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(54) DERIVATIVES OF 9-FLUOROPREDNISOLONE

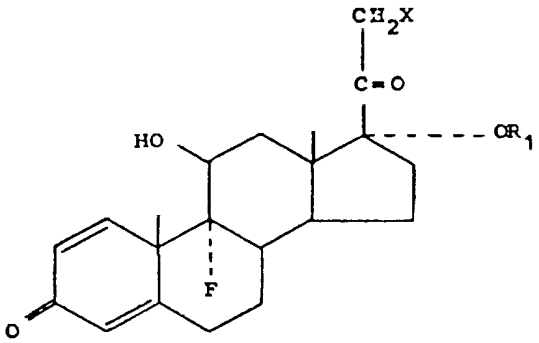
(71) We, SCHERING AKTIENGESELLSCHAFT, a Body Corporate organised according to the laws of the Federal Republic of Germany, of Berlin and Bergkamen, the Federal Republic of Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

The invention relates to derivatives of 9-fluoroprednisolone, a process for their production and pharmaceutical preparations containing these active substances.

9-Fluoroprednisolone (9α-fluoro-11β, 17α,21-trihydroxy-1, 4-pregnadiene-3,2-dione) has been known for a long time. (See, for example, J.Amer. Chem. Soc., 77, 1955, 4181). This corticoid is not a suitable active substance for pharmaceutical preparations which are used for the topical treatment of inflammatory diseases since it has very strong systemic effects.

The present invention is based on the observation that hitherto unknown derivatives of 9-fluoroprednisolone have only weak systemic action but, when administered topically, they have, surprisingly, a strong anti-inflammatory action that generally exceeds that of the most effective commercial corticoids.

The present invention provides a derivative of 9-fluoroprednisolone of the general formula (I)



(I),

wherein

R_1 represents a group of the general formula RCO− in which R represents a hydrogen atom or an alkyl group or a cycloalkyl or cycloakylalkyl group or an alkyl-substituted cycloalkyl or cycloalkylalkyl group, and R_1 has from 1 to 8 carbon atoms, or in which R represents an aryl or aralkyl group or an alkyl-substituted aryl or aralkyl group, and R_1 has up to 9 carbon atoms, and

X represents a fluorine or chlorine atom or a group of the general formula R'COO− which has from 3 to 8 carbon atoms and in which R' represents an alkyl group or a cycloalkyl or cycloalkylalkyl group or an alkyl-substituted cycloalkyl or cycloalkylalkyl group.

Thus, for example, R_1 may represent a formyl group or a alkanoyl or cycloalkanecarbonyl group having up to 8 carbon atoms or a benzoyl group or a phenylalkanoyl group having up to 9 carbon atoms, and X may represent a fluorine or chlorine atom or an alkanoyloxy or cycloalkanecarbonyloxy group having from 3 to 8 carbon atoms.

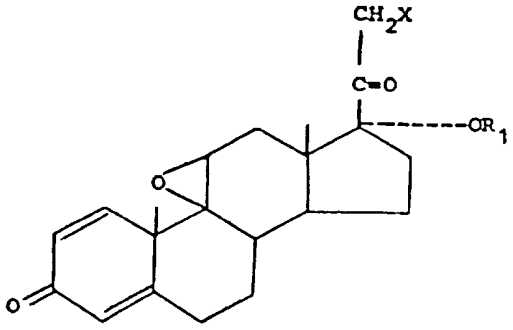
An acyl group represented by R_1 and an acyloxy group represented by X may be derived from a cyclic carboxylic acid or from an open-chained (straight-chained or branched-chained) carboxylic acid, such as, for example, butyric acid, isobutyric acid, valeric acid, isovaleric acid, trimethylacetic acid, caproic acid, t-butylacetic acid, cyclopentanecarboxylic acid, cyclohexanecarboxylic acid or caprylic acid or, in the case of R_1, from formic acid, acetic acid or propionic acid.

Particularly preferred alkanoyl groups R_1 and alkanoyloxy groups X are those that are derived from an alkanecarboxylic acid containing up to 6 carbon atoms.

9-Fluoroprednisolone derivatives of the general formula (I) where X represents a chlorine atom are, for example:
17α-acetoxy-21-chloro-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione,
21-chloro-9α-fluoro-11β-hydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione,
17α-butyryloxy-21-chloro-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.
21-chloro-9α-fluoro-11β-hydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione,
21-chloro-9α-fluoro-11β-hydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione and
17α-benzoyloxy-21-chloro-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.
9,21-Difluoroprednisolone derivatives of the general formula (I) are, for example,
17α-acetoxy-9α,21-difluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione,
9α,21-difluoro-11β-hydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione,
17α-butyryloxy-9α,21-difluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione and
9α,21-difluoro-11β-hydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione.
9-Fluoroprednisolone derivatives of the general formula (I) with X representing a group of the formula R'COO– are preferably those in which the radicals R_1 and X together have 5 to 14 carbon atoms. Such fluoroprednisolone derivatives are, for example:
17α-acetoxy-9α-fluoro-11β-hydroxy-21-propionyloxy-1,4-pregnadiene-3,20-dione,
17α-acetoxy-21-butyryloxy-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione,
17α-acetoxy-9α-fluoro-11β-hydroxy-21-isobutyryloxy-1,4-pregnadiene-3,20-dione,
17α-acetoxy-9α-fluoro-11β-hydroxy-21-valeryloxy-1,4-pregnadiene-3,20-dione,
21-butyryloxy-9α-fluoro-11β-hydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione,
17α-benzoyloxy-21-butyryloxy-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione,
9α-fluoro-11β-hydroxy-17α,21-diisobutyryloxy-1,4-pregnadiene-3,20-dione and
9α-fluoro-11β-hydroxy-17α,21-divaleryloxy-1,4-pregnadiene-3,20-dione.

The present invention also provides a process for the manufacture of the 9-fluoroprednisolone derivatives of the general formula (I) wherein

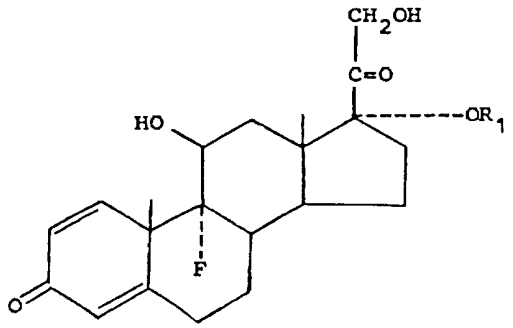
a) the epoxide ring of a compound of the general formula (II)



(II),

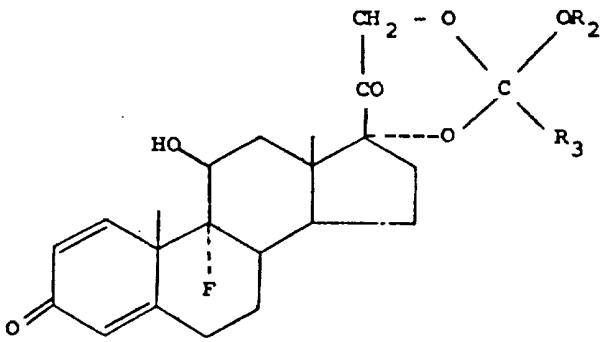
in which R_1 and X have the meanings given above is opened with hydrogen fluoride, or

b) a 9-fluoro derivative of the general formula (III)



(III),

in which R_1 has the meaning given above, is halogenated or esterified in the 21-position, or c) for the production of a 9-fluoroprednisolone derivative of the general formula (I) wherein X represents a fluorine or chlorine atom, an ortho ester of the general formula (IV)



(IV),

wherein R_3 represents a hydrogen atom, an alkyl group or a cycloalkyl group having up to 7 carbon atoms or a phenyl group and R_2 represents an alkyl group having 1 to 4 carbon atoms, is cleaved with a trimethylsilyl halide or a triphenylmethyl halide.

The process of the invention according to process variants (a) and (b) may be carried out in a manner known *per se* under the conditions described in U.S. Specifications Nos. 3,678,034, 3,718,671 and 3,828,083. The starting compounds for these processes may be produced under the conditions described in U.S. Specification No. 3,152,154 and in German Offenlegungsschriften Nos. 23 40 591 and 20 55 221.

The process of the invention according to process variant (a) may likewise be carried out under conditions known *per se* preferably by reacting a compound of general formula (II) with hydrogen fluoride contained in an inert solvent. Suitable inert solvents are, for example, ethers (e.g. diethyl ether, diisopropyl ether, tetrahydrofuran or pyridine) and chlorinated hydrocarbons (e.g. methylene chloride, chloroform, carbon tetrachloride or tetrachloroethane).

The process of the invention according to process variant (b) may likewise be carried out under conditions known *per se*.

Thus, for example, a hydroxy steroid of the general formula (III) may be esterified with an acyl chloride or acid anhydride in the presence of an acid, such as, for example, hydrogen chloride, *p*-toluenesulphonic acid or trifluoroacetic acid, or in the presence of a base such, for example, as potassium carbonate, pyridine, collidine, or *p*-dimethylaminopyridine.

A preferred method of chlorinating a compound of the general formula (III) comprises esterifying the 21-hydroxy group with a sulphonic acid, preferably with methanesulphonic acid or *p*-toluenesulphonic, and then exchanging the sulphonic acid group for chlorine. The 21-hydroxy group is esterified, for example, by causing a sulphonic acid chloride to act on the compound of formula (III) in the presence of an organic base, such, for example, as pyridine, or in the presence of an aqueous alkali. The sulphonic acid group is exchanged for a chlorine atoms preferably by reacting the 21-sulphonic acid ester with alkali metal chloride such as, for example, lithium chloride, in the presence of a polar solvent such, for example, as dimethylformamide.

The process of the invention according to process variant (c) may likewise be carried out under conditions known *per se*.

The cleavage of an ortho ester of the general formula (IV) is preferably effected with trimethylsilyl fluoride, trimethylsilyl chloride or triphenylmethyl chloride, advantageously in a inert solvent such, for example, as a dipolar aprotic solvent (e.g. dimethylformamide, N-methylpyrrolidone, dimethyl sulphoxide or hexamethylphosphoric acid triamide), an ether (e.g. diethyl ether, diisopropyl ether, tetrahydrofuran, dioxan or glycol dimethyl ether), a chlorinated hydrocarbon (e.g. methylene chloride, chloroform or tetrachloroethane), a hydrocarbon (e.g. benzene, toluene or cyclohexane) or a mixture of any two or more of these solvents.

The starting compound for the process according to the invention can thus be produced in a simple manner and with high yields from prednisolone which can itself be synthesised relatively easily from diosgenin. The result of this is that compounds of the invention can be produced from diosgenin at relatively low expenditure and with a total yield of approximately 15 %. In contrast, the syntheses of the known highly effective corticoids from diosgenin require considerably more expenditure and the total yields obtained are significantly lower (approximately 0.5 to 5 %). In view of the growing difficulties in

obtaining a sufficient quantity of suitable starting materials for the corticoid syntheses and with regard to the high cost of active substances, which is the disadvantage of corticoid-containing medicament specialities, this is not without significance.

As already mentioned, when the compounds of the invention are administered topically they have a very strong anti-inflammatory activity but have only weak action when administered systemically.

The anti-inflammatory activity was determined as follows: A hyperaemia was produced on human skin in the following manner.

Part of the *Stratum corneum* on the backs of male and female volunteers was stripped off by applying and tearing off 20 times from the same place a portion of "Tesa" (Registered Trade Mark) self-adhesive tape 2 cm wide and a pronounced hyperaemia was thus produced.

Approximately 50 mg of the ointment preparations were applied to marked 4 cm^2 zones inside the stripped area.

In order to obtain comparable starting values relative numbers were used since the colour of the untreated skin, as also the reddening of the hyperaemic area, differs from case to case.

The colour value of the untreated skin was set at 100 and that of the stripped skin at 0.

The skin colour value of the skin under vasoconstriction (100) was determined on a relative scale.

Relatively slight, average and a high degree of vasoconstriction were rated accordingly between 0 and 100.

The average values, which were derived from investigations of the various test persons and from various regions of the back, are given in the following Table A.

The systemic activity of the compounds was determined using the adjuvant-oedema test as follows:

SPF rats weighing 130 to 150 g were injected in the right hind leg with 0.1 ml of a 0.5 % *Mycobacterium butyricum* suspension (obtainable from the American firm Difko) in order to produce a focus of inflammation. The volume of the rats' legs was measured before injection and again 24 hours after injection to determine the extent of the oedema. Different quantities of the test substance were then administered orally to the rats. After a further 24 hours the volume of the legs was determined once again.

From the leg volumes obtained the quantity of test substance necessary to achieve 50 % healing of the oedema in the leg was determined in the normal manner.

The results obtained in the tests are given in the following Table A:

TABLE A

No.	Substance	Vasoconstriction test: Concentration %	Results after 4 hours	Results after 8 hours	Adjuvant-oedema test ED_{50}
I	6α,9α-Difluoro-11β-hydroxy-21-valeryloxy-1,4-pregnadiene-3,20-dione(=Diflucortolone-valerate)	0.1 %	58	68	0.04 mg/kg
		0.001 %	54	66	
		0.00001 %	32	36	
II	21-Acetoxy-9α-fluoro-11β-hydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione (DOS 20 55 221)	0.1 %	55	66	3.8 mg/kg
		0.001 %	52	63	
		0.00001 %	31	42	
III	17α-Acetoxy-9α-fluoro-11β-hydroxy-21-hexanoyloxy-1,4-pregnadiene-3,20-dione	0.1 %	67	78	7.7 mg/kg
		0.001 %	60	74	
		0.00001 %	23	36	
IV	17α-Acetoxy-9α-fluoro-11β-hydroxy-21-trimethylacetoxy-1,4-pregnadiene-3,20-dione	0.1 %	57	74	7.0 mg/kg
		0.001 %	57	68	
		0.00001 %	33	42	
V	9α-Fluoro-11β-hydroxy-17α,21-dipropionyloxy-1,4-pregnadiene-3,20-dione	0.1 %	65	83	5.0 mg/kg
		0.001 %	58	76	
		0.00001%	39	47	

TABLE A (continued)

No.	Substance	Vasoconstriction test Concentration %	Results after 4 hours	Results after 8 hours	Adjuvant-oedema test ED_{50}
VI	21-Butyryloxy-9α-fluoro-11β-hydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione	0.1 %	62	83	5.7 mg/kg
		0.001%	58	76	
		0.00001 %	43	47	
VII	9α-Fluoro-11β-hydroxy-17α-propionyloxy-21-valeryloxy-1,4-pregnadiene-3,20-dione	0.1 %	60	75	6.0 mg/kg
		0.001 %	57	76	
		0.00001 %	40	43	
VIII	17α-Benzoyloxy-9α-fluoro-11β-hydroxy-21-propionyloxy-1,4-pregnadiene-3,20-dione	0.1 %	62	78	over 10 mg/kg
		0.001 %	59	70	
		0.00001 %	40	43	
IX	17α-Benzoyloxy-21-butyryloxy-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione	0.1 %	68	82	over 10 mg/kg
		0.001 %	67	80	
		0.00001 %	51	58	
X	17α-Benzoyloxy-21-chloro-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione	0.1 %	60	72	over 10 mg/kg
		0.001 %	56	64	
		0.00001 %	43	45	

Similar results are obtained if the systemic activity of the 9-fluoroprednisolone derivatives according to the invention is determined using the known thymolysis test or the known sodium/potassium retention test.

In combination with the carriers conventionally used in galenical pharmacy compounds of the invention are suitable for the local treatment of contact dermatitis, eczemas of the most varied types, neurodermatoses, erythrodermia, burns, *Pruritis vulvae et ani*, rosacea, *Erthematodes cutaneus*, psoriasis, *Lichen ruber planus et verrucosus* and similar skin diseases.

Accordingly, the present invention also provides a pharmaceutical preparation which comprises a compound of the general formula (I), in admixture or conjunction with a pharmaceutically suitable carrier.

The pharmaceutical preparations may be produced in a conventional manner by converting the active substances with suitable additives into the desired form of administration, such as, for example, solutions, lotions, ointments, creams or plasters. In the preparations formulated in this manner the concentration of active substance depends on the form of administration. An active substance concentration of 0.001 to 1 % is preferably used in the case of lotions and ointments.

The present invention further provides a method of treating an animal to relieve inflammation, which comprises applying a compound or preparation of the invention to the affected area.

In addition, compounds of the invention, optionally in combination with the conventional carriers and auxiliary agents, are also very suitable for the production of inhalants which can be used for the therapy of allergic diseases of the respiratory system, such as, for example, bronchial asthma or rhinitis.

A compound or preparation of the present invention may also be used to alleviate inflammation caused by a medicament used for treating a non-inflammatory disease.

Accordingly, the present invention provides a pharmaceutical composition which comprises a compound of the general formula (I) in admixture with a medicament for the treatment of a non-inflammatory disease but which is liable to have an inflammatory action, and a pharmaceutical preparation which comprises this composition in admixture or conjunction with a pharmaceutically suitable carrier.

The present invention further provides a pack which comprises a compound of the general formula (I), or a pharmaceutical preparation containing this, and a medicament for the treatment of a non-inflammatory disease but which is liable to have an inflammatory action.

The following Examples illustrate the invention:

I-SYNTHESES

Example 1

a) 5 g of 9α-fluoroprednisolone are added to 500 mg of pyridine tosylate, twice concentrated to dryness *in vacuo* with benzene, in 500 ml of benzene and 40 ml of N,N-dimethylformamide. At a bath temperature of 130°C 50 ml of solvent are distilled off and 6 ml of orthoacetic acid triethyl ester are added. The remainder of the benzene is distilled off within 2.5 hours and after the addition of 2.4 ml of pyridine the whole is concentrated *in vacuo*. 17α,21-(1-ethoxyethylidenedioxy)-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione is isolated as a yellow oily epimer mixture.

b) A solution of the oil is thus obtained in 150 ml of methanol is refluxed for 1 hour at 90°C with a mixture of 54 ml of 0.1 N acetic acid and 6 ml of 0.1 N aqueous sodium acetate solution. The mixture is concentrated to dryness *in vacuo*, added to water and extracted with ethyl acetate. The organic extracts are washed with water, dried and evaporated in vacuo. Yield: 9g of 17α-acetoxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione as a foam.

c) 3.0 g of 17α-acetoxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione are stirred in 17 ml of pyridine and 8 ml of propionic anhydride for 1.5 hours at room temperature. After precipitating with ice water filtration is effected, the residue is taken up in methylene chloride and is evaporated after washing and drying over sodium sulphate. 4.9 g are isolated which are chromatographed on 450 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 2.96 g of 17α-acetoxy-9α-fluoro-11β-hydroxy-21-propionyloxy-1,4-pregnadiene-3,20-dione. Melting point 219°C. $[\alpha]_D^{25} = +81°$ (pyridine). UV:$\varepsilon_{239} = 15100$ (methanol).

Example 2

4.5 g of 17α-acetoxy-9α-fluoro-11β,21-dihydroxy-1.4-pregnadiene-3,20-dione are stirred overnight at room temperature in 50 ml of pyridine and 25 ml of butyric anhydride. The reaction product is precipitated with ice water, filtered off and dissolved in methylene

chloride. The solution is washed with water, dried over sodium sulphate and concentrated *in vacuo*. The residue is chromatographed on 700 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 3.6 g of 17α-acetoxy-21-butyryloxy-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione. Melting point 218°C.

Example 3

1.0 g of 17α-acetoxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione is reacted as in Example 2 in 10 ml of pyridine with 6 ml of valeric anhydride instead of butyric anhydride. Yield: 680 mg of 17α-acetoxy-9α-fluoro-11β-hydroxy-21-valeryloxy-1,4-pregnadiene-3,20-dione. Melting point 213°C.

Example 4

3.0 g of 17α-acetoxy-9α-fluoro-11β, 21-dihydroxy-1,4-pregnadiene-3,20-dione in 30 ml of pyridine are stirred with 15 ml of caproic anhydride for 1.5 hours at room temperature. The mixture is worked up as in Example 2. The crude product is purified on 450 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). 2.36 g of 17α-acetoxy-9α-fluoro-21-hexanoyloxy-11β-hydroxy-1,4-pregnadiene-3,20-dione. Melting point 222°C. $[\alpha]_D^{25}$ = + 820 (pyridine). UV:ε_{239} = 15500 (methanol).

Example 5

3.0 g of 17α-acetoxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione are stirred with 15 ml of trimethylacetic anhydride in 30 ml of pyridine for 48 hours at room temperature. As described in Example 2, the crude product is isolated and chromatographed on 700 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). Yield: 2.06 g of 17α-acetoxy-9α-fluoro-11β-hydroxy-21-trimethylacetoxy-1,4-pregnadiene-3,20-dione. Melting point 227°C. $[\alpha]_D^{25}$ = +79° (pyridine). UV:ε_{239} = 15500 (methanol).

Example 6

5.0 g of 9α-fluoro-11β,21-dihydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione, produced as in Example 1a and 1b from 9α-fluoroprednisolone using orthopropionic acid triethyl ester instead of orthoacetic acid triethyl ester, are stirred in 50 ml of pyridine with 25 ml of propionic anhydride for 2 hours at room temperature. The mixture is worked up as described in Example 2. 4.8 g of crude product are purified on 450 g of silica gel with a methylene chloride/acetone gradient (0-15%). Yield: 4.62 g of 9α-fluoro-11β-hydroxy-17α,21-dipropionyloxy-1,4-pregnadiene-3,20-dione. Melting point 191°C. $[\alpha]_D^{25}$ = +51° (chloroform). UV:ε_{239} = 15700 (methanol).

Example 7

5.0 g of 9α-fluoro-11β,21-dihydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione are reacted as in Example 2 with butyric anhydride. The crude product is chromatographed on 450 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). 4.93 g of 21-butyryloxy-9α-fluoro-11β-hydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione. Melting point 179°C. $[\alpha]_D^{25}$ = +51° (chloroform). UV:ε_{239} = 15700 (methanol).

Example 8

5 g of 9α-fluoro-11β,21-dihydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione are reacted as in Example 2 with valeric anhydride instead of butyric anhydride. The whole is likewise worked up as described in Example 2. The crude product is purified on 750 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 5.03 g of 9α-fluoro-11β-hydroxy-17α-propionyloxy-21-valeryloxy-1,4-pregnadiene-3,20-dione. Melting point 190°C. $[\alpha]_D^{25}$ = +54° (chloroform). UV:ε_{239} = 15800 (methanol).

Example 9

5.0 g of 9α-fluoro-11β,21-dihydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione are reacted as in Example 2 with caproic anhydride instead of butyric anhydride. The crude product weighing 5.8 g is purified on 700 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). 4.32 g of 9α-fluoro-21-hexanoyloxy-11β-hydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione are isolated. Melting point 208°C. $[\alpha]_D^{25}$ = +52° (chloroform). UV:ε_{239} = 15900 (methanol).

Example 10

5.0 g of 9α-fluoro-11β-,21-dihydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione are reacted and worked up as in Example 2 with trimethylacetic anhydride instead of butyric anhydride 5.9 g of crude product are chromatographed on 450 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). Yield: 2.23 g of 9α-fluoro-11β-

hydroxy-17α-propionyloxy-21-trimethylacetoxy-1,4-pregnadiene-3,20-dione. Melting point 214°C. $[\alpha]_D^{25}$ = +53° (chloroform). UV:ε_{239} = 15700 (methanol).

Example 11

a) 25 g of 9α-fluoroprednisolone are stirred overnight at room temperature in 250 ml of pyridine and 125 ml of butyric anhydride. After precipitating with ice water filtration is effected and the residue is dissolved in methylene chloride. The solution is washed in water, dried over sodium sulphate and concentrated *in vacuo*. The residue is chromatographed on 2.5 kg of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 23.1 g of 21-butyryloxy-9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione.

b) 100 ml of a 5 % solution of methyl lithium in ether are added dropwise at 0°C under argon to a suspension of 24 g of copper (I) iodide in 480 ml of dry tetrahydrofuran. The yellow mixture is cooled to −30°C and a solution of 22.3 g of 21-butyryloxy-9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione in 400 ml of dry tetrahydrofuran is added. The whole is stirred for 3 - 4 hours at this temperature. The excess reagent is destroyed with an aqueous ammonium chloride solution. After extraction with methylene chloride the organic phase is washed, dried over sodium sulphate and evaporated *in vacuo*. Yield: 20.3 g of 17α-butyryloxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione.

c) 2.0 g of 17α-butyryloxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione are reacted, worked up and purified as in Example 1c with propionic anhydride. 1.4 g of 17α-butyryloxy-9α-fluoro-11β-hydroxy-21-propionyloxy-1,4-pregnadiene-3,20-dione are isolated. Melting point 146°C.

Example 12

1.5 g of 17α-butyryloxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione are reacted as in Example 2 with valeric anhydride instead of butyric anhydride to form 17α-butyryloxy-9α-fluoro-11β-hydroxy-21-valeryloxy-1,4-pregnadiene-3,20-dione. Melting point 220°C.

Example 13

1.4 g of 17α-butyryloxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione are stirred overnight at room temperature in 15 ml of pyridine and 10 ml of oenanthic anhydride. The mixture is then stirred into ice water and extracted with methylene chloride. The extract is washed with water, dried over sodium sulphate and evaporated *in vacuo*. The excess oenanthic acid in the residue is removed by distillation with steam. The crude product is chromatographed on 250 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). 790 mg of 17α-butyryloxy-9α-fluoro-21-heptanoyloxy-11β-hydroxy-1,4-pregnadiene-3,20-dione are isolated.

Example 14

4.5 g of 17α-butyryloxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione are reacted as Example 2 except that isobutyric anhydride is used instead of butyric anhydride. The crude product is purified on 700 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). Yield: 2.1 g of 17α-butyryloxy-9α-fluoro-11β-hydroxy-21-isobutyryloxy-1,4-pregnadiene-3,20-dione.

Example 15

a) 3 g of 9α-fluoroprednisolone are stirred overnight at room temperature in 30 ml of pyridine and 15 ml of valeric anhydride. The mixture is then stirred into ice water and extracted with methylene chloride. The extract is washed with water, dried over sodium sulphate and evaporated *in vacuo*. The excess valeric acid is removed from the residue by distillation with steam. The crude product is chromatographed on 300 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 2.87 g of 9α-fluoro-11β,17α-dihydroxy-21-valeryloxy-1,4-pregnadiene-3,20-dione.

b) 2 g of 9α-fluoro-11β,17α-dihydroxy-21-valeryloxy-1,4-pregnadiene-3,20-dione are converted as in Example 11b with lithium dimethyl cuprate to form 1.86 g of 9α-fluoro-11β,21-dihydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione.

c) 1.8 g of 9α-fluoro-11β,21-dihydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione are reacted as in Example 2, except that propionic anhydride is used instead of butyric anhydride, to form 920 mg of 9α-fluoro-11β-hydroxy-21-propionyloxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione. Melting point 206°C.

Example 16

3.4 g of 9α-fluoro-11β,21-dihydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione are treated as in Example 2 with butyric anhydride and is worked up in an appropriate manner.

1.96 g of 21-butyryloxy-9α-fluoro-11β-hydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione are isolated. Melting point 234°C.

Example 17

A solution of 2.0 g of 9α-fluoro-11β,21-dihydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione in 20 ml of pyridine is stirred with 10 ml of caproic anhydride for 1.5 hours at room temperature. The reaction product is precipitated with ice water, filtered off and dissolved in methylene chloride. The solution is washed with water, dried and evaporated *in vacuo*. The residue, 1.96 g of crude product, is chromatographed on 200 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). Yield: 1.58 g of 9α-fluoro-21-hexanoyloxy-11β-hydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione.

Example 18

a) 12 g of 9α-fluoroprednisolone are reacted as in Example 11a, except that isobutyric anhydride is used instead of butyric anhydride, to form 10.4 g of 9α-fluoro-11β,17α-dihydroxy-21-isobutyryloxy-1,4-pregnadiene-3,20-dione.

b) 10 g of 9α-fluoro-11β,17α-dihydroxy-21-isobutyryloxy-1,4-pregnadiene-3,20-dione are converted as in Example 11b with lithium dimethyl cuprate to form 6.9 g of 9α-fluoro-11β,21-dihydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione.

c) 2.1 g of 9α-fluoro-11β,21-dihydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione are reacted as in Example 1c with propionic anhydride to form 1.3 g of 9α-fluoro-11β-hydroxy-17α-isobutyryloxy-21-propionyloxy-1,4-pregnadiene-3,20-dione.

Example 19

1.2 g of 9α-fluoro-11β,21-dihydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione are reacted with butyric anhydride, worked up and chromatographed as in Example 2. 670 mg of 21-butyryloxy-9α-fluoro-11β-hydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione are isolated.

Example 20

a) 5.0 g of 9α-fluoro-11β,17α-dihydroxy-21-trimethylacetoxy-1,4-pregnadiene-3,20-dione are converted as in Example 11b with lithium dimethyl cuprate to form 3.4 g of 9α-fluoro-11β,21-dihydroxy-17α-trimethylacetoxy-1,4-pregnadiene-3,20-dione.

b) 2.4 g of 9α-fluoro-11β,21-dihydroxy-17α-trimethylacetoxy-1,4-pregnadiene-3,20-dione are reacted as in Example 1c with propionic anhydride to form 1.2 g of 9α-fluoro-11β-hydroxy-21-propionyloxy-17α-trimethylacetoxy-1,4-pregnadiene-3,20-dione.

Example 21

3.1 g of 17α-benzoyloxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione produced from 9α-fluoroprednisolone as in Example 1a and 1b using orthobenzoic acid triethyl ester instead of orthoacetic acid triethyl ester are stiired in 30 ml of pyridine and 15 ml of propionic anhydride for 1 hour at room temperature. The whole is worked up as in Example 1c. The crude product is purified on 450 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). Yield: 1.34 g of 17α-benzoyloxy-9α-fluoro-11β-hydroxy-21-propionyloxy-1,4-pregnadiene-3,20-dione. Melting point 235°C (decomposition). $[\alpha]_D^{25}$ = +22°(pyridine). UV:ε_{234} = 28800 (methanol).

Example 22

3.0 g of 17α-benzoyloxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione are reacted and worked up as in Example 2 in 30 ml of pyridine and 15 ml of butyric anhydride. After purifying the crude product on 450 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). 1.9 g of 17α-benzoyloxy-21-butyryloxy-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione are isolated. Melting point 218°C (decomposition). $[\alpha]_D^{25}$ = +21° (pyridine). UV:ε_{234} = 28900 (methanol).

Example 23

2.8 g of 17α-benzoyloxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione are reacted and worked up as in Example 2 except that valeric anhydride is used instead of butyric anhydride. The crude product is purified on 450 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). 1.81 g of 17α-benzoyloxy-9α-fluoro-11β-hydroxy-21-valeryloxy-1,4-pregnadiene-3,20-dione are obtained. Melting point 208°C. $[\alpha]_D^{25}$ = 22° (pyridine). UV:ε_{234} = 29000 (methanol).

Example 24

2.1 g of 17α-benzoyloxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione are reacted and worked up as in Example 2 with isobutyric anhydride instead of butyric anhydride. The crude product is chromatographed on 200 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). 1.09 g of 17α-benzoyloxy-9α-fluoro-11β-hydroxy-21-isobutyryloxy-1,4-pregnadiene-3,20-dione are obtained.

Example 25

1.8 g of 17α-benzoyloxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione are reacted as in Example 2, with trimethylacetic anhydride instead of butyric anhydride, worked up in an appropriate manner and chromatographed as described in Example 2. 720 mg of 17α-benzoyloxy-9α-fluoro-11β-hydroxy-21-trimethylacetoxy-1,4-pregnadiene-3,20-dione are isolated.

Example 26

10 ml of hexamethylphosphoric acid triamide are stirred with 1.3 ml of thionyl chloride for 30 minutes at 0°C. 800 mg of 17α-acetoxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione are then added and stirring is continued for 5.5 hours at 0°C. The mixture is added to ice water, extracted with ethyl acetate and the extracts are washed neutral with sodium hydrogen carbonate and water. The whole is dried over sodium sulphate and after concentration *in vacuo* 1 g of crude product is isolated which is purified on 65 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 535 mg of 17α-acetoxy-21-chloro-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione. Melting point 265°C (decomposition). $[\alpha]_D^{25}$ = +101° (pyridine). UV:ε_{239} = 15800 (methanol).

Example 27

1.2 g of 9α-fluoro-11β,21-dihydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione are reacted with thionyl chloride in hexamethylphosphoric acid triamide as in Example 26. The crude product is chromatographed on 150 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 860 mg of 21-chloro-9α-fluoro-11β-hydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione. Melting point 229°C (decomposition). $[\alpha]_D^{25}$ = +98° (pyridine). UV:ε_{239} = 15900 (methanol).

Example 28

950 mg of 9α-fluoro-11β,21-dihydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione are treated as in Example 26 with thionyl chloride in hexamethylphosphoric acid triamide. The crude product is purified on 120 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 520 mg of 21-chloro-9α-fluoro-11β-hydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione. Melting point 216°C.

Example 29

2.5 g of 17α-benzoyloxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione are reacted as in Example 26 and the crude product is purified on 250 g of silica gel with a methylene chloride/acetone gradient (0-12 % acetone). Yield: 1.1 g of 17α-benzoyloxy-21-chloro-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione. Melting point 256°C (decomposition). $[\alpha]_D^{25}$ = +15° (pyridine). UV:ε_{234} = 28600 (methanol).

Example 30

a) A suspension of 8.7 g of 21-fluoro-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione in 100 ml of diethylene glycol dimethyl ether is stirred with 12 g of N,N-dimethylaminopyridine and 8.8 ml of acetanhydride for 6.5 hours at 80°C. The reaction mixture is diluted with methylene chloride and washed with 2 N hydrochloric acid. After distillation with steam extraction is effected with methylene chloride, drying is effected over sodium sulphate and after evaporation 7.9 g of 17α-acetoxy-21-fluoro-1,4,9(11)-pregnatriene-3,20-dione are isolated.

b) 7.6 of 17α-acetoxy-21-fluoro-1,4,9(11)-pregnatriene-3,20-dione are dissolved in 76 ml of dioxan and 7.2 g of N-bromosuccinimide are added. After the dropwise addition of 38 ml of 10 % aqueous perchloric acid stirring is continued for 30 minutes at room temperature and the reaction solution is added to a solution of 3.5 g of sodium hydrogen sulphite in 350 ml of water. The precipitate is sucked off and 10 g of 17α-acetoxy-9α-bromo-21-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione are obtained after drying.

c) 10 g of the above crude product are refluxed for 2 hours at 110°C in 600 ml of ethanol with 14.0 g of potassium acetate. The reaction solution is concentrated *in vacuo* and is added to ice water. The precipitate is filtered off and the crude product is purified on 700 g of silica gel with a methylene chloride/acetone gradient (0-6 % acetone). Yield: 3.4 g of

17α-acetoxy-9,11β-epoxy-21-fluoro-1,4-pregnadiene-3,20-dione.
d) 31 ml of a 70 % $(HF)_n$/pyridine solution are cooled to −60°C and a solution of 3 g of 17α-acetoxy-9,11β-epoxy-21-fluoro-1,4-pregnadiene-3,20-dione in 3 ml of pyridine is added. The reaction solution is stirred for 10 hours at −5°C and then stored for 3 days in a refrigerator. The whole is added to ammoniacal ice water and the precipitate is filtered off. The crude product is purified on 350 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 2.15 g of 17α-acetoxy-9α,21-difluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione. Melting point 276°C (decomposition) $[\alpha]_D^{25}$ = + 16° (chloroform). UV:ε_{239} = 15800 (methanol).

Example 31
a) 5 g of 21-fluoro-17α-propionyloxy-1,4,9(11)-pregnatriene-3,20-dione are produced as in Example 30a from 7.9 g of 21-fluoro-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione and propionic anhydride and these 5 g are reacted with N-bromosuccinimide under the conditions described in Example 30b. Yield: 8.5 g of 9α-bromo-21-fluoro-11β-hydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione.
b) 8.5 g of the above crude product are reacted with potassium acetate under the conditions described in Example 30c. The crude product is purified on 700 g of silica gel with a methylene chloride/acetone gradient (0-6 % acetone). Yield: 5.3 g of 9,11β-epoxy-21-fluoro-17α-propionyloxy-1,4-pregnadiene-3,20-dione.
c) 5.0 g of 9,11β-epoxy-21-fluoro-17α-propionyloxy-1,4-pregnadiene-3,20-dione are treated as in Example 30d with 70 % $(HF)_n$/pyridine solution. The reaction product is purified on 700 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 3.98 g of 9α,21-difluoro-11β-hydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione. Melting point 214°C. $[\alpha]_D^{25}$ = + 15° (chloroform). UV:ε_{239} = 15800 (methanol).

Example 32
a) 20.0 g of 17α-butyryloxy-21-fluoro-1,4,9(11)-pregnatriene-3,20-dione, produced as in Example 30a from 21-fluoro-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione and butyric anhydride, are treated with N-bromosuccinimide as in Example 30b. Yield: 24.9 g of 9α-bromo-17α-butyryloxy-21-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.
b) The above crude product is treated with potassium acetate under the conditions described in Example 30c. 16.1 g of 17α-butyryloxy-9,11β-epoxy-21-fluoro-1,4-pregnadiene-3,20-dione are isolated.
c) 15.1 g of 17α-butyryloxy-9,11β-epoxy-21-fluoro-1,4-pregnadiene-3,20-dione are treated as in Example 30d with 70 % $(HF)_n$/pyridine solution. The crude product is purified on 1.5 kg of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). 13.4 g of 17α-butyryloxy-9α,21-difluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione are obtained. Melting point 126°C. $[\alpha]_D^{25}$ = + 11° (chloroform). UV:ε_{239} = 15300 (methanol).

Example 33
a) 7.1 g of 21-fluoro-17α-valeryloxy-1,4,9(11)-pregnatriene-3,20-dione are produced as in Example 30a from 9.0 g of 21-fluoro-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione and valeric anhydride and these 7.1 g are treated as in Example 30b with N-bromosuccinimide. Yield: 8.7 g 9α-bromo-21-fluoro-11β-hydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione.
b) 6.0 g of the above crude product are reacted as in Example 30c with potassium acetate. After purifying the reaction product on 700 g of silica gel with a methylene chloride/acetone gradient (0-5 % acetone) 4.2 g of 9,11β-epoxy-21-fluoro-17α-valeryloxy-1,4-pregnadiene-3,20-dione are obtained.
c) 3.1 g of 9α,21-difluoro-11β-hydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione are produced as in Example 30d by the reaction of 3.8 g of 9,11β-epoxy-21-fluoro-17α-valeryloxy-1,4-pregnadiene-3,20-dione with a 70 % $(HF)_n$/pyridine solution, which 3.1 g are obtained after purification on 450 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Melting point 139°C. $[\alpha]_D^{25}$ = + 10° (chloroform). UV:ε_{239} = 15800 (methanol).

Example 34
a) Under the conditions described in Example 30a 7.3 g of 21-fluoro-17α-hexanoyloxy-1,4,9(11)-pregnatriene-3,20-dione are produced from 8.9 g of 21-fluoro-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione and caproic anhydride which 7.3 g are reacted as in Example 30b with N-bromosuccinimide. Yield: 8.2 g of 9α-bromo-21-fluoro-17α-hexanoyloxy-11β-hydroxy-1,4-pregnadiene-3,20-dione.
b) 8.0 g of the above crude product are treated as in Example 30c with potassium acetate and the crude product is purified with a methylene chloride/acetone gradient (0-5 % acetone). 5.8 g of 9,11β-epoxy-21-fluoro-17α-hexanoyloxy-1,4-pregnadiene-3,20-dione are

isolated.
c) 3.2 g of 9,11β-epoxy-21-fluoro-17α-hexanoyloxy-1,4-pregnadiene-3,20-dione are treated, as described in Example 30d, with a 70 % $(HF)_n$/pyridine solution. The reaction product is purified on 350 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 2.6 g of 9α,21-difluoro-17α-hexanoyloxy-11β-hydroxyl-1,4-pregnadiene-3,20-dione.

Example 35
a) 6.2 g of 21-fluoro-17α-isobutyryloxy-1,4,9(11)-pregnatriene-3,20-dione are produced as in Example 30a from 8.1 g of 21-fluoro-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione and isobutyric anhydride, which 6.2 g are reacted as in Example 30b with N-bromosuccinimide. Yield: 6.9 g of 9α-bromo-21-fluoro-11β-hydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione.
b) 6.0 g of the above crude product are reacted as in Example 30c with potassium acetate and the reaction product is purified on 600 g of silica gel with a methylene chloride/acetone gradient (0-5 % acetone). 4.1 g of 9,11β-epoxy-21-fluoro-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione are obtained.
c) 3.5 g of 9, 11β-epoxy-21-fluoro-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione are reacted as in Example 30d with a 70 % $(HF)_n$/pyridine solution. The crude product is purified on 400 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 2.9 g of 9α,21-difluoro-11β-hydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione.

Example 36
a) 8.0 g of 21-fluoro-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione are added to a mixture of 80 ml of isovaleric acid and 32 ml of trilfuoroacetic anhydride and then stirred for 2.5 hours at 80°C. The whole is then added to hot water in order to destroy the excess anhydride and is afterwards extracted with methylene chloride. After neutralising with 1 % pyridine/water and drying over sodium sulphate the whole is evaporated *in vacuo*. The substance is dissolved in a small quantity of pyridine, added to ice water and the pyridine is neutralised with dilute hydrochloric acid. After working up in the usual manner 5.8 g of 21-fluoro-17α-isovaleryloxy-1,4,9(11)-pregnatriene-3,20-dione are isolated.
b) 5.3 g of 21-fluoro-17α-isovaleryloxy-1,4,9(11)-pregnatriene-3,20-dione are treated as in Example 30b with N-bromosuccinimide. 6.2 g of 9α-bromo-21-fluoro-11β-hydroxy-17α-isovaleryloxy-1,4-pregnadiene-3,20-dione are obtained.
c) 6.0 g of the above crude product are reacted as in Example 30c with potassium acetate. The reaction product is purified on 600 g of silica gel with a methylene chloride/acetone gradient (0-5 % acetone). Yield: 3.7 g of 9,11β-epoxy-21-fluoro-17α-isovaleryloxy-1,4-pregnadiene-3,20-dione.
d) Under the conditions in Example 30d 3 g of 9,11β-epoxy-21-fluoro-17α-isovaleryloxy-1,4-pregnadiene-3,20-dione are reacted with a 70 % $(HF)_n$/pyridine solution. The crude product is purified on 300 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 2.1 g of 9α,21-difluoro-11β-hydroxy-17α-isovaleryloxy-1,4-pregnadiene-3,20-dione.

Example 37
a) As described in Example 30a 8.7 g of 21-fluoro-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione and trimethylacetic anhydride are reacted to form 6.3 g of 21-fluoro-17α-trimethylacetoxy-1,4,9(11)-pregnatriene-3,20-dione, which 6.3 g are treated as in Example 30b with N-bromosuccinimide. After working up in the usual manner 6.5 g of 9α-bromo-21-fluoro-11β-hydroxy-17α-trimethylacetoxy-1,4-pregnadiene-3,20-dione are isolated.
b) 6.0 g of the above crude product are reacted as in Example 30c with potassium acetate and the crude product is purified on 600 g of silica gel with a methylene chloride/acetone gradient (0-5 % acetone). Yield: 3.1 g of 9,11β-epoxy-21-fluoro-17α-trimethylacetoxy-1,4-pregnadiene-3,20-dione.
c) 1.9 g of 9α,21-difluoro-11β-hydroxy-17α-trimethylacetoxy-1,4-pregnadiene-3,20-dione are produced as in Example 30d from 3.0 g of 9,11β-epoxy-21-fluoro-17α-trimethylacetoxy-1,4-pregnadiene-3,20-dione by reaction with a 70 % $(HF)_n$/pyridine solution, which 1.9 g are obtained after purification on 300 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone).

Example 38

a) 7.0 g of 21-fluoro-17α-(3-phenylpropionyloxy)-1,4,9(11)-pregnatriene-3,20-dione are produced as in Example 30a from 15.4 g of 21-fluoro-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione and 3-phenylpropionic acid chloride, which 7.0 g are reacted as in Example 30b with N-bromosuccinimide. Yield: 6.9 g of 9α-bromo-21-fluoro-11β-hydroxy-17α-(3-phenylpropionyloxy)-1,4-pregnadiene-3,20-dione.

b) 6.5 g of the above crude product are reacted with potassium acetate under the conditions of Example 30c. The crude product is purified on 650 g of silica gel with a methylene chloride/acetone gradient (0-5 % acetone). Yield: 3.8 g of 9,11β-epoxy-21-fluoro-17α-(3-phenylpropionyloxy)-1,4-pregnadiene-3,20-dione.

c) 3.5 g of 9,11β-epoxy-21-fluoro-17α-(3-phenylpropionyloxy)-1,4-pregnadiene-3,20-dione are treated as in Example 30d with a 70 % $(HF)_n$/pyridine solution and the crude product is purified on 400 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 2.1 g of 9α,21-difluoro-11β-hydroxy-17α-(3-phenylpropionyloxy)-1,4-pregnadiene-3,20-dione.

Example 39

a) 5.8 g of 17α-cyclopentanecarbonyloxy-21-fluoro-1,4,9(11)-pregnatriene-3,20-dione are produced as in Example 36 from 9.1 g of 21-fluoro-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione, 91 ml of cyclopentanecarboxylic acid and 44 ml of trifluoroacetic anhydride, which 5.8 g are treated as in Example 30b with N-bromosuccinimide. After working up in the normal manner 6.1 g of 9α-bromo-17α-cyclopentanecarbonyloxy-21-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione are isolated.

b) 6.0 g of the above crude product are reacted as in Example 30c with potassium acetate and the crude product is purified on 600 g of silica gel with a methylene chloride/acetone gradient (0-5 % acetone). 4.5 g of 17α-cyclopentanecarbonyloxy-9,11β-epoxy-21-fluoro-1,4-pregnadiene-3,20-dione are obtained.

c) 4.0 g of 17α-cyclopentanecarbonyloxy-9,11β-epoxy-21-fluoro-1,4-pregnadiene-3,20-dione are reacted as in Example 30d with a 70 % $(HF)_n$/pyridine solution. The crude product is purified on 400 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone). Yield: 2.8 g of 17α-cyclopentanecarbonyloxy-9α,21-difluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.

Example 40

a) 5.8 g of 17α-cyclohexanecarbonyloxy-21-fluoro-1,4,9(11)-pregnatriene-3,20-dione are produced under the conditions of Example 36 from 9.2 g of 21-fluoro-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione, 92 ml of cyclohexanecarboxylic acid and 40 ml of trifluoroacetic anhydride, which 5.8 g are reacted as in Example 30b with N-bromosuccinimide. Yield: 6.1 g of 9α-bromo-17α-cyclohexanecarbonyloxy-21-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.

b) 6.0 g of the above crude product are reacted as in Example 30c with potassium acetate and the crude product is purified on 600 g of silica gel with a methylene chloride/acetone gradient (0-5 % acetone). Yield: 3.4 g of 17α-cyclohexanecarbonyloxy-9,11β-epoxy-21-fluoro-1,4-pregnadiene-3,20-dione.

c) 2.4 g of 17α-cyclohexanecarbonyloxy-9α,21-difluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione are produced as in Example 30d from 3.1 g of 17α-cyclohexanecarbonyloxy-9,11β-epoxy-21-fluoro-1,4-pregnadiene-3,20-dione by reaction with a 70 % $(HF)_n$/pyridine solution, which 2.4 g are obtained after purification on 300 g of silica gel with a methylene chloride/acetone gradient (0-15 % acetone).

Example 41

1 g of 17α,21-(α-ethoxybenzylidenedioxy)-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione is stirred in 40 ml of dimethylformamide with 4 ml of trimethylsilyl flouride for 2 hours at room temperature. After precipitating with ice water and working up in the usual manner the whole is evaporated *in vacuo*. The crude product is purified on 120 g of silica gel with a methylene chloride/acetone gradient (0-10 % acetone). Yield 240 mg of 17α-benzoyloxy-9α,21-difluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.

II PHARMACEUTICAL PREPARATIONS

Example 42

Composition of an ointment

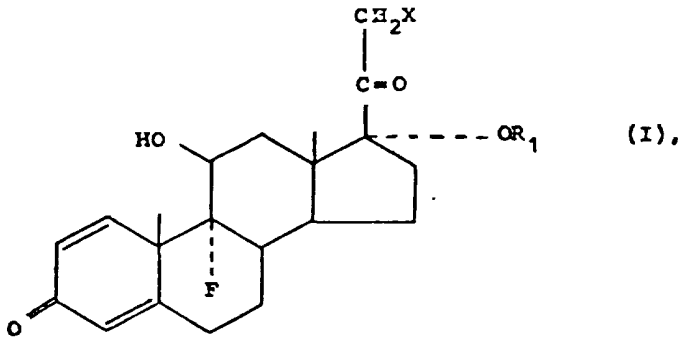
0.03 % of 9α-fluoro-11β-hydroxy-17α,21-dipropionyloxy-1,4-pregnadiene-3,20-dione
2.50 % Allercur hexachlorophenate, micronised, particle size approximately 8 μ
(Allercur = Trade Mark for 1-p-chlorobenzyl-2-pyrrolidylmethylbenzimidazole)

6.00 % Hostaphat KW 340 (Trade Mark) (tert. ester of O-phosophoric acid and wax alcohol tetra-glyclo ether)
0.10 % sorbic acid
10.00 % neutral oil (Migloyol 812 (Trade Mark))
3.50 % stearyl alcohol
1.50 % wool fat, anhydrous DAB 6
76.36 % desalted water

Example 43
Production of an inhalant
1.000g of micronised 9α-fluoro-11β-hydroxy-17α,21-dipropionyloxy-1,4-pregnadiene-3,20-dione (average particle size smaller than 7 μ) and 39.00 g of ground lactose are mixed together. A dose of 20 mg of inhalant is used per inhalation.

WHAT WE CLAIM IS:

1. A compound of the general formula (I)



(I),

wherein

R_1 represents a group of the general formula RCO– in which R represents a hydrogen atom or an alkyl group or a cycloalkyl or cycloalkylalkyl group or an alkyl-substituted cycloalkyl or cycloalkylalkyl group, and R_1 has from 1 to 8 carbon atoms, or in which R represents an aryl or aralkyl group or an alkyl-substituted aryl or aralkyl group, and R_1 has up to 9 carbon atoms.

X represents a fluorine or chlorine atom or a group of the general formula R'COO– which has from 3 to 8 carbon atoms and in which R' represents an alkyl group or a cycloalkyl or cycloalkylalkyl group or an alkyl-substituted cycloalkyl or cycloalkylalkyl group.

2. A compound as claimed in claim 1, wherein R_1 represents a formyl group or an alkanoyl or cycloalkanecarbonyl group having up to 8 carbon atoms or a benzoyl group, and X represents a fluorine or chlorine atom or an alkanoyloxy or cycloalkanecarbonyloxy group having from 3 to 8 carbon atoms.

3. A compound as claimed in claim 1 or claim 2, wherein R_1 represents a benzoyl group or an alkanoyl group having up to 6 carbon atoms.

4. A compound as claimed in any one of claims 1 to 3, wherein X represents a fluorine or chlorine atom or an alkanoyloxy group having up to 6 carbon atoms.

5. 17α-Acetoxy-9α-fluoro-11β-hydroxy-21-propionyloxy-1,4-pregnadiene-3,20-dione.

6. 17α-Acetoxy-21-butyryloxy-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.

7. 17α-Acetoxy-9α-fluoro-11β-hydroxy-21-valeryloxy-1,4-pregnadiene-3,20-dione.

8. 17α-Acetoxy-9α-fluoro-21-hexanoyloxy-11β-hydroxy-1,4-pregnadiene-3,20-dione.

9. 17α-Acetoxy-9α-fluoro-11β-hydroxy-21-trimethylacetoxy-1,4-pregnadiene-3,20-dione.

10. 9α-Fluoro-11β-hydroxy-17α,21-dipropionyloxy-1,4-pregnadiene-3,20-dione.

11. 21-Butyryloxy-9α-fluoro-11β-hydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione.

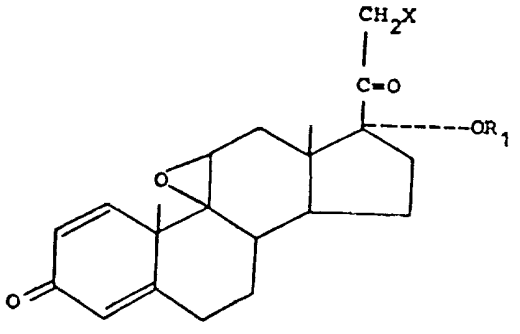
12. 9α-Fluoro-11β-hydroxy-17α-propionyloxy-21-valeryloxy-1,4-pregnadiene-3,20-dione.

13. 9α-Fluoro-21-hexanoyloxy-11β-hydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione.

14. 9α-Fluoro-11β-hydroxy-17α-propionyloxy-21-trimethylacetoxy-1,4-pregnadiene-3,20-dione.

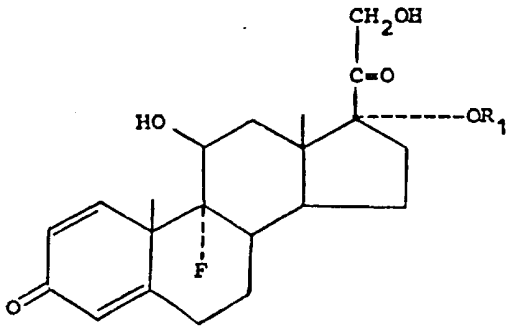
15. 17α-Butyryloxy-9α-fluoro-11β-hydroxy-21-propionyloxy-1,4-pregnadiene-3,20-dione.

16. 17α-Butyryloxy-9α-fluoro-11β-hydroxy-21-valeryloxy-1,4-pregnadiene-3,20-dione.
17. 17α-Butyryloxy-9α-fluoro-21-heptanoyloxy-11β-hydroxy-1,4-pregnadiene-3,20-dione.
18. 17α-Butyryloxy-9α-fluoro-11β-hydroxy-21-isobutyryloxy-1,4-pregnadiene-3,20-dione.
19. 9α-Fluoro-11β-hydroxy-21-propionyloxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione.
20. 21-Butyryloxy-9α-fluoro-11β-hydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione.
21. 9α-Fluoro-21-hexanoyloxy-11β-hydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione.
22. 9α-Fluoro-11β-hydroxy-17α-isobutyryloxy-21-propionyloxy-1,4-pregnadiene-3,20-dione.
23. 21-Butyryloxy-9α-fluoro-11β-hydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione.
24. 9α-Fluoro-11β-hydroxy-21-propionyloxy-17α-trimethylacetoxy-1,4-pregnadiene-3,20-dione.
25. 17α-Benzoyloxy-9α-fluoro-11β-hydroxy-21-propionyloxy-1,4-pregnadiene-3,20-dione.
26. 17α-Benzoyloxy-21-butyryloxy-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.
27. 17α-Benzoyloxy-9α-fluoro-11β-hydroxy-21-valeryloxy-1,4-pregnadiene-3,20-dione.
28. 17α-Benzoyloxy-9α-fluoro-11β-hydroxy-21-isobutyryloxy-1,4-pregnadiene-3,20-dione.
29. 17α-Benzoyloxy-9α-fluoro-11β-hydroxy-21-trimethylacetoxy-1,4-pregnadiene-3,20-dione.
30. 17α-Acetoxy-21-chloro-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.
31. 21-Chloro-9α-fluoro-11β-hydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione.
32. 21-Chloro-9α-fluoro-11β-hydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione.
33. 17α-Benzoyloxy-21-chloro-9α-fluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.
34. 17α-Acetoxy-9α,21-difluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.
35. 9α,21-Difluoro-11β-hydroxy-17α-propionyloxy-1,4-pregnadiene-3,20-dione.
36. 17α-Butyryloxy-9α,21-difluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.
37. 9α,21-Difluoro-11β-hydroxy-17α-valeryloxy-1,4-pregnadiene-3,20-dione.
38. 9α,21-Difluoro-17α-hexanoyloxy-11β-hydroxy-1,4-pregnadiene-3,20-dione.
39. 9α,21-Difluoro-11β-hydroxy-17α-isobutyryloxy-1,4-pregnadiene-3,20-dione.
40. 9α,21-Difluoro-11β-hydroxy-17α-isovaleryloxy-1,4-pregnadiene-3,20-dione.
41. 9α,21-Difluoro-11β-hydroxy-17α-trimethylacetoxy-1,4-pregnadiene-3,20-dione.
42. 9α,21-Difluoro-11β-hydroxy-17α-(3'-phenylpropionyloxy)-1,4-pregnadiene-3,20-dione.
43. 17α-Cyclopentanecarbonyloxy-9α,21-difluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.
44. 17α-Cyclohexanecarbonyloxy-9α,21-difluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.
45. 17α-Benzoyloxy-9α,21-difluoro-11β-hydroxy-1,4-pregnadiene-3,20-dione.
46. A process for the manufacture of a compound as claimed in claim 1 wherein a) the epoxide ring of a compound of the general formula (II)



(II),

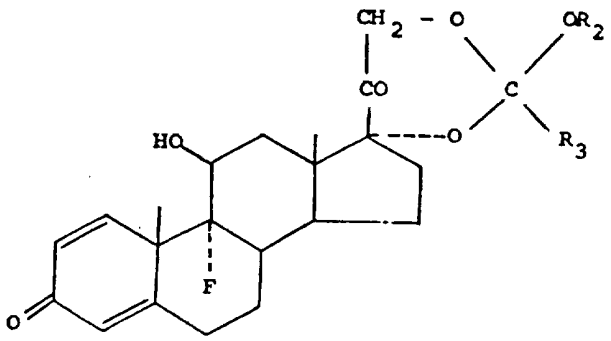
in which X and R_1 have the meanings given in claim 1 is opened with hydrogen fluoride, or
b) a 9-fluoro derivative of the general formula (III)



(III),

wherein R_1 has the meaning given in claim 1, is halogenated or esterified in the 21-position, or

c) for the production of a 9-fluoroprednisolone derivative of the general formula (I) wherein X represents a fluorine or chlorine atom, an ortho ester of the general formula (IV)



(IV),

wherein R_3 represents a hydrogen atom, an alkyl group or a cycloalkyl group having up to 7 carbon atoms or a phenyl group and R_2 represents an alkyl group having 1 to 4 carbon atoms, is cleaved with a trimethylsilyl halide or a triphenylmethyl halide.

47. A process as claimed in claim 46, carried out substantially as described in any one of the Examples 1 to 41 herein.

48. A compound as claimed in claim 1, whenever obtained by a process claimed in claim 46 or claim 47.

49. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 45 and 48, in admixture or conjunction with a pharmaceutically suitable carrier.

50. A pharmaceutical preparation as claimed in claim 49, which is in the form of an ointment.

51. A pharmaceutical preparation as claimed in claim 50, substantially as described in Example 42 herein.

52. A pharmaceutical preparation as claimed in claim 49, which is in the form of an inhalant.

53. An inhalant as claimed in claim 52, substantially as described in Example 43 herein.

54. A pharmaceutical composition which comprises a compound as claimed in any one of claims 1 to 45 and 48, and a medicament for the treatment of a non-inflammatory disease but which is liable to have an inflammatory action.

55. A pharmaceutical preparation which comprises a composition as claimed in claim 54, in admixture or conjunction with a pharmaceutically suitable carrier.

56. A pack which comprises a compound as claimed in any one of claims 1 to 45 and 48, or a preparation as claimed in any one of claims 49 to 53, and a medicament for the treatment of a non-inflammatory disease but which is liable to have an inflammatory action.

57. A method of treating a non-human animal to relieve inflammation, which comprises applying to the affected area a compound as claimed in any one of claims 1 to 45 and 48 or a preparation or composition as claimed in any one of claims 49 to 53.

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