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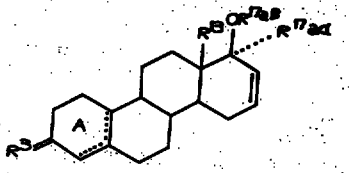
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(54) D-HOMO STEROIDS

(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 steroids. More particularly, the invention is concerned with D-homosteroids, a process for the manufacture thereof, pharmaceutical preparations containing same and starting materials used in the manufacture of said D-homosteroids.

The D-homosteroids provided by the present invention have the following general formula

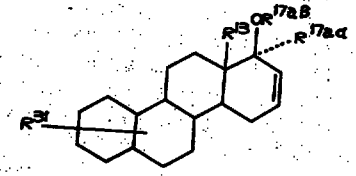


(I)

wherein R^3 represents an oxo, (H,H) or (α-H, β-O-acyl), grouping, R^{13} represents a lower alkyl group, $R^{17a\beta}$ represents a hydrogen atom or an acyl or lower alkyl group and $R^{17a\alpha}$ represents a hydrogen atom or a lower alkyl, ethylnyl, 1-propynyl, vinyl, chloroethynyl, butadiynyl or propadienyl group and wherein the broken line in the A-ring denotes an additional carbon-carbon bond in the 4,5- or 5(10)-position.

According to the process provided by the present invention, the D-homosteroids of formula I are manufactured by

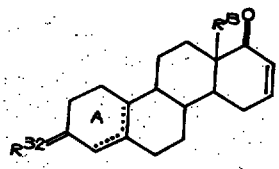
(a) hydrolysing a compound of the general formula



(II)

wherein R^{13}, $R^{17a\beta}$ and $R^{17a\alpha}$ have the significance given earlier and R^{31} represents a moiety hydrolysable to form a 3-keto-Δ^4 or 3-keto-$\Delta^{5(10)}$ grouping,
or

(b) reacting a compound of the general formula



(III)

wherein R^{13} and the broken line in the A-ring have the significance given earlier and R^{32} represents a (H,H) or (α-H, β-O-acyl) grouping,
with anorganometallic compound furnishing a lower alkyl, ethynyl, 1-propynyl, vinyl, chloroethynyl, butadiynyl, or propadienyl group, or

(c) reducing the keto group in a compound of formula III hereinbefore to a hydroxy group.

As used in this specification, the term "acyl" denotes an acyl group derived from an organic acid; for example, an alkanecarboxylic acid such as acetic acid, propionic acid, caproic acid or valeric acid, oxalic acid, succinic acid, citric acid or an aromatic carboxylic acid such as benzoic acid.

A lower alkyl group contains up to 7 carbon atoms and can be straight-chain or branched-chain. Examples of such lower alkyl groups are the methyl, ethyl, propyl, isopropyl and butyl groups and isomers of the latter. Preferred lower alkyl groups denoted by R^{13} are the methyl and ethyl groups.

Examples for the moiety denoted by R^{31} are 3-alkoxy (e.g. 3-methoxy)-$\Delta^{2,5(10)}$, 3-alkylthio (e.g. 3-methylthio)-$\Delta^{2,5(10)}$, 3-sec.amino (e.g. pyrrolidino)-$\Delta^{2,5(10)}$, 3-alkylenedioxy (e.g. ethylenedioxy)-$\Delta^{5(10)}$, -Δ^4 or -Δ^5, or 3-alkylene-dithio (e.g. 3-ethylenedithio)-$\Delta^{5(10)}$, -Δ^4 or -Δ^5 groupings.

A preferred group of D-homosteroids of formula I are those wherein R^3 represents an oxo group, R^{13} represents a methyl or ethyl group and the double bond in ring A is present in the 4,5-position. More especially pre-

ferred are such D-homosteroids of formula I wherein $R^{17a\alpha}$ represents a hydrogen atom or an ethylnyl, chloroethylnyl or butadiynyl group and $R^{17a\beta}$ represents a hydrogen atom.

Examples of D-homosteroids of formula I in which R^3 represents a (H,H) or (α-H, β-O-acyl) grouping are:

17aβ - hydroxy - 13 - methyl - gona - 4,16-diene;
17aα - ethynyl - 17aβ - hydroxy - 13-methyl - gona - 4,16 - diene;
17aα - ethynyl - 13 - ethyl - 17aβ - hydroxy-gona - 4,16 - diene;
17aβ - acetoxy - 17aα - ethylnyl - 13-ethyl - gona - 4,16 - diene;
3β,17$\alpha\beta$ - diacetoxy - 13 - methyl - gona-4,16 - diene;
3β,17aβ - diacetoxy - 17aα - ethynyl - 13-methyl - gona - 4,16 - diene and
3β,17aβ - diacetoxy - 17aα - ethylnyl - 13-ethyl - gona - 4,16 - diene.

The hydrolysis of a compound of formula II according to embodiment (a) of the present process can be carried out in a manner known per se using an acid; for example, a mineral acid such as hydrochloric acid or a carboxylic acid such as oxalic acid. A particularly suitable hydrolysis medium is an aqueous-alcoholic solution (e.g. methanol/water) which may contain other solvents (e.g. chloroform).

The reaction of a compound of formula III with an organometallic compound according to embodiment (b) of the present process can be carried out in manner known per se. The organometallic compound can be a Grignard compound (e.g. ethynylmagnesium bromide, propynylmagnesium bromide or vinylmagnesium bromide) or an alkali organometallic compound such as sodium acetylide, potassium acetylide, lithium acetylide or vinyllithium.

The reduction of a compound of formula III according to embodiment (c) of the present process can be carried out in a manner known per se with complex metal hydrides [e.g. di(lower alkyl)-aluminium hydrides such as diisobutylaluminium hydride; tri(lower alkoxy)-aluminiums such as triisopropoxy-aluminium; lithium aluminium hydride; sodium aluminium or sodium (boro) hydride; trimethoxy- or tributoxy-(lithium aluminium hydride)]. Suitable solvents for this reduction are hydrocarbons such as cyclohexane, benzene and toluene or ethers such as diethyl ether and tetrahydrofuran.

The starting materials of formulae II and III can be prepared as follows or in an analogous manner.

A) Preparation of 3-methoxy-D-homo-19-nor - 17aα - pregna - 2,5(10),16 - trien - 20-yn-17a-ol

a) A boiling solution of 44 g of 3-methoxy--D-homooestra-1,3,5(10)-trien-17a-one in 100 ml of dichloromethane and 200 ml of methanol was treated with a suspension of 62 g of cupric bromide in 40 ml of methanol and 30 ml of dichloromethane and the mixture was stirred for 5 hours under reflux. The crystalline precipitate was filtered over "Speedex" under suction, rinsed with dichloromethane and the filtrate was concentrated to dryness on a rotary evaporator. The residue was taken up in dichloromethane, washed three times with water and the aqueous phases were extracted twice more with dichloromethane. The organic phases were dried over sodium sulphate and concentrated on a rotary evaporator. The crude 17β - bromo - 3 - methoxy-D - homooestra - 1,3,5(10) - trien - 17a - one was crystallised from dichloromethane/hexane; melting point 183°—184°C; $[\alpha]_D^{25} = +32°$ (c=1.0 in chloroform).

b) A solution of 49 g of 17β - bromo - 3-methoxy - D - homooestra - 1,3,5(10) - trien-17a - one in 400 ml of dimethylformamide was treated with 43.5 g of lithium bromide and with 18.5 g of lithium carbonate and the mixture stirred at 110°C (bath temperature) for 10 hours under argon. The mixture was poured on to ice-water and extracted three times with dichloromethane. The organic extracts were back-washed twice with water, dried over sodium sulphate and concentrated on a rotary evaporator. The last traces of dimethylformamide were removed at 70°C/0.5 Torr. Crystallisation from dichloro-methane/acetone gave 3 - methoxy - D - homooestra-1,3,5(10),16 - tetraen - 17a - one; melting point 161°—162°C; $[\alpha]_D^{25} = \pm 0°$ (c=1.0 in chloroform).

c) A solution of 36.5 g of 3 - methoxy-D - homooestra - 1,3,5(10),16 - tetraen - 17a-one in 750 ml of absolute tetrahydrofuran was treated portionwise with 3.8 g of lithium aluminium hydride while stirring in an argon atmosphere at 0°—5°C. After stirring at 0°C for 2 hours, the mixture was treated carefully with ethyl acetate and then with ice-water and filtered over "Speedex" under suction. The filtrate was extracted three times with ethyl acetate, the organic phases washed twice with water, dried over sodium sulphate and concentrated to dryness on a rotary evaporator. Crystallisation of the crude product from ether/hexane yielded 3 - methoxy - D - homo-oestra - 1,3,5(10),16 - tetraen - 17aβ - ol; melting point 100°—101°C; $[\alpha]_D^{25} = +28°$ (c=1.0 in chloroform).

d) A solution of 33 g of 3 - methoxy - D-homooestra - 1,3,5(10),16 - tetraen - 17β - ol in 300 ml of absolute tetrahydrofuran and 300 ml of tert.butanol was added dropwise within 15 minutes to 750 ml of absolute liquid ammonia at —33°C. 10.2 g of sodium were added portionwise to the milky suspension. The dark-blue mixture was stirred for 2 hours at —33°C, carefully treated with

100 ml of methanol and freed from ammonia by slowly warming to room temperature. The mixture was poured on to ice-water and extracted with dichloromethane. The organic phases were back-washed twice with water, dried over sodium sulphate and evaporated to dryness on a rotary evaporator. Crystallisation from ether/hexane yielded 3-methoxy-D-homooestra - 2,5(10),16 - trien - 17aβ - ol; melting point 119°—120°C; $[\alpha]_D^{25}=+90°$ (c=1.0 in chloroform).

e) A solution of 16 g of 3 - methoxy - D-homooestra - 2,5(10),16 - trien - 17aβ - ol in 200 ml of benzene was treated with a suspension of 50 g of silver carbonate on "Speedex" [M. Fétizon et al J. Org. Chem. *36*, 1341 (1971)] in 40 ml of benzene and the mixture was heated to reflux for 3 hours under argon. The black precipitate was filtered off under suction, rinsed with ether and the filtrate concentrated to dryness on a rotary evaporator. Crystallisation from ether/hexane yielded 3 - methoxy - D - homooestra - 2,5(10),16-trien - 17a - one; melting point 149°—151°C; $[\alpha]_D^{25}=-86°$ (c=0.95 in chloroform).

f) A solution of 3.7 g of 3 - methoxy - D-homooestra - 2,5(10),16 - trien - 17a - one in 75 ml of absolute tetrahydrofuran was treated with 3.4 g of lithium acetylide-ethylenediamine complex and the mixture was stirred for 90 minutes at 25°C under argon. The mixture was poured on to ice-water and extracted three times with ether/ethyl acetate (ca 1:1). The organic phases were washed with water, dried over sodium sulphate and evaporated to dryness on a rotary evaporator. There was obtained 3-methoxy - D - homo - 19 - nor-17aα - pregna - 2,5(10),16 - trien - 20 - yn-17a - ol; melting point 139°—140°C (from hexane); $[\alpha]_D^{25}=-86°$ (c=0.816 in chloroform).

B) Preparation of 13 - ethyl - 3 - methoxy-D - homo - 18,19 - dinor - 17aα - pregna-2,5(10),16 - trien - 20 - yn - 17a - ol.

a) A boiling solution of 25 g of 13 - ethyl-3 - methoxy - D - homogona - 1,3,5(10)-trien - 17a - one [prepared from 13 - ethyl-3 - methoxygona - 1,3,5(10) - trien - 17 - one by 1) conversion into the corresponding 17-cyanohydrin and 2) reduction of the cyanohydrin to the corresponding primary amine and N-nitrosation with nitrous acid with simultaneous ring expansion [see Helv. Chim. Acta. *24* 295$_E$ (1941)]] in 50 ml of dichloromethane and 100 ml of methanol was treated with a suspension of 36.2 g of cupric bromide in 20 ml of dichloromethane and 20 ml of methanol and the mixture was stirred for 18 hours under reflux. The crystalline precipitate was filtered over "Speedex" under suction, thoroughly rinsed with dichloromethane and the filtrate was evaporated to dryness on a rotary evaporator. The residue was taken up in dichloromethane, washed three times with water and the aqueous phases were extracted a further twice with dichloromethane. After drying over sodium sulphate the dichloromethane solutions were concentrated on a rotary evaporator, the 13 - ethyl - 17 - bromo-3 - methoxy - D - homogona - 1,3,5(10)-trien - 17a - one crystallising out. Further crystalline α-bromoketone was obtained from the mother liquors after chromatography on 1 kg of silica gel with benzene/2% ethyl acetate as the eluant. 28 g of α-bromoketone were dissolved in 400 ml of dimethylformamide, treated with 20.4 g of lithium bromide and 8.3 g of lithium carbonate and the mixture was stirred at 110°C (bath temperature) for 7 hours under argon. The mixture was poured on to ice-water and extracted once with ether/dichloromethane (2:1) and twice with ether. The organic extracts were back-washed twice with water, dried over sodium sulphate and evaporated on a rotary evaporator. After chromatography on 700 g of silica gel with benzene as the eluant and crystallisation from dichloromethane/acetone, there was obtained 13 - ethyl - 3 - methoxy - D - homogona-1,3,(10),6 - tetraen - 17a - one; melting point 169° — 170°C; $[\alpha]^{589.25}=-20°$ (c=0.103 in dioxane).

b) A solution of 12 g of 13 - ethyl - 3-methoxy - D - homogona - 1,3,5(10),16-tetraen - 17a - one in 400 ml of absolute tetrahydrofuran was treated portionwise with 1.6 g of lithium aluminium hydride under an argon atmosphere while stirring at 0°—5°C. After stirring at 0°C for 60 minutes, the mixture was treated carefully with ethyl acetate, then with ice-water and filtered over "Speedex" under suction. The filtrate was extracted three times with ethyl acetate, the organic phases washed twice with water, dried over sodium sulphate and evaporated to dryness on a rotary evaporator. After chromatography of the crude product on 1 kg of silica gel (0.06—0.2 mm) with hexane/ethyl acetate (7:1) as the eluant, there was obtained 13-ethyl - 3 - methoxy - D - homogona-1,3,5(10),16 - tetraen - 17aβ - ol; melting point 138°—139°C (from ether); $[\alpha]_{589}^{25}=+18°$ (c=0.099 in dioxane).

c) A solution of 9 g of 13 - ethyl - 3-methoxy - D - homogona - 1,3,5(10),16-tetraen - 17aβ - ol in 100 ml of absolute tetrahydrofuran and 100 ml of tert.butanol was added dropwise within 20 minutes to 250 ml of absolute liquid ammonia at −33°C. 4.5 g of sodium were added portionwise to the milky suspension. The dark-blue mixture was stirred for 4.5 hours at −33°C, treated carefully with 50 ml of methanol and freed from ammonia by slowly warming to room temperature. The mixtures was poured into ice-water and extracted three times with dichloromethane. The organic phases were back-washed twice with water, dried over sodium sulphate and evaporated to dryness on a rotary evaporator. There

was obtained 13 - ethyl - 3 - methoxy - D-homogona - 2,5(10),16 - trien - 17aβ - ol; melting point 166°—170°C (from dichloromethane).

c) A solution of 1 g of 13 - ethyl - 3-methoxy - D - homogona - 2,5(10),16 - trien-17aβ - ol in 100 ml of benzene was treated with a suspension of 15 g of silver carbonate on "Speedex" in ca 100 ml of benzene and the mixture was heated at reflux under argon for 48 hours. The mixture was filtered, the filtrate evaporated and the residue chromatographed on 30 g of Alox neutral (activity III) using benzene for the elution, there being obtained 13 - ethyl - 3 - methoxy - D - homogona-2,5(10),16 - trien - 17a - one; melting point 168°—172°C.

e) A solution of 0.9 g of crude 13 - ethyl-3 - methoxy - D - homogona - 2,5(10),16-trien - 17a - one in 20 ml of absolute tetrahydrofuran was added to a suspension of ethynylmagnesium bromide prepared from 1 g of magnesium shavings, 4 ml of ethyl bromide and excess dry acetylene in 30 ml of tetrahydrofuran. The mixture was stirred under acetylene for 20 hours at 25°C, carefully decomposed with ice-water and filtered over "Speedex" under suction. The filtrate was extracted three times with ether, the organic phases washed with water, dried over magnesium sulphate and evaporated to dryness on a rotary evaporator to give 13 - ethyl-3 - methoxy - D - homo - 18,19 - dinor-17aα - pregna - 2,5(10),16 - trien - 20 - yn-17a - ol.

C) Preparation of 13 - ethyl - 17a - hydroxy-D - homo - 18,19 - dinor - 17aα - pregna-5(10),16 - dien - 20 - yn - 3 - one ethyleneketal.

a) A suspension of 3.1 g of 13 - ethyl - 3-methoxy - D - homogona - 2,5(10),16 - trien-17aβ - ol in 30 ml of dichloromethane and 25 ml of ethyleneglycol was reduced to a volume of ca 30 ml on a rotary evaporator and treated with 15 ml of glacial acetic acid. After stirring for 18 hours under argon at 25°C, the homogeneous solution was poured into ice-cold aqueous 3-N sodium hydroxide and the alkaline phase extracted three times with ether. The organic phases were washed three times with water, dried over magnesium sulphate and concentrated to dryness on a rotary evaporator. After chromatography on 120 g of silica gel (0.06—0.2 mm) with hexane/ethyl acetate (5:1) as the eluant, there was obtained amorphous 13 - ethyl - 17aβ - hydroxy - D-homogona - 5(10),16 - dien - 3 - one ethyleneketal.

b) A solution of 3.68 g of 13 - ethyl - 17aβ-hydroxy - D - homogona - 5(10),16 - dien-3 - one ethyleneketal in 60 ml of pyridine was treated at 5°C with 30 ml of a 1 molar solution of chromium trioxide in pyridine/water (10:1). After stirring for 18 hours at 25°C, the mixture was treated with ice-water and ether, filtered over "Speedex" under a vacuum and the aqueous phase of the filtrate extracted three times with ether. The organic phases were washed three times with water, dried over magnesium sulphate and evaporated on a rotary evaporator. After chromatography on 100 g of silica gel (0.06—0.02 mm) with hexane/ethyl acetate as the eluant, there was obtained 13 - ethyl - D - homogona-5(10),16 - diene - 3,17a - dione - 3 - ethylene - ketal; melting point 86°—88°C (from ether); $[\alpha]_{589}^{25} = +52°$ (c=0.105 in dioxane).

c) A solution of 2.6 g of 13 - ethyl - D-homogona - 5(10),16 - diene - 3,17a - dione 3 - ethyleneketal in 30 ml of absolute tetrahydrofuran was added to a suspension of ethynylmagnesium bromide prepared from 2 g of magnesium shavings, 8 ml of ethyl bromide and excess dry acetylene in 100 ml of tetrahydrofuran. The mixture was stirred under acetylene at 25°C for 20 hours, carefully decomposed with ice-water, covered with ether and converted into a homogeneous two-phase system by the addition of aqueous 3-N sulphuric acid. The aqueous phase was extracted three times with ether, the organic extracts washed once with aqueous bicarbonate solution and once with water, dried over magnesium sulphate and evaporated to dryness on a rotary evaporator. There was obtained crude 13 - ethyl - 17a - hydroxy - D - homo - 18,19-dinor - 17aα - pregna - 5(10),16 - dien - 20-yn - 3 - one ethyleneketal in the form of a yellow foam.

D) Preparation of 17aβ - hydroxy - D-homooestra - 5(10),16 - dien - 3 - one ethylene ketal.

13.3 ml of a ca 0.75-M solution of diisobutylaluminium hydride in toluene were added at 0°C with stirring under argon to a solution of 3.3 g of D - homooestra - 5(10),16-diene - 3,17a - dione 3 - ethyleneketal in 50 ml of benzene. After stirring for 45 minutes at 0°C, the mixture was poured on to ice-water and extracted three times with ether. The organic phases were back-washed twice with water, dried over sodium sulphate and concentrated on a rotary evaporator. Crystallisation from ether followed by chromatography of the mother liquor on silica gel yielded respectively 2.85 g and 0.37 g of 17aβ - hydroxy - D - homooestra - 5(10),16-dien - 3 - one ethyleneketal; melting point 166°—168°C.

E) Preparation of 13 - ethyl - 17aβ-hydroxy - D - homogona - 5(10),16 - dien-3 - one 3 - ethyleneketal.

13.3 ml of a ca 0.75-M solution of diisobutylaluminium hydride in toluene were added at 0°C with stirring under argon to a solution of 3.4 g of 13 - ethyl - D - homogona - 5(10),16 - diene - 3,17a - dione 3 - ethylene-

ketal in 50 ml of benzene. After stirring for 60 minutes at 0°C, the mixture was poured on to ice-water and extracted three times with ether. The organic phases were washed twice with water, dried over sodium sulphate and concentrated on a rotary evaporator. After chromatography on silica gel, there was obtained 3.2 g of amorphous 13 - ethyl - 17$\alpha\beta$-hydroxy - D - homogona - 5(10),16 - dien-3 - one 3 - ethyleneketal.

The D-homosteroids of formula I possess a hormonal activity, i.e. a strongly gestagenic and ovulation-inhibitory activity. They can be used, for example, as fertility inhibitors or cycle regulators. For this, dosages of 0.01—0.1 mg/kg may be administered. Furthermore, an androgenic activity has been observed, especially in D-homosteroids of formula I wherein $R^{17a\alpha}$ represents a hydrogen atom.

The D-homosteroids of formula I can be used in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier which 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 or petroleum jelly. 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 following Examples illustrate the present invention:

Example 1

A solution of 3.9 g of crude 3 - methoxy-D - homo - 19 - nor - 17aα - pregna-2,5(10),16 - trien - 20 - yn - 17a - ol in 9 ml of methanol and 50 ml of chloroform was treated with 1.8 g of oxalic acid in 50 ml of water. After stirring at 25°C for 3 hours, the mixture was poured on to an ice-cold aqueous bicarbonate solution, the methanol was removed on a rotary evaporator and the aqueous phase was extracted three times with ether/ethyl acetate (1:1). The organic phases were washed twice with water, dried over sodium sulphate and concentrated to dryness on a rotary evaporator. After chromatography on 250 g of Alox (neutral III) with dichloromethane as the eluant, there was obtained 17a - hydroxy - D - homo - 19 - nor - 17aα-pregna - 5(10),16 - dien - 20 - yn - 3 - one; melting point 182°—184°C (from hexane); $[\alpha]_{589}^{25} = -31°$C (c=0.100 in dioxane).

Example 2

A solution of 3.2 g of crude 3 - methoxy-D - homo - 19 - nor - 17aα - pregna 2,5(10),16 - trien - 20 - yn - 17a - ol in 40 ml of methanol was treated with 1.6 ml of concentrated hydrochloric acid and with 2 ml of water and kept at 25°C for 18 hours. The mixture was poured on to brine, extracted three times with dichloromethane, the organic phases were washed once with bicarbonate solution, dried over sodium sulphate and concentrated to dryness on a rotary evaporator. After chromatography on 150 g of Alox (neutral III) with hexane/ethyl acetate (4:1) as the eluant, there was obtained 17a - hydroxy-D - homo - 19 - nor - 17aα - pregna - 4,16-dien - 20 - yn - 3 - one; melting point 190°—191°C; $[\alpha]_{589}^{25} = -202°$ (c=0.102 in dioxane).

Example 3

A solution of 3 g of crude 13 - ethyl-17a hydroxy - D - homo - 18,19 - dinor-17aα - pregna - 5(10),16 - dien - 20 - yn - 3-one ethylene - ketal in 40 ml of methanol was treated with 0.5 ml of concentrated hydrochloric acid and 1 ml of water. After standing at 25°C for 2.5 hours, the mixture was neutralised with an aqueous bicarbonate solution, the methanol was removed on a rotary evaporator and the aqueous residue was extracted with dichloromethane. The organic phases were washed with water, dried over sodium sulphate and concentrated to dryness on a rotary evaporator. After chromatography on 100 g of Alox (neutral II) with dichloromethane as the eluant, there was obtained 13-ethyl - 17a - hydroxy - D - homo - 18,19-dinor - 17aα - pregna - 4,16 - dien - 20 - yn-3 - one; melting point 227°—230°C (from dichloromethane/methanol); $[\alpha]_{589}^{25} = -197°$ (c=0.072 in dioxane).

Example 4

A solution of 0.9 g of crude 13 - ethyl-3 - methoxy - D - homo - 18,19 - dinor-17aα - pregna - 2,5(10)16 - trien - 20 - yn-17a - ol in 20 ml of methanol was treated with 0.4 ml of concentrated hydrochloric acid and 1 ml of water. After 4 hours, the mixture was worked up as described in Example 3. There was obtained 13 - ethyl - 17a-hydroxy - D - homo - 18,19 - dinor - 17aα-pregna - 4,16 - dien - 20 - yn - 3 - one.

Example 5

A suspension of 3.2 g of 17aβ - hydroxy-D - homooestra - 5(10),16 - dien - 3 - one ethyleneketal in 15 ml of methanol was treated with 4 ml of 1-N and with 0.4 ml of concentrated aqueous hydrochloric acid and the mixture stirred at 0°C for 15 hours, a homogeneous solution resulting. The methanol was evaporated on a rotary evaporator, the residue was treated with ice-water and then extracted three times with dichloromethane. After washing with bicarbonate solution, drying over sodium sulphate and concentration on a rotary evaporator, the crude product obtained was adsorbed on 100 g of silica gel (0.06-0.2 mm). Elution with dichloromethane/1% ether

yielded 2.5 g of 17aβ - hydroxy - D - homooestra - 4,16 - dien - 3 - one; melting point 132°C—133°C; $[\alpha]_{589}^{25} = +29°$ (c=0.100 in dioxane).

Example 6

A solution of 3 g of 3 - methoxy - D-homooestra - 2,5(10),16 - trien - 17aβ - ol in 15 ml of methanol was treated with 30 ml of 1-N aqueous hydrochloric acid and kept at 25°C for 15 hours. The methanol was evaporated on a rotary evaporator and the aqueous residue extracted three times with dichloromethane. The organic phases were washed with bicarbonate solution, dried over sodium sulphate and concentrated on a rotary evaporator. There were obtained 2.8 g of 17aβ - hydroxy - D - homooestra - 4,16-dien - 3 - one; melting point 132°—133°C.

Example 7

A solution of 3.14 g of 13 - ethyl - 3-methoxy - D - homogona - 2,5(10),16 - trien-17aβ - ol in 150 ml of methanol was treated with 10 ml of 1-N and with 3 ml of concentrated aqueous hydrochloric acid and stirred at 25°C for 12 hours. The methanol was evaporated on a rotary evaporator and the aqueous residue extracted three times with dichloromethane. The organic phases were washed with bicarbonate solution, dried over sodium sulphate and concentrated on a rotary evaporator. There were obtained 2.9 g of 13 - ethyl - 17aβ - hydroxy - D - homogona - 4,16 - dien - 3 - one; melting point 191°—192°C.

Example 8

A suspension of 3.2 g of 13 - ethyl - 17aβ-hydroxy - D - homogona - 5(10),16 - dien-3 - one in 20 ml of methanol was treated with 5 ml of 1-N and 0.3 ml of concentrated aqueous hydrochloric acid and stirred for 2 hours. The homogeneous solution was kept at +5°C for 2.5 days, after which 0.93 g of crystalline 13 - ethyl - 17aβ - hydroxy - D - homogona - 4,16 - dien - 3 - one had separated. After the usual working-up of the filtrate and chromatography on silica gel, there were obtained a further 1.0 g of 13 - ethyl - 17aβ-hydroxy - D - homogona - 4,16 - dien - 3-one; melting point 191°—192°C; $[\alpha]_{589}^{25} = +12°$ (c=0.101 in dioxane).

Example 9

12 ml of a ca 2-M ethereal solution of n-butyllithium were added while stirring under argon at −20°C to a solution of 1.16 g of trans-1,2-dichloroethylene in 20 ml of ether. After stirring at −20°C for 30 minutes a solution of 1 g of 13 - ethyl - D - homogona-5(10),16 - diene - 3,17a - dione 3 - ethylene-ketal in 20 ml of ether was added with stirring and the mixture stirred for 2 hours at 0°C and for 1.5 hours at 25°C. The mixture was poured into an ice-cold aqueous ammonium chloride solution and extracted three times with ether. The organic phases were washed with water, dried over sodium sulphate and concentrated on a rotary evaporator. The 1.5 g of crude substance obtained were crystallised from dichloromethane/ether to give 0.48 g of 13 - ethyl - 21 - chloro-17a - hydroxy - D - homo - 18,19 - dinor-17aα - pregna - 5(10),16 - dien - 20 - yn - 3-one ethylene-ketal, a further 0.47 g of same being obtained after chromatography of the mother liquor on silica gel; melting point 191°—192°C; $[\alpha]_{589}^{25} = -143°$ (c=0.102 in dioxane).

A solution of 0.5 g of 13 - ethyl - 21-chloro - 17a - hydroxy - D - homo - 18,19-dinor - 17aα - pregna - 5(10),16 - dien - 20-yn - 3 - one ethyleneketal in 20 ml of methanol was treated with 10 ml of 1-N aqueous hydrochloric acid and stirred at 25°C for 24 hours. After removal of the methanol on a rotary evaporator, the residue was partitioned between ether and aqueous bicarbonate solution, the ethereal phases were washed with water, dried over sodium sulphate and concentrated on a rotary evaporator. Crystallisation from ether/hexane yielded 0.35 g of 13-ethyl - 21 - chloro - 17a - hydroxy - D-homo - 18,19 - dinor - 17aα - pregna - 4,16-dien - 20 - yn - 3 - one; melting point 198°—199°C; $[\alpha]_{589}^{25}$.

Example 10

7.5 ml of a ca 1.5-M solution of methyllithium were added with stirring under argon at 0°C to a solution of 3.4 g of 13 - ethyl-D - homogona - 5(10),16 - diene - 3,17a-dione 3-ethyleneketal in 20 ml of tetrahydrofuran. After stirring at 0°C for 1 hour the mixture was poured into ice-water and extracted four times with ether. The ethereal phases were washed with water, dried over sodium sulphate and evaporated on a rotary evaporator. The 4 g of crude substance obtained were adsorbed on 150 g of silica gel (0.06—0.2 mm) and eluted with dichloromethane to give 2.8 g of amorphous 13-ethyl-17aβ - hydroxy 17a - methyl - D - homogona-5(10),16 - dien - 3 - one ethyleneketal.

A solution of 2.5 g of 13 - ethyl - 17aβ-hydroxy - 17a - methyl - D - homogona-5(10),16 - dien - 3 - one ethyleneketal in 30 ml of methanol was treated with a solution of 0.25 g of oxalic acid in 10 ml of water and kept at 5°C for 4 days and at 25°C for 24 hours. The mixture was made slightly alkaline with an aqueous ammonia solution, the methanol was removed on a rotary evaporator and the aqueous residue was extracted with dichloromethane. The organic phases were washed with water, dried over sodium sulphate and evaporated on a rotary evaporator. The residue was adsorbed on 150 g of silica gel (0.06—0.2 mm) and eluted with

benzene to give 0.12 g of 13 - ethyl - 17aβ-hydroxy - 17a - methyl - D - homogona-4,16 - dien - 3 - one; melting point 159°—160°C; $[\alpha]=_{589}{}^{25}=-54°$ (c=0.099 in dioxane).

The following Example illustrates a pharmaceutical preparation containing a D-homosteroid of formula I:

Example A

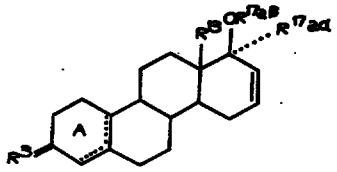
A tablet for oral administration of the following composition can be manufactured:

13 - Ethyl - 17a - hydroxy-D-homo-18,19-dinor-17aα pregna - 4,16 - dien - 20-yn - 3 - one	1 mg
Lactose	60 mg
Starch	37 mg
Talcum	1.8 mg
Magnesium stearate	0.2 mg
Total weight	100 mg

The word "Speedex" used herein is a Trade Mark.

WHAT WE CLAIM IS:—

1. A D-homosteroid of the general formula



(I)

wherein R^3 represents an oxo, (H,H) or (α-H, β-O-acyl) grouping, R^{13} represents a lower alkyl group, $R^{17a\beta}$ represents a hydrogen atom or an acyl or lower alkyl group and $R^{17a\alpha}$ represents a hydrogen atom or a lower alkyl, ethynyl, 1-propynyl, vinyl, chloroethynyl, butadiynyl or propadienyl group and wherein the broken line in the A-ring denotes an additional carbon-carbon bond in the 4,5- or 5(10)-position.

2. A D-homosteroid according to claim 1, wherein R^3 represents an oxo, (H,H) or (α-H β-O-acyl) grouping, R^{13} represents a lower alkyl group, $R^{17a\beta}$ represents a hydrogen atom or an acyl or lower alkyl group and $R^{17a\alpha}$ represents an ethynyl, 1-propynyl, vinyl, chloroethynyl or propadienyl group and wherein the broken line in the A-ring denotes an additional carbon-carbon bond in the 4,5- or 5(10)-position.

3. A D-homosteroid according to claim 1 or claim 2, wherein R^3 represents an oxo group, R^{13} represents a methyl or ethyl group and the double bond in ring A is present in the 4,5-position.

4. A D-homosteroid according to claim 1 or claim 3, wherein $R^{17a\alpha}$ represents a hydrogen atom or an ethynyl, chloroethynyl or butadiynyl group and $R^{17a\beta}$ represents a hydrogen atom.

5. 17a - Hydroxy - D - homo - 19 - nor-17aα - pregna - 5(10)16 - dien - 20 - yn - 3-one.

6. 17a - Hydroxy - D - homo - 19 - nor-17aα - pregna - 4,16 - dien - 20 - yn - 3-one.

7. 13 - Ethyl - 17a - hydroxy - D - homo-18,19 - dinor - 17aα - pregna - 4,16 - dien-20 - yn - 3 - one.

8. 17aβ - Hydroxy - D - homooestra - 4,16-dien - 3 - one.

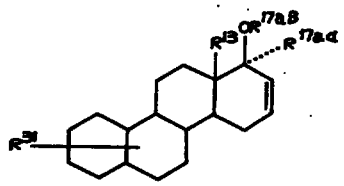
9. 13 - Ethyl - 17aβ - hydroxy - D - homogona - 4,16 - dien - 3 - one.

10. 13 - Ethyl - 21 - chloro - 17a-hydroxy - hydroxy - D - homo - 18,19 - dinor - 17aα - pregna - 4,16 - dien - 20 - yn-3 - one.

11. 13 - Ethyl - 17aβ - hydroxy - 17a-methyl - D - homogona - 4,16 - dien - 3-one.

12. A process for the manufacture of D-homosteroids of formula I given in claim 1, which process comprises

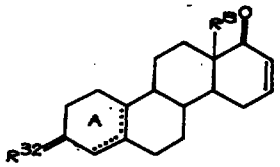
(a) hydrolysing a compound of the general formula



(II)

wherein R^{13}, $R^{17a\beta}$ and $R^{17a\alpha}$ have the significance given in claim 1 and R^{31} represents a moiety hydrolysable to form a 3-keto-Δ^4 or 3-keto-$\Delta^{5(10)}$ grouping, or

(b) reacting a compound of the general formula



(III)

wherein R^{13} and the broken line in the A-ring have the significance given in claim 1 and R^{32} represents a (H,H) or (α-H, β-O-acyl) grouping,

with an organometallic compound furnishing a lower alkyl, ethynyl, 1-propynyl, vinyl, chloroethynyl, butadiynyl or propadienyl group, or

(c) reducing the keto group in a compound of formula III given earlier in this claim to a hydroxy group.

13. A process according to claim 12, wherein a D-homosteroid as claimed in claim 2 is manufactured according to embodiment (a) or (b) of said process.

benzene to give 0.12 g of 13 - ethyl - 17aβ-hydroxy - 17a - methyl - D - homogona-4,16 -dien - 3 - one; melting point 159°—160°C; $[\alpha]=_{589}{}^{25}=-54°$ (c=0.099 in dioxane).

The following Example illustrates a pharmaceutical preparation containing a D-homosteroid of formula I:

Example A

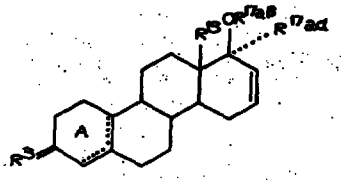
A tablet for oral administration of the following composition can be manufactured:

13 - Ethyl - 17a - hydroxy-D-homo-18,19-dinor-17aα pregna - 4,16 - dien - 20-yn - 3 - one	1 mg
Lactose	60 mg
Starch	37 mg
Talcum	1.8 mg
Magnesium stearate	0.2 mg
Total weight	100 mg

The word "Speedex" used herein is a Trade Mark.

WHAT WE CLAIM IS:—

1. A D-homosteroid of the general formula



(I)

wherein R^3 represents an oxo, (H,H) or (α-H, β-O-acyl) grouping, R^{13} represents a lower alkyl group, $R^{17a\beta}$ represents a hydrogen atom or an acyl or lower alkyl group and $R^{17a\alpha}$ represents a hydrogen atom or a lower alkyl, ethynyl, 1-propynyl, vinyl, chloroethynyl, butadiynyl or propadienyl group and wherein the broken line in the A-ring denotes an additional carbon-carbon bond in the 4,5- or 5(10)-position.

2. A D-homosteroid according to claim 1, wherein R^3 represents an oxo, (H,H) or (α-H β-O-acyl) grouping, R^{13} represents a lower alkyl group, $R^{17a\beta}$ represents a hydrogen atom or an acyl or lower alkyl group and $R^{17a\alpha}$ represents an ethynyl, 1-propynyl, vinyl, chloroethynyl or propadienyl group and wherein the broken line in the A-ring denotes an additional carbon-carbon bond in the 4,5- or 5(10)-position.

3. A D-homosteroid according to claim 1 or claim 2, wherein R^3 represents an oxo group, R^{13} represents a methyl or ethyl group and the double bond in ring A is present in the 4,5-position.

4. A D-homosteroid according to claim 1 or claim 3, wherein $R^{17a\alpha}$ represents a hydrogen atom or an ethynyl, chloroethynyl or butadiynyl group and $R^{17a\beta}$ represents a hydrogen atom.

5. 17a - Hydroxy - D - homo - 19 - nor-17aα - pregna - 5(10)16 - dien - 20 - yn - 3-one.

6. 17a - Hydroxy - D - homo - 19 - nor-17aα - pregna - 4,16 - dien - 20 - yn - 3-one.

7. 13 - Ethyl - 17a - hydroxy - D - homo-18,19 - dinor - 17aα - pregna - 4,16 - dien-20 - yn - 3 - one.

8. 17aβ - Hydroxy - D - homooestra - 4,16-dien - 3 - one.

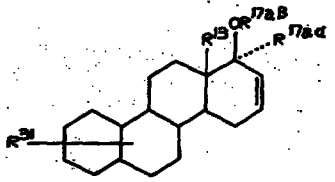
9. 13 - Ethyl - 17aβ - hydroxy - D - homogona - 4,16 - dien - 3 - one.

10. 13 - Ethyl - 21 - chloro - 17a-hydroxy - hydroxy - D - homo - 18,19 - dinor - 17aα - pregna - 4,16 - dien - 20 - yn-3 - one.

11. 13 - Ethyl - 17aβ - hydroxy - 17a-methyl - D - homogona - 4,16 - dien - 3-one.

12. A process for the manufacture of D-homosteroids of formula I given in claim 1, which process comprises

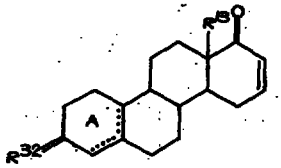
(a) hydrolysing a compound of the general formula



(II)

wherein R^{13}, $R^{17a\beta}$ and $R^{17a\alpha}$ have the significance given in claim 1 and R^{31} represents a moiety hydrolysable to form a 3-keto-Δ^4 or 3-keto-$\Delta^{5(10)}$ grouping, or

(b) reacting a compound of the general formula



(III)

wherein R^{13} and the broken line in the A-ring have the significance given in claim 1 and R^{32} represents a (H,H) or (α-H, β-O-acyl) grouping,

with an organometallic compound furnishing a lower alkyl, ethynyl, 1-propynyl, vinyl, chloroethynyl, butadiynyl or propadienyl group, or

(c) reducing the keto group in a compound of formula III given earlier in this claim to a hydroxy group.

13. A process according to claim 12, wherein a D-homosteroid as claimed in claim 2 is manufactured according to embodiment (a) or (b) of said process.

14. A process according to claim 12 or claim 13, wherein a D-homosteroid as claimed in claim 3 is manufactured.

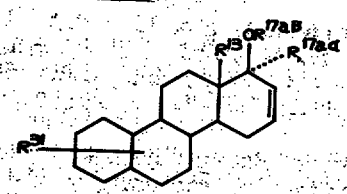
15. A process according to claim 12 or claim 14, wherein a D-homosteroid as claimed in claim 4 is manufactured.

16. A process for the manufacture of D-homosteroids of formula I given in claim 1, substantially as hereinbefore described with reference to any one of Examples 1 to 10 inclusive.

17. A D-homosteroid of formula I given in claim 1, when manufactured by the process claimed in any one of claims 12 to 16 inclusive.

18. A pharmaceutical preparation containing a D-homosteroid of formula I as claimed in claim 1 in association with a compatible pharmaceutical carrier.

19 A compound of the general formula



(II)

wherein R^{13} represents a lower alkyl group, $R^{17a\beta}$ represents a hydrogen atom, $R^{17a\alpha}$ represents a hydrogen atom or a lower alkyl, ethynyl, 1-propynyl, vinyl, chloroethynyl, butadiynyl or propadienyl group and R^{31} represents a 3,3 - alkylenedioxy - $\Delta^{5(10)}$ or 3-alkoxy - $\Delta^{2,5(10)}$ grouping.

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