PATENT SPECIFICATION

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Complete Specification entitled (54) 15a, 16a-METHYLENE-4-PREGNENE

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Related Art (56) Nil

The following statement is a full description of this invention, including the best method of performing it known to us:

X810-72-ND-19 P.C.
The present invention is concerned with new 15\(\alpha\),16\(\alpha\)-methylene-\(\Delta^4\)-pregnenes and with their manufacture and use.

The invention provides 15\(\alpha\),16\(\alpha\)-methylene-\(\Delta^4\)-pregnenes of the general formula I

\[
\begin{align*}
\text{CH}_3 \\
\text{R}^1 \text{CO} \\
\text{H} \\
\text{R}^2 \\
\end{align*}
\]

in which \(\text{R}^1\) represents a lower alkyl group and \(\text{R}^2\) represents an acyl group.

It is to be understood in the description and claims herein that the term "acyl group" includes a group obtainable not only from an organic carboxylic acid such as an aliphatic carboxylic acid or a heterocyclic carboxylic acid (but excluding organic sulphonic acids) but also from an oxygen-containing inorganic acid by the removal of a hydroxyl group.

As lower alkyl groups there come into consideration those having 1 to 5 carbon atoms. There may be mentioned, for example, the methyl, ethyl, propyl, butyl and pentyl groups. Preferred groups represented by \(\text{R}^1\) are the methyl and ethyl groups.

As acyl groups represented by \(\text{R}^2\) there come into consideration physiologically tolerable acid groups, which
are derived from acids customarily used for esterifying steroid alcohols. There may be mentioned, inter alia, organic carboxylic acids containing 1 to 18 carbon atoms that belong to the aliphatic, alicyclic, aromatic or heterocyclic series, and which may be saturated or unsaturated, monobasic, dibasic or polybasic and/or substituted, and as examples of substituents there may be mentioned alkyl, hydroxyl, oxo or amino groups or halogen atoms. The usual inorganic acids may also be mentioned.

The compounds of the present invention possess valuable hormone properties. Thus, for example, 17-acetoxy-15α,16α-methylene-19-nor-Δ⁴-pregnen-3,20-dione (I) and 17-acetoxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnen-3,20-dione (II) are markedly superior in their progesterone activity to known gestagens. They exhibit in the fertilization-inhibiting test, when administered subcutaneously, a superior action as compared with known compounds, as is shown by the following comparison with 17β-acetoxy-17α-ethynyl-Δ⁴-oestrone-3-one (III) and 17β-hydroxy-18-methyl-17α-ethynyl-Δ⁴-oestrone-3-one (IV).

Table 1
Fertilization-inhibiting test.

<table>
<thead>
<tr>
<th></th>
<th>Relative action (progesterone = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I 17-Acetoxy-15α,16α-methylene-19-nor-Δ⁴-pregnen-3,20-dione</td>
<td>30</td>
</tr>
<tr>
<td>II 17-Acetoxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnen-3,20-dione</td>
<td>30</td>
</tr>
<tr>
<td>III 17β-Acetoxy-17α-ethynyl-Δ⁴-oestrone-3-one</td>
<td>0.3</td>
</tr>
</tbody>
</table>
The higher esters are also distinguished by a protracted action, as shown by the results of the usual protracted Clauberg tests. Thus, for example, 17-hexanoyloxy-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione (V) and 17-hexanoyloxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione (VII) are markedly superior to the corresponding desmethylene compounds 17-hexanoyloxy-19-nor-Δ⁴-pregnene-3,20-dione (VI) and 17-hexanoyloxy-18-methyl-19-nor-Δ⁴-pregnene-3,20-dione (VIII).

Table 2

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Substance</th>
<th>Dose [mg]</th>
<th>McPhail-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>17-Hexanoyloxy-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione</td>
<td>3</td>
<td>3.8 (7th day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0 (13th day)</td>
</tr>
<tr>
<td>VI</td>
<td>17-Hexanoyloxy-19-nor-Δ⁴-pregnene-3,20-dione</td>
<td>3</td>
<td>3.3 (7th day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.3 (13th day)</td>
</tr>
<tr>
<td>VII</td>
<td>17-Hexanoyloxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione</td>
<td>1</td>
<td>3.5 (8th day)</td>
</tr>
<tr>
<td>VIII</td>
<td>17'-Hexanoyloxy-18-methyl-19-nor-Δ⁴-pregnene-3,20-dione</td>
<td>1</td>
<td>3.2 (8th day)</td>
</tr>
</tbody>
</table>
The superior gestagenic and fertilization-preventing action of the compounds of the present invention makes them suitable for use in medicinal preparations or as medicaments or in or as contraceptives.

The present invention accordingly also provides a pharmaceutical preparation which comprises a compound of the general formula I, in admixture or conjunction with a pharmaceutically suitable carrier. The preparation may be in the form of a contraceptive preparation.

The present invention further provides a method of contraception, wherein there is administered in a contraceptive dose to a female mammal, especially a female of the human species, a compound of the general formula I.

The present invention further provides a system which comprises a compound of the general formula I together with instructions, which instructions require the administration of the compound in a contraceptive dose to a female mammal, especially a female of the human species.

By a female mammal is to be understood herein a female of the human species or a female commercially reared animal.

When the compounds of the present invention are used, for example, in contraceptive preparations, they are used either in combination with an oestrogenically active hormone component, for example ethynyl-oestradiol, or as the sole active component at a daily dosage for females of the human species within the range of from 0.01 to 2 mg. For pharmaceutical use the new compounds may
be worked up with the additives, carrier substances and taste correctives customarily used in galenical pharmacy by methods known per se into the usual forms of application. For oral administration there may be mentioned more especially tablets, dragées, capsules, pills, suspensions or solutions, and for parenteral administration especially oily solutions, for example solutions in sesame oil or castor oil, which may also contain a diluent, for example benzyl benzoate or benzyl alcohol. The concentration of the active substance in the contraceptive preparations so formulated depends on the form of application. Thus, a tablet preferably contains 0.01 to 5 mg, and solutions for parenteral administration contain 0.1 to 10 mg per ml of solution.

The present invention further provides a process for the manufacture of 15α, 16α-methylene-4-pregnenes of the general formula I, wherein a 17-hydroxy-15α, 16α-methylene-Δ^4-pregnene of the general formula II
in which $R^1$ has the meaning given above, is esterified. The esterification may be carried out in a manner known per se.

The esterification of the 17-hydroxy group may be carried out by methods familiar to those skilled in the art. There may be mentioned, for example, esterification with an acid or a reactive acid derivative, for example an anhydride or halide, or mixtures thereof, in the presence of a strongly acidic esterification catalyst, for example para-toluene sulphonie acid, perchloric acid or trifluoracetic acid, or in the presence of a basic esterification catalyst, for example pyridine, collidine or quinoline, at temperatures preferably above room temperature.

The starting compounds of the general formula II may be prepared in the manner described in the following Examples A and B:


46.2 grams of natural 18-methyl-19-nor-Δ4,16-pregnadiene-3,20-dione were heated under reflux in 2.5 litres of benzene with 37.1 grams of 2,2-dimethyl-1,3-propanediol and 2.7 grams of para-toluene sulphonie acid for 6 hours with a water separator. After cooling, the reaction solution was washed with a saturated solution of sodium bicarbonate and water, dried over sodium sulphate and evaporated to dryness in vacuo. The residue so obtained was chromatographed over silica gel and there were obtained, after recrystallization from diisopropyl ether, 28.6 grams of natural 3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-
18-methyl-19-nor-$\Delta^5,16$- or $\Delta^5(10),16$-pregnadien-20-one melting at 145 - 155°C.
38.2 grams of natural 3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-18-methyl-19-nor-Δ⁵,16-orΔ⁵(10),16-pregnadien-20-one, dissolved in 229 ml of tetrahydrofuran, were added dropwise during the course of 30 minutes to a solution, cooled to -20°C, of 29.2 grams of potassium tert.-butylate in 343 ml of dimethylformamide, 57 ml of absolute tert.-butanol and 22.9 ml of trimethyl phosphite while introducing oxygen. The mixture was then stirred for a further hour at -20°C while introducing oxygen. The reaction solution was then stirred into ice-water rendered weakly acid with acetic acid, and the precipitate that separated out was filtered off, washed well with water, dissolved in methylene chloride, and dried over sodium sulphate. The residue obtained after evaporating the solution was chromatographed over silica gel, and there were obtained, after recrystallization from diisopropyl ether/methylene chloride, 15.5 grams of natural 17-hydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-18-methyl-19-nor-Δ⁵,15- or Δ⁵(10),15-pregnadien-20-one melting at 202 - 214°C.

14.0 grams of natural 17-hydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-18-methyl-19-nor-Δ⁵,15- or Δ⁵(10),15-pregnadien-20-one were dissolved in 140 ml of absolute tetrahydrofuran, 14.0 grams of lithium tri-tert.-butoxyalanate were added, and the whole was allowed to stand for 1 hour at room temperature. The reaction solution was stirred into ice-water, acidified with dilute sulphuric acid, and extracted with methylene chloride. The crude product obtained after drying and evaporating the extract was chromatographed over silica gel, and there were obtained 13.0 grams of natural 17,20Δ-dihydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-18-methyl-19-nor-Δ⁵,15- or Δ⁵(10),15-pregnadiene.
10.4 grams of natural 17,20\(\Delta^5\)-dihydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-18-methyl-19-nor-\(\Delta^5,15\)- or \(\Delta^5(10)15\)-pregnadiene in 185 ml of absolute ether and 185 ml of absolute ethylene glycol dimethyl ether were heated under reflux for 5 hours with 16.8 ml of methylene iodide and 20.8 grams of zinc-copper. The mixture was then diluted with methylene chloride, washed with a saturated solution of ammonium chloride and water, dried over sodium sulphate, and evaporated to dryness in vacuo. The residue was chromatographed over silica gel, and there were obtained 6.8 grams of natural 17,20\(\Delta^5\)-dihydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-18-methyl-15\(\Delta\),16\(\Delta\)-methylen-19-nor-\(\Delta^5\)- or \(\Delta^5(10)\)-pregnene.

To 3.0 grams of natural 17,20\(\Delta^5\)-dihydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-18-methyl-15\(\Delta\),16\(\Delta\)-methylen-19-nor-\(\Delta^5\)- or \(\Delta^5(10)\)-pregnene in 90 ml of dimethyl sulphoxide and 8.25 ml of triethylamine there was added while stirring at 15°C during the course of 15 minutes a solution of 6.0 grams of pyridine-\(\text{SO}_3^-\) complex in 22.5 ml of dimethyl sulphoxide, and then the whole was further stirred for 1 hour at room temperature. The mixture was then stirred into ice-water rendered weakly acid with acetic acid, and the precipitate that separated was filtered off, washed with water and taken up in methylene chloride. The residue obtained after drying and evaporating was chromatographed over silica gel, and there was obtained 2.8 grams of natural 17-hydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-18-methyl-15\(\Delta\),16\(\Delta\)-methylen-19-nor-\(\Delta^5\)- or \(\Delta^5(10)\)-pregnen-20-one.
To 2.4 grams of natural 17-hydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-18-methyl-15α,16α-methylene-19-nor-Δ5-or Δ5(10)-pregnen-20-one in 120 ml of methanol there were added 2.4 grams of oxalic acid dissolved in 2.4 ml of water, and the whole was heated under reflux for 2.5 hours. After bringing about precipitation with ice-water, the precipitate that separated was filtered off, washed with water and taken up in methylene chloride. After drying and evaporating, the residue was recrystallized from ethyl acetate, and there were obtained 1.43 grams of natural 17-hydroxy-18-methyl-15α,16α-methylene-19-nor-Δ4-pregnene-3,20-dione melting at 207-209.5°C.

UV: \( \varepsilon_{240} = 17,400. \)

**B:** 17-Hydroxy-15α,16α-methylene-19-nor-Δ4-pregnene-3,20-dione

5.0 grams of 19-nor-Δ4,16-pregnadiene-3,20-dione in 250 ml of benzene were heated under reflux with a water separator for 2 hours with 4.0 grams of 2,2,-dimethyl-1,3-propanediol and 300 mg of para-toluene sulphonie acid. Working up was carried out as described in Example A. After chromatography over silica gel there were obtained 4.9 grams of 3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-19-nor-Δ5,16- or Δ5(10),16-pregnadien-20-one.

UV: \( \varepsilon_{239} = 9,200. \)

5.0 grams of 3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-19-nor-Δ5,16- or Δ5(10),16-pregnadien-20-one were reacted with potassium tert.-butylate solution, oxygen and trimethyl phosphate at -5°C and worked up as described in Example A.
By chromatography over silica gel and recrystallization from diisopropyl ether/methylene chloride there were obtained 1.5 grams of 17-hydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-19-nor-Δ⁵,¹⁵- or Δ⁵(10),¹⁵-pregnadien-20-one melting at 241 - 249°C.

44.5 grams of 17-hydroxy-3,3-(2',2'-dimethyl-1'-3'-propylenedioxy)-19-nor-Δ⁵,¹⁵- or Δ⁵(10),¹⁵-pregnadien-20-one in 440 ml of absolute tetrahydrofuran were reacted with 45 grams of lithium tri-tert.-butoxy-alanate and worked up as described in Example A. After chromatography over silica gel there were obtained 37.6 grams of 17,20β-dihydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-19-nor-Δ⁵,¹⁵- or Δ⁵(10),¹⁵-pregnadiene.

35.6 grams of 17,20β-dihydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-19-nor-Δ⁵,¹⁵- or Δ⁵(10),¹⁵-pregnadiene in 475 ml of absolute ether and 475 ml of ethylene glycol dimethyl ether were heated under reflux for 6.5 hours while stirring with 57.3 ml of methylene iodide and 71.2 grams of zinc-copper. Working up was carried out as described in Example A. After chromatography over silica gel there were obtained 17.7 grams of 17,20β-dihydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-15Δ,16Δ-methylene-19-nor-Δ⁵- or Δ⁵(10)-pregnene.

To 4.2 grams of 17,20β-dihydroxy-3,3-(2',2'-dimethyl-1',3'-propylenedioxy)-15Δ,16Δ-methylene-19-nor-Δ⁵- or Δ⁵(10)-pregnene in 126 ml of dimethyl sulfoxide and 11.55 ml of triethylamine there was added while stirring at 15°C during the course of 20 minutes a solution of 8.4 grams of pyridine-SO₃-complex in 31.5 ml of dimethyl sulfoxide, and then the
whole was stirred for 1 hour at room temperature. Working up was carried out as described in Example A. After chromatography over silica gel there were obtained 3.1 grams of 17-hydroxy-3,3-(2',2' -dimethyl-l',3'-propylenedioxy)-15a,16a-methylene-19-nor-Δ⁵ or Δ⁵(10)-pregnen-20-one.

3.0 grams of 17-hydroxy-3,3-(2',2' -dimethyl-l',3'-propylenedioxy)-15a,16a-methylene-19-nor-Δ⁵ or Δ⁵(10)-pregnen-20-one in 150 ml of methanol were reacted with 3.0 grams of oxalic acid in 30 ml of water and worked up as described in Example A. By recrystallization from ethyl acetate there were obtained 1.7 grams of 17-hydroxy-15a,16a-methylene-19-nor-Δ⁴-pregnene-3,20-dione melting at 199 -202.5°C.

UV: ε 240 = 17,000.

The following Examples illustrate the invention:-

Example 1

500 mg of natural 17-hydroxy-18-methyl-15a,16a-methylene-19-nor-Δ⁴-pregnene-3,20-dione in 10 ml of acetic anhydride were stirred with 250 mg of para-toluene sulphonylic acid for 18 hours in a current of nitrogen at room temperature. The whole was then stirred into ice-water containing pyridine, and the precipitate that separated was filtered off with suction, washed with water, and taken up in methylene chloride. The residue obtained after drying and evaporating was, for the purpose of enol-acetate splitting, taken up in 15 ml of ethanol, 1.5 ml of sulphuric acid of 8% strength by volume were added, and the whole was heated under reflux for 30 minutes. After precipitating with ice-water the precipitate
was filtered off, washed with water, and taken up in methylene chloride. The residue obtained after drying and evaporating was chromatographed over silica gel, and there were obtained 205 mg of natural 17-acetoxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione melting at 163 - 165°C.

UV: $\varepsilon_{240} = 17,000$.

Example 2

To 325 mg of natural 17-hydroxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione in 10 ml of absolute benzene and 0.65 ml of caproic anhydride there was added 0.003 ml of perchloric acid of 70% strength, and the whole was stirred for 2 hours at room temperature. The mixture was then diluted with ether, washed with water, dried and evaporated to dryness. For the purpose of enolester splitting the residue was taken up in 10 ml of methanol, 2.5 ml of 2N-hydrochloric acid were added, and the whole was heated for 1 hour under reflux. After cooling, the mixture was diluted with ether, washed until neutral with water, dried, and evaporated to dryness. The residue was chromatographed over silica gel, and there were obtained 260 mg of natural 17-nexanoyloxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione in the form of an oil.

UV: $\varepsilon_{240} = 16,400$.

Example 3

To 300 mg of natural 17-hydroxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione in 10 ml of absolute
benzene and 0.6 ml of caprylic anhydride there was added 0.003 ml of perchloric acid of 70% strength, and the whole was stirred for 2 hours at room temperature. Working up and also enol-ester splitting were carried out as described in Example 2. After chromatography over silica gel there were obtained 210 mg of natural 17-octanoyloxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione in the form of an oil.

UV: ε 240 = 16,500.

Example 4

450 mg of 17-hydroxy-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione in 9 ml of acetic anhydride were reacted with 225 mg of para-toluene sulphonic acid and worked up as described in Example 1. By chromatography over silica gel and recrystallization from isopropyl ether there were obtained 285 mg of 17-acetoxy-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione melting at 221 - 223.5°C.

UV: ε 240 = 17,000.

Example 5

To 500 mg of 17-hydroxy-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione in 15 ml of absolute benzene and 1 ml of caproic anhydride there was added 0.005 ml of perchloric acid of 70% strength, and the whole was stirred for 1 hour at room temperature. Working up was carried out as described in Example 2. By chromatography over silica gel and recrystallization from isopropyl ether there were obtained 380 mg of 17-hexanoyloxy-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione melting at
Example 6

400 mg of 17-hydroxy-15\(\alpha\),16\(\alpha\)-methylene-19-nor-\(\Delta^4\)-pregnene-3,20-dione in 15 ml of absolute benzene and 0.8 ml of caprylic anhydride were reacted with 0.003 ml of perchloric acid of 70% strength and worked up in the manner described in Example 3. After chromatography over silica gel there were obtained 270 mg of 17-octanoyloxy-15\(\alpha\),16\(\alpha\)-methylene-19-nor-\(\Delta^4\)-pregnene-3,20-dione in the form of an oil.

UV: \(\varepsilon_{240} = 17,000\).

Example 7

1 gram of 17-hydroxy-18-methyl-15\(\alpha\),16\(\alpha\)-methylene-19-nor-\(\Delta^4\)-pregnene-3,20-dione was introduced at 5\(^\circ\)C into a mixture of 1.2 grams of undecanoic acid in 30 ml of absolute benzene and 1.1 ml of trifluoracetic anhydride, and the whole was heated for 2 hours at 60\(^\circ\)C. After cooling, the mixture was diluted with ether, and the solution was washed in succession with a saturated solution of sodium bicarbonate, an N/10 solution of sodium hydroxide and water, and dried and evaporated in vacuo. The residue was dissolved in 20 ml of methanol, 0.2 ml of concentrated hydrochloric acid was added, and the whole was heated under reflux for 45 minutes. The solution was diluted with ether, washed until neutral with water, and evaporated in vacuo. After chromatography over silica gel there was obtained 0.9 gram of 17-undecanoyloxy-18-methyl-15\(\alpha\),16\(\alpha\)-methylene-19-nor-\(\Delta^4\)-pregnene-3,20-dione.
in the form of an oil.
UV: $\epsilon_{240} = 16,700$.

**Example 8**

A solution of 910 mg of 17-hydroxy-15α,16α-methylene-19-nor-$\Delta^4$-pregnene-3,20-dione in 19 ml of collidine and 5 grams of lauric anhydride was heated at the boil for 5 hours under nitrogen. After cooling, the mixture was poured into ice-water and extracted with methylene chloride. The extract was washed with dilute hydrochloric acid, a solution of sodium bicarbonate and water, and then dried and evaporated in vacuo. The residue was chromatographed over silica gel. There were obtained 410 mg of 17-dodecanoyloxy-15α,16α-methylene-19-nor-$\Delta^4$-pregnene-3,20-dione in the form of a slightly yellow viscous oil.
UV: $\epsilon_{240} = 16,500$.

**Example 9**

1 gram of 17-hexanoyloxy-18-methyl-15α,16α-methylene-19-nor-$\Delta^4$-pregnene-3,20-dione was dissolved in sesame oil. The solution was made up to 1,000 ml with sesame oil, filtered under sterile conditions and introduced in the usual manner under aseptic conditions into 1 ml-ampoules. After sterilization was then carried out for 2 hours at 120°C.

**Example 10**

10 grams of 17-hexanoyloxy-15α,16α-methylene-19-nor-$\Delta^4$-pregnene-3,20-dione were dissolved in a mixture of castor oil and benzyl benzoate (6:4), and the solution was then made up to 1,000 ml. After filtering the solution under
sterile conditions it was introduced in the usual manner under aseptic conditions into 1 ml-ampoules. The ampoules were then after-sterilized for 2 hours at 120°C.

Example 11

2 grams of 17-acetoxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnen-3,20-dione were dissolved in a mixture of castor oil and benzyl benzoate (6 : 4), and then made up to 1,000 ml of solution. After filtration under sterile conditions the solution was introduced in the usual manner under aseptic conditions into 1- or 2-ml-ampoules. The ampoules were then after-sterilized for 2 hours at 120°C.

Example 12 (Composition of a tablet)

0.02 mg of 17-acetoxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnen-3,20-dione

63.68 mg of lactose
15.0 mg of Avicel
1.0 mg of talcum
0.3 mg of magnesium stearate

80.00 mg total weight of the tablet.

Example 13 (Composition of a push-fit, 2-part capsule).

0.100 mg of 17-acetoxy-15α,16α-methylene-19-nor-Δ⁴-pregnen-3,20-dione were mixed with 200 - 210 mg of lactose and introduced into push-fit, 2-part capsules of size 3.
Example 14 (Composition of a dragee)

1.000 mg of 17-acetoxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione

31.000 mg of lactose

18.425 mg of maize starch

2.060 mg of polyvinyl-pyrrolidone 25

0.010 mg of p-hydroxybenzoic acid methyl ester

0.005 mg of p-hydroxybenzoic acid propyl ester

2,500 mg of talcum

55,000 mg total weight of the tablet, which was coated with the usual sugar mixture to weight about 90 mg.

Example 15 (Composition of a tablet)

0.030 mg of 17α-ethynyl-oestradiol

0.100 mg of 17-acetoxy-18-methyl-15α,16α-methylene-19-nor-Δ⁴-pregnene-3,20-dione

33.000 mg of lactose

18.000 mg of maize starch

2.100 mg of polyvinyl-pyrrolidone

1.670 mg of talcum

0.100 mg of magnesium stearate

55,000 mg total weight, which was made up with the usual sugar mixture to about 90 mg.
Example 16 (Composition of dragées for stage-combination preparation)

1st Stage
0.050 mg of 17α-ethynyl-oestradiol
0.020 mg of 17-acetoxy-18-methyl-15α,16α-methylene-19-nor-Δ4-pregnene-3,20-dione
33.180 mg of lactose
18.000 mg of maize starch
2.100 mg of polyvinyl-pyrrolidone
1.650 mg of talcum

55.000 mg total weight, which was made up with the usual sugar mixture to about 90 mg.

2nd Stage
0.050 mg of 17α-ethynyl-oestradiol
0.050 mg of 17-acetoxy-18-methyl-15α,16α-methylene-19-nor-Δ4-pregnene-3,20-dione
33.150 mg of lactose
18.000 mg of maize starch
2.100 mg of polyvinyl-pyrrolidone
1.650 mg of talcum

55.000 mg total weight, which was made up with the usual sugar mixture to about 90 mg.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A 15α, 16α-methylene-Δ^4^-pregnene of the general formula I

in which R^1 represents a lower alkyl group and R^2 represents an acyl group.

2. A compound as claimed in claim 1, wherein R^1 represents a methyl or ethyl group.


11. A process for the manufacture of a 15\(\alpha\),16\(\alpha\)-methylene-\(\Delta^4\)-pregnene of the general formula I

\[
\begin{align*}
\text{CH}_3 & \\
\mid & \\
R^1 & \text{CO} \\
\mid & \\
O-R^2 & \\
\text{H} & \\
& \\
\text{0} & \\
\end{align*}
\]

(I),

in which \(R^1\) represents a lower alkyl group and \(R^2\) represents an acyl group, wherein a 17-hydroxy-15\(\alpha\),16\(\alpha\)-methylene-\(\Delta^4\)-pregnene of the general formula II

\[
\begin{align*}
\text{CH}_3 & \\
\mid & \\
R^1 & \text{CO} \\
\mid & \\
\text{OH} & \\
\text{H} & \\
& \\
\text{0} & \\
\end{align*}
\]

(II),
in which \( R^1 \) has the meaning given above, is esterified.

12. A process as claimed in claim 11, conducted substantially as described in any one of Examples 1 to 8 herein.

13. A pharmaceutical preparation which comprises a 15\( \alpha \),16\( \alpha \)-methylene-\( \Delta^4 \)-pregnene as claimed in claim 1 or 2, in admixture or conjunction with a pharmaceutically suitable carrier.

14. A pharmaceutical preparation which comprises the 15\( \alpha \),16\( \alpha \)-methylene-\( \Delta^4 \)-pregnene claimed in any one of claims 3 to 10, in admixture or conjunction with a pharmaceutically suitable carrier.

15. A preparation as claimed in claim 13 or 14, which is in the form of a contraceptive preparation.

16. A preparation as claimed in claim 15, which also contains an oestrogenically active compound.

17. A preparation as claimed in claim 16, wherein the oestrogenically active compound is ethynyl-oestradiol.

18. A preparation as claimed in any one of claims 13 to 17, which is in a form suitable for oral administration.

19. A preparation as claimed in claim 18, which is in the form of a tablet, dragée, capsule, pill, suspension or solution.

20. A preparation as claimed in claim 19, which is in the form of a tablet containing 0.01 to 5 mg of the active substance.

21. A preparation as claimed in any one of claims 13 to 17, which is in a form suitable for parenteral administration.
22. A preparation as claimed in claim 21, which is in the form of a solution.
23. A preparation as claimed in claim 22, which is in the form of an oily solution.
24. A preparation as claimed in claim 22 or 23, containing 0.1 to 10 mg of active substance per ml of solution.
25. A pharmaceutical preparation having a composition substantially as described in any one of Examples 9 to 16 herein.
26. A method of contraception, wherein there is administered in a contraceptive dose to a female mammal, as hereinbefore defined, a 15α,16α-methylene-Δ⁴-pregnene as claimed in claim 1 or 2.
27. A method of contraception, wherein there is administered in a contraceptive dose to a female mammal, as hereinbefore defined, the 15α,16α-methylene-Δ⁴-pregnene claimed in any one of claims 3 to 10.
28. A method as claimed in claim 26 or 27, wherein the female mammal is a female of the human species.
29. A method as claimed in claim 28, wherein the 15α,16β-methylene-Δ⁴-pregnene is administered in a daily dosage within the range of from 0.01 to 2 mg.

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