

PATENT SPECIFICATION

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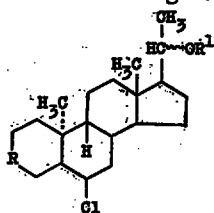
NO DRAWINGS

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(54) $9\beta,10\alpha$ -STEROIDS AND A PROCESS FOR THE PREPARATION 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 $9\beta,10\alpha$ -steroids and a process for the preparation thereof.

The $9\beta,10\alpha$ -steroids provided by the invention have the following formula



- I
 15 wherein R is a 3-keto- Δ^4 -, a 3-keto- $\Delta^{4,6}$ -, a 3-keto- $\Delta^{1,4}$ -, a 3-keto- $\Delta^{3,4,6}$ -, a 3-alkoxy- $\Delta^{3,5}$ -, a 3-alkoxy- $\Delta^{4,6}$ -, a 3-acyloxy- $\Delta^{3,5}$ -, a 3-acyloxy- $\Delta^{4,6}$ -, a 3-acyloxy- $\Delta^{2,4,6}$ -, or a 3-hydroxy- $\Delta^{4,6}$ -system and R¹ is hydrogen or acyl.

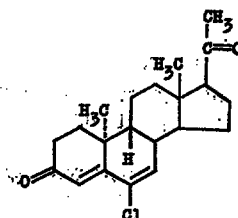
- 20 As used herein the term "alkoxy" denotes aliphatic, cycloaliphatic, aromatic or araliphatic etherified hydroxy groups having up to 10 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tertiary butoxy, cyclopentyloxy, cyclohexyloxy, phenoxy and benzyloxy. The term "acyl" denotes a radical
 25 derived from a saturated or unsaturated aliphatic, cycloaliphatic, araliphatic or aromatic carboxylic acid of up to 20 carbons formed by removal of the hydroxy moiety from the carboxyl group. The acid may be saturated,
 30 unsaturated, straight or branched chain and includes formic acid, acetic acid, privalic acid, propionic acid, butyric acid, valeric acid, caproic acid, enanthic acid, oleic acid, palmitic acid, stearic acid, succinic acid, malonic

acid, citric acid and benzoic acid. The term "acyloxy" denotes an acyloxy group in which the acyl moiety is as defined earlier.

The 20-(hydroxy or acyloxy) group can either have an α - or β -configuration. A preferred group of $9\beta,10\alpha$ -steroids represented by formula I comprises those wherein R is a 3-keto- $\Delta^{4,6}$ - or a 3-keto- $\Delta^{1,4,6}$ -system and R¹ is hydrogen or alkanoyl containing up to 6 carbon atoms, preferably acetyl.

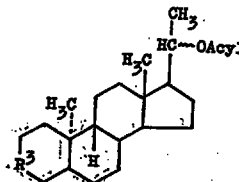
According to the process provided by this invention, the $9\beta,10\alpha$ -steroids of formula I are prepared by

(A) treating the $9\beta,10\alpha$ -steroid of the formula



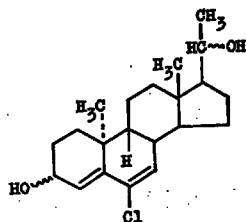
II
 with a reducing agent to give a $9\beta,10\alpha$ -steroid of formula I in which R is a 3-hydroxy- $\Delta^{4,6}$ -system and R¹ is hydrogen or

(B) treating a $9\beta,10\alpha$ -steroid of the formula



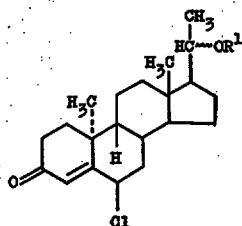
III
 wherein R³ is a 3-acyloxy- $\Delta^{3,5}$ -, a 3-alkoxy- $\Delta^{3,5}$ - or a 3-keto- $\Delta^{4,6}$ -system, with a chlorinating agent to give a $9\beta,10\alpha$ -steroid of formula I in which R is a 3-keto- Δ^4 -system and R¹ is acyl when a $9\beta,10\alpha$ -

- 5 steroid of formula III in which R^3 is a 3-acyloxy- $\Delta^{3,5}$ - or a 3-alkoxy- $\Delta^{3,5}$ -system is used or a $9\beta,10\alpha$ -steroid of formula I in which R is a 3-keto- $\Delta^{4,6}$ -system and R^1 is acyl when a $9\beta,10\alpha$ -steroid of formula III in which R^3 is a 3-keto- $\Delta^{4,6}$ -system is used or (C) selectively oxidizing a 3-hydroxy- $9\beta,10\alpha$ -steroid of the formula



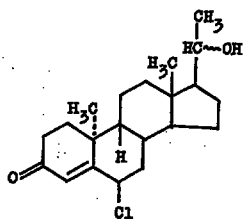
IV

- 10 to the corresponding 3-ketone or (D) dehydrogenating a Δ^4 - $9\beta,10\alpha$ -steroid of the formula



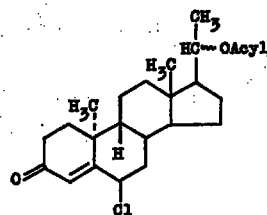
V

- 15 wherein R^1 has the significance given earlier, or a 6(7)-dehydro derivative thereof in at least one of the positions 1(2) and 6(7) or (E) acylating the 20-hydroxy group of a $9\beta,10\alpha$ -steroid of the formula



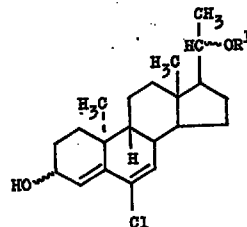
VI

- or a 1(2)- or 6(7)-dehydro or 1(2), 6(7)-bisdehydro derivative thereof or (F) saponifying the $9\beta,10\alpha$ -steroid of the formula



VII

- or a 1(2)- or 6(7)-dehydro or 1(2), 6(7)-bisdehydro derivative thereof or (G) acylating a free hydroxy group of a $9\beta,10\alpha$ -steroid of the formula



VIII

- wherein R^1 has the significance given earlier, or

- (H) alkylating the 3-hydroxy group of a $9\beta,10\alpha$ -steroid of formula VIII or

- (I) enol-etherifying a $9\beta,10\alpha$ -steroid of formula V or

- (J) enol-esterifying a $9\beta,10\alpha$ -steroid of formula V or a 6(7)-dehydro derivative thereof.

The various embodiments of the foregoing process will now be described in detail.

(A) When it is desired to prepare a 3,20-dihydroxy-derivative of formula I, a $9\beta,10\alpha$ -steroid of formula II can be treated with a reducing agent such as a complex metal hydride, e.g., lithium aluminium hydride, sodium borohydride or diisobutyl aluminium hydride, by means known to the art.

(B) A $9\beta,10\alpha$ -steroid of formula III wherein R^3 is a 3-acyloxy- $\Delta^{3,5}$ - or 3-alkoxy- $\Delta^{3,5}$ -system is treated with a chlorinating agent to yield a $9\beta,10\alpha$ -steroid of formula I in which R is a 3-keto- $\Delta^{4,6}$ -system and R^1 is acyl. Exemplary of the chlorinating agents which may be employed are chlorine, N-chloroimides or N-chloroamides such as N-chlorosuccinimide or N-chloroacetamide. $9\beta,10\alpha$ -Steroids of formula III wherein R^3 represents a 3-keto- $\Delta^{4,6}$ -system can be chlorinated by treatment with chromyl chloride, and then the intermediate reaction product can be dehydrated with an acidic reagent such as a hydrogen halide, e.g., hydrogen chloride or hydrogen bromide, to yield a $9\beta,10\alpha$ -steroid of formula I in which R is a 3-keto- $\Delta^{4,6}$ -system and R^1 is acyl. Suitable solvents are inert organic solvents such as ethers, e.g. dioxan or tetrahydrofuran, lower alkanolic acids, e.g. acetic acid, or di-(lower alkyl) ketones, e.g., acetone. Further, $9\beta,10\alpha$ -steroids of formula III wherein R^3 is a 3-keto- $\Delta^{4,6}$ -system can be chlorinated by first converting same to a corresponding 6,7-epoxide by reaction with a peracid such as perphthalic acid. The 6,7-epoxide, upon treatment with hydrogen chloride, yields the 6-chloro-7-hydroxy-derivative which can then be further reacted by dehydration as described hereinbefore to yield the 6(7) double bond.

(C) A 3-hydroxy- $9\beta,10\alpha$ -steroid of formula IV can be converted to the corresponding 3-keto derivative of formula I by selectively

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oxidizing the 3-hydroxy group. The selective oxidation can be effected by means of manganese dioxide or dichlorodicyanobenzoquinone.

5 (D) A Δ^4 -9 β ,10 α -steroid of formula V can be dehydrogenated to yield the corresponding Δ^1 or Δ^6 derivatives of formula I. Suitable reagents for effecting the dehydrogenation of the 6(7)-position include benzoquinones, preferably dichlorodicyanobenzoquinone in dioxan which contains in solution about 1% to 10% of mineral acid, e.g. hydrogen chloride. The dehydrogenation can be conveniently carried out in other organic solvents such as di-lower alkyl ketones, e.g. acetone, or lower alcohols, e.g., amylalcohol, or hydrocarbons such as benzene. A preferred method for introducing the 1(2) double bond comprises treatment with dichlorodicyanobenzoquinones in dioxan containing small amounts (about 0.1% to 1.0%) of mineral acid, e.g., hydrogen chloride. Additionally, the 1(2) double bond can be introduced by treatment with selenium dioxide in a lower alkyl alcohol solvent such as tertiary butanol or amyl alcohol. Alternatively, to introduce a 6(7) double bond the compounds represented by formula V can be converted to the corresponding 3-enol ethers by means known to the art followed by treatment with manganese dioxide.

25 (E) and (G) The 20-hydroxy group of a 9 β ,10 α -steroid of formula VI or a 1(2)- or 6(7)-dehydro or 1(2), 6(7)-bisdehydro derivative thereof or a free hydroxy group of a 9 β ,10 α -steroid of formula VIII can be acylated by treatment with an acylating agent, for example, a reactive acyl derivative such as an acyl anhydride or halide (i.e. fluoride, chloride, bromide or iodide) in the presence of a suitable organic base, preferably pyridine.

40 (F) The acyloxy group of a 9 β ,10 α -steroid of formula VII or a 1(2)- or 6(7)-dehydro or 1(2),6(7)-bisdehydro derivative thereof can be saponified by means of a mild base, preferably an alkali carbonate or hydrogen carbonate.

50 (H) and (I) The alkylation of the 3-hydroxy group of a 9 β ,10 α -steroid of formula VIII or the enol-etherification of a 9 β ,10 α -steroid of formula V can be effected by the reaction of the starting steroid with the desired alcohol, e.g., methanol, ethanol, benzyl alcohol or cyclohexyl alcohol, in the presence of p-toluenesulphonic acid. Other convenient methods of preparing the ether derivatives include reacting the starting material of formula V or VIII with an orthoformic acid ester in the presence of a mineral acid such as hydrogen chloride or with a dialkoxypropane, e.g., 2,2-dimethoxypropane, in methanol/dimethylformamide solvent using p-toluenesulphonic acid as the catalyst.

65 (J) The 3-enol-esterification of a 9 β ,10 α -steroid of formula V or of a 6(7)-dehydro

derivative thereof can be effected by treatment with an acylating agent such as isopropenyl acetate in the presence of a catalyst such as p-toluenesulphonic acid.

The starting materials used in embodiments (A) and (B) of the foregoing process, insofar as they are not known or their preparation has not heretofore been described, can be obtained according to methods known to those skilled in the art.

The 9 β ,10 α -steroids represented by formula I are characterized by a high degree of endocrinological usefulness. They are hormonally active, more specifically as progestational agents or anti-estrogenic agents. Moreover, they influence gonadotropin secretion and/or production. The 9 β ,10 α -steroids of formula I come into consideration, e.g., for treatment of menstrual disorders. They can be used in the form of conventional pharmaceutical preparations. These conventional pharmaceutical preparations containing the 9 β ,10 α -steroids of formula I can contain them in admixture with conventional organic or inorganic inert carrier materials suitable for enteral or parenteral administration such as, for example, water, gelatin, lactose, starch, talc, vegetable oil, gums, polyalkylene glycols and petroleum jelly. These preparations can be in conventional solid forms such as tablets, dragées or capsules or in conventional liquid forms such as solutions, suspensions or emulsions. They can be subjected to conventional pharmaceutical expedients such as sterilization and/or can contain conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting or emulsifying agents, salts for adjusting the osmotic pressure or buffers. They can also contain other active ingredients including other hormonally active ingredients.

The following examples are illustrative of the invention but are not limitative thereof. All temperatures are stated in °C. Optical rotation values are taken in dioxan, c=0.1.

EXAMPLE 1.

A solution of 28 g of sodium borohydride in 400 ml of water is added over a 10 minute period to a solution of 6-chloro-9 β ,10 α -pregna-4,6-diene-3,20-dione in 700 ml of dioxan and 2000 ml of methanol cooled to 0°. The reaction solution is subsequently stirred at 0° for an additional 30 minutes, then poured onto 10 litres of ice-water and 50 ml of acetic acid and extracted three times with methylene chloride. The organic extracts are combined, washed with water, dried with sodium sulphate and evaporated to dryness in vacuum. The residue is recrystallized twice from alcohol yielding pure 6-chloro-3 α ,20 β - dihydroxy - 9 β ,10 α - pregna - 4,6-diene, m.p. 142—144°. $[\alpha]_D^{25} = -148^\circ$.

The mother liquors from the above reaction, consisting primarily of 6-chloro-3 ξ ,20 ξ - dihydroxy - 9 β ,10 α - pregna - 4,6-

diene, are dissolved in 1000 ml of chloroform and stirred at room temperature for 3 hours with 100 g of manganese dioxide. The reaction mixture is filtered and the residue is then rinsed with chloroform. The combined filtrates are evaporated in vacuum and the residue chromatographed on 600 g of silica gel with hexane/acetone. Elution with hexane/acetone (92:8) and recrystallization from ether yields 6-chloro-20 β -hydroxy-9 β ,10 α -pregna-4,6-dien-3-one, (m.p. 180—182°). $[\alpha]_D^{25} = -440^\circ$.

Further elution with hexane/acetone (9:1) yields 6-chloro-20 α -hydroxy-9 β ,10 α -pregna-4,6-dien-3-one, m.p. 156.5—158.5° (from ether). $[\alpha]_D^{25} = -435^\circ$.

EXAMPLE 2.

A solution of 5.0 g of 6-chloro-20 α -hydroxy-9 β ,10 α -pregna-4,6-dien-3-one and 4.23 g of 2,3-dichloro-5,6-dicyanobenzoquinone in 200 ml of dioxan containing 0.2% of hydrogen chloride is stirred at room temperature for 6 hours. 200 g of sodium carbonate are then added and the mixture is heated to reflux for 30 minutes. The cooled reaction mixture is filtered and the residue is rinsed with dioxan. The combined filtrates are treated with the same volume of benzene and filtered through a column of 100 g of aluminium oxide (act. I). The substance is completely eluted with acetic ester. The combined eluates, after evaporation in vacuum yield 5.0 g of residue which is chromatographed on 250 g of silica gel. Elution with ether/hexane (2:1) yields 6-chloro-20 α -hydroxy-9 β ,10 α -pregna-1,4,6-trien-3-one, m.p. 159—161° (acetone/hexane). $[\alpha]_D^{25} = -254^\circ$.

EXAMPLE 3.

Using similar procedures to those described in Example 2, 6-chloro-20 β -hydroxy-9 β ,10 α -pregna-4,6-dien-3-one yields 6-chloro-20 β -hydroxy-9 β ,10 α -pregna-1,4,6-trien-3-one, m.p. 209—210° (acetone/hexane).

EXAMPLE 4.

A mixture of 1.5 g of 6-chloro-20 β -hydroxy-9 β ,10 α -pregna-4,6-dien-3-one, 40 ml of pyridine and 40 ml of acetic anhydride is held at room temperature for 4 hours and subsequently evaporated to dryness in vacuum. The residue, recrystallized from acetone/hexane, yields 6-chloro-20 β -acetoxy-9 β ,10 α -pregna-4,6-dien-3-one, m.p. 190—192°. $[\alpha]_D^{25} = -303^\circ$.

EXAMPLE 5.

According to the methods described in Example 4, 6-chloro-20 β -hydroxy-9 β ,10 α -pregna-1,4,6-trien-3-one yields 6-chloro-20 β -acetoxy-9 β ,10 α -pregna-1,4,6-trien-3-one, m.p. 250—252°. $[\alpha]_D^{25} = -156^\circ$.

EXAMPLE 6.

According to the methods described in Example 4, 6-chloro-3 α ,20 β -dihydroxy-9 β ,10 α -pregna-4,6-diene yields 6-chloro-3 α ,20 β -diacetoxy-9 β ,10 α -pregna-4,6-diene, m.p. 134—135°. $[\alpha]_D^{25} = -47^\circ$.

EXAMPLE 7.

A solution of 1.0 g of 6-chloro-3 α ,20 β -dihydroxy-9 β ,10 α -pregna-4,6-diene in 100 ml of ethanol is, after the addition of 0.5 g of p-toluenesulphonic acid, heated at 50° for 1 hour. The reaction mixture is poured on to ice-cold, dilute sodium bicarbonate solution and extracted with ether. The ether extracts are washed with water, dried with sodium sulphate and evaporated in vacuum. The residue is chromatographed on silica gel. 3 β -ethoxy-6-chloro-20 β -hydroxy-9 β ,10 α -pregna-4,6-diene is first eluted with hexane/acetone. The subsequent fractions yield 3 α -ethoxy-6-chloro-20 β -hydroxy-9 β ,10 α -pregna-4,6-diene, $n_{20} = 20500$. Acetylation of 3 α -ethoxy-6-chloro-20 β -hydroxy-9 β ,10 α -pregna-4,6-diene in accordance with the methods of Example 4 yields 20 β -acetoxy-3 α -ethoxy-6-chloro-9 β ,10 α -pregna-4,6-diene, m.p. 125—126° (hexane). $[\alpha]_D^{25} = -73^\circ$.

EXAMPLE 8.

A solution of 19.5 g of potassium acetate in 400 ml of 85% acetic acid is added with stirring over a 10 minute period to a solution of 11.40 g of 3,20 α -diacetoxy-9 β ,10 α -pregna-3,5-diene in 200 ml of ether which is cooled to -5°. A solution of 2.42 g of chlorine in 56 ml of glacial acetic acid is subsequently added dropwise over a 10 minute period at -5°. The mixture is then stirred for an additional 10 minutes, poured on ice-water and extracted with ether. The ether extract is washed neutral with sodium carbonate solution and water, dried with sodium sulphate and evaporated to dryness in vacuum. The residue is chromatographed on 500 g of silica gel. Elution with hexane/ether (3:1) yields 20 α -acetoxy-6 β -chloro-9 β ,10 α -pregn-4-en-3-one, m.p. 185—187° (from acetone/isopropyl ether).

The starting material, 3,20 α -diacetoxy-9 β ,10 α -pregna-3,5-diene, can be prepared as follows:

A mixture of 100 ml of isopropenyl acetate and 200 ml of benzene is added dropwise with stirring over a 6 hour period to a boiling solution of 9.0 g of 20 α -hydroxy-9 β ,10 α -pregn-4-en-3-one and 0.9 g of p-toluenesulphonic acid in 400 ml of abs. benzene while 300 ml of benzene are simultaneously distilled off via a Vigreux column. The cooled reaction mixture is then treated with 2 ml of pyridine. The precipitate which separates out is filtered off and the filtrate is evaporated to dryness in vacuum below 40°. There is

obtained 3,20 α - diacetoxy - 9 β ,10 α - pregna-3,5-diene which is directly used for the chlorination.

EXAMPLE 9.

- 5 According to the methods described in Example 2, 20 α - acetoxy - 6 - chloro-9 β ,10 α - pregna - 4,6 - dien - 3 - one yields 20 α - acetoxy - 6 - chloro - 9 β ,10 α -pregna - 1,4,6 - trien - 3 - one, m.p. 145—156° (from ether). $[\alpha]_D^{25} = -247^\circ$.

EXAMPLE 10.

- A mixture of 8.90 g of 20 α - acetoxy - 6 β - chloro - 9 β ,10 α - pregn - 4 - en-3-one, 0.5 g of p-toluenesulphonic acid, 8.5 ml of orthoformic acid ethyl ester and 120 ml of abs. dioxan is held at 25° for 15 hours with the exclusion of light. The reaction mixture is then added over a 15 minute period with stirring to a mixture of 45 g of manganese dioxide, 450 ml of glacial acetic acid and 36 ml of water. The reaction mixture is subsequently stirred at room temperature for 2 hours, poured onto a large amount of ice-water and extracted with methylene chloride. The organic extracts are washed neutral with water, dried with sodium sulphate and evaporated to dryness in vacuum. The residue is chromatographed on silica gel yielding 20 α - acetoxy - 6 - chloro - 9 β ,10 α -pregna - 4,6 - dien - 3 - one on elution with hexane/acetone (9:1). M.p. 159—160° (from acetone/hexane). $[\alpha]_D^{25} = -403^\circ$.

EXAMPLE 11.

- A solution of 5.3 ml of chromyl chloride in 10 ml of methylene chloride is added within 45 minutes with good stirring to a solution of 3.50 g of 20 α - acetoxy - 9 β ,10 α -pregna - 4,6 - dien - 3 - one in 100 ml of methylene chloride cooled to -15°. It is stirred at -15° for an additional 3 hours. The brown precipitate is subsequently filtered off and washed several times with cold methylene chloride. The filter cake is introduced with stirring into a solution of 21 g of sodium acetate and 25.7 g of sodium pyrosulphite in 300 ml of ice-water and 150 ml of ethyl acetate are immediately added. The mixture is stirred for 40 minutes, the organic phase is then separated off and the aqueous phase extracted twice more with ethyl acetate. The combined organic extracts are washed neutral with dilute sodium acetate solution and water, dried with Na₂SO₄ and evaporated in vacuum. The residue is dissolved in 50 ml of dioxan which contains 2% of hydrogen chloride and held at room temperature for 15 hours. For the work-up, the mixture is poured onto ice-water and extracted with ethyl acetate. The extract is washed neutral with dilute sodium bicarbonate solution in water, dried with sodium sulphate and evaporated in vacuum. After chromatography on silica gel and recrystallization from acetone/hexane,

the crude product yields 20 α -acetoxy-6-chloro - 9 β ,10 α - pregna - 4,6 - dien - 3 - one, m.p. 159—160°.

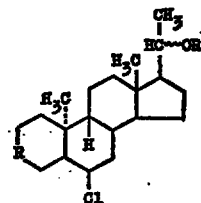
EXAMPLE 12.

Tablets for oral administration can be prepared using the following ingredients:

6 - chloro - 20 α - hydroxy-9 β ,10 α - pregna - 1,4,6-triene - 3 - one	5 mg	70
lactose	60 mg	
starch	33 mg	
talc	1.8 mg	75
magnesium stearate	0.2 mg	
total	100.0 mg	

WHAT WE CLAIM IS:—

1. A 9 β ,10 α -steroid of the formula



I

wherein R is a 3-keto $\Delta^{4,6}$, a 3-keto- $\Delta^{4,6}$, a 3-keto- $\Delta^{1,4}$, a 3-keto- $\Delta^{1,4,6}$, a 3-alkoxy- $\Delta^{3,5}$, a 3-alkoxy- $\Delta^{4,6}$, a 3-acyloxy- $\Delta^{3,5}$, a 3-acyloxy- $\Delta^{4,6}$, a 3-acyloxy- $\Delta^{2,4,6}$ or a 3-hydroxy- $\Delta^{4,6}$ -system and R¹ is hydrogen or acyl.

2. A 9 β ,10 α -steroid as set forth in claim 1, wherein R is a 3-keto- $\Delta^{4,6}$ or a 3-keto- $\Delta^{1,4,6}$ -system and R¹ is hydrogen or alkanoyl containing up to 6 carbon atoms.

3. 6 - Chloro - 3 α ,20 β - dihydroxy-9 β ,10 α - pregna - 4,6 - diene. 90
4. 6 - Chloro - 20 β - hydroxy - 9 β ,10 α -pregna - 4,6 - dien - 3 - one.
5. 6 - Chloro - 20 α - hydroxy - 9 β ,10 α -pregna - 4,6 - dien - 3 - one. 95
6. 6 - Chloro - 20 α - hydroxy - 9 β ,10 α -pregna - 1,4,6 - trien - 3 - one.
7. 6 - Chloro - 20 β - hydroxy - 9 β ,10 α -pregna - 1,4,6 - trien - 3 - one.
8. 6 - Chloro - 20 β - acetoxy - 9 β ,10 α -pregna - 4,6 - dien - 3 - one. 100
9. 6 - Chloro - 20 β - acetoxy - 9 β ,10 α -pregna - 1,4,6 - trien - 3 - one.
10. 6 - Chloro - 3 α ,20 β - diacetoxy-9 β ,10 α - pregna - 4,6 - diene. 105
11. 3 α - Ethoxy - 6 - chloro - 20 β -hydroxy - 9 β ,10 α - pregna - 4,6 - diene.
12. 20 β - Acetoxy - 3 α - ethoxy - 6-chloro - 9 β ,10 α - pregna - 4,6 - diene.
13. 20 α - Acetoxy - 6 β - chloro - 9 β ,10 α -pregn - 4 - en - 3 - one. 110
14. 20 α - Acetoxy - 6 - chloro - 9 β ,10 α -pregna - 1,4,6 - trien - 3 - one.
15. 20 α - Acetoxy - 6 - chloro - 9 β ,10 α -pregna - 4,6 - dien - 3 - one. 115



obtained 3,20 α - diacetoxy - 9 β ,10 α - pregna-3,5-diene which is directly used for the chlorination.

EXAMPLE 9.

- 5 According to the methods described in Example 2, 20 α - acetoxy - 6 - chloro-9 β ,10 α - pregna - 4,6 - dien - 3 - one yields 20 α - acetoxy - 6 - chloro - 9 β ,10 α -pregna - 1,4,6 - trien - 3 - one, m.p. 145—156° (from ether). $[\alpha]_D^{25} = -247^\circ$.

EXAMPLE 10.

- A mixture of 8.90 g of 20 α - acetoxy - 6 β - chloro - 9 β ,10 α - pregn - 4 - en-3-one, 0.5 g of p-toluenesulphonic acid, 8.5 ml of orthoformic acid ethyl ester and 120 ml of abs. dioxan is held at 25° for 15 hours with the exclusion of light. The reaction mixture is then added over a 15 minute period with stirring to a mixture of 45 g of manganese dioxide, 450 ml of glacial acetic and 36 ml of water. The reaction mixture is subsequently stirred at room temperature for 2 hours, poured onto a large amount of ice-water and extracted with methylene chloride. The organic extracts are washed neutral with water, dried with sodium sulphate and evaporated to dryness in vacuum. The residue is chromatographed on silica gel yielding 20 α - acetoxy - 6 - chloro - 9 β ,10 α -pregna - 4,6 - dien - 3 - one on elution with hexane/acetone (9:1). M.p. 159—160° (from acetone/hexane). $[\alpha]_D^{25} = -403^\circ$.

EXAMPLE 11.

- A solution of 5.3 ml of chromyl chloride in 10 ml of methylene chloride is added within 45 minutes with good stirring to a solution of 3.50 g of 20 α - acetoxy - 9 β ,10 α -pregna - 4,6 - dien - 3 - one in 100 ml of methylene chloride cooled to -15°. It is stirred at -15° for an additional 3 hours. The brown precipitate is subsequently filtered off and washed several times with cold methylene chloride. The filter cake is introduced with stirring into a solution of 21 g of sodium acetate and 25.7 g. of sodium pyrosulphite in 300 ml of ice-water and 150 ml of ethyl acetate are immediately added. The mixture is stirred for 40 minutes; the organic phase is then separated off and the aqueous phase extracted twice more with ethyl acetate. The combined organic extracts are washed neutral with dilute sodium acetate solution and water, dried with Na₂SO₄ and evaporated in vacuum. The residue is dissolved in 50 ml of dioxan which contains 2% of hydrogen chloride and held at room temperature for 15 hours. For the work-up, the mixture is poured onto ice-water and extracted with ethyl acetate. The extract is washed neutral with dilute sodium bicarbonate solution in water, dried with sodium sulphate and evaporated in vacuum. After chromatography on silica gel and recrystallization from acetone/hexane,

the crude product yields 20 α -acetoxy-6-chloro - 9 β ,10 α - pregna - 4,6 - dien - 3 - one, m.p. 159—160°.

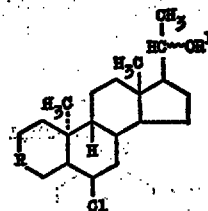
EXAMPLE 12.

Tablets for oral administration can be prepared using the following ingredients:

6 - chloro - 20 α - hydroxy-9 β ,10 α - pregna - 1,4,6-triene - 3 - one	5 mg	70
lactose	60 mg	
starch	33 mg	
talc	1.8 mg	75
magnesium stearate	0.2 mg	
total	100.0 mg	

WHAT WE CLAIM IS:—

1. A 9 β ,10 α -steroid of the formula



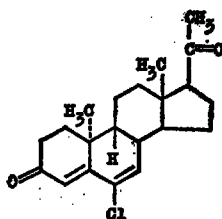
- wherein R is a 3-keto- $\Delta^{4,6}$, a 3-keto- $\Delta^{1,4,6}$, a 3-keto- $\Delta^{1,4}$, a 3-keto- $\Delta^{1,4,6}$, a 3-alkoxy- $\Delta^{3,6}$, a 3-alkoxy- $\Delta^{4,6}$, a 3-acyloxy- $\Delta^{3,6}$, a 3-acyloxy- $\Delta^{4,6}$, a 3-acyloxy- $\Delta^{2,4,6}$ or a 3-hydroxy- $\Delta^{4,6}$ -system and R¹ is hydrogen or acyl.
2. A 9 β ,10 α -steroid as set forth in claim 1, wherein R is a 3-keto- $\Delta^{4,6}$ or a 3-keto- $\Delta^{1,4,6}$ -system and R¹ is hydrogen or alkanoyl containing up to 6 carbon atoms.
3. 6 - Chloro - 3 α ,20 β - dihydroxy-9 β ,10 α - pregna - 4,6 - diene.
4. 6 - Chloro - 20 β - hydroxy - 9 β ,10 α -pregna - 4,6 - dien - 3 - one.
5. 6 - Chloro - 20 α - hydroxy - 9 β ,10 α -pregna - 4,6 - dien - 3 - one.
6. 6 - Chloro - 20 α - hydroxy - 9 β ,10 α -pregna - 1,4,6 - trien - 3 - one.
7. 6 - Chloro - 20 β - hydroxy - 9 β ,10 α -pregna - 1,4,6 - trien - 3 - one.
8. 6 - Chloro - 20 β - acetoxy - 9 β ,10 α -pregna - 4,6 - dien - 3 - one.
9. 6 - Chloro - 20 β - acetoxy - 9 β ,10 α -pregna - 1,4,6 - trien - 3 - one.
10. 6 - Chloro - 3 α ,20 β - diacetoxy-9 β ,10 α - pregna - 4,6 - diene.
11. 3 α - Ethoxy - 6 - chloro - 20 β -hydroxy - 9 β ,10 α - pregna - 4,6 - diene.
12. 20 β - Acetoxy - 3 α - ethoxy - 6-chloro - 9 β ,10 α - pregna - 4,6 - diene.
13. 20 α - Acetoxy - 6 β - chloro - 9 β ,10 α -pregn - 4 - en - 3 - one.
14. 20 α - Acetoxy - 6 - chloro - 9 β ,10 α -pregna - 1,4,6 - trien - 3 - one.
15. 20 α - Acetoxy - 6 - chloro - 9 β ,10 α -pregna - 4,6 - dien - 3 - one.



16. A pharmaceutical preparation comprising a $9\beta,10\alpha$ -steroid as formulated in claim 1 in association with a compatible pharmaceutical carrier.

17. A process for the preparation of the $9\beta,10\alpha$ -steroids formulated in claim 1, which process comprises

(A) treating the $9\beta,10\alpha$ -steroid of the formula

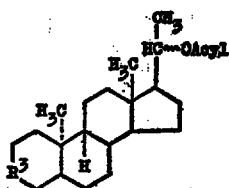


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II

with a reducing agent to give a $9\beta,10\alpha$ -steroid of formula I in claim 1 in which R is a 3-hydroxy- $\Delta^{4,6}$ -system and R¹ is hydrogen or

(B) treating a $9\beta,10\alpha$ -steroid of the formula



15

III

wherein R³ is a 3-acyloxy- $\Delta^{4,6}$ -, or 3-alkoxy- $\Delta^{4,6}$ -, or a 3-keto- $\Delta^{4,6}$ -system,

with a chlorinating agent to give a $9\beta,10\alpha$ -steroid of formula I in claim 1 in which R

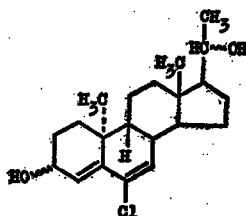
is a 3-keto- $\Delta^{4,6}$ -system and R² is acyl when a $9\beta,10\alpha$ -steroid of formula III in which R³

is a 3-acyloxy- $\Delta^{4,6}$ -, or a 3-alkoxy- $\Delta^{4,6}$ -system is used or a $9\beta,10\alpha$ -steroid of formula I in

claim 1 in which R is a 3-keto- $\Delta^{4,6}$ -system and R¹ is acyl when a $9\beta,10\alpha$ -steroid of formula

III in which R³ is a 3-keto- $\Delta^{4,6}$ -system is used or

(C) selectively oxidizing a 3-hydroxy- $9\beta,10\alpha$ -steroid of the formula

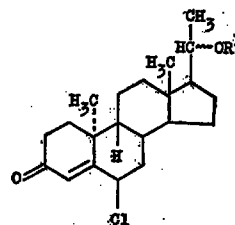


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IV

to the corresponding 3-ketone or

(D) dehydrogenating a Δ^4 - $9\beta,10\alpha$ -steroid of the formula

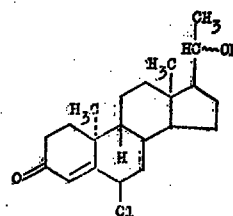


V

wherein R¹ has the significance given in claim 1, 35

or a 6(7)-dehydro derivative thereof in at least one of the positions 1(2) and 6(7) or

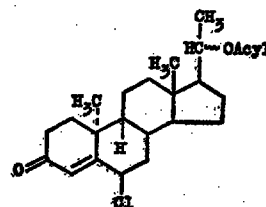
(E) acylating the 20-hydroxy group of a $9\beta,10\alpha$ -steroid of the formula 40



VI

or a 1(2)- or 6(7)-dehydro or 1(2), 6(7)-bis-hydro derivative thereof or

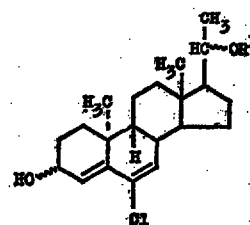
(F) saponifying the $9\beta,10\alpha$ -steroid of the formula 45



VII

or a 1(2)- or 6(7)-dehydro or 1(2), 6(7)-bis-hydro derivative thereof or

(G) acylating a free hydroxy group of a $9\beta,10\alpha$ -steroid of the formula 50



VIII

wherein R¹ has the significance given in claim 1, 55

or

(H) alkylating the 3-hydroxy group of a $9\beta,10\alpha$ -steroid of formula VIII or



- (I) enol-etherifying a $9\beta,10\alpha$ -steroid of formula V or
- (J) enol-esterifying a $9\beta,10\alpha$ -steroid of formula V or a 6(7)-dehydro derivative thereof.
- 5 18. A process as set forth in claim 17, wherein a 6 - chloro - 3,20 - dihydroxy- $9\beta,10\alpha$ - pregna - 4,6 - diene is selectively oxidized to the corresponding 3-ketone.
- 10 19. A process as set forth in claim 17, wherein 6 - chloro - $9\beta,10\alpha$ - pregna - 4,6 - diene - 3,20 - dione is reduced with a complex metal hydride.
- 15 20. A process as set forth in claim 17, wherein a 6 - chloro - 20 - hydroxy- $9\beta,10\alpha$ - pregna - 4,6 - dien - 3 - one is dehydrogenated in the 1(2)-position.
- 20 21. A process as set forth in claim 17, wherein 20α - acetoxy - 6 - chloro - $9\beta,10\alpha$ - pregna-4,6-dien-3-one is dehydrogenated in the 1(2)-position.
- 25 22. A process as set forth in claim 17, wherein 6 - chloro - 20β - hydroxy - $9\beta,10\alpha$ - pregna - 4,6 - dien - 3 - one is acetylated.
- 23. A process as set forth in claim 17, wherein 6 - chloro - 20β - hydroxy - $9\beta,10\alpha$ - pregna - 1,4,6 - trien - 3 - one is acetylated.
- 24. A process as set forth in claim 17, wherein 6 - chloro - $3\alpha,20\beta$ - dihydroxy- $9\beta,10\alpha$ - pregna - 4,6 - diene is acetylated.
- 25. A process as set forth in claim 17, wherein the 3-hydroxy group of 6-chloro- $3\alpha,20\beta$ - dihydroxy - $9\beta,10\alpha$ - pregna - 4,6 - diene is ethylated.
- 26. A process as set forth in claim 17, wherein $3,20\alpha$ - diacetoxy - $9\beta,10\alpha$ - pregna-3,5-diene is chlorinated.
- 27. A process as set forth in claim 17, wherein 20α - acetoxy - 6β - chloro - $9\beta,10\alpha$ - pregn-4-en-3-one is dehydrogenated in the 6(7)-position.
- 28. A process as set forth in claim 17, wherein 20α - acetoxy - $9\beta,10\alpha$ - pregna-4,6-dien-3-one is chlorinated.
- 29. A process for the preparation of the $9\beta,10\alpha$ -steroids formulated in claim 1, substantially as hereinbefore described with reference to Examples 1 to 11.
- 30. $9\beta,10\alpha$ -Steroids as formulated in claim 1, when prepared by the process claimed in any one of claims 17 to 29 inclusive.

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