PATENT SPECIFICATION (11) 1 563 638

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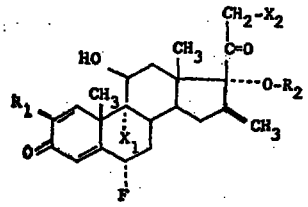
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(19)

(54) 21-HALOGENOPREGNANE COMPOUNDS

(71) We, CIBA-GEIGY AG, a Swiss body corporate, of 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 invention relates to the manufacture of new polyhalogenated steroids, especially 9α,21 - dihalogeno - 11β,17α - dihydroxy - 6α - fluoro - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione compounds of the formula



(I)

in which X_1 represents chlorine or fluorine, X_2 represents bromine or chlorine, R_1 represents hydrogen or chlorine and R_2 represents the acyl radical Ac of a carboxylic acid, or salts of such compounds having salt-forming properties, as well as to the new compounds themselves or salts of such compounds having salt-forming properties and also to pharmaceutical compositions which contain the new compounds, and the use thereof.

Carbon-containing compounds and radicals designated throughout this specification as "lower" contain not more than 7 carbon atoms.

An acyl group Ac is preferably derived from the carboxylic acids customary in steroid chemistry, for example those containing up to and including 18 carbon atoms, and is in particular derived from corresponding aliphatic cycloaliphatic, cycloaliphatic-aliphatic, aromatic or araliphatic carboxylic acids. The radical Ac is, in particular, lower alkanoyl, such as lower alkanoyl which is substituted or unsubstituted, for example by free or etherified or esterified hydroxy, such as lower alkoxy, for example methoxy or ethoxy, or phenoxy, or halogen, for example chlorine, or carboxyl, i.e. a straight-chain or branched lower alkanoyl, for example acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, 2-ethyl-butyryl, 2,2- or 3,3-dimethylbutyryl, hexanoyl or heptanoyl, or hydroxy-lower alkanoyl, for example 3-hydroxypropionyl, phenoxy-lower alkanoyl, for example phenoxyacetyl, halogeno-lower alkanoyl, for example chloro-acetyl, or carboxy-lower alkanoyl, for example 3-carboxypropionyl or 4-carboxy-butyryl, alkenoyl, for example undecylenoyl, cycloalkyl-lower alkanoyl, for example cyclopentylpropionyl or cyclohexylacetyl, substituted or unsubstituted benzoyl, for example benzoyl, or substituted or unsubstituted phenyl-lower alkanoyl or phenyl-lower alkenoyl, for example phenylacetyl.

Salts of compounds of the formula I having salt-forming groups are those of such compounds which contain corresponding groups, which are optionally in the form of a salt, in an acyl radical Ac, above all the corresponding pharmaceutically useful non-toxic salts which are usually water-soluble. Compounds of the formula I having salt-forming properties are, in particular, those in which R_2 represents carboxy-lower alkanoyl radical Ac. Such compounds can in particular be in the form of a metal salt, for example in the form of an alkali metal salt, such as a sodium salt or potassium salt. The sodium salt of a compound of the formula I in which R_2 represents 3-carboxypropionyl is particularly preferred.

The compounds of the present invention have valuable pharmacological properties. Thus they are distinguished by a pronounced anti-antiflammatory action, whilst having a reduced systemic action. Accordingly, for example, when applied locally in the raw cotton wool granuloma test on rats, inhibition of the inflammatory

processes can be observed in the dosage range between about 0.001 and about 0.10 mg per cotton wool pellet. The first indications of a systemic action, however, are only apparent at, or even above, the upper limit of this dosage range, namely in the decrease in weight of the thymus at a dose above 0.03 mg per cotton wool pellet of the adrenals at a dose above 0.1 mg per cotton wool pellet, and of the entire body only at a dose of 1 mg per cotton wool pellet. On topical administration (rat's ear test of Tonelli), ED_{50} is approx. 10 to 30 mcg/ml.

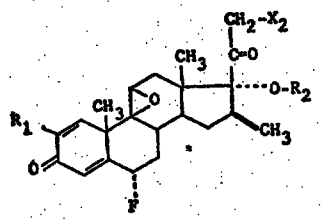
On account of these biological properties, the new compounds can be used in all indications for which glucocorticoid steroids with anti-inflammatory properties are suitable. In particular, they are suitable for use as anti-inflammatory glucocorticoids for topical application, for example for the treatment of inflammatory dermatoses, such as eczemas, or dermatides, or dermatoses which are partially corticoid-resistant, for example psoriasis. They can also be used as useful intermediate products for obtaining other useful substances, especially other pharmacologically active steroids.

The invention preferably relates to those compounds of the formula I in which X_1 represents fluorine or chlorine, X_2 represents chlorine, R_1 represents hydrogen and R_2 represents lower alkanoyl, for example propionyl.

The invention relates above all to compounds of the formula I in which X_1 represents fluorine or chlorine, X_2 represents chlorine, R_1 represents chlorine and R_2 represents lower alkanoyl, for example propionyl.

The invention above all relates most particularly to the compounds of the formula I mentioned in the examples.

The compounds according to the invention of the formula I can be manufactured in a manner which is known per se, for example by treating a compound of the formula



(II)

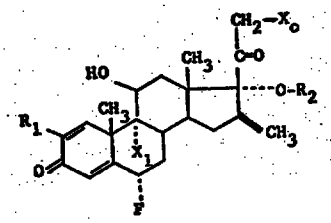
with a hydrogen halide of the formula $H—X_1$ (III) and, if desired converting a compound of the formula I, which is obtainable according to the process and has salt-forming properties, into a salt, and/or converting a salt, which is obtainable according to the process, of a salt-forming compound of the formula I into the free compound of the formula I or into another salt.

Cleavage of the 9β,11β-oxide group in a starting material of the formula II by treatment with a hydrogen halide of the formula III, that is to say with hydrogen chloride or hydrogen fluoride, is carried out in a manner which is known per se, advantageously using an anhydrous hydrogen halide, optionally in the presence of an inert solvent, such as chloroform, tetrahydrofurane or, in particular, dimethylformamide, or also hydrogen fluoride in aqueous solution.

In place of the hydrogen halide of the formula III, it is also possible to use an agent which releases hydrogen fluoride or hydrogen chloride, such as the salt of such an acid with a tertiary organic base, for example pyridine, or, especially if hydrogen fluoride is used, a similar suitable addition compound. A particularly advantageous process is described in U.S. Patent 3,211,758, wherein hydrogen fluoride is used in the form of an adduct with a carbamic acid derivative or thiocarbamic acid derivative, especially with urea.

The starting materials of the formula II can be obtained in a manner which is known per se, for example by eliminating water from a 6α - fluoro - 11β - hydroxy - 16β - methyl - 2 - R_1 - 17α - OR_2 - 21 - X_2 - pregna - 1,4 - diene - 3,20 - dione compound, for example by treatment with a suitable acid chloride, such as phosphorus oxychloride or methanesulphonyl chloride, in the presence of a base, for example pyridine, adding hypobromous acid (which, for example, is used in the form of N-bromoacetamide or N-bromosuccinimide) onto the 9,11-double bond of the 6α - fluoro - 16β - methyl - 2 - R_1 - 17α - OR_2 - 21 - X_2 - pregna - 1,4,9(11) - triene - 3,20 - dione compound which is thus obtainable and eliminating hydrogen bromide from the corresponding 9α, 11β-bromohydrin compound by treatment with a base, for example an alkali metal carbonate or alkali metal hydroxide, for example potassium carbonate or potassium hydroxide, with formation of the desired starting material of the formula II. In the above intermediate products, R_1, R_2 and X_2 have the abovementioned meanings.

The new compounds of the formula I can also be obtained by converting the group X_0 in a compound of the general formula



(IV)

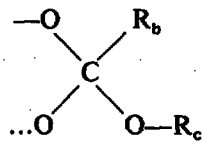
in which X_0 represents a group which can be converted into a halogen atom X_2, into a halogen atom X_2 and, if desired, carrying out the additional process steps.

A group X_0 which can be converted into a halogen atom X_2 is the group —O—R_a, in which R_a represents the acyl radical of an organic sulphonic acid. The replacement of the sulphonyloxy group —O—R_a by the halogen atom X_2 is effected in a manner which is known per se. The acyl radical R_a of an organic sulphonic acid is, in particular, the acyl radical of an aliphatic or carboxylic, optionally unsaturated sulphonic acid or of an aromatic sulphonic acid. Such acids are, inter alia, unsubstituted or substituted, for example halogenated, lower alkanesulphonic acids, cycloalkanesulphonic acids, in which the cycloalkyl radical can be monocyclic or polycyclic, or benzenesulphonic acids which are unsubstituted or substituted by lower alkyl, for example methyl, lower alkoxy, for example methoxy, halogen, for example chlorine or bromine, and/or nitro. Typical examples of such acids are trifluoromethanesulphonic acid, (+) - camphor - 10 - sulphonic acid, 4 - bromobenzenesulphonic acid and 3 - nitrobenzenesulphonic acid and especially p-toluenesulphonic acid and, in particular, methanesulphonic acid.

The substitution reaction is usually carried out by treating the starting material with an alkali metal halide of the formula M—X_2 (V), in which M represents an alkali metal, in the presence of an aprotic organic solvent which has a dielectric constant of 29 or higher. An alkali metal M which can be used is, preferably, lithium. Aprotic organic solvents which can be used are, in particular, di-lower alkyl sulphoxides, for example dimethyl sulphoxide, N,N-di-lower alkylamides of lower aliphatic carboxylic acids, for example N,N-dimethylformamide or N,N-dimethylacetamide, lower alkanenitriles or lower alkenenitriles, for example acetonitrile, hexa-lower alkylphosphoramides, for example hexamethylphosphortriamide, or, above all when using starting materials of the formula IV in which R_2 represents hydrogen, also ketones, especially aliphatic or cycloaliphatic ketones containing up to and including 10 carbon atoms such as corresponding alkanones, for example acetone, 2-butanone, 2- or 3-pentanone, 2-hexanone or 4-decanone, or cycloalkanones containing up to and including 8 ring carbon atoms, for example cyclopentanone or cyclohexanone, or mixtures of such solvents.

The reaction is appropriately carried out between room temperature and the boiling point of the reaction mixture and is effected with at least one equivalent of the alkali metal halide of the formula V.

A further group X_0 which can be converted into a halogen atom X_2 is hydroxyl and also a radical which, together with —O—R_2, forms an etherified hydroxymethylenedioxy group of the formula



(IVa)

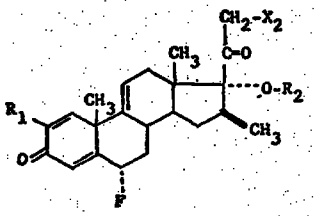
in which R_b represents hydrogen or an organic radical, especially an aliphatic hydrocarbon radical, such as lower alkyl, for example methyl or ethyl, and R_c forms an organic radical, especially an aliphatic hydrocarbon radical, such as lower alkyl, for example methyl or ethyl.

The replacement of a hydroxyl group X_0 by halogen X_2 and also of the group of the formula IVa by X_2 in the 21-position with a simultaneous formation of an esterified hydroxyl in the 17α-position of the formula —O—CO—R_b can be carried out in a manner which is known per se, for example by treatment with a phosphine, such as a tri-lower alkylphosphine, or preferably triphenylphosphine, and a carbon tetrahalide, preferably carbon tetrachloride, and also bromotrichloromethane. The reaction is preferably carried out in a dipolar aprotic medium, for example in the presence of a corresponding solvent of the amide type, such as dimethyl formamide, dimethylacetamide, 1 - methyl - 2 - pyrrolidone or hexamethylphosphortriamide, with cooling or warming, for example in a temperature range between about 10°C and about 125°C and, if necessary, in a closed vessel and/or in an inert gas atmosphere.

The starting materials of the formula IV are known or can be manufactured in a manner which is known per se, for example compounds of the formula IV, in which X_0 represents organic sulphonyloxy, can be manufactured by converting the 21-hydroxyl group in a 6α - fluoro - 11β,21 - dihydroxy - 16β - methyl - 2 - R_1 - 9α - X_1 - 17α - OR_2 - pregna - 1,4 - diene - 3,20 - dione compound into the desired organic sulphonyloxy group —OR_a by treatment with a reactive derivative of an organic sulphonic acid of the formula R_a—OH(VI), especially with a corresponding sulphonic acid chloride of the formula R_a—Cl (VIa), in the presence of a base, for example pyridine; and compounds of the formula IV in which X_0 and —O—R_2 together form a group of the formula IVa can be manufactured by treating a 6α -

fluoro - 11β, 17α,21 - trihydroxy - 16β - methyl - 2 - R_1 - 9α - X_1 - pregna - 1,4 - diene - 3,20 - dione compound with a suitable orthocarboxylic acid ester, for example triethyl orthoformate or triethyl orthopropionate, in the presence of a strong acid, for example p-toluenesulphonic acid, and advantageously with removal of the alcohol which is set free, for example by azeotropic distillation.

The new compounds of the formula I in which X_1 represents chlorine can also be obtained by adding hypochlorous acid onto the 9,11-double bond of a compound of the formula



(VII)

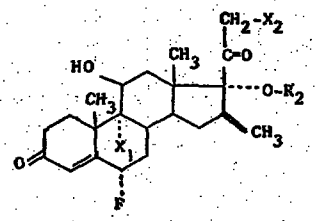
and, if desired, carrying out the additional process steps.

According to the above reaction, the elements of hypochlorous acid are added onto the 9,11-double bond of the starting materials of the formula VII in a manner which is known per se. The reaction is carried out, for example, with aqueous hypochlorous acid, or a hypochlorous acid donor, such as a N-chlorocarboxylic acid amide or imide (cf. U.S. Patent Specification 3,057,886), can be used. The reaction is carried out in an inert solvent, such as a tertiary alcohol, for example tert. butanol, an ether, for example diethyl ether, methyl isopropyl ether, dioxane or tetrahydrofurane, or a ketone, for example acetone, in the presence of water and optionally of a strong acid.

The addition of hypochlorous acid to the 9,11-double bond of the starting material of the formula VII can also be carried out in a non-aqueous medium. A particularly advantageous embodiment of this modification is the use of lower alkyl hypochlorites, above all tert.-butyl hypochlorite, in an inert, water-immiscible solvent, for example a nitro-hydrocarbon, usually in the presence of perchloric acid (cf. German Patent Specification 2,011,559).

The starting materials of the formula VII can be manufactured in a manner which is known per se, for example by eliminating water from a 6α - fluoro - 11β - hydroxy - 16β - methyl - 2 - R_1 - 17α - OR_2 - 21 - X_2 - pregna - 1,4 - diene - 3,20 - dione compound, for example by treatment with a suitable acid chloride, such as phorphorus oxychloride or methanesulphonyl chloride, in the presence of a base, for example pyridine.

The new compounds of the formula I in which R_1 represents hydrogen can also be obtained by introducing the 1,2-double bond into a compound of the formula



(VIII)

and, if desired, carrying out the additional measures.

The introduction of the 1,2-double bond can be carried out by dehydrogenation, for example by treatment with a suitable dehydrogenating quinone, such as 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone.

The 1,2-dehydrogenation of starting materials of the formula VIII can also be effected by treatment with selenium dioxide or microbiologically, for example with suitable microorganisms, such as *Corynebacterium simplex* or *Septomyxa affinis*.

The starting materials of the formula VIII have valuable pharmaceutical properties analogous to those of end products of the formula I and can also be used in the same way as these latter. The compounds of the formula VIII, in which X_1, X_2 and R_2 have the above meanings, also form an object of the present invention. They are obtained by means of the process described above, starting in each case from 1,2-saturated, 2-unsubstituted compounds of the type of formula II, IV or VII, and carrying out the corresponding reaction. Thus they can be obtained for example by converting the 21-hydroxyl group of a 6α - fluoro - 11β,21 - dihydroxy - 16β - methyl - 9α - X_1 - 17α - OR_2 - pregn - 4 - ene - 3,20 - dione compound (i.e. a compound of the formula IV type) for example by treatment with a suitable sulphonic acid derivative, such as methanesulphonyl chloride, into a 21-organic sulphonyloxy group, and treating the intermediate with a lithium halide, for example lithium chloride.

A compound of the formula I which is obtainable according to the process can be converted into another compound of the formula I in a manner which is known per se.

Thus, for example, in a compound of the formula I in which R_1 represents hydrogen, the latter can be replaced by chlorine. For this purpose it is possible to add one molecule of chlorine onto the 1,2-double bond in such a compound and to split off one mole of hydrogen chloride from the intermediate 1,2 - dichlor - pregn - 4 -

ene - 3,20 - dione. The addition of chlorine to the 1,2-double bond can be effected by treatment with elementary chlorine or with a mixture of two different chlorine-containing compounds, one of which releases positive chlorine and the other releases negative chlorine.

The treatment with elementary chlorine can be carried out in an inert organic solvent, for example an ether, such as dioxane or tetrahydrofurane, a halogenated hydrocarbon, for example methylene chloride, or a carboxylic acid, especially a lower aliphatic carboxylic acid, such as acetic acid or propionic acid, or a derivative thereof, such as an acid amide, for example dimethylformamide, or a nitrile, such as a lower alkaenitrile, for example acetonitrile. Advantageously, it is also possible to use mixtures of such solvents, especially mixtures of an ether, such as dioxane, with one of the lower alkanecarboxylic acids mentioned. The chlorination is usually carried out using the stoichiometric amount of chlorine at low temperature, say between −50°C and +30°C, for example at between −20°C and +10°C, and with the exclusion of light.

In a particularly preferred embodiment, the compound of the formula I in which R_1 represents hydrogen, is dissolved in one of the above solvents, for example dioxane, and treated with a solution of chlorine in a lower aliphatic carboxylic acid, for example propionic acid, and this solution is then left to stand, for example at the indicated temperature.

In a mixture of two different chlorinating agents, reagents which can set free positive chlorine are chlorinated acid amides or acid imides, such as chlorosuccinimide or chloroacetamide, and reagents which yield negative chlorine are, for example, hydrogen chloride and also alkali metal chlorides.

The elimination of hydrogen chloride from the intermediate 1,2 - dichloro - pregn - 4 - ene - 3,20 - dione is advantageously effected by treatment with a base. Examples of suitable bases are tertiary organic nitrogen bases, such as lower aliphatic amines, for example a tri-lower alkylamine, such as triethylamine, hetero-aromatic bases, for example pyridine or collidine, or mixed aliphatic-aromatic bases, such as N,N-di-lower alkyl-aniline, for example N,N-dimethylaniline. The reaction is preferably carried out with an excess of the base, which at the same time can be used as solvent. However, it is also possible to use inorganic bases, such as, in particular, the alkali metal salts or alkaline earth metal salts which are also used for hydrolysis of the 11β-trifluoroacetate described below, for example potassium acetate or bicarbonate or sodium acetate or bicarbonate, in aqueous-alcoholic solution, as well as the corresponding hydroxides. The dehydrochlorination is preferably carried out in a temperature range between about 20°C and about 100°C. Advantageously, those agents and reaction conditions are chosen which have no influence on the other functional groups, especially those in the 17-position and/or 21-position.

Before adding chlorine onto the 1,2-double bond in a compound of the formula I, in which R_1 represents hydrogen, the 11β-hydroxyl group is advantageously protected, for example by esterification, preferably in the form of a trifluoroacetoxy group, a compound of the formula I in which R_1 represents hydrogen being reacted in a manner which is known per se with a suitable reactive derivative of an acid, for example with trifluoroacetyl chloride or trifluoroacetic anhydride. It is known that the trifluoroacetyl group can be split off easily by solvolysis, for example by hydrolysis or alcoholysis, for example by treatment with alkali metal hydroxides, carbonates, bicarbonates or acetates or alkaline earth metal hydroxides, carbonates, bicarbonates or acetates, in a suitable medium, for example an alcoholic, such as methanolic, or aqueous-alcoholic medium. A particular method of carrying out the solvolysis of the 11-trifluoroacetoxy group is described in German Patent Specification 1,593,519. This procedure can be used mainly because it leaves intact any esterified hydroxyl group which may be present in the 17α-position and consists in treating the 11β-trifluoroacetoxy compound, in a lower alkanol, with the salt of an acid which has a pKa value in the range of from about 2.3 to about 7.3, for example with an alkali metal azide, for example sodium azide or potassium azide, or an alkali metal formate, for example sodium formate or potassium formate. If appropriate, this salt can also be used only in catalytic amounts. Furthermore, the 11β-trifluoroacetyl group can also be removed by treatment with other bases, for example with amines and especially with hetero-aromatic bases, such as pyridine or collidine. Finally, the cleavage of the trifluoroacetoxy group by treatment with silica gel according to the process described in German Offenlegungsschrift 2,144,405 is also possible.

Liberation of the 11β-hydroxyl group from the protected form can be effected immediately after the addition of chlorine to the 1,2-double bond or at the same time as the dehydrochlorination by means of a base, but if desired, it can also be effected only subsequently to this step as a separate operation.

Compounds of the formula I which are obtainable according to the process and have salt-forming properties, that is to say which contain an acyl group R_2 which is suitable for forming a salt, can be converted into their salts in a manner which is known per se. Accordingly those compounds in which R_2 represents a carboxy-lower alkanoyl radical can be converted into their salts by treatment with a suitable base, such as a metal hydroxide, carbonate or bicarbonate, especially an alkali metal hydroxide, carbonate or bicarbonate, such as sodium hydroxide, carbonate or bicarbonate or potassium hydroxide, carbonate or bicarbonate (the equivalent amount of the base preferably being used), usually in an aqueous or aqueous-alcoholic medium.

Conversely, a salt, which is obtainable according to the process, of a compound of the formula with salt-forming properties can be converted into the free compound, the corresponding salt with a base, for example, by treatment with an acid, such as an inorganic acid (for example by acidifying a solution of the salt in an aqueous or aqueous-organic medium to a pH value of about 1—2).

The starting materials used in the above process steps are preferably those which result in the compounds described above as being particularly preferred.

The present invention also relates to pharmaceutical compositions which contain, as active ingredient, a compound according to the invention of the formula I, or a salt of such a compound with salt-forming properties, and to a process for the manufacture of such pharmaceutical compositions.

Suitable pharmaceutical compositions are in particular those for topical application, such as creams, ointments, pastes, foams, tinctures and solutions, which contain from about 0.005% to about 0.1% of the active compound, and also compositions for oral administration, for example tablets, coated tablets and capsules, and those for parenteral administration.

Creams are oil-in-water emulsions which contain more than 50% of water. Fatty alcohols are chiefly used as oleaginous base, for example lauryl, cetyl or stearyl alcohol, fatty acids, for example palmitic or stearic acid, liquid to solid waxes, for example isopropyl myristate, wool wax or bees-wax, and/or hydrocarbons, for example petroleum jelly (petrolatum) or paraffin oil. Suitable emulsifiers are surface-active substances with primarily hydrophilic properties, such as corresponding non-ionic emulsifiers, for example fatty acid esters of polyalcohols or ethylene oxide adducts thereof, such as polyglycerol fatty acid esters or polyoxyethylene sorbitan fatty acid esters (Tweens—Registered Trade Mark); polyoxyethylene fatty alcohol ethers or esters, or corresponding ionic emulsifiers, such as alkali metal salts of fatty alcohol sulphates, for example sodium lauryl sulphate, sodium cetyl sulphate or sodium stearyl sulphate, which are customarily used in the presence of fatty alcohol, for example cetyl alcohol or stearyl alcohol. Additives to the water phase include agents which reduce water loss through evaporation, for example polyalcohols, such as glycerol, sorbitol, propylene glycol and/or polyethylene glycols, as well as preservatives, perfumes etc.

Ointments are water-in-oil emulsions which contain up to 70%, preferably however approx. 20% to about 50%, of water or aqueous phase. The oleaginous phase comprises chiefly hydrocarbons, for example petroleum jelly, paraffin oil and/or hard paraffins, which contain preferably hydroxy compounds suitable for improving the water-absorption, such as fatty alcohols or esters thereof, for example cetyl alcohol or wool wax alcohols, or wool wax. Emulsifiers are corresponding lipophilic substances, such as sorbitan fatty acid esters (Spans—Registered Trade Mark), for example sorbitan oleate and/or sorbitan isostearate. Additives to the water phase include humectants, such as polyalcohols, for example glycerol, propylene glycol, sorbitol and/or polyethylene glycol, and preservatives, perfumes etc.

Greasy ointments are anhydrous and contain as base in particular hydrocarbons, for example paraffin, petroleum jelly and/or liquid paraffins, furthermore natural or partially synthetic fat, for example coconut fatty acid triglycerides, or preferably hardened oils, for example hydrated ground nut or castor oil, and also fatty acid partial esters of glycerol, for example glycerol mono- and distearate, and, for example, the fatty alcohols, emulsifiers and/or additives for increasing the water-absorption mentioned in connection with the ointments.

Pastes are creams and ointments containing powdered ingredients which absorb secretions, such as metal oxides, for example titanium oxide or zinc oxide, and talc and/or aluminium silicates whose purpose it is to bind moisture or secretion present.

Foams are administered from pressurised dispensers and are liquid oil-in-water emulsions in aerosol form, with halogenated hydrocarbons, such as chlorofluoro-lower alkanes, for example dichlorodifluoromethane and dichlorotetrafluoroethane being used as propellants. For the oleaginous phase there are used,

inter alia, hydrocarbons, for example paraffin oil, fatty alcohols, for example cetyl alcohol, fatty acid esters, for example isopropyl myristate, and/or other waxes. As emulsifiers there are used, inter alia, mixtures of those emulsifiers with primarily hydrophilic properties, such as polyoxyethylene sorbitan fatty acid esters (Tweens—Registered Trade Mark), and those with primarily lipophilic properties, such as sorbitan fatty acid esters (Spans—Registered Trade Mark). In addition, the conventional additives are used, such as preservatives etc.

Tinctures and solutions generally have an aqueous ethanolic base to which are added, inter alia, polyalcohols, for example glycerol, glycols, and/or polyethylene glycol, as humectants for reducing water loss, and fat-restoring substances such as fatty acid esters with lower polyethylene glycols, i.e. lipophilic substances which are soluble in the aqueous mixture as substitute for fatty substances which are taken from the skin with the ethanol, and, if necessary, other assistants and additives.

The pharmaceutical compositions for topical application are obtained in known manner, for example by dissolving or suspending the active substance in the base or in a part thereof, if necessary. When processing the active substance in the form of a solution, it is usually dissolved in one of the two phases before the emulsification, and when processing the active substance in the form of a suspension, it is mixed with a part of the base before the emulsification and than added to the remainder of the formulation.

In addition to the pharmaceutical compositions which can be applied topically, other suitable preparations are those for enteral, for example oral, and parenteral administration to warm-blooded animals and which contain the active substance as sole ingredient or together with a pharmaceutically acceptable carrier. These pharmaceutical compositions contain about 0.01% to about 10% of active substance and are in dosage unit form, such as coated tablets, tablets, capsules, suppositories or ampoules. They are obtained in known manner, for example by conventional mixing, granulating, coating, dissolving or lyophilising methods.

The dosage of active substance depends on the species of warm-blooded animal, the age, and the individual condition as well as on the mode of application.

The new compounds the formula I and the salts of such compounds with salt-forming properties are useful in medicine, preferably for treating inflammations, chiefly an anti-inflammatory glucocorticoids for local application, normally in the form of pharmaceutical compositions, especially in the form of pharmaceutical compositions for topical application.

The following Examples describe the invention in more detail, without in any way restricting the scope thereof.

Example 1

230 mg of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone (DDQ) are added to a solution of 228 mg of 21 - chloro - 6α, 9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate in 11.4 ml of dioxane, which is then refluxed for 20 hours in a nitrogen atmosphere. The reaction mixture is concentrated in a water jet vacuum and the amorphous residue is chromatographed on 100 times its weight of silica gel (stepped column). The fractions eluted with a 99:1 mixture of methylene chloride/methanol yield the pure 21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate which melts at 220°—221°C after recrystallisation from methylene chloride/ether.

The 17-monopropionate used as starting material is prepared as follows:

A suspension of 1 g of 21 - chloro - 9β,11β - epoxy - 17α - hydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate in 5.4 ml of dioxane and 1.4 ml of triethyl orthoformate is treated with 0.9 ml of a solution consisting of 277 mg of p-toluenesulphonic acid, 2.7 ml of dioxane and 0.55 ml of ethyl alcohol and stirred for 90 minutes at room temperature. After addition of 3.8 ml of pyridine, the reaction mixture is diluted with ethyl acetate, washed 3 times with a saturated solution of sodium chloride, dried and concentrated in a water jet vacuum. The crude 3 - ethyl - enol ether (3 - ethoxy - 21 - chloro - 9β,11β - epoxy - 17α - hydroxy - 16β - methyl - pregna - 3,5 - dien - 20 - one - 17 - propionate) is dissolved in a mixture of 50 ml of tetrahydrofurane and 10 ml of water and the solution is treated for 40 minutes at room temperature with gaseous perchloroyl fluoride. After nitrogen has subsequently been introduced over the course of 10 minutes, the reaction solution is diluted with ethyl acetate, washed successively with 10% potassium iodide solution, 10% sodium thiosulphate solution and 3 times with a saturated solution of sodium chloride, then dried and concentrated in a water jet vacuum. The crude product is chromatographed on 100 times its weight of silica gel (stepped column).

The column is eluted with a 90:10 mixture of toluene/ethyl acetate. Recrystallisation from methylene chloride/ether of the

fractions obtained yields 21 - chloro - 6α - fluoro - 9β,11β - epoxy - 17α - hydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate which melts at 174—177°C.

14.5 ml of a reagent prepared by mixing 10 g of urea with 13.25 g of anhydrous liquid hydrogen fluoride are poured over 720 mg of the above compound in a plastic vessel. The reaction mixture is stirred for 3 hours with ice cooling, then poured onto 55 ml of an ice-cold saturated solution of ammonia, weakly acidified with acetic acid and extracted twice with chloroform. The organic phases are combined, washed with the ice-cold sodium hydroxide solution, dried and concentrated in a water jet vacuum. The crude product is chromatographed on 100 times its weight of silica gel (stepped column). The column is eluted with 90:10 mixture of toluene/ethyl acetate. Recrystallisation from methylene chloride/ether of the fractions obtained yields 21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate which melts at 212°—213°C.

Example 2

A solution of 3.7 g of 21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methylpregna - 1,4 - diene - 3,20 - dione - 17-propionate in 30 ml of dioxane is treated with 1.85 ml of a solution which is prepared by introeucing 7.7 g of chlorine gas into 100 ml of propionic acid. The reaction mixture is allowed to stand for 5 days at 3—4°C. It is then diluted with chloroform, washed successively with a 10% potassium iodide solution, a 10% sodium thiosulphate solution, dilute sodium hydroxide solution and water, dried, and concentrated in a water jet vacuum. The crude 1ξ2ξ - 21 - trichloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methylpregn - 4 - ene - 3,20 - dione - 17 - propionate is dissolved in methylene chloride to remove HCl and filtered through a column of 37 g of basic alumina (activity 2). The eluted solution is concentrated and recrystallised from methylene chloride to yield 2,21 - dichloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methylpregna - 1,4 - diene - 3,20 - dione - 17 - propionate which melts at 202°—204°C.

Example 3

A solution of 350 mg of 9α,21 - dichloro - 6α - fluoro - 11β,17 - dihydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate and 525 mg of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone in 17.5 ml of dioxane is refluxed for 20 hours in an atmosphere of nitrogen. The cooled mixture is filtered and the filtrate is evaporated. The residue is dissolved in methylene chloride and filtered through 15 times its weight of neutral alumina (activity 2). The filtrate is concentrated and purified by preparative thin-layer chromatography (on silica gel, 3 developings by a 9:1 mixture of toluene/methanol as eluant). The desired zone is localised by ultra-violet light having a wavelength of 254 nm, eluted from the adsorbent with ethyl acetate and recrystallised from methylene chloride/ether, affording the desired 9α,21 - dichloro - 6α - fluoro - 11β,17 - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate which melts, with decomposition, at 212°—213°C.

The starting steroid is obtained as follows:

Hydrogen chloride gas is introduced at 0°C in the course of 30 minutes into a solution of 400 mg of 21 - chloro - 6α - fluoro - 9β,11 - epoxy - 17 - hydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dionepropionate in 20 ml of chloroform. The mixture is allowed to stand for a further 30 minutes at 0°C, diluted with chloroform, washed with an ice-cold saturated sodium hydrocarbonate solution, dried and concentrated in vacuo. The crude 9α,21 - dichloro - 6α - fluoro - 11β,17 - dihydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate can be used without purification for the dehydrogenation reaction.

Example 4

Hydrogen chloride gas is introduced at 0°C in the course of 30 minutes into a solution of 2.8 g of 21 - chloro - 6α - fluoro - 9β,11 - epoxy - 17 - hydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dionepropionate in 140 ml of chloroform. The mixture is allowed to stand for a further 30 minutes at 0°C, diluted with chloroform, washed with an ice-cold saturated sodium hydrocarbonate solution, dried and evaporated in vacuo. The crude product is chromatographed on 100 times its weight of silica gel (stepped column). The desired product is eluted with a 99:1 mixture of toluene/methanol. Crystallisation from methylene chloride/ether yields 9α,21 - dichloro - 6α - fluoro - 11β,17 - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate which melts, with decomposition, at 212°—213°C and is identical with the product of Example 3.

The starting steroid is obtained as follows:

A mixture of 3 g of 21 - chloro - 16α - fluoro - 9β,11 - epoxy - 17 - hydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dionepropionate and 3 g of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone in 150 ml of dioxane is refluxed for 20 hours in an

atmosphere of nitrogen. The cooled mixture is filtered, and the filtrate concentrated.

The residue is dissolved in methylene chloride and filtered through 15 times its weight of neutral alumina (activity II). The filtrate is concentrated, affording the crude 21 - chloro - 6α - fluoro - 9β,11 - epoxy - 17 - hydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dionepropionate which can be treated with hydrogen chloride without further purification.

Example 5

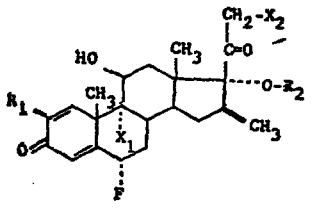
An ointment containing 0.1% of 21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate can be prepared as follows:

Composition	%
21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate	0.1
white petroleum jelly	45.0
liquid paraffin	19.6
cetyl alcohol	5.0
bees-wax	5.0
sorbitane sesquioleate	5.0
p-hydroxybenzoic acid ester	0.2
perfume	0.1
water	20.0

The fatty substances and emulsifiers are melted together. The preservative is dissolved in water and the solution is emulsified into the fatty melt at elevated temperature. After cooling, a suspension of the active compound in part of the fatty melt is incorporated into the emulsion and the perfume is then added.

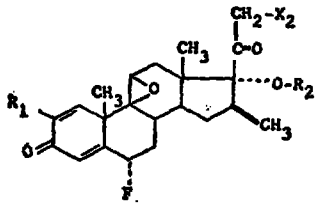
WHAT WE CLAIM IS:—

1. A process for the manufacture of a 9α,21 - dihalogeno - 11β,17α - dihydroxy - 6α - fluoro - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione compound of the formula



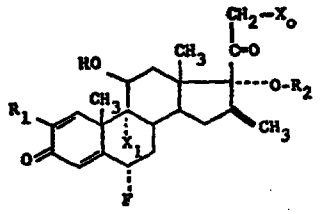
(I)

in which X_1 represents chlorine or fluorine, X_2 represents bromine or chlorine, R_1 represents hydrogen or chlorine and R_2 represents the acyl radial Ac of a carboxylic acid, or a salt of such a compound with salt-forming properties, which process comprises (a) treating a compound of the formula



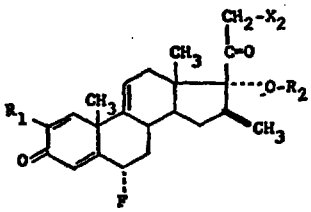
(II)

with a hydrogen halide of the formula H—X_1, (III) or with an agent which donates the hydrogen halide HX, or (b) converting the group X_0 in a compound of the general formula



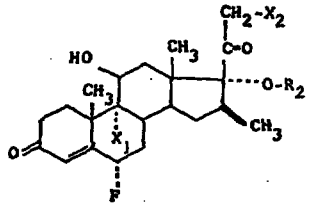
(IV)

in which X_0 represents a group which can be converted into a halogen atom X_2, into a halogen atom X_2, or (c) in order to obtain a compound of the formula I in which X_1 represents chlorine adding hypochlorous acid onto the 9,11-double bond of a compound of the formula



(VII)

or (d) in order to obtain a compound of the formula I in which R_1 is hydrogen, introducing the 1,2-double bond into a compound of the formula



(VIII)

and, if desired, converting a compound of the formula I, which is obtainable according to the process and has salt-forming properties, into a salt, and/or converting a salt, which is obtainable according to the process, of a salt-forming compound of the formula I into the free compound of the formula I or into another salt.

2. A process according to process variant (b) of Claim 1 wherein the sulphonyloxy group —O—R_a is replaced by chlorine in a compound of the formula IV, in which X_0 means the group —O—R_a, in which R_a

atmosphere of nitrogen. The cooled mixture is filtered, and the filtrate concentrated.

The residue is dissolved in methylene chloride and filtered through 15 times its weight of neutral alumina (activity II). The filtrate is concentrated, affording the crude 21 - chloro - 6α - fluoro - 9β,11 - epoxy - 17 - hydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dionepropionate which can be treated with hydrogen chloride without further purification.

Example 5

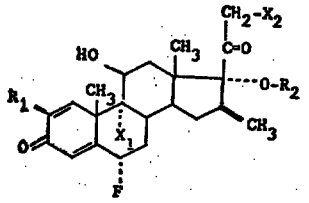
An ointment containing 0.1% of 21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate can be prepared as follows:

Composition	%
21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate	0.1
white petroleum jelly	45.0
liquid paraffin	19.6
cetyl alcohol	5.0
bees-wax	5.0
sorbitane sesquioleate	5.0
p-hydroxybenzoic acid ester	0.2
perfume	0.1
water	20.0

The fatty substances and emulsifiers are melted together. The preservative is dissolved in water and the solution is emulsified into the fatty melt at elevated temperature. After cooling, a suspension of the active compound in part of the fatty melt is incorporated into the emulsion and the perfume is then added.

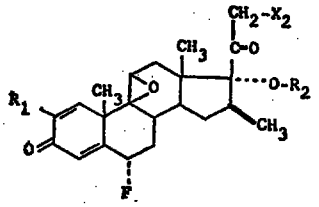
WHAT WE CLAIM IS:—

1. A process for the manufacture of a 9α,21 - dihalogeno - 11β,17α - dihydroxy - 6α - fluoro - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione compound of the formula



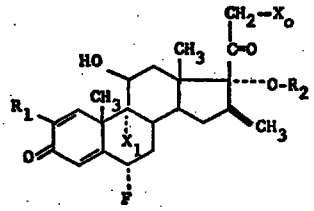
(I)

in which X_1 represents chlorine or fluorine, X_2 represents bromine or chlorine, R_1 represents hydrogen or chlorine and R_2 represents the acyl radial Ac of a carboxylic acid, or a salt of such a compound with salt-forming properties, which process comprises (a) treating a compound of the formula



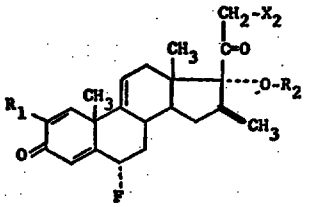
(II)

with a hydrogen halide of the formula H—X_1, (III) or with an agent which donates the hydrogen halide HX, or (b) converting the group X_0 in a compound of the general formula



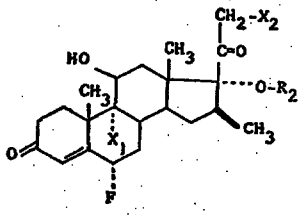
(IV)

in which X_0 represents a group which can be converted into a halogen atom X_2, into a halogen atom X_2, or (c) in order to obtain a compound of the formula I in which X_1 represents chlorine adding hypochlorous acid onto the 9,11-double bond of a compound of the formula



(VII)

or (d) in order to obtain a compound of the formula I in which R_1 is hydrogen, introducing the 1,2-double bond into a compound of the formula



(VIII)

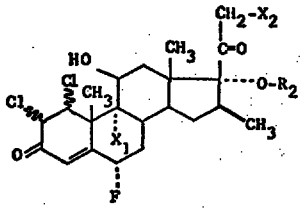
and, if desired, converting a compound of the formula I, which is obtainable according to the process and has salt-forming properties, into a salt, and/or converting a salt, which is obtainable according to the process, of a salt-forming compound of the formula I into the free compound of the formula I or into another salt.

2. A process according to process variant (b) of Claim 1 wherein the sulphonyloxy group —O—R_a is replaced by chlorine in a compound of the formula IV, in which X_0 means the group —O—R_a, in which R_a

represents the acyl radical of an organic sulphonic acid.

3. A process according to process variant (c) of Claim 1, wherein a compound of the formula VII is treated with hypochlorous acid or a hypochlorous acid donor.

4. A process for the production of a compound of the formula I, in which R_1 is chlorine, wherein chlorine is added onto the 1,2-double bond of a compound of formula I, in which R_1 represents hydrogen and hydrogen chloride is split off from the resulting intermediate of the formula



in which R_2 represents the acyl radical Ac of a carboxylic acid, X_1 represents chlorine or fluorine and X_2 represents bromine or chlorine, and in which process the 11-hydroxyl group is, if necessary, in a temporarily protected form, in which case the protective group is removed at any desired stage.

5, A process according to Claim 4, wherein the reaction is carried out while temporarily protecting the 11β-hydroxyl group by conversion into the trifluoroacetate.

6. A process according to any one of Claims 1 to 3 for the manufacture of a compound of the formula I in which X_1 represents fluorine or chlorine, X_2 represents chlorine, R_1 represents hydrogen and R_2 represents lower alkanoyl.

7. A process according to any one of Claims 1 to 5 for the manufacture of a compound of the formula I in which X_1 represents fluorine or chlorine, X_2 represents bromine or chlorine, and R_1 represents chlorine.

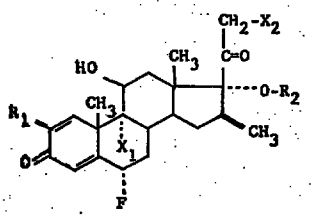
8. A process according to any one of Claims 1 to 5 for the manufacture of a compound of the formula I in which X_1 represents fluorine or chlorine, X_2 represents chlorine, R_1 represents hydrogen or chlorine and R_2 represents lower alkanoyl of 2 to 5 carbon atoms.

9. A process according to any one of Claims 1 to 5 for the manufacture of 2,21 - dichloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate.

10. A process according to any one of Claims 1 to 3 for the manufacture of 9α,21 - dichloro - 6α - fluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate.

11. A process according to any one of Claims 1 to 3 for the manufacture of 21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate.

12. 9α,21 - dihalogeno - 11β,17α - dihydroxy - 6α - fluoro - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione compounds of the formula



(I)

wherein X_1 represents chlorine or fluorine, X_2 represents bromine or chlorine, R_1 represents hydrogen or chlorine and R_2 represents the acyl radical Ac of a carboxylic acid, and 2-unsubstituted 1,2-dihydro derivatives thereof.

13. A compound of the formula I according to Claim 12 wherein X_1 represents fluorine, X_2 represents chlorine, R_1 represents hydrogen and R_2 represents lower alkanoyl, and 1,2-dihydro derivatives thereof.

14. A compound of the formula I according to Claim 12, wherein X_1 represents chlorine or fluorine, each of X_2 and R_1 represents chlorine and R_2 represents lower alkanoyl.

15. A compound according to either of Claims 13 or 14, wherein lower alkanoyl contains 2 to 5 carbon atoms.

16. 2,21 - dichloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate.

17. 21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate.

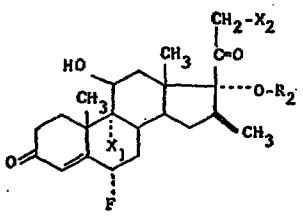
18. 21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate.

19. 9α,21 - dichloro - 6α - fluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate.

20. 9α,21 - dichloro - 6α - fluoro - 11β,17α - dihydroxy - 16β - methylpregn - 4 - ene - 3,20 - dione - 17 - propionate.

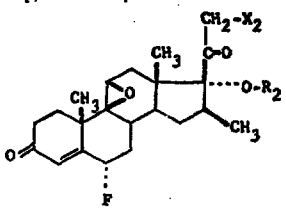
21. A pharmaceutical composition which contains at least one of the compounds described in Claims 16 to 24 and at least one pharmaceutical carrier.

22. A process for the manufacture of 9α,21 - dihalogeno - 11β,17α - dihydroxy - 6α - fluoro - 16β - methyl - pregn - 4 - ene - 3,20 - dione compounds of the formula



(VIII)

wherein X_1 represents chlorine or fluorine, X_2 represents bromine or chlorine, and R_2 represents the acyl radical Ac of a carboxylic acid, which process comprises a treating a compound of the formula

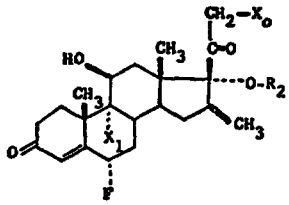


(IIA)

with a hydrogen halide of the formula

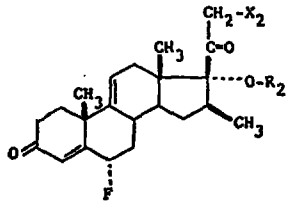
$$H—X_1 \qquad (III)$$

in which X_1 represents chlorine or fluorine, or with a corresponding donor of $H—X_1$, or (b) in a compound of the general formula



(IVA)

in which X_0 represents a group which can be converted into the halogen atom X_2, converting the group X_0 into the halogen atom X_2, or (c) in order to obtain a compound of the formula VIII, in which X_1 represents chlorine, adding hypochlorous acid onto the 9,11-double bond of a compound of the formula



(VIIA)

23. A process according to process variant (b) of Claim 22 wherein a compound of the formula VIA, in which X_0 is the group $—O—R_a$, in which R_a is the acyl of an organic sulphonic acid, the group $—O—R_a$ is replaced by chlorine.

24. A process according to process variant (c) of Claim 22, wherein a compound of the formula VIIA is treated with hypochlorous acid or a donor thereof.

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