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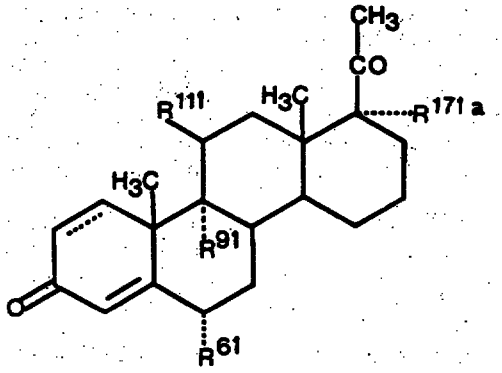
(19)

(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 pharmaceutical preparations having inflammation-inhibiting activity and containing a D-homosteroid of the pregnane series and with a process for the manufacture of said pharmaceutical preparations.

In accordance with the present invention it has been found that D-homosteroids of the pregnane series of the general formula



(I')

wherein the broken line in the 1,2-position denotes an optional carbon-carbon bond; R^{61} represents a hydrogen, fluorine or chlorine atom or a methyl group; R^{91} represents a hydrogen, fluorine, chlorine or bromine atom; R^{171a} represents a hydroxy or acyloxy group and R^{111} represents a hydroxy or acyloxy group or a fluorine or chlorine atom with the proviso that, in the case of 9,11-dihalo compounds, the atomic number of R^{111} must be less than or equal to that of R^{91}, have inflammation-inhibiting activity.

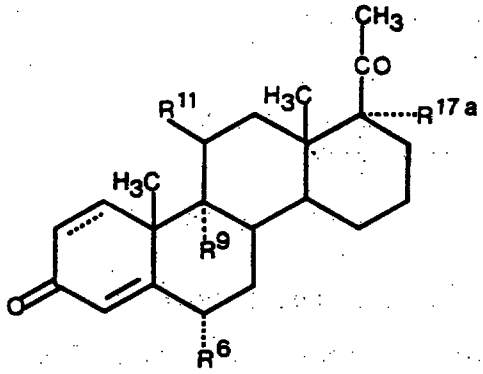
The present invention is based on the foregoing finding and is concerned with with pharmaceutical preparations having inflammation-inhibiting activity and containing as essential active ingredient a D-homosteroid of formula I', and with a process for the manufacture of these pharmaceutical preparations, which process comprises mixing a D-homosteroid of formula I' as essential active ingredient with a pharmaceutically acceptable carrier material.

The following D-homosteroids of formula I'

11β, 17a - dihydroxy - D - homopregn - 4 - ene - 3,20 - dione,

11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione and 6α - fluoro - 11β,17a - dihydroxy - D - homopregn - 4 - ene - 3,20 - dione and their preparation are described in Belgian Patent Specification No. 797 412.

Among the D-homosteroids of formula I', those of the general formula



(I)

wherein the broken line in the 1,2-position denotes an optional carbon-carbon bond; R^6 represents a hydrogen, fluorine or chlorine atom or a methyl group; R^9 represents a hydrogen, fluorine, chlorine or bromine atom; R^{11} represents a hydroxy or acyloxy group or a fluorine or chlorine atom and R^{17a} represents a hydroxy or acyloxy group, with the proviso that, in the case of 9,11-dihalo compounds, the atomic number of R^{11} must be less than or equal to that of R^9 and, where R^6 represents a hydrogen atom in a 11,17a-dihydroxy compound or where R^6 represents a fluorine atom in a 11,17a - dihydroxy - 4 - ene compound, R^9 must represent a fluorine, chlorine or bromine atom, are preferred in the practice of the present invention.

An acyloxy group can be derived from a saturated or unsaturated aliphatic carboxylic acid, a cycloaliphatic, araliphatic or an aromatic carboxylic acid preferably containing up to 15 carbon atoms. Examples of such acids are formic acid, acetic acid, trifluoroacetic acid, pivalic acid, propionic acid, butyric acid, caproic acid, oenanthic acid, undecylenic acid, oleic acid, cyclopentylpropionic acid, cyclohexylpropionic acid, phenylacetic acid and benzoic acid. Especially preferred acyloxy groups are alkanoyloxy groups containing from 1 to 7 carbon atoms.

A preferred group of D-homosteroids of formula I comprises those in which R^{11} represents a hydroxy group. Moreover, those D-homosteroids of formula I in which R^9 represents a hydrogen, fluorine or chlorine atom are preferred. D-homosteroids of formula I containing a double bond in the 1,2-position are also preferred.

Examples of D-homosteroids of formula I for use in the present invention are:

11β - Butyryloxy - 17a - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,

11β - trifluoroacetoxy - 17a - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,

17a - butyryloxy - 11β - trifluoroacetoxy - D - homopregna - 1,4 - diene - 3,20 - dione,

17a - butyryloxy - 11β - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,

6α - fluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,

6α - chloro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,

6α-fluoro - 17a - hydroxy - 11β - trifluoroacetoxy - D - homopregna - 1,4 - diene - 3,20 - dione,

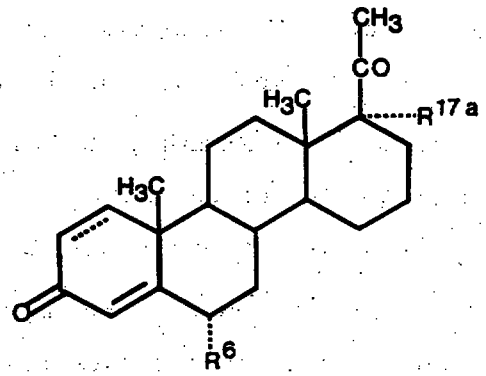
17a - butyryloxy - 6α - fluoro - 11β - trifluoroacetoxy - D - homopregna - 1,4 - diene - 3,20 - dione,

17a - butyryloxy - 6α - fluoro - 11β - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,

17a - valeroyloxy - 6α - chloro - 11β - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,

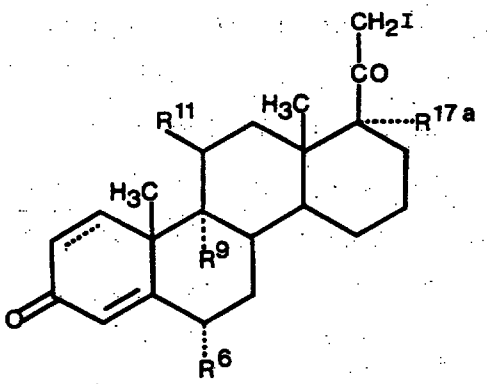
9 - fluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,
9 - chloro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,
9 - bromo - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,
9 - fluoro - 17a - hydroxy - 11β - propionyloxy - D - homopregna - 1,4 - diene - 3,20 - dione,
17a - butyryloxy - 9 - fluoro - 11β - propionyloxy - D - homopregna - 1,4 - diene - 3,20 - dione,
9 - fluoro - 17a - hydroxy - 11β - trifluoroacetoxy - D - homopregna - 1,4 - diene - 3,20 - dione,
17a - butyryloxy - 9 - fluoro - 11β - trifluoroacetoxy - D - homopregna - 1,4 - diene - 3,20 - dione,
17a - butyryloxy - 9 - fluoro - 11β - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,
9 - chloro - 11β - hydroxy - 17a - propionyloxy - D - homopregna - 1,4 - diene - 3,20 - dione,
9 - chloro - 11β - fluoro - 17a - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,
17a - butyryloxy - 9 - chloro - 11β - fluoro - D - homopregna - 1,4 - diene - 3,20 - dione,
11β,17a - dihydroxy - 6α - methyl - D - homopregn - 4 - ene - 3,20 - dione,
17a - butyryloxy - 11β - hydroxy - 6α - methyl - D - homopregn - 4 - ene - 3,20 - dione,
11β,17a - dihydroxy - 6α - methyl - D - homopregna - 1,4 - diene - 3,20 - dione,
17a - butyryloxy - 11β - hydroxy - 6α - methyl - D - homopregna - 1,4 - diene - 3,20 - dione,
6α - methyl - 11β,17a - dipropionyloxy - D - homopregna - 1,4 - diene - 3,20 - dione,
9 - fluoro - 11β,17a - dihydroxy - 6α - methyl - D - homopregn - 4 - ene - 3,20 - dione,
17a - butyryloxy - 9 - fluoro - 11β - hydroxy - 6α - methyl - D - homopregn - 4 - ene - 3,20 - dione,
9 - fluoro - 11β,17a - dihydroxy - 6α - methyl - D - homopregna - 1,4 - diene - 3,20 - dione,
9 - fluoro - 11β - hydroxy - 6α - methyl - 17a - valeroyloxy - D - homopregna - 1,4 - diene - 3,20 - dione,
11β,17a - dibutyryloxy - 9 - chloro - 6α - methyl - D - homopregna - 1,4 - diene - 3,20 - dione,
9 - chloro - 6α - fluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,
6α,9 - difluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,
6α,9 - difluoro - 11β - hydroxy - 17a - propionyloxy - D - homopregna - 1,4 - diene - 3,20 - dione,
6α - chloro - 9 - fluoro - 11β,17a - divaleroyloxy - D - homopregna - 1,4 - diene - 3,20 - dione,
9 - chloro - 11β - fluoro - 17a - hydroxy - 6α - methyl - D - homopregna - 1,4 - diene - 3,20 - dione,
9 - chloro - 11β - fluoro - 6α - methyl - 17a - valeroyloxy - D - homopregna - 1,4 - diene - 3,20 - dione,
9,11β - dichloro - 6α - methyl - 17a - propionyloxy - D - homopregn - 4 - ene - 3,20 - dione,
9 - chloro - 6α,11β - difluoro - 17a - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,
17a - butyryloxy - 9 - chloro - 6α,11β - difluoro - D - homopregna - 1,4 - diene - 3,20 - dione,
6α,9,11β - trichloro - 17a - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione,
6α,9 - dichloro - 11β - fluoro - 17a - valeroyloxy - D - homopregna - 1,4 - diene - 3,20 - dione.

The D-homosteroids of formula I may be prepared by
(a) hydroxylating a D-homosteroid of the general formula



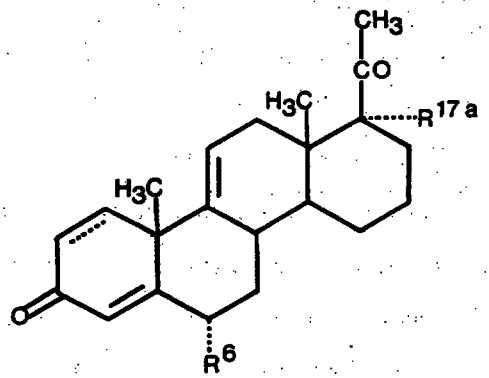
(II)

in the 11-position by means of microorganisms or enzymes produced therefrom, or
(b) replacing the iodine atom in a D-homosteroid of the general formula



(III)

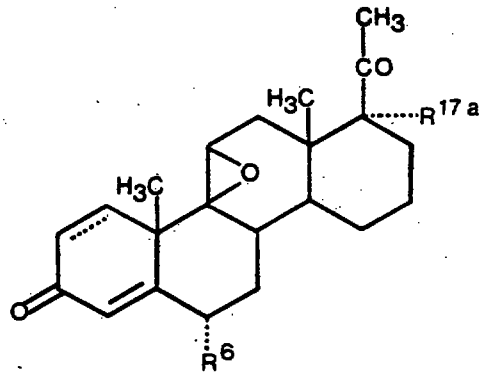
by a hydrogen atom,
or
(c) dehydrogenating a 1,2-saturated D-homosteroid of formula I in the 1,2-position,
or
(d) adding Cl_2, ClF, BrF, BrCl or hypochlorous or hypobromous acid to the 9,11-double bond of a D-homosteroid of the general formula



(IV),

or

(e) treating a D-homosteroid of the general formula



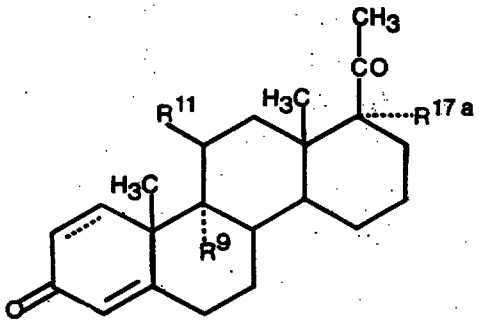
(V)

with hydrogen fluoride, hydrogen chloride or hydrogen bromide, or

(f) saponifying an acyloxy group in a D-homosteroid of formula I in which at least one of R^{17a} and R^{11} represents an acyloxy group, or

(g) isomerising a 6β - (fluoro, chloro or methyl) - D - homosteroid corresponding to formula I to the 6α - isomer, or

(h) fluorinating or chlorinating a D-homosteroid of the general formula

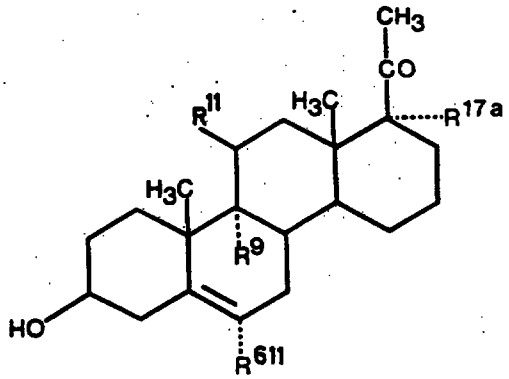


(VI)

in the 6-position, or

(i) acylating an 11β- or 17a-hydroxy group in a D-homosteroid of formula I in which at least one of R^{11} and R^{17a} represents a hydroxy group, or

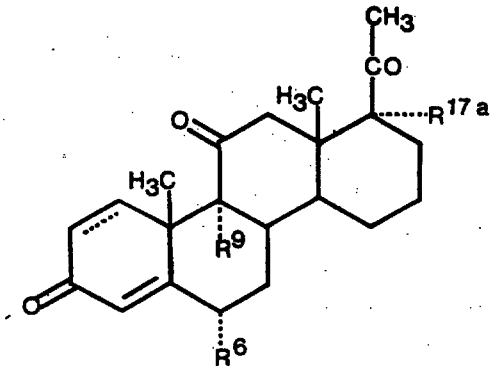
(j) oxidising the 3-hydroxy-Δ^5 - grouping in a D - homosteroid of the general formula



(VIII)

to the 3-keto-Δ^4-grouping, or

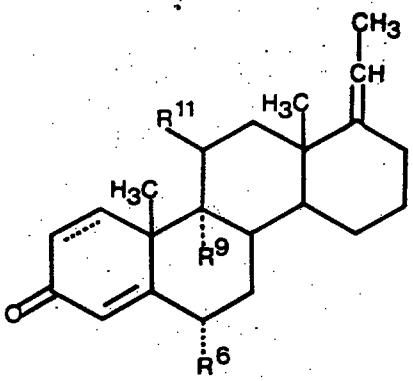
(k) reducing the 11-keto group in a D-homosteroid of the general formula



(IX)

to the hydroxy group with protection of the 3- and 20-keto group, or

(l) oxidising the 17a(20)-double bond in a D-homosteroid of the general formula

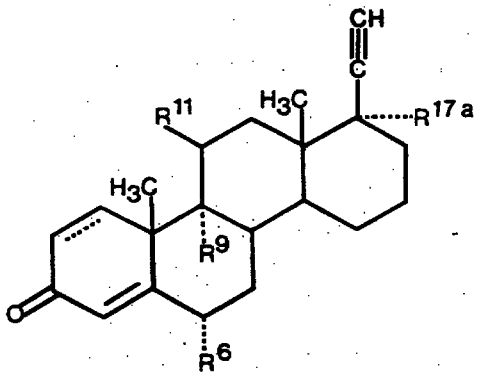


(X)

to the hydroxyketone grouping, or

(m) methylating a D-homosteroid of formula VI in the 6-position, or

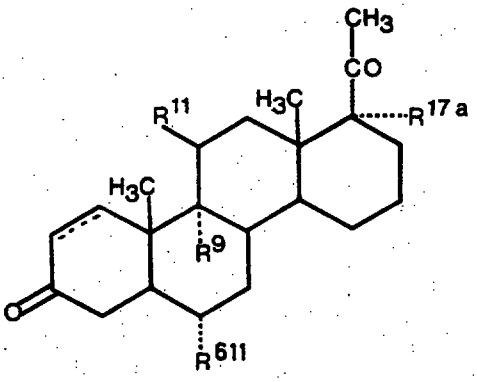
(n) converting the 17β-ethynyl group in a D-homosteroid of the general formula



(XI)

into the acetyl group, or

(o) dehydrogenating a D-homosteroid of the general formula



(XII)

in the 4-position;

in which formulae R^6, R^9, R^{11}, R^{17a} and the broken line in the 1,2-position have the significance given earlier and R^{611} represents a hydrogen atom or a methyl group.

The hydroxylation of a D-homosteroid of formula II in accordance with process (a) can be carried out according to methods known per se for the microbial 11-hydroxylation of steroids. For this 11-hydroxylation there can be used microorganisms of the taxonomic groups Fungi and Schizomycetes, especially of the sub-groups Ascomycetes, Phycomycetes, Basidiomycetes and Actinomycetales. There can also be used mutants produced in a chemical manner (e.g. by treatment with nitrite) or in a physical manner (e.g. by irradiation) as well as cell-free enzyme preparations obtained from the microorganisms. Especially suitable microorganisms for the 11β-hydroxylation are those of the genera Curvularia (e.g. C. lunata NRRL 2380 and NRRL 2178; ATCC 13633, 13432, 14678, IMI 77007, IFO 2811), Absidia (e.g. A. coerula IFO 4435), Colletotrichum (e.g. C. pisi ATCC 12520), Pellicolaria (e.g. P. filamentosa IFO 6675), Streptomyces (e.g. S. Fradiae ATCC 10745), Cunninghamella (e.g. C. bainieri ATCC 9244, C. verticellata ATCC 8983, C. elegans NRRL 1392 and ATCC 9245, C. blakesleeana ATCC 8688, 8688a, 8688b, 8983 and C. echinulata ATCC 8984), Pycnosporium (e.g. sp. ATCC 12231), Verticillium (e.g. V. theobromae CBS 39858), Aspergillus (e.g. A. quadrilieatus JAM 2763), Trichothecium (e.g. T. roseum ATCC 12519) and Phoma (e.g. sp. ATCC 13145).

The replacement of the iodine atom in a D-homosteroid of formula III by a hydrogen atom in accordance with process (b) can be carried out by treatment with a reduction agent such as sodium hydrogen sulphite.

The 1,2,-dehydrogenation of a 1,2-saturated D-homosteroid of formula I in accordance with process (c) can be carried out in a manner known per se; for example, in a microbiological manner or using a dehydrogenating agent such as iodine pentoxide, periodic acid, selenium dioxide, 2,3-dichloro-5,6-dicyanobenzoquinone, chloranil 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).

In carrying out processes (d) and (e) a D-homosteroid of formula IV or V is conveniently dissolved in a suitable solvent (e.g. an ether such as tetrahydrofuran or dioxan, a chlorinated hydrocarbon such as methylene chloride or chloroform, or a ketone such as acetone) and left to react with the reagent which is added thereto. Hypochlorous or hypobromous acid is conveniently generated in situ; for example, from N-bromo- or N-chloroamides or imides such as N-chlorosuccinimide or N-bromoacetamide and a strong acid, preferably perchloric acid. Process (e) is preferred for the preparation of 9 - fluoro - 11 - hydroxy - D - homosteroids of formula I.

The saponification of an acyloxy group in a D-homosteroid of formula I in accordance with process (f) can be carried out in a manner known per se; for example, with aqueous-methanolic potassium carbonate solution or sodium hydrogen carbonate solution.

The isomerisation of 6β - (fluoro, chloro or methyl) - D - homosteroid corresponding to formula I, especially a 6β - (fluoro or chloro) - D - homosteroid, in accordance with process (g) can be carried out by treatment with an acid, especially a mineral acid such as hydrochloric acid, in a solvent (e.g. dioxan or glacial acetic acid).

The fluorination or chlorination of a D-homosteroid of formula VI in the 6-position in accordance with process (h) can be carried out in a manner known per se. A 6,7-saturated D-homosteroid of formula VI can be fluorinated or chlorinated by reaction with a fluorinating or chlorinating agent such as a N-chloroamide or imide (e.g. N-chlorosuccinimide) or with elemental chlorine [see J. Am. Chem. Soc. *72*, 4534 (1950)]. This embodiment of the process is preferably carried out by converting a 6,7-saturated D-homosteroid of formula VI into a 3-enol ester or 3-enol ether (e.g. the 3-enol acetate) and reacting the 3-ester or 3-enol ether with chlorine [see J. Am. Chem. Soc. *82*, 1230 (1960)], with a N-chloroimide [see J. Am. Chem. Soc. *82*, 1230 (1960); *77*, 3827 (1955)] or with perchloryl fluoride [see J. Am Chem. Soc. *81*, 5259 (1959); Chem. and Ind. *1959*, 1317]. Trifluoromethylhypofluorite can also be used as the fluorinating agent.

Insofar as the previously described fluorination or chlorination yields an isomer mixture (i.e. a mixture of 6α and 6β-(fluoro or chloro) - D - homosteroids, the mixture can be separated into the pure isomers according to known methods such as chromatography.

The acylation of an 11β- and/or 17a-hydroxy group in a D-homosteroid of formula I in accordance with process (i) can be carried out in a manner known per se; for example, by treatment with an acylating agent such as an acyl chloride or anhydride in the presence of an acid binding agent (e.g. pyridine or triethylamine) and a suitable catalyst (e.g. p-dimethylaminopyridine) or in the presence of a strong acid catalyst (e.g. p-toluenesulphonic acid). As the solvent for the acylation there may be mentioned organic solvents which do not contain hydroxyl groups (e.g. chlorinated hydrocarbons such as methylene chloride or hydrocarbons such as benzene). When the acylation is carried out in basic medium in the presence of p-dimethylaminopyridine, then the 11β-hydroxy group can be selectively acylated in the presence of the 17a-hydroxy group.

The oxidation of the 3-hydroxy-Δ^5-grouping in a D-homosteroid of formula VIII in accordance with process (J) can be carried out according to the Oppenauer procedure (e.g. using aluminium isopropylate) or by means of oxidising agents such as chromium trioxide (e.g. Jones' reagent) or according to the Pfitzner-Moffatt procedure using dimethyl - sulphoxide/dicyclohexyl-carbodiimide (the initially obtained Δ^5-3-ketone requiring subsequent isomerisation to the Δ^4-3-ketone) or by means of pyridine/sulphur trioxide.

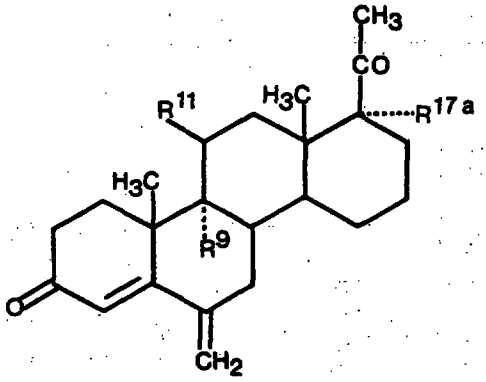
In carrying out process (k), the keto groups in the 3- and 20-positions of a D-homosteroid of formula IX are first protected (e.g. as the semicarbazone). Where a 1,2-double bond is present, the 3-keto group can also be protected by the formation of an enamine. The protecting groups can subsequently be removed by acid hydrolysis. A $\Delta^{1,4}$-3-ketone can also be converted into a $\Delta^{1,3,5}$-3-enamine using a secondary amine in the presence of titanium tetrachloride. The reduction of the 11keto group of a thus-protected D-homosteroid can be carried out using a complex metal hydride such as lithium aluminium hydride, sodium borohydride or diisobutyl aluminium hydride.

The oxidation of the 17(20)-double bond in a D-homosteroid of formula X in accordance with process (l) can be carried out, for example, with an oxidising agent such as a tertiary amine N-oxide peroxide in tert.butanol/pyridine in the presence of catalytic amounts of osmium tetroxide. Examples of tertiary amine N-oxide peroxides which can be used in this embodiment are N-methylmorpholine N-oxide peroxide and triethylamine oxide peroxide. The 17(20)-double bond can also be oxidised with an oxidising agent such as osmium tetroxide or permanganate to give a 17,20-glycol which can be further oxidised to the hydroxyketone with an oxidising agent such as chromic acid.

The methylation of a D-homosteroid of formula VI in the 6-position in accordance with process (n) can be carried out, for example, by converting a D-homosteroid of formula VI into a 3-enol ether (e.g. by treatment with an orthoformic acid ester such as ethyl orthoformate in the presence of an acid such as p-toluenesulphonic acid, if desired, with addition of the corresponding alcohol; or by treatment with a dialkoxypropane such as 2,2-dimethoxypropane in methanol/dimethylformamide in the presence of p-toluenesulphonic acid) and reacting the 3-enol ether with a tetrahalomethane (e.g. CBr_4, CCl_2Br_2 or CCl_3Br)

to give a trihalomethyl-Δ^4-3-ketone. A trihalomethyl-Δ^4-3-ketone can be dehydrohalogenated with a base such as collidine to give a dihalomethylene-Δ^4-3-ketone which can be converted by catalytic hydrogenation under mild conditions (e.g. using a $Pd/SrCO_3$ catalyst) into a 6α - methyl - Δ^4 - 3 - ketone.

Another methylation procedure consists in conveting a 1,2-saturated D-homosteroid of formula VI into a 3-enol ether as described earlier and reacting this 3-enol ether in a manner known per se to give a corresponding 6-formyl derivative, reducing the formyl group with sodium borohydride to the hydroxymethyl group and finally dehydrating the product obtained with cleavage of the enol ether, there being obtained a 6-methylene-D-homosteroid of the general formula



(VII)

wherein R^9, R^{11} and R^{17a} have the significance given earlier.

6-Methylene-D-homosteroids of formula VII can also be obtained by converting a 1,2-saturated D-homosteroid of formula VI into a 3-enamine (e.g. the 3-pyrrolidinium enamine), hydroxy-methylating the 3-enamine with formaldehyde and cleaving water from the hydroxymethylation product using an acid such as p-toluenesulphonic acid.

A 6-methylene-D-homosteroid of formula VII can be catalytically hydrogenated to give a corresponding 6-methyl-D-homosteroid of formula I in a manner known per se; for example, using a known hydrogenation catalyst.

The conversion of the 17β-ethynyl group in a D-homosteroid of formula XI into the acetyl group in accordance with process (n) can be carried out in the presence of a suitable catalyst such as p-toluenesulphonamide - mercury or with acid ion exchangers activated with mercury salts.

In accordance with process (o) a D-homosteroid of formula XII can be dehydrogenated in the 4-position or 1,4-position by bromination and subsequent dehydrobromination.

The starting materials used in the foregoing process, insofar as they are not known or insofar as their preparation is not described hereinafter, can be prepared in analogy to known methods or methods described in the Examples hereinafter.

The D-homosteroids of formula I possess inflammation-inhibiting activity and can accordingly be used, for example, for the treatment of inflammatory conditions such as eczemas.

In general, pharmaceutical preparations for internal administration can contain 0.01% to 5.0% of a D-homosteroid of formula I. The daily dosage can vary between 0.05 mg and 10.0 mg depending on the condition to be treated and the duration of the desired treatment. The amount of D-homosteroid of formula I in topical preparations lies, in general, in the range of from 0.0001 wt.% to 5 wt.%, advantageously in the range of from 0.001 wt.% to 0.5 wt.% and preferably in the range of from 0.01 wt.% to 0.25 wt.%.

The D-homosteroids of formula I can be used as medicaments 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, percutaneous or parenteral administration such as, for example, water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkyleneglycols, petroleum jelly etc. The pharmaceutical preparations can be made up, for example, as salves or 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 the variation of the osmotic pressure or buffers. They can also contain still other therapeutically valuable materials.

The following Examples illustrate the manner in which the D-homosteroids of formula I can be prepared:

Example 1

100 mg of 11β,17a - acetoxy - D - homopregn - 4 - en - 20 - yn - 3 - one and 200 mg of mercury - p - toluenesulphonamide were boiled at reflux for 20 hours in 5 ml of alcohol. The mixture was poured into dilute hydrochloric acid and extracted three times with methylene chloride. The organic phases were washed with dilute sodium chloride solution, dried and evaporated. Chromatography of the residue on silica gel gave 11β,17a - diacetoxy - D - homopregn - 4 - ene - 3,20 - dione;

UV: ε_{242}=16250

NMR: signals at

δ=1.08 ppm (S) 3H 1.24 „ (S) 3H	18—Me, 19—Me
2.02 „ (S) 3H 2.09 „ (S) 3H 2.13 „ (S) 3H	—$COCH_3$ and 2x—$OOCCH_3$
5.47 „ (m) 1H	H_{11}eq
5.70 „ (m) 1H	H_4

The starting material can be prepared as follows:

3β,17a - trihydroxy - D - homopregn - 5 - en - 20 - yne is oxidised according to the Oppenauer procedure to give 11β,17a - dihydroxy - D - homopregn - 4 - en - 20 - yn - 3 - one and this is subsequently converted in acetic acid anhydride and acetic acid in the presence of catalytic amounts of p-toluenesulphonic acid into 11β,17a-diacetoxy - D - homopregn - 4 - en - 20 - yn - 3 - one.

Example 2

1g of 11β - acetoxy - 6α - fluoro - D - homopregna - 4,17a(20) - dien - 3 - one, 22 ml of tert. butanol, 1.5 ml of pyridine, 4.3 mg of osmium tetroxide and 5.3 ml of N-methylmorpholine oxide hydrogen peroxide solution [L. Fieser, M. Fieser, Reagents for Organic Syntheses 690 (1967)] were stirred at 25°C. After 24 hours, 2.5 mg of osmium tetroxide and 3.0 ml of N-methylmorpholine oxide hydrogen peroxide solution were added. After a further 24 hours, there were added while stirring 20 ml of 2-N hydrochloric acid, 1.5 g of thiourea and 50 ml of methylene chloride. The aqueous phase was separated and extracted a further twice with methylene chloride. The methylene chloride solutions were washed with water and dilute sodium chloride solution, dried over sodium sulphate and evaporated. Chromatography of the residue on silica gel gave 11β - acetoxy - 6α - fluoro - 17a - hydroxy - D - homopregn - 4 - ene - 3,20 - dione of melting point 202°—203°C; UV: ε_{234}=15900; $[\alpha]_D$=+98° (c=0.1% in dioxan).

The starting material can be prepared as follows:

11β-Hydroxy-D-homopregna-4,17a(20)-dien-3-one is converted in ether and acetic acid anhydride in the presence of perchloric acid into 3,11β - diacetoxy - D - homopregna - 3,5,17a(20) - triene from which by treatment with perchloryl fluoride and subsequent isomerisation there is obtained 11β - acetoxy - 6α - fluoro - D - homopregna - 4,17a(20) - dien - 3 - one.

Example 3

400 mg of 11β,17a - diacetoxy - 3β - hydroxy - D - homopregn - 5 - en - 20 - one were heated to boiling in 5 ml of cyclohexanone and 30 ml of toluene. 5 ml were distilled off. After the addition of 600 mg of aluminium tritert. butylate, the mixture was boiled at reflux under argon for 6 hours. The mixture was poured on to 2-N hydrochloric acid and extracted three times with toluene. The organic phases were washed neutral with sodium hydrogen carbonate solution and sodium chloride solution, dried and evaporated. Chromatography of the residue on silica gel gave 11β,17a - diacetoxy - D - homopregn - 4 - ene - 3,20 - dione which was identical with the product obtained according to Example 1.

The starting material can be prepared as follows:

3β,11β - Dihydroxy - D - homoandrost - 5 - en - 17a - one is reacted at reflux with ethynylmagnesium bromide in tetrahydrofuran. Chromatographical

purification of the reaction mixture gives 17aβ - ethynyl - 3β,11β,17aα - trihydroxy - D - homoandrost - 5 - ene of melting point 232°—234°C; $[\alpha]_D$=—77° (c=0.1% in dioxan).

From the foregoing 17aβ - ethynyl - 3β,11β,17aα - trihydroxy - D - homoandrost - 5 - ene there is obtained with mercury - p - toluene - sulphonamide in boiling alcohol 3β,11β,17a - trihydroxy - D - homopregn - 5 - en - 20 - one of melting point 244°—247°C; $[\alpha]_D$=—101° (c=0.1% in dioxan).

The foregoing 3β,11β,17a - trihydroxy - D - homopregn - 5 - en - 20 - one is converted with acetic acid anhydride and a catalytic amount of perchloric acid in ethyl acetate into 3β,11β,17a - triacetoxy - D - homopregn - 5 - en - 20 - one from which there is obtained by partial saponification with potassium carbonate in methanol 11β,17a - diacetoxy - 3β - hydroxy - D - homopregn - 5 - en - 20 - one.

Example 4

4.9 g of 9 - fluoro - 11β,17a - dihydroxy - 21 - iodo - D - homopregna - 1,4 - diene - 3,20 - dione, 80 ml of ether, 80 ml of benzene, 40 ml of water and 40 ml of saturated sodium hydrogen sulphite solution were stirred at 25°C for 30 hours. The mixture was diluted with ethyl acetate. The aqueous phase was separated and extracted twice with ethyl acetate. The ethyl acetate solutions were washed twice with sodium chloride solution, dried over sodium sulphate and evaporated. Filtration on silica gel and crystallisation from acetone/hexane gave 9 - fluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 268°—269°C; UV: ε_{329}=15200; $[\alpha]_D$=+67° (c=0.1% in methanol).

The starting material can be prepared by reacting 9 - fluoro - D - homoprednisolone [melting point 241°—246°C; $[\alpha]_D$=+101° (c=0.1% in dioxan); UV: ε_{238}=14540] with methane-sulphonyl chloride in pyridine to give 9 - fluoro - 11β,17a - dihydroxy - 21 - methanesulphonyloxy - D - homopregna - 1,4 - diene - 3,20 - dione and reacting this with sodium iodide in acetone to give 9 - fluoro - 11β,17a - dihydroxy - 21 - iodo - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 190°C (decomposition); [α]=+118° (c=0.1% in dioxan); UV: ε_{238}=15750.

In an analogous manner from 6α fluoro - 11β,17a - dihydroxy - 21 - iodo - D - homopregna - 1,4 - diene - 3,20 - dione [melting point 175°—177°C; UV: ε_{243}=15830; $[\alpha]_D$=+121° (c=0.1% in dioxan] there was obtained 6α - fluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 183°—184°C; UV: ε_{242}=14400; $[\alpha]_D$=+56° (c=0.1% in dioxan); and from 6α,9 - difluoro - 11β,17a - dihydroxy - 21 - iodo - D - homopregna - 1,4 - dien - 3,20 - dione [melting point 189°—190°C; UV: ε_{238}=16750; $[\alpha]_D$=+115° (c=0.1% in dioxan)] there was obtained 6α,9 - difluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 230°—231°C; UV: ε_{238}=16000; $[\alpha]_D$+57° (c=0.1% in dioxan).

Example 5

60 mg of 9,11β - epoxy - 17a - hydroxy - D - homo - 9β - pregna - 1,4 - diene - 3,20 - dione were stirred at 25°C for 15 minutes in 1.5 ml of glacial acetic acid and 0.15 ml of 37% hydrochloric acid. The mixture was poured into dilute sodium hydrogen carbonate solution and extracted three times with methylene chloride. The methylene chloride solutions were washed twice with dilute sodium chloride solution, dried and evaporated. From acetone there was obtained 9 - chloro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 265°—270°C (decomposition); UV: ε_{240}=15080; $[\alpha]_D$=+94° (c=0.1% in dimethylsulphoxide).

Example 6

340 mg of 17a - hydroxy - D - homopregna - 1,4,9(11) - triene - 3,20 - dione and 330 mg of N-chlorosuccinimide were stirred at 25°C for 6 hours in 3.5 ml of a solution of 1 part of urea and 1 part of hydrogen fluoride. The mixture was poured into water and extracted three times with methylene chloride. The organic phases were washed twice with dilute sodium chloride solution, which contained 1% sodium hydrogen carbonate and 1% sodium sulphite, dried and evaporated. Chromatography on silica gel gave 9 - chloro - 11β - fluoro - 17a - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 296°—297°C; $[\alpha]_D$=+85° (c=0.1% in dioxan); UV: ε_{238}=15870.

Example 7

100 mg of 9,11β - epoxy - 17a - hydroxy - D - homo - 9β - pregna - 1,4 - diene - 3,20 - dione were stirred at 25°C for 1 hour in 2 ml of a solution of 1 part of urea and 1.3 parts of hydrogen fluoride. The mixture was poured into water and extracted with methylene chloride as usual. Chromatography of the crude product on silica gel gave 9 - fluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 268°—269°C; UV: ε_{239}=15200; [α]=+67° (c=0.1% in methanol).

The starting material, 9,11β - epoxy - 17a - hydroxy - D - homo - 9β - pregna - 1,4 - diene - 3,20 - dione [melting point 179°—180°C; UV: ε_{248}=16060; $[\alpha]_D$=—15° (c=0.1% in dioxan)], is obtained from 9 - bromo - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione and potassium acetate in alcohol after heating to reflux for several hours.

Example 8

170 mg of 17a - hydroxy - D - homopregna - 1,4,9(11) - triene - 3,20 - dione and 130 mg of N-bromoacetamide were treated in 8.2 ml of dioxan and 1.65 ml of water with 0.84 ml of 10% perchloric acid. After 15 minutes, 435 mg of sodium sulphite were added and the mixture was diluted with water and a large amount of methylene chloride. The aqueous phase was extracted three times with methylene chloride, the methylene chloride solutions were washed twice with dilute sodium chloride solution, dried over sodium sulphate and evaporated. The resulting 9 - bromo - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione melted at 215°C (decomposition). UV: ε_{242}=14050; $[\alpha]_D$=+91° (c=0.09% in dimethysulphoxide).

The starting material, 17a - hydroxy - D - homopregna - 1,4,9(11) - triene - 3,20 - dione [melting point 190°—191°C; UV: ε_{239}=15500; $[\alpha]_D$=—80° (c=0.1% in dioxan)], is obtained from 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione by reaction with methanesulphonyl chloride and sulphur dioxide in pyridine and dimethylformamide.

Example 9

1 g of 9 - fluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione, 375 mg of 4 - dimethylaminopyridine, 5 ml of triethylamine and 5 ml of propionic acid anhydride were stirred at 25°C for 2 hours under argon. After the addition of 5 ml of water, the mixture was stirred for 10 minutes, then poured into 2—N hydrochloric acid and extracted three times with methylene chloride. the methylene chloride solutions were washed neutral with water, dried over sodium sulphate and evaporated. Chromatography of the residue on silica gel gave 9 - fluoro - 17a - hydroxy - 11β - propionyloxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 201°—202°C; UV: ε_{238}=15500; $[\alpha]_D$=+93° (c=0.1% in dioxan).

Example 10

490 mg of 9 - fluoro - 17a - hydroxy - 11β - propionyloxy - D - homopregna - 1,4 - diene - 3,20 - dione were stirred at 40°C for 4.5 hours in 5 ml of butyric acid and 2 ml of trifluoroacetic acid anhydride. The mixture was poured into 5% aqueous pyridine, acidified after 10 minutes with hydrochloric acid and extracted with methylene chloride. The organic phases were washed neutral with sodium hydrogen carbonate solution and dilute sodium chloride solution, dried and evaporated. Chromatography of the residue on silica gel gave 17a - butyryloxy - 9 - fluoro - 11β - propionyloxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 199°—200°C; UV: ε_{238}=16550; $[\alpha]_D$=+71° (c=1% in dioxan).

In an analogous manner, from 9 - chloro - 11β - fluoro - 17a - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione there was obtained 17a - butyryloxy - 9 - chloro - 11β - fluoro - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 170°—171°C; UV: ε_{238}=15750; $[\alpha]_D$=+43° (c=1% in dioxan).

Example 11

1 g of 6α - fluoro - 11β,17a - dihydroxy - D - homopregn - 4 - ene - 3,20 - dione and 660 mg of selenium dioxide were stirred at reflux for 24 hours under argon in 50 ml of tert. butanol and 0.5 ml of glacial acetic acid. The mixture was filtered and evaporated. The residue was dissolved in ethyl acetate and washed

successively with sodium hydrogen carbonate solution, water, ice-cold ammonium sulphide solution, dilute ammonia, water, dilute hydrochloric acid and water. The ethyl acetate solution was dried over sodium sulphate and evaporated in vacuo. Chromatography on silica gel gave 6α - fluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 183°—184°C; UV: ε_{242}=14400; $[\alpha]_D$=+56° (c=0.1% in dioxan).

Example 12

40 mg of 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione, 15 mg of 4 - dimethylaminopyridine, 0.2 ml of triethylamine and 0.2 ml of butyric acid anhydride were stirred at 25°C for 2 hours under argon. After the addition of 0.2 ml of water, the mixture was stirred for 10 minutes, then poured into 2-N hydrochloric acid and extracted three times with methylene chloride. The methylene chloride solutions were washed neutral with water, dried over sodium sulphate and evaporated. Preparative thin-layer chromatography gave non-crystalline 11β - butyryloxy - 17a - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione.

UV: ε_{242}=14000
NMR: 1.21 ppm S 3H } 18_{Me}, 19_{Me}
1.37 „ S 3H }
5.50 „ m 1H 11αH

Example 13

1 g of 11β,17a - diacetoxy - D - homopregn - 4 - ene - 3,20 - dione was dissolved in 10 ml of ethyl orthoformate and 10 ml of absolute alcohol and treated with 10 mg of p-toluenesulphonic acid in 1 ml of alcohol. After 10 minutes, 2 drops of pyridine were added to the mixture and the resulting mixture was poured into dilute sodium hydrogen carbonate solution and extracted with methylene chloride. The methylene chloride solution was washed with water, dried over sodium sulphate and evaporated to dryness. The crude 3 - ethoxy - 11β,17a - dihydroxy - D - homopregna - 3,5 - dien - 20 - one was gasified in 40 ml of dimethylformamide and 4 ml of water with perchloryl fluoride until enol ether could no longer be detected in a thin-layer chromatogram. The mixture was evaporated in vacuo and the residue, a mixture of the two isomeric 11β,17a - diacetoxy - 6 - fluoro - D - homopregn - 4 - ene - 3,20 - diones, left to stand at 25°C for 30 minutes in 100 ml of glacial acetic acid and 1 ml of 33% hydrogen bromide in glacial acetic acid. After the addition of 5 ml of pyridine, the mixture was evaporated in vacuo. Chromatography of the residue on silica gel gave 11β,17a - diacetoxy - 6α - fluoro - D - homopregn - 4 - ene - 3,20 - dione of melting point 236°—237°C; $[\alpha]_D$=+25° (c=0.1% in dioxan); UV: ε_{232}=16100.

Example 14

1.1 g of 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione were dissolved at −10°C in 6.2 ml of pyridine and 0.474 ml of trifluoroacetic acid anhydride and stirred at 0°C for 50 minutes under argon. The mixture was poured into dilute hydrochloric acid and extracted three times with methylene chloride. The methylene chloride solutions were washed neutral with sodium hydrogen carbonate solution and sodium chloride solution, dried and evaporated. Chromatography on silica gel gave pure non-crystalline 17a - hydroxy - 11β - trifluoroacetoxy - D - homopregna - 1,4 - diene - 3,20 - dione; UV: ε_{239}=14200; $[\alpha]_D$=+84° (c=0.1% in dioxan).

Example 15

1.2 g of 17a - hydroxy - 11β - trifluoroacetoxy - D - homopregna - 1,4 - diene - 3,20 - dione were dissolved in a mixture of 12 ml of butyric acid and 4.8 ml of trifluoroacetic acid anhydride and stirred at 50°C for 4 hours. The mixture was poured into aqueous pyridine, stirred for 10 minutes, acidified with 2-N hydrochloric acid and extracted three times with methylene chloride. The methylene chloride solutions were washed neutral with sodium hydrogen carbonate solution and sodium chloride solution, dried over sodium sulphate and evaporated. Chromatography of the residue on silica gel gave pure 17a - butyryloxy - 11β - trifluoroacetoxy - D - homopregna - 1,4 - diene - 3,20 - dione as a foam. UV: ε_{240}=13900; $[\alpha]_D$=+41° (c=0.1% in dioxan).

Example 16

1.1 g of 17a - butyryloxy - 11β - trifluoroacetoxy - D - homopregna - 1,4 - diene - 3,20 - dione were treated in 55 ml of methanol and 4.2 ml of water with 4.2 ml of saturated sodium hydrogen carbonate solution and stirred at 25°C for 48 hours. The methanol was evaporated and the residue taken up in methylene chloride and water. The methylene chloride solution was washed with dilute sodium chloride solution, dried and evaporated. There was obtained 17a - butyryloxy - 11β - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione as a foam which was pure according to thin-layer chromatography. UV: ε_{244}=13940; $[\alpha]_D$=+22° (c=0.1% in dioxan).

Example 17

In an analogous manner to Examples 14—16, from 9 - fluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione there was obtained 17a - butyryloxy - 9 - fluoro - 11β - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 187°—188°C; UV: ε_{240}=14000; $[\alpha]_D$=+13° (c=1% in dioxan); and from 6α,9 - difluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione there was obtained 17a - butyryloxy - 6α,9 - difluoro - 11β - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 224°—225°C; UV: ε_{238}=16400; $[\alpha]_D$=+14° (c=0.1% in dioxan).

Example 18

In analogy to Examples 14—16, from 6α - fluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione there was obtained 17a - butyryloxy - 6α - fluoro - 11β - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 168°—169°C; UV: ε_{242}=16600; $[\alpha]_D$=+13° (c=0.1% in dioxan).

Example 19

If, in Example 15, there is used acetic acid, propionic acid or valeric acid in place of butyric acid, then there are obtained from 9 - fluoro - 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione in analogy to Examples 14—16 17a - acetoxy - 9 - fluoro - 11β - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 232°—233°C; UV: ε_{239}=13900; $[\alpha]_D$=+29° (c=0.1% in dioxan); 9 - fluoro - 11β - hydroxy - 17a - propionyloxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 204°—205°C; UV: ε_{238}=15100; $[\alpha]_D$=+23° (c=0.1% in dioxan); and 9 - fluoro - 11β - hydroxy - 17a - valeroyloxy - D - homopregna - 1,4 - diene - 3,20 - dione of melting point 144°—146°C; UV: ε_{239}=15400; $[\alpha]_D$=+17° (c=0.1% in dioxan).

Example 20

300 mg of 11β,17a - dihydroxy - 6 - methylene - D - homopregn - 4 - ene - 3,20 - dione, 150 mg of 5% palladium/carbon, 1.5 ml of cyclohexene and 15 ml of ethanol were boiled at reflux for 8.5 hours under argon. The mixture was cooled to 25°C, treated with 0.75 ml of 25% hydrochloric acid and stirred for 1 hour. The catalyst was filtered off and the filtrate evaporated. Chromatography on silica gel gave 11β,17a - dihydroxy - 6α - methyl - D - homopregn - 4 - ene - 3,20 - dione of melting point 223°—225°C; UV: ε_{242}=14100; $[\alpha]_D$=+46° (c=0.1% in dioxan).

The starting material can be prepared as follows:

11β,17a - Dihydroxy - D - homopregn - 4 - ene - 3,20 - dione is reacted in boiling methanol with pyrrolidine to give 11β,17a - dihydroxy - 3 - (1 - pyrrolidinyl) - D - homopregna - 3,5 - dien - 20 - one. This is reacted with formalin in benzene and methanol to give 11β,17a - dihydroxy - 6β - hydroxymethyl - D - homopregn - 4 - ene - 3,20 - dione. Treatment with hydrochloric acid in dioxan gives 11β,17a - dihydroxy - 6 - methylene - D - homopregn - 4 - ene - 3,20 - dione.

Example 21

A 2 litre Erlenmeyer flask containing 500 ml of nutrient solution (sterilised for 30 minutes at 120°C in an autoclave) comprising 1% cornsteep liquor, 1% soya powder and 0.005% soya oil, adjusted to pH 6.2, is inoculated with a lyophilised culture of Curvularia lunata (NRRL 2380) and shaken on a rotary shaker at 30°C for 72 hours. a 20 litre stainless steel fermenter containing 15 litres of a medium (sterilised at 121°C and 1.1 atmospheres) comprising 1% cornsteep liquor, 0.5% starch sugar and 0.005% soya oil, adjusted to pH 6.2, is then inoculated with the

aforementioned pre-culture. Cultivation is carried out for 24 hours at 29°C with aeration (10 litres/minute), at 0.7 atmospheres and while stirring (220 revolutions/minute) with the addition of a silicon oil (Silicon SH) as an anti-foam agent. 1litre of the culture broth is transferred under sterile conditions into 14 litres of a medium (sterilised as described earlier) comprising 1% cornsteep liquor, 1.25% soya powder and 0.005% soya oil and cultivated under the same conditions. After 12 hours, there is added a solution of 4 g of 17aα - acetoxy - D - homo - 4 - pregnene - 3,20 - dione in 100 ml of dimethylformamide. After 52 hours, the content of the fermenter is extracted twice by stirring with (10 litres of methyl isobutyl ketone each time and the extract evaporated at 50°C (bath temperature) in vacuo. In order to remove the silicon oil, the residue is washed several times with hexane and separated from unreacted starting material by column chromatography on silica gel [gradient elution: hexane+hexane/ethyl acetate 1+(1/1)]. The 17aα - acetoxy - 11β - hydroxy - D - homo - 4 - pregnene - 3,20 - dione is recrystallised from isopropyl ether; melting point 234°/235°—237°C, ε_{242}=16700.

Example 22

A 2 litre Erlenmeyer flask containing 500 ml of a nutrient solution (sterilised for 30 minutes at 120°C in an autoclave) comprising 1.5% peptone, 1.2% cornsteep and 0.2% magnesium sulphate, adjusted to pH 6.5, is inoculated with a lyophilised culture of Bacillus lentus (ATCC 13805) and shaken at 30°C for 24 hours. A 20 litre stainless steel fermenter containing 15 litres of a liquid nutrient medium (sterilised at 121°C and 1.1 atmospheres) comprising 0.2% yeast extract, 1% cornsteep liquor and 0.1% starch sugar, adjusted to pH 7.0, is then inoculated with the aforementioned pre-culture. Cultivation is carried out at 29°C with aeration and stirring and with the addition of a silicon oil (Silicon SH) as an anti-foam agent. After a growth-phase of 6 hours, there is added a solution of 1.6 g of 17aα - acetoxy - 11β - hydroxy - D - homo - 4 - pregnene - 3,20 - dione in 50 ml of dimethylformamide. After 15 hours, the content of the fermenter is extracted twice with 10 litres of methyl isobutyl ketone each time and the extract evaporated in vacuo. In order to remove the silicon oil, the residue is washed with hexane and recrystallised from acetone/diisopropyl ether in the presence of active carbon, there being obtained 17aα - acetoxy - 11β - hydroxy - D - homo - 1,4 - pregnadiene - 3,20 - dione of melting point 218°/219°—220°C and ε_{244}=15100.

The following Example illustrates a pharmaceutical preparation provided by the present invention and the manufacture thereof:

Example A

The D-homosteroids of formula I' can be made up, for example, in the form of salves as follows:

D-Homosteroid	0.01—1 wt.%
Liquid paraffin	10.0 wt.%
White soft paraffin ad	100 parts by weight

The D-homosteroid is ground with a portion of the liquid paraffin in a ball mill until a particle size of less than 5 μ is achieved. The paste is diluted and the mill washed out with the remaining liquid paraffin. The suspension is added to the molten colourless soft paraffin at 50°C and stirred until the mass is cold, there being obtained a homogeneous salve.

WHAT WE CLAIM IS:—

1) A pharmaceutical preparation having inflammation-inhibiting activity and containing a pharmaceutical acceptable carrier and, as essential active ingredient, a D-homosteroid of the general formula

aforementioned pre-culture. Cultivation is carried out for 24 hours at 29°C with aeration (10 litres/minute), at 0.7 atmospheres and while stirring (220 revolutions/minute) with the addition of a silicon oil (Silicon SH) as an anti-foam agent. 1litre of the culture broth is transferred under sterile conditions into 14 litres of a medium (sterilised as described earlier) comprising 1% cornsteep liquor, 1.25% soya powder and 0.005% soya oil and cultivated under the same conditions. After 12 hours, there is added a solution of 4 g of 17aα - acetoxy - D - homo - 4 - pregnene - 3,20 - dione in 100 ml of dimethylformamide. After 52 hours, the content of the fermenter is extracted twice by stirring with (10 litres of methyl isobutyl ketone each time and the extract evaporated at 50°C (bath temperature) in vacuo. In order to remove the silicon oil, the residue is washed several times with hexane and separated from unreacted starting material by column chromatography on silica gel [gradient elution: hexane+hexane/ethyl acetate 1+(1/1)]. The 17aα - acetoxy - 11β - hydroxy - D - homo - 4 - pregnene - 3,20 - dione is recrystallised from isopropyl ether; melting point 234°/235°—237°C, ε_{242}=16700.

Example 22

A 2 litre Erlenmeyer flask containing 500 ml of a nutrient solution (sterilised for 30 minutes at 120°C in an autoclave) comprising 1.5% peptone, 1.2% cornsteep and 0.2% magnesium sulphate, adjusted to pH 6.5, is inoculated with a lyophilised culture of Bacillus lentus (ATCC 13805) and shaken at 30°C for 24 hours. A 20 litre stainless steel fermenter containing 15 litres of a liquid nutrient medium (sterilised at 121°C and 1.1 atmospheres) comprising 0.2% yeast extract, 1% cornsteep liquor and 0.1% starch sugar, adjusted to pH 7.0, is then inoculated with the aforementioned pre-culture. Cultivation is carried out at 29°C with aeration and stirring and with the addition of a silicon oil (Silicon SH) as an anti-foam agent. After a growth-phase of 6 hours, there is added a solution of 1.6 g of 17aα - acetoxy - 11β - hydroxy - D - homo - 4 - pregnene - 3,20 - dione in 50 ml of dimethylformamide. After 15 hours, the content of the fermenter is extracted twice with 10 litres of methyl isobutyl ketone each time and the extract evaporated in vacuo. In order to remove the silicon oil, the residue is washed with hexane and recrystallised from acetone/diisopropyl ether in the presence of active carbon, there being obtained 17aα - acetoxy - 11β - hydroxy - D - homo - 1,4 - pregnadiene - 3,20 - dione of melting point 218°/219°—220°C and ε_{244}=15100.

The following Example illustrates a pharmaceutical preparation provided by the present invention and the manufacture thereof:

Example A

The D-homosteroids of formula I' can be made up, for example, in the form of salves as follows:

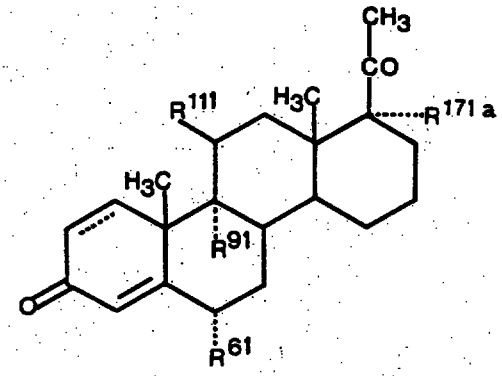
D-Homosteroid	0.01—1 wt.%
Liquid paraffin	10.0 wt.%
White soft paraffin ad	100 parts by weight

The D-homosteroid is ground with a portion of the liquid paraffin in a ball mill until a particle size of less than 5 μ is achieved. The paste is diluted and the mill washed out with the remaining liquid paraffin. The suspension is added to the molten colourless soft paraffin at 50°C and stirred until the mass is cold, there being obtained a homogeneous salve.

WHAT WE CLAIM IS:—

1) A pharmaceutical preparation having inflammation-inhibiting activity and containing a pharmaceutical acceptable carrier and, as essential active ingredient, a D-homosteroid of the general formula

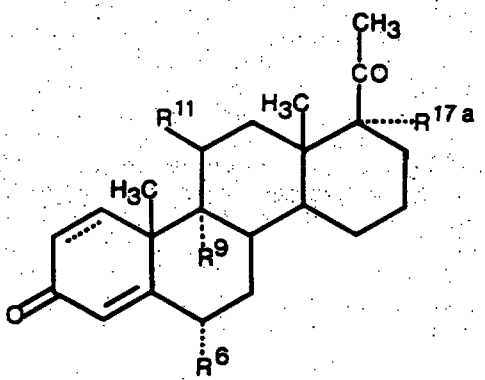
* C L M S *



(I')

wherein the broken line in the 1,2 - position denotes an optional carbon-carbon bond; R^{61} represents a hydrogen, fluorine or chloring atom or a methyl group; R^{91} represents a hydrogen, fluorine, chlorine or bromine atom; R^{171a} represents a hydroxy or acyloxy group and R^{111} represents a hydroxy or acyloxy group or a fluorine or chlorine atom with the proviso that, in the case of 9,11-dihalo compounds, the atomic number of R^{111} must be less than or equal to that of R^{91}.

2) A pharmaceutical preparation according to claim 1, wherein said D-homosteroid has the general formula



(I)

wherein the broken line in the 1,2-position denotes an optional carbon-carbon bond; R^6 represents a hydrogen, fluorine or chlorine atom or a methyl group; R^9 represents a hydrogen, fluorine, chlorine or bromine atom; R^{11} represents a hydroxy or acyloxy group or a fluorine or chlorine atom and R^{17a} represents a hydroxy or acyloxy group, with the proviso that, in the case of 9,11-dihalo compounds, the atomic number of R^{11} must be less than or equal to that of R^9 and, where R^6 represents a hydrogen atom in a 11,17a-dihydroxy compound or R^6 represents a fluorine atom in a 11,17a-dihydroxy-4-ene compound, R^9 must represent a fluorine, chlorine or bromine atom.

3) A pharmaceutical preparation according to claim 1, wherein the D-homosteroid is 11β,17a - dihydroxy - D - homopregn - 4 - ene - 3,20 - dione, 11β,17a - dihydroxy - D - homopregna - 1,4 - diene - 3,20 - dione or 6α - fluoro - 11β,17a - dihydroxy - D - homopregn - 4 - ene - 3,20 - dione.

4) A pharmaceutical preparation according to claim 1 wherein the D-homosteroid is 17a - Butyryloxy - 9 - fluoro - 11β - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione or 17a - Butyryloxy - 11β - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione.

5) A process for the manufacture of pharmaceutical preparations having inflammation-inhibiting activity, which process comprises mixing a D-homosteroid of formula I' given in claim 1 with a pharmaceutically acceptable carrier material.

6) A process according to claim 5, wherein a D-homosteroid of formula I given in claim 2 is mixed with a pharmaceutically acceptable carrier material.

7) A process according to claim 5, wherein 11β,17a - dihydroxy - D - homopregn - 4 - ene - 3,20 - dione, 11β,17a - dihydroxy - D - homopregna -

1,4 - diene - 3,20, dione or 6α - fluoro - 11β,17a - dihydroxy - D - homopregn - 4 - ene - 3,20 - dione is mixed with a pharmaceutically acceptable carrier material.

8) A process according to claim 5, wherein 17a - Butyryloxy - 9 - fluoro - 11β - hydroxy - D - homopregna - 1,4 - diene - 320 - dione or 17a - Butyryloxy - 11β - hydroxy - D - homopregna - 1,4 - diene - 3,20 - dione is mixed with a pharmaceutically acceptable carrier material.

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