

PATENT SPECIFICATION

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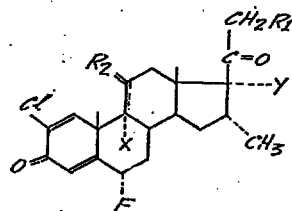
NO DRAWINGS

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(54) HALOGENO-PREGNADIENES AND PROCESS FOR THE MANUFACTURE THEREOF

- (71) We, CIBA-GEIGY AG, formerly known as Ciba Limited, a body corporate organised according to the laws of Switzerland, 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:—
 10 The present invention provides a halogeno-pregnadiene of the general formula (I)



- in which R_1 represents a free, esterified or etherified hydroxyl group, R_2 represents a free hydroxyl group or the acetoxy group in α or β position together with a hydrogen atom, X represents a hydrogen or fluorine atom or $R_2 + X$ represents a 9,11-double bond or a 9 β ,11 β -oxido group and Y represents a hydrogen atom or a free or esterified hydroxyl group, and R_1 taken together with Y represents a cyclic ester group of a dicarboxylic or an orthocarboxylic acid.
 25 The above-mentioned esterified hydroxyl groups are primarily derived from an organic carboxylic acid of the aliphatic, alicyclic, aromatic or heterocyclic series, especially those which contain up to 18 carbon atoms, for example, formic, acetic, propionic, or butyric acid; a valeric acid, for example, n-valeric acid; trimethylacetic or trifluoroacetic acid; a caproic acid, for example, β -trimethylpropionic acid or diethylacetic acid; oenanthic caprylic, pelargonic, or capric acid; an undecylic acid, for example, undecylenic acid; a lauric, myristic, palmitic or stearic acid, for example, oleic acid; cyclo-

propane-, cyclobutane-, cyclopentane- or cyclohexane-carboxylic acid; cyclopropyl-methanecarboxylic, cyclohexylethanecarboxylic; a cyclopentyl-, cyclohexyl- or phenyl-acetic or propionic acid; a benzoic acid; a phenoxyalkanoic acid, for example, phenoxy-acetic acid; a dicarboxylic acid, for example, succinic or phthalic acid; quinolic acid, furan-2-carboxylic, 5-tertiary butyl-furan-2-carboxylic, 5-bromo-furan-2-carboxylic acid, nicotinic or isonicotinic acid; a sulphonic acid, for example, benzenesulphonic acid or inorganic acid, for example, phosphoric or sulphuric acid.

The ester groups may alternatively be derived from orthocarboxylic acid, for example, orthoformic, orthoacetic or orthopropionic acid, and these acids, as well as the above-mentioned dicarboxylic acids, may furnish cyclic 17,21-esters.

As etherified hydroxyl groups there may be specially mentioned those derived from an alcohol with up to 8 carbon atoms, for example, lower aliphatic alkanols, ethanol, methanol, propanol, isopropanol; a butyl or amyl alcohol, or from an araliphatic alcohol, especially from a monocyclic aryl-lower aliphatic alcohol, for example, benzyl alcohol, or from a heterocyclic alcohol, for example, α -tetrahydropyranol or -furanol.

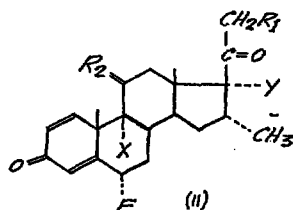
The compounds of the above general formula (I) possess valuable pharmacological properties, *inter alia* apart from a thymolytic effect and an inhibiting effect upon the sup-
 70 rarenals especially an antiphlogistic effect as can be shown in animal tests, for example, on rats, by the test for foreign bodies in a granuloma. The compounds of the invention may therefore be used as corticosteroid analogues, especially as antiphlogistics. The compounds of the invention are also valuable intermediates for the manufacture of other useful substances, especially compounds that display a pharmacological activity.

Particularly advantageous is $\Delta^{1,4}$ -2-chloro-6 α ,9 α - difluoro - 16 α - methyl - 3,20 - dioxo - 11 β ,17 α - dihydroxy - 21 - acetoxy - pregnadiene which, for example, on sub-

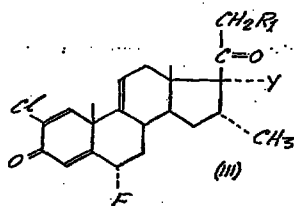
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cutaneous administration in doses of from 0.1 to 1.0 mg/kg to the rat produces a distinct anti-inflammatory effect.

- 5 The compounds of the above general formula (I) are accessible in known manner; more especially, they are obtained when in a compound of the general formula (II)



- 10 in which R_1 and Y have the above meanings, chlorine is added on the 1,2-double bond and from the resulting 1,2-dichloro-preg-4-ene hydrogen chloride is eliminated, whereby compounds of the formula (I) are obtained in which R_2 represents a free hydroxy group or the acetoxy group together with a hydro-
15 gen atom and X represents a hydrogen or a fluorine atom, and, if compounds having a double bond in position 9,11 are desired, water is eliminated from a compound having
20 in the 11-position a hydroxy group and in the 9-position a hydrogen atom, and, if a compound having the epoxy group in the 9 β , 11 β -position is desired, in a compound of the general formula (III)



- 25 in which R_1 and Y have the same meaning as in formula (I), hypobromous acid is added on to the 9,11-double bond, from the resulting bromohydrin hydrogen bromide is eliminated by treatment with a basic agent and, if a corresponding 9 α -fluoro-11 β -hydroxy
30 compound is desired, in the resulting 9 β , 11 β - oxido compound the 9 β ,11 β - oxido group is split with hydrogen fluoride or a hydrogen fluoride donor, and, if
35 desired, in a resulting compound, free hydroxyl groups are esterified and/or the 21-hydroxyl group is etherified and/or esterified or etherified hydroxyl group are converted into free hydroxyl groups.
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The addition of chlorine on to the 1,2-double bond is carried out in known manner, where the term "known" as used here and

throughout the specification means used in the art or described in the literature of the art; for example, the chlorination is performed in an inert solvent, for example, dioxane, in the presence of a lower aliphatic carboxylic acid, for example, propionic acid, at a lower temperature in the dark. The elimination of hydrogen chloride from the 1,2-dichloro compound is achieved by treatment with a base, preferably a tertiary organic nitrogen base, for example, triethylamine, pyridine or collidine.

For the hypobromination for example, N-bromosuccinimide is used, preferably in the presence of perchloric acid. The dehydrobromination of the resulting bromohydrin to furnish the 9 β ,11 β -oxido compound with a basic agent is advantageously carried out with an alkali metal acetate, for example, sodium acetate, in a lower aliphatic alcohol, for example, methanol or ethanol. The resulting 9 β ,11 β -oxido group is split with hydrogen fluoride in the known manner, using anhydrous hydrogen fluoride, if desired in an inert solvent, for example, chloroform, tetrahydrofuran or especially dimethylformamide, or aqueous hydrofluoric acid. It is also possible to use a hydrogen fluoride donor, for example, a salt of this acid with a tertiary organic base, for example, pyridine, or a derivative of hydrofluoric acid. A particularly favourable process has been described in USA Specification No. 3,211,758, where hydrofluoric acid in the form of an adduct with a carbamic acid or thiocarbamic acid, especially with urea, is used.

The dehydrating agent used in the manufacture of the compound of the formula (III) from the corresponding 11 α - or 11 β -hydroxy compound saturated in the 9,11-position by elimination of water may be, for example, phosphorus oxychloride in pyridine, or an N-halogenamide or N-halogenimide, for example, N-bromosuccinimide and sulphur dioxide under anhydrous conditions, preferably in pyridine.

If desired, the present invention includes the esterification of the free hydroxyl groups present in the 17 α - or 21-positions. Both the 17 α - or 21-monoester and 17 α -21-diester may be manufactured. To manufacture the 21-monoester, the 21-hydroxy compound is treated in known manner with a reactive functional carboxylic acid derivative, preferably with one of the above-mentioned acids, for example, a lower aliphatic carboxylic acid, for example, with an acid anhydride or an acid halide, for instance in a tertiary base, for example pyridine.

A free hydroxyl group in position 17 α may be selectively esterified in known manner, for example: The 17 α ,21-diester is prepared by acylation with a carboxylic acid anhydride, or instance acetic anhydride, with addition of a strong acid, especially an

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aromatic sulphonic acid, for example, p-toluenesulphonic acid, as catalyst, and the 21-ester group is then hydrolyzed under mild alkaline conditions, using, for instance, a solution of an alkali carbonate or bicarbonate in an aqueous aliphatic alcohol, such as methanol or ethanol.

17 α -Monoesters are also accessible by the following known route: When a compound of the formula (I), that contains free hydroxyl groups in positions 17 α and 21, is reacted with an orthoester of the type



(where R' represents a hydrogen atom or an alkyl radical and R'' an alkyl radical, preferably with an orthoalkanoic acid ester) in the presence of a strong acid, for example, p-toluenesulphonic acid, as catalyst in an inert solvent, for example, benzene, a cyclic 17 α , 21-ortho-ester is obtained. By hydrolyzing with a weak organic acid, for example, oxalic acid, the 21-ester bond is then selectively hydrolyzed and 17 α -monoester is obtained.

The present process includes if desired, also the etherification of a free hydroxyl group in position 21 in known manner, preferably with a reactive derivative of one of the afore-mentioned alcohols. For example, by using dihydropyran in a solvent that is inert to the reaction, for example, tetrahydrofuran, diethyl ether or chloroform, in the presence of phosphorus oxychloride, the 21-tetrahydropyranyl ether is obtained.

The compounds of the above formula (II) to (V) to be used as starting materials are known or can be prepared in known manner.

The present invention is also concerned with the manufacture of pharmaceutical preparations for use on human and veterinary medicine containing the pharmacologically active substance of the invention described above as active ingredients in conjunction or admixture with a pharmaceutically suitable carrier. Suitable carriers are organic or inorganic substances suitable for enteral, for example oral, parenteral or topical administration. Suitable carriers are substances that do not react with the compounds of the invention, for example, water, gelatin, lactose, starches, magnesium stearate, talcum, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, white petroleum jelly, cholesterol or other known medicinal carriers. The pharmaceutical preparations may be in solid form, for example, tablets, dragées or capsules, or in liquid or semiliquid form, solutions, for example, oily injection solutions in ampoules, suspensions, emulsions, ointments, salves or creams. These pharmaceutical preparations may be sterilized and/or contain assistants, for example, preserving, stabilizing, wetting or emulsifying agents, salts for regulating the osmotic pressure or

buffers. They may also contain further pharmaceutically useful substances. The compounds of the invention may also be used as starting materials for the manufacture of other useful compounds.

The compounds of this invention may also be used as additives to animal fodders.

The following Examples illustrate the invention.

EXAMPLE 1

30.0 Grams of $\Delta^{1,4}$ -6 α -fluoro-16 α -methyl-11 β ,17 α -dihydroxy-21-acetoxy-3,20-dioxopregnadiene [paramethasone acetate] are dissolved in 1500 ml of dioxane. The solution is cooled until dioxane begins to crystallize, then 150 ml of a solution of 84 g of chlorine in 1 litre of propionic acid are tipped in and the mixture is kept for 2 days at a temperature within the range of from 0 to 5°C in the dark. The reaction solution is then poured into 15 litres of water, extracted with 4 $\times$ 1 litre of methylenechloride and the extracts are washed successively with water, saturated aqueous sodium bicarbonate solution and once more with water. The washed, combined extracts are dried over sodium-sulphate, filtered and completely evaporated under vacuum at a bath temperature of from 30° to 35°C, to yield 48.2 g of Δ^4 -6 α -fluoro-1,2-dichloro-16 α -methyl-11 β ,17 α -dihydroxy-21-acetoxy-3,20-dioxopregnene. $[\alpha]_D^{20} = +57^\circ$ ($c=0.9\%$ in dioxane). λ_{max} in rectified alcohol 250 m μ ($\epsilon=10,500$). The dichloride is unstable and decomposes when left to stand at room temperature.

A solution of the resulting 48.2 g of Δ^4 -6 α -fluoro-1,2-dichloro-16 α -methyl-11 β ,17 α -dihydroxy-21-acetoxy-3,20-dioxopregnene in 1/2 litre of pyridine is kept for 20 hours at room temperature, during which its colour gradually turns from pink to yellowish brown. The reaction solution is then poured into a mixture of 3 kg of ice, 10 litres of water and 2 litres of concentrated hydrochloric acid. The whole is extracted with 5 $\times$ 1 litre of methylenechloride and the extracts are washed successively with water, saturated aqueous sodium bicarbonate solution and once more with water; the extracts are then combined, dried over sodium sulphate, filtered and completely evaporated under vacuum. For purification the residue is mixed with a small quantity of active carbon and recrystallized from methanol, to yield 21.0 g of $\Delta^{1,4}$ -6 α -fluoro-2-chloro-16 α -methyl-11 β ,17 α -dihydroxy-21-acetoxy-3,20-dioxopregnadiene melting at 232–233°C. $[\alpha]_D^{20} = +55^\circ$ ($c=1\%$ in dioxane). λ_{max} in ethanol 251 m μ ($\epsilon=14,700$).

The infrared spectrum (Nujol) displays absorption bands, *inter alia*, at 2.76, 2.86, 5.71, 5.77, 6.00, 6.09, 8.14, 9.41, 9.60, 9.92 and 10.87 μ .

EXAMPLE 2

While stirring a solution of 32.4 g. of $\Delta^{1,4}$ -6 α -fluoro-2-chloro-16 α -methyl-11 β ,17 α -dihydroxy-21-acetoxy-3,20-dioxopregnadiene in 165 ml of pyridine under nitrogen a solution of 17.1 g of N-bromosuccinimide in 285 ml of pyridine is run in during the course of 10 minutes at a temperature of from 20° to 25°C. The brownish reaction solution is then cooled to -12° to -13°C. Then, while providing a permanent, successively increased cooling from an initial temperature of -12°C to -20°C, over a period of 50 to 70 minutes, a moderate current of sulphur dioxide is introduced until active bromine can no longer be detected in the reaction solution, and the introduction of sulphur dioxide is then continued for 15 to 20 minutes. The cooling is then discontinued and over a period of 1 1/2 to 2 hours a total of 2.25 litres of water is run into the brown, partially crystalline reaction mixture at first slowly and then more rapidly, during which the temperature gradually rises to 20 to 25°C and the reaction product crystallizes out slowly from the solution which temporarily turns clear. The product is suctioned off, washed with 1 litre of water and dried under vacuum at a temperature of from 50° to 60°C. Yield: 29.1 g of $\Delta^{1,4,9(11)}$ -6 α -fluoro-2-chloro-16 α -methyl-17 α -hydroxy-21-acetoxy-3,20-dioxopregnatriene melting at 128 to 132°C. $[\alpha]_D^{20} = -8^\circ$ (c=1.0% in chloroform). λ_{max} in rectified alcohol 247 m μ ($\epsilon=15,900$).

EXAMPLE 3

While stirring a solution of 5.00 g. of $\Delta^{1,4,9(11)}$ -2-chloro-6 α -fluoro-16 α -methyl-3,20-dioxo-17 α -hydroxy-21-acetoxy-pregnatriene in 60 ml of absolute dioxane and 7.5 ml of 0.5N-perchloric acid in the dark at a temperature of from 18° to 20°C, a solution of 2.34 g of N-bromoacetamide in 40 ml of absolute dioxane is added dropwise over a period of 15 minutes and the whole is then stirred for 4 hours under nitrogen in the dark at room temperature. Then, within 10 minutes, 15 ml of 10% sodium thiosulphate solution (loss of colour) and then within 15 minutes 100 ml of water are added dropwise at a temperature from 18° to 20°C. A solution of 1.5 g of sodium hydroxide in 15 ml of water and 10 ml of methanol are added at about 20°C and the redish mixture is stirred for 1 hour under nitrogen at room temperature. At about 10°C, over a period of 30 minutes, 400 ml of water are added dropwise; the precipitate is suctioned off, rinsed with water, dissolved in methylenechloride, the solution dried over sodium sulphate and evaporated to dryness under a water-jet vacuum. The yellow foam (4.64g) is sprinkled with ether and recrystallized from a mixture of methylenechloride+

methanol+ether, to furnish 3.18 g of pure $\Delta^{1,4}$ -2-chloro-6 α -fluoro-16 α -methyl-9 β ,11 β -oxido-3,20-dioxo-17 α ,21-dihydroxypregnadiene melting at 200 to 202°C. $[\alpha]_D^{20} = -10^\circ \pm 1^\circ$ (c=0.964). Ultraviolet spectrum: λ_{max} 254 m μ ($\epsilon=15,500$). Infrared spectrum, bands, *inter alia*, at 2.77, 2.85, 5.84, 5.97, 6.03, 6.20, 8.80, 9.37, 9.90, 10.10, 10.95 and 11.87 μ .

EXAMPLE 4

A solution of 1.80 grams of $\Delta^{1,4}$ -2-chloro-6 α -fluoro-16 α -methyl-9 β ,11 β -oxido-3,20-dioxo-17 α ,21-dihydroxypregnadiene in 10 ml of pyridine and 10 ml of acetic anhydride is kept for 15 hours at room temperature. The clear, yellow solution is poured into ice water and stirred for 30 minutes, and then extracted twice with chloroform. The organic phases are successively washed with water, dilute sulphuric acid/ice, water, saturated sodium bicarbonate solution/ice and with water until the washings run neutral, dried over sodium sulphate and evaporated to dryness under a water-jet vacuum. The resulting yellowish oil (1.89g) is sprinkled with ether and redissolved once from methylenechloride+ether, to yield 1.23g of pure 21-acetate of the above starting material, melting at 184°C. Ultraviolet spectrum: $\lambda_{max}=254$ m μ ($\epsilon=15,400$) [in ethanol]. $[\alpha]_D^{20} = +5^\circ \pm 2^\circ$ (c=0.580 in chloroform). Infrared spectrum, bands, *inter alia*, at 2.75, 5.70, 5.75, 5.96, 6.18, 7.25, 8.12, 9.40, 9.93 and 10.95 μ .

EXAMPLE 5

2.62 Grams of the acetate obtained in Example 4 are introduced into a polyethylene vessel containing 60 ml of urca-hydrogen fluoride adduct (1:1.325) and stirred for 40 hours with exclusion of air by means of a Teflon (Trade Mark) magnetic stirrer at 3°C ($\pm 1^\circ$ C). The suspension is stirred into a mixture of 700 g of ice and 200 ml of concentrated ammonia and then adjusted with glacial acetic acid to pH 7. The precipitate is suctioned off, rinsed with water, dissolved in chloroform, the solution is dried over sodium sulphate and evaporated to dryness under a water-jet vacuum. The resulting brown crystals (about 2.8 g) are dissolved in a 4:1-mixture of toluene and ethyl acetate and filtered through 120g of silicagel. The fractions which crystallize in a gelatinous form are dissolved with heating in methylenechloride, concentrated under atmospheric pressure and a small quantity of ether is added, to yield 1.06 g of pure $\Delta^{1,4}$ -2-chloro-6 α ,9 α -difluoro-16 α -methyl-3,20-dioxo-11 β ,17 α -dihydroxy-21-acetoxy-pregnadiene melting at (202°) 204°C. According to thin-layer chromatography the mother liquor likewise contains 95% of this product. $[\alpha]_D^{20} = +48^\circ \pm 2^\circ$ (c=0.497). Ultraviolet

spectrum: $\lambda_{\max}=246 \text{ m}\mu$ ($\epsilon=15,800$). Infrared spectrum (Nujol) bands, *inter alia*, at 2.82, 5.70, 5.76, 6.15, 7.83, 8.74, 9.37, 9.91, 10.50, 10.95 and 11.25μ .

EXAMPLE 6

9.4 g of $\Delta^{1,4}$ -6 α -fluoro-2-chloro-16 α -methyl-11 β ,17 α -dihydroxy-21-acetoxy-3,20-dioxopregnadiene are dissolved in 400 ml of methanol by heating to the boil while introducing nitrogen. The resulting solution is cooled under nitrogen to a temperature of from 1° to 3°C and, within 15 to 30 minutes, a solution of 1.7g of sodium bicarbonate in 50 ml of water is added dropwise. Stirring of the reaction solution is continued overnight at 1° to 3°C under nitrogen, the reaction product crystallizing out gradually. The course of hydrolysis is observed by means of thin layer chromatography on silica gel using toluene+ethyl acetate 1:1 as running agent. After 10 to 15 hours' saponification it is no longer possible to detect any starting material in the reaction solution. The mixture is then poured into 2 litres of water. There follow several extractions with methylene chloride, and the extracts are washed repeatedly with water and dried over sodium sulphate, filtered and evaporated completely. A yield of 7.65 g of crystalline crude product melting at 175°C is obtained. The product is pure according to thin-layer chromatography (silica gel, toluene+ethyl acetate 1:1). For further purification, the crude product which has a slight yellow tint is crystallized from ethyl acetate, and 2.87 g of $\Delta^{1,4}$ -6 α -fluoro-2-chloro-16 α -methyl-11 β ,17 α ,21-tri-hydroxy-3,20-dioxo-pregnadiene of melting point (180°C) 181–182°C are obtained.

On concentration of the mother liquor further quantities of the same product are obtained.

EXAMPLE 7

9.0 Grams of $\Delta^{1,4}$ -6 α ,9 α -difluoro-16 α -methyl-11 β ,17 α -dihydroxy-21-acetoxy-3,20-dioxo-pregnadiene (flumethasone acetate) are dissolved in 750 ml of pure dioxan with the application of heat. After cooling until crystallization of the dioxan sets in, 66 ml of a solution of 36 g of chlorine in 500 ml of pure propionic acid are added all at once and the whole is allowed to stand in the dark at a temperature of from 0° to 5°C for 7 days. The reaction solution is poured into 3 litres of iced water. The batch is extracted with 3×500 ml of methylene chloride and the extracts washed successively with water, saturated aqueous sodium bicarbonate solution, and water. The extracts are then combined and dried over sodium sulphate, filtered, and evaporated completely under reduced pressure at a bath tempera-

ture of 30–35°C. There are obtained 11.7 g of Δ^4 -6 α ,9 α -difluoro-1,2-dichloro-16 α -methyl-11 β ,17 α -dihydroxy-21-acetoxy-3,20-dioxo-pregnene. The IR spectrum (methylene chloride) exhibits absorption bands *inter alia* at 2.80, 3.95, 5.75, 5.95, 7.25, 8.20, 8.85, 9.45, 9.60, 10.05 and 11.35μ .

The dichloride is unstable and decomposes when allowed to stand at room temperature.

11.7 g of Δ^4 -6 α ,9 α -difluoro-1,2-dichloro-16 α -methyl-11 β ,17 α -dihydroxy-21-acetoxy-3,20-dioxopregnene are dissolved in 150 ml of pure pyridine and the solution allowed to stand at room temperature for 24 hours, when the colour gradually changes from pink to yellow to brown. The reaction solution is then poured into 1 litre of ice-cooled normal hydrochloric acid. The batch is then extracted with 5×250 ml of methylene chloride and the extracts are washed successively and repeatedly with ice-cooled, normal hydrochloric acid, water, ice-cooled, saturated sodium bicarbonate solution, and water. The extracts are then combined and dried over sodium sulphate, filtered, and completely evaporated under reduced pressure. The resulting, partly crystalline crude product (10g) is chromatographed on 750 g of silica gel (diameter of column, 6 cm), elution being performed with toluene+ethyl acetate 95:5, then 90:10, and finally 80:20. From the first runnings (fractions 69–80) there is obtained on concentration, 0.7g of $\Delta^{1,4}$ -6 α ,9 α -difluoro-2-chloro-16 α -methyl-17 α -hydroxy-11 β ,21-diacetoxy-3,20-dioxo-pregnadiene of melting point (240°C) 246–250°C; $[\alpha]_D^{20}+90^\circ$ ($c=1\%$ in dioxan) and $\lambda_{\max}$ (rectified alcohol) 245 $\text{m}\mu$ ($\epsilon=14600$). The fractions 86–115 are jointly evaporated completely and the residue recrystallized from rectified alcohol to obtain 2.4 g of $\Delta^{1,4}$ -6 α ,9 α -difluoro-2-chloro-16 α -methyl-11 β ,17 α -dihydroxy-21-acetoxy-3,20-dioxo-pregnadiene which melts between 200 and 210°C; $[\alpha]_D^{20}+61^\circ$ ($c=1\%$ in dioxan) and $\lambda_{\max}$ (rectified alcohol) 246 $\text{m}\mu$ ($\epsilon=16100$). When the mother liquors are concentrated, further quantities of the same compound are obtained.

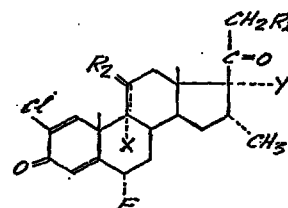
EXAMPLE 8

18.0 Grams of $\Delta^{1,4}$ -6 α ,9 α -difluoro-16 α -methyl-11 β ,17 α -dihydroxy-21-trimethylacetoxy-3,20-dioxo-pregnadiene are dissolved in 1500 ml of pure dioxan. The solution is cooled until crystallization of the dioxan sets in, and then 90 ml of a solution of 72 g of chlorine in 1000 ml of propionic acid are added all at once, and the whole allowed to stand in the dark at 0–5°C for 7 days. The batch is worked up as described in Example 1, and 22.7 g of Δ^4 -6 α ,9 α -di-

- fluoro - 1,2 - dichloro - 16 α - methyl - 11 β , 17 α - dihydroxy - 21 - trimethylacetoxo - 3,20-dioxo-pregnene obtained which melt at 200°C with decomposition.
- 5 The 22.7 g of this product are covered with 300 ml of pure, dry pyridine, a clear, pale-brown solution forming immediately. The solution is allowed to stand at room temperature for 2 days and then worked up as described in Example 2. The resulting brownish, crystalline crude product (20.9 g) is chromatographed on 2300 g of silica gel (diameter of column, 12 cm) with toluene + ethyl acetate 95:5. The first runnings are separated (fractions 10—25), and the fractions 38—61 then evaporated and the residue recrystallized from ethyl acetate. There are obtained 4.68 g of $\Delta^{1,4}$ - 6 α ,9 α - difluoro - 2 - chloro - 16 α - methyl - 11 β ,17 α - dihydroxy - 21 - trimethylacetoxo - 3,20 - dioxo-pregnadiene of melting point (242°C) 243—244°C; $[\alpha]_D^{20} + 58^\circ$ (c=0.8% in dioxan) and λ_{max} (rectified alcohol) 247 m μ (ϵ =16200). When the mother liquor is concentrated, further quantities of utilizable material are obtained.
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| white petroleum jelly (petrolatum) | 65% | 65 |
| higher aliphatic alcohols (waxes) | 10% | |
| polyoxyethylene-sorbitan derivative (sorbitan-fatty acid ester) | 4.6% | |
| preservative | 0.2% | |
| perfume | 0.1% | 70 |
| water | 20% | |
| $\Delta^{1,4}$ -2-chloro-6 α ,9 α -difluoro-16 α -methyl-3,20-dioxo-11 β ,17 α -dihydroxy-21-acetoxypregnadiene | 0.1% | 75 |
- The fats and emulsifiers are fused together, the preservatives dissolved in water and the solution is emulsified in the fat melt at an elevated temperature. After cooling, a suspension of the active ingredient in part of the fat melt is worked into the emulsion and then the perfume is added.
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WHAT WE CLAIM IS:—

1. Process for the manufacture of a halogeno-pregnadiene of the general formula I 85

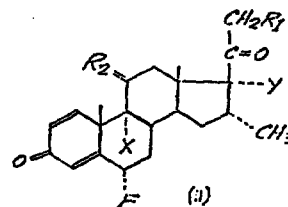


(I)

in which R₁ represents a free, esterified or etherified hydroxyl group, R₂ represents a free hydroxyl group or the acetoxo group in α - or β -position together with a hydrogen atom, X represents a hydrogen or fluorine atom or R₂+X represents a 9,11-double bond or a 9 β ,11 β -oxido group and Y represents a hydrogen atom or a free or esterified hydroxyl groups, and R₁ taken together with Y represents a cyclic ester group of a dicarboxylic or an orthocarboxylic acid, wherein in a compound of the general formula

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(II)

in which R₁ and Y have the above meanings, chlorine is added on to the 1,2-double bond and from the resulting 1,2-dichloro-pregn-4-ene hydrogen chloride is eliminated, whereby compounds of the formula (I) are

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EXAMPLE 10

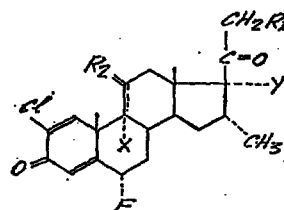
- Pharmaceutical preparation in the form of an ointment for topical administration, containing $\Delta^{1,4}$ - 2 - chloro - 6 α ,9 α - difluoro - 16 α - methyl - 3,20 - dioxo - 11 β ,17 α - dihydroxy-21-acetoxypregnadiene, consisting of:
- 60



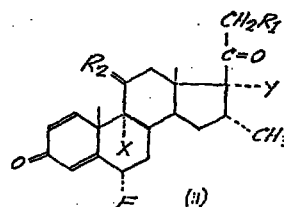
- fluoro - 1,2 - dichloro - 16 α - methyl - 11 β , 17 α - dihydroxy - 21 - trimethylacetoxy - 3,20-dioxo-pregnene obtained which melt at 200°C with decomposition.
- 5 The 22.7 g of this product are covered with 300 ml of pure, dry pyridine, a clear, pale-brown solution forming immediately. The solution is allowed to stand at room temperature for 2 days and then worked up as described in Example 2. The resulting brownish, crystalline crude product (20.9 g) is chromatographed on 2300 g of silica gel (diameter of column, 12 cm) with toluene+ethyl acetate 95:5. The first runnings are separated (fractions 10—25), and the fractions 38—61 then evaporated and the residue recrystallized from ethyl acetate. There are obtained 4.68 g of $\Delta^{1,4}$ - 6 α ,9 α - difluoro - 2 - chloro - 16 α - methyl - 11 β ,17 α - dihydroxy - 21 - trimethylacetoxy - 3,20 - dioxo-pregnadiene of melting point (242°C) 243—244°C; $[\alpha]_D^{20} + 58^\circ$ ($c=0.8\%$ in dioxan) and λ_{max} (rectified alcohol) 247 m μ ($\epsilon=16200$). When the mother liquor is concentrated, further quantities of utilizable material are obtained.
- 10
- 15
- 20
- 25
- white petroleum jelly (petrolatum) 65% 65
higher aliphatic alcohols (waxes) 10%
polyoxyethylene-sorbitan derivative (sorbitan-fatty acid ester) 4.6%
preservative 0.2%
perfume 0.1% 70
water 20%
 $\Delta^{1,4}$ -2-chloro-6 α ,9 α -difluoro-16 α -methyl-3,20-dioxo-11 β ,17 α -dihydroxy-21-acetoxypregnadiene 0.1% 75
- The fats and emulsifiers are fused together, the preservatives dissolved in water and the solution is emulsified in the fat melt at an elevated temperature. After cooling, a suspension of the active ingredient in part of the fat melt is worked into the emulsion and then the perfume is added.
- WHAT WE CLAIM IS:—
1. Process for the manufacture of a halogeno-pregnadiene of the general formula I 85

EXAMPLE 9

- 14.3 g of the obtained product (2-chloro-flumethasone-21-acetate) are dissolved in 950 ml of methanol by warming to the boil in a current of nitrogen. The solution is then cooled in an atmosphere of nitrogen to a temperature of from 0° to 5°C and a solution of 2 g of sodium bicarbonate in 38 ml of water is added dropwise in the course of 10 minutes. The batch is then stirred at 0°—5°C for 2—3 days in an atmosphere of nitrogen. The reaction product gradually crystallizes out during this period. The progress of the saponification is checked by thin layer chromatography on silica gel using toluene-acetone 1:1 as eluting agent. After completion of the reaction the batch is concentrated under diminished pressure at 30° (bath temperature) to a volume of 200—300 ml and is then poured on to 1500 ml of water. The reaction mixture is extracted several times with ethyl acetate, the extracts are repeatedly washed with water, dried and filtered and evaporated to dryness. There is thus obtained the crystalline 2-chloro-flumethasone melting at 220°—222°C (with decomposition). The product is unitary according to thin layer chromatogram (silicagel toluene-acetone 1:1) $[\alpha]_D^{20} + 40^\circ$ ($c=0.97\%$ in dioxan) $\lambda_{max}=245$ m μ (15000) in ethanol.
- 30
- 35
- 40
- 45
- 50
- 55
- 15
- 20
- 25
- 30
- 35
- 40
- 45
- in which R₁ represents a free, esterified or etherified hydroxyl group, R₂ represents a free hydroxyl group or the acetoxy group in α - or β -position together with a hydrogen atom, X represents a hydrogen or fluorine atom or R₂+X represents a 9,11-double bond or a 9 β ,11 β -oxido group and Y represents a hydrogen atom or a free or esterified hydroxyl groups, and R₁ taken together with Y represents a cyclic ester group of a dicarboxylic or an orthocarboxylic acid, wherein in a compound of the general formula



(I)

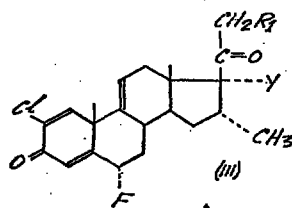


(II)

- EXAMPLE 10
Pharmaceutical preparation in the form of an ointment for topical administration, containing $\Delta^{1,4}$ - 2 - chloro - 6 α ,9 α - difluoro - 16 α - methyl - 3,20 - dioxo - 11 β ,17 α - dihydroxy-21-acetoxypregnadiene, consisting of:
- 60
- in which R₁ and Y have the above meanings, chlorine is added on to the 1,2-double bond and from the resulting 1,2-dichloropregn-4-ene hydrogen chloride is eliminated, whereby compounds of the formula (I) are
- 100
- 50



- obtained in which R_2 represents a free hydroxy group or the acetoxy group together with a hydrogen atom and X represents a hydrogen or a fluorine atom, and, if compounds having a double bond in position 9,11 are desired, water is eliminated from a compound having in the 11-position, a hydroxy group and in the 9-position a hydrogen atom, and if a compound having the epoxy group in the 9 β ,11 β -position is desired in a compound of the general formula



- in which R_1 and Y have the same meanings as in formula (I), hypobromous acid is added on to the 9,11-double bond, from the resulting bromohydrin hydrogen bromide is eliminated by treatment with a basic agent and, if a corresponding 9 α -fluoro-11 β -hydroxy compound is desired, in the resulting 9 β ,11 β -oxido compound the 9 β ,11 β -oxido group is split with hydrogen fluoride or a hydrogen fluoride donor and, if desired, in a resulting compound, free hydroxy groups are esterified and/or the 21-hydroxy group is etherified and/or esterified or etherified hydroxyl groups are converted into free hydroxyl groups.
2. Process according to claim 1, wherein the addition of chlorine to the 1,2-double bond is performed in a *per se* conventional manner in an inert solvent in the presence of a carboxylic acid.
3. Process according to claim 2, wherein the chlorination is performed in the presence of a lower aliphatic carboxylic acid.
4. Process according to claim 3, wherein the chlorination is performed in the presence of propionic acid.
5. Process according to claim 1, wherein the elimination of hydrogen chloride from a 1,2-dichloro compound is performed by treatment with a base.
6. Process according to claim 5, wherein the base is triethylamine, pyridine or collidine.
7. Process according to claim 1, wherein N-bromo-succinimide is used for the addition of hypobromic acid.
8. Process according to claim 7, wherein the N-bromo-succinimide is used for the addition of hypobromic acid in the presence of perchloric acid.
9. Process according to claim 1, wherein for the elimination of hydrogen bromide from

the bromohydrin there is used an alkali metal acetate in a lower aliphatic alcohol as solvent.

10. Process according to claim 1, wherein for the splitting of the 9 β ,11 β -oxido group there is used hydrogen fluoride in an inert solvent.

11. Process according to claim 10, wherein a solution of hydrogen fluoride in chloroform, tetrahydrofuran, or water is used.

12. Process according to claim 10, wherein a solution of hydrogen fluoride in dimethylformamide is used.

13. Process according to claim 1, wherein for the splitting of the 9 β ,11 β -oxido group hydrogen fluoride is used in the form of an adduct with urea.

14. Process according to claim 1, wherein the 11 β - or 11 α -hydroxy group is split off by treatment with a dehydrating agent.

15. Process according to claim 14, wherein the dehydrating agent used is phosphorus oxychloride in pyridine or an N-halogenamide and sulfur dioxide.

16. Process according to claim 1, wherein a resulting compound with a free hydroxy group in the positions 17 and 21 is converted into its 21-monoester.

17. Process according to claim 1, wherein a resulting compound with a free hydroxy group in the positions 17 and 21 is converted into its 17,21-diester.

18. Process according to claim 1, wherein a resulting compound with a free hydroxy group in the positions 17 and 21 is converted into its 17-monoester.

19. Process according to any one of claims 16 to 18, wherein in the esterification a reactive functional derivative of an acid of the aliphatic, aromatic, cycloaliphatic, araliphatic or heterocyclic series having up to 18 carbon atoms is used.

20. Process according to claim 19, wherein a lower aliphatic acid derivative is used.

21. Process according to claim 20, wherein a derivative of acetic acid is used.

22. Process according to claim 20, wherein a derivative of propionic acid is used.

23. Process according to claim 16 or any one of claims 19 to 22, wherein esterification in the 21-position is brought about by the action of an acid anhydride in pyridine.

24. Process according to claim 17 or any one of claims 19 to 22, wherein bis-esterification in the 17- and 21-positions is brought about by the action of an acid anhydride in the presence of a strong acid as catalyst.

25. Process according to any one of claims 18 to 22, wherein the 17,21-diester is first prepared and the 21-ester group then hydrolyzed by mild alkaline treatment.

26. Process according to any one of claims 18 to 22, wherein by treatment of a 17,21-dihydroxy compound with an ortho-alkanoic acid ester the cyclic 17,21-ortho-ester is pre-



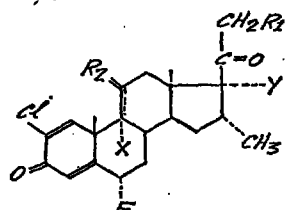
pared which is then hydrolyzed in 21-position by treatment with a strong acid.

27. Process according to claim 1, wherein a 21-hydroxy compound is etherified in 21-position by treatment with a reactive functional derivative of a lower aliphatic alcohol.

28. Process according to claim 1, wherein a 21-hydroxy compound is converted into the 21-tetrahydropyranyl ether by treatment with dihydropyran in the presence of phosphorus oxychloride.

29. Process for the manufacture of steroids of the general formula (I) conducted substantially as described in any one of the Examples 1 to 9 herein.

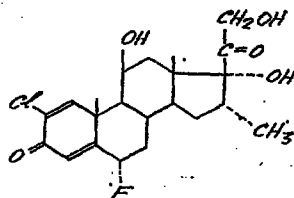
30. A compound of the general formula (I)



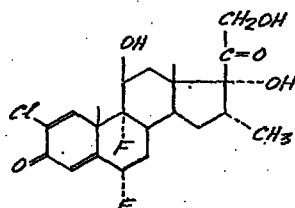
in which R_1 represents a free, esterified or etherified hydroxyl group, R_2 represents a free hydroxyl group or the acetoxy group in α or β position together with a hydrogen atom, X represents a hydrogen or fluorine atom or $R_2 + X$ represents a 9,11-double bond or a 9 β ,11 β -oxide group and Y represents a hydrogen atom or a free esterified hydroxyl group, and R_1 taken together with Y represents a cyclic ester group of a dicarboxylic or an orthocarboxylic acid.

31. A compound of the formula claimed in claim 30, an esterified hydroxyl group of which is derived from a carboxylic acid having up to 18 carbon atoms.

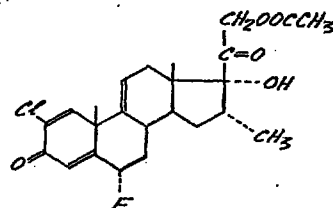
32. The compound of the formula



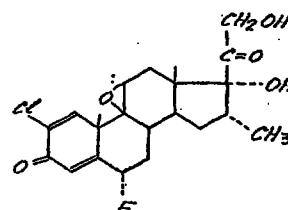
33. The compound of the formula



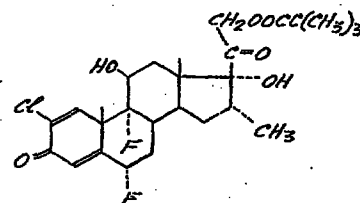
34. The compound of the formula



35. The compound of the formula



36. The compound of the formula



37. An ester of a compound claimed in any one of claims 32 to 36 derived from a carboxylic acid having up to 18 carbon atoms.

38. The 21-acetate of the compound claimed in claim 32.

39. The 21-acetate of the compound claimed in claim 35.

40. The 21-acetate of the compound claimed in claim 33.

41. A pharmaceutical preparation containing as active principle a compound claimed in any one of claims 30 to 40 in admixture or conjunction with a pharmaceutically suitable carrier.

42. A pharmaceutical preparation according to claim 41 for oral, parenteral or topical application.

43. A pharmaceutical preparation according to claim 41 in the form of an oily injection solution in ampoules.

44. A pharmaceutical preparation according to claim 1 in the form of tablets.

45. A pharmaceutical preparation according to claim 1 in the form of a salve or cream.

46. A pharmaceutical preparation as claimed in claim 1 and as described in Example 10 herein.



* C L M S *

47. A compound of the general formula
(I) obtained by the process claimed in any
one of claims 1 to 29.

48. A compound of the general formula
5 (I) and which is described in any one of
the Examples 1 to 9 herein.

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ERRATA

SPECIFICATION No. 1,245,292

Page 8, line 25, *after free insert or*
Page 8, lines 65, 67 and 70, *for 1 read 41*

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4th April, 1974

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