

PATENT SPECIFICATION

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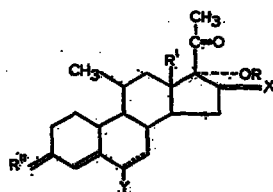


(54) 11 β -METHYL-19-NORPREGNENE COMPOUNDS

(71) 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:—

The present invention is concerned with 17 α - (hydroxy or acyloxy) - 11 β - methyl - 19 - norpregn - 4 - en - 20 - ones, related compounds and the processes for their preparation.

The compounds of the invention are represented by the following general formula

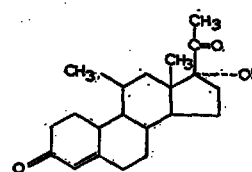


wherein R is a hydrogen atom, a formyl radical or an alkanoyl radical in which the alkyl portion contains from 1 to 6 carbon atoms; R' is an alkyl radical containing from 1 to 7 carbon atoms; R'' is an oxo group, or a hydroxy radical or an alkanoyloxy radical in the β -configuration in which the alkyl portion contains from 1 to 6 carbon atoms, together with a hydrogen atom; Y is a hydrogen or chlorine atom or a methyl group; and the dotted line indicates an optional 6(7) double bond; and X is H₂ or when Y is a hydrogen atom and the 6(7) bond is saturated X is H₂ or a methylene radical.

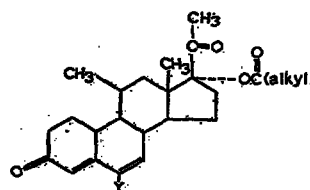
Illustrative of the alkyl radicals encompassed by the foregoing structural representation are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and the branched-chain groups isomeric therewith.

Typical of the alkanoyl radicals represented in that formula are acetyl, propionyl, butyryl, valeryl, caproyl, heptanoyl and the branched-chain isomers thereof.

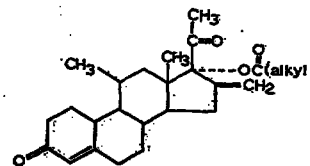
In one embodiment the invention provides compounds of the general formula



wherein R is a hydrogen atom, a formyl radical or an alkanoyl radical in which the alkyl portion contains from 1 to 6 carbon atoms. In another embodiment the invention provides compounds of the general formula

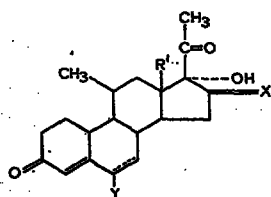


wherein Y is a hydrogen or chlorine atom or a methyl group; and the alkyl radicals contain from 1 to 6 carbon atoms. In yet another embodiment the invention provides compounds of the general formula

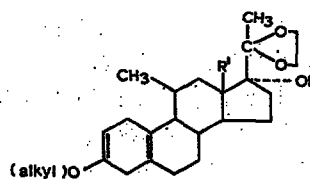


wherein the alkyl radicals contain from 1 to 6 carbon atoms.

The 17-acyloxy compounds of formula (I) wherein R'' is an oxo group are conveniently prepared by the acylation of the corresponding 17-hydroxy compounds of the general formula



(II)



(III)

wherein R', X and Y have the same meanings here and throughout the specification as previously described above. This acylation can be conducted by conventional methods using the appropriate acid anhydride or acid halide in the presence of a strong acid, *e.g.* *p*-toluenesulphonic acid. Under such conditions it is possible that some 3-enol acetate will be formed in the reaction. To improve the yield obtained by these conventional methods, one can dissolve the reaction product obtained in an alcohol such as methanol and treat it with a small amount of a concentrated mineral acid such as concentrated hydrochloric acid thus affecting reconversion of the 3-enol acetate to the 3-keto- Δ^4 system. Since this side reaction can occur upon use of these conventional methods of acylation, it is preferable to employ a method of acylation, which is known to those skilled in the art to avoid this enol acetate conversion. Such a method is that comprising the use of a complex formed from a combination of a metalloid halide (*e.g.* phosphorus or antimony pentachloride), an organic acid halide and a halogenated aliphatic solvent (*e.g.*, chloroform, carbon tetrachloride, dichloroethane, trichloroethylene and analogs) under anhydrous conditions. The reaction is suitably conducted by adding the steroid to the complex in a lower nitroparaffin solvent which has a high dielectric constant (*e.g.* nitromethane) and cooling the reaction mixture for example to a temperature of from 0 to 5°C. A specific illustration of this preferred acylation procedure is the formation of the complex by the combination of 1,1,2-trichlorotrifluoroethane, antimony pentachloride and acetyl chloride to which is added nitromethane succeeded by 17 α -hydroxy-11 β -methyl-19-norpregn-4-ene-3,20-dione. After reaction at 0 to 5°C. for 15 minutes and maintenance of the mixture at room temperature for 45 minutes, the resultant product obtained is 17 α -acetoxy-11 β -methyl-19-norpregn-4-ene-3,20-dione.

The 17 α -acyloxy compounds of formula (I) wherein R and R' are defined as hereinbefore; R'' is an oxo group; Y is a hydrogen atom; X is H₂; and the optional 6(7) double bond is saturated can be alternatively prepared by the strong acid hydrolysis of a corresponding 17 α -acyloxy compound chosen from those having the following general structure

wherein the alkyl radical contains from 1 to 6 carbon atoms; and R and R' are defined as hereinbefore. Hydrolysis in this instance will simultaneously remove the 20-ketal function and generate the 3-keto- Δ^4 moiety. It can be suitably effected with a strong acid such as hydrochloric acid and is exemplified by the reaction of 17 α -acetoxy-3-methoxy-11 β -methyl-19-norpregn-2,5(10)-dien-20-one 20-ethylene ketal in methanol with hydrochloric acid to yield 17 α -acetoxy-11 β -methyl-19-norpregn-4-ene-3,20-dione. It will be noted that in formula (III) when R represents a hydrogen atom the desired 17 α -hydroxy material can also be obtained by this strong acid hydrolysis method.

A further method for obtaining the 17 α -hydroxy compound of formula (I) wherein X is H₂; Y is a hydrogen atom; R' is an alkyl radical containing 1 to 7 carbon atoms; R'' is an oxo group, and the 6(7) position is saturated involves the oxidation of the corresponding 17 α ,20-dihydroxy compound with a chromic acid oxidizing agent such as Jones' reagent. This reaction is depicted by the reaction of 17 α ,20-dihydroxy-11 β -methyl-19-norpregn-4-ene-3-one in dimethylformamide with Jones' reagent (an aqueous solution 8N in chromium trioxide and 8N in sulphuric acid) and manganese dichloride tetrahydrate to yield 17 α -hydroxy-11 β -methyl-19-norpregn-4-ene-3,20-dione.

The 17 α ,20-dihydroxy-11 β -methyl-19-norpregn-4-ene-3-ones, which are useful precursors to the 17 α -hydroxy and subsequent 17 α -acyloxy compounds of formula (I), can be prepared by the following synthetic scheme from already described starting materials such as a 3-alkoxy-13 β -alkyl-17 α -ethyl-17 β -hydroxy-11 β -methylgon-1,3,5(10)-triene. The initial step consists of the dehydration of the aforementioned starting material with reagent such as thionyl chloride in pyridine to yield the corresponding 17(20)-dehydro compound. That substance is hydroxylated, suitably with osmium tetroxide in pyridine to afford the 17 α ,20-diol, which is submitted to the Birch reduction, using lithium in liquid ammonia, to afford the 2,5(10)-diene-3-enol ether. Hydrolysis of that enol ether produces the corresponding 3-keto- Δ^4 intermediate which serves as the starting material

for the Jones' reagent oxidation reaction which provides the 17 α -hydroxy compounds of formula (I). Acylation then yields the 17 α -acyloxy compounds of formula (I) and thus completes the synthetic scheme. That sequence of reactions is specifically illustrated by the dehydration of 17 α - ethyl - 11 β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3-methyl ether with thionyl chloride in pyridine to afford 11 β - methyl - 19 - norpregna - 1,3,5(10), - 17(20) - tetraen - 3 - ol 3-methyl ether, which is hydroxylated with osmium tetroxide in pyridine to yield 11 β - methyl - 19 - norpregna - 1,3,5(10) - triene - 3,17 α ,20 - triol - 3-methyl ether. Birch reduction of that substance, using lithium in liquid ammonia, affords 11 β - methyl - 19 - norpregna - 2,5(10) - diene - 3,17 α ,20 - triol 3-methyl ether, which is hydrolyzed with dilute hydrochloric acid in methanol, thus producing 17 α ,20 - dihydroxy - 11 β - methyl - 19 - norpregn - 4 - en - 3 - one.

The 3 - alkoxy - 11 β - methyl - 19 - norpregna - 2,5(10) - dien - 20 - one 20-ethylene ketal intermediates of formula (III) which serve as suitable starting materials for the strong acid hydrolysis yielding the corresponding 17 α -hydroxy or 17 α -acyloxy compounds of formula (I) can be prepared by the following sequence beginning with 11 β - methyl - 19 - norpregna - 1,3,5(10) - triene - 3,17 α ,20 - triol 3-alkyl ethers (prepared as indicated above). This sequence involves the oxidation of the 20-hydroxy group *prior* to Birch reduction, ketalization of the resulting 20-keto group, then Birch reduction to give the desired starting materials suitable for obtaining the 17-hydroxy compound of this invention, while a subsequent step of acylation is required to obtain the suitable starting material for obtaining the 17-acyloxy compounds of this invention. That process is exemplified by the oxidation of 11 β - methyl - 19 - norpregna - 1,3,5(10) - triene - 3,17 α ,20 - triol 3-methyl ether with chromic acid and manganese chloride, reaction of the resulting 20-ketone with ethylene glycol in the presence of *p*-toluenesulphonic acid, Birch reduction of the 20-ethylene ketal thus produced, and optional subsequent acetylation with the acetyl chloride-antimony pentachloride complex hereinbefore described and hydrolysis of the ketal and end ether moieties with hydrochloric acid to yield the aforementioned 17 α - acetoxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

The 16-methylene derivatives of formula (I) wherein R'' is an oxo group are conveniently prepared by a sequence of reactions which uses 3 - alkoxy - 11 β - methyl - 19 - norpregna - 1,3,5(10),16 - tetraen - 20 - ones as starting materials. Reaction of those 16-dehydro compounds with diazomethane affords the corresponding 16,17 - [3',1' - (2' - pyrazoline)] derivatives, which are pyrolyzed by heating at high temperature to produce the corresponding 16 - methyl - 16 - dehydro com-

pounds. The latter substance are peroxidized with a peracid in an alkaline medium, *e.g.* alkaline hydrogen peroxide, and the resulting 16 α ,17 α -epoxides are cleaved with a strong acid such as *p* - toluene - sulphonic acid, to afford the desired 16 - methylene - 17 α - hydroxy substances. Those materials are subjected to the Birch reduction to yield the corresponding 11 β - methyl - 16 - methylene - 19 - norpregna - 2,5(10) - diene - 3,17,20 - triol 3-alkyl ethers which upon hydrolysis, for example with hydrochloric acid in methanol, yield the corresponding 3 - keto - Δ^4 substances. These latter materials can serve as the starting materials for the Jones' reagent oxidation which provides the 17 α -hydroxy compounds of formula (I) as described hereinabove and which upon acylation, according to the aforementioned methods, provides the desired 17 α -acyloxy compounds of formula (I).

The 6-dehydro compounds of formula (I) wherein X is H₂; Y is a hydrogen atom; R' is an alkyl radical containing 1 to 7 carbon atoms; and R'' is an oxo group; can be prepared by the following method which uses a starting material 17 α - alkanoyloxy/hydroxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione or a 13-homologue thereof. That material is converted to the corresponding 3,5-diene enol ether by conventional methods known to those skilled in the art. Thus, *e.g.* by treatment with an orthoformic ester; reaction with an appropriate alcohol utilizing a suitable carrier such as isooctane for the azeotropic removal of the water formed; or transesterification of a preformed alkyl ether, prepared by either of the first mentioned conventional methods with an appropriate alcohol in the presence of an acid catalyst. The resulting 17 α - alkanoyloxy/hydroxy - 3 - alkoxy - 11 β - methyl - 19 - norpregna - 3,5 - dien - 20 - one is then subjected to oxidation with the manganese dioxide reagent (preparation of this reagent as given in U.S. Patent No. 3,194,803) or with 2,3 - dichloro - 5,6 - dicyanobenzoquinone. The reaction can be conducted at room temperature to elevated temperatures, for example, temperatures of from 15°C to 60°C are suitable, and reaction time can vary from 15 minutes to 2 hours. Inert organic solvents are, in general, suitable for use in this procedure; particularly preferred is a nonpolar organic solvent medium such as benzene, toluene, xylene, methylene chloride or carbon tetrachloride. The oxidation results in the formation of the desired 17 α - alkanoyloxy/hydroxy - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione.

The aforementioned enol ethers, *i.e.* the 17 α - alkanoyloxy/hydroxy - 3 - alkoxy - 11 β - methyl - 19 - norpregna - 3,5 - dien - 20 - ones also can serve as starting materials for the 6 α -methyl derivatives of formula (I). Thus, these 3,5 - dien - 3 - alkyl ethers are subjected to the Vilsmeier reaction to afford

the corresponding 6-iminium intermediate which upon hydrolysis yields the corresponding 6-formyl compound. That formyl compound can be suitably reduced with hydrogen and a hydrogenation catalyst or with an alkali metal borohydride in methanol or with diborane to provide the 6-hydroxymethyl derivative thereof. Hydrolysis and concomitant dehydrogenation of that 6 hydroxymethyl derivative with, for example, aqueous acetic acid or hydrochloric acid and methanol provides the corresponding 6 - methylene- Δ^4 - 3 - one compound. That 6 - methylene - Δ^4 - 3 - one serves as the starting material which upon hydrogenation gives the 6 β -methyl compound which is epimerized to the desired 6 α -methyl derivative with a suitable acid. Alternatively, the 6-formyl derivative resulting from the above-mentioned reactions can be subjected to reduction and subsequent acid treatment to provide the 3 - keto - Δ^4 - 6 α - methyl compound directly. A further variation of this procedure would be the treatment of the 6-methylene compound with a reducing agent such as palladium and cyclohexene followed directly in the same reaction vessel with acidification to provide the 3 - keto - Δ^4 - 6 α - methyl compound immediately without isolation of the 6 β -methyl intermediate.

The 6 - methyl - 6 - dehydro compounds can be prepared from the aforementioned 6-methylene derivatives by suitable isomerization treatment with, for example, sodium acetate, ethanol, and a palladium-on-carbon catalyst with a reaction time of 1 to 24 hours.

The 6 α -chloro compounds of formula (I) wherein R'' is an oxo group can be prepared by treating the aforementioned 3,5-diene 3-alkyl ethers with a hypochlorous acid or an agent capable of liberating this acid. Other suitable agents include alkali metal salts of hypochlorous acid or N-chloro amides or imides for example N-chlorosuccinimide in the presence of sodium acetate, acetic acid and water, preferably at temperatures near 0°C for periods up to several hours. The hypochlorous acid treatment provides the corresponding 6 β ' - chloro - 3 - keto - Δ^4 derivative which upon subsequent strong mineral acid epimerization under anhydrous conditions yields the desired 6 α -chloro derivative. Preferably, acid treatment is employed upon the compound dissolved in an organic acid such as acetic acid. Suitable strong mineral acids include dry hydrogen chloride while reaction times can be several hours at temperatures preferably between 5 and 20°C.

The 6 - chloro - 6 - dehydro compounds can be obtained by three conventional methods. In one such method the aforementioned 6 α - chloro - 3 - keto - Δ^4 compounds serve as starting materials. The starting materials are subjected to dehydrogenation with a dehydrogenating agent suitable for the introduction of a 6,7-dehydro linkage into a 3 - keto - Δ^4

steroidal system. Suitable agents include substituted quinones such as 2,3 - dichloro - 5,6 - dicyanobenzo - quinone, 2,6 - dichloro - *p* - benzoquinone, 1,4 - naphtho - quinone, *p* - toluquinone, *p* - benzoquinone, 1,2-naphthoquinone or chloranil. Suitable solvent mediums are tertiary butanol and xylene as well as other appropriate inert, organic or inorganic solvents.

Alternatively the desired 6 - chloro - Δ^4 derivatives can be obtained from the corresponding 6 - chloro - 3 - keto - Δ^4 compounds by formation of the corresponding enol ether by any of the methods described above followed by manganese dioxide oxidation of that ether to provide the desired compounds. Thirdly, and preferably, the 6 - chloro - 6 - dehydro compounds can be prepared from the corresponding 3 - keto - Δ^4 compounds. In this procedure the 3 - keto - Δ^4 compounds are first epoxidized to the corresponding 6 α ,7 α - oxido - 3 - keto - Δ^4 compound with a peracid, for example monopero-phthalic acid and a mixture of methylene chloride in chloroform and ether. These epoxides are then opened by the addition of the elements of a hydrogen chloride. Suitable solvent mediums for this reaction are lower aliphatic carboxylic acids, ketones, ethers, and halogenated hydrocarbons or mixtures of such solvents typically acetic acid, propionic acid, acetone, methylene chloride, chloroform or tetrahydrofuran. The 6 β ' - chloro - 7 α - hydroxy compound formed by this addition of the elements of chloride hydrogen is dehydrated with conventional dehydrating agents (*i.e.* hydrochloric acid) to provide the desired 6 - chloro - 3 - keto - Δ^4 compound of formula (I).

Each of the methods discussed hereinabove for the preparation of the various 6-derivatives of formula (I) are suitable not only for the direction preparation of the 17-acyloxy derivative of formula (I) but likewise for the 17-hydroxy compounds which can be utilized as precursors to the 17-acyloxy compounds in the preferred acylation method of this invention.

The starting materials for the compound of the invention wherein the 13 β -alkyl group contains more than one carbon atom are prepared by synthetic methods not involving a resolution stage and are therefore obtained as *dl*-mixtures. Resolution of these *dl* compounds to afford the individual *d* and *l* enantiomorphs which is necessary for the preparation of the 8 β , 9 α , 13 β , 14 α -steroids of the invention is conveniently effected by esterification of an 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 and strychnine.

Reduction of the 3-keto compounds of formula (I) wherein R'' is an oxo group, typically

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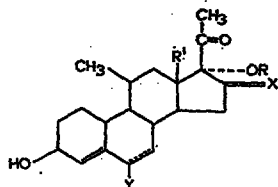
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with a metallic reducing agent such as lithium tri - (tertiary - butoxy) aluminium hydride, or an alkali metal borohydride together with a small quantity of water, affords the corresponding 3-hydroxy compounds of the following structural formula



wherein R, R', X, Y and the dotted line have the same meanings as hereinbefore described.

For example, 17 α - acetoxy - 11 β - methyl - 19 - norpregn - 4 - en - 3,20 - dione is contacted with lithium tri(tertiarybutoxy) aluminium hydride in tetrahydrofuran at room temperature to afford 17 α - acetoxy - 3 β - hydroxy - 11 β - methyl - 19 - norpregn - 4 - en - 20 - one. Acylation of those 3-ols with an alkanolic acid anhydride in the presence of a suitable acid acceptor affords the corresponding 3 β -alkanoates. 17 α - Acetoxy - 3 β - hydroxy - 11 β - methyl - 19 - norpregn - 4 - en - 20 - one is thus contacted with acetic anhydride and pyridine to yield 3 β ,17 α - diacetoxy - 11 β - methyl - 19 - norpregn - 4 - en - 20 - one.

The latter 3 β -hydroxy and 3 β -alkanoxyloxy compounds, like the corresponding 3-keto compounds, exhibit hormonal properties, for example, as anti-fertility agents.

The compounds of this invention are useful as a result of their valuable pharmacological properties. They are, for example, potent progestational and estrogen-inhibitory agent. The pharmacological activity of the novel compounds of formula (I) is specifically illustrated by the progestational activity of a representative species, 17 α - acetoxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione when assayed in the rabbit according to the Clauberg assay at subcutaneously administered doses ranging from 0.0002 to 0.05 milligrams. Relative to the standard, i.e. progesterone, it possesses a potency of 10—20 $\times 10^3\%$. The anti-estrogenic activity of the compounds of formula (I) is again specifically illustrated by the representative species named above which when assayed according to the method of Edgren and Calhoun, *Proc. Soc. Exp. Biol. Med.*, 94, 537 (1957), in the mouse, at subcutaneously administered doses ranging from 0.001 to 0.1 mg., exhibited a potency of about 10,000% relative to the standard, i.e. progesterone.

In the following Examples which are intended to illustrate the present 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.

17 α - Acetoxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

To 7 parts of 1,1,2-trichlorotrifluoroethane was added, with stirring, 1.76 parts of antimony pentachloride and the mixture was cooled to 0 to 5 $^{\circ}\text{C}$., at which time 0.5 part of acetyl chloride was added dropwise. Stirring was continued at that temperature for 15 minutes, at the end of which time 8 parts of nitromethane were added. To the resulting two-phase system was then added 0.68 part of 17 α - hydroxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione and that reaction mixture was stirred for 15 minutes at 0 to 5 $^{\circ}\text{C}$., then for 45 minutes at room temperature. The solution was again cooled to 0 to 5 $^{\circ}\text{C}$., and a solution of 3 parts of sodium acetate in 8 parts of water added. Stirring at room temperature was continued for 30 minutes, at the end of which time the mixture was extracted with chloroform. The chloroform layer was separated, washed successively with dilute aqueous sodium bicarbonate and water, then dried over anhydrous sodium sulphate. Distillation of that solution under reduced pressure afforded the crude product, which was purified by chromatography on silica gel followed by elution with 10% ethyl acetate in benzene. Evaporation of the eluate to dryness afforded a solid, which was further purified by recrystallization from ether, thus producing crystalline 17 α - acetoxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione, melting at 190 to 191 $^{\circ}\text{C}$.

Substitution of a molecular equivalent quantity of the appropriate 17-hydroxy compound for the starting material used in the foregoing acylation procedure provides according to the details given above the following products of formula (I).

Use of 17 α - hydroxy - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione affords 17 α - acetoxy - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione.

Similarly, 6 - chloro - 17 α - hydroxy - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione reacts - in the above acylation procedure to yield 17 α - acetoxy - 6 - chloro - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione.

Acylation of 6 α - chloro - 17 β - hydroxy - 11 β - methyl - 19 - norpregna - 4 - ene - 3,20 - dione provides 17 α - acetoxy - 6 α - chloro - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

Reaction of 17 α - hydroxy - 6 α ,11 β - dimethyl - 19 - norpregn - 4 - ene - 3,20 - dione in the foregoing procedure yields 17 α - acetoxy - 6 α ,11 β - dimethyl - 19 - norpregn - 4 - ene - 3,20 - dione.

Likewise, use of 17 α - hydroxy - 6,11 β - dimethyl - 19 - norpregna - 4,6 - diene - 3,20 - dione provides 17 α - acetoxy - 6,11 β - dimethyl - 19 - norpregna - 4,6 - diene - 3,20 - dione.

Acylation of 17 α - hydroxy - 11 β - methyl - 16 - methylene - 19 - norpregn - 4 - ene - 3,20 - dione provides 17 α - acetoxy - 11 β - methyl - 16 - methylene - 19 - norpregn - 4 - ene - 3,20 - dione.

Substitution of a molecular equivalent quantity of *n*-butyryl chloride for the acetyl chloride used in the foregoing procedure provides 17 α - *n* - butyryloxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

EXAMPLE 2.

17 α - Acetoxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

One part of 17 α - hydroxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione was dissolved in 52.5 parts of acetic acid. To that solution was added 10.8 parts of acetic anhydride and 1 part of *p*-toluenesulphonic acid monohydrate. The resulting reaction mixture was stirred until all the *p*-toluenesulphonic acid had been dissolved and was thereafter maintained at room temperature for 24 hours. Thereupon, the solution was poured into 500 parts of water and stirred for 2 hours. The resultant solidified product was filtered off, dissolved in 180 parts of ethyl acetate, washed successively with dilute sodium bicarbonate solution and water, dried over sodium sulphate and distilled to dryness to yield the crude product, 17 α - acetoxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione, which is characterized by infrared maxima in chloroform at 5.80, 5.82, 6.02 and 6.20 microns. To improve the yield by facilitating complete conversion of any 3-enol acetate formed in the reaction, one can distill the crude reaction product in methanol and treat it with a small amount of concentrated hydrochloric acid for a period of 2 to 3 hours at room temperature.

EXAMPLE 3.

17 α - Hydroxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

To 3 parts of 17 α - hydroxy - 3 - methoxy - 11 β - methyl - 19 - norpregna - 2,5(10) - dien - 20 - one 20-ethylene ketal and 144 parts of methanol was added 18 parts by volume of a 2N hydrochloric acid solution. The resultant reaction mixture was refluxed for 30 minutes. Thereafter, the solution was cooled and neutralized by the addition of 3.6 parts of potassium carbonate in 30 parts of water. Removal of solvent *in vacuo* left a residue which was thereupon dissolved in 450 parts of ethyl acetate, successively washed with water until neutralized, dried over sodium sulphate and distilled to dryness to afford the crude product. Recrystallization from acetone afforded 17 α - hydroxy - 11 β - methyl - 19 - norpregn -

4 - ene - 3,20 - dione, which is characterized by infrared maxima, in chloroform solution, at 5.82, 6.02 and 6.20 microns.

Substitution of a molecular equivalent quantity of 17 α - acetoxy - 3 - methoxy - 11 β - methyl - 19 - norpregna - 2,5(10) - dien - 20 - one 20-ethylene ketal for the abovementioned starting material yield upon strong acid hydrolysis, as detailed in the foregoing paragraph, 17 α - acetoxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

EXAMPLE 4.

17 α - Hydroxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

To a mixture containing 7 parts by volume of an aqueous solution, 8N in chromium trioxide and 8N in sulphuric acid, 0.9 part of manganese dichloride tetrahydrate, and 13.5 parts of dimethylformamide, cooled to 0 to 5°C., was added with stirring a solution of 1.33 parts of 17 α ,20 - dihydroxy - 11 β - methyl - 19 - norpregn - 4 - en - 3 - one in 31.5 parts of dimethylformamide. The mixture was then allowed to warm to room temperature and was stirred at the latter temperature for 3 hours. At the end of that time it was carefully poured, with stirring, into ice water and the precipitate which formed was collected by filtration, washed on the filter with water and dried in air to afford 17 α - hydroxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione, which exhibited nuclear magnetic resonance peaks at about 50, 60, 68, 136.5 and 352 cycles per second.

EXAMPLE 5.

17 α - Hydroxy - 11 β - methyl - 16 - methylene - 19 - norpregn - 4 - ene - 3,20 - dione.

To a solution of 10 parts of 3 - methoxy - 11 β - methyl - 19 - norpregn - 1,3,5(10),16 - tetraen - 20 - one in 100 parts of methylene chloride was added portionwise over a period of 8 hours, 10 parts of nitrosomethylurea and a solution of 2 parts of potassium hydroxide and 6.7 parts of potassium carbonate in 9.7 parts of water. The reaction mixture was kept at 0 to 5°C. during the addition, then allowed to stand at room temperature for 12 hours. Activated alumina was added slowly to decompose excess diazomethane and the mixture filtered. The filtrate was evaporated to dryness *in vacuo* and the residue crystallized from hexane. Recrystallization from a solution of methylene chloride and methanol affords 3-methoxy - 11 β - methyl - 16,17 - [3',1' - (2' - pyrazolino)] - 19 - norpregna - 1,3,5(10) - trien - 20 - one.

A flask containing 10 parts of 3 - methoxy - 11 β - methyl - 16 - 17 - [3',1' - (2' - pyrazolino)] - 19 - norpregna - 1,3,5(10) - trien - 20 - one was heated *in vacuo* in an oil bath at 180°C. for 30 minutes. The solid residue was recrystallized twice from methylene chloride-methanol solutions to afford 11 β ,16 -

dimethyl - 3 - methoxy - 19 - norpregna - 1,3,5(10),16 - tetraen - 20 - one.

To a solution of 20 parts of 11 β ,16 - dimethyl - 3 - methoxy - 19 - norpregna - 1,3,5(10),16 - tetraen - 20 - one in 4000 parts of methanol, cooled to 0°C., were added 316.8 parts of 30% hydrogen peroxide and a solution of 5.1 parts of potassium carbonate in 250 parts of water. After 8 hours the solution was neutralized with acetic acid, concentrated *in vacuo* and poured into water. After recrystallization from methanol there was afforded 16 α ,17 α - epoxy - 3 - methoxy - 11 β ,16 β - dimethyl - 19 - norpregna - 1,3,5(10) - trien - 20 - one.

Thirtyfour parts of 16 α ,17 α - epoxy - 3 - methoxy - 11 β ,16 β - dimethyl - 19 - norpregna - 1,3,5(10) - trien - 20 - one were dissolved in a mixture of 1056 parts of benzene. From this solution, 250 parts by volume of the solvent were evaporated. The residue was treated with 2.4 parts of *p*-toluenesulphonic acid and boiled for 6 hours under reflux using a water separator. After cooling, the mixture was washed with a solution of 5% sodium bicarbonate with water and evaporated *in vacuo*. The residue was washed with a mixture of benzene and low boiling petroleum ether. The crystals were filtered with suction, washed with the same solvent and recrystallized from methanol to yield 17 α - hydroxy - 11 β - methyl - 3 - methoxy - 16 - methylene - 19 - norpregna - 1,3,5(10) - trien - 20 - one.

To 88 parts of liquid ammonia was added dropwise, over a period of 10 minutes, a solution of 2.3 parts of 17 α - hydroxy - 11 β - methyl - 3 - methoxy - 16 - methylene - 19 - norpregna - 1,3,5(10) - trien - 20 - one dissolved in 112 parts of tetrahydrofuran containing 16 parts of isopropyl alcohol. After the addition was complete, metallic lithium was added portionwise while the reaction mixture was vigorously stirred. Stirring was continued for approximately 1 hour following completion of the addition and 6.4 parts of ethanol were then carefully added dropwise over a period of 20 minutes. Removal of the solvents by evaporation under a nitrogen atmosphere affords a slurry, which was diluted with ether, then washed with water. Drying of that ether solution over anhydrous sodium sulphate followed by distillation of the solution to dryness and azeotropic distillation with benzene afforded 11 β - methyl - 16 - methylene - 19 - norpregna - 2,5(10) - diene - 3,17 α ,20 - triol 3-methyl ether.

A mixture containing 2.37 parts of 11 β - methyl - 16 - methylene - 19 - norpregna - 2,5(10) - diene - 3,17 α ,20 - triol 3-methyl ether, 80 parts of methanol and 10 parts by volume of 2N hydrochloric acid was heated at the reflux temperature for 30 minutes, then cooled to 0 to 5°C. and a solution of 2 parts of potassium carbonate in approximately 10 parts of water added. The methanol was distilled

led under reduced pressure and the resulting residue extracted into ethyl acetate. The organic solution resulting was washed with water, dried over anhydrous sodium sulphate, then distilled to dryness under reduced pressure to afford 17 α ,20 - dihydroxy - 11 β - methyl - 16 - methylene - 19 - norpregn - 4 - en - 3 - one.

To a mixture containing 7 parts by volume of an aqueous solution (8N in chromium trioxide and 8N in sulphuric acid), 0.9 part of manganese dichloride tetrahydrate and 13.5 parts of dimethylformamide, cooled to 0 to 5°C., was added with stirring a solution of 1.33 parts of 17 α ,20 - dihydroxy - 11 β - methyl - 16 - methylene - 19 - norpregn - 4 - en - 3 - one in 31.5 parts of dimethylformamide. The mixture was then allowed to warm to room temperature and was stirred at the latter temperature for 3 hours. At the end of that time it was carefully poured with stirring into ice water and the precipitate which formed collected by filtration, washed on the filter with water and dried in air to afford 17 α - hydroxy - 11 β - methyl - 16 - methylene - 19 - norpregn - 4 - ene - 3,20 - dione, which is characterized by infra-red maxima, in chloroform solution, at about 5.84, 6.02 (broad), and 6.19 microns.

EXAMPLE 6.

17 α - Acetoxy - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione.

To a solution of 20.5 parts of 17 α - acetoxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione and 19.7 parts of ethylorthoformate in 115 parts of dioxane and 5.6 parts of ethanol was added 0.22 part of *p*-toluenesulphonic acid monohydrate, and the resulting mixture was stored at room temperature for one and one-half hours. The reaction mixture was neutralized by the addition of about 0.3 part of fused sodium acetate, then evaporated to dryness *in vacuo*. Trituration of the residue with methanol resulted in crystallization of 17 α - acetoxy - 3 - ethoxy - 11 β - methyl - 19 - norpregna - 3,5 - dien - 20 - one.

To a solution of one part of 17 α - acetoxy - 3 - ethoxy - 11 β - methyl - 19 - norpregna - 3,5 - dien - 20 - one in 44 parts of benzene was added 5 parts of manganese dioxide and the resulting reaction mixture was stirred for 40 minutes. The insoluble material was removed by filtration and washed on the filter with benzene. Concentration of the filtrate to dryness under nitrogen afforded a crystalline residue. Fractional crystallization of this residue from methanol resulted in 17 α - acetoxy - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione, which was characterized by infrared maxima, in chloroform solution, at 5.78, 5.83, 6.01, 6.22 and 6.28 microns.

Similarly, substitution of a molecular equivalent quantity of 17 α - hydroxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione for the steroid employed in paragraph one of

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this example provides 3 - ethoxy - 17 α - hydroxy - 11 β - methyl - 19 - norpregna - 3,5 - dien - 20 - one which in accordance with the method described above in paragraph two affords 17 α - hydroxy - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione.

REFERENCE EXAMPLE

Preparation and purification of the starting material:

17 α - Acetoxy - 11 β - methyl - 6 - methylene - 19 - norpregn - 4 - ene - 3,20 - dione

The Vilsmeier reagent was prepared by adding a solution of 2 parts of phosgene in 20 parts of ethylene dichloride to a stirred solution of 3 parts of distilled dimethylformamide in 10 parts of anhydrous ethylene dichloride. The addition was completed in a dropwise manner, over a period of 30 minutes while the temperature was maintained between 0 and 5°C. 10 Minutes after the formation of a white precipitate, accompanied by the evolution of carbon dioxide, 6 parts of 17 α - acetoxy - 3 - methoxy - 11 β - methyl - 19 - norpregna - 3,5 - dien - 20 - one in 30 parts of ethylene dichloride containing 0.5 parts of pyridine was added, in total, to the reagent slurry. Stirring was continued at 0 to 20°C. for 1 hour, after which time 4 parts of a 5% aqueous solution of sodium acetate was added and the mixture was stirred vigorously for a further period of 10 minutes and then poured into water. Sufficient ether was added to produce an upper organic phase and the two phases were separated. Impurities in the ether phase were removed by repeated washing with water and the extracts were dried. After solvent removal, the residual crude 6-formyl derivative was purified from methanol.

One part of a 5% platinum-on-charcoal catalyst was hydrogenated in methanol. To the catalyst was added 2 parts of the above prepared formyl derivative and 2 parts of sodium acetate combined together in 10 parts of methanol. The resulting mixture was hydrogenated until one equivalent proportion of hydrogen had been absorbed. Thereupon the catalyst was removed, water was added and the crude product was extracted with ether and purified from aqueous methanol containing a trace of pyridine to afford the 6-hydroxymethyl derivative.

One part of the above prepared 6 - hydroxy - methyl 3-enol ether in 10 parts of 80% aqueous acetic acid was heated for 10 minutes at 85 to 100°C. Upon addition of water a crude product was obtained which was purified according to the procedure of D. Burn *et al*, Tetrahedron 20,597(1964), which is known to those skilled in the art, to yield the desired 17 α - acetoxy - 11 β - methyl - 6 - methylene - 19 - norpregn - 4 - ene - 3,20 - dione.

EXAMPLE 7

17 α - Acetoxy - 6 α ,11 β - dimethyl - 19 - norpregn - 4 - ene - 3,20 - dione. 65

Two parts of 17 α - acetoxy - 11 β - methyl - 6 - methylene - 19 - norpregn - 4 - ene - 3,20 - dione in 56 parts of methanol was hydrogenated in the presence of a pre-hydrogenated 2% palladium-on-carbon catalyst. The hydrogenation was allowed to proceed until one molecular equivalent of hydrogen had been absorbed; thereupon the catalyst was removed and the product was obtained upon extraction with ether. Crystallization from aqueous methanol gave 17 α - acetoxy - 6 β ,11 β - dimethyl - 19 - norpregn - 4 - ene - 3,20 - dione. 70

A slow stream of dry hydrogen chloride was introduced into a suspension of 3 parts of the above-prepared 6 β -methyl compound and about 50 parts of glacial acetic acid, while the temperature was maintained below 10°C. After 1 hour the mixture was poured into 100 parts of water containing about 36 parts of potassium acetate and was cooled. The precipitate was collected by filtration, washed with water, dried and recrystallized from acetone-hexane, thus yielding 17 α - acetoxy - 6 α ,11 β - dimethyl - 19 - norpregn - 4 - ene - 3,20 - dione, which is characterized by infrared maxima in chloroform solution at about 5.78, 5.83, 6.01 and 6.22 microns. 80

EXAMPLE 8.

17 α - Acetoxy - 6 α ,11 β - dimethyl - 19 - norpregn - 4 - ene - 3,20 - dione. 95

A solution of 11 part of 17 α - acetoxy - 6 - formyl - 3 - methoxy - 11 β - methyl - 19 - norpregna - 3,4 - dien - 20 - one and 1.6 parts of cyclohexene in 16 parts of ethanol was heated under reflux and stirred with 0.3 part of a 5% palladium-on-carbon catalyst. After 2½ hours the reaction mixture was filtered and evaporated to dryness to afford the crude residue which upon crystallization from aqueous methanol containing about 11% hydrochloric acid gave 17 α - acetoxy - 6 α ,11 β - dimethyl - 19 - norpregn - 4 - ene - 3,20 - dione, which is identical to the product obtained in Example 7. 100

EXAMPLE 9.

17 α - Acetoxy - 6 α ,11 β - dimethyl - 19 - norpregn - 4 - ene - 3,20 - dione. 115

A solution of 1 part of 17 α - acetoxy - 11 β - methyl - 6 - methylene - 19 - norpregn - 4 - ene - 3,20 - dione and 2.4 parts of cyclohexene in 40 parts of ethanol was heated under reflux and stirred with 0.2 parts of a 5% palladium-on-carbon catalyst for 3 hours. The catalyst was removed by filtration and 1.2 parts of concentrated hydrochloric acid was added to the filtrate, which was then concentrated under reduced pressure and diluted with water. Crystallization of the product from aqueous methanol gave 17 α - 120

acetoxy - 6 α ,11 β - dimethyl - 19 - norpregn - 4 - ene - 3,20 - dione, which is identical to the product obtained in Example 7.

EXAMPLE 10.

5 17 α - Acetoxy - 6,11 β - dimethyl - 19 - norpregna - 4,6 - diene - 3,20 - dione.

A mixture of 10 parts of 17 α - acetoxy - 11 β - methyl - 6 - methylene - 19 - norpregn - 4 - ene - 3,20 - dione, 5 parts of sodium acetate, 1.5 parts of 5% palladium-on-carbon catalyst and 120 parts of ethanol was stirred under reflux for 20 hours until isomerization was complete. The catalyst was removed, and the product obtained on dilution with water was crystallized from a mixture of dichloromethane and methanol to yield 17 α - acetoxy - 6,11 β - dimethyl - 19 - norpregna - 4,6 - diene - 3,20 - dione, which is characterized by infrared maxima, in chloroform, at about 5.78, 5.83, 6.01, 6.22 and 6.28 microns.

EXAMPLE 11.

17 α - Acetoxy - 6 α - chloro - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

25 A mixture of 5 parts of 17 α - acetoxy - 3 - methoxy - 11 β - methyl - 19 - norpregna - 3,5 - dien - 20 - one, 3 parts of anhydrous sodium acetate, 80 parts of acetone and 32 parts of water was cooled to 0 to 5°C. and then treated with 6.4 parts of N-chlorosuccinimide and 2 parts of glacial acetic acid. The mixture was stirred for 30 minutes at a temperature of 0 to 5°C. diluted with 300 parts of water and kept overnight in the refrigerator. The precipitate formed was collected, washed with water, dried *in vacuo* and recrystallized from acetone. There was thus obtained 17 α - acetoxy - 6 β - chloro - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

A slow stream of dry hydrogen chloride was introduced into a suspension of 3 parts of the above compound and 50 parts of glacial acetic acid, while the temperature was maintained below 10°C. After 1 hour, the mixture was poured into 100 parts of water containing 35 parts of potassium acetate and cooled. The precipitate was collected by filtration, washed with water, dried and recrystallized from a mixture of acetone and hexane, thus yielding 17 α - acetoxy - 6 α - chloro - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione, which is characterized by infrared maxima in chloroform solution at about 5.76, 5.82, 5.94 and 6.18 microns.

EXAMPLE 12.

17 α - Acetoxy - 6 - chloro - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione.

60 A solution of 2.5 parts of 17 α - acetoxy - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione in about 200 parts of methylene chloride was treated with 125 parts by volume

of a 5% solution of monoperphthalic acid in ether and the mixture was kept at room temperature for 24 hours; the solution was washed with 5% aqueous sodium carbonate solution and water, dried over anhydrous sodium sulphate and concentrated until crystallization started. After cooling, the precipitate was collected by filtration and dried in air. Subsequent chromatography on silica gel afforded 17 α - acetoxy - 11 β - methyl - 6 α ,7 α - oxido - 19 - norpregn - 4 - ene - 3,20 - dione.

A solution of 2 parts of the above prepared 6 α ,7 α - oxido compound in 105 parts of acetic acid was treated with 6 parts of concentrated hydrochloric acid and the mixture was kept at room temperature for 6 hours. The product was precipitated with water, collected by filtration and recrystallized from a mixture of acetone and hexane, to afford 17 α - acetoxy - 6 - chloro - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione, which is characterized by infrared maxima in chloroform solution at about 5.78, 5.83, 6.02, 6.23 and 6.30 microns.

EXAMPLE 13.

3 β ,17 α - Diacetoxy - 11 β - methyl - 19 - norpregn - 4 - en - 20 - one.

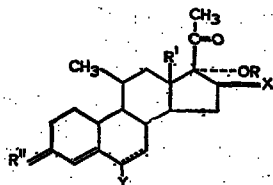
To a cooled solution of 0.5 part of 17 α - acetoxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione in 4.5 parts of tetrahydrofuran was added 0.9 part of lithium tri-(tertiary-butoxy) aluminium hydride. The reaction vessel was stoppered and the mixture was maintained at room temperature for 2 hours, with stirring. It was then cooled on an ice bath and neutralized by the addition of 1.9 parts of acetic acid in 10 parts of water. Upon extraction with chloroform, the chloroform extract was washed successively with water and saturated sodium bicarbonate solution, dried over sodium sulphate and distilled to dryness to yield the crude 3-hydroxy steroid, namely 17 α - acetoxy - 3 - hydroxy - 11 β - methyl - 19 - norpregn - 4 - en - 20 - one.

0.5 Part of the aforementioned 3-hydroxy material was dissolved in 3.9 parts of pyridine. To this solution was added 3.2 parts of acetic anhydride and the resulting reaction mixture was allowed to stand at room temperature for 5 hours. Thereafter, the reaction mixture was poured into ice water and the precipitate which formed was filtered off and redissolved in chloroform. The chloroform solution was washed successively with water and sodium bicarbonate solution, then dried over sodium sulphate and distilled to dryness. The crude product was recrystallized from acetone to yield 3 β ,17 α - diacetoxy - 11 β - methyl - 19 - norpregn - 4 - en - 20 - one which is characterized by nuclear magnetic resonance peaks, in deuterochloroform, at 44 (singlet); 58 and 66 (doublet); 122 (singlet, 6 protons); 126 (singlet, 3 protons); 317 (multiplet); and 323 (singlet) cycles per second.



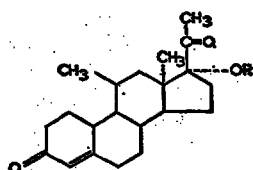
WHAT WE CLAIM IS:—

1. Compounds of the general formula



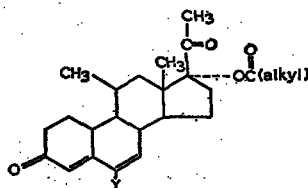
- 5 wherein R is a hydrogen atom, a formyl radical or an alkanoyl radical in which the alkyl portion contains from 1 to 6 carbon atoms; R' is an alkyl radical containing from 1 to 7 carbon atoms; R'' is an oxo group, or a hydroxy radical or an alkanoyloxy radical in the β -configuration in which the alkyl portion contains from 1 to 6 carbon atoms together with a hydrogen atom; Y is a hydrogen or chlorine atom or a methyl group; and the dotted line indicates an optional 6(7) double bond; and X is H₂ or when Y is a hydrogen atom and the 6(7) bond is saturated X is H₂ or a methylene radical.

2. Compounds of the general formula



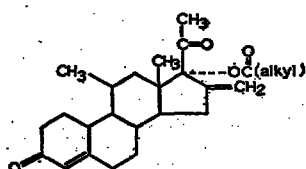
- 20 wherein R is a hydrogen atom, a formyl radical or an alkanoyl radical in which the alkyl portion contains from 1 to 6 carbon atoms.

3. Compounds of the general formula



- 25 wherein Y is a hydrogen or chlorine atom or a methyl group; and the alkyl radicals contain from 1 to 6 carbon atoms.

4. Compounds of the general formula



- 30 wherein the alkyl radicals contain from 1 to 6 carbon atoms.

5. 17 α - Hydroxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

6. 17 α - Acetoxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

- 35 7. 17 α - Acetoxy - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione.

8. 17 α - Acetoxy - 6 - chloro - 11 β - methyl - 19 - norpregna - 4,6 - diene - 3,20 - dione.

9. 17 α - Acetoxy - 6 α - chloro - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione.

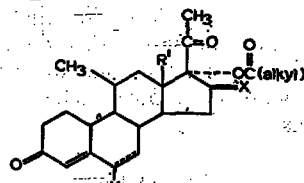
10. 17 α - Acetoxy - 6 α ,11 β - dimethyl - 19 - norpregn - 4 - ene - 3,20 - dione.

11. 17 α - Acetoxy - 6,11 β - dimethyl - 19 - norpregna - 4,6 - diene - 3,20 - dione.

12. 17 α - Acetoxy - 11 β - methyl - 16 - methylene - 19 - norpregn - 4 - ene - 3,20 - dione.

13. 3 β ,17 α - Diacetoxy - 11 β - methyl - 19 - norpregn - 4 - en - 20 - one.

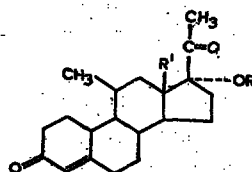
14. The process for the preparation of a compound of the general formula



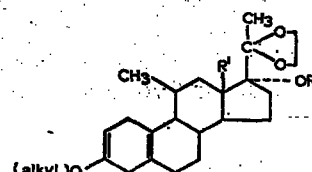
wherein R', X, Y and the dotted line have the meanings defined in Claim 1 which comprises acylating the corresponding 17 α -hydroxy compound.

15. A process as claimed in Claim 13 wherein the acylating agent is the complex formed from a metalloid halide, an organic acid halide and a halogenated aliphatic solvent and wherein the reaction is conducted in the presence of a lower nitroparaffin which has a high dielectric constant and under anhydrous conditions.

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

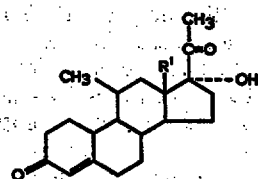


wherein R and R' have the meanings defined in Claim 1, which comprises the strong acid hydrolysis of a compound of the general formula



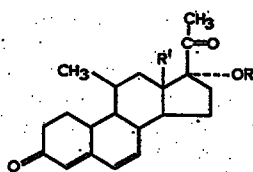
wherein R and R' are defined as above and the alkyl radicals contain 1 to 6 carbon atoms.

17. A process for the preparation of a compound of the general formula



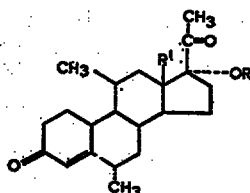
wherein R' is an alkyl radical containing 1 to 7 carbon atoms; which comprises the chromic acid oxidation of the corresponding

- 5 17 α ,20-dihydroxy compound.
18. A process for the preparation of a compound of the general formula

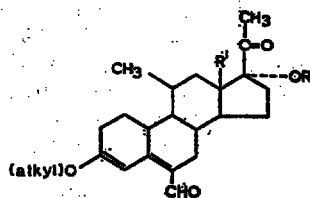


- wherein R and R' have the meanings defined in Claim 1 which comprises the oxidation with manganese dioxide or 2,3 - dichloro - 5,6 - dicyanobenzoquinone of the corresponding
15 17 α - alkanoyloxy/hydroxy - 3 - alkoxy - 11 β - methyl - 19 - norpregna - 3,5 - dien - 20 - one.

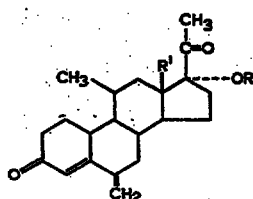
19. A process for the preparation of a compound of the general formula



- wherein R and R' have the meanings defined in Claim 1, which comprises
20 a) the reduction of a compound of the general formula



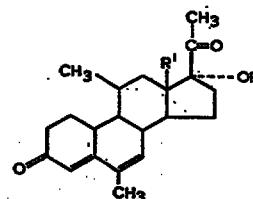
- followed by acidification of the 6 β -methyl intermediate thus obtained; or
25 b) reduction of a compound of the general formula



followed by acidification of the isolated or unisolated 6 β -methyl intermediate.

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20. A process for the preparation of a compound of the general formula

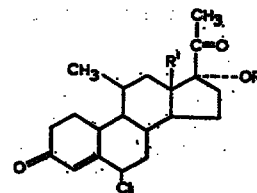


wherein R is a hydrogen atom, a formyl radical or an alkanoyl radical wherein the alkyl portion contains 1 to 6 carbon atoms, and R' is an alkyl radical containing 1 to 7 carbon atoms; which is characterized by the isomerization of the corresponding 6-methylene compound of the formula depicted under 19b above.

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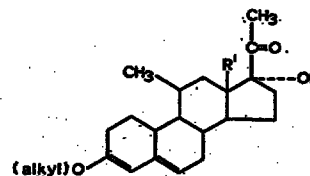
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21. A process for the preparation of a compound of the general formula



wherein R and R' have the meanings defined in Claim 1 which comprises contacting a 3,5-diene 3-enol ether of the general formula

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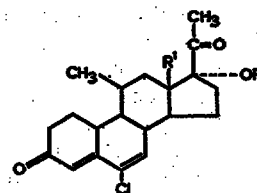


wherein R and R' are defined as above and the alkyl radicals contain from 1 to 6 carbon atoms, with a hypochlorous acid or an agent capable of liberating this acid, followed by epimerization with strong mineral acid of the 3 - keto - Δ^4 - 6 β - chloro derivative thus obtained.

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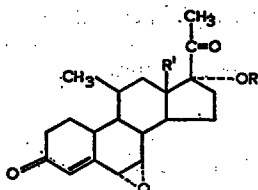
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22. A process for the preparation of a compound of the general formula



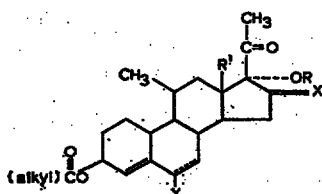
wherein R and R' have the meanings defined in Claim 1, which comprises the addition of the elements of hydrogen chloride to a compound of the general formula

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wherein R and R' are defined as above if followed by the dehydration of the resulting 6 β -chloro - 7 α - hydroxy compound thus formed.

- 5 23. The process for the preparation of a compound of the general formula



where R, R', X, Y and the dotted line have the meanings defined in Claim 1, which comprises the acylation of the corresponding 3-hydroxy compound.

- 10 24. A process for the preparation of 17 α - acetoxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione which comprises acylation of 17 α - hydroxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione with a complex formed by the combination of antimony pentachloride, 1,1,2-trichlorotrifluoroethane and acetyl chloride.

- 20 25. A process for the preparation of 17 α - acetoxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione which comprises the acylation of 17 α - hydroxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione with acetic anhydride in the presence of *p*-toluenesulphonic acid monohydrate and acetic acid followed by hydrochloric acid treatment of the resulting crude material.

- 30 26. A process for the preparation of 17 α - hydroxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione which comprises the strong acid hydrolysis of 17 α - hydroxy - 3 - methoxy - 11 β - methyl - 19 - norpregn - 2,5(10) - dien - 20 - one 20-ethylene ketal with hydrochloric acid.

- 40 27. A process for the preparation of 17 α - hydroxy - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione which comprises the oxidation of 17 α ,20 - dihydroxy - 11 β - methyl - 19 - norpregn - 4 - en - 3 - one with a chromic acid oxidizing agent.

- 45 28. A process for the preparation of 17 α - acetoxy - 11 β - methyl - 19 - norpregn - 4,6 - diene - 3,20 - dione which comprises the oxidation of 17 α - acetoxy - 3 - ethoxy -

11 β - methyl - 19 - norpregn - 3,5 - dien - 20 - one with manganese dioxide.

29. A process for the preparation of 17 α - acetoxy - 6 α ,11 β - dimethyl - 19 - norpregn - 4 - ene - 3,20 - dione which comprises the hydrogenation of 17 α - acetoxy - 11 β - methyl - 6 - methylene - 19 - norpregn - 4 - ene - 3,20 - dione with hydrogen and a pre-hydrogenated palladium-on-carbon catalyst, followed by hydrogen chloride treatment of the resulting 6 β -methyl compound.

30. A process for the preparation of 17 α - acetoxy - 6 α ,11 β - dimethyl - 19 - norpregn - 4 - ene - 3,20 - dione which comprises the reduction of 17 α - acetoxy - 6 - formyl - 3 - methoxy - 11 β - methyl - 19 - norpregn - 3,5 - dien - 20 - one with cyclohexene in the presence of ethanol and a palladium-on-carbon catalyst, followed by hydrochloric acid treatment of the crude residue.

31. A process for the preparation of 17 α - acetoxy - 6,11 β - dimethyl - 19 - norpregn - 4,6 - diene - 3,20 - dione which comprises the isomerization of 17 α - acetoxy - 11 β - methyl - 6 - methylene - 19 - norpregn - 4 - ene - 3,20 - dione with sodium acetate and a palladium-on-carbon catalyst.

32. Process for the preparation of 17 α - acetoxy - 6 α - chloro - 11 β - methyl - 19 - norpregn - 4 - ene - 3,20 - dione which comprises the chlorination of 17 α - acetoxy - 3 - methoxy - 11 β - methyl - 19 - norpregn - 3,5 - dien - 20 - one with N-chlorosuccinimide, followed by treatment with hydrochloric acid in the presence of acetic acid of the resulting 6 β -chloro compound.

33. A process for the preparation of 17 α - acetoxy - 6 - chloro - 11 β - methyl - 19 - norpregn - 4,6 - diene - 3,20 - dione which comprises contacting 17 α - acetoxy - 11 β - methyl - 6 α ,7 α - oxido - 19 - norpregn - 4 - ene - 3,20 - dione with hydrochloric acid in the presence of acetic acid.

34. A process for the preparation of 3 β , 17 α - diacetoxy - 11 β - methyl - 19 - norpregn - 4 - en - 20 - one which comprises the acylation of 17 α - acetoxy - 3 β - hydroxy - 11 β - methyl - 19 - norpregn - 4 - en - 20 - one with acetic anhydride in the presence of pyridine.

35. A process for the production of compounds as claimed in Claims 1 to 4 substantially as described with reference to any of the Examples.

ELKINGTON AND FIFE,
Chartered Patent Agents,
High Holborn House,
52/54 High Holborn,
London WC1V 6SH.
Agents for the Applicants.