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PATENT SPECIFICATION

926,472



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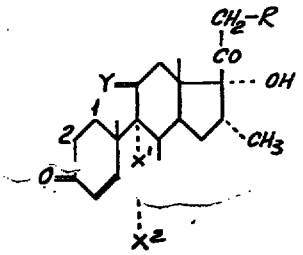
COMPLETE SPECIFICATION

New Halogen-Pregnenes and a process for their manufacture

We, CIBA LIMITED, a body corporate organised according to the Laws of Switzerland, of Basel, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new halogeno-pregnenes, a process for their manufacture and pharmaceutical preparations containing them.

The present invention provides halogeno-pregnene compounds of the formula



in which R represents a free or esterified hydroxyl group, Y represents an oxo group, or a hydrogen atom together with a free or esterified hydroxyl group, X^1 represents a hydrogen atom or a chlorine or fluorine atom, and X^2 represents a chlorine or fluorine atom, and the corresponding compounds with an additional double bond in the 1:2-position.

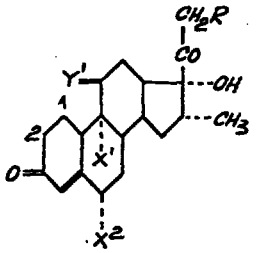
In the esters the acid radicals are those of saturated or unsaturated aliphatic or cycloaliphatic, aromatic or heterocyclic carboxylic acids, for example of formic acid, acetic acid, propionic acid, butyric acids, valeric acids such as *n*-valeric acid or trimethylacetic acid, caproic acids such as β-trimethylpropionic acid, oenanthic, caprylic, pelargonic, capric, undecylic acids, for example of undecylenic acid, lauric, myristic, palmitic or stearic acids, for example of oleic acid, cyclopropyl-, cyclobutyl-, cyclopentyl- and cyclohexyl-carboxylic acid, cyclopropylmethyl-carboxylic acid, cyclobutylmethyl-carboxylic acid, cyclopentyl-ethyl-carboxylic acid, cyclohexylethyl-carboxylic acid, cyclopentyl-, cyclohexyl- or phenyl-acetic or -propionic acid, of benzoic acid, phenoxyalkane acids such as phenoxyacetic acid, parachloro-phenoxyacetic acid, 2:4-dichlorophenoxyacetic acid, 4-tertiary butyl-phenoxyacetic acid, 3-phenoxy-propionic acid, 4-phenoxy-butyric acid, of furan-2-carboxylic acid, 5-tertiarybutyl-furan-2-carboxylic acid, 5-bromo-furan-2-carboxylic acid, of nicotinic acids, of β-ketocarboxylic acids for example acetoacetic, propionylacetic, butyrylacetic or caprionylacetic acid, of amino acids, for example diethylamino-acetic acid or aspartic acid. Instead of carboxylic acid radicals there may be present those of sulphonic acids, or those of phosphoric, sulphuric or hydrohalic acids.

Special importance is attached to those esters that contain a group imparting solubility in water, for example a carboxyl or amino group, since they may be used in preparing aqueous solutions. The resulting semi-esters are derived from dicarboxylic acids, for example from oxalic, succinic, maleic, glutaric, dimethyl-glutaric, pimelic, acetone-dicarboxylic, acetylenedicarboxylic, phthalic, tetrahydrophthalic, hexahydrophthalic, endomethylene-tetrahydrophthalic, endomethylene-hexahydrophthalic, endoxyhexahydrophthalic, endoxytetrahydrophthalic, camphoric, cyclopropane-, cyclobutane-dicarboxylic, diglycollic, ethylene-bis-glycollic, polyethylene-bisglycollic, thioglycollic, furan-, dihydrofuran-, tetrahydrofuran-dicarboxylic acids, quinolic, cinchomeronic acid, or from the polyethyleneglycol-monoalkyl ether semi-esters of the aforementioned dicarboxylic acids.

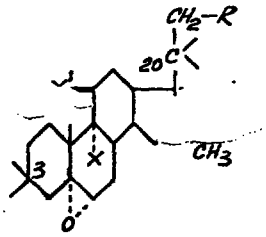
The products of the present process are distinguished by their high biological action. Special mention is deserved by the 6α-chloro- and 6α-fluoro derivatives of 16α-methyl-hydrocortisone, 16α-methyl-cortisone, 16α-methyl-prednisolone and 16α-methyl-prednisone, of

- fluoro - 16α - methylhydrocortisone, 9α-fluoro - 16α - methyl - cortisone, 9α - fluoro-16α - methyl - prednisolone and 9α - fluoro-16α - methyl prednisone as well as the corresponding 21-esters such as 21-trimethylacetates, 21-cyclopentylpropionates, 21-phenylpropionates and the 21-esters of dicarboxylic acids, for example of succinic acid, which display a high activity in the liver glycogen and the granuloma tests. In contradistinction to various corticosteroids not substituted in the 6α- and 16α-position, the afore-mentioned 6α-halogen-16α-methylpregnenes do not, or at most only very slightly, have the side-action of sodium retention.

The present invention also provides a process for the manufacture of a compound of the formula



in which R, X^1, X^2 and Y^1 have the meanings given above, or a 1-dehydro-derivative of such a compound, wherein a compound of the formula



in which R represents a free or esterified hydroxyl group, X represents a hydrogen, chlorine or fluorine atom, Y^1 represents an oxo group, or a hydrogen atom together with a free or esterified hydroxyl group and which contains a ketalized oxo group in the 3-position and a free or ketalized oxo group in the 20-position, is treated with hydrogen chloride or hydrogen fluoride or a salt thereof with a pyridine compound, a ketalized oxo group or groups in the 3- or 3:20-positions is or are converted into a free oxo group or groups, a resulting 5α-hydroxy-6β-chloro- or 5α-hydroxy-6β-fluoro compound is dehydrated, a resulting Δ⁴ - 3 - oxo - 6β - chloropregnene or Δ⁴-3-oxo-6β-fluoropregnene is isomerized in the 6-position, and, if desired, the resulting compound is dehydrogenated in the 1:2-position by a known method for the introduction of a 1:2-double bond into a steroid, and at any stage in the process esterified hydroxyl groups are hydrolyzed or free hydroxyl groups are esterified and/or an 11-hydroxy compound is dehydrogenated to an 11-oxo-compound. The word "known" is to be understood in this Specification as designating methods in actual use or described in the literature on the subject.

The reaction according to the invention of the starting materials with hydrochloric or hydrofluoric acid is performed in an organic solvent, for example in an alcohol, ketone, ether, halogenated hydrocarbon such as methylene chloride or chloroform, preferably in a lower aliphatic carboxylic acid, for example glacial acetic acid or propionic acid, or in a mixture of the aforementioned solvents, advantageously at a temperature ranging from 0 to 30°C. Under these conditions the starting materials are directly converted into the desired Δ⁴-3-oxo-6α-halogeno-pregnenes, first the 5α:6α-epoxide being split, then the 3-ketal hydrolyzed to the 3-oxo-5α-hydroxy-6β-halogeno-pregnane, the latter compound being dehydrated to the Δ⁴-3-oxo-6β-halogeno-pregnene and finally isomerization in the 6-position to the Δ⁴-3-oxo-6α-halogeno-pregnene being performed. Depending on the reaction conditions — for example when hydrochloric acid in acetone is used — 3-oxo-5α-hydroxy-6β-halogeno-pregnanes are obtained together with the final products. The former are converted into the desired Δ⁴-3-oxo-6α-halogeno-pregnenes, for example, by treatment with hydrochloric acid in glacial acetic acid.

When the starting material is treated with a pyridine salt of hydrochloric or hydrofluoric acid, for example with pyridine hydrochloride or collidine hydrochloride, the reaction comes to a standstill at the stage of the 3-oxo-5α-hydroxy-6β-halogeno-pregnanes or of the corresponding 3-mono- or 3:20-diketals. To convert these intermediate products into the Δ⁴-3-oxo-6α-halogeno-pregnenes they are, for example, treated with hydrochloric or hydrofluoric acid in the presence of glacial acetic acid or of a mixture of glacial acetic acid and chloroform.

The introduction of the 1:2-double bond can be performed by treatment with a selenium compound having a dehydrogenating action or by treatment with an aerobic culture of microorganisms capable of causing dehydrogenation in the 1:2-position.

A ~~prefered~~ preferred selenium compound of dehydrogenating action is selenium dioxide, for example in sublimed form, or selenious acid. The reaction is performed in an aqueous or non-aqueous solvent. Preferred organic solvents are those which at the temperature selected for the reaction react at most only a little with the selenium compound having a dehydrogenating action. Solvents that have proved especially advantageous are tertiary alcohols,

for example tertiary butanol or tertiary amyl alcohol, in the presence of a base, for example, a tertiary organic amine, for example pyridine or collidine. If required, the reaction mixture is heated under superatmospheric pressure or boiled under reflux. On completion of the reaction the mixture is filtered off from the selenium formed, and from the filtrate the reaction product is isolated by a known method.

To introduce the 1:2-double bond microbiologically, use is made of an aerobic culture of Fusarium solani, Fusarium caucasicum, Calonectria decora, Alternaria passiflorae, Ophiobolus heterostrophus, Ophiobolus Miyabeanus, Didymella lycopersici or of Corynebacterium simplex. For the performance of the microbiological process the starting material may be incubated with a culture of the above-mentioned microorganisms under aerobic conditions known *per se*. The organism is grown in a surface culture or, industrially more advantageously, in a submerged culture, with shaking or stirring. The cultures contain assimilable carbon, more especially carbohydrates, and may also contain growth promoting substances such as cornsteep liquor or beer wort, and inorganic salts. Thus, natural, synthetic or semi-synthetic nutrient solutions can be used. The process is simplest to perform in practice as described hereinbelow without limiting the invention thereto: The organism is grown in an apparatus and under conditions similar to those known in the manufacture of antibiotics as the so-called deep-tank process. When the culture has developed, the selected specified starting material is added in the form of a fine dispersion or solution, for example in methanol or ethylene-glycol, and incubation continued. Finally, the mycelium is separated, the filtrate and/or the mycelial mass is extracted and from the extract the $\Delta^{1:4}$-pregnadiene compound is isolated in a manner known *per se*, for example by a demixing process, adsorption, chromatography, crystallization, or conversion into a functional derivative, for example an ester. The same reactions can also be performed when the active enzymes from appropriate aerobic cultures of the aforementioned organisms have been first isolated and used with exclusion of the growing culture. Thus, for example, the mycelium formed by an appropriate areobic culture of the said organisms can be separated, suspended in water or in a buffer solution, the selected starting material added to the suspension obtained, and the whole then incubated.

To prepare the esters—above all the 21-esters—use is made of the afore-mentioned acids, or of their halides, anhydrides, thiol derivatives or ketones; transesterification methods are also applicable. To prepare the water-soluble salts, the semi-esters are reacted in a manner known *per se*, for example with a hydroxide, carbonate or bicarbonate of an alkali metal, more especially with sodium bicarbonate, or with an organic base such as ethanolamine, diethanolamine, triethanolamine, dibenzylethylene-diamine, ephedrine, or α-1-phenyl-2-methylaminopropane. It is a special advantage of these semi-esters that they form relatively stable aqueous solutions with the specified organic or inorganic bases.

Esterified hydroxyl groups in a resulting compound can be converted into free hydroxyl groups by chemical or enzymatic hydrolysis, for example with the use of an acid or basic agent or by reesterification.

To convert an 11-hydroxy compound into the corresponding 11-ketone use is made of a conventional dehydrogenating agent, for example chromium trioxide in glacial acetic acid or pyridine.

The 5α:6α-oxido-3-mono- and -3:20-diketals are new. They can be prepared for example, from the 16α-methyl-allopregnanes described in Specification No. 22984/59 (Serial No. 924,252) in the following manner:

The said 16α-methylallopregnanes are brominated in a conventional manner in the 2- and 4-positions, the 4-bromine atom is split off with the formation of a 4:5-double bond, and the 2-bromine atom is eliminated by reduction. The resulting Δ^4-3-oxo-16α-methylpregnene is then ketalized in the 3- or 3- and 20-positions, for example by being treated with ethylene-glycol or methyl-ethyldioxolane and an acid catalyst such as paratoluenesulphonic acid in boiling benzene or toluene. The ketal is then converted into the corresponding 5α:6α-oxido-16α-methyl-pregnane by oxidation with a per-compound, for example, peracetic acid, perbenzoic acid or mono-perphthalic acid.

The new compounds can be used as medicaments, for example in the form of pharmaceutical preparations which contain the active substance in admixture or conjunction with a pharmaceutical organic or inorganic, solid or liquid carrier suitable for enteral or parenteral administration; the content of the active ingredient is advantageously about 0.03 to 60 per cent by weight. As carriers such substances come into consideration as do not react with the new compounds, such as for instance water, gelatine, lactose, starch, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, cholesterol or other known carriers. The pharmaceutical preparations can be in the form, for instance, of tablets or dragees, or in liquid form as solutions, suspensions or emulsions, for example in the form of an ampoule or of an aqueous solution within an ampoule. They may be sterilized and/or contain auxiliary substances, such as preserving, stabilizing, wetting or emulsifying agents, salts for the modification of osmotic pressure or buffers. They may also contain other therapeutically useful substances. The

preparations are obtained in the customary way.

The following Examples illustrate the invention.

EXAMPLE 1

A slow current of dry hydrogen chloride gas is introduced at about 15°C for 2 hours into a suspension of 2 grams of 3-ethylenedioxy-5α:6α - oxido - 16α - methylpregnane-17α:21-diol-11,20-dione-21-acetate in 100 cc of glacial acetic acid. The reaction solution is then poured into ice water and the precipitated product is extracted with methylene chloride, the extract is washed with water, sodium carbonate solution and water, dried over sodium sulphate and evaporated *in vacuo*. Crystallization of the residue from acetone + hexane yields Δ^4-6α-chloro-16α-methylpregnene - 17α:21 - diol - 3:11:20 - trione - 21-acetate.

A solution of the above acetate in 20 cc of methanol is cooled in a nitrogen atmosphere to 0°C, and 12.5 mg of sodium methylate are added. After 15 minutes at 0°C the solution is neutralized with acetic acid, evaporated *in vacuo* and treated with water. The precipitate formed is suctioned off, dried and crystallized from acetone to yield Δ^4-6α-chloro-16α-methylpregnene-17α:21-diol-3:11:20-trione.

2 grams of this compound are dissolved in 15 cc of pyridine and treated at 0°C dropwise with 5 cc of trimethylacetic acid chloride. The mixture is allowed to stand overnight at room temperature, water is added, and the mixture shaken for 2 hours. It is then extracted with ether, washed with dilute hydrochloric acid, dilute sodium bicarbonate solution and water, dried over sodium sulphate and evaporated *in vacuo*. The residue is Δ^4-6α-chloro-16α-methylpregnene - 17α:21 - diol-3:11:20-trione-21-trimethylacetate.

In similar manner there is prepared, for example the 21-acetate, 21-cyclopentylpropionate, β-phenylpropionate and 21-hemisuccinate.

By the procedure described above there are obtained from 3:20-bisethylenedioxy-5α:6α-oxido-9α-chloro- and -9α-fluoro-16α-methylpregnane - 17α:21 - diol - 11 - one - 21-acetate the Δ^4-6α:9α-dichloro- and Δ^4-6α-chloro - 9α - fluoro - 16α - methylpregnene-17α:21 - diol - 3:11:20 - trione - 21 - acetate respectively.

EXAMPLE 2

A suspension of 2 grams of 3-ethylenedioxy-5α:6α - oxido - 16α - methyl - pregnane-17α:21 - diol - 11:20 - dione - 21 - acetate in 100 mg of glacial acetic acid is treated with 3 grams of hydrofluoric acid at a temperature below 15°C. The whole is kept for 4 hours at 15°C and then poured over ice, extracted with methylene chloride, washed with water, sodium bicarbonate solution and water, dried over sodium sulphate and evaporated to dryness *in vacuo*. Crystallization from acetone + hexane yields Δ^4 - 6α - fluoro - 16α - methylpregnene - 17α:21 - diol - 3:11:20 - trione-21-acetate. The product can be converted into the 21-hydroxy compound as described in Example 1.

When the starting material used above is treated with hydrofluoric acid in a dioxane + pyridine solution instead of in glacial acetic acid, the Δ^4 - 6β - fluoro - 16α - methylpregnene - 17α:21 - diol - 3:11:20 - trione-21-acetate is obtained which can be converted by isomerization into the Δ^4-6α-fluoro-16α-methyl - pregnene - 17α:21 - diol - 3:11:20-trione-21-acetate by treatment with hydrogen chloride + glacial acetic acid as described in Example 1.

In similar manner there is obtained from 3-ethylenedioxy - 5α:6α - oxido - 16α - methylpregnane - 11β:17α:21 - triol - 20 - one - 21-acetate the Δ^4 - 6β - fluoro - 16α - methylpregnene - 11β:17α:21 - triol - 3:20 - dione-21-acetate which is isomerized with hydrogen chloride + glacial acetic acid to the Δ^4-6α-fluoro - 16α - methyl - pregnene-11β:17α:21-triol - 3:20 - dione - 21 - acetate, which can be converted into the 21-hydroxy compound as described in Example 1.

EXAMPLE 3

5 grams of 3:20-bisethylenedioxy-5α,6α-oxido - 9α - fluoro - 16α - methylpregnane-11β:17α:21 - triol - 21 - acetate are dissolved in 250 cc of glacial acetic acid. A current of dry hydrogen chloride is introduced into the solution for 2 hours at 15°C. The whole is then poured into ice water, extracted with methylene chloride, washed with water, dilute sodium bicarbonate solution and water, dried over sodium sulphate and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone + hexane yields Δ^4-6α-chloro-9α-fluoro - 16α - methyl - pregnene-11β:17α:21-triol - 3:20 - dione - 21 - acetate.

When the starting material used above is reacted with hydrogen fluoride in glacial acetic acid + chloroform instead of with hydrogen chloride in glacial acetic acid, Δ^4-6α:9α-difluoro - 16α - methyl-pregnene-11β:17α:21-triol - 3:20 - dione - 21 - acetate is obtained. These 21-acetates can be converted into the 21-hydroxy compounds as described in Example 1.

EXAMPLE 4

A slow current of dry hydrogen chloride is introduced for 2 hours at 15°C into a solution of 2 grams of 3:30-bis-ethylenedioxy-5α:6α-oxido - 16α - methyl - pregnane-11β:17α:21-triol-21-acetate. The reaction solution is then poured into ice water, extracted with methylene chloride, washed with water, dilute sodium bicarbonate solution and water, and the methylene chloride solution is dried over sodium sulphate and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone + hexane yields Δ^4 - 6α - chloro - 16α-

thyl - pregnene - 11β:17α:21 - triol-20-dione-21-acetate.

As described in Example 1, the resulting acetate can be hydrolysed to the Δ⁴-6α-chloro-16α - methyl - pregnene - 11β:17α:21 - triol-3:20-dione and esterified to the corresponding 21-trimethyl acetate.

The 11β-hydroxyl group in the Δ⁴-6α-chloro - 16α - methyl - pregnene-11β:17α:21-triol-3:20-dione-21-acetate can be oxidized thus:

A solution of 150 mg of chromium trioxide in 5 cc of acetic acid of 80% strength is added dropwise with stirring, at a temperature below 15°C, to a solution of 1 gram of the above compound in 30 cc of glacial acetic acid. The mixture is kept for 2 hours at room temperature, poured into ice water, and the precipitate is separated, washed with water, dried and crystallized from acetone + hexane to yield Δ⁴ - 6α - chloro - 16α - methyl - pregnene-17α:21-diol-3:11:20-trione-21-acetate.

Example 5

5 grams of 3:20-bisethylenedioxy-5α:6α-oxido - 16α - methyl - pregnane-11β:17α:21-triol are suspended in 200 cc of acetone, 10 cc of concentrated hydrochloric acid are added, and the mixture is stirred for 1½ hours at room temperature, poured into ice water, extracted with methylene chloride, the extract is washed with water, dilute sodium bicarbonate and water, dried and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone + hexane yields a mixture of 5α-hydroxy - 6β - chloro - 16α - methylpregnane-11β:17α:21 - triol - 3:20 - dione.3:20-dione and Δ⁴ - 6β - chloro - 16α - methylpregene-11β:17α:21-triol-3:20-dione.

1 gram of the above product is dissolved in 50 cc of glacial acetic acid, the solution is cooled to about 15°C and for 4 hours a current of dry hydrogen chloride gas is introduced into it. The whole is then poured into ice water, extracted with methylene chloride, washed with water, sodium bicarbonate solution and water, dried and evaporated *in vacuo*. The residue is Δ⁴ - 6α - chloro - 16α - methyl-pregnene-11β:17α:21-triol-3:20-dione.

Example 6

4.11 grams of 6α - chloro - 16α - methyl-hydrocortisone are dissolved in 15 cc of pyridine and cooled to 0°C. A solution of 1.2 grams of cyclopropyl-carboxylic acid chloride in 5 cc of pyridine is then added under nitrogen in the course of 30 minutes. The whole is allowed to stand overnight at room temperature under nitrogen. The reaction solution is then poured on to a mixture of finely disintegrated ice and hydrochloric acid. The reaction product is taken up in a mixture of chloroform and tetrahydrofuran (3:2). The extract is washed with water, dilute hydrochloric acid, sodium bicarbonate solution and again with water, dried over sodium sulphate, filtered and evaporated. The resulting 6α-chloro - 16α - methyl - hydrocortisone - 21-cyclopropyl-carboxylic acid ester is recrystallized from acetone-methanol; the product gives no direct blue coloration with blue tetrazol and dilute sodium hydroxide solution.

In an analogous manner the reaction of cyclopropyl-carboxylic acid chloride in pyridine with 6α - fluoro - 16α - methyl - hydrocortisone yields 6α - fluoro - 16α - methyl-hydrocortisone - 21 - cyclopropyl - carboxylic acid ester, with 6α - chloro - 9α - fluoro - 16α-methyl - hydrocortisone the 6α - chloro - 9α-fluoro - 16α - methyl - hydrocortisone - 21-cyclopropyl - carboxylic acid ester, with 6α:9α - dichloro - 16α - methyl - hydrocortisone the 6α:9α - dichloro - 16α - methyl-hydrocortisone - 21 - cyclopropyl - carboxylic acid ester, with 6α:9α - difluoro - 16α-methyl - hydrocortisone the 6α:9α - difluoro-16α - methyl - hydrocortisone - 21 - cyclopropyl - carboxylic acid ester, with 6α-chloro-16α - methyl - cortisone the 6α - chloro - 16α-methyl - cortisone - 21 - cyclopropyl - carboxylic acid ester, with 6α - fluoro - 16α-methyl - cortisone the 6α - fluoro - 16α-methyl - cortisone - 21 - cyclopropyl - carboxylic acid ester, with 6α - chloro - 9α-fluoro - 16α - methyl - cortisone the 6α-chloro - 9α - fluoro - 16α - methyl - cortisone-21 - cyclopropyl - carboxylic acid ester, with 6α:9α - dichloro - 16α - methyl - cortisone the 6α:9α - dichloro - 16α - methyl-cortisone-12 - cyclopropyl - carboxylic acid ester and with 6α:9α - difluoro - 16α - methyl-cortisone the 6α:9α - difluoro - 16α - methyl-cortisone-21-cyclopropyl-carboxylic acid ester; the products give no direct blue coloration with blue tetrazol and dilute sodium hydroxide solution.

Example 7

4.11 grams of 6α - chloro - 16α - methyl-hydrocortisone are heated in 50 cc of pyridine with 2.0 grams of succinic acid anhydride on a boiling water bath for 30 minutes under nitrogen. After cooling, the mixture is poured on to ice-water, acidified with glacial acetic acid, the precipitated reaction product is allowed to stand overnight, suction-filtered, washed with water and dried. 4.7 grams of 6α - chloro - 16α - methyl - hydrocortisone-21-hemisuccinate are obtained.

In order to prepare the water-soluble sodium salt of 6α - chloro - 16α - methyl - hydrocortisone - 21 - hemisuccinate 0.51 gram of 6α - chloro - 16α - methyl - hydrocortisone-21-hemi-succinate is dissolved in 11 cc of 0.1N-sodium bicarbonate, filtered clean and lyophilized. 0.5 gram of the sodium salt of 6α - chloro - 16α - methyl - hydrocortisone-21-hemisuccinate is obtained.

In an analogous manner from 6α-chloro-16α - methyl - hydrocortisone and triethanolamine there is obtained the triethanolamine

salt of 6α - chloro - 16α - methyl - hydrocortisone - 21 - hemisuccinate and with diethanolamine the corresponding diethanolamine salt of 6α-chloro-16α-methyl-hydrocortisone-21-hemisuccinate.

By working in the same manner there is obtained by reacting succinic acid anhydride with 6α - fluoro - 16α - methyl - hydrocortisone the 6α - fluoro - 16α - methyl hydrocortisone-21-hemisuccinate and from the latter the water-soluble sodium salt of 6α-fluoro-16α-methyl - hydrocortisone - 21 - hemisuccinate, with 6α - chloro - 9α - fluoro - 16α - methyl-hydrocortisone the 6α - chloro - 9α - fluoro-16α - methyl - hydrocortisone - 21 - hemisuccinate and from the latter the water-soluble sodium salt of 6α-chloro-9α-fluoro-16α-methyl - hydrocortisone - 21 - hemisuccinate, with 6α:9α - dichloro - 16α - methyl - hydrocortisone the 6α:9α - dichloro - 16α - methyl-hydrocortisone - 21 - hemisuccinate and from the later the water-soluble sodium salt of 6α:9α - dichloro - 16α - methyl - hydrocortisone-21-hemisuccinate, and with 6α:9α-difluoro - 16α - methyl - hydrocortisone the 6α:9α - difluoro - 16α - methyl - hydrocortisone-21-hemisuccinate and from the latter the water-soluble sodium salt of 6α:9α-difluoro - 16α - methyl - hydrocortisone - 21-hemisuccinate.

EXAMPLE 8

0.80 gram of liquid sulphur trioxide is added dropwise to 30 cc of dry pyridine in a nitrogen atmosphere at −10° to −5°C. To the resulting pyridine-sulphur trioxide adduct in pyridine there are added in the course of 30 minutes with continuous cooling 4.1 grams of 6α - chloro - 16α - methyl - cortisol dissolved in 30 cc of dry pyridine. The reaction mixture is first stirred for 1 to 2 hours at 0°C, the pyridine-sulphur trioxide adduct gradually dissolving, and then maintained another 2 to 3 hours at room temperature. The pyridine is then distilled off to a great extent under reduced ~~presure~~ at a bath temperature of 40°C at the most. The resulting residue is ~~digested~~ repeatedly with dry ether until crystallization sets in, the crystalline magma is covered with dry ether and allowed to stand overnight. The reaction mixture is suction-filtered, the crystallizate dissolved in 100 cc of methanol and the solution titrated with N-sodium methylate until the pH = 9. The sodium sulphate precipitating on titration is separated and the filtrate concentrated under reduced pressure at a bath temperature of 40°C at the most, the concentrated solution cooled to −40° to −50°C and poured slowly into ether with stirring. The resulting crystalline suspension is suction-filtered after being allowed to cool overnight.

There is obtained the sodium salt of 6α-chloro - 16α - methyl - cortisol - 21 - hemisulphate which is readily soluble in water and exhibits no direct blue coloration with blue tetrazol and dilute sodium hydroxide solution in the cold.

0.5 gram of the sodium salt of 6α-chloro-16α - methyl - cortisol - 21 - hemisulphate is dissolved in 50 cc of methanol and allowed to flow slowly through a column of "Amberlite" (Registered Trade Mark) JR—120 prepared with dilute hydrochloric acid and methanol. The column is washed with methanol until the filtrate is practically not absorbed in the ultraviolet spectrum at 240 mμ. The filtrate is concentrated under reduced pressure at a bath temperature of 40°C at the most, diluted with ether, 6α - chloro - 16α - methyl - cortisol-21-hemisulphate precipitating. After being allowed to stand overnight in a refrigerator, the crystallizate is suction-filtered and dried. 6α - chloro - 16α - methyl - ~~coritsol~~ - 21-hemisulphate is obtained which dissolves in dilute sodium bicarbonate solution to form a clear solution and with blue tetrazol and dilute sodium hydroxide solution exhibits no direct blue coloration in the cold.

In an analogous manner by reacting the pyridine-sulphur trioxide adduct with 6α-fluoro - 16α - methyl - cortisol and 6α-fluoro-16α - methyl - ~~coritsone~~ respectively there are obtained 6α - fluoro - 16α - methyl - cortisol-21-hemisulphate and 6α - fluoro - 16α-methyl-~~coritsone~~-21-hemisulphate respectively and from the latter the water-soluble sodium salts of 6α - fluoro - 16α - methyl - cortisol - 21-hemisulphate and 6α - fluoro - 16α - methyl-~~coritsone~~ - 21 - hemisulphate, with 6α-chloro-9α - fluoro - 16α - methyl - cortisol and 6α-chloro - 9α - fluoro - 16α - methyl - cortisone respectively 6α - chloro - 9α - fluoro - cortisol-21-hemisulphate and 6α - chloro - 9α - fluorocortisone - 21 - hemisulphate respectively, and from the latter the water-soluble sodium salts of 6α - chloro - 9α - fluoro - 16α-methyl-cortisol - 21 - hemisulphate and 6α - chloro-9α - fluoro - 16α - methyl - cortisone - 21-hemisulphate, and with 6α:9α - difluoro-16α - methyl - cortisol and 6α:9α - difluoro-16α - methyl - cortisone and 6α:9α-dichloro-16α - methyl - cortisol and 6α:9α - dichloro-16α - methyl - cortisone the 6α:9α - difluoro-16α - methyl - cortisol - 21 - hemisulphate, the 6α:9α - difluoro - 16α - methyl - cortisone-21 - hemisulphate, the 6α:9α - dichloro - 16α-methyl - cortisol - 21 - hemisulphate and 6α:9α - dichloro - 16α - methyl - cortisone-21-hemisulphate and their water-soluble sodium salts; the products exhibit no direct blue coloration with blue tetrazol and dilute sodium hydroxide solution in the cold.

EXAMPLE 9

A suspension of 500 mg of Δ⁴-16α-methyl-6α - chloro - pregnene - 17α:21 - diol-3:11:20 - trione - 21 - acetate in 25 cc of anhydrous tertiary butanol, 150 mg of selenium dioxide and 0.05 cc of pyridine is refluxed for 70 hours in an atmosphere of nitrogen.

...ne mixture is cooled, diluted with 50 cc of ...ic acid ethyl ester, filtered over "Celite" (Registered Trade Mark) and the filter residue is thoroughly washed with acetic acid ethyl ester. The combined ethyl acetate solutions are evaporated to dryness *in vacuo*, the residue is treated with water and then filtered. The dried residue is adsorbed on a column of 25 grams of washed alumina and the column is then eluted with benzene + ether, and ether, the fractions are combined, evaporated to dryness and crystallized from acetone + hexane, to yield 150 mg of $\Delta^{1:4}$-16α-methyl-6α-chloro-pregnadiene - 17α:21 - diol - 3:11:20-trione-21-acetate.

A solution of 100 mg of the resulting acetate in 20 cc of methanol is cooled with ice to 0°C, and in an atmosphere of nitrogen treated with 12.5 mg of sodium methylate. The solution is kept for 15 minutes at 0°C, neutralized with acetic acid, evaporated almost to dryness and diluted with water. The precipitate is collected and recrystallized from acetone to yield $\Delta^{1:4}$-16α - methyl - 6α - chloro - pregnadiene-17α:21-diol-3:11:20-trione.

Instead of with sodium methylate, the hydrolysis can be performed with an equal amount of sodium hydroxide or potassium hydroxide.

In an analogous manner the $\Delta^{1:4}$-16α-methyl - 6α - fluoro - pregnadiene - 17α:21-diol-3:11:20-trione can be prepared.

Example 10

500 mg of $\Delta^{1:4}$ - 16α - methyl - 6α - chloro-pregnadiene - 17α:21 - diol - 3:11:20-trione are dissolved in 5 cc of pyridine, mixed with 0.5 cc of acetic anhydride, and the mixture is kept for 4 hours at room temperature and then poured into water. It is extracted with methylene dichl... the extra... washed with dilute hydrochloric acid, wa... sodium bicarbonate solution and once more with water, dried over sodium sulphate and evaporated to dryness. Recrystallization of the residue from acetone + hexane yields $\Delta^{1:4}$-16α-methyl-6α - chloro - pregnadiene - 17α:21 - diol-3:11:20-trione-21-acetate.

When acetic anhydride is replaced in this Example by trimethyl acetic acid anhydride, cyclopentylpropionic acid anhydride, phenylpropionic acid anhydride or succinic acid anhydride, there are obtained respectively the corresponding 21-trimethyl-acetate, 21-cyclopentylpropionate, 21 - phenylpropionate and 21-hemisuccinate of $\Delta^{1:4}$ - 16α - methyl - 6α-chloro - pregnadiene - 17α:21 - diol-3:11:20-trione.

Example 11

A mixture of 500 mg of Δ^{4}-16α-methyl-6α-chloro - pregnene - 11β:17α:21 - triol-3:20-dione-21-acetate, 25 cc of anhydrous tertiary butanol, 150 mg of selenium dioxide and 0.05 cc of pyridine is refluxed for 70 hours in a nitrogen atmosphere. The reaction mixture is cooled and then diluted with 50 cc of acetic acid ethyl ester and filtered over "Celite," the filter residue is thoroughly washed with acetic acid ethyl ester, and the combined filtrates are evaporated to dryness *in vacuo*. The residue is treated with water, filtered, the residue is dried and absorbed on a column of 25 grams of washed alumina, and the crystalline fractions are eluted with benzene + ether and ether. The fractions are combined and recrystallized from acetone + hexane to yield $\Delta^{1:4}$-16α-methyl-6α-chloro - pregnadiene-11β:17α:21-triol-3:20-dione-21-acetate.

100 mg of the resulting acetate are dissolved in 20 cc of methanol, cooled to 0°C in a nitrogen atmosphere, and mixed with 12.5 mg of sodium methylate. The solution is kept for 15 minutes at 0°C and then neutralized with acetic acid, evaporated to dryness *in vacuo* and diluted with water. The precipitate is filtered off and recrystallized from acetone to yield $\Delta^{1:4}$ - 16α - methyl - 6α - chloro-pregnadiene-11β:17α:21-triol-3:20-dione.

Example 12

3.5 grams of $\Delta^{1:4}$ - 16α - methyl - 6α-chloro-pregnadiene - 11β:17α - 21 - triol - 3:20-dione are heated in 50 cc of pyridine with 2.0 grams of succinic acid anhydride under nitrogen for 30 minutes on a boiling water bath. The mixture is allowed to cool, poured into dilute, ice-cold hydrochloric acid, suction-filtered, washed with dilute hydrochloric acid and then with water, dried and recrystallized from methanol to yield $\Delta^{1:4}$ - 16α - methyl-6α - chloro - pregnadiene - 11β:17α:21-triol-3:20-dione-21-hemisuccinate.

To prepare the water-soluble sodium salt of $\Delta^{1:4}$ - 16α - methyl - 6α - chloro - pregnadiene - 11β:17α:21 - triol - 3:20 - dione-21-hemisuccinate 0.5 gram of $\Delta^{1:4}$-16α-methyl-6α - chloro - pregnadiene - 11β:17α:21-triol-3:20-dione-21-hemisuccinate is dissolved in 11 cc of 0.1N-sodium bicarbonate solution, filtered clear and then lyophillized in the usual manner to yield 0.54 gram of the sodium salt of $\Delta^{1:4}$ - 16α - methyl - 6α - chloro - pregnadiene - 11β:17α:21 - triol - 3:20 - dione-21-hemisuccinate.

In an analogous manner the triethanolamine salt of $\Delta^{1:4}$ - 16α - methyl - 6α - chloro-pregnadiene - 11β:17α:21 - triol - 3:20-dione-21-hemisuccinate is obtained from triethanolamine and $\Delta^{1:4}$ - 16α - methyl - 6α-chloro - pregnadiene - 11β:17α:21 - triol-3:20-dione-21-hemisuccinate.

Example 13

A mixture of 500 mg of Δ^{4} - 16α - methyl-6α - fluoro - pregnene - 11β:17α:21 - triol-3:20-dione-21-acetate, 25 cc of anhydrous tertiary butanol, 150 mg of selenium dioxide and 0.05 cc of pyridine is refluxed for 70 hours in an atmosphere of nitrogen. The mixture is cooled, diluted with 50 cc of acetic acid ethyl

ester, filtered over "Celite," and the residue is thoroughly washed with acetic acid ethyl ester. The filtrate and the washings are combined, washed with water, dried over sodium sulphate, filtered, and evaporated to dryness under diminished pressure. The residue is treated with water, the precipitate is filtered off, dried and adsorbed on 25 grams of washed alumina. The fractions obtained by elution with benzene + ether and ether and recrystallization from acetone + hexane yield $\Delta^{1:4}$-16α-methyl - 6α - fluoro-pregnadiene-11β:17α:21-triol - 3:20 - dione - 21 - acetate which can be hydrolysed to yield $\Delta^{1:4}$-16α-methyl-6α-fluoro - pregnadiene - 11α:17α:21 - triol-3:20-dione as described in Examples 9 and 11.

EXAMPLE 14

A mixture of 3 grams of Δ^4 - 16α - methyl-6α-chloro-9α-fluoro - pregnene - 11β:17α:21-triol - 3:20 - dione - 21 - acetate, 150 cc of anhydrous tertiary butanol, 900 mg of selenium dioxide and 0.3 cc of pyridine is refluxed for 70 hours under nitrogen, then cooled and diluted with acetic acid ethyl ester. The mixture is filtered through "Celite," the residue washed with acetic acid ethyl ester, the filtrate and the washings are combined and evaporated to dryness under reduced pressure. The residue is treated with water, the precipitate is filtered off, dried and then adsorbed on 150 grams of washed alumina. The fractions obtained with benzene + ether and ether are combined, evaporated and crystallized from acetone + hexane to yield $\Delta^{1:4}$ - 16α-methyl - 6α - chloro - 9α - fluoro - pregnadiene - 11β:17α:21 - triol - 3:20 - dione-21-acetate.

The 11β-hydroxyl group can be oxidized thus:

A solution of 150 mg of chromium trioxide in 5 cc of acetic acid of 80% strength is added dropwise with thorough stirring at a temperature below 20°C to a solution of 1 gram of $\Delta^{1:4}$ - 16α - methyl - 6α - chloro - 9α - fluoro-pregnadiene - 11β:17β:21 - triol - 3:20-dione-21-acetate in 30 cc of acetic acid. The mixture is kept for 2 hours at room temperature, then poured into ice water, the precipitate is filtered off, washed with water, dried and recrystallized from acetone + hexane to yield $\Delta^{1:4}$ - 16α - methyl - 6α - chloro - 9α-fluoro - pregnadiene - 17α:21 - diol-3:11:20-trione-21-acetate.

EXAMPLE 15

A solution of 1 gram of $\Delta^{1:4}$ - 16α - methyl-6α - chloro - 9α - fluoro - pregnadiene-11β:17α:21 - triol - 3:20 - dione - 21-acetate in 200 cc of methanol is cooled to 0°C and mixed with 120 mg of sodium methylate under nitrogen. The mixture is kept for 15 minutes at 0°C, neutralized with acetic acid, evaporated almost to dryness and diluted with water. The precipitate is filtered off and recrystallized from acetone to yield $\Delta^{1:4}$-16α-methyl - 6α - chloro - 9α - fluoro - pregnadiene-11β:17α:21-triol-3:20-dione.

The 21-acetates described in Example 14, can be hydrolysed to the corresponding 21-hydroxy compounds in a similar manner.

EXAMPLE 16

A mixture of 1 gram of $\Delta^{1:4}$ - 16α - methyl-6α - chloro - 9α - fluoro - pregnadiene-11β:17α:21 - triol - 3:20 - dione, 20 cc of pyridine and 1 cc of trimethylacetic acid chloride is kept overnight at room temperature and then poured into water. It is extracted with acetic acid ethyl ester, the acetic acid ethyl ester solution is washed with water, dilute hydrochloric acid, water, sodium bicarbonate solution and again with water, dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The resulting $\Delta^{1:4}$-16α-methyl - 6α - chloro - 9α - fluoropregnadiene-11β:17α:21 - triol - 3:20 - dione - 21-trimethylacetate is recrystallized from methanol.

EXAMPLE 17

A mixture of 1 gram of Δ^4 - 16α - methyl-6α:9α - difluoropregnene - 11β:17α:21-triol - 3:20 - dione - 21 - acetate, 50 cc of anhydrous tertiary butanol, 300 mg of selenium dioxide and 0.1 cc of pyridine is refluxed for 70 hours under nitrogen, cooled, diluted with acetic acid ethyl ester and filtered through "Celite." The filter residue is thoroughly washed with ethyl acetate, the washing combined with the filtrate and evaporated to dryness under reduced pressure. The residue is treated with water, the precipitate is filtered off, dried and chromatographed, to yield $\Delta^{1:4}$ - 16α - methyl - 6α:9α - difluoro-pregnadiene - 11β:17α:21 - triol - 3:20-dione-21-acetate.

The 11β-hydroxy group can be oxidized thus:

A solution of 1 gram of $\Delta^{1:4}$ - 16α - methyl-6α:9α - difluoro - pregnadiene - 11β:17α:21-triol - 3:20 - dione - 21 - acetate in 300 cc of acetic acid is mixed dropwise with stirring at a temperature below 20°C with a solution of 150 mg of chromium trioxide in 6 cc of acetic acid of 80% strength. The mixture is kept for 2 hours at room temperature, poured over ice, the precipitate is filtered off, washed with water, dried and recrystallized from acetone + hexane, to yield $\Delta^{1:4}$-16α-methyl-6α:9α - difluoro - pregnadiene - 17α:21-diol-3:11:20-trione-21-acetate. The above 21-acetates can be converted into the 21-hydroxy compounds as described in Example 1.

EXAMPLE 18

30 cultures of Corynebacterium simplex ATCC 6946 are prepared on a 0.1% yeast extract in distilled water (which is distributed in portions of 30 cc each per Erlenmeyer flask of 125 cc capacity) by inoculating the media

with a 24-hour-old culture on the same medium, and incubating for 24 hour at 28°C.

To each of these cultures is added 1 cc of an ethanolic solution of Δ^4 - 16α - methyl-6α - chloro - pregnene - 11β:17α:21 - triol-3:20-dione-21-acetate containing 10 mg of the steroid and having been prepared in distilled ethanol and without application of heat shortly before use. Incubation is continued for 48 hours with stirring and at an even temperature of 28°C. In other tests the incubation period was extended to 72 hours, the same result being achieved.

The content of the flasks is then divided into 3 portions, each portion is extracted 5 times with 500 cc of methylene dichloride, the extracts are combined, washed with water, dried over anhydrous sodium sulphate, filtered and evaporated to dryness under diminished pressure and at a low temperature. The product obtained in this manner contains the $\Delta^{1:4}$-16α - methyl - 6α - chloro - pregnadiene-11β:17α:21-triol-3:20-dione.

This crude product is dissolved in 3 cc of pyridine, mixed with 3 cc of acetic anhydride, kept for 24 hours at room temperature, poured into water and extracted with methylene dichloride. The extract is washed with dilute hydrochloric acid, with potassium carbonate solution of 5% strength and with water, dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The residue is adsorbed on a column of 15 grams of washed alumina and eluted with benzene + ether (80:20) to yield 70 mg of $\Delta^{1:4}$-16α-methyl-6α-chloro-pregnadiene - 11β:17α:21 - triol - 3:20-dione-21-acetate.

When the microbiologically produced crude product is purified directly by adsorption on 15 grams of silica and elution of the column with chloroform + ether, the $\Delta^{1:4}$-16α-methyl-6α - chloro - pregnadiene - 11β:17α:21-triol-3:20-dione is obtained.

The Δ^4-pregnene compounds used in Examples 9, 13, 14 and 17 can be dehydrogenated in 1:2-position in an analogous manner.

In identical manner, but with the use of cultures of Didymella lycopersici, the aforementioned starting materials can be dehydrogenated in the 1:2-position.

EXAMPLE 19

4.09 grams of 1-dehydro-6α-chloro-16α-methyl-hydrocortisone are dissolved in 10 cc of pyridine and cooled to 0°C; a solution of 1.2 grams of cyclopropyl-carboxylic acid chloride in 5 cc of pyridine is added in the course of 30 minutes under nitrogen. The whole is allowed to stand overnight at room temperature under nitrogen and the reaction solution is then poured on to a mixture of finely disintegrated ice and hydrochloric acid. The reaction product is taken up in a mixture of chloroform and tetrahydrofuran (3:2). The extract is washed with water, dilute hydrochloric acid, sodium bicarbonate solution and several times with water, dried over sodium sulphate, filtered and evaporated. The resulting 1 - dehydro - 6α - chloro - 16α - methyl-hydrocortisone - 21 - cyclopropyl - carboxylic acid ester is recrystallized from acetone-methanol; the product exhibits no direct blue coloration with blue tetrazol and 2N-sodium hydroxide solution in the cold.

In an analogous manner by reacting 1-dehydro - 6α - fluoro - 16α - methyl - hydrocortisone and cyclopropyl - carboxylic acid chloride in pyridine there is obtained 1-dehydro - 6α - fluoro - 16α - methyl - hydrocortisone - 21 - cyclopropyl - carboxylic acid ester which exhibits no direct blue coloration with blue tetrazol and 2N-sodium hydroxide solution in the cold.

EXAMPLE 20

4.09 grams of 1-dehydro-6α-chloro-16α-methyl-hydrocortisone are dissolved in 10 cc of pyridine; the solution is cooled to 0°C. A solution of 1.4 grams of trimethylacetic acid chloride in 10 cc of pyridine is added dropwise in the course of 20—30 minutes under nitrogen. After being allowed to stand overnight at room temperature under nitrogen, the reaction solution is poured onto ice-water. It is acidified with dilute hydrochloric acid and the reaction product taken up in a mixture of chloroform and tetrahydrofuran (3:2). The extract is washed with dilute hydrochloric acid, water, dilute sodium carbonate solution and water, dried over sodium sulphate, filtered and evaporated. After recrystallizing the residue from a mixture of ether and methylene chloride there is obtained 1 - dehydro - 6α - chloro-16α - methyl - hydrocortisone - 21 - trimethyl acetate which exhibits no direct blue coloration with blue tetrazol and 2N-sodium hydroxide solution in the cold.

In an analogous manner by reacting 1-dehydro - 6α - fluoro - 16α - methyl - hydrocortisone and trimethylacetyl chloride in pyridine there is obtained 1-dehydro-6α-fluoro-16α - methyl - hydrocortisone - 21 - trimethyl acetate which exhibits no direct blue coloration with blue tetrazol and 2N-sodium hydroxide solution.

EXAMPLE 21

4.10 grams of 1-dehydro-6α:9α-difluoro-16α-methyl-hydrocortisone are heated in 50 cc of pyridine with 2.0 grams of succinic acid anhydride on a boiling water bath for 30 minutes under nitrogen. After cooling, the reaction mixture is poured into ice-water, acidified with glacial acetic acid, the precipitated reaction product suction-filtered after being allowed to stand overnight, washed with water and dried. There is obtained 1-dehydro-6α:9α - difluoro - 16α - methyl - hydrocortisone-21-hemisuccinate.

To prepare the water-soluble sodium salt of 1 - dehydro - 6α:9α - difluoro - 16α - methyl-

hydrocortisone - 21 - hemisuccinate 0.51 gram of 1 - dehydro - 6α:9α - difluoro - 16α-methyl-hydrocortisone-21-hemisuccinate is dissolved in 11 cc of 0.1N-sodium bicarbonate, filtered clean and lyophilized in known manner. 0.5 gram of the sodium salt of 1-dehydro-6α:9α-difluoro - 16α - methyl - hydrocortisone - 21-hemisuccinate is obtained.

In an analogous manner from diethanolamine and 1 - dehydro - 6α:9α - difluoro-16α - methyl - hydrocortisone - 21 - hemisuccinate there is obtained the diethanolamine salt of 1 - dehydro - 6α:9α - difluoro - 16α-methyl - hydrocortisone - 21 - hemisuccinate.

Working in the same way and reacting succinic acid anhydride with 1-dehydro-6α-chloro - 9α - fluoro - 16α - methyl - hydrocortisone there is obtained 1-dehydro-6α-chloro - 9α - fluoro - 16α - methyl - hydrocortisone - 21 - hemisuccinate and from the latter the water-soluble sodium salt of 1-dehydro - 6α - chloro - 9α - fluoro - 16α-methyl - hydrocortisone - 21 - hemisuccinate, with 1 - dehydro - 6α:9α - difluoro - 16α-methyl - cortisone 1 - dehydro - 6α:9α - difluoro - 16α - methyl - cortisone - 21 - hemisuccinate and from the latter the sodium salt of 1 - dehydro - 6α:9α - difluoro - 16α-methyl - cortisone - 21 - hemisuccinate, and with 1 - dehydro - 6α - chloro - 9α - fluoro-16α - methyl - cortisone 1 - dehydro - 6α-chloro - 9α - fluoro - 16α - methyl - cortisone-21-hemisuccinate and from the latter the sodium salt of 1 - dehydro - 6α - chloro - 9α-fluoro - 16α - methyl - cortisone - 21 - hemisuccinate.

EXAMPLE 22

0.80 gram of liquid sulphur trioxide is introduced dropwise into 30 cc of dry pyridine at −10° to −5°C in a nitrogen atmosphere. Into the resulting pyridine-sulphur trioxide adduct in pyridine there are added 4.0 grams of 6α-fluoro - 16α - methyl - prednisolone dissolved in 30 cc of dry pyridine in the course of 30 minutes with continuous cooling. The reaction mixture is first stirred for 1—2 hours at 0°C, the pyridine-sulphur trioxide adduct gradually dissolving, and then maintained for another 2—3 hours at room temperature. The pyridine is then distilled off to a great extent under reduced pressure at a bath temperature of 40°C at the most. The resulting residue is digested repeatedly with dry ether until crystallization sets in, the crystalline magma covered with dry ether and allowed to stand overnight. The reaction product is suction-filtered, the crystallizate dissolved in 100 cc of methanol and the solution titrated with N-sodium methylate to pH = 9. The sodium sulphate which precipitates on titration is separated and the filtrate concentrated under reduced pressure at a bath temperature of 40°C at the most, the concentrated solution cooled to −40°C to −50°C and slowly introduced into ether with stirring. The resulting crystalline suspension is suction-filtered after cooling. There are obtained 3 to 3.5 grams of the sodium salt of 6α - fluoro - 16α - methyl-prednisolone - 21 - hemisulphate which dissolves to form a clear solution in water and exhibits no direct blue coloration with blue tetrazol and dilute sodium hydroxide solution in the cold.

0.5 gram of the sodium salt of 6α-fluoro-16α - methyl - prednisolone - 21 - hemisulphate is dissolved in 50 cc of methanol and allowed to flow slowly through a column of "Amberlite" JR—120 prepared with dilute hydrochloric acid and methanol; the column is washed with methanol until the filtrate is practically not absorbed in the ultraviolet spectrum at 240 mμ. The filtrate is concentrated under reduced pressure at a bath temperature of 40°C at the most, diluted with ether, 6α-fluoro - 16α - methyl - prednisolone-21-hemisulphate precipitating. After being allowed to stand overnight in a refrigerator, the crystallizate is suction-filtered and dried. 0.4 gram of 6α - fluoro - 16α - methyl-prednisolone - 21 - hemisulphate is obtained which dissolved in dilute sodium bicarbonate to form a clear solution and exhibits no direct blue coloration with blue tetrazol and dilute sodium hydroxide solution in the cold.

0.4 gram of 6α - fluoro - 16α - methyl-prednisolone - 21 - hemisulphate is dissolved in 30 cc of methanol, and a solution of diazomethane in ether is added with cooling by means of ice-water until the yellow colour pesists. Glacial acetic acid is then added dropwise until decoloration takes place and the mixture is then concentrated under reduced pressure until crystallization sets in. After being allowed to stand overnight in a refrigerator, the crystallizate is suction-filtered. 0.2 gram of the methyl ester of 6α-fluoro-16α-methyl - prednisolone - 21 - hemisulphate is obtained; from the mother liquor there are obtained further quantities of the methyl ester after concentration.

In an analogous manner by reacting the pyridine-sulphur trioxide adduct with 6α-chloro - 16α - methyl - prednisolone there is obtained 6α - chloro - 16α - methyl - prednisolone-21-hemisulphate and from the latter the water-soluble sodium salt of 6α-chloro-16α - methyl - prednisolone - 21 - hemisulphate, with 6α - chloro - 16α - methyl-prednisone 6α - chloro - 16α - methyl - prednisone-21-hemisulphate and from the latter the water-soluble sodium salt of 6α - chloro - 16α-methyl - prednisone - 21 - hemisulphate, with 6α - fluoro - 16α - methyl - prednisone 6α-fluoro - 16α - methyl - prednisone - 21 - hemisulphate and from the latter the water-soluble sodium salt of 6α-fluoro-16α-methylprednisone-21 - hemisulphate, with 6α:9α - difluoro-16α - methyl - prednisone and -prednisolone 6α:9α - difluoro - 16α - methyl - prednisone-21-hemisulphate and -prednisolone-21-hemi-

hate and from the latter the water-soluble sodium salts of 6α:9α - difluoro - 16α-methyl - prednisone - 21 - hemisulphate and of 6α:9α - difluoro - 16α - methyl - prednisolone - 21 - hemisulphate, and with 6α-chloro - 9α - fluoro - 16α - methyl - prednisone and -prednisolone 6α - chloro - 9α - fluoro-16α - methyl - prednisone - 21 - hemisulphate and 6α - chloro - 9α - fluoro - 16α - methyl-prednisolone - 21 - hemisulphate and from the latter the water-soluble sodium salts of 6α - chloro - 9α - fluoro - 16α - methyl - prednisone - 21 - hemisulphate and 6α - chloro-9α - fluoro - 16α - methyl - prednisolone - 21-hemisulphate.

The starting materials used in the preceding Examples can be prepared, for example, as follows:

3 - ethylenedioxy - 5α:6α - oxido - 16α-methyl - pregnane - 17α:21 - diol-11:20-dione-21-acetate.

A solution of 3 grams of the 16α-methyl-allopregnane - 17α:21 - diol - 3:11:20-trione - 21 - acetate, described in Specification No. 22984/59 (Serial No. 924,252) in 400 cc of glacial acetic acid is treated with a few drops of hydrobromic acid in glacial acetic acid and then with 3 grams of bromine in 5 cc of glacial acetic acid. When the reaction solution has lost its colour, it is poured into ice water and extracted with methylene chloride, washed with sodium bicarbonate solution and water, the solvent is dried over sodium sulphate and cautiously evaporated *in vacuo*. The residue is crude 2:4-dibromo-16α-methyl-allopregnane - 17α:21 - diol-3:11:20-dione-21-acetate.

0.3 cc of bromine is added with cooling to 7.5 cc of ac[illegible]. After discoloration has occurred, 0.7 gram of sodium carbonate is added. The whole is filtered and the filtrate is added to 30 cc of acetone containing 7 grams of iodine. The resulting solution is heated for several minutes at the boil, 1.5 grams of the above dibromide are added and the mixture is boiled for 2½ hours. 1.4 grams of oxalic acid are added and the mixture is boiled for another hour, allowed to cool, 30 cc of ethyl acetate are added, and the precipitate is filtered off. The filtrate is washed with water, sodium bicarbonate solution and water. The iodine-containing solution is then discolorized by adding 3.5 grams of zinc dust and 0.5 cc of glacial acetic acid. It is then filtered, and the filtrate is washed with sodium bicarbonate solution and water, dried and evaporated. The resulting residue is Δ^4-16α-methyl-pregnene-17α:21 - diol - 3:11:20 - trione - 21 -acetate.

A mixture of 0.5 grams of Δ^4-16α-methyl-pregnene - 17α:21 - diol - 3:11:20 - trione-21-acetate, 20 cc of benzene, 4 cc of ethyleneglycol and 60 mg of para-toluenesulphonic acid is boiled for 8 hours while continuously removing the water formed. The reaction solution is cooled and diluted with benzene, washed with sodium bicarbonate solution and water, dried and evaporated *in vacuo*. Crystallization of the residue from acetone + hexane yields Δ^5 - 3 - ethylenedioxy - 16α - methyl-pregnene - 17α:21 - diol - 11:20 - dione-21-acetate.

A cooled solution of 1 gram of the above ketal in 10 cc of chloroform is mixed with an ethereal solution containing 1.2 equivalents of monoperphthalic acid, and the mixture is kept for 18 hours at 0—5°C. Water is then added and the organic layer separated, washed with ice-cold sodium bicarbonate solution and water, dried over sodium sulphate and cautiously evaporated *in vacuo*. The resulting 3 - ethylenedioxy - 5α:6α - oxido-16α - methyl - pregnane - 17α:21 - diol-11:20 - dione - 21 - acetate can be purified by crystallization from acetone + hexane.

In an analogous manner 9α-chloro- and 9α-fluoro - 16α - methyl - allopregnane - 17α:21-diol - 3:11:20 - trione - 21 - acetate, respectively, yield the 3-ethylenedioxy-5α:6α-oxido-9α - chloro- and the 3 - ethylenedioxy - 5α:6α-oxido - 9α - fluoro - 16α - methyl - pregnane-17α:21 - diol - 11:20 - dione - 21 - acetate, respectively.

3:20 - bisethylenedioxy - 5α:6α - oxido - 16α-methyl - pregnane - 11β:17α:21 - triol-21-acetate.

A mixture of 5 grams of Δ^4-16α-methyl-pregnene - 17α:21 - diol - 3:11:20 - trione, 300 cc of benzene, 35 cc of ethylene glycol and 250 mg of para-toluenesulphonic acid is refluxed for 12 hours while continuously removing the water formed. After cooling, 50 cc of 2N-sodium carbonate solution and 200 cc of water are added, the benzolic layer is separated and washed with water. Evaporation of the benzolic solution yields Δ^5-3:20-bis-ethylenedioxy - 16α - methyl - pregnene-17α:21-diol-11-one which can be used for the reaction of the next stage without purification.

The above crude diketal is dissolved in 150 cc of tetrahydrofuran and stirred dropwise into a solution of 1.5 grams of lithium aluminium hydride in 100 cc of tetrahydrofuran. The mixture is then refluxed for 30 minutes. After cooling, the surplus lithium aluminium hydride is destroyed by the careful, dropwise addition of ethyl acetate. 15 cc of saturated sodium sulphate solution and solid sodium sulphate are then added, the mixture is filtered and the organic solvent is evaporated *in vacuo*. The residue is Δ^5 - 3:20 - bisethylenedioxy-16α-methyl-pregnene-11β:17α/21-triol.

The resulting diol is dissolved in 30 cc of pyridine, mixed with 5 cc of acetic anhydride and kept overnight at room temperature, then poured into water, extracted with ethyl acetate, the extract is washed with water, dilute hydrochloric acid and sodium bicarbonate solution and water, dried over sodium sulphate and

diketal

evaporated *in vacuo*. The resulting Δ^5-3:20-bisethylenedioxy - 16α - methyl - pregnene-11β:17α:21-triol-21-acetate is dissolved in 800 cc of ether and 300 cc of chloroform and mixed at 0°C wtih a chloroform solution containing 1.1 equivalents of perbenzoic acid. The reaction solution is kept overnight at room temperature and then washed three times with 500 cc of a sodium carbonate solution of 5% strength and then with water, dried and evaporated *in vacuo*. Chromatography of the residue over alumina and crystallization from acetone + hexane yields 3:20-bisethylenedioxy-5α:6α - oxido - 16α - methyl - pregnene-11β:17α:21-triol-21-acetate.

3:20-bisethylenedioxy-5α:6α-oxido-9α-fluoro-16α - methyl - pregnane - 11β:17α:21-triol-21-acetate.

A solution of 3 grams of the 9α-fluoro-16α-methyl - allopregnane - 11β:17α:21 - triol-3:20-dione-21-acetate, described in Specification No. 22984/59 (Serial No. 924,252), in 400 cc of glacial acetic acid is treated with a few drops of hydrobromic acid in glacial acetic acid and then with 3 grams of bromine in 5 cc of glacial acetic acid. When the reaction solution has become colourless, it is poured into ice water and extracted with methylene chloride, washed with sodium bicarbonate solution and water, the solvent is dried over sodium sulphate and cautiously evaporated *in vacuo*, to yield 2:4 - dibromo - 9α - fluoro-16α - methyl - pregnane - 11β:17α:21 - triol-3:20-dione-21-acetate.

0.6 cc of bromine is added with cooling to 15 cc of acetone. After discoloration, 1.4 grams of sodium bicarbonate are added and the mixture is filtered. The filtrate is combined with a solution of grams of iodine in 60 cc of acetone, boiled for 10 minutes, 3 grams of the above dibromide are added, and the mixture is boiled for 3 hours on a water bath. 2.8 grams of oxalic acid are added and the mixture is boiled for another hour, then cooled, diluted with 100 cc of ethyl acetate, the precipitate is filtered off and the filtrate washed with water, sodium bicarbonate solution and water, dried and evaporated *in vacuo*. The resulting residue is Δ^4 - 9α - fluoro - 16α - methyl-pregnene - 11β:17α:21 - triol - 3:20 - dione-21-acetate. Its conversion into Δ^5 - 3:20 - bisethylenedioxy - 9α - fluoro - 16α - methyl-pregnene - 11β:17α:21 - triol - 21 - acetate and 3:20 - bisethylenedioxy - 5α:6α - oxido-9α - fluoro - 16α - methyl - pregnane-11β:17α:21 - ~~trial~~ triol - 21 - acetate is conducted as described above.

In a similar manner 9α - chloro - 16α-methyl - allopregnane - 11β:17α:21 - triol-3:20 - dione - 21 - acetate yields 3:20-bisethylenedioxy - 5α:6α - oxido - 9α - chloro-16α - methyl - pregnane - 11β:17α:21 - triol-21-acetate.

2:4 - dibromo - 11α:17α - dihydroxy - 16α-methyl - 21 - acetoxy - allopregnane-3:20-dione.

A solution of 5.05 grams of 11α:17α-dihydroxy - 16α - methyl - 21 - acetoxy-allopregnane - 3:20 - dione described in Specification No. 22984/59 (Serial No. 924,252), in 60 cc of glacial acetic acid is mixed with 5.4 cc of a 4.47N-solution of hydrogen bromide in glacial acetic acid, and 15.5 cc of a 3.32N-solution of bromine in glacial acetic acid is then stirred in during the course of 10 minutes at an internal temperature of 15 to 16°C. The mixture is stirred for 10 minutes at an internal temperature of 20 to 22°C and then poured into 360 cc of water, filtered and thoroughly washed with water. The resulting filter cake is dried in a water-jet vacuum over potassium hydroxide and sulphuric acid, to yield 6 grams of crude 2:4 - dibromo - 11α:17α - dihydroxy-16α - methyl - 21 - acetoxy - allopregnane-3:20-dione in the form of a colourless powder.

The aqueous mother liquor is extracted 3 times with 160 cc of methylene chloride, and the organic solutions are then washed once with 700 cc of saturated sodium bicarbonate solution and once with 200 cc of water, dried and evaporated in a water-jet vacuum at a bath temperature of 30 to 40°C. In this manner a further amount of the afore-mentioned 2:4-dibromo compound is obtained.

As described for the corresponding 11-keto compound at the beginning of this Example, the above dibromide is converted into Δ^4-16α-methyl - 11α:17α - dihydroxy - 21 - acetoxy-pregnene-3:20-dione which, on ketalization with ethyleneglycol and para-toluenesulphonic acid, yields Δ^5 - 3 - ethylenedioxy - 16α-methyl - 11α:17α - dihydroxy - 21 - acetoxy-pregnene-20-one which is oxidized with monoperphthalic acid to yield the corresponding 5:6α-epoxide. By means of pyridine + chromic acid this compound can be oxidized to yield the 3 - ethylenedioxy - 5α:6α - oxido - 16α-methyl - pregnane - 17α:21 - diol - 11:20-dione-21-acetate described hereinbefore.

Bromination in an analogous manner of $\Delta^{9(11)}$ - 16α - methyl - allopregnene - 17α:21-diol - 3:20 - dione - 21 - acetate yields $\Delta^{9(11)}$-16α - methyl - 2:4 - dibromo - allopregnene-17α:21 - diol - 3:20 - dione - 21 - acetate which is converted into $\Delta^{4:9(11)}$-16α-methyl-pregnadiene - 17α:21 - diol - 3:20 - dione-21-acetate in the manner described above. Additive combination of the latter compound with hypobromous acid in the presence of perchloric acid, alkaline treatment and cleavage of the resulting 9:11β-epoxide with hydrofluoric acid, yields the Δ^4-9α-fluoro-16α-methyl - pregnene - 11β:17α:21 - triol-3:20-dione-21-acetate described above.

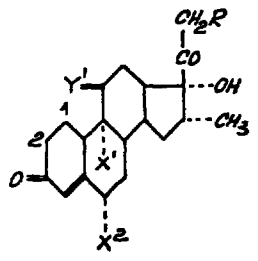
EXAMPLE 23

0.56 cc of trimethyl acetic acid chloride are dissolved under an atmosphere of nitrogen and with stirring at 0° in 10 cc of pure dry pyridine. To the clear and colourless solution so obtained there is added during a period of 5 minutes a solution of 0.5 g of 6α-fluoro-16α-methyl-prednisolone in 5 cc of pure, dry pyridine while stirring continuously, the addition being effected at 0° and in atmosphere of nitrogen. The reaction solution is then allowed to stand for a period of 8 hours at 0° under nitrogen; after this period there cannot be detected any free 6α - fluoro - 16α - methyl - prednisolone with the method of the thin layer chromatogram according to E. Stahl (solvent system benzene-ethyl acetate 3:7; indicator 50% sulphuric acid). The reaction solution is then poured into ice water and acidified with diluted hydrochloric acid. The reaction products are extracted with ethyl acetate and the organic solution is washed consecutively with diluted hydrochloric acid, with water, diluted sodium carbonate solution and water; then it is dried over anhydrous sodium sulphate, filtered and evaporated. The white, micro-crystalline residue (0.62 g) is crystallized from a mixture of ether and methylene chloride; 0.48 g of pure 6α - fluoro - 16α - methyl - prednisolone-21-trimethyl-acetate is so obtained, which gives no blue coloration with tetrazolium-blue and 2N-sodium hydroxide in the cold. F. 198—200° (under decomposition starting at about 190°) λ_{max} (absolute alcohol) 243—244 mμ ($\varepsilon = 15^{1}800$).

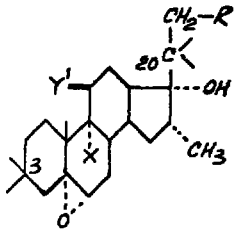
In an analogous manner 6α:9α-difluoro-16α-methyl - prednisolone - 21 - trimethyl-acetate is obtained by reacting 6α:9α-difluoro-16α-methyl - prednisolone with trimethyl acetic acid chloride in pyridine at 0° (yield 92—93%). The product shows dimorphism; one of the two modifications melts at 229—230° (decomposition starting from 220°), the other melts at 254—255° (decomposition starting from 251°) $[\alpha]_D^{29} = +72{,}7° \pm 1°$ ($c = 1{,}034\%$ in dioxane) λ_{max} (absolute alcohol) 238—239 mμ, $\varepsilon = 16^{1}600$—$16^{1}900$.

WHAT WE CLAIM IS:—

1. A process for the manufacture of a halogen-pregnene of the formula



in which R represents a free or esterified hydroxyl group, Y^1 represents an oxo group, or a hydrogen atom together with a free or esterified hydroxyl group, X^1 represents a hydrogen atom or a chlorine or fluorine atom and X^2 represents a chlorine or fluorine atom, or a 1-dehydro-derivative of such a compound wherein a compound of the formula



in which R represents a free or esterified hydroxyl group, X represents a hydrogen atom or a chlorine or fluorine atom, Y^1 represents an oxo group or a hydrogen atom together with a free or esterified hydroxyl group, and which compound contains in the 3-position a ketalized oxo group and in the 20-position a free or ketalized oxo group, is treated with hydrogen chloride or hydrogen fluoride or a salt thereof with a pyridine compound, a ketalized oxo group or groups in the 3- or 3:20-positions is or are converted into a free oxo group or groups, the 5α-hydroxy-6β-halogen compound so obtained is dehydrated, the resulting Δ^4 - 3 - oxo - 6β - halogen-pregnene is isomerized in the 6-position, and, if desired, the resulting compound is dehydrogenated in the 1:2-position by a known method for the introduction of a 1:2-double bond into a steroid, and at any stage in the process esterified hydroxyl groups are ~~hydrolized~~ hydrolyzed or free hydroxyl groups esterified and/or an 11-hydroxy compound is oxidised to an 11-oxo-compound.

2. A process as claimed in claim 1, wherein the treatment with hydrogen chloride or hydrogen fluoride is carried out in glacial acetic acid or in a mixture of glacial acetic acid and chloroform.

3. A process as claimed in claim 1, wherein pyridine hydrochloride or collidine hydrochloride is used as the salt of hydrogen chloride.

4. A process as claimed in claim 1, 2 or 3, wherein the 5α - hydroxy - 6β - halogen-pregnane is converted into a Δ^4-3-oxo-6α-halogen-pregnene by treatment with hydrogen chloride in glacial acetic acid or in a mixture of glacial acetic acid and chloroform.

5. A process as claimed in any one of claims 1—4, wherein selenium dioxide is used for the 1:2-dehydrogenation.

6. A process as claimed in claim 5, wherein the 1:2-dehydrogenation is carried out in a tertiary alcohol.

7. A process as claimed in claim 6, wherein the tertiary alcohol is tertiary butanol or tertiary amyl alcohol.

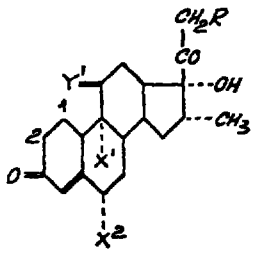
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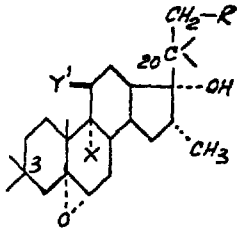
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WHAT WE CLAIM IS:—

1. A process for the manufacture of a halogen-pregnene of the formula



in which R represents a free or esterified hydroxyl group, Y^1 represents an oxo group, or a hydrogen atom together with a free or esterified hydroxyl group, X^1 represents a hydrogen atom or a chlorine or fluorine atom and X^2 represents a chlorine or fluorine atom, or a 1-dehydro-derivative of such a compound, wherein a compound of the formula



in which R represents a free or esterified hydroxyl group, X represents a hydrogen atom or a chlorine or fluorine atom, Y^1 represents an oxo group or a hydrogen atom together with a free or esterified hydroxyl group, and which compound contains in the 3-position a ketalized oxo group and in the 20-position a free or ketalized oxo group, is treated with hydrogen chloride or hydrogen fluoride or a salt thereof with a pyridine compound, a ketalized oxo group or groups in the 3- or 3:20-positions is or are converted into a free oxo group or groups, the 5α-hydroxy-6β-halogen compound so obtained is dehydrated, the resulting Δ^4 - 3 - oxo - 6β - halogen-pregnene is isomerized in the 6-position, and, if desired, the resulting compound is dehydrogenated in the 1:2-position by a known method for the introduction of a 1:2-double bond into a steroid, and at any stage in the process esterified hydroxyl groups are ~~hydrolized~~ hydrolyzed or free hydroxyl groups esterified and/or an 11-hydroxy compound is oxidised to an 11-oxo-compound.

2. A process as claimed in claim 1, wherein the treatment with hydrogen chloride or hydrogen fluoride is carried out in glacial acetic acid or in a mixture of glacial acetic acid and chloroform.

3. A process as claimed in claim 1, wherein pyridine hydrochloride or collidine hydrochloride is used as the salt of hydrogen chloride.

4. A process as claimed in claim 1, 2 or 3, wherein the 5α - hydroxy - 6β - halogen-pregnane is converted into a Δ^4-3-oxo-6α-halogen-pregnene by treatment with hydrogen chloride in glacial acetic acid or in a mixture of glacial acetic acid and chloroform.

5. A process as claimed in any one of claims 1—4, wherein selenium dioxide is used for the 1:2-dehydrogenation.

6. A process as claimed in claim 5, wherein the 1:2-dehydrogenation is carried out in a tertiary alcohol.

7. A process as claimed in claim 6, wherein the tertiary alcohol is tertiary butanol or tertiary amyl alcohol.

8. A process as claimed in claim 5, wherein the dehydrogenation is carried out in the presence of a tertiary base.

9. A process as claimed in claim 8, wherein the tertiary base is pyridine or collidine.

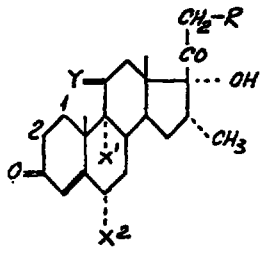
10. A process as claimed in any one of claims 1—4, wherein the 1:2-dehydrogenation is carried out with the aid of a 1:2-dehydrogenating micro-organism.

11. A process as claimed in claim 10, wherein one of the following organisms is used for the 1:2-dehydrogenation: Fusarium solani, Fusarium caucasicum, Calonectria decora, Alternaria passiflorae, Phiobolus heterostrophus, Phiobolus miyabeanus, Didymella lycopersici or Corynebacterium simplex.

12. A process as claimed in any one of claims 1—11, wherein a 21-hydroxy-compound so obtained is converted into its 21-trimethyl acetate, 21 - cyclopentyl - propionate, 21β-phenyl - propionate, 21 - hemisuccinate, 21-cyclopropyl-carboxylate or 21-hemisulphate.

13. A process for the manufacture of a halogen-pregnene conducted substantially as described in any one of the Examples herein.

14. A halogen-pregnene of the formula



in which R represents a free or esterified hydroxyl group, Y represents an oxo group, or a hydrogen atom together with a free or esterified hydroxyl group, X^1 represents a hydrogen atom or a chlorine or fluorine atom, and X^2 represents a chlorine or fluorine atom, or a 1-dehydro-derivative of such a compound.

15. Δ^4 - 6α - Chloro - 16α - methyl - pregnene-17α:21-diol-3:11:20-trione.

16. Δ^4 - 6α - Fluoro - 16α - methyl - pregnene-17α:21-diol-3:11:20-trione.

17. Δ^4 - 6α - Chloro - 16α - methyl - pregnene-11β:17α:21-triol-3:20-dione.

18. Δ^4 - 6α - Chloro - 9α - fluoro - 16α-methyl - pregnene - 11β:17α:21 - triol-3:20-dione.

19. Δ^4 - 6α - Fluoro - 16α - methyl - pregnene-11β:17α:21-triol-3:20-dione.

20. Δ^4 - 6α:9α - Difluoro - 16α - methyl-pregnene - 11β:17α:21 - triol - 3:20 - dione.

21. $\Delta^{1:4}$ - 16α - Methyl - 6α - chloro - pregnadiene-17α:21-diol-3:11:20-trione.

22. $\Delta^{1:4}$ - 16α - Methyl - 6α - fluoro-pregnadiene-17α:21-diol-3:11:20-trione.

23. $\Delta^{1:4}$ - 16α - Methyl - 6α - chloro - pregnadiene-11β:17α:21-triol-3:20-dione.

24. $\Delta^{1:4}$ - 16α - Methyl - 6α - fluoro-pregnadiene-11β:17α:21-triol-3:20-dione.

25. $\Delta^{1:4}$ - 16α - Methyl - 6α:9α - difluoro-pregnadiene-17α:21-diol-3:11:20-trione.

26. $\Delta^{1:4}$ - 16α - Methyl - 6α - chloro - 9α-fluoro - pregnadiene - 17α:21 - diol-3:11:20-trione.

27. $\Delta^{1:4}$ - 16α - Methyl - 6α:9α - difluoro-pregnadiene-11β:17α:21-triol-3:20-dione.

28. $\Delta^{1:4}$ - 16α - Methyl - 6α - chloro - 9α-fluoro - pregnadiene - 11β:17α:21 - triol-3:20-dione.

29. An ester of the compound claimed in any one of claims 15—28.

30. The 21-trimethyl-acetate, 21-cyclopentyl-propionate, 21β-phenyl-propionate, or 21-hemisuccinate of the compound claimed in any one of claims 15—28.

31. The 21-trimethyl-acetate of $\Delta^{1:4}$ - 6α-fluoro-16α-methyl-pregnadiene - 11β:17α:21-triol-3:20-dione.

32. The 21-trimethyl-acetate of $\Delta^{1:4}$-6α:9α-difluoro-16α-methyl-pregnadiene-11β:17α:21-triol-3:20-dione.

33. A halogenopregnane as claimed in claim 14 and described in any one of Examples 1 to 5 and 9 to 18 herein.

34. A halogenopregnane as claimed in claim 14 and described in any one of Examples 6 to 8 and 19 to 22 herein.

35. A pharmaceutical preparation which comprises a compound as claimed in claim 14 in admixture or conjunction with a pharmaceutical carrier suitable for enteral or parenteral administration.

36. A pharmaceutical preparation which comprises any one of the compounds claimed in the claims 15—33 in admixture or conjunction with a pharmaceutical carrier suitable for enteral or parenteral administration.

37. A pharmaceutical preparation which comprises a halogenopregnane as claimed in claim 34 in admixture or conjunction with a pharmaceutical carrier suitable for enteral or parenteral administration.

38. A pharmaceutical preparation as claimed in claim 35, 36 or 37, which contains 0.03—60 per cent by weight of the said compound in admixture with the said carrier.

39. A pharmaceutical preparation as claimed in any one of claims 35—38, which is in the form of a tablet.

40. A pharmaceutical preparation as claimed in any one of claims 35—38, which is in the form of an oil ampoule.

* C L M S *

A pharmaceutical preparation as claimed one of claims 35—38, which is in the of an aqueous solution within an ampoule.

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ERRATA

SPECIFICATION No. 926,472

Page 2, line 99, *for* "prefered" *read* "preferred"
Page 3, line 124, *insert* "oil" *after* "an" (first occurrence)
Page 4, line 10, *for* "11,20" *read* "11:20"
Page 6, line 22, *for* "later" *read* "latter"
Page 6, line 45, *for* "presure" *read* "pressure"
Page 6, line 47, *for* "digesed" *read* "digested"
Page 6, line 83, *for* "coritsol" *read* "cortisol"
Page 6, lines 92, 95 and 99, *for* "coritsone" *read* "cortisone"
Page 7, line 71, *for* "absorbed" *read* "adsorbed"
Page 9, line 26, *for* "24" *read* "20,"
Page 11, line 122, *for* "diol" *read* "diketal"
Page 12, line 56, *for* "trial" *read* "triol"
Page 13, lines 81 and 82, *for* "hydro-lized" *read* "hydro-lyzed"

THE PATENT OFFICE
1st February 1965

