

PATENT SPECIFICATION

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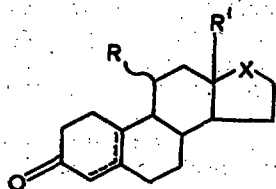
International Classification:—C 07 c 169/02

COMPLETE SPECIFICATION

11-Alkyl Steroids

We, G. D. SEARLE & CO., a Corporation organized and existing under the laws of the State of Delaware, United States of America, of Post Office Box 5110, Chicago, Illinois, 60680, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel steroidal derivatives characterised by an 11-alkyl substituent and a process for their preparation. The novel compounds of the present invention are (optionally 17-hydrocarbon-substituted)-11, 13 β -dialkylgon-4-en-3-ones and the corresponding $\Delta^{5(10)}$ compounds of the following general formula



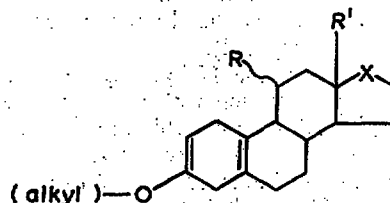
(I)

wherein R and R' are alkyl radicals containing 1 to 7 carbon atoms; X is a carbonyl, β -hydroxymethylene, β -alkanoyloxymethylene, α -(aliphatic hydrocarbon)- β -hydroxymethylene or α -(aliphatic hydrocarbon)- β -alkanoyloxymethylene radical; the wavy line indicates that the alkyl substituent at the 11-position can possess either the α or β stereochemical configuration; and the dotted lines indicate the presence of a double bond between carbon atoms 4 and 5 or carbon atoms 5 and 10; and the antipodal enantiomers and racemates of those compounds of the above formula wherein R' is an alkyl group containing from 2 to 7 carbon atoms.

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The aliphatic hydrocarbon radicals and the alkanoyl radicals encompassed by the X term are preferably lower with from 1 to 7 carbon atoms. The hydrocarbon radicals are exemplified by alkyl radicals such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and the branched-chain groups isomeric therewith; alkenyl radicals such as vinyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, and the corresponding branched-chain isomers; and alkynyl radicals such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl and the corresponding branched-chain isomeric groups.

The compounds of formula (I) can be conveniently prepared by the hydrolysis of a compound of the general formula



(II)

wherein R, R' and X are as defined above and the alkyl radical contains 1 to 7 carbon atoms, the said compound being in the form of a racemate when R' is an alkyl group containing from 2 to 7 carbon atoms, by treating said compound with an acid in a hydroxylic medium.

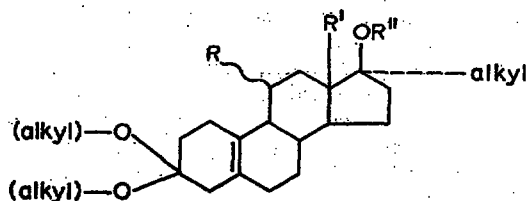
Use of mild acids, for example monocarboxylic acids such as acetic acid and dicarboxylic acids such as oxalic acid, affords the $\Delta^{5(10)}$ compounds of formula (I). Isomerisation of said $\Delta^{5(10)}$ products with a basic reagent (e.g., sodium hydroxide or sodium methoxide in aqueous methanol) or an acidic reagent (e.g., hydrochloric or *p*-toluenesulphonic acid in

aqueous methanol) provides the Δ^4 compounds of formula (I).

When a strong acid is employed for the hydrolysis, for example a mineral acid such as aqueous hydrochloric or sulphuric acid in the presence of methanol, cleavage of the enol ether function at position 3, ketonisation of the resulting 3-enol and rearrangement of the 5(10) double bond into conjugation with the 3-ketone takes place as a single operation in a single reaction vessel without the necessity of isolating the $\Delta^{5(10)}$ compound, which is formed as an intermediate product.

For the hydrolysis reaction of the present invention the time of reaction and reaction temperature employed are interdependent. Thus, the use of heat, though not required, simply serves to promote the reaction.

For those compounds of formula (I) wherein X is an α -alkyl- β -hydroxymethylene or α -alkyl- β -alkanoyloxymethylene radical, an equally suitable starting material is a ketal of the general formula



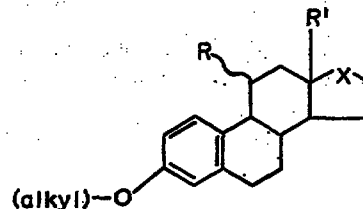
wherein R'' is a hydrogen atom or an alkanoyl radical, which upon acid hydrolysis, as described above, yields the desired Δ^4 or $\Delta^{5(10)}$ compound of formula (I).

Esterification of the 17-hydroxy compounds of the present invention with an alkanoyl acid anhydride or halide, preferably in the presence of a suitable acid acceptor, results in the corresponding 17-alkanoates. 17- α -Ethinyl-17 β -hydroxy-11 β -methylestr-4-en-3-one is thus heated with acetic anhydride and pyridine to afford 17 β -acetoxy-17 α -ethinyl-11 β -methylestr-4-en-3-one.

Oxidation of the compounds of formula (I) wherein X is a β -hydroxymethylene radical, suitably with aluminium isopropoxide and cyclohexanone in toluene, provides an alternative route to the corresponding 17-keto compounds.

Those $\Delta^{5(10)}$ compounds wherein X is an α -(alkenyl/alkyl)- β -(hydroxy/alkanoyloxy)-methylene radical can be alternatively prepared from the corresponding $\Delta^{5(10)}$ compounds possessing a 17 α -alkenyl substituent by reduction with hydrogen and a hydrogenation catalyst. Partial reduction with the absorption of 1 molecular equivalent of hydrogen provides the 17 α -alkenyl derivatives, while complete reduction with the absorption of at least 2 molecular equivalents of hydrogen affords the corresponding 17 α -alkyl compounds.

The starting materials of formula (II) are prepared by the reduction of the corresponding estratrienes of the general formula



with an alkali metal-liquid ammonia combination. Typically, 3-methoxy-11 β -methylestr-1,3,5(10)-trien-17 β -ol in tetrahydrofuran is contacted with sodium and liquid ammonia to afford 3-methoxy-11 β -methylestr-2,5(10)-dien-17 β -ol. The optional ketal starting materials are prepared from the aforementioned 3-alkoxyestra-2,5(10)-dienes by reaction with an alkanol in the presence of an acid.

For example, use of methanol and *p*-toluenesulphonic acid, accompanied by heat, would provide the dimethyl ketal.

The compounds of the present invention wherein the 13 β -alkyl group contains more than 1 carbon atom, i.e., ethyl and higher homologous radicals, are obtained as *dl* mixtures. Since their intermediate precursors of formula (II) are themselves *dl*-mixtures having been prepared by total synthetic methods not involving or resolution stage. Resolutions of these *dl* compounds to afford the individual *d* and *l* enantiomorphs is conveniently effected by esterification of the hydroxy group with a dibasic acid anhydride such as succinic or phthalic anhydride to afford the corresponding acid ester which is resolved by means of an optically active amine such as brucine, morphine, quinine, quinidine or strychnine.

The compounds of formula (I) display valuable pharmacological properties. They are hormonal agents, for example, as is evidenced by their anabolic, androgenic and progestational properties. In addition, they lack the desoxycorticosterone acetate inhibitory activity characteristic of related substances.

In the following examples, which illustrate the invention, temperatures are given in degrees centigrade ($^{\circ}\text{C}$.) and quantities of materials are expressed in parts by weight unless otherwise noted. The relationship between parts by weight and parts by volume is the same as that existing between grams and millilitres.

EXAMPLE 1

A solution containing 6 parts of 3-methoxy-11 β -methylestr-2,5(10)-dien-17 β -ol, 800 parts of methanol and 200 parts of 4M hydrochloric acid was heated just below the reflux temperature for about 40 minutes, then was cooled and neutralised by the addition of aqueous sodium bicarbonate.

Extraction of that aqueous mixture with ether afforded an organic solution, which was dried over anhydrous magnesium sulphate and concentrated to dryness under reduced pressure. Trituration of the resulting residue with ether-hexane afforded crystals of 17 β -hydroxy-11 β -methylestr-4-en-3-one, melting at about 158—160°. This compound exhibited an ultraviolet absorption maximum at about 241.5 millimicrons with a molecular extinction coefficient of about 15,800.

Substitution of molecular equivalent quantities of the appropriate 3-alkoxyestra-2,5(10)-diene of formula (II) for the steroidal starting material utilised above yielded, according to the strong acid hydrolysis procedure described above, the following products from the respective steroidal starting material named:

Use of 3-methoxy-11 β -methylestra-2,5(10)-dien-17-one afforded 11 β -methylestr-4-ene-3,17-dione, which exhibited infra-red absorption maxima in potassium bromide at about 5.72, 5.95, and 6.97 microns.

Use of *dl*-13 β -ethyl-3-methoxy-11 β -methylgona-2,5(10)-dien-17 β -ol yielded *dl*-13 β -ethyl-17 β -hydroxy-11 β -methylgon-4-en-3-one.

Hydrolysis of 11 β -ethyl-3-methoxyestra-2,5(10)-dien-17 β -ol in accord with the above procedure yielded 11 β -ethyl-17 β -hydroxyestr-4-en-3-one.

EXAMPLE 2

To 0.6 parts of 17 α -ethynyl-3-methoxy-11 β -methylestra-2,5(10)-dien-17 β -ol dissolved in 80 parts of methanol was added a solution of 20 parts of 4N hydrochloric acid in 20 parts of water.

That solution was heated on the steam bath for about 10 minutes, then was cooled and neutralised by the addition of aqueous sodium bicarbonate. Concentration of that solution to dryness afforded the crude product, which was treated with decolourising carbon, then was recrystallised from ether-hexane to afford 17 α -ethynyl-17 β -hydroxy-11 β -methylestr-4-en-3-one, melting at about 220°. This compound exhibited infra-red absorption maxima, in potassium bromide, at about 2.92, 3.06 and 5.98 microns.

Substitution of a molecular equivalent quantity of the appropriate starting material of formula (II) afforded according to the above procedure the following products:

Use of *dl*-13 β -ethyl-17 α -ethynyl-3-methoxy-11 β -methylgona-2,5(10)-dien-17 β -ol afforded *dl*-13 β -ethyl-17 α -ethynyl-17 β -hydroxy-11 β -methylgon-4-en-3-one.

Similarly, an equivalent molecular quantity of 11 β -ethyl-17 α -ethynyl-3-methoxyestra-2,5(10)-dien-17 β -ol yielded 11 β -ethyl-17 α -ethynyl-17 β -hydroxyestr-4-en-3-one.

The acidic hydrolysis of an equivalent quantity of 3-methoxy-11 β -methyl-17 α -vinylestra-2,5(10)-dien-17 β -ol by the procedure described above resulted in 17 β -

hydroxy-11 β -methyl-17 α -vinylestr-4-en-3-one.

Likewise 3-methoxy-11 β -methyl-17 α -propynylestra-2,5(10)-dien-17 β -ol, upon strong acid hydrolysis according to the above procedure, resulted in 17 β -hydroxy-11 β -methyl-17 α -propynylestr-4-en-3-one.

Use of 3-methoxy-11 β -methyl-17 α -propynylestra-2,5(10)-dien-17 β -ol provided 17 β -hydroxy-11 β -methyl-17 α -propynylestr-4-en-3-one.

EXAMPLE 3

To 0.6 parts of 3-methoxy-11 β ,17 α -dimethylestra-2,5(10)-dien-17 β -ol dissolved in 90 parts of methanol was added 25 parts by volume of 4M hydrochloric acid, and the resulting mixture was distilled slowly over a period of about 45 minutes, then was neutralised by the addition of aqueous sodium bicarbonate and extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulphate, then was distilled to dryness under reduced pressure. The resulting residue was purified by adsorption on a silica gel chromatographic column followed by elution with 10—25% ethyl acetate in benzene. Recrystallisation from ether-hexane of the eluted fractions afforded 17 β -hydroxy-11 β ,17 α -dimethylestr-4-en-3-one, melting at about 125—126°. This compound exhibited nuclear magnetic resonance peaks at about 61, 69, 73 and 352 cycles per second.

When an equivalent molecular quantity of 17 β -hydroxy-11 β ,17 α -dimethylestr-5(10)-en-3-one 3-dimethyl ketal was substituted for the starting material utilised above and that strong acid hydrolysis procedure was repeated, there was obtained 17 β -hydroxy-11 β ,17 α -dimethylestr-4-en-3-one, which was identical to the product obtained in the preceding paragraph.

Similarly, the substitution of an equivalent quantity of *dl*-13 β -ethyl-3-methoxy-11 β ,17 α -dimethylgona-2,5(10)-dien-17 β -ol yielded *dl*-13 β -ethyl-17 β -hydroxy-11 β ,17 α -dimethylgon-4-en-3-one.

Use of 11 β -ethyl-3-methoxy-17 α -methylestra-2,5(10)-dien-17 β -ol yielded 11 β -ethyl-17 β -hydroxy-17 α -methyl-estr-4-en-3-one according to the procedure described hereinabove.

EXAMPLE 4

To about 2 parts of 17 α -ethyl-3-methoxy-11 β -methylestra-2,5(10)-dien-17 β -ol, dissolved in 160 parts of methanol, was added 40 parts of 2M hydrochloric acid. That solution was heated at a temperature just below the reflux point in a nitrogen atmosphere for about 10 minutes, then was neutralised by the addition of aqueous sodium bicarbonate and concentrated by distillation under reduced pressure. Extraction of that residual mixture with benzene afforded an organic solution, which was dried over anhydrous magnesium sulphate,

then distilled to dryness under reduced pressure. The resulting crude product was purified by preparative thin layer chromatography on silica gel. The chromatogram was developed with 15% ethyl acetate in benzene, and the silica gel fraction containing the desired product was stirred with ethyl acetate for about 10 minutes. The ethyl acetate extract was concentrated to dryness to afford 17 α -ethyl-17 β -hydroxy-11 β -methylestr-4-en-3-one, melting at about 58—61°. This compound exhibited an ultra-violet absorption maximum at about 241.5 millimicrons with a molecular extinction coefficient of about 16,700.

EXAMPLE 5

One-half part of 3-methoxy-11 α ,17 α -dimethylmethylestra-2,5(10)-dien-17 β -ol was dissolved in approximately 40 parts of methanol.

To that solution was added 10 parts by volume of 2M hydrochloric acid. The resulting mixture was heated at approximately 70° for about 45 minutes, then was neutralised by the addition of excess aqueous sodium bicarbonate. That aqueous mixture was extracted with chloroform, and the chloroform layer was separated and concentrated to dryness under reduced pressure. The resulting residue was triturated with ether to afford crystalline 17 β -hydroxy-11 α ,17 α -dimethylestr-4-en-3-one, melting at about 195—197°. The compound displayed an ultra-violet absorption maximum at about 242 millimicrons with a molecular extinction coefficient of about 17,800.

EXAMPLE 6

5 Parts of 17 α -ethynyl-3-methoxy-11 β -methylestra-2,5(10)-dien-17 β -ol, 1000 parts by volume of an 80% solution of aqueous methanol and 100 parts of acetic acid were stirred in a nitrogen atmosphere, and warmed for about 1/2 hour. To that mixture were added water, excess saturated aqueous sodium bicarbonate and chloroform. The chloroform layer was separated, dried over magnesium sulphate and concentrated to dryness. Trituration with ether gave, as crystals, 17 α -ethynyl-17 β -hydroxy-11 β -methylestr-5(10)-en-3-one melting at about 176—177° and exhibiting infrared maxima, in chloroform, at about 2.76, 3.01, and 5.84 microns.

Similarly, substitution of 3-methoxy-11 β ,17 α -dimethylestra-2,5(10)-dien-17 β -ol for the starting material used above afforded, according to the described mild acidic hydrolysis, 17 β -hydroxy-11 β ,17 α -dimethylestr-5(10)-en-3-one.

Similarly use of 3-methoxy-11 β -methyl-17 α -vinylestra-2,5(10)-dien-17 β -ol afforded

according to the above described procedure 17 β -hydroxy-11 β -methyl-17 α -vinylestr-5(10)-en-3-one.

EXAMPLE 7

The isomerisation of an equivalent quantity of 17 β -hydroxy-11 β ,17 α -dimethylestr-5(10)-en-3-one with 4M hydrochloric acid in methanol according to the procedure described in Example 3 above resulted in 17 β -hydroxy-11 β ,17 α -dimethylestr-4-en-3-one, which was identical with the product of that example.

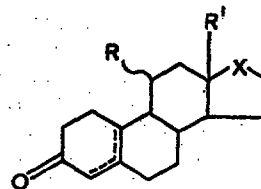
EXAMPLE 8

A mixture of 2 parts of 17 α -ethynyl-17 β -hydroxy-11 β -methylestr-4-en-3-one, 20 parts of acetic anhydride and 40 parts of pyridine was heated at 90—100° for about 2 hours, then was cooled and poured carefully into water. The resulting aqueous mixture was extracted with benzene, and the organic layer was separated, washed with water, dried over anhydrous sodium sulphate and stripped of solvent under reduced pressure to afford 17 β -acetoxyl-17 α -ethynyl-11 β -methylestr-4-en-3-one.

Substituting an equivalent quantity of propionic anhydride and otherwise proceeding according to the process described above there was produced 17 α -ethynyl-11 β -methyl-17 β -propionyloxyestr-4-en-3-one.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



wherein R and R' are alkyl radicals containing 1 to 7 carbon atoms; X is a carbonyl, β -hydroxymethylene, β -alkanoyloxymethylene, α -(aliphatic hydrocarbon)- β -hydroxymethylene or α -(aliphatic hydrocarbon)- β -alkanoyloxymethylene radical; the wavy line indicating that the alkyl substituent at the 11-position can possess either the α or β stereochemical configuration; and the dotted line indicating the presence of a double bond between carbon atoms 4 and 5 or carbon atoms 5 and 10; and the antipodal enantiomers and racemates of those compounds of the above formula wherein R' is an alkyl group containing from 2 to 7 carbon atoms.

2. Compounds of the general formula

then distilled to dryness under reduced pressure. The resulting crude product was purified by preparative thin layer chromatography on silica gel. The chromatogram was developed with 15% ethyl acetate in benzene, and the silica gel fraction containing the desired product was stirred with ethyl acetate for about 10 minutes. The ethyl acetate extract was concentrated to dryness to afford 17 α -ethyl-17 β -hydroxy-11 β -methylene-4-en-3-one, melting at about 58—61°. This compound exhibited an ultra-violet absorption maximum at about 241.5 millimicrons with a molecular extinction coefficient of about 16,700.

EXAMPLE 5

One-half part of 3-methoxy-11 α ,17 α -dimethylmethylene-2,5(10)-dien-17 β -ol was dissolved in approximately 40 parts of methanol.

To that solution was added 10 parts by volume of 2M hydrochloric acid. The resulting mixture was heated at approximately 70° for about 45 minutes, then was neutralised by the addition of excess aqueous sodium bicarbonate. That aqueous mixture was extracted with chloroform, and the chloroform layer was separated and concentrated to dryness under reduced pressure. The resulting residue was triturated with ether to afford crystalline 17 β -hydroxy-11 α ,17 α -dimethylene-4-en-3-one, melting at about 195—197°. The compound displayed an ultra-violet absorption maximum at about 242 millimicrons with a molecular extinction coefficient of about 17,800.

EXAMPLE 6

5 Parts of 17 α -ethynyl-3-methoxy-11 β -methylene-2,5(10)-dien-17 β -ol, 1000 parts by volume of an 80% solution of aqueous methanol and 100 parts of acetic acid were stirred in a nitrogen atmosphere, and warmed for about 1/2 hour. To that mixture were added water, excess saturated aqueous sodium bicarbonate and chloroform. The chloroform layer was separated, dried over magnesium sulphate and concentrated to dryness. Trituration with ether gave, as crystals, 17 α -ethynyl-17 β -hydroxy-11 β -methylene-5(10)-en-3-one melting at about 176—177° and exhibiting infrared maxima, in chloroform, at about 2.76, 3.01, and 5.84 microns.

Similarly, substitution of 3-methoxy-11 β ,17 α -dimethylene-2,5(10)-dien-17 β -ol for the starting material used above afforded, according to the described mild acidic hydrolysis, 17 β -hydroxy-11 β ,17 α -dimethylene-5(10)-en-3-one.

Similarly use of 3-methoxy-11 β -methyl-17 α -vinylestra-2,5(10)-dien-17 β -ol afforded

according to the above described procedure 17 β -hydroxy-11 β -methyl-17 α -vinylestra-5(10)-en-3-one.

EXAMPLE 7

The isomerisation of an equivalent quantity of 17 β -hydroxy-11 β ,17 α -dimethylene-5(10)-en-3-one with 4M hydrochloric acid in methanol according to the procedure described in Example 3 above resulted in 17 β -hydroxy-11 β ,17 α -dimethylene-4-en-3-one, which was identical with the product of that example.

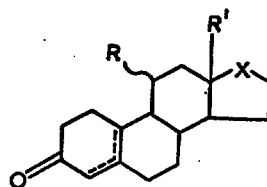
EXAMPLE 8

A mixture of 2 parts of 17 α -ethynyl-17 β -hydroxy-11 β -methylene-4-en-3-one, 20 parts of acetic anhydride and 40 parts of pyridine was heated at 90—100° for about 2 hours, then was cooled and poured carefully into water. The resulting aqueous mixture was extracted with benzene, and the organic layer was separated, washed with water, dried over anhydrous sodium sulphate and stripped of solvent under reduced pressure to afford 17 β -acetoxy-17 α -ethynyl-11 β -methylene-4-en-3-one.

Substituting an equivalent quantity of propionic anhydride and otherwise proceeding according to the process described above there was produced 17 α -ethynyl-11 β -methyl-17 β -propionyloxy-4-en-3-one.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



wherein R and R' are alkyl radicals containing 1 to 7 carbon atoms; X is a carbonyl, β -hydroxymethylene, β -alkanoyloxymethylene, α -(aliphatic hydrocarbon)- β -hydroxymethylene or α -(aliphatic hydrocarbon)- β -alkanoyloxymethylene radical; the wavy line indicating that the alkyl substituent at the 11-position can possess either the α or β stereochemical configuration; and the dotted line indicating the presence of a double bond between carbon atoms 4 and 5 or carbon atoms 5 and 10; and the antipodal enantiomers and racemates of those compounds of the above formula wherein R' is an alkyl group containing from 2 to 7 carbon atoms.

2. Compounds of the general formula

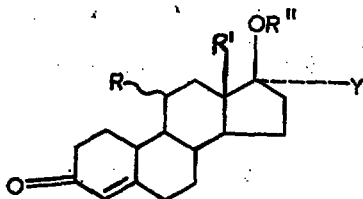




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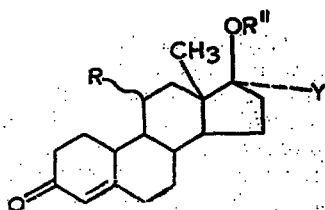
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wherein R and R' are alkyl radicals containing 1 to 7 carbon atoms; Y is a hydrogen atom or an aliphatic hydrocarbon radical; R'' is a hydrogen atom or an alkanoyl radical; the wavy line indicating that the alkyl substituent at the 11-position can possess either the α or β stereochemical configuration; and the antipodal enantiomers and racemates of those compounds of the above formula wherein R' is an alkyl group containing from 2 to 7 carbon atoms.

3. Compounds as claimed in Claim 2 wherein Y is a hydrogen atom or a lower aliphatic hydrocarbon radical with from 1 to 7 carbon atoms and R'' is a hydrogen atom or a lower alkanoyl radical with from 1 to 7 carbon atoms.

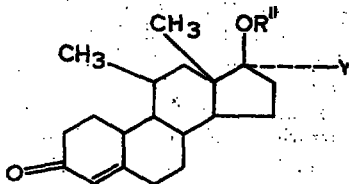
4. Compounds of the general formula



wherein R is an alkyl radical containing 1 to 7 carbon atoms; Y is a hydrogen atom or an aliphatic hydrocarbon radical; R'' is a hydrogen atom or an alkanoyl radical; the wavy line indicating that the alkyl substituent at the 11-position can possess either the α or β stereochemical configuration.

5. Compounds as claimed in Claim 4 wherein Y is a hydrogen atom or a lower aliphatic hydrocarbon radical with from 1 to 7 carbon atoms and R'' is a hydrogen atom or a lower alkanoyl radical with from 1 to 7 carbon atoms.

6. Compounds of the general formula

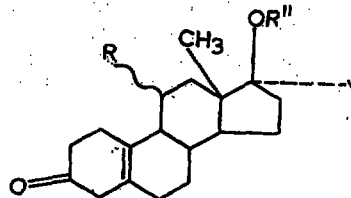


wherein Y is a hydrogen atom or an aliphatic hydrocarbon radical and R'' is a hydrogen atom or an alkanoyl radical.

7. Compounds as claimed in claim 6 wherein Y is a hydrogen atom or a lower aliphatic

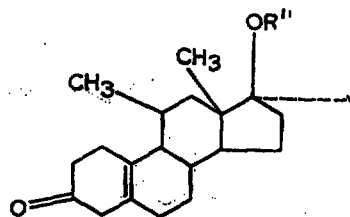
hydrocarbon radical with from 1 to 7 carbon atoms and R'' is a hydrogen atom or a lower alkanoyl radical with from 1 to 7 carbon atoms.

8. Compounds of the general formula



wherein R is an alkyl radical containing 1 to 7 carbon atoms; Y is a hydrogen atom or an aliphatic hydrocarbon radical; R'' is a hydrogen atom or an alkanoyl radical; the wavy line indicating that the alkyl substituent at the 11-position can possess either the α or β stereochemical configuration.

9. Compounds of the general formula



wherein Y is a hydrogen atom or an aliphatic hydrocarbon radical; and R'' is a hydrogen atom or an alkanoyl radical.

10. 17β - hydroxy - $11\beta, 17\alpha$ - dimethylestr-4-en-3-one.

11. 17β - hydroxy - 11β - methylestr - 4-en-3-one.

12. 17α - ethyl - 17β - hydroxy - 11β - methylestr-4-en-3-one.

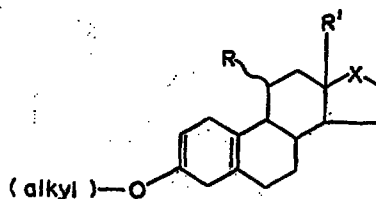
13. 17α - ethynyl - 17β - hydroxy - 11β - methylestr-4-en-3-one.

14. 17β - hydroxy - $11\alpha, 17\alpha$ - dimethylestr-4-en-3-one.

15. 11β - methylestr - 4 - ene - 3,17 - dione.

16. 17α - ethynyl - 17β - hydroxy - 11β - methylestr-5(10)-en-3-one.

17. A process for the preparation of the compounds claimed in Claim 1 which comprises the hydrolysis of a compound of the general formula



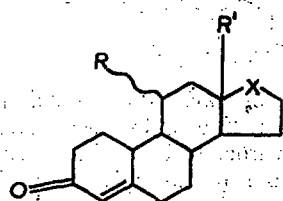
wherein R, R', X and the wavy line have the meanings given in Claim 1 and the alkyl radical



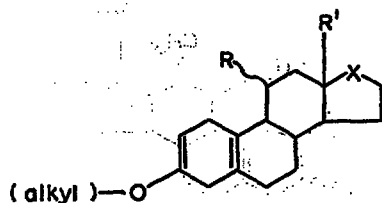
contains 1 to 7 carbon atoms, the said compound being in the form of a racemate when R' is an alkyl group containing 2 to 7 carbon atoms, with an acid in a hydroxylic medium, and if desired, where the group R' contains

from 2 to 7 carbon atoms, the product is resolved to yield the antipodal enantiomers.

18. A process as claimed in Claim 17 for the preparation of compounds of the general formula

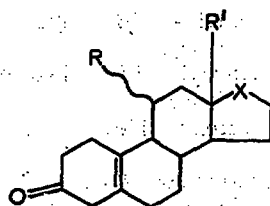


wherein R, R', X, and the wavy line have the meanings given in Claim 1, which comprises the hydrolysis of a compound of the general formula

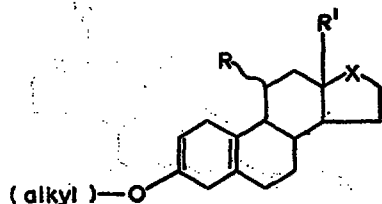


wherein the alkyl radical contains 1 to 7 carbon atoms with a strong acid in a hydroxylic medium.

19. A process as claimed in Claim 17 for the preparation of compounds of the general formula



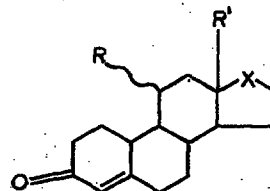
wherein R, R', X, and the wavy line have the meanings given in claim 1, which comprises the hydrolysis of a compound of the general formula



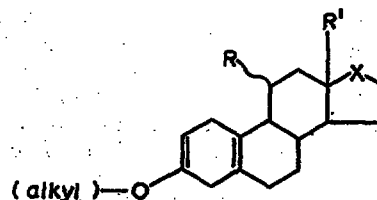
wherein the alkyl radical contains 1 to 7

carbon atoms, with a mild mono- or dicarboxylic acid in a hydroxylic medium.

20. A process as claimed in claim 17 for the preparation of a compound of the general formula



wherein R, R', X, and the wavy line have the meanings given in claim 1, which comprises the hydrolysis of a compound of the general formula



wherein the alkyl radical contains 1 to 7 carbon atoms, with a mild mono- or dicarboxylic acid in a hydroxylic medium, followed by the isomerisation with a basic or acidic reagent of the $\Delta^5(10)$ product thereby obtained.

21. A process as claimed in claim 18 for the preparation of 17 α -ethynyl-17 β -hydroxy-11 β -methylestr-4-en-3-one which comprises the hydrolysis of 17 α -ethynyl-3-methoxy-11 β -methylestr-2,5(10)-dien-17 β -ol with dilute hydrochloric acid in the presence of methanol.

22. A process as claimed in claim 18 for the preparation of 17 β -hydroxy-11 β ,17 α -dimethylestr-4-en-3-one which comprises the hydrolysis of 3-methoxy-11 β ,17 α -dimethylestr-2,5(10)-dien-17 β -ol with dilute hydrochloric acid in the presence of methanol.

23. A process as claimed in claim 18 for the preparation of 17 α -ethyl-17 β -hydroxy-11 β -methylestr-4-en-3-one which comprises the hydrolysis of 17 α -ethyl-3-methoxy-11 β -methylestr-2,5(10)-dien-17 β -ol with dilute hydrochloric acid in the presence of methanol.

24. A process as claimed in claim 19 for the preparation of 17 α -ethynyl-17 β -hydroxy-11 β -methylestr-5(10)-en-3-one which comprises the hydrolysis of 17 α -ethynyl-3-methoxy-11 β -methylestr-2,5(10)-dien-17 β -ol with acetic acid in the presence of methanol.

25. A process as claimed in claim 20 for the preparation of 17 β -hydroxy-11 β ,17 α -di-



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- methylestr - 4 - en - 3 - one which comprises the hydrolysis of 3 - methoxy - 11 β ,17 α - dimethylestra - 2,5(10) - dien - 17 β - ol with acetic acid in the presence of methanol,
- 5 followed by isomerisation with dilute hydrochloric acid, in the presence of methanol, of the resultant 17 β - hydroxy - 11 β ,17 α - dimethylestr - 5(10) - en - 3 - one.
26. A process for the preparation of the compounds claimed in claim 1 substantially as described with reference to any one of the Examples. 10

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