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PATENT SPECIFICATION

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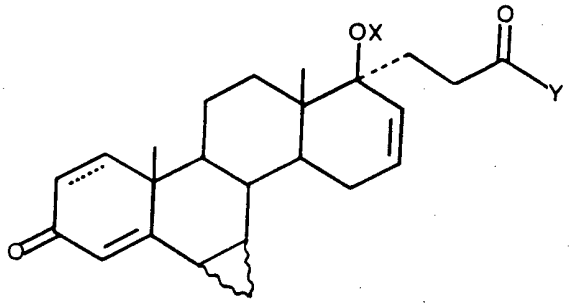
(54) D-HOMOSTEROIDS

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, 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 D-homosteroids. More particularly, the invention is concerned with D-homosteroids, a process for the manufacture thereof and pharmaceutical preparations containing same.

The D-homosteroids provided by the present invention are compounds of the general formula



(I)

wherein the dotted line in the A-ring represents an optional carbon-carbon bond and X and Y together represent an oxygen-carbon bond or X represents a hydrogen atom and Y represents a hydroxy group, and salts thereof.

Of particular interest are the compounds of formula I in which X represents a hydrogen atom and Y represents a hydroxy group and salts thereof, especially the alkali metal salts (e.g. the potassium or sodium salts), the ammonium salts and the alkaline earth metal salts (e.g. the calcium salts), the potassium salts being preferred.

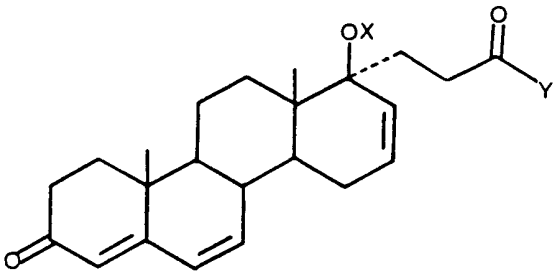
Also preferred are the 1,2-saturated compounds of formula I and the 6β,7β-compounds of formula I, for example 17α - hydroxy - 6β,7β - methylene - 3 - oxo - D - homo - 17α - pregna - 4,16 - diene - 21 - carboxylic acid, and salts thereof; for example, potassium 17α - hydroxy - 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21 - carboxylate.

Examples of other compounds of formula I are:

6β,7β - Methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21,17a - carbolactone and

6α,7α - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21,17a - carbolactone.

According to the process provided by the present invention, the D-homosteroids aforesaid (i.e. the compounds of formula I and salts thereof) are manufactured by methylenating a D-homosteroid of the general formula



(II)

wherein X and Y have the significance given earlier, or a salt thereof in the 6,7-position and, if desired, dehydrogenating a resulting compound of formula I or a salt thereof in the 1,2-position, or cleaving the lactone ring in a compound of formula I in which X and Y together represent an oxygen-carbon bond and isolating the product in the form of the free acid or a salt thereof, or lactonising a compound of formula I in which X represents a hydrogen atom and Y represents a hydroxy group or a salt thereof.

The methylenation of a D-homosteroid of formula II or of a salt of a compound of formula II in which X represents a hydrogen atom and Y represents a hydroxy group (e.g. an alkali metal, ammonium or alkaline earth metal salt) can be carried out in a manner known per se; for example, by means of trimethylsulphoxonium iodide in the presence of a base such as sodium hydride or potassium tert.butylate in an aprotic dipolar solvent (e.g. dimethylsulphoxide, tetrahydrofuran, hexamethylphosphoric acid triamide, dimethylformamide or mixtures thereof) at a temperature between about 0°C and 50°C, conveniently at room temperature.

The 1,2-dehydrogenation of a compound of formula I or of a salt thereof can be carried out in a manner known per se; for example, in a microbiological manner or by means of dehydrogenating agents such as selenium dioxide, 2,3 - dichloro - 5,6 - dicyanobenzo - quinone, chloranil, thallium triacetate or lead tetraacetate. Suitable microorganisms for the 1,2-dehydrogenation are, for example, Schizomycetes, especially those of the genera Arthrobacter (e.g. A. simplex ATCC 6946), Bacillus (e.g. B. lentus ATCC 13805 and B. sphaericus ATCC 7055), Pseudomonas (e.g. P. aeruginosa IFO 3505), Flavobacterium (e.g. F. flavescens IFO 3058), Lactobacillus (e.g. L. brevis IFO 3345) and Nocardia (e.g. N. opaca ATCC 4276).

The cleavage of the lactone ring present in a compound of formula I can be carried out in a manner known per se; for example, by means of a base such as potassium hydroxide or sodium hydroxide in a solvent (e.g. an alcohol such as methanol, ethanol or isopropanol) at a temperature between about 0°C and the reflux temperature of the mixture, conveniently at about 50°C. The thus-obtained salts, which correspond to the bases used, can be converted by acidification (e.g. by means of hydrochloric acid) into the free acids of formula I. The latter can be converted into salts by treatment with suitable bases.

The lactonisation of a compound of formula I in which X represents a hydrogen atom and Y represents a hydroxy group or of a salt thereof can be carried out in a manner known per se; for example, by means of a strong acid such as hydrochloric acid, sulphuric acid or p-toluenesulphonic acid in a solvent (e.g. water, an alcohol such as methanol, or mixtures thereof) at a temperature between about −50°C and 100°C, conveniently at room temperature.

The starting materials of formula II in which X represents a hydrogen atom and Y represents a hydroxy group and salts thereof can be prepared by cleaving the lactone ring present in a corresponding compound of formula II, the cleavage being carried out in the same manner as described earlier in connection with the cleavage of the lactone ring present in a compound of formula I.

The D-homosteroids provided by the present invention exhibit pharmacological activity. Inter alia, they have diuretic activity and are suitable for blocking the action of aldosterone or of desoxycorticosterone acetate. They can accordingly be used, for example, as potassium-sparing diuretics or for the flushing of oedemas. They may be administered, for example, in a dosage of from about 0.1 mg/kg to 10 mg/kg per day.

The D-homosteroids provided by the present invention show advantages,

especially in relation to side-effects, over known compounds having aldosterone-antagonistic activity. Thus, it has been shown that potassium 17a - hydroxy - 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21 - carboxylate has a comparable aldosterone-antagonistic activity to the known spironolactone (7α - acetylthio - 3 - oxo - 17α - pregn - 4 - ene - 21,17 - carbolactone), but has substantially less antiandrogenic and gestagenic side-effects.

The D-homosteroids provided by the present invention can be used as medicaments; for example, in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier material. This carrier material can be an organic or inorganic inert carrier material suitable for enteral or parenteral administration such as, for example, water, gelatine, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkyleneglycols, petroleum jelly etc. The pharmaceutical preparations can be made up in a solid form (e.g. as tablets, dragées, suppositories or capsules) or in a liquid form (e.g. as solutions, suspensions or emulsions). The pharmaceutical preparations may be sterilised and/or may contain adjuvants such as preserving, stabilising, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They can also contain still other therapeutically valuable substances.

The pharmaceutical preparations can be prepared in a manner known per se by mixing a compound of formula I or a salt thereof with non-toxic, inert, solid and/or liquid carrier materials which are customary in such preparations and which are suitable for therapeutic administration (e.g. the carrier materials previously named) and, if desired, bringing the mixture into the desired dosage form.

The following Examples illustrate the process provided by the present invention:

Example 1

96.64 g of trimethylsulphoxonium iodide are dry-mixed in a nitrogen atmosphere with 18.2 g of a 55% sodium hydride dispersion. Subsequently, while cooling to 15°—17°C, 300 ml of dimethylsulphoxide are added dropwise within 10 minutes. After completion of the hydrogen evolution, the suspension is stirred under nitrogen at room temperature for 3.5 hours. 77.4 g of 3 - oxo - D - homo - 17aα - pregna - 4,6,16 - triene - 21,17a - carbolactone dissolved in 500 ml of dimethylsulphoxide are added dropwise at room temperature within 15 minutes. The brown-red solution is stirred at room temperature under nitrogen for 113 hours. For the working-up, the mixture containing the sodium 17a - hydroxy - 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21 - carboxylate and sodium 17a - hydroxy - 6α,7α - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21 - carboxylate is acidified with 100 ml of glacial acetic acid, poured into water and extracted with methylene chloride. The crude product is dissolved in 200 ml of methanol. 10 ml of 1-N hydrochloric acid are added thereto. After stirring at room temperature for 1 hour, the solution is neutralised with sodium bicarbonate, concentrated on a rotary evaporator, poured into water and extracted with methylene chloride. By chromatography on silica gel using ether for the elution and subsequent crystallisation from acetone/hexane there are obtained 15 g of 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21,17a - carbolactone; melting point 226°—229°C, UV: λ_{max} 265 nm, ε=19000, $[\alpha]_D$=−219° (c=0.101 in methanol) and 15 g of 6α,7α - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21,17a - carbolactone; melting point 231°—233°C, UV: λ_{max} 257.5 nm, ε=17300, $[\alpha]_D$=+82° (c=0.102 in methanol).

The foregoing methylenation can be carried out using, in place of sodium hydride as the base and dimethylsulphoxide as the solvent, sodium hydride and dimethylsulphoxide/tetrahydrofuran or potassium tert.butylate and dimethylformamide, hexamethylphosphoric acid triamide or dimethylsulphoxide.

Example 2

169.2 g of trimethylsulphoxonium iodide and 31.95 g of a 55% sodium hydride dispersion are dry-mixed in an argon atmosphere. While cooling to 15°C there are slowly added 693 ml of dimethylsulphoxide. The resulting suspension is stirred at room temperature for 3.5 hours. There is then added dropwise while cooling to room temperature a solution of 58 g of potassium 17a - hydroxy - 3 - oxo - D - homo - 17aα - pregna - 4,6,16 - triene - 21 - carboxylate in 462 ml of dimethylsulphoxide. After 24 hours, there are added while cooling 162 ml of acetic acid and the mixture is poured into water. The precipitate is filtered off and washed with a small amount of water. The residue is taken up in ethanol, evaporated and dried. The crude product is dissolved in 273 ml of methanol, acidified with 6 ml of

1-N hydrochloric acid and held at room temperature for 60 minutes. The solution is poured into water and extracted with ethyl acetate. The crude product is chromatographed on silica gel with hexane/ether (1:1) and ether. After crystallisation from acetate/hexane, there are obtained 13 g of 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21,17a - carbolactone and 10 g of 6α,7α - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21,17a - carbolactone.

The foregoing methylenation can be carried out using, in place of sodium hydride as the base and dimethylsulphoxide as the solvent, sodium hydride and dimethylsulphoxide/tetrahydrofuran or potassium tert.butylate and dimethylformamide, hexamethylphosphoric acid triamide or dimethylsulphoxide.

The starting material can be prepared as follows:

50 g of 3 - oxo - D - homo - 17aα - pregna - 4,6,16 - triene - 21,17a - carbolactone are suspended in 750 ml of isopropanol and 55.7 ml of aqueous 2.49-N potassium hydroxide solution are added thereto. The suspension is boiled at reflux under argon for 40 minutes, a solution being obtained. The solution is concentrated with repeated addition of isopropanol. There is obtained potassium 17a - hydroxy - 3 - oxo - D - homo - 17aα - pregna - 4,6,16 - triene - 21 - carboxylate which, after crystallisation from ethanol/ethyl acetate, melts at 210°—215°C (with decomposition); UV: λ_{max}=256.5 nm, ε=12480.

Example 3

60.6 g of 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21,17a - carbolactone are suspended in 745 ml of isopropanol and 69.55 ml of 2.33-N potassium hydroxide solution and boiled at reflux under argon for 40 minutes. The solution is gradually cooled down to +5°C, the potassium salt crystallising out. The crystallisate is filtered off, washed with 100 ml of cold isopropanol and dried in vacuo. There are obtained 47 g of potassium 17a - hydroxy - 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21 - carboxylate; melting point 254°—256°C (with decomposition); UV; λ_{max}=267 nm, ε=17000.

Example 4

20 mg of potassium 17a - hydroxy - 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21 - carboxylate are dissolved in 0.6 ml of methanol and 0.2 ml of 0.1-N hydrochloric acid and held at room temperature under argon for 10 minutes, a portion of the product crystallising out. The mixture is poured into 20 ml of water. The precipitate is filtered off and washed neutral with a small amount of water and dried. There are thus obtained 15 mg of crude product which, after gas chromatography, consists exclusively of 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21,17a - carbolactone.

Example 5

A solution of 2.5 g of 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21,17a - carbolactone and 1.9 g of 2,3 - dichloro - 5,6 - dicyanobenzoquinone in 250 ml of dioxan is heated under reflux for 18 hours. The solution is treated with 250 ml of ethyl acetate and subsequently filtered through 100 g of aluminium oxide. The substance is eluted completely with a further 300 ml of ethyl acetate. The filtrate is evaporated in vacuo and the residue is chromatographed on 250 g of silica gel. Elution with methylene chloride containing 2% acetone yields 1.3 g of pure 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 1,4,16 - triene - 21,17a - carbolactone; melting point 261°—263°C; $[\alpha]_D^{25}$=−171° (c=0.1 in dioxan), ε_{243}=12200.

Example 6

In a manner analogous to that described in Example 5, from 6α,7α - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21,17a - carbolactone there is obtained pure 6α,7α - methylene - 3 - oxo - D - homo - 17aα - pregna - 1,4,16 - triene - 21,17a - carbolactone; melting point 232°—233°C; $[\alpha]_D^{25}$=+4° (c=0.1 in dioxan), ε_{244}=13100.

The following Examples illustrate typical pharmaceutical preparations containing the D-homosteroids provided by the present invention:

Example A

A tablet for oral administration can contain the following ingredients:

Compound of formula I or salt thereof	25 mg
Maize starch	100 mg
Lactose	50 mg
Polyvinylpyrrolidone	15 mg
Magnesium stearate	2 mg

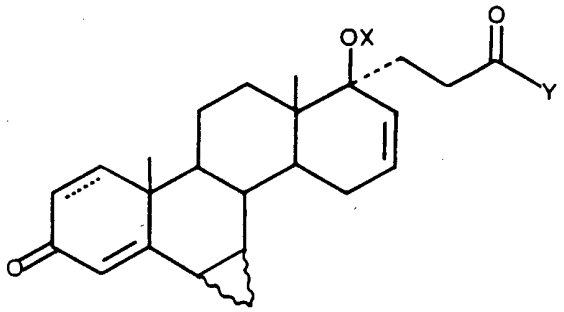
Example B

A capsule for oral administration can contain the following ingredients:

Compound of formula I or salt thereof	25 mg
Maize starch	125 mg
Lactose	125 mg

WHAT WE CLAIM IS:—

1. Compounds of the general formula



(I)

wherein the dotted line in the A-ring represents an optional carbon-carbon bond and X and Y together represent an oxygen-carbon bond or X represents a hydrogen atom and Y represents a hydroxy group, and salts thereof.

2. Compounds of formula I according to claim 1, wherein X represents a hydrogen atom and Y represents a hydroxy group, and salts thereof.

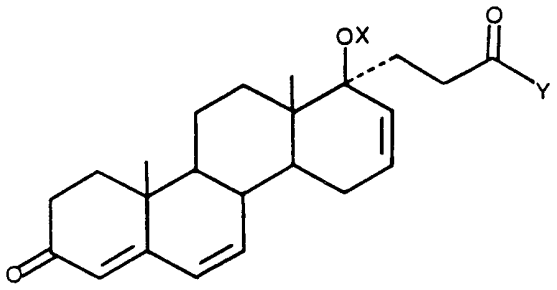
3. 1,2-Saturated compounds of formula I according to claim 1 or claim 2, and salts thereof.

4. 6β,7β-Compounds of formula I according to claim 1, claim 2 or claim 3, and salts thereof.

5. 17a - Hydroxy - 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21 - carboxylic acid and salts thereof.

6. Potassium 17a - hydroxy - 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21 - carboxylate.

7. A process for the manufacture of the compounds of formula I given in claim 1, and salts thereof, which process comprises methylenating a D-homosteroid of the general formula



(II)

wherein X and Y have the significance given in claim 1, or a salt thereof in the 6,7-position and, if desired, dehydrogenating a resulting compound of formula I or a salt thereof in the 1,2-position, or cleaving the lactone ring in a compound of formula I in which X and Y together represent an oxygen-carbon bond and isolating the product in the form of the free acid or a salt thereof, or lactonising a

compound of formula I in which X represents a hydrogen atom and Y represents a hydroxy group or a salt thereof.

8. A process according to claim 7, wherein a compound of formula I in which X represents a hydrogen atom and Y represents a hydroxy group or a salt thereof is manufactured.

9. A process according to claim 7 or claim 8, wherein a 1,2-saturated compound of formula I or a salt thereof is manufactured.

10. A process according to claim 7, claim 8 or claim 9, wherein a 6β,7β-compound of formula I or a salt thereof is manufactured.

11. A process according to any one of claims 7 to 10 inclusive, wherein 17a - hydroxy - 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21 - carboxylic acid or a salt thereof is manufactured.

12. A process according to any one of claims 7 to 11 inclusive, wherein potassium 17a - hydroxy - 6β,7β - methylene - 3 - oxo - D - homo - 17aα - pregna - 4,16 - diene - 21 - carboxylate is manufactured.

13. A process for the manufacture of the compounds of formula I given in claim 1 and salts thereof, substantially as hereinbefore described with reference to any one of Examples 1 to 6.

14. Compounds of formula I given in claim 1 and salts thereof, when manufactured by the process claimed in any one of claims 7 to 13 inclusive or by an obvious chemical equivalent thereof.

15. A pharmaceutical preparation containing a compound of formula I given in claim 1 or a salt thereof in association with a compatible pharmaceutical carrier material.

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