b | H | H | H | Me | H | H | Me | H | R | $\Delta^{4,9}$ | + |
| 17 | H | H | vinyl | Me | H | Me | H | H | S | $\Delta^{4,9}$ | ++ |
| 18 | H | H | vinyl | Me | H | H | Me | H | R | $\Delta^{4,9}$ | + |

**10β-Methyl compounds**

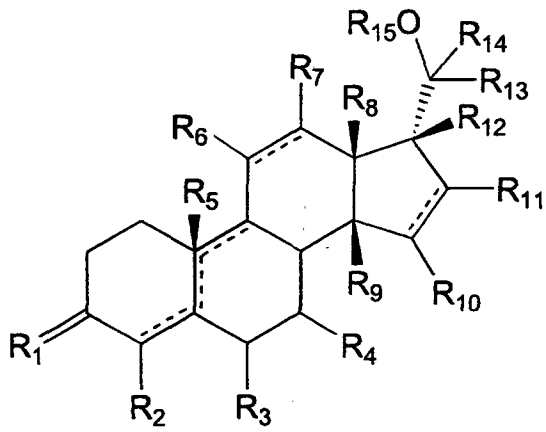
| Ex. | $R_4$ | $R_5$ | $R_6$ | $R_8$ | $R_{12}$ | $R_{13}$ | $R_{14}$ | $R_{15}$ | Conf. (20) | Unsat | Rating |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 | H | Me | H | Me | H | H | H | H | - | $\Delta^4$ | + |
| 19 | H | Me | H | Me | H | H | H | Ac | - | $\Delta^4$ | + |

Claims:

(70)

1. A steroid compound, or a pharmaceutically acceptable salt or ester thereof, having a hydroxymethyl moiety at carbon atom no. 17, characterised in that the steroid compound has a 14β,17α-configuration, with the proviso that the compound is not any one of 2-hydroxy-14β,17α-19-norpregn-4-en-3-on, (3β,5α,14β,17α)-pregna-3,20-diol, (3β,14β,17α)-pregna-5,9(11)-dien-3,20-diol, and (14β,17α)-20-hydroxy-19-norpregn-4-en-3-one.

2. A compound according to claim 1, satisfying the structural formula:




Formula I

wherein

$R_1$ is O, (H,H), (H,OR), NOR, with R being hydrogen, $(C_{1-6})$ alkyl, $(C_{1-15})$ acyl;

$R_2$ is hydrogen, $(C_{1-6})$ alkyl, or halogen;

$R_3$ is hydrogen, $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl, or $(C_{2-6})$ alkynyl;

$R_4$ is hydrogen, halogen, or cyano; or $R_4$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl or $(C_{2-6})$ alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_5$ is hydrogen, or $(C_{1-6})$ alkyl;

$R_6$ is hydrogen, $(C_{1-6})$ alkoxy, or halogen; or $R_6$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl, $(C_{2-6})$ alkynyl, a $(C_{1-6})$ alkylidene group, or a $(C_{2-6})$ alkenylidene group, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_7$ is hydrogen, or $(C_{1-6})$ alkyl;

$R_8$ is $(C_{1-6})$ alkyl;

$R_9$ is hydrogen, halogen or cyano; or $R_9$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl, or $(C_{2-6})$ alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_{10}$ is hydrogen, ($C_{1-6}$) alkoxy, halogen, or cyano; or $R_{10}$ is ($C_{1-6}$) alkyl, ($C_{2-6}$) alkenyl or ($C_{2-6}$) alkynyl, each optionally substituted by hydroxy, ($C_{1-4}$) alkoxy, oxo, halogen, or cyano;

$R_{11}$ is hydrogen, ($C_{1-6}$) alkoxy, halogen, or cyano; or $R_{11}$ is ($C_{1-6}$) alkyl, ($C_{2-6}$) alkenyl or ($C_{2-6}$)alkynyl, each optionally substituted by hydroxy, ($C_{1-4}$)alkoxy, oxo, halogen, or cyano;

$R_{12}$ is hydrogen, halogen, or cyano; or $R_{12}$ is ($C_{1-6}$) alkyl, ($C_{2-6}$) alkenyl, ($C_{2-6}$) alkynyl, each optionally substituted by hydroxy, ($C_{1-4}$) alkoxy, oxo, halogen, or cyano;

$R_{13}$ and $R_{14}$ are independently hydrogen, cyano, or phenyl, the latter optionally substituted by hydroxy, ($C_{1-4}$) alkoxy, ($C_{1-4}$) alkyl or halogen; or $R_{13}$ and $R_{14}$ are independently ($C_{1-6}$) alkyl, ($C_{2-6}$) alkenyl, ($C_{3-6}$) cycloalkyl, ($C_{5-6}$) cycloalkenyl or ($C_{2-6}$) alkynyl, each optionally substituted by hydroxy, ($C_{1-4}$) alkoxy, phenyl, oxo, halogen, or cyano; or $R_{13}$ and $R_{14}$ together with the carbon atom at which they are placed form a ($C_{3-6}$) cycloalkane ring or a ($C_{5-6}$) cycloalkene ring;

$R_{15}$ is hydrogen, $SO_3H$, ($C_{1-6}$) alkyl, ($C_{1-15}$) acyl; and

the dotted lines indicate optional bonds.

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

$R_1$ is O;

$R_2$, $R_3$, $R_5$, $R_6$, $R_7$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, and $R_{14}$ all are hydrogen;

$R_4$ is H or methyl;

$R_8$ is methyl;

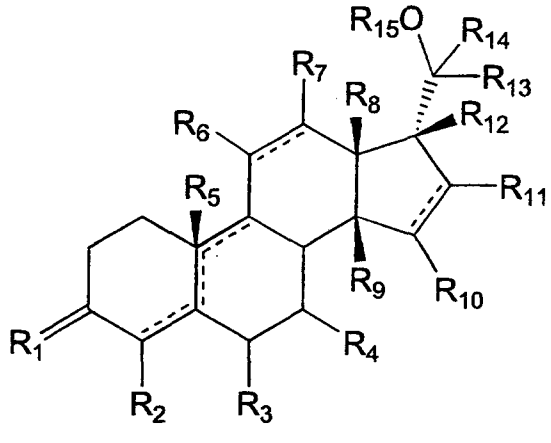
$R_{13}$ is hydrogen, or $C_{1-2}$ (alkyl) with the configuration at carbon atom no. 20 being S;

$R_{15}$ is H or ($C_{1-15}$) acyl;

and wherein a double bond is present between carbon atoms nos. 4 and 5, and optionally also between carbon atoms nos. 9 and 10.

4. A (14β,17α)-17-(hydroxymethyl) steroid for use as a medicine.

5. A compound satisfying the structural formula:




Formula I

wherein

$R_1$ is O, (H,H), (H,OR), NOR, with R being hydrogen, $(C_{1-6})$ alkyl, $(C_{1-15})$ acyl;

$R_2$ is hydrogen, $(C_{1-6})$ alkyl, or halogen;

$R_3$ is hydrogen, $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl, or $(C_{2-6})$ alkynyl;

$R_4$ is hydrogen, halogen, or cyano; or $R_4$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl or $(C_{2-6})$ alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_5$ is hydrogen, or $(C_{1-6})$ alkyl;

$R_6$ is hydrogen, $(C_{1-6})$ alkoxy, or halogen; or $R_6$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl, $(C_{2-6})$ alkynyl, a $(C_{1-6})$ alkylidene group, or a $(C_{2-6})$ alkenylidene group, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_7$ is hydrogen, or $(C_{1-6})$ alkyl;

$R_8$ is $(C_{1-6})$ alkyl;

$R_9$ is hydrogen, halogen or cyano; or $R_9$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl, or $(C_{2-6})$ alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_{10}$ is hydrogen, $(C_{1-6})$ alkoxy, halogen, or cyano; or $R_{10}$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl or $(C_{2-6})$ alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_{11}$ is hydrogen, $(C_{1-6})$ alkoxy, halogen, or cyano; or $R_{11}$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl or $(C_{2-6})$alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$alkoxy, oxo, halogen, or cyano;

$R_{12}$ is hydrogen, halogen, or cyano; or $R_{12}$ is $(C_{1-6})$ alkyl, $(C_{2-6})$ alkenyl, $(C_{2-6})$ alkynyl, each optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, oxo, halogen, or cyano;

$R_{13}$ and $R_{14}$ are independently hydrogen, cyano, or phenyl, the latter optionally substituted by hydroxy, $(C_{1-4})$ alkoxy, $(C_{1-4})$ alkyl or halogen; or $R_{13}$ and $R_{14}$ are independently $(C_{1-6})$

alkyl, ($C_{2-6}$) alkenyl, ($C_{3-6}$) cycloalkyl, ($C_{5-6}$) cycloalkenyl or ($C_{2-6}$) alkynyl, each optionally substituted by hydroxy, ($C_{1-4}$) alkoxy, phenyl, oxo, halogen, or cyano; or $R_{13}$ and $R_{14}$ together with the carbon atom at which they are placed form a ($C_{3-6}$) cycloalkane ring or a ($C_{5-6}$) cycloalkene ring;

$R_{15}$ is hydrogen, $SO_3H$, ($C_{1-6}$) alkyl, ($C_{1-15}$) acyl; and

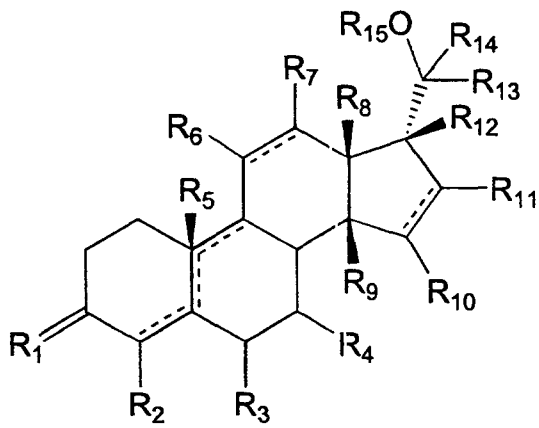
the dotted lines indicate optional bonds;

for use as a medicine.

6. The use of a steroid compound, or a pharmaceutically acceptable salt or ester thereof, having a hydroxymethyl moiety at carbon atom no. 17, and having a 14β,17α-configuration, for the preparation of a medicament for treating androgen insufficiency.

7. The use of a steroid compound, or a pharmaceutically acceptable salt or ester thereof, having a hydroxymethyl moiety at carbon atom no. 17, and having a 14β,17α-configuration, for the preparation of a medicament for male contraception.

8. A use according to claim 6 or 7, characterised in that the (14β,17α)-17-(hydroxymethyl) steroid satisfies the structural formula:




Formula I

wherein

$R_1$ is O, (H,H), (H,OR), NOR, with R being hydrogen, ($C_{1-6}$) alkyl, ($C_{1-15}$) acyl;

$R_2$ is hydrogen, ($C_{1-6}$) alkyl, or halogen;

$R_3$ is hydrogen, ($C_{1-6}$) alkyl, ($C_{2-6}$) alkenyl, or ($C_{2-6}$) alkynyl;

$R_4$ is hydrogen, halogen, or cyano; or $R_4$ is ($C_{1-6}$) alkyl, ($C_{2-6}$) alkenyl or ($C_{2-6}$) alkynyl, each

optionally substituted by hydroxy, ($C_{1-4}$) alkoxy, oxo, halogen, or cyano;

$R_5$ is hydrogen, or ($C_{1-6}$) alkyl;

$R_6$ is hydrogen, ($C_{1-6}$) alkoxy, or halogen; or $R_6$ is ($C_{1-6}$) alkyl, ($C_{2-6}$) alkenyl, ($C_{2-6}$) alkynyl, a ($C_{1-6}$) alkylidene group, or a ($C_{2-6}$) alkenylidene group, each optionally substituted by hydroxy, ($C_{1-4}$) alkoxy, oxo, halogen, or cyano;

$R_7$ is hydrogen, or ($C_{1-6}$) alkyl;

$R_8$ is ($C_{1-6}$) alkyl;

$R_9$ is hydrogen, halogen or cyano; or $R_9$ is ($C_{1-6}$) alkyl, ($C_{2-6}$) alkenyl, or ($C_{2-6}$) alkynyl, each optionally substituted by hydroxy, ($C_{1-4}$) alkoxy, oxo, halogen, or cyano;

$R_{10}$ is hydrogen, ($C_{1-6}$) alkoxy, halogen, or cyano; or $R_{10}$ is ($C_{1-6}$) alkyl, ($C_{2-6}$) alkenyl or ($C_{2-6}$) alkynyl, each optionally substituted by hydroxy, ($C_{1-4}$) alkoxy, oxo, halogen, or cyano;

$R_{11}$ is hydrogen, ($C_{1-6}$) alkoxy, halogen, or cyano; or $R_{11}$ is ($C_{1-6}$) alkyl, ($C_{2-6}$) alkenyl or ($C_{2-6}$)alkynyl, each optionally substituted by hydroxy, ($C_{1-4}$)alkoxy, oxo, halogen, or cyano;

$R_{12}$ is hydrogen, halogen, or cyano; or $R_{12}$ is ($C_{1-6}$) alkyl, ($C_{2-6}$) alkenyl, ($C_{2-6}$) alkynyl, each optionally substituted by hydroxy, ($C_{1-4}$) alkoxy, oxo, halogen, or cyano;

$R_{13}$ and $R_{14}$ are independently hydrogen, cyano, or phenyl, the latter optionally substituted by hydroxy, ($C_{1-4}$) alkoxy, ($C_{1-4}$) alkyl or halogen; or $R_{13}$ and $R_{14}$ are independently ($C_{1-6}$) alkyl, ($C_{2-6}$) alkenyl, ($C_{3-6}$) cycloalkyl, ($C_{5-6}$) cycloalkenyl or ($C_{2-6}$) alkynyl, each optionally substituted by hydroxy, ($C_{1-4}$) alkoxy, phenyl, oxo, halogen, or cyano; or $R_{13}$ and $R_{14}$ together with the carbon atom at which they are placed form a ($C_{3-6}$) cycloalkane ring or a ($C_{5-6}$) cycloalkene ring;

$R_{15}$ is hydrogen, $SO_3H$, ($C_{1-6}$) alkyl, ($C_{1-15}$) acyl; and

the dotted lines indicate optional bonds.

9. A pharmaceutical formulation comprising a compound as defined in any one of the preceding claims, and a pharmaceutically acceptable carrier.

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 claim 9.

ABSTRACT

The disclosed invention relates to the unexpected finding of novel steroids which are characterized by a configuration opposite to that of natural steroids, viz. 14α,17β. These steroids according to the invention are (14β,17α)-17-(hydroxymethyl) steroids, and they are found to have in common an androgenic activity. They can be used for the preparation of an agent for male contraception, as well as for the preparation of a medicament for the treatment of androgen insufficiency.

**TRADUCCION:** Se traduce la carátula y las reivindicaciones anexas a una copia de la solicitud de patente europea Nº 9920665.0, escrita en inglés para el invento denominado: **ANDROGENOS NOVEDOSOS.**

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**A N E X O S**

**OFICINA DE PATENTES EUROPEA**

**Certificado**

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. 99200665.0

Por el Presidente de la Oficina de Patentes Europea

(Firmado Ilegible)

**I.L.C. HATTEN-HECKMAN**

La Haya, 20/03/00

HH
107

**OFICINA DE PATENTES EUROPEA**

Página 2 del certificado

Solicitud Nº 99200665.0 Fecha de presentación 08/03/99

Solicitante(s)

**AKZO NOBEL N.V.**

6824 BM Arnhem

Holanda

Título del invento: **14-β, 17-α- HYDOXYMETIL ESTEROIDES ANDROGENOS**

Prioridades reivindicadas

País Fecha Archivo Nº

Clasificación Internacional de Patente:

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 NOVEDOSOS**

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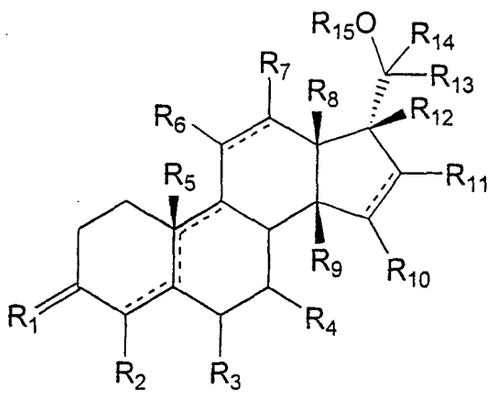
## REIVINDICACIONES

1. Un compuesto esteroide, o una sal o éster del mismo farmacéuticamente aceptable, con una mitad de hidroximetilo en átomo de carbón N° 17, CARACTERIZADO porque el compuesto esteroide tiene una configuración 14β,17α, con la condición que el compuesto no es ninguno de (2- hidroxi- 14β,17α- 19- norpregn- 4- en- 3- on, (3β,5α,14β,17α)- pregna- 3,20- diol, (3β,14β,17α)- pregna- 5,9(11)- dien- 3,20- diol, y (14β,17α)- 20- hidroxi- 19- norpregn- 4- en- 3- uno.

2, Un compuesto de acuerdo con la Reivindicación 1, que satisface la fórmula estructural:




Formula I

CARACTERIZADO porque

$R_1$ es O, (H,H), (H,OR), NOR, con R siendo hidrógeno, $(C_{1-6})$ alquilo, $(C_{1-15})$ acilo;

$R_2$ es hidrógeno, $(C_{1-6})$ alquilo, o halógeno;

$R_3$ es hidrógeno, $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo, o $(C_{2-6})$ alquinilo;

$R_4$ es hidrógeno, halógeno, o ciano; o $R_4$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo o $(C_{2-6})$ alquilino, cada uno opcionalmente sustituido por hidroxi $(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

$R_5$ es hidrógeno, o $(C_{1-6})$ alquilo;

$R_6$ es hidrógeno, $(C_{1-6})$ alcoxi, o halógeno; o $R_6$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo, $(C_{2-6})$ alquinilo, un grupo $(C_{1-6})$ alquiloideno, o un grupo $(C_{2-6})$ alquiniloideno, cada opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

$R_7$ es hidrógeno, o $(C_{1-6})$ alquilo;

$R_8$ es $(C_{1-6})$ alquilo;

$R_9$ es hidrógeno, halógeno o ciano; o $R_9$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo, o $(C_{2-6})$ alquinilo, cada uno opcionalmente sustituido por (hidroxi, $(C_{1-4})$ alcoxi, oxo, halógeno o ciano;

$R_{10}$ es hidrógeno, $(C_{1-6})$ alcoxi, halógeno, o ciano; o $R_{10}$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo o $(C_{2-}$

$_{6}$) alquinilo, cada uno opcionalmente sustituido por hidroxi, ($C_{1-4}$) alcoxi, oxo, halógeno, o ciano;

$R_{11}$ es hidrógeno, ($C_{1-6}$) alcoxi, halógeno, o ciano; o $R_{11}$ es ($C_{1-6}$) alquilo, ($C_{2-6}$) alquenilo o ($C_{2-6}$) alquinilo, cada uno opcionalmente sustituido por hidroxi, ($C_{1-4}$) alcoxi, oxo, halógeno, o ciano;

$R_{12}$ es hidrógeno, halógeno, o ciano; o $R_{12}$ es ($C_{1-6}$) alquilo, ($C_{2-6}$) alquenilo, ($C_{2-6}$) alquinilo, cada uno opcionalmente sustituido por hidroxi, ($C_{1-4}$) alcoxi, oxo, halógeno, o ciano;

$R_{13}$ y $R_{14}$ are son independientemente hidrógeno, ciano, o fenilo, el último opcionalmente sustituido por hidroxi, ($C_{1-4}$) alcoxi, ($C_{1-4}$) alquilo o halógeno; o $R_{13}$ y $R_{14}$ son independientemente ($C_{1-6}$) alquilo, ($C_{2-6}$) alquenilo ($C_{3-6}$) cicloalquilo ($C_{5-6}$) cicloalquenilo ($C_{2-6}$) alquinilocada uno opcionalmente sustituido por hidroxi ($C_{1-4}$) alcoxi, fenilo fenilo, oxo, halógeno, o ciano; o $R_{13}$ y $R_{14}$ junto con el átomo de carbón en el cual se ubican forman un anillo ($C_{3-6}$) cicloalcane o un anillo ($C_{5-6}$) de cicloalqueno

$R_{15}$ es hidrógeno, $SO_3H$, ($C_{1-6}$) alquilo ($C_{1-15}$) acilo y

las líneas punteadas indican los enlaces opcionales.

3, Un compuesto de acuerdo a la Reivindicación 2, CARACTERIZADO porque

$R_1$ es O;

$R_2$, $R_3$, $R_5$, $R_6$, $R_7$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, y $R_{14}$ son todos hidrógeno;

$R_4$ es H o metilo

$R_8$ es metilo

$R_{13}$ es hidrógeno, o $C_{1-2}$ alquilo con la configuración en el átomo de carbón N° 20, siendo S;

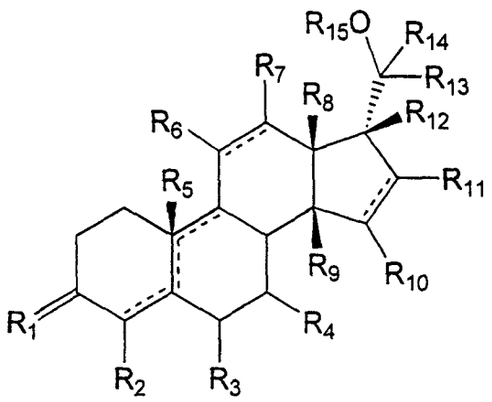
$R_{15}$ es H o ($C_{1-15}$) acilo;

y en donde hay presente un enlace doble entre átomos de carbón Nos. 4 y 5, y opcionalmente también entre los átomos de carbón Nos. 9 y 10.

4, Un esteroide (14β,17α)- 17- hidroximetilo, CARACTERIZADO por su uso como medicamento.

5. Un compuesto que satisface la fórmula estructural:

HA
110




Formula I

en donde

$R_1$ es O, (H,H), (H,OR), NOR, con R siendo hidrógeno, $(C_{1-6})$ alquilo $(C_{1-15})$ acilo

$R_2$ es hidrógeno, $(C_{1-6})$ alquilo o halógeno;

$R_3$ es hidrógeno, $(C_{1-6})$ alquilo $(C_{2-6})$ alquenilo $(C_{2-6})$ alquinilo

$R_4$ es hidrógeno, halógeno, o ciano $R_4$ es $(C_{1-6})$ alquilo $(C_{2-6})$ alquenilo $(C_{2-6})$ alquinilo, cada uno

opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxioxo, halógeno, o ciano;

$R_5$ es hidrógeno, o $(C_{1-6})$ alquilo;

$R_6$ es hidrógeno, $(C_{1-6})$ alcoxio halógeno; o $R_6$ es $(C_{1-6})$ alquilo $(C_{2-6})$ alquenilo $(C_{2-6})$ alquinilo un grupo $(C_{1-6})$ alquiloideno o un grupo $(C_{2-6})$ alquiniloideno cada uno opcionalmente sustituido por hidroxi,

$(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

$R_7$ es hidrógeno, o $(C_{1-6})$ alquilo;

$R_8$ es $(C_{1-6})$ alquilo;

$R_9$ es hidrógeno, halógeno o ciano; o $R_9$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo, o $(C_{2-6})$ alquinilo, cada uno opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

$R_{10}$ es hidrógeno, $(C_{1-6})$ alcoxi, halógeno, o ciano; o $R_{10}$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo o $(C_{2-6})$ alquinilo, cada uno opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

$R_{11}$ es hidrógeno, $(C_{1-6})$ alcoxi, halógeno, o ciano; o $R_{11}$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo o $(C_{2-6})$ alquinilo, cada uno opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

$R_{12}$ es hidrógeno, halógeno, o ciano; o $R_{12}$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo, $(C_{2-6})$ alquinilo, cada uno opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

115
111

$R_{13}$ y $R_{14}$ son independientemente hidrógeno, ciano, o fenilo, el último opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, $(C_{1-4})$ alquilo o halógeno; o $R_{13}$ y $R_{14}$ son independientemente $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo, $(C_{3-6})$ cicloalquilo, $(C_{5-6})$ cicloalquenilo o $(C_{2-6})$ alquinilo, cada uno opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, fenilo, oxo, halógeno, o ciano; o $R_{13}$ y $R_{14}$ junto con el átomo de carbón en el cual se ubican formando un anillo $(C_{3-6})$ cicloalcane o un anillo $(C_{5-6})$ cicloalqueno;

$R_{15}$ es hidrógeno, $SO_3H$, $(C_{1-6})$ alquilo, $(C_{1-15})$ acilo;

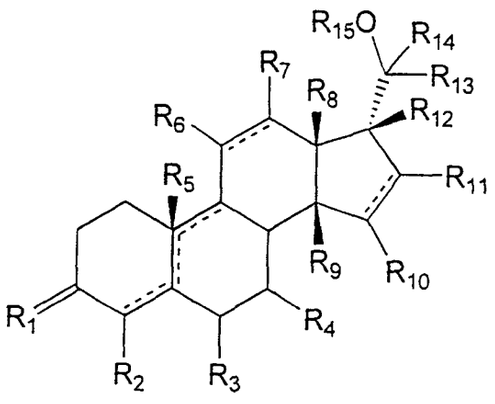
y las líneas punteadas indican enlaces opcionales;

para su uso como medicamento.

6, El uso de un compuesto esteroide, o una sal o éster del mismo farmacéuticamente aceptable, con una porción de (hidroximetilo) en el átomo de carbón N° 17, y con una configuración 14β,17α, para la preparación de un medicamento para tratar insuficiencia andrógena.

7, El uso de un compuesto esteroide, o una sal o éster del mismo farmacéuticamente aceptable, CARACTERIZADO porque tiene una porción de hidroximetilo en el átomo de carbón N° 17, y que tiene una configuración 14β,17α, para la preparación de un medicamento para la (anticoncepción masculina.

8, Un uso de acuerdo a la Reivindicación 6 o 7, CARACTERIZADO porque el esteroide (14β,17α)- 17- (hidroximetilo) satisface la fórmula estructural:




Formula I

en donde

$R_1$ es O, (H,H), (H,OR), NOR, siendo R hidrógeno, $(C_{1-6})$ alquilo, $(C_{1-15})$ acilo;

$R_2$ es hidrógeno, $(C_{1-6})$ alquilo, o halógeno;

$R_3$ es hidrógeno, $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo, o $(C_{2-6})$ alquinilo;

$R_4$ es hidrógeno, halógeno, o ciano; o $R_4$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo o $(C_{2-6})$ alquinilo, cada uno opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

$R_5$ es hidrógeno, o $(C_{1-6})$ alquilo;

$R_6$ es hidrógeno, $(C_{1-6})$ alcoxi, o halógeno; o $R_6$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo, $(C_{2-6})$ alquinilo, un grupo $(C_{1-6})$ alquiloideno, o un grupo $(C_{2-6})$ alquiniloideno, cada uno opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

$R_7$ es hidrógeno, o $(C_{1-6})$ alquilo;

$R_8$ es $(C_{1-6})$ alquilo;

$R_9$ es hidrógeno, halógeno o ciano; o $R_9$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo, o $(C_{2-6})$ alquinilo, cada uno opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

$R_{10}$ es hidrógeno, $(C_{1-6})$ alcoxi, halógeno, o ciano; o $R_{10}$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo o $(C_{2-6})$ alquinilo, cada uno opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

$R_{11}$ es hidrógeno, $(C_{1-6})$ alcoxi, halógeno, o ciano; o $R_{11}$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo o $(C_{2-6})$ alquinilo, cada uno opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

$R_{12}$ es hidrógeno, halógeno, o ciano; o $R_{12}$ es $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo, $(C_{2-6})$ alquinilo, cada uno opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, oxo, halógeno, o ciano;

$R_{13}$ y $R_{14}$ son independientemente hidrógeno, ciano, o fenilo, el último opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, $(C_{1-4})$ alquilo o halógeno; o $R_{13}$ y $R_{14}$ son independientemente $(C_{1-6})$ alquilo, $(C_{2-6})$ alquenilo, $(C_{3-6})$ cicloalquilo, $(C_{5-6})$ cicloalquenilo o $(C_{2-6})$ alquinilo, cada uno opcionalmente sustituido por hidroxi, $(C_{1-4})$ alcoxi, fenilo, oxo, halógeno, o ciano; o $R_{13}$ y $R_{14}$ junto con el átomo de carbón en el cual se ubican forman un anillo $(C_{3-6})$ cicloalcano o un anillo $(C_{5-6})$ cicloalqueno;

$R_{15}$ es hidrógeno, $SO_3H$, $(C_{1-6})$ alquilo, $(C_{1-15})$ acilo; y

las líneas punteadas indican uniones opcionales.

9, Una formulación farmacéutica, CARACTERIZADA porque comprende un compuesto como se define en cualquiera de las reivindicaciones anteriores, y un portador farmacéuticamente aceptable.

10. Un kit para anticoncepción masculina que comprende un medio para la administración de un progestágeno y un medio para la administración de un andrógino, CARACTERIZADO porque el segundo medio es una formulación farmacéutica, de acuerdo a la reivindicación 9,