



PATENT SPECIFICATION

NO DRAWINGS

1.190.240

Date of Application (No. 52842/67) and filing Complete Specification: 21 Nov., 1967.

Application made in United States of America (No. 596,090) on 22 Nov., 1966.

Complete Specification Published: 29 April, 1970.

Index at acceptance:—C2 U (4A1, 4B2, 4C2, 4C4, 4X)

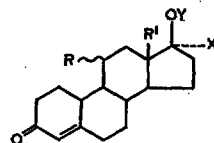
International Classification:—C 07 c 169/02

COMPLETE SPECIFICATION

17-(Unsaturated Hydrocarbon-Substituted) 11,13 β -Dialkylgon-4-Ene-3,17 β -Diols and Esters thereof

We, G. D. SEARLE & Co., a Corporation organised 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:—

The present invention relates to compounds of the general formula



(II)

in *d*, *l* or *dl* form or in a mixture of these forms, (X, Y, R and R' are here and throughout the text defined as hereinbefore) with a reducing agent capable of converting a carbonyl function to a carbinol function without affecting unsaturated linkages. Suitable reducing agents include metallic hydrides such as lithium aluminium hydride, sodium borohydride, potassium borohydride, lithium tri-(tertiary - butoxy) aluminium hydride and diisobutyl aluminium hydride. This reaction can be carried out at room temperature, preferably in the presence of a suitable inert organic solvent such as tetrahydrofuran.

The starting materials of formula (II) are described and claimed in our co-pending application No. 54774/66 (Serial No. 1,169,938).

When Y of formula (II) is hydrogen, the product of the reduction reaction described above is the 3,17-diol of formula (I). Esterification of that substance by reaction with an alkanolic acid anhydride or halide at room temperature, preferably in the presence of a suitable acid acceptor, for example pyridine, provides the corresponding 3-monoalkanoate of formula (I), wherein Z is an alkanoyl radical and Y is a hydrogen atom. By esterification of that 3,17-diol at elevated temperature, there are produced the 3,17-bisalkanoates of formula (I), wherein both Y and Z represent an alkanoyl radical.

On the other hand, when Y of formula (II) represents an alkanoyl radical, reduction according to the method described above provides the 17-monoalkanoates of formula (I). Esterification thereof, at room temperature,

(I)
in *d*, *l* or *dl* form or in a mixture of these forms, wherein R and R' are alkyl radicals; X is an unsaturated aliphatic hydrocarbon radical; Y and Z are hydrogen atoms or alkanoyl radicals; the wavy line indicates the alternative α or β stereochemical configuration; and each of the alkyl, unsaturated aliphatic hydrocarbon and alkanoyl radicals contain less than 8 carbon atoms.

The alkyl radicals symbolised by R and R' are exemplified by methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and the branched-chain radicals isomeric therewith.

Typical of the alkanoyl radicals signified by the Y and Z terms are formyl, acetyl, propionyl, butyryl, valeryl, caproyl, heptanoyl and the branched-chain isomers thereof.

The unsaturated aliphatic hydrocarbon radicals denoted by X are typified by ethynyl, vinyl, propynyl, allyl, butynyl, propargyl and methallyl.

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

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provides the 3,17-bisalkanoates, i.e., the compounds of formula (I) wherein Y and Z represent alkanoyl radicals.

5 The compounds of formula (I) wherein X represents an alkenyl radical can be alternatively prepared by contacting the corresponding compound of formula (I), wherein X represents an alkynyl radical, with hydrogen in the presence of a hydrogenation catalyst such as
10 palladium-on-carbon until one molecular equivalent of hydrogen has been consumed.

When the compounds of the present invention are prepared from starting materials having a 13 β -alkyl group containing more than one carbon atom, these starting materials are obtained by a total synthetic method not involving a resolution stage and are thus *dl* mixtures. Compounds according to the invention derived therefrom wherein the 13 β -alkyl group contains more than one carbon atom are thus also obtained as *dl* mixtures. Resolutions of these *dl* compounds to provide the individual *d* and *l* enantiomorphs is conveniently effected by esterification of the hydroxy group with a dibasic 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.

30 The compounds of the present invention are useful in consequence with their valuable pharmacological properties. In particular, they are hormonal agents as is evidenced by their potent progestational and decidual activity.

35 In the following examples, which are intended to illustrate and not limit the present invention, temperatures are given in degrees centigrade ($^{\circ}\text{C}$.) and quantities of materials are expressed in parts by weights, unless otherwise noted. The relationship between parts by weight and parts by volume is the same as that existing between grams and milliliters.

EXAMPLE 1

45 To a solution of one part of 17 α -ethynyl-17 β -hydroxy-11 β -methylestr-4-en-3-one in 27 parts of tetrahydrofuran was added 4 parts of lithium tri-(tertiary-butoxy) aluminium hydride, and the resulting reaction mixture was stirred at room temperature for about 2 hours.
50 The mixture was then poured with stirring into an aqueous mixture containing 40 parts of water, 20 parts of ice and 10.5 parts of acetic acid. Extraction with chloroform yielded an organic solution, which was washed successively with aqueous sodium chloride and aqueous sodium bicarbonate, then dried over anhydrous magnesium sulphate and distilled to dryness under reduced pressure. The resulting crude product was purified by recrystallisation from ether-hexane to yield 17 α -ethynyl-11 β -methylestr-4-ene-3 β ,17 β -diol, melting at
60 175–180 $^{\circ}$. This compound exhibits infrared absorption maxima, in a potassium bromide disc, at 2.82, 2.90, 3.06, 7.21, 9.34, 9.67, and

9.98 microns and nuclear magnetic resonance peaks at about 58, 67, 154, 250 and 325 cycles per second.

Substitution of a molecular equivalent quantity of each of the below listed reactants in place of the steroidal starting material employed in the above reduction reaction yields, according to the procedure there detailed, the following products.

Use of *dl*-17 α -ethynyl-13 β -ethyl-17 β -hydroxy-11 β -methylgon-4-en-3-one affords *dl*-17 α -ethynyl-13 β -ethyl-11 β -methylgon-4-ene-3 β ,17 β -diol, which is characterised by infrared maxima, in potassium bromide, at 2.82, 2.92 and 3.06 microns.

Reduction of 11 β -ethyl-17 α -ethynyl-17 β -hydroxyestr-4-en-3-one by the procedure described above results in 11 β -ethyl-17 α -ethynylestr-4-ene-3 β ,17 β -diol, which is characterised by infrared maxima, in potassium bromide, at 2.83, 2.93 and 3.05 microns.

Reduction of 11 β -ethyl-17 α -ethynyl-17 β -hydroxyestr-4-en-3-one by the procedure described above results in 11 β -ethyl-17 α -ethynylestr-4-ene-3 β ,17 β -diol, which is characterised by infrared maxima, in potassium bromide, at 2.83, 2.93 and 3.05 microns.

Similarly, employing 17 β -hydroxy-11 β -methyl-17 α -vinylestr-4-en-3-one there is obtained 11 β -methyl-17 α -vinylestr-4-ene-3 β ,17 β -diol, which is characterised by infrared maxima, in chloroform solution, at 2.9 and 6.0 microns.

Use of 17 β -hydroxy-11 β -methyl-17 α -propynylestr-4-en-3-one yields 11 β -methyl-17 α -propynylestr-4-ene-3 β ,17 β -diol characterised by infrared maxima, in chloroform solution, at 2.73, 6.00 and 6.18 microns.

Similarly, the reduction of 17 β -hydroxy-11 β -methyl-17 α -propynylestr-4-en-3-one according to the procedure described above, affords 11 β -methyl-17 α -propynylestr-4-ene-3 β ,17 β -diol, which is characterised by infrared maxima, in chloroform solution, at 2.72 and 6.0 microns.

In a similar manner, use of 17 β -hydroxy-11 α -methyl-17 α -vinylestr-4-en-3-one in the process described above yields 11 α -methyl-17 α -vinylestr-4-ene-3 β ,17 β -diol, which is characterised by infrared maxima, in chloroform solution, at 2.9 and 6.0 microns.

Reduction of 17 α -ethynyl-17 β -hydroxy-11 α -methylestr-4-en-3-one in accord with the above procedure results in 17 α -ethynyl-11 α -methylestr-4-ene-3 β ,17 β -diol, which is characterised by infrared maxima, in chloroform solution at 2.82, 2.92 and 3.05 microns.

Use of 17 β -acetoxy-17 α -ethynyl-11 α -methylestr-4-en-3-one yields, upon

reduction as detailed above, 17 α - ethynyl - 11 α - methylestr - 4 - ene - 3 β ,17 β - diol 17-acetate, which is characterised by infrared maxima, in chloroform solution, at 2.72, 3.05 and 5.73 microns.

EXAMPLE 2

A mixture containing one part of 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol, 5 parts of acetic anhydride and 10 parts of pyridine was heated on the steam bath for about 18 hours, then cooled and concentrated to dryness under reduced pressure. The resulting solid residue was extracted with ether, and the ether solution washed several times with saturated aqueous sodium chloride, then dried over anhydrous magnesium sulphate and concentrated to dryness under reduced pressure. Purification by recrystallisation from methanol yielded pure 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol, 3,17-diacetate, melting at 148°.

Substitution of a molecular equivalent quantity of each of the below listed reactants in place of the reactants used in the above example yields, according to the esterification procedure described above, the following products.

Use of propionic anhydride and 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol yields, upon esterification, 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol 3,17-dipropionate, which is characterised by infrared maxima in chloroform solution at 3.03 and 5.80 (broad) microns.

Use of *dl* - 17 α - ethynyl - 13 β - ethyl - 11 β - methylgon - 4 - ene - 3 β ,17 β - diol and acetic anhydride yields *dl* - 17 α - ethynyl - 13 β - ethyl - 11 β - methylgon - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima, in chloroform solution at 3.06, 5.73 and 5.78 microns.

Esterification of 11 β - ethyl - 17 α - ethynylestr - 4 - ene - 3 β ,17 β - diol by the above procedure results in 11 β - ethyl - 17 α - ethynylestr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima, in chloroform solution, at 3.05, 5.73 and 5.78 microns.

The reaction of 11 β - methyl - 17 α - vinyl - estr - 4 - ene - 3 β ,17 β - diol with acetic anhydride according to the above procedure results in 11 β - methyl - 17 α - vinyl - estr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima, in chloroform solution, at 5.78 and 6.0 microns.

Similarly, use of 11 β - methyl - 17 α - propynylestr - 4 - ene - 3 β ,17 β - diol in the foregoing procedure results in 11 β - methyl - 17 α - propynylestr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima in chloroform solution at 5.78 (broad) microns.

Similarly esterification of 11 β - methyl - 17 α - propenylestr - 4 - ene - 3 β ,17 β - diol in the above procedure results in 11 β - methyl -

17 α - propenylestr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima in chloroform solution at 5.73 and 5.78 microns.

Use of 17 α - ethynyl - 11 α - methylestr - 4 - ene - 3 β ,17 β - diol affords 17 α - ethynyl - 11 α - methylestr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima in chloroform solution at 3.03, 5.74 and 5.78 microns.

Similarly, esterification of 11 α - methyl - 17 α - vinyl - estr - 4 - ene - 3 β ,17 β - diol according to the above procedure yields 11 α - methyl - 17 α - vinyl - estr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima in chloroform solution at 5.78 and 6.0 microns.

EXAMPLE 3

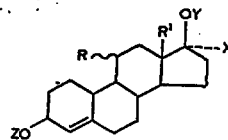
A mixture containing one part of 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol 17-acetate, 5 parts of acetic anhydride and 10 parts of pyridine was maintained at room temperature for about 4 hours and then concentrated to dryness under reduced pressure. The resulting solid residue was extracted with ether, and the ether solution washed several times with saturated aqueous sodium chloride, then dried over magnesium sulphate and concentrated to dryness under reduced pressure. Purification by recrystallisation from methanol yielded pure 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, melting at 148°.

EXAMPLE 4

A solution of 4 parts of 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol in 200 parts of pyridine was shaken with 0.4 part of 5% palladium-on-carbon catalyst at atmospheric pressure and room temperature until one molecular equivalent of hydrogen was absorbed. The catalyst was removed by filtration, and the filtrate evaporated to dryness at reduced pressure to yield 11 β - methyl - 17 α - vinyl - estr - 4 - ene - 3 β ,17 β - diol, which is characterised by infrared maxima in chloroform solution at 2.9 and 6.0 microns.

WHAT WE CLAIM IS:—

1. A compound of the general formula



in *d*, *l* or *dl* form or in a mixture of these forms,

wherein R and R' are alkyl radicals; X is an unsaturated aliphatic hydrocarbon radical; Y and Z are hydrogen atoms or alkanoyl radicals; the wavy line indicates the alternative α or β stereochemical configuration; and each of the alkyl, unsaturated aliphatic hydrocarbon and alkanoyl radicals contain less than 8 carbon atoms.

reduction as detailed above, 17 α - ethynyl - 11 α - methylestr - 4 - ene - 3 β ,17 β - diol 17-acetate, which is characterised by infrared maxima, in chloroform solution, at 2.72, 3.05 and 5.73 microns.

EXAMPLE 2

A mixture containing one part of 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol, 5 parts of acetic anhydride and 10 parts of pyridine was heated on the steam bath for about 18 hours, then cooled and concentrated to dryness under reduced pressure. The resulting solid residue was extracted with ether, and the ether solution washed several times with saturated aqueous sodium chloride, then dried over anhydrous magnesium sulphate and concentrated to dryness under reduced pressure. Purification by recrystallisation from methanol yielded pure 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol, 3,17-diacetate, melting at 148°.

Substitution of a molecular equivalent quantity of each of the below listed reactants in place of the reactants used in the above example yields, according to the esterification procedure described above, the following products.

Use of propionic anhydride and 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol yields, upon esterification, 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol 3,17-dipropionate, which is characterised by infrared maxima in chloroform solution at 3.03 and 5.80 (broad) microns.

Use of *dl* - 17 α - ethynyl - 13 β - ethyl - 11 β - methylgon - 4 - ene - 3 β ,17 β - diol and acetic anhydride yields *dl* - 17 α - ethynyl - 13 β - ethyl - 11 β - methylgon - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima, in chloroform solution at 3.06, 5.73 and 5.78 microns.

Esterification of 11 β - ethyl - 17 α - ethynylestr - 4 - ene - 3 β ,17 β - diol by the above procedure results in 11 β - ethyl - 17 α - ethynylestr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima, in chloroform solution, at 3.05, 5.73 and 5.78 microns.

The reaction of 11 β - methyl - 17 α - vinyl - estr - 4 - ene - 3 β ,17 β - diol with acetic anhydride according to the above procedure results in 11 β - methyl - 17 α - vinyl - estr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima, in chloroform solution, at 5.78 and 6.0 microns.

Similarly, use of 11 β - methyl - 17 α - propynylestr - 4 - ene - 3 β ,17 β - diol in the foregoing procedure results in 11 β - methyl - 17 α - propynylestr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima in chloroform solution at 5.78 (broad) microns.

Similarly esterification of 11 β - methyl - 17 α - propenylestr - 4 - ene - 3 β ,17 β - diol in the above procedure results in 11 β - methyl -

17 α - propenylestr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima in chloroform solution at 5.73 and 5.78 microns.

Use of 17 α - ethynyl - 11 α - methylestr - 4 - ene - 3 β ,17 β - diol affords 17 α - ethynyl - 11 α - methylestr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima in chloroform solution at 3.03, 5.74 and 5.78 microns.

Similarly, esterification of 11 α - methyl - 17 α - vinyl - estr - 4 - ene - 3 β ,17 β - diol according to the above procedure yields 11 α - methyl - 17 α - vinyl - estr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which is characterised by infrared maxima in chloroform solution at 5.78 and 6.0 microns.

EXAMPLE 3

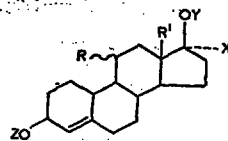
A mixture containing one part of 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol 17-acetate, 5 parts of acetic anhydride and 10 parts of pyridine was maintained at room temperature for about 4 hours and then concentrated to dryness under reduced pressure. The resulting solid residue was extracted with ether, and the ether solution washed several times with saturated aqueous sodium chloride, then dried over magnesium sulphate and concentrated to dryness under reduced pressure. Purification by recrystallisation from methanol yielded pure 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, melting at 148°.

EXAMPLE 4

A solution of 4 parts of 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol in 200 parts of pyridine was shaken with 0.4 part of 5% palladium-on-carbon catalyst at atmospheric pressure and room temperature until one molecular equivalent of hydrogen was absorbed. The catalyst was removed by filtration, and the filtrate evaporated to dryness at reduced pressure to yield 11 β - methyl - 17 α - vinyl - estr - 4 - ene - 3 β ,17 β - diol, which is characterised by infrared maxima in chloroform solution at 2.9 and 6.0 microns.

WHAT WE CLAIM IS:—

1. A compound of the general formula

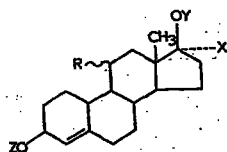


in *d*, *l* or *dl* form or in a mixture of these forms,

wherein R and R' are alkyl radicals; X is an unsaturated aliphatic hydrocarbon radical; Y and Z are hydrogen atoms or alkanoyl radicals; the wavy line indicates the alternative α or β stereochemical configuration; and each of the alkyl, unsaturated aliphatic hydrocarbon and alkanoyl radicals contain less than 8 carbon atoms.



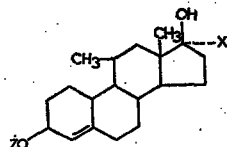
2. A compound of the general formula



in *d*, *l* or *dl* form or in a mixture of these forms,

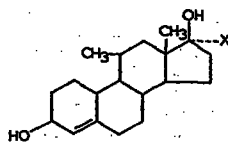
- 5 wherein X denotes an unsaturated aliphatic hydrocarbon radical; Y and Z are hydrogen atoms or alkanoyl radicals; R is an alkyl radical; the wavy line indicates the alternative α or β stereochemical configuration; and each of
10 the alkyl, unsaturated aliphatic hydrocarbon and alkanoyl radicals contain less than 8 carbon atoms.

3. A compound of the general formula



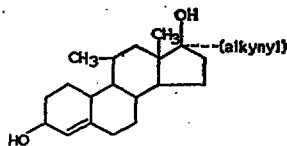
- 15 in *d*, *l* or *dl* form or in a mixture of these forms, wherein X is an unsaturated aliphatic hydrocarbon radical; Y and Z are hydrogen atoms or alkanoyl radicals; and the aliphatic unsaturated hydrocarbon and alkanoyl radicals contain
20 less than 8 carbon atoms.

4. A compound of the general formula



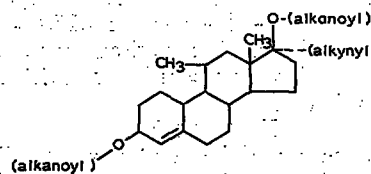
- 25 in *d*, *l* or *dl* form or in a mixture of these forms, wherein X is an unsaturated aliphatic hydrocarbon radical containing less than 8 carbon atoms.

5. A compound of the general formula



in *d*, *l* or *dl* form or in a mixture of these forms, wherein the alkynyl radical contains less than
30 8 carbon atoms.

- 35 6. A compound of the general formula

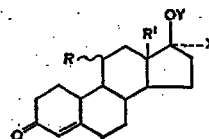


in *d*, *l* or *dl* form or in a mixture of these forms, wherein the alkynyl and alkanoyl radicals contain less than 8 carbon atoms.

7. 17α - Ethynyl - 11β - methylestr - 4 - ene - $3\beta,17\beta$ - diol.

8. 17α - Ethynyl - 11β - methylestr - 4 - ene - $3\beta,17\beta$ - diol 3,17-diacetate.

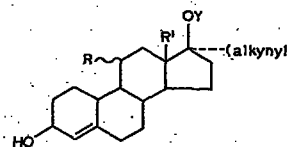
9. The process for the preparation of compounds as claimed in claim 1 which comprises contacting a compound of the general
40 formula



in *d*, *l* or *dl* form or in a mixture of these forms,

with a reducing agent capable of converting a carbonyl function to a carbinol function without affecting unsaturated linkages, followed by, when desired, esterification thereof to provide
50 the corresponding 3-monoalkanoates and 3,17-bisalkanoates thereof.

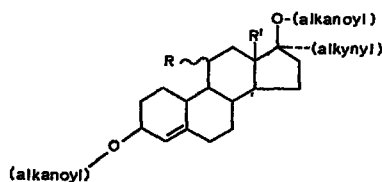
10. The process for the preparation of a compound of the general formula



in *d*, *l* or *dl* form or in a mixture of these forms, wherein R, R' and Y have the meanings defined in claim 1 and the wavy line indicates the alternative α or β stereochemical configuration; and the alkynyl radical contains less than 8 carbon atoms, which comprises contacting the corresponding 3-keto compound with a reducing agent capable of converting a carbonyl function of a carbinol function without affecting unsaturated linkages.

11. The process for the preparation of a compound of the general formula

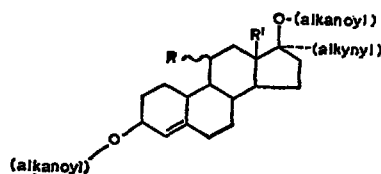




in *d*, *l* or *dl* form or in a mixture of these forms,

5 wherein *R* and *R'* and the wavy line have the meanings defined in claim 1, and each of the alkyl, alkynyl and alkanoyl radicals contain less than 8 carbon atoms, which comprises esterifying, at or near room temperature, the corresponding 3-hydroxy compound.

10 12. The process for the preparation of a compound of the general formula



in *d*, *l* or *dl* form or in a mixture of these forms,

15 wherein *R*, *R'* and the wavy line have the meanings defined in claim 1, and each of the alkyl, alkynyl and alkanoyl radicals contain less than 8 carbon atoms, which comprises esterifying, at elevated temperature, the corresponding 3,17 - dihydroxy compound.

20 13. The process for the preparation of 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol which comprises the reduction of 17 α - ethynyl - 17 β - hydroxy - 11 β - methylestr - 4 - en - 3 - one with lithium tri - (tertiarybutoxy) aluminium hydride.

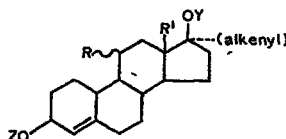
25 14. The process for the preparation of 17 α - ethynyl - 11 β - methylestr - 4 - ene -

3 β ,17 β - diol 3,17-diacetate which comprises the esterification of 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol 17-acetate at or near room temperature.

15. The process for the preparation of 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol 3,17-diacetate, which comprises the esterification of 17 α - ethynyl - 11 β - methylestr - 4 - ene - 3 β ,17 β - diol at an elevated temperature.

16. The process according to claim 14 or 15 wherein the esterification is conducted with acetic anhydride, in the presence of pyridine.

17. The process for the preparation of compounds of the general formula



in *d*, *l* or *dl* form or in a mixture of these forms,

wherein *R*, *R'*, *Y*, *Z* and the wavy line have the meanings defined in claim 1, which comprises the reduction of the corresponding 17 α -alkynyl compound with hydrogen in the presence of a hydrogenation catalyst until at least one molecular equivalent of hydrogen has been absorbed.

18. A process as claimed in claim 9 substantially as described with reference to any of the Examples.

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