(54) Titre : 14,15-CYCLOPROPANO-ANDROSTANES INSATURES, LEUR PROCEDE DE PRODUCTION ET COMPOSITIONS PHARMACEUTIQUES CONTENANT CES COMPOSES
(54) Title: UNSATURATED 14,15-CYCLOPROPANO-ANDROSTANES

(57) Abrégé/Abstract:
The invention relates to new, unsaturated 14, 15-cyclopropano-androstanes of the general formula (I) (see formula I) to their synthesis and to pharmaceutical compositions, containing these compounds. The compounds of formula (I) have gestagenic and/or androgenic activity.
Abstract of the Disclosure

The invention relates to new, unsaturated 14, 15-cyclopropano-androstanes of the general formula (I)

![Chemical Structure](image)

(I)

to their synthesis and to pharmaceutical compositions, containing these compounds.

The compounds of formula (I) have gestagenic and/or androgenic activity.
UNSATURATED 14,15 CYCLOPROPANO-ANDROSTANES

The invention relates to new unsaturated 14,15-cyclopropano-androstanes, a method for their production and pharmaceutical compositions containing these compounds. Unsaturated 14,15-cyclopropano-androstanes of the following formula

![Chemical Structure](image)

are described in PCT published patent application WO 99/67275.

In that formula:

- $R_1$ is a hydrogen atom, a hydroxy group, an alkyloxy, acyloxy, alyloxy or alkylaryloxy group, an $-\text{OCONHR}_9$ or $-\text{OCOOR}_9$ group, in which $R_9$ represents a hydrogen atom, an alkyl, aryl, aralkyl or alkylaryl group with, in each case, 1 to 10 carbon atoms;

- $R_2$ represents a hydrogen atom, a hydroxyl group, an alkyl, acyl, aryl, aralkyl or alkyaryl group with, in each case, 1 to 10 carbon atoms;

- a $-(\text{CH}_2)_n\text{CH}_2\text{Y}$ group with $n = 0, 1$ or 2, in which $Y$ represents a fluorine, chlorine, bromine or iodine atom, a cyano, azido or rhodanide group, an $-\text{OR}_{10}$ or $-\text{SR}_{10}$ group, in which $R_{10}$ represents a hydrogen atom, an alkyl, aryl, aralkyl or alkylaryl group with, in each case, 1 to 10 carbon atoms, or a COR$_9$ acyl group in which $R_9$ represents an alkyl, aryl, aralkyl or alkylaryl group with, in each case, 1 to 10 carbon atoms, a $-\text{OR}_9$ group, in which $R_9$ represents a hydrogen atom, an alkyl, aryl, aralkyl or alkylaryl group with, in each case, 1 to 10 carbon atoms;

- a $-\text{(CH}_2)_m\text{CH=CH(CH}_2)_n\text{R}_8$ group, in which $m = 0, 1, 2$ or 3 and $n = 0, 1$ or 2 and $R_8$ represents a hydrogen atom or an alkyl, aryl, aralkyl or alkylaryl group with, in each case, 1 to 10 carbon atoms, or a hydroxy group, an alkoxy group or an acyloxy group with, in each case, 1 to 10 carbon atoms;
a \((CH_2)_nC=CR_{11}\) group in which \(n = 0, 1,\) or 2 and \(R_{11}\) represents a hydrogen atom, a fluorine, chlorine, bromine or iodine atom, or an alkyl, aryl, aralkyl or alkylaryl group with, in each case, 1 to 10 carbon atoms; or \(R_1\) and \(R_2\) independently of one another, represent a keto, methylene or difluoromethylene group;

there possibly being a double bond between C-6 and C-7;

if there is an \(\alpha\) or \(\beta\) cyclopropano group X between C-14 and C-15, X representing \(CZ_2\) in which \(Z\) represents a hydrogen, fluorine, chlorine, bromine or iodine atom;

\(R_3\) and \(R_4\) independently of one another represent a hydrogen atom, an \(\alpha\) or \(\beta\) alkyl group with 1 to 10 carbon atoms; and

\(R_5\) represents an alkyl group with 1 to 3 carbon atoms.

From E.P. 768,316, steroids are known with a 14,15 methylene group, which have progesterone activity and, with that, in combination with at least one suitable estrogen, are suitable for hormonal contraception and menopausal hormone replacement therapy (HRT), as well as for the treatment of endometriosis and gestagen-dependent tumors.

With this state of the art as background, it is an object of the present invention to provide new, unsaturated, 14,15-cyclopropano-androstanes.
This objective is accomplished by unsaturated 14,15-cyclopropano-androstanes of the general formula (I)

\[
\begin{align*}
\text{R}_1 & \text{ is a hydrogen atom, a hydroxy group, a C}_{1-10} \text{ alkyl, a C}_{1-10} \text{ alkoxy, a C}_{1-15} \text{ acyloxy, a C}_{4-15} \text{ aryloxy, a C}_{7-15} \text{-aralkyloxy or a C}_{7-15} \text{ alkylaryloxy group;} \\
\text{R}_2 & \text{ represents a hydrogen atom, a hydroxy group, a C}_{1-10} \text{ alkyl group, a C}_{1-10} \text{ acyl group, a C}_{1-10} \text{ acyloxy group, a C}_{6-15} \text{ aryl group, a C}_{7-15} \text{ aralkyl group, a C}_{7-15} \text{ alkylaryl group,} \\
& \text{or a } -(\text{CH}_2)_n\text{CH}_2\text{Y group, in which } n = 0, 1 \text{ or } 2 \text{ and } \text{Y represents a halogen atom or a cyano, azido or rhodanide group,} \\
& \text{or a } -(\text{CH}_2)_m\text{CH}=\text{CH}(\text{CH}_2)_p\text{R}_6 \text{ group in which } m = 0, 1, 2 \text{ or } 3, p = 0, 1 \text{ or } 2 \text{ and } \text{R}_6 \text{ represents a hydrogen atom, a C}_{1-10} \text{ alkyl group, a C}_{6-15} \text{ aryl group, a C}_{7-15} \text{ aralkyl group, a C}_{7-15} \text{ alkylaryl group, a hydroxyl group, a C}_{1-10} \text{ alkoxy group or a C}_{1-10} \text{ acyloxy group,} \\
& \text{or a } -(\text{CH}_2)_o\text{C}=\text{CR}_7 \text{ group in which } o = 0, 1 \text{ or } 2 \text{ and } \text{R}_7 \text{ represents a hydrogen atom, a halogen atom, a C}_{1-10} \text{ alkyl group, a C}_{6-15} \text{ aryl group, a C}_{7-15} \text{ aralkyl group, a C}_{7-15} \text{ alkylaryl group or a C}_{1-10} \text{ acyl group;} \\
& \text{or } \text{R}_1 \text{ and } \text{R}_2 \text{ together represent a keto group, a methylene group, a difluoromethylene group or, with inclusion of C-17, a spirooxirene or a 2,2-dimethyl-1,3-dioxolane;}
\end{align*}
\]
R₃ represents a hydrogen atom, an α-C₁₋₁₀ alkyl group or a β-C₁₋₁₀ alkyl group;
R₄ represents a halogen atom or an azido or rhodanide group, a hydroxy group or a
perfluoroalkyl group;
R₅ represents a C₁₋₄ alkyl group;
in which there is an α-cyclopropano group or a β-cyclopropano group between C-14 and
C-15; and
in which optionally there is a double bond between C-1 and C-2;

with the proviso that, if there is a double bond in the 1,2 position in the molecule, then R₄
also can be a hydrogen atom in addition to the meanings given above;

and pharmaceutically-acceptable salts thereof.

Surprisingly, it was found that the inventive, unsaturated 14,15-
cyclopropano-androstanes of the general formula (I) are compounds with gestagenic
and/or androgenic activity.

Within the sense of the invention, pharmaceutically-tolerated salts
preferably are alkali or alkaline earth salts, especially sodium, potassium or ammonium
salts. These salts can be synthesized by standard techniques and methods, which are well
known in the art.

Within the sense of the invention, a "C₁₋₄ or C₁₋₁₀ alkyl group" is
understood to be a branched or linear alkyl group with 1 to 4 or 1 to 10 carbon atoms. As
examples, a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl or t-butyl, n-pentyl,
i-pentyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl or 2,3-
dimethylbutyl group are mentioned.

Within the sense of the application, the concept of "C₁₋₁₀ alkoxy group" is
understood to include cyclic or acyclic groups, the alkyl portion of which contains 1 to 10
carbon atoms. "Cyclic groups" are understood to include also heterocyclic groups, which may have one or two hetero atoms in the ring, which may be a nitrogen atom, an oxygen atom or a sulfur atom. A methoxy group, an ethoxy group or an n- or iso-propoxy group or an iso- or t-butoxy, a 1'-methoxy-cyclopent oxy or a tetrahydropyranoxy group are examples.

In the sense of the application, the concept of "C\textsubscript{1-10} or C\textsubscript{1-15} acyl or acyloxy group" is understood to be a group with 1 to 10 or 1 to 15 carbon atoms of the linear or branched alkane carboxylic acids, such as formic acid, acetic acid, propionic acid, butyric acid, iso-butyric acid, heptanoic acid or undecanoic acid.

Within the sense of the application, the concept of a "C\textsubscript{6-15} aryl group" is understood to include a substituted or unsubstituted aryl group with 6 to 15 carbon atoms, such as a phenyl group, a substituted phenyl group, such as a halogenated phenyl group or a nitrophenyl group, or a naphthyl group.

Within the sense of the application, the concept of a "C\textsubscript{4-15} aryloxy group" is understood to include a carbocyclic or heterocyclic group with 4 to 15 carbon atoms. Examples are a benzyloxy group, a 1- or 2-naphthinyloxy group, a 2- or 3-furanyloxy group, a 2- or 3-thienyl group and a 2-, 3- or 4-pyridinyloxy group.

Within the sense of the application, the concept of a "C\textsubscript{7-15} alkylaryl group" is understood to include an aryl group, which is substituted by an alkyl group, the two groups together having 7 to 15 carbon atoms. The aryl group may have additional substituents, such as a halogen atom. Examples are a toluenyl group (methylphenyl group), a halogenated toluenyl group, an ethylphenyl group, a dimethylphenyl group or a trimethylphenyl group.
Within the sense of the application, the concept of a "C₇₋₁₅ alkylaryloxy group" is understood to be a "C₇₋₁₅ aralkyl group", such as a 3- or a 4-methylphenyloxy group, which is extended by an oxygen atom.

Within the sense of the application, the concept of a "C₇₋₁₅ aralkyl group" is understood to include an alkyl group, which is substituted by an aryl group, the two groups together having 7 to 15 carbon atoms. The aryl group may have further substituents, such as a halogen atom. Examples are a free or an aromatically-substituted benzyl group, such as a benzyl group or a halogenated benzyl group.

Within the sense of the application, the concept of "C₇₋₁₅ aralkyloxy group" is understood to include "C₇₋₁₅ aralkyl groups", which has been extended by an oxygen atom, such as a benzyloxy group.

Within the sense of the invention, the concept of "halogen" comprises a fluorine, chlorine, bromine or iodine atom.

Within the sense of the invention, the concept of "pseudohalogen" comprises a cyanate, rhodanide, cyano or azido group.

Within the sense of the invention, the concept of "perfluoroalkyl group" comprises a branched or linear fluoroalkyl group with 1 to 3 carbon atoms, such as a trifluoromethyl, pentafluoroethyl, heptafluoro-n-propyl or heptafluoro-i-propyl group.

R₁ represents preferably a hydroxy or acyloxy group, especially a hydroxy group, formyloxy group, acetyloxy group, propionyloxy group, n-butyryloxy group, i-butyryloxy group, heptanyloxy group or undecanyl group.

If R₂ represents a −(CH₂)ₙCH₂Y group, n preferably is 1 and Y preferably represents a fluorine atom, a cyano or rhodanide group.
If R₂ is a \((\text{CH}_2)\_m\text{CH}=\text{CH}(\text{CH}_2)\_n\text{R}_6\) group, \(m\) preferably is 1 and \(R_6\) preferably represents a methyl or ethyl group, or a methoxy or ethoxy group.

If \(R_2\) represents a \((\text{CH}_2)\_o\text{C}≡\text{CR}_7\) group, \(o\) preferably is 1 and \(R_7\) preferably represents a fluorine atom or a methyl or ethyl group.

It is particularly preferred if \(R_2\) represents a hydrogen atom or a C₁₋₆ alkyl group, especially a methyl or ethyl group.

\(R_3\) preferably represents a C₁₋₄ alkyl group, especially a methyl group.

\(R_4\) preferably represents a fluorine, chlorine or bromine atom, or a trifluoromethyl or hydroxy group.

\(R_5\) preferably represents a methyl or ethyl group.

The most preferred compounds are the following:

- 4-chloro-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
- 4-chloro-17α-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
- 4-chloro-17β-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
- 4-chloro-17α-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
- 4-bromo-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
- 4-bromo-17α-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
- 4-bromo-17β-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
- 4-bromo-17α-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
- 4-fluoro-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
- 4-fluoro-17α-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
4,17β-dihydroxy-14α,15α-methylene-androst-4-ene-3-one,
4,17α-dihydroxy-14α,15α-methylene-androst-4-ene-3-one,
4,17β-dihydroxy-14β,15β-methylene-androst-4-ene-3-one,
4,17α-dihydroxy-14β,15β-methylene-androst-4-ene-3-one,
4-trifluoromethyl-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
4-trifluoromethyl-17α-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
4-trifluoromethyl-17β-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
4-trifluoromethyl-17α-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
17β-hydroxy-14α,15α-methylene-androsta-1,4-diene-3-one,
17α-hydroxy-14α,15α-methylene-androsta-1,4-diene-3-one,
17β-hydroxy-14β,15β-methylene-androsta-1,4-diene-3-one,
17α-hydroxy-14β,15β-methylene-androsta-1,4-diene-3-one,
4-chloro-17α-hydroxy-14α,15α-methylene-androsta-1,4-diene-3-one,
4-chloro-17β-hydroxy-14α,15α-methylene-androsta-1,4-diene-3-one,
4-chloro-17β-hydroxy-14β,15β-methylene-androsta-1,4-diene-3-one
or 4-chloro-17α-hydroxy-14β,15β-methylene-androsta-1,4-diene-3-one.

The inventive compounds and their pharmaceutically-acceptable salts can be synthesized by a process wherein compounds of formula (II):

![Chemical Structure](image)

wherein R₁, R₂, R₃ and R₅ have the meanings given above, and there is an α-cyclopropano group or a β-cyclopropano group between C-14 and C-15;
in which the 4,5 double bond is epoxidized with hydrogen peroxide under alkaline conditions, and the resulting epoxide mixture is treated in a suitable solvent with acids of the formula HR₈ in which R₈ represents a halogen atom or a cyano, azido or rhodanide group.

Moreover, the corresponding 4-bromo compounds can also be prepared by addition of bromine to compounds of general formula (II) by carrying out the reaction with bromine, N-bromosuccinimide or N-bromoacetamide in acetic acid/ethyl ether in the presence of a proton acceptor, for example collidine (X.S. Fei et al., J. Chem Soc., Perkin Trans.1, 1998, 1139-1142).

4-Hydroxy compounds are obtained by reacting the epoxide mixture above with catalytic amounts of mineral acid, such as sulfuric acid (P. S. Furth et. al. J. Enzyme Inhibition, 1990, Vol. 4, 131-135).

Compounds of the general formula (I) with an additional double bond in the 1,2 position can be obtained easily by methods known to those skilled in the art, such as the dehydrogenation of the 4-ene-3-one system by means of 2,3-dichloro-5,6-dicyanobenzoquinone in a suitable solvent, such as dioxane, toluene or t-butanol.

4-Trifluormethyl compound of the general formula (I) can be obtained by the reaction of the 4-bromo compounds of the general formula (I), which are mentioned above, with methyl 2,2-difluoro-2-(fluorosulfonyl)acetate in dimethylformamide in the presence of CuI (X. S. Fei et al., J. Chem. Soc., Perkin Trans.
1, 1998, 1139-1142). The starting compounds of formula (II) can be synthesized by known methods or by the method described in the German application with the application No. 198 27 523.4 (PCT/DE99/01794). The introduction of the groups, which are analogous to the groups R1, R2, R3 and R5 occurring there and are claimed here, is described in the protective right mentioned.

Pharmaceutical compositions for the oral, rectal, subcutaneous, intravenous or intramuscular applications, which contain at least one compound of the general formula (I) and/or their acid addition salts as active ingredient, together with the conventional vehicles and diluents are also an object of the present invention.

Pharmaceutical preparations of the invention are prepared with the usual solid or liquid vehicles and/or diluents and the inactive ingredients, the use of which is generally customary in accordance with the desired type of application, in a suitable dosage and by a known procedure. In the case of a preferred oral form of administration, preferably tablets, film-coated tablets, coated tablets, capsules, pills, powders, solutions or suspensions are prepared also in sustained release form. In addition, parenteral forms of medicinal drugs, such as injection solutions or suspensions, can also be considered.

Medicinal drug forms as tablets can be obtained for example by mixing the active ingredient with the known inert materials, such as dextrose, sugar, sorbitol, mannitol, polyvinylpyrrolidone, disintegrants such as corn starch or alginic acid, binders such as starch or gelatin, lubricants such as magnesium stearate or talc and/or agents, which can achieve a sustained release effect, such as carboxypolymethylene, carboxymethylcellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets may also consist of several layers.

Similarly, coated tablets can be prepared by coating cores, prepared similarly to the tablets, with agents used in conventional tablet coatings, such as
polyvinylpyrrolidone or shellac, gum arabic, talc, titanium dioxide or sugar. The tablet coating may consist of several layers, the inert materials, named above, for example being used.

To improve the taste, the solutions or suspensions with the inventive active ingredient can be mixed with materials such as saccharin, cyclamate or sugar and/or with aromatic and flavoring materials such as vanillin or orange extract. Moreover, they may be mixed with suspending agents, such as sodium carboxymethylcellulose, or preservatives, such as p-hydroxybenzoic acid.

Capsules can be prepared by mixing medicinal drugs with vehicles, such as lactose or sorbitol, which are then brought into the capsules.

Suppositories are prepared preferably by mixing active ingredients with suitable vehicles, such as neutral fats or polyethylene glycols or their derivatives.

The pharmaceutical forms of preparations furthermore can be percutaneous forms, such as transdermal therapeutic systems (TTS) or gels, sprays or ointments or intranasal forms, such as nose sprays or oral nose drops.

The inventive 14,15-cyclopropanoandrostanes of the general formula (I) are compounds with hormonal (gestagenic and/or androgenic) activity.

For example, the compound of the general formula (I), in which $R_1$ is a hydroxyl group, $R_2$ and $R_3$ are hydrogen atoms, $R_3$ is a methyl group and $X$ is a $\text{CH}_2$ group and the 14,15 cyclopropane ring is in the $\alpha$ position, namely 4-chloro-17$\beta$-hydroxy-14$\alpha$,15$\alpha$-methylene-androst-4-ene-3-one is an androgen.

The 4-chloro-17$\beta$-hydroxy-14$\alpha$,15$\alpha$-methylene-androst-4-ene-3-one binds to the extent of 42% ± 3% to the androgen receptor of the rat prostate (reference
substance 17β-hydroxy-17α-methyl-estra-4,9,11-triene-3-one; R 1881). On the other hand, there is practically no binding to the progesterone receptor of the rabbit uterus (reference substance: progesterone). It was possible to demonstrate distinct androgenic activity in the Hershberger test. On the other hand, there is hardly any gestagenic activity in the pregnancy maintenance test.

These test results open up various possibilities for the inventive compounds of the general formula (I) for fertility control in men, hormone replacement therapy (HRT) in men and women or the treatment of hormonally induced diseases in men and women, such as endometriosis, breast cancer or hypogonadism.

The following examples are intended to explain the invention in greater detail without limiting it.

**Examples**

**Example 1**

**17β-Hydroxy-4,5-epoxy-14α,15α-methylene-androstan-3-one**

**Synthesis of 4,5-Epoxides**

17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one (2 g) is dissolved in 80 mL of methanol and treated at 0°C with 26 mL of a hydrogen peroxide solution (35%). While stirring, 5.2 mL of a 10% sodium hydroxide solution are added, the stirring being continued at 0°C for 30 hours. The reaction solution is mixed with 50 mL of dichloromethane and 25 mL of water and the organic phase is removed, washed with semi-concentrated thiosulfate solution, dried and evaporated to dryness. The residue obtained consists of a mixture of 4α,5α- or 4β,5β- epoxides and is used in the subsequent step without further purification.
Example 2

17α-Hydroxy-4,5-epoxy-14α,15α-methylene-androstan-3-one

The compound, named above, can be obtained from 17α-hydroxy-14α,15α-methylene-androst-4-ene-3-one by a method, similar to that of Example 1.

Example 3

4-Chloro-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one

17β-hydroxy-4,5-epoxy-14α,15α-methylene-androstan-3-one (1.5 g) is dissolved in 150 mL of acetone and treated at 0°C with 5.5 mL of concentrated hydrochloric acid. After 24 hours at 0°C, the reaction mixture is neutralized with sodium carbonate solution and the acetone is evaporated. The residue is extracted with dichloromethane. The organic extracts are dried and concentrated. After crystallization from ethanol, 4-chloro-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one is obtained.

^1H-NMR: 0.12 (1H, dd, J=5.5, 3.3 Hz, CH₂-bridge), 0.22 (1H, dd, J=8.2, 5.5 Hz, CH₂-bridge), 0.99 (3H, s, H-18), 1.30 (3H, s, H-19), 3.49 (1H, dd, J=9.3, 7.1 Hz, H-17).

Example 4

4-Chloro-17α-hydroxy-14α,15α-methylene-androst-4-ene-3-one

17α-Hydroxy-14α,15α-methylene-androst-4-ene-3-one is reacted by a method, similar to that of Example 3.

^1H-NMR: 0.32 (1H, dd, J=7.7, 4.9 Hz, CH₂-bridge), 0.72 (1H, dd, J=4.4, 3.3 Hz, CH₂-bridge), 0.99 (3H, s, H-18), 1.29 (3H, s, H-19), 3.80 (1H, d, J=6.0 Hz, H-17).
Example 5

4,17β-Dihydroxy-14α,15α-methylene-androst-4-ene-3-one

An epoxide mixture (3.5 g), 17β-hydroxy-4,5-epoxy-14α,15α-methylene-androstan-3-one, (step 1) is dissolved in 50 mL of acetic acid, which contains 2% by volume of concentrated sulfuric acid. The solution is allowed to stand for 3 days at 10°C. After that, it is treated with 200 mL ethyl acetate and neutralized with sodium carbonate solution. The organic phase is dried and concentrated. The residue is dissolved in 100 mL of methanol, treated with 4 g of potassium hydroxide, refluxed for 1 hour and then cooled. After neutralization with 50% acetic acid, it is poured into 1 L of water and the crystals are filtered off with suction, 4,17β-Dihydroxy-14α,15α-methylene-androst-4-ene-3-one being obtained.

$^1$H-NMR: 0.13 (1H, dd, J=5.6, 3.2 Hz, CH$_2$-bridge), 0.24 (1H, dd, J=8.3, 5.6 Hz, CH$_2$-bridge), 0.99 (3H, s, H-18), 1.30 (3H, s, H-19), 3.50 (1H, dd, J=9.4, 6.8 Hz, H-17), 6.10 (1H, s, 4-OH).

Example 6

4-Bromo-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one

The target compound is synthesized in a manner similar to the synthesis of 4-Chloro-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one, 48% hydrobromic acid being used instead of hydrochloric acid.

$^1$H-NMR: 0.12 (1H, dd, J=5.5, 3.3 Hz, CH$_2$-bridge), 0.21 (1H, dd, J=8.4, 5.4 Hz, CH$_2$-bridge), 1.00 (3H, s, H-18), 1.33 (3H, s, H-19), 3.49 (1H, dd, J=9.3, 7.1 Hz, H-17).
Example 7

4-Trifluoromethyl-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one

4-Bromo-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one (1.5 g) is dissolved in 180 mL of dimethylformamide and stirred at 75°C for 12 hours with 1 g of CuI as well as 2.8 mL of methyl 2,2-difluoro-2-(fluorosulfonyl)acetate. After working up and chromatographic purification, 4-Trifluoromethyl-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one is obtained.

$^1$H-NMR: 0.14 (1H, dd, J=5.5, 3.0 Hz, CH$_2$-bridge), 0.25 (1H, dd, J=8.2, 5.8 Hz, CH$_2$-bridge), 1.00 (3H, s, H-18), 1.32 (3H, s, H-19), 3.51 (1H, m, H-17).

$^{19}$F-NMR: -55.3 (3F, s, 4-F$_2$C).

Example 8

17β-Hydroxy-14α,15α-methylene-androsta-1,4-diene-3-one

17β-Hydroxy-14α,15α-methylene-androst-4-ene-3-one (4 g) in 160 mL of toluene is stirred for 6 days at 85°C with 3.2 g of 2,3-dichloro-5-6-dicyanobenzoquinone. The precipitate is filtered off, washed with a little toluene and the filtrates and washings are evaporated to dryness. The residue is purified by chromatography, 17β-Hydroxy-14α,15α-methylene-androsta-1,4-diene-3-one being obtained.

$^1$H-NMR: 0.13 (1H, dd, J=5.6, 3.2 Hz, CH$_2$-bridge), 0.24 (1H, dd, J=8.3, 5.6 Hz, CH$_2$-bridge), 0.98 (3H, s, H-18), 1.35 (3H, s, H-19), 3.50 (1H, m, H-17), 6.06 (1H, m, H-4); 6.22 (1H, dd, J=12.09; 1.65 Hz, H{2}), 7.04 (1H, d, J=9.9 Hz, H-1).
Example 9

4-Chloro-17β-hydroxy-14α,15α-methylene-androsta-1,4-diene-3-one

This compound is prepared from 4-chloro-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one by a method similar to that of Example 6.

$^1$H-NMR: 0.13 (1H, dd, J=5.6, 3.2 Hz, CH$_2$-bridge), 0.24 (1H, dd, J=8.3, 5.6 Hz, CH$_2$-bridge), 0.98 (3H, s, H-18), 1.35 (3H, s, H-19), 3.50 (1H, m, H-17), 6.22 (1H, dd, J=12.09, 1.65 Hz, H{2}), 7.04 (1H, d, J=9.9 Hz, H-1).
The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. Unsaturated 14,15-cyclopropano-androstanes of the general formula (I):

wherein:

- $R_1$ is a hydrogen atom, a hydroxy group, a C$_{1-10}$ alkyl, a C$_{1-10}$ alkoxy, a C$_{1-15}$ acyloxy, a C$_{4-15}$ aryloxy, a C$_{7-15}$-arylalkoxy or a C$_{7-15}$ alkylaryloxy group;
- $R_2$ represents a hydrogen atom, a hydroxy group, a C$_{1-10}$ alkyl group, a C$_{1-10}$ acyl group, a C$_{1-10}$ acyloxy group, a C$_{6-15}$ aryl group, a C$_{7-15}$ aralkyl group, a C$_{7-15}$ alkylaryl group, or a $-(CH_2)_nCH_2Y$ group, in which $n = 0$, 1 or 2 and $Y$ represents a halogen atom or a cyano, azido or rhodanide group,
- or a $-(CH_2)_mCH=CH(CH_2)_pR_6$ group in which $m = 0$, 1, 2 or 3, $p = 0$, 1 or 2 and $R_6$ represents a hydrogen atom, a C$_{1-10}$ alkyl group, a C$_{6-15}$ aryl group, a C$_{7-15}$ aralkyl group, a C$_{7-15}$ alkylaryl group, a hydroxyl group, a C$_{1-10}$ alkoxy group or a C$_{1-10}$ acyloxy group,
- or a $-(CH_2)_nC=CR_7$ group in which $o = 0$, 1 or 2 and $R_7$ represents a hydrogen atom, a halogen atom, a C$_{1-10}$ alkyl group, a C$_{6-15}$ aryl group, a C$_{7-15}$ aralkyl group, a C$_{7-15}$ alkylaryl group or a C$_{1-10}$ acyl group;
- or $R_1$ and $R_2$ together represent a keto group, a methylene group, a difluoromethylene group or, with inclusion of C-17, a spirooxiran or a 2,2-dimethyl-1,3-dioxolane;
- $R_3$ represents a hydrogen atom, an $\alpha$-C$_{1-10}$ alkyl group or a $\beta$-C$_{1-10}$ alkyl group;
- $R_4$ represents a halogen atom or an azido or rhodanide group, a hydroxy group or a perfluoroalkyl group;
- $R_5$ represents a C$_{1-4}$ alkyl group;
in which there is an α-cyclopropano group or a β-cyclopropano group between C-14 and C-15; and

in which optionally there is a double bond between C-1 and C-2;

with the proviso that, if there is a double bond in the 1,2 position in the molecule, then R₄ also can be a hydrogen atom in addition to the meanings given above;

and pharmaceutically-acceptable salts thereof.

2. Unsaturated 14,15-cyclopropano-androstanes as defined in claim 1, wherein R₁ is a hydroxy group or an acyloxy group.

3. Unsaturated 14,15-cyclopropano-androstanes as defined in 2, wherein the acyloxy group is a formyloxy, acetyloxy, a propionyloxy, n-butyryloxy, isobutyryloxy, heptanyloxy or an undecanyloxy group.

4. Unsaturated 14,15-cyclopropano-androstanes as defined in claim 1, 2 or 3, wherein R₂ is a hydrogen atom or a C₁₋₆ alkyl group.

5. Unsaturated 14,15-cyclopropano-androstanes as defined in 4, wherein the alkyl group is a methyl group or an ethyl group.

6. Unsaturated 14,15-cyclopropano-androstanes as defined in claim 1, 2 or 3, wherein R₂ is a \(-(CH₂)ₙCH₂Y\) group, n is 1 and Y represents a fluorine atom, or a cyano or rhodanide group.

7. Unsaturated 14,15-cyclopropano-androstanes as defined in claim 1, 2 or 3, wherein R₂ is a \(-(CH₂)ₘCH=CH(CH₂)ₙR₆\) group, m is 1 and R₆ represents a methyl, ethyl, methoxy or ethoxy group.
8. Unsaturated 14,15-cyclopropano-androstanes as defined in claim 1, 2 or 3, wherein 
R₂ is a \(-(\text{CH}_2)_n\text{C}=\text{CR}_7\) group, n is 1, and R₇ represents a fluorine atom or a methyl or 
ethyl group.

9. Unsaturated 14,15-cyclopropano-androstanes as defined in any one of claims 1 to 8, 
wherein R₃ is C₁₋₄ alkyl group.

10. Unsaturated 14,15-cyclopropano-androstanes as claim 9, wherein R₃ is a methyl 
group.

11. Unsaturated 14,15-cyclopropano-androstanes as defined in any one of claims 1 to 10, 
wherein R₄ is a fluorine atom, a chlorine atom, a bromine atom, a hydroxy group or a 
trifluoromethyl group.

12. Unsaturated 14,15-cyclopropano-androstanes as defined in any one of claims 1 to 10, 
wherein R₄ is a fluorine atom, a chlorine atom, a bromine atom, an azido group or a 
rhodanide group.

13. Unsaturated 14,15-cyclopropano-androstanes as defined in any one of claims 1 to 12, 
wherein R₅ is a methyl group or an ethyl group.

14. An unsaturated 14,15-cyclopropano-androstan compound as defined in claim 1 
which is:
4-chloro-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
4-chloro-17α-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
4-chloro-17β-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
4-chloro-17α-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
4-bromo-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
4-bromo-17α-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
4-bromo-17β-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
4-bromo-17α-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
4-fluoro-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
4-fluoro-17α-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
4-fluoro-17β-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
4-fluoro-17α-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
4,17β-dihydroxy-14α,15α-methylene-androst-4-ene-3-one,
4,17α-dihydroxy-14α,15α-methylene-androst-4-ene-3-one,
4,17β-dihydroxy-14β,15β-methylene-androst-4-ene-3-one,
4,17α-dihydroxy-14β,15β-methylene-androst-4-ene-3-one,
4-trifluoromethyl-17β-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
4-trifluoromethyl-17α-hydroxy-14α,15α-methylene-androst-4-ene-3-one,
4-trifluoromethyl-17β-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
4-trifluoromethyl-17α-hydroxy-14β,15β-methylene-androst-4-ene-3-one,
17β-hydroxy-14α,15α-methylene-androsta-1,4-diene-3-one,
17α-hydroxy-14α,15α-methylene-androsta-1,4-diene-3-one,
17β-hydroxy-14β,15β-methylene-androsta-1,4-diene-3-one,
17α-hydroxy-14β,15β-methylene-androsta-1,4-diene-3-one,
4-chloro-17α-hydroxy-14α,15α-methylene-androsta-1,4-diene-3-one,
4-chloro-17β-hydroxy-14α,15α-methylene-androsta-1,4-diene-3-one,
4-chloro-17β-hydroxy-14β,15β-methylene-androsta-1,4-diene-3-one
or 4-chloro-17α-hydroxy-14β,15β-methylene-androsta-1,4-diene-3-one.

15. A process for the synthesis of 14,15-cyclopropano-androstanes as defined in any one
of claims 1 to 14, wherein compounds of formula (II):

![Formula (II)](image)

wherein R₁, R₂, R₃ and R₅ are as defined in the said one of claims 1 to 14, and there
is an α-cyclopropano group or a β-cyclopropane group between C-14 and C-15;
in which process the 4,5 double bond is epoxidized with hydrogen peroxide under
alkaline conditions, and the resulting epoxide mixture is treated in a suitable solvent with
acids of the formula HR₈ in which R₈ represents a halogen atom or a cyano, azido or rhodanide group, or is reacted with catalytic amounts of a mineral acid, to obtain 4-bromo compounds, and, optionally, the obtained 4-bromo compounds are reacted with methyl 2,2-difluoro-2-(fluorosulfonyl) acetate in dimethylformamide in the presence of CuI.

16. A process as defined in claim 15, wherein R₈ is a fluorine, chlorine or bromine atom.

17. A process as defined in claim 15, wherein R₈ is an azido or rhodanide group.

18. Use of a compound as defined in any one of claims 1 to 14 in the manufacture of a pharmaceutical composition.

19. A pharmaceutical composition comprising an unsaturated 14,15-cyclopropano-androstane or a pharmaceutically-acceptable salt thereof as defined in any one of claims 1 to 14, and a pharmaceutically-acceptable carrier.

20. Use of an unsaturated 14,15-cyclopropano-androstane or a pharmaceutically-acceptable salt thereof as defined in any one of claims 1 to 14, for hormone-replacement therapy in a man or woman in need of such therapy.

21. Use of an unsaturated 14,15-cyclopropano-androstane as defined in any one of claims 1 to 14 for controlling fertility in a man.

22. Use of an unsaturated 14,15-cyclopropano-androstane or a pharmaceutically-acceptable salt thereof as defined in any one of claims 1 to 14 for treating a hormone-induced disease suffered by a man or a woman.

23. Use as defined in claim 22, wherein said hormone-induced disease is endometriosis, breast cancer or hypogonadism.