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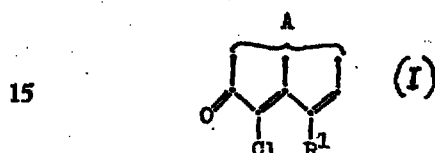


(54) NOVEL HALOGENATED STEROIDS AND A PROCESS
 FOR THE MANUFACTURE THEREOF

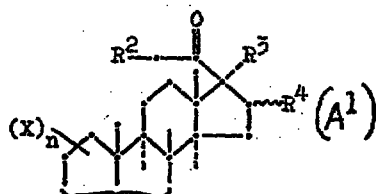
(71) We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESellschaft, a Swiss Company of 124-184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with novel halogenated steroids and a process for the manufacture thereof.

The novel halogenated steroids provided by the present invention may be generically formulated thus:



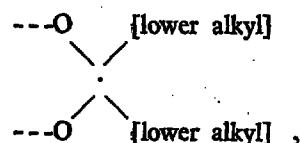
wherein R¹ represents a fluorine, chlorine or bromine atom or a lower-alkyl group and A represents (i) a grouping of the formula



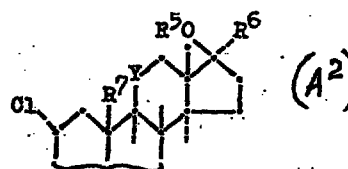
20 in which n stands for 0 or 1, X represents an unsaturation between the carbon atoms in the 1- and 2-positions or a 2-chloro substituent or a 1 α ,2 α - methylene group, R² represents a hydrogen or fluorine atom, R³ represents a hydrogen atom or a hydroxy, lower-alkoxy, lower alkanoyloxy, difluoroacetyl, dichloroacetyl or lower-alkyl group, R⁴ represents a lower-alkylidene group or an

[Price 5s. 0d. (25p)]

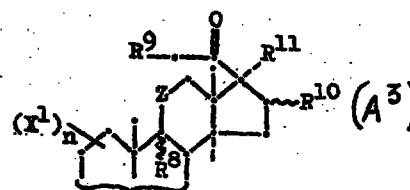
α -chloromethyl group, (the latter, only when n stands for 0 or 1, X represents an unsaturation between the carbon atoms in the 1- and 2-positions or a 2-chloro substituent, R² represents a hydrogen atom and R³ represents a hydroxy or lower-alkanoyloxy group), or R³ and R⁴ together represent a grouping of the formula



or (ii) a grouping of the formula

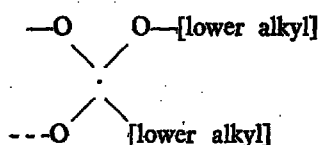


40 in which R⁵ represents a hydrogen atom or a lower-alkanoyl group, R⁶ represents a hydrogen atom or a lower-alkyl, mono-unsaturated lower-aliphatic hydrocarbyl or monounsaturated halo-(lower aliphatic hydrocarbyl) group, R⁷ represents a hydrogen atom or the methyl group and Y represents a methylene, β - hydroxy - methylene, α - hydroxy - methylene or carbonyl group, or (iii) a grouping of the formula

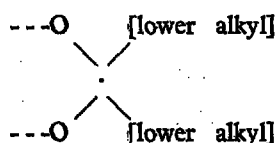


50 in which n has the significance given earlier,

- 5 X^1 represents an unsaturation between the carbon atoms in the 1- and 2-positions or a 2-chloro substituent, R^8 represents an α -hydrogen, α -fluorine, α -chlorine or α -bromine atom, R^9 represents a hydrogen atom, the hydroxy group, the dihydrogen phosphate ester thereof or an alkali-metal salt thereof or a lower-alkanoyloxy group, R^{10} represents a lower-alkylidene, α -chloromethyl or α -fluoromethyl group or an α -chloro or α -fluoro substituent, R^{11} represents a hydroxy or lower-alkanoyloxy group or R^9 and R^{11} together represent a grouping of the formula



- 15 or, when R^9 represents a hydrogen atom, R^{10} and R^{11} together represent a grouping of the formula



- 20 and Z represents a carbonyl, β -hydroxy-methylene, α -hydroxy-methylene, or α -sulphonyloxy-methylene group or, when R^8 represents an α -hydrogen atom and R^9 is other than a hydrogen atom, a methylene group or, when R^8 represents an α -chlorine atom, a β -chloro-methylene group, or Z and R^8 together represent an unsaturation between the 9- and 11-carbon atoms or a 9 β ,11 β -oxido group.

- 30 The term 'lower alkyl' is used in this description and in the accompanying claims to mean both straight-chain and branched-chain saturated hydrocarbon groups which contain up to 8 carbon atoms (e.g. methyl, ethyl, *tert*butyl and octyl). The term 'mono-unsaturated lower-aliphatic hydrocarbyl'
- 35 means both alkenyl and alkynyl groups containing up to 7 carbon atoms such as allyl, 2-methyl-allyl and ethynyl. The term 'monounsaturated halo-(lower aliphatic hydrocarbyl)' means alkenyl and alkynyl groups containing up to 7 carbon atoms which are bromo- or chloro-substituted (e.g. 2-chloro-ethynyl and 3-chloro-2-methyl-allyl). The term 'lower alkoxy' means groups which can be designated at $\text{---O---[lower alkyl]}$ where 'lower alkyl' has the meaning given earlier; that is to say, groups such as methoxy and ethoxy. The term 'lower alkylidene' indicates a straight-chain or
- 40 branched-chain hydrocarbon group containing up to 7 carbon atoms whose terminal

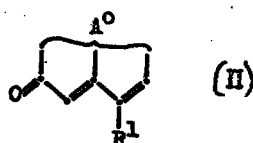
carbon atom has two free valency bonds (e.g. methylene and isopropylidene with methylene being especially preferred). The term 'lower alkanoyl' means the acyl residue of an alkane carboxylic acid containing up to 8 carbon atoms such as acetyl, butyryl and caprylyl. The term 'lower alkanoyloxy' means an alkanoyloxy group containing up to 8 carbon atoms. The term 'alkali metal' has its usual meaning and includes such metals at lithium, sodium and potassium. The term 'sulphonyloxy' means alkylsulphonyloxy groups containing up to 7 carbon atoms such as mesyloxy and arylsulphonyloxy groups such as tosyloxy.

Halogenated steroids of formula I which contain grouping A^1 or A^2 are useful as progestational agents. When R^3 represents a hydrogen atom or the hydroxy group, they can be administered parenterally and, when R^3 represents a lower-alkoxy, lower-alkanoyloxy, difluoro-acetyl, dichloro-acetyl or lower-alkyl group, they can be administered orally or parenterally. The preferred halogenated steroids within this group are those containing grouping A^1 in which R^1 represents a chlorine or fluorine atom, R^2 has the significance given earlier, R^3 represents a lower-alkoxy, lower-alkanoyloxy or lower-alkyl group, R^4 represents the methylene group and n stands for O.

Halogenated steroids of formula I which contain grouping A^3 are useful as corticoid agents when X^1 represents an unsaturation between the carbon atoms in the 1- and 2-positions and when Z represents the methylene, carbonyl, β -hydroxy-methylene or β -chloro-methylene group. Those halogenated steroids in which Z represents the methylene group are useful as mineralocorticoids and those in which Z represents the carbonyl, β -hydroxy-methylene or β -chloro-methylene group are useful as glucocorticoids (i.e. as anti-inflammatory and thymolytic agents). The halogenated steroids which are useful as mineralocorticoids can be administered orally, parenterally or, particularly when Z contains a β -hydroxy or β -chloro moiety, topically. Of those halogenated steroids which are useful as anti-inflammatory and thymolytic agents, the especially preferred members are those in which R^1 represents a chlorine or fluorine atom, R^2 represents an α -fluorine, α -chlorine or α -bromine atom, R^3 represents the dihydrogen phosphate ester or a lower-alkanoyloxy group, R^{10} represents the methylene group, R^{11} represents a hydroxy group, n stands for O and Z represents the β -hydroxymethylene group.

According to the process provided by the invention, the novel halogenated steroids aforesaid are manufactured by:

(a) treating a steroid of the formula



, wherein R^1 has the significance given earlier and A^0 represents grouping A^1 , A^2 or A^3 hereinbefore in which X (if present) represents a $1\alpha,2\alpha$ - methylene group, X^1 is absent and the 2-position of grouping A^3 is unsubstituted, with chlorine and a proton acceptor so as to insert a chlorine atom at the 4-position or

(b) treating a 2 - unsubstituted - 1(2) - saturated steroid of formula I with a chlorinating agent so as to insert a chlorine atom at the 2-position or

(c) dehydrogenating in the 1(2)-position a steroid of formula I containing grouping A^1 or A^3 in which n stands for O or

(d) oxidising the 11 - hydroxy group of a steroid of formula I containing grouping A^2 or A^3 in which Y or Z as the case may be represents the hydroxy - methylene group so as to convert said group into a carbonyl group or

(e) esterifying the 11α - hydroxy group of a steroid of formula I containing grouping A^3 in which Z represents an α - hydroxy - methylene group with a sulphonic acid or

(f) splitting off an 11α -sulphonyloxy group or an 11β -hydroxy group an a 9-hydrogen atom from a steroid of formula I containing grouping A^3 in which Z represents an α -sulphonyloxy-methylene or β - hydroxy - methylene group and R^8 represents an α - hydrogen atom so as to introduce a 9(11) - double bond or

(g) treating a steroid of formula I containing grouping A^3 in which Z and R^8 together represent an unsaturation between the 9- and 11-carbon atoms with hydrochlorous acid or hydrobromous acid so as to insert a chlorine or bromine atom respectively at the 9-position and a hydroxyl group at the 11-position or

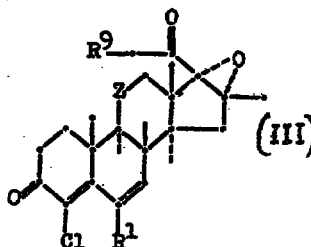
(h) treating a steroid of formula I containing grouping A^3 in which Z represents a hydroxy-methylene group and R^8 represents an α - chlorine or α - bromine atom with a dehydrohalogenating agent so as to form a $9\beta,11\beta$ - oxido group or

(i) treating a steroid of formula I containing grouping A^3 in which Z and R^8 together represent a $9\beta,11\beta$ - oxido group with hydrogen fluoride, hydrogen chloride, hydrogen bromide or a chlorinating agent so as to introduce the relevant halogen atom at the 9-position and a hydroxyl group or chlorine atom at the 11-position or

(j) esterifying a steroid of formula I which contains at least one free hydroxy group in the 17- or 21-position or

(k) saponifying a 17- and/or 21-esterified steroid of formula I or

l) treating a steroid of the formula



wherein R^1 , R^9 and Z have the significance given earlier, with a strong acid so as to yield a 16 - methylene - 17 α - hydroxy product.

The chlorination procedure according to process (a) is suitably carried out by intermixing chlorine and a reaction medium which contains the steroid starting material of formula II, preferably in solution. The treatment with chlorine can be carried out in the presence of a proton acceptor such as, for example, an N,N - di(lower alkyl) - lower alkanamide such as N,N - dimethyl - formamide or N,N - dimethyl - acetamide or or a lower - alkylene oxide such as ethylene oxide or propylene oxide in a solvent such as a lower - alkanic acid (e.g. propionic acid or acetic acid). Alternatively, the proton acceptor can be added subsequently to the mixture of the chlorine with the steroid starting material. In this case, a 6 - substituted dichloro intermediate is formed. Conveniently, this intermediate is not purified but is dehydrochlorinated by treatment with a proton acceptor such as a nitrogen - containing heterocyclic base (e.g. picoline or pyridine).

When the proton acceptor is initially present during the chlorination, it can also serve as the solvent for the steroid starting material of formula II. Alternatively, and indeed preferably, the reaction medium can contain other solvents. These solvents can conveniently be inert organic solvents; for example, ethers such as lower - alkyl ethers (e.g. diethyl ether) or dioxan, chlorinated hydrocarbons such as chloroform or carbon tetrachloride. The chlorine can be introduced into the reaction mixture by conventional techniques; for example, a solution containing the chlorine can be introduced into the reaction mixture. A chlorine - containing lower - alkanic acid solution (e.g. chlorine in propionic acid) is suitable for this purpose. The treatment with chlorine is suitably carried out at a low temperature, preferably between about -40°C and room temperature and more preferably between about -30°C and 0°C . Another embodiment comprises treating the steroid starting material in chloroform with chlorine in carbon tetra-

chloride, preferably between about 0°C and room temperature, followed by removal of the solvent and treatment with a heterocyclic nitrogen - containing base such as pyridine or picoline.

Hydroxy groups present in the steroid starting material can be esterified after the chlorination has taken place. Alternatively the chlorination can be carried out using starting materials containing ester groups. When chlorinating steroid starting materials in which Y or Z represents a β - hydroxy - methylene group it is preferable to protect the hydroxy group prior to chlorination; for example, by acylation to form the corresponding 11β - formyloxy or trifluoroacetoxy steroid. After the chlorination, the 11β - hydroxy group can be regenerated by conventional methods. When the 9-position carries a halogen atom such as fluorine (i.e. R⁸ is other than hydrogen) it is preferable to carry out the chlorination without protecting the 11β - hydroxy group if present. In addition to the foregoing, other known techniques can be used to protect labile groups prior to the chlorination procedure.

It will be appreciated that the aforementioned chlorination procedure, when applied to 2 - unsubstituted - 1(2) - saturated steroid starting materials, may yield as a by-product 2,4 - dichloro - steroids of formula I. 2,4 - dichloro - steroids of formula I can also be manufactured according to process (b) by chlorinating a 2 - unsubstituted - 1(2) - saturated - 4 - chloro - steroid of formula I using a chlorinating agent such as chlorine or N - chloro - succinimide.

The dehydrogenation procedure according to process (c) can be brought about by treatment with selenious acid or by a reaction sequence consisting of chlorination and dehydrochlorination, the latter step being carried out, for example, by treatment with lithium chloride in N,N - dimethyl - formamide.

The oxidation of an 11 - hydroxymethylene group according to process (d) can be carried out in accordance with methods known per se; for example, with chromic acid.

Examples of sulphonic acids which are useful for the esterification of an 11 - hydroxy group according to process (e) are methanesulphonic acid and *paratoluene* - sulphonic acid. The esterification can be carried out in accordance with methods known per se, suitably by treating the 11 - hydroxy - steroid with a reactive sulphonic acid derivative such as the chloride in the presence of a proton acceptor such as pyridine.

The introduction of a 9(11) - double bond according to process (f) can be carried out by treating a 11α - sulphonyloxy steroid in the presence of a catalyst, preferably a weak base such as a salt of a lower-alkanoic acid,

in an anhydrous organic solvent such as acetic acid or in N,N - dimethyl - formamide which can itself serve as the catalyst. The dehydration of an 11β - hydroxy - steroid can be carried out using, for example, thionyl chloride in pyridine.

The addition of hydrochlorous acid or hydrobromous acid to a 9(11) double bond of a steroid starting material according to process (g) is suitably carried out using the hydrohalous acid generated in situ; for example, by reacting the $\Delta^{9(11)}$ - steroid with an N - halo - amide such as N - chloro- or N - bromo - acetamide in the presence of an aqueous acid (e.g. an aqueous mineral acid as perchloric acid).

The conversion of a 9α - (bromo or chloro) - 11 - hydroxy - steroid into the corresponding $9\beta,11\beta$ - oxido - steroid in accordance with process (h) is carried out by treatment with a dehydrohalogenating agent such as an alkali - metal hydroxide solution.

A suitable chlorinating agent for converting a $9\beta,11\beta$ - oxido - steroid into a corresponding $9\alpha,11\beta$ - dichloro - steroid according to process (i) is a solution of chlorine in carbon tetrachloride.

The esterification of a free hydroxy group according to process (j) can be carried out in a known manner; for example, using a reactive acid derivative such as a halide or an anhydride.

The saponification of a 17- or 21-esterified hydroxy group in accordance with process (k) can be carried out using a weak basic agent such as an alkali - metal carbonate or dicarbonate.

The cleavage of the $16\alpha,17\alpha$ - oxido group and subsequent dehydration according to process (l) can be carried out by treating the steroid starting material of formula III in an anhydrous solvent in the presence of a strong acid such as trifluoroacetic acid.

The halogenated steroids provided by this invention are characterised by a high degree of endocrinological utility with a selectivity of action characterised by minimal side-effects. Thus, the endocrinologically useful halogenated steroids of this invention can be administered internally (e.g. orally or parentally) with dosages adjusted to individual requirements. The halogenated steroids can be administered pharmaceutical preparations; for example, in solid or liquid forms such as tablets, pills, capsules, solutions, suspensions or emulsions. The pharmaceutical preparations contain conventional pharmaceutical carriers and excipients such as water, talc, corn starch, polyalkyleneglycols, emulsifying agents, buffering agents, agents for the adjustment of osmotic pressure and petroleum jelly. Although it is preferred to administer the endocrinologically useful halogenated steroids of this invention internally, those having progestational or anti-inflammatory

utility can also be administered topically. For this purpose (i.e. topical administration) they can be administered in conventional topical administration forms such as ointments or creams in combination with conventional topical carriers such as petroleum or stearic acid. The pharmaceutical preparations containing the halogenated steroids of this invention can be subjected to conventional pharmaceutical processes such as sterilisation. Also, they can contain other active substances. Moreover, the endocrinologically active halogenated steroids can be administered as feed additives and for this purpose they can be admixed with conventional animal feeds or conventional animal feed premixes.

The majority of the steroid starting materials for the foregoing process are known or are members of known classes of steroids. In any event, the steroid starting materials can be prepared by known methods such as, for example, those described in certain of the following Examples.

The following Examples illustrate the process provided by the invention:

EXAMPLE 1

(i) 11.3 ml (5% excess) of a 0.87-molar solution of chlorine in carbon tetrachloride were added dropwise at 0°C to a solution of 3.9 g of 6 - chloro - 17 α - acetoxy - 16 - methylene - pregna - 4,6 - diene - 3,20 - dione in 25 ml of alcohol-free chloroform. The resulting solution was stirred at 0°C for 1 hour, then the solvents were removed under reduced pressure. The resulting foam was treated with 10 ml of dry pyridine and stirred at room temperature for 2 hours. 200 ml of ether were subsequently added and the mixture was extracted with two 150 ml portions of 1-N hydrochloric acid. The ether solution was then dried and the solvent was removed under reduced pressure. The residue was triturated with ether to give 2.4 g of material which was chromatographed on 100 g of silica gel. Elution with 2% (ethyl acetate)/benzene gave 2 α ,4,6 - trichloro - 17 α - acetoxy - 16 - methylene - pregna - 4,6 - diene - 3,20 - dione which after crystallization from (methylene chloride)/ether melted at 235°—238°C (with decomposition beginning at 225°C). Further elution with 5% (ethyl acetate)/benzene gave 4,6-dichloro-17 α -acetoxy-16 - methylene - pregna - 4,6 - diene - 3,20 - dione which after crystallization from (methylene chloride)/ether melted at 218°—219°C.

(ii) A solution of 0.250 g of 2 α ,4,6 - trichloro - 17 α - acetoxy - 16 - methylene - pregna - 4,6 - diene - 3,20 - dione, 0.1 g of lithium chloride and 3 ml of dry N,N - dimethyl - formamide was heated at reflux under a nitrogen atmosphere for 0.5 hour.

The solution was then cooled and poured into 100 ml of ice-water. The solid was filtered off and air-dried. The crude material thus obtained was chromatographed on 6 g of neutral alumina (grade I). Elution with 1:1 solution of petroleum ether (boiling range=60°—90°C) and methylene chloride and finally methylene chloride gave 4,6 - dichloro - 17 α - acetoxy - 16 - methylene - pregna - 1,4,6 - triene - 3,20 - dione as a light-yellow product which after crystallization from ether/(methylene chloride) melted at 225°—228°C.

EXAMPLE 2

2.8 ml of a 1.0-M solution of chlorine in carbon tetrachloride were added at 0°C to 1.05 g of 6 - chloro - 16 α ,17 α - isopropylidenedioxy - pregna - 4,6 - diene - 3,20 - dione in 10 ml of alcohol - free chloroform. After 1 hour at 3°C, solvents were removed under reduced pressure and the residue was treated with 12 ml of pyridine. After standing at room temperature for 2 hours, the pyridine was removed under vacuum and the residue was taken up in methylene chloride, washed with 2 - N hydrochloric acid and water, dried with magnesium sulphate and concentrated under reduced pressure. The residue was chromatographed on silica gel and the purified material obtained was recrystallized from acetone/hexane to yield 4,6 - dichloro - 16 α ,17 α - isopropylidenedioxy - pregna - 4,6 - diene - 3,20 - dione.

EXAMPLE 3

A) The preparation of the starting material:

A mixture of 2 g of 6 α - fluoro - 16 α ,17 α - isopropylidenedioxy - pregna - 4 - ene - 3,11,20 - trione, 2 g of chloranil and 150 ml of *tert*butanol was heated at reflux for 18 hours. The cooled solution was then diluted with 300 ml of chloroform, washed three times with cold 5% sodium hydroxide solution and with water and dried over magnesium sulphate. The solvent was subsequently removed under reduced pressure and the crude 6 - fluoro - 16 α ,17 α - isopropylidenedioxy - pregna - 4,6 - diene - 3,11,20 - trione obtained was purified by chromatography on neutral alumina followed by crystallization from (methylene chloride)/ether.

B) The process:

17 ml of a 0.6 - molar solution of chlorine in carbon tetrachloride were added at 0°C to a solution of 4.16 g of 6 - fluoro - 16 α ,17 α - isopropylidenedioxy - pregna - 4,6 - diene - 3,11,20 - trione in 50 ml of alcohol-free chloroform. The resulting mixture was allowed to stand at 0°C for 1 hour. The solvent was then removed under reduced pressure and the residue treated with 6 ml of dry

pyridine. After 1 hour at room temperature, 200 ml of ether were added and the mixture was washed with 1 - N hydrochloric acid. The ether solution was dried over magnesium sulphate and the solvent was removed under reduced pressure. Chromatographic purification of the residue on silica gel followed by crystallization of the product from (methylene chloride)/ether gave 4 - chloro - 6 - fluoro - 16 α ,17 α - isopropylidenedioxy - pregna - 4,6 - diene - 3,11,20 - trione.

EXAMPLE 4

A) The preparation of the starting material: Treatment of 21 - acetoxy - 6 α - fluoro - 16 α - fluoromethyl - 17 α - hydroxy - pregn - 4 - ene - 3,11,20 - trione in accordance with the procedure described in Example 3A gave 21 - acetoxy - 6 - fluoro - 16 α - fluoromethyl - 17 α - hydroxy - pregna - 4,6 - diene - 3,11,20 - trione.

B) The process:

Chlorination of 21 - acetoxy - 6 - fluoro - 16 α - fluoromethyl - 17 α - hydroxy - pregna - 4,6 - diene - 3,11,20 - trione in accordance with the procedure described in Example 3B gave 21 - acetoxy - 4 - chloro - 6 - fluoro - 16 α - fluoromethyl - 17 α - hydroxy - pregna - 4,6 - diene - 3,11,20 - trione.

EXAMPLE 5

A) The preparation of the starting material: Treatment of 21 - acetoxy - 6 α ,16 α - difluoro - 17 α - hydroxy - pregn - 4 - ene - 3,11,20 - trione in accordance with the procedure described in Example 3A gave 21 - acetoxy - 6,16 α - difluoro - 17 α - hydroxy - pregna - 4,6 - diene - 3,11,20 - trione.

B) The process:

Chlorination of 21 - acetoxy - 6,16 α - difluoro - 17 α - hydroxy - pregna - 4,6 - diene - 3,11,20 - trione in accordance with the procedure described in Example 3B gave 21 - acetoxy - 4 - chloro - 6,16 α - difluoro - 17 α - hydroxy - pregna - 4,6 - diene - 3,11,20 - trione.

EXAMPLE 6

A) The preparation of the starting material: A mixture of 15 g 16 α - chloromethyl - 17 α - acetoxy - pregn - 4 - ene - 3,20 - dione, 150 ml of dioxan (purified over alumina), 20 ml of triethyl orthoformate, 10 ml of ethanol and 1.5 ml of concentrated sulphuric acid was stirred at room temperature in the absence of light. After 2 hours, the resulting mixture was poured with stirring into 3 litres of ice and water containing excess sodium bicarbonate. The resulting precipitate was filtered off, well washed with water and dissolved in methylene chloride. The methylene chloride solution was dried

and concentrated to a semi-solid residue which could be crystallized from ether to give 17 α - acetoxy - 16 α - chloromethyl - 3 - ethoxy - pregna - 3,5 - dien - 20 - one but which normally is used directly for the next reaction.

A solution of the foregoing crude 17 α - acetoxy - 16 α - chloromethyl - 3 - ethoxy - pregna - 3,5 - dien - 20 - one in 670 ml of acetone was cooled to 5°C. A solution of 14.2 g of sodium acetate in 240 ml of water was added thereto, followed by 27.6 g of N - chloro - succinimide and 17.2 ml of acetic acid. After stirring for an additional 1.5 hours, the mixture was poured into 8 litres of water and ice. After stirring for an additional hour, the resulting slurry was filtered and the precipitate was dissolved in methylene chloride. The solution was dried, then the solvent was removed and the residue crystallized from (methylene chloride)/ether to give 6 β - chloro - 16 α - chloromethyl - 17 α - acetoxy - pregn - 4 - ene - 3,20 - dione.

A mixture of 10.0 g of 6 β - chloro - 16 α - chloromethyl - 17 α - acetoxy - pregn - 4 - ene - 3,20 - dione, 50 ml of tetrahydrofuran (purified over alumina), 18 ml of triethyl orthoformate, 5 ml of ethanol and 100 g of paratoluene - sulphonic acid was stirred at room temperature for 1.5 hours in the absence of light. The resulting mixture was then added in the course of 10 minutes to a stirred suspension of 45 g of activated manganese dioxide in 450 ml of acetic acid and 35 ml of water. The resulting mixture was stirred for an additional hour and then filtered. The solid was well washed with methylene chloride and the combined filtrate and washings were concentrated under vacuum. The oily residue was diluted with methylene chloride, washed three times with 5% sodium bicarbonate solution and once with water, dried and concentrated. The residue was crystallized with ether and then recrystallized from acetone/hexane to give purified 6 - chloro - 16 α - chloromethyl - 17 α - acetoxy - pregna - 4,6 - diene - 3,20 - dione.

B) The process:

A solution of 1.00 g of 6 - chloro - 16 α - chloromethyl - 17 α - acetoxy - pregna - 4,6 - diene - 3,20 - dione in 22 ml of N,N - dimethyl - formamide and 11 ml of ether is cooled to 0°C and 2.55 mmol of chlorine dissolved in propionic acid are added thereto. The resulting solution is kept in the refrigerator for 12 hours and then at room temperature for 8 hours. It is then diluted with (methylene chloride)/ether (2:5) and washed with water, 5% sodium bicarbonate solution and water, dried and evaporated. The residue is crystallized from (methylene chloride)/hexane to give purified 4,6 - dichloro -

16 α - chloromethyl - 17 α - acetoxy - pregna - 4,6 - diene - 3,20 - dione.

EXAMPLE 7

A) The preparation of the starting material:
Treatment of 21 - acetoxy - 17 α - hydroxy - 16 - methylene - pregn - 4, ene - 3,11,20 - trione in accordance with the procedure described in the first paragraph of Example 6A gave 21 - acetoxy - 3 - ethoxy - 17 α - hydroxy - 16 - methylene - pregna - 3,5 - diene - 11,20 - dione.

Treatment of 21 - acetoxy - 3 - ethoxy - 17 α - hydroxy - 16 - methylene - pregna - 3,5 - diene - 11,20 - dione in accordance with the procedure described in the second paragraph of Example 6A gave 21 - acetoxy - 6 β - chloro - 17 α - hydroxy - 16 - methyl - pregn - 4 - ene - 3,11,20 - trione.

Treatment of 21 - acetoxy - 6 β - chloro - 17 α - hydroxy - 16 - methylene - pregn - 4 - ene - 3,11,20 - trione in accordance with the third paragraph of Example 6A gave 21 - acetoxy - 6 - chloro - 17 α - hydroxy - 16 - methylene - pregna - 4,6 - diene - 3,11,20 - trione.

B) The process:

Chlorination of 21 - acetoxy - 6 - chloro - 17 α - hydroxy - 16 - methylene - pregna - 4,6 - diene - 3,11,20 - trione in accordance with Example 6B gave 21 - acetoxy - 4,6 - dichloro - 17 α - hydroxy - 16 - methylene - pregna - 4,6 - diene - 3,11,20 - trione.

EXAMPLE 8

A) The preparation of the starting material:
83.0 g of semicarbazide hydrochloride and 104 ml of pyridine were added to a stirred solution of 58.0 g of 21 - acetoxy - 6 - chloro - 17 α - hydroxy - pregna - 4,6 - diene - 3,11,20 - trione in 2.3 litres of methanol. The resulting mixture was heated at reflux overnight in a nitrogen atmosphere. Approximately one half of the solvent was then removed under reduced pressure and the residual mixture was diluted with 2 litres of water. The resulting precipitate was allowed to digest for 0.25 hour, then filtered off, well washed with water and dried under reduced pressure to yield 69.0 g of solid 21 - acetoxy - 6 - chloro - 17 α - hydroxy - pregn - 4,6 - dien - 3,11,20 - trione 3,20 - bis - semicarbazone.

A solution of 69.0 g of the foregoing bis-semicarbazone in 690 ml of trifluoroacetic acid was stirred and heated at reflux for 85 minutes. The resulting mixture was then cooled to room temperature and the solvent was removed under reduced pressure to yield 21 - acetoxy - 6 - chloro - pregna - 4,6,16 - triene - 3,11,20 - trione 3,20 - bis - (semicarbazone) as an oil.

The foregoing crude oil was dissolved in 1.4 litres of 50% acetic acid and to the

resulting solution were added 140 ml of 50% pyruvic acid and 69.0 g of anhydrous sodium acetate. The resulting mixture was stirred and heated at 100°C for 1.25 hours under nitrogen, then cooled to room temperature and poured into 3.2 litres of water. The resulting mixture was extracted twice with chloroform. The organic layers were washed once with water, twice with 10% potassium bicarbonate and once with brine. The combined organic layers were dried over sodium sulphate and concentrated to dryness under reduced pressure to yield 60 g of 21 - hydroxy - 6 - chloro - pregna - 4,6,16 - triene - 3,11,20 - trione as an oil.

The foregoing oil was dissolved in 300 ml of dry pyridine and 60 ml of distilled acetic anhydride. The solution obtained was allowed to stand at room temperature for 3 hours and was then added to 3 litres of 3 - N hydrochloric acid and 500 g of ice. The mixture was extracted three times with ether/ (methylene chloride) (3:1). The organic layers were washed once with 1 - N hydrochloric acid, with 5% sodium bicarbonate solution and once with brine. The combined organic layers were dried with sodium sulphate and concentrated under reduced pressure to give 52.0 g of 6 - chloro - 21 - acetoxy - 16 - methyl - pregna - 4,6,16 - triene as a pale yellow foam.

A solution of diazomethane (from 105 g of nitrosomethyl - urea) in 1.5 litres of ether was added over a period of 10 minutes to a solution of 52.0 g of 6 - chloro - 21 - acetoxy - pregna - 4,6,16 - triene - 3,11,20 - trione in 520 ml of dry tetrahydrofuran. The resulting mixture was allowed to stand at room temperature for 1.5 hours, whereupon a precipitate emerged. The solvent was removed under reduced pressure to give a yellow solid which was crystallized once from (methylene chloride)/ether to yield 44.0 g of 6 - chloro - 21 - acetoxy - 16 α ,17 α - methyleneazo - pregna - 4,6 - diene - 3,11,20 - trione as yellow crystals of melting point 194°—197°C (with decomposition).

44 g of crystallized 6 - chloro - 21 - acetoxy - 16 α ,17 α - methyleneazo - pregna - 4,6 - diene - 3,11,20 - trione were placed in an evacuated 3-litre flask which was heated in an oil-bath at 175°—188°C for 0.5 hour. The resulting mixture was then cooled to room temperature. The resulting crude oil was crystallized once from (methylene chloride)/ether to yield 20.28 g of 6 - chloro - 21 - acetoxy - 16 - methyl - pregna - 4,6,16 - triene - 3,11, 20 - trione as yellow crystals of melting point 155°—160°C. An additional 13.5 g of the same substance were obtained from the mother liquors.

A solution of 5.0 g of 6 - chloro - 21 - acetoxy - 16 - methyl - pregna - 4,6,16 - triene - 3,11,20 - trione in 320 ml of alcohol-free chloroform was cooled to 0°C. To the

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solution were added 11.6 ml of a 1.10-molar solution of chlorine in carbon tetrachloride. The resulting mixture was allowed to stand at 0°C for 0.75 hour, then the solvent was removed under reduced pressure. The resulting pale yellow solid was crystallized once from (methylene chloride)/ether to yield 3.59 g of a trichloro intermediate as pale yellow crystals of melting point 211°—213.5°C.

26.0 g of disodium hydrogen phosphate were added to a cooled (0°C) solution of 3.40 g of the said trichloro intermediate in 140 ml of methylene chloride. To the resulting stirred suspension there were rapidly added 8.20 ml of the peroxytrifluoroacetic acid solution prepared by adding 5.1 ml of trifluoro - acetic acid over a period of 10 minutes to a cold solution of 0.82 ml of 90% hydrogen peroxide in 5 ml of methylene chloride. The resulting mixture was stirred at 0°C for 3.5 hours and was then diluted with 400 ml of water. The mixture obtained was extracted twice with methylene chloride. The organic layers were washed once with water and once with brine, combined, dried with sodium sulphate and concentrated under reduced pressure to yield 3.60 g of a colourless oil.

The foregoing colourless oil was dissolved in 27 ml of dry pyridine and the solution was allowed to stand at room temperature for 1.5 hours, then the pyridine was removed under reduced pressure. The residue was dissolved in methylene chloride and the organic solution was washed twice with 1 - N hydrochloric acid solution, once with 5% sodium bicarbonate solution and once with brine. The organic layers were combined, dried with sodium sulphate and concentrated under reduced pressure to give 3.5 g of 4,6 - dichloro - 21 - acetoxy - 16 α ,17 α - oxido - 16 β - methyl - preña - 4,6 - diene - 3,11,20 - trione.

B) The process:

12 ml of trifluoroacetic acid were added to a warm solution of 2.50 g of 4,6 - dichloro - 21 - acetoxy - 16 α ,17 α - oxido - 16 β - methyl - preña - 4,6 - diene - 3,11,20 - trione in 60 ml of dry benzene. The resulting mixture was heated at reflux under nitrogen for 5 hours, then diluted with ether/(methylene chloride) (3:1). The organic layer was washed twice with 5% sodium bicarbonate solution and once with brine, dried with sodium sulphate and concentrated under reduced pressure to yield a solid. Two crystallizations from (methylene chloride)/(ethyl acetate) gave 520 mg of 4,6 - dichloro - 21 - acetoxy - 17 α - hydroxy - 16 - methylene - preña - 4,6 - diene - 3,11,20 - trione as colourless crystals of melting point 267°—270°C. Concentration of the mother liquor yielded an additional 390 mg of the same substance.

EXAMPLE '9.

A) The preparation of the starting material:

3.30 ml of a 0.90-molar solution of chlorine in glacial acetic acid was added dropwise over 2 minutes to a solution of 1.20 g of 4,6 - dichloro - 21 - acetoxy - 16 α ,17 α - oxido - 16 β - methyl - preña - 4,6 - diene - 3,11,20 - trione in 20 ml of glacial acetic acid. The resulting mixture was allowed to stand at room temperature for 1 hour and was then diluted with 75 ml of water. The resulting precipitate was filtered off, washed with water and dried to yield 1.18 g of 2,4,6 - trichloro - 21 - acetoxy - 16 α ,17 α - oxido - 16 β - methyl - preña - 4,6 - diene - 3,11,20 - trione as a colourless solid.

B) The process:

(i) A solution of 1.00 g of 2,4,6 - trichloro - 21 - acetoxy - 16 α ,17 α - oxido - 16 β - methyl - preña - 4,6 - diene - 3,11,20 - trione in 25 ml of dry benzene and 5.0 ml of trifluoroacetic acid was heated at reflux under nitrogen for 10 hours. The resulting mixture was cooled to room temperature, diluted with ether/(methylene chloride) (3:1), washed twice with 5% sodium bicarbonate solution and once with brine, dried with sodium sulphate and concentrated to yield an oil which was chromatographed over silica gel in benzene. Elutions with benzene/(ethyl acetate) and evaporation of the solvent gave the crude product. Crystallization from (ethyl acetate)/ether gave 230 mg of 2,4,6 - trichloro - 21 - acetoxy - 17 α - hydroxy - 16 - methylene - preña - 4,6 - diene - 3,11,20 - trione of melting point 271°—274°C.

(ii) 100 g of anhydrous lithium carbonate were added to a stirred solution of 140 mg of 2,4,6 - trichloro - 21 - acetoxy - 17 α - hydroxy - 16 - methylene - preña - 4,6 - diene - 3,11,20 - trione in 3.0 ml of dry N,N - dimethyl - formamide. The resulting mixture was stirred and heated under nitrogen at 125°C for 4 hours and at 151°C for 0.25 hour. The cooled mixture was then diluted with water and was extracted twice with methylene chloride. The organic layers were washed with brine, combined, dried with sodium sulphate and concentrated. The resulting oil (140 mg) was dissolved in 1 ml of pyridine and 0.20 ml of acetic anhydride. The solution was allowed to stand at room temperature for 3 hours, then diluted with cold 3 - N hydrochloric acid and extracted once with ether/(methylene chloride) (3:1) and once with methylene chloride. The organic layers were washed once with 1 - N hydrochloric acid, once with 5% sodium bicarbonate solution and once with brine, combined, dried with sodium sulphate and concentrated to yield an oil which was chromatographed on 10.0 g of activated magnesium silicate in benzene. Elution with benzene/(ethyl acetate) gave material which was crystallized once from (ethyl acetate)/

ether to yield 4,6'- dichloro - 21 - acetoxy - 17 α - hydroxy - 16 - methylene - prena - 1,4,6 - triene - 3,11,20 - trione.

The following Examples are illustrative of pharmaceutical preparations containing the novel derivatives provided by the invention:

EXAMPLE A

In a tablet formulation, each tablet contains 2.0 mg of 17 α - acetoxy - 4,6 - dichloro - 16 - methylene - prena - 4,6 - diene - 3,20 - dione, 121.5 mg of lactose, 70.5 mg of corn starch, 8.0 mg of pregelatinized corn starch and 3.0 mg of calcium stearate and has a total weight of 205.0 mg.

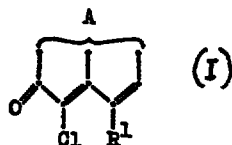
EXAMPLE B

In a capsule formulation, each capsule contains 5 mg of 17 α - acetoxy - 4,6 - dichloro - 16 - methylene - prena - 4,6 - diene - 3,20 - dione, 178 mg of lactose, 37 mg of corn starch and 5 mg of talc and has a total net weight of 225 mg.

Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to the claims of Patent No. 1,131,443.

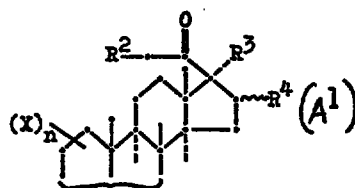
WHAT WE CLAIM IS:—

1) Halogenated steroids of the general formula



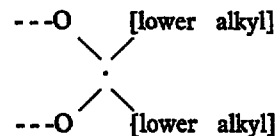
, wherein R¹ represents a fluorine, chlorine or bromine atom or a lower-alkyl group and A represents

(i) a grouping of the formula

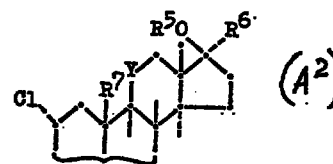


, in which n stands for 0 or 1, X represents an unsaturation between the carbon atoms in the 1- and 2-positions or a 2 - chloro substituent or a 1 α ,2 α - methylene group, R² represents a hydrogen or fluorine atom, R³ represents a hydrogen atom or a hydroxy, lower-alkoxy, lower-alkanoyloxy, difluoro-acetyl, dichloromethyl group, (the latter, only R⁴ represents a lower-alkylidene group or an α - chloromethyl group, (the latter, only when n stands for 0 or 1, X represents an unsaturation between the carbon atoms in the 1- and 2-positions or a 2 - chloro substituent,

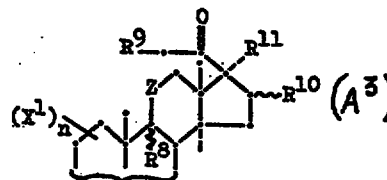
R³ represents a hydrogen atom and R³ represents a hydroxy or lower - alkanoyloxy group), or R³ and R⁴ together represent a grouping of the formula



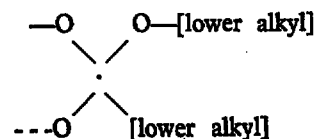
or (ii) a grouping of the formula



, in which R⁵ represents a hydrogen atom or a lower - alkanoyl group, R⁶ represents a hydrogen atom or a lower - alkyl, monosaturated low - aliphatic hydrocarbyl or monosaturated halo - (lower aliphatic hydrocarbyl) group, R⁷ represents a hydrogen atom or the methyl group and Y represents a methylene, β - hydroxy - methylene, α - hydroxy - methylene or carbonyl group, or (iii) a grouping of the formula



in which n has the significance given earlier in this claim, X¹ represents an unsaturation between the carbon atoms in the 1- and 2-positions or a 2 - chloro substituent, R⁸ represents an α - hydrogen, α - fluorine, α - chlorine or α - bromine atom, R⁹ represents a hydrogen atom, the hydroxy group, the dihydrogen phosphate ester thereof or an alkali - metal salt thereof or a lower - alkanoyloxy group, R¹⁰ represents a lower - alkylidene, α - chloromethyl or α - fluoro-methyl group or an α - chloro or α - fluoro substituent, R¹¹ represents a hydroxy or lower - alkanoyloxy group or R⁹ and R¹¹ together represent a grouping of the formula





ether to yield 4,6 - dichloro - 21 - acetoxy - 17 α - hydroxy - 16 - methylene - pregna - 1,4,6 - triene - 3,11,20 - trione.

The following Examples are illustrative of pharmaceutical preparations containing the novel derivatives provided by the invention:

EXAMPLE A

In a tablet formulation, each tablet contains 2.0 mg of 17 α - acetoxy - 4,6 - dichloro - 16 - methylene - pregna - 4,6 - diene - 3,20 - dione, 121.5 mg of lactose, 70.5 mg of corn starch, 8.0 mg of pregelatinized corn starch and 3.0 mg of calcium stearate and has a total weight of 205.0 mg.

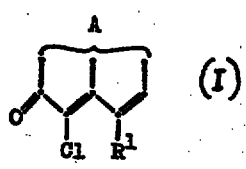
EXAMPLE B

In a capsule formulation, each capsule contains 5 mg of 17 α - acetoxy - 4,6 - dichloro - 16 - methylene - pregna - 4,6 - diene - 3,20 - dione, 178 mg of lactose, 37 mg of corn starch and 5 mg of talc and has a total net weight of 225 mg.

Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to the claims of Patent No. 1,131,443.

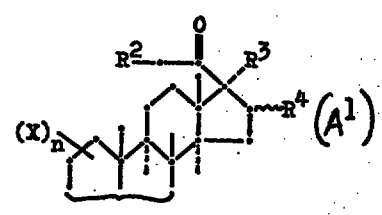
WHAT WE CLAIM IS:—

1) Halogenated steroids of the general formula



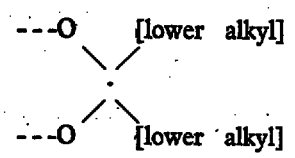
, wherein R¹ represents a fluorine, chlorine or bromine atom or a lower-alkyl group and A represents

(i) a grouping of the formula

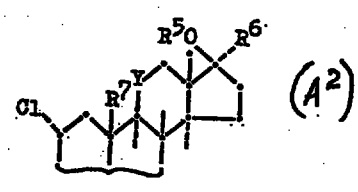


, in which n stands for 0 or 1, X represents an unsaturation between the carbon atoms in the 1- and 2-positions or a 2 - chloro substituent or a 1 α ,2 α - methylene group, R² represents a hydrogen or fluorine atom, R³ represents a hydrogen atom or a hydroxy, lower-alkoxy, lower-alkanoyloxy, difluoroacetyl, dichloromethyl group, (the latter, only R⁴ represents a lower-alkylidene group or an α - chloromethyl group, (the latter, only when n stands for 0 or 1, X represents an unsaturation between the carbon atoms in the 1- and 2-positions or a 2 - chloro-substituent,

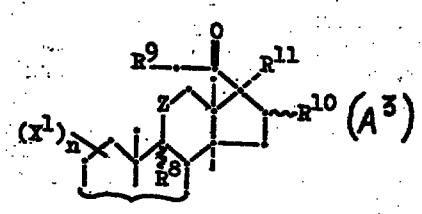
R³ represents a hydrogen atom and R³ represents a hydroxy or lower - alkanoyloxy group), or R³ and R⁴ together represent a grouping of the formula



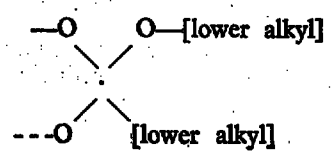
or (ii) a grouping of the formula



, in which R⁵ represents a hydrogen atom or a lower - alkanoyl group, R⁶ represents a hydrogen atom or a lower - alkyl, monosaturated low - aliphatic hydrocarbonyl or monosaturated halo - (lower aliphatic hydrocarbonyl) group, R⁷ represents a hydrogen atom or the methyl group and Y represents a methylene, β - hydroxy - methylene, α - hydroxy - methylene or carbonyl group, or (iii) a grouping of the formula

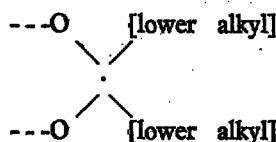
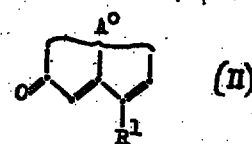


in which n has the significance given earlier in this claim, X¹ represents an unsaturation between the carbon atoms in the 1- and 2-positions or a 2 - chloro substituent, R⁸ represents an α - hydrogen, α - fluorine, α - chlorine or α - bromine atom, R⁹ represents a hydrogen atom, the hydroxy group, the dihydrogen phosphate ester thereof or an alkali - metal salt thereof or a lower - alkanoyloxy group, R¹⁰ represents a lower - alkylidene, α - chloromethyl or α - fluoro-methyl group or an α - chloro or α - fluoro substituent, R¹¹ represents a hydroxy or lower - alkanoyloxy group or R⁹ and R¹¹ together represent a grouping of the formula





or, where R⁹ represents a hydrogen atom, R¹⁰ and R¹¹ together represent a grouping of the formula



5 and Z represents a carbonyl, β - hydroxy - methylene, α - hydroxy - methylene or α - sulphonyloxy - methylene group or, when R⁸ represents an α - hydrogen atom and R⁹ is other than a hydrogen atom, a methylene group or, when R⁸ represents an α - chlorine atom, a β - chloro - methylene group, or Z and R⁸ together represent an unsaturation between the 9- and 11-carbon atoms or a 9 β -11 β - oxido group.

15 2) A halogenated steroid of formula I given in claim 1 containing grouping A¹ in which R¹ represents a chlorine or fluorine atom, R³ represents a lower - alkoxy, lower - alkanoyloxy or lower - alkyl group, R⁴ represents the methylene group and n stands for 0.

20 3) A halogenated steroid of formula I given in claim 1 containing grouping A³ in which R¹ represents a chlorine or fluorine atom, R³ represents an α - fluorine, α - chlorine or α - bromine atom, R⁹ represents the dihydrogen phosphate ester group or a lower - alkanoyloxy group, R¹⁰ represents the methylene group and R¹¹ represents the hydroxy group, n stands for 0 and Z represents the β - hydroxymethylene group.

25 4) A 4,6 - dichloro - 17 α - (lower alkanoyloxy) - 16 - methylene - pregna - 4,6 - diene - 3,20 - dione as set forth in claim 1.

30 5) 4,6 - Dichloro - 17 α - acetoxy - 16 - methylene - pregna - 4,6 - diene - 3,20 - dione.

35 6) 4,6 - Dichloro - 17 α - acetoxy - 16 - methylene - pregna - 1,4,6 - triene - 3,20 - dione.

40 7) 2 α ,4,6 - Trichloro - 17 α - acetoxy - 16 - methylene - pregna - 4,6 - diene - 3,20 - dione.

45 8) 4,6 - Dichloro - 21 - acetoxy - 17 α - hydroxy - 16 - methylene - pregna - 4,6 - diene - 3,11,20 - trione.

50 9) 2,4,6 - Trichloro - 21 - acetoxy - 17 α - hydroxy - 16 - methylene - pregna - 4,6 - diene - 3,11,20 - trione.

10) A pharmaceutical preparation comprising a halogenated steroid as set forth in claim 1 in association with a compatible pharmaceutical carrier.

55 11) A process for the manufacture of the halogenated steroids set forth in claim 1, which process comprises:

(a) treating a steroid of the formula

, wherein R¹ has the significance given in claim 1 and A⁰ represents grouping A¹, A² or A³ given in claim 1 in which X (if present) represents a 1 α ,2 α - methylene group, X¹ is absent and the 2-position of grouping A² is unsubstituted with chlorine and a proton acceptor so as to insert a chlorine atom at the 4-position or

(b) treating a 2-unsubstituted 1(2)-saturated steroid of formula I given in claim 1 with a chlorinating agent so as to insert a chlorine atom at the 2-position or

(c) dehydrogenating in the 1(2)-position a steroid of formula I given in claim 1 containing grouping A¹ or A³ in which n stands for 0 or

(d) oxidising the 11 - hydroxy group of a steroid of formula I given in claim 1 containing grouping A² or A³ in which Y or Z as the case may be represents the hydroxymethylene group so as to convert said group into a carbonyl group or

(e) esterifying the 11 α - hydroxy group of a steroid of formula I given in claim 1 containing grouping A³ in which Z represents an α - hydroxy - methylene group with a sulphonic acid or

(f) splitting off a 11 α - sulphonyloxy group or a 11 β - hydroxy group and a 9 - hydrogen atom from a steroid of formula I given in claim 1 containing grouping A³ in which Z represents an α - sulphonyloxy - methylene or β - hydroxy - methylene group and R⁸ represents an α - hydrogen atom so as to introduce a 9(11) - double bond or

(g) treating a steroid of formula I given in claim 1 containing grouping A³ in which Z and R⁸ together represent an unsaturation between the 9- and 11-carbon atoms with hydrochlorous acid or hydrobromous acid so as to insert a chlorine or bromine atom respectively at the 9-position and a hydroxyl group at the 11-position or

(h) treating a steroid of formula I given in claim 1 containing grouping A³ in which Z represents a hydroxymethylene group and R⁸ represents an α - chlorine or α - bromine atom with a dehydrohalogenating agent so as to form a 9 β ,11 β - oxido group or

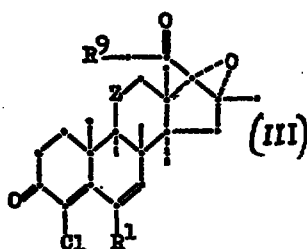
(i) treating a steroid of formula I given in claim 1 containing grouping A³ in which Z and R⁸ together represent a 9 β ,11 β - oxido group with hydrogen fluoride, hydrogen chloride, hydrogen bromide or a chlorinating agent so as to introduce the relevant halogen atom at the 9-position and a hydroxyl group or chlorine atom at the 11-position or

(j) esterifying a steroid of formula I given



in claim 1^r which contains at least one free hydroxy group in the 17- or 21-position or (k) saponifying a 17- and/or 21-esterified steroid of formula I given in claim 1 or

5 (l) treating a steroid of the formula



, wherein R¹, R⁹ and Z have the significance given in claim 1, with a strong acid so as to yield a 16 - methylene - 17 α - hydroxy product.

10 12) A process as set forth in claim 11, wherein a steroid starting material of formula II containing grouping A¹ in which R¹ represents a chlorine or fluorine atom, R⁹ represents a lower-alkoxy, lower-alkanoyloxy or lower-alkyl group, R⁴ represents the methylene group and *n* stands for O, is chlorinated so as to yield a steroid according to claim 2.

20 13) A process as set forth in claim 11, wherein a steroid of formula I given in claim 1 containing grouping A³ in which R¹ represents a chlorine or fluorine atom, R⁹ represents the dihydrogen phosphate ester group or a lower-alkanoyloxy group, R¹⁰ represents the methylene group, R¹¹ represents a hydroxy group, *n* stands for O and Z and R⁸ together represent a 9 β ,11 β - oxido group, is treated with hydrogen fluoride, hydrogen chloride or hydrogen bromide so as to yield a steroid according to claim 3.

30 14) A process as set forth in claim 11, wherein a steroid of formula I given in claim 1 containing grouping A³ in which R¹ represents a chlorine or fluorine atom, R⁹ re-

presents the dihydrogen phosphate ester group or a lower-alkanoyloxy group, R¹⁰ represents the methylene group, R¹¹ represents a hydroxy group, *n* stands for O and Z and R⁸ together represent an unsaturation between the carbon atoms in the 9- and 11-positions, is treated with hydrochlorous acid or hydrobromous acid so as to yield a steroid according to claim 3 in which R⁸ represents a chlorine or bromine atom.

15) A process as set forth in claim 11, wherein a 6 - chloro - 17 α - (lower alkanoyloxy) - 16 - methylene - pregna - 4,6 - diene - 3,20 - dione is chlorinated.

16) A process as set forth in claim 11, wherein 4,6 - dichloro - 17 α - hydroxy - 16 - methylene - pregna - 4,6 - diene - 3,20 - dione is esterified with a lower-alkanoic acid.

17) A process as set forth in claim 11, wherein 4,6 - dichloro - 17 α - acetoxy - 16 - methylene - pregna - 4,6 - diene - 3,20 - dione is dehydrogenated in the 1(2)-position.

18) A process as set forth in claim 11, wherein 4,6 - dichloro - 21 - acetoxy - 16 α - 17 α - oxido - 16 β - methyl - pregna - 4,6 - diene - 3,11,20 - trione is treated with trifluoroacetic acid so as to yield the steroid as set forth in claim 8.

19) A process as set forth in claim 11, wherein 2,4,6 - trichloro - 21 - acetoxy - 16 α ,17 α - oxido - 16 β - methyl - pregna - 4,6 - diene - 3,11,20 - trione is treated with trifluoroacetic acid so as to yield the steroid as set forth in claim 9.

20) A process for the manufacture of the halogenated steroids claimed in claim 1, substantially as described with reference to the Examples.

21) Halogenated steroids as set forth in claim 1, when manufactured by the process claimed in any one of claims 11 to 20 inclusive.

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Patent Agent,

For F. HOFFMANN-LA ROCHE & CO.,
Aktiengesellschaft.