

1063.816

PATENT SPECIFICATION

NO DRAWINGS

1063.816



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COMPLETE SPECIFICATION

10 α -Methyl Steroids

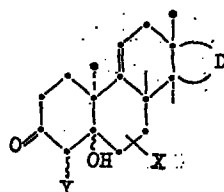
We, F. HOFFMANN-LA ROCHE & Co., Aktiengesellschaft, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following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

The present invention relates to 10 α -methyl steroids. More particularly, the invention is concerned with a process for the manufacture of 9 α 10 α - and 9 β ,10 α -steroids of the androstane and pregnane series and with novel steroids useful in said process.

Natural steroids possess a 9 α ,10 β -stereochemical configuration. Steroid compounds possessing the unnatural 9 α ,10 α - or 9 β ,10 α -configuration represent a pharmaceutically valuable class of compounds which, even though numerous members are known, cannot be obtained except by cumbersome and lengthy procedures. In fact, the only known methods for obtaining steroids possessing the unnatural 9 β ,10 α -configuration involve at least one photochemical reaction. Such photochemical reactions involve irradiation with ultraviolet light of strong intensity for long periods of time and, in comparison with purely chemical reactions, are very inefficient and give only small yields.

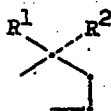
According to the process provided by the invention, 9 α ,10 α - and 9 β ,10 α -steroids of the androstane and pregnane series are manufactured by catalytically hydrogenating a 10 α - $\Delta^{9(11)}$ -steroid of the androstane or pregnane series and, if desired, introducing a double bond into the 4,5-position of the hydrogenation product.

One class of useful starting materials comprises the 5-hydroxy-10 α -androst(or pregn)-9(11)-en-3-ones. Preferred compounds within this class are those of the formula



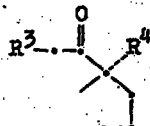
I

wherein X represents a hydrogen or halogen atom or a lower-alkyl group in the 6- or 7-position, Y is a hydrogen atom or a lower-alkyl group and D represents a moiety of the formula



Ia

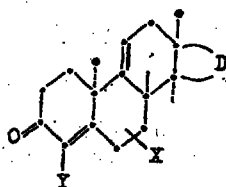
or



Ib

in which R^1 represents a hydroxy or esterified hydroxy group, R^2 represents a hydrogen atom or a lower-alkyl group or R^1 together with R^2 represents an oxo group, R^3 represents a hydrogen or halogen atom or a hydroxy or esterified hydroxy group and R^4 represents a hydrogen or halogen atom or a lower-alkyl, hydroxy or esterified hydroxy group.

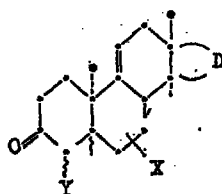
Another class of useful starting materials comprises the 10α -androsta(or pregna)-4,9(11)-dien-3-ones. Preferred compounds within this class are those of the formula



II

wherein X, Y and D have the significance given earlier.

Other preferred starting materials are those of the formula

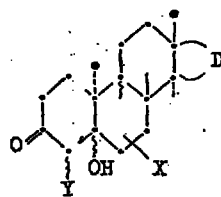


III

wherein X, Y and D have the significance given earlier.

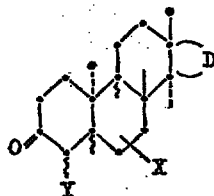
Especially preferred starting materials are those in which X represents a hydrogen atom or a lower-alkyl group in the 6- or 7-position and those in which X represents a halogen atom in the 7-position.

The catalytic hydrogenation of starting materials of formula I leads to $9\alpha,10\alpha$ - and $9\beta,10\alpha$ -steroids of the formula



IV'

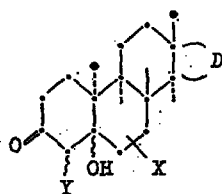
wherein X, Y and D have the significance given earlier, and the catalytic hydrogenation of the starting materials of formulae II and III leads to $9\alpha,10\alpha$ - and $9\beta,10\alpha$ -steroids of the formula



V

wherein X, Y and D have the significance given earlier.

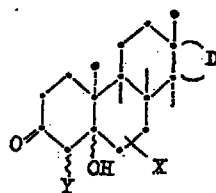
The $9\alpha,10\alpha$ - and $9\beta,10\alpha$ -steroids of formula IV may be respectively formulated thus



IVa

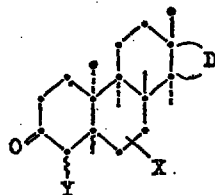
10 and

10



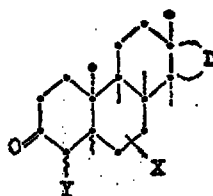
IVb

and the $9\alpha,10\alpha$ - and $9\beta,10\alpha$ -steroids of formula V may be respectively formulated thus



Va

and



Vb

In formulae IVa, IVb, Va and Vb, X, Y and D have the significance given earlier.

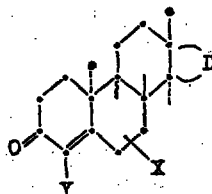
The catalytic hydrogenation involves the saturation of the 9(11)-double bond and of any 4,5-double bond of the starting materials. The hydrogen atom inserted at the 9-position can assume either the 9 α - or 9 β -stereoconfiguration. The use of starting materials of formulae I and III wherein the 5-hydroxy substituent or the 5-hydrogen atom as the case has the 5 α -configuration favours the formation of 9 α -hydrogenation products, whereas the use of starting materials of formulae I and III containing a 5 β -hydroxy substituent or a 5 β -hydrogen atom as the case may be favours the insertion of a 9 β -hydrogen atom.

The catalytic hydrogenation can suitably be effected by hydrogenation in the presence of a metal catalyst; for example, a noble metal catalyst such as platinum, palladium, ruthenium or rhodium. The hydrogenation can be effected in neutral, acid or alkaline medium. Thus, for example, the hydrogenation can be effected with platinum in glacial acetic acid, if desired with the addition of a strong acid (for example, a mineral acid such as a hydrohalic acid such as hydrobromic acid) or with platinum or palladium/carbon in an organic solvent such as ethanol, hexane or dioxan, if desired with the addition of an acid or a base such as an alkali-metal hydroxide or an alkaline-earth-metal hydroxide (for example, potassium hydroxide or sodium hydroxide). Though noble metal catalysts are preferred, other metal catalysts such as RANEY-nickel or RANEY-cobalt are also suitable. For these latter catalysts it is especially suitable to effect the hydrogenation in neutral or alkaline media, for example, in a lower-alkanol such as ethanol or methanol, with or without addition of a base such as an alkaline-earth-metal hydroxide or an alkali-metal hydroxide such as potassium hydroxide or sodium hydroxide. The hydrogenation can be effected at room temperature and normal pressure. If desired, however, it can also be carried out at elevated temperatures and/or at elevated pressures.

Besides the foregoing influence of the stereoconfiguration at the 5-position on the stereospecificity of the hydrogenation of the 9-position, it has been found that hydrogenation by means of platinum in acidic medium (especially in glacial acetic acid) favours the formation of the 9 β -configuration, whereas the use of platinum or other noble metal catalysts in a neutral medium results predominantly in the formation of products having the 9 α -configuration. Moreover, the amount of the catalyst has also been found to affect the selectivity of the hydrogenation. Thus, the greater the amount of, for example, platinum catalyst used the greater will be the proportion of hydrogenation product containing the 9 β -configuration. For example, it has been found that the decrease of the starting material-to-catalyst weight ratio from 1:1 to 1:5 raises the amount of the 9 β -isomer by a factor of 2.

The separation of the hydrogenation products into the $9\alpha,10\alpha$ -fractions and the $9\beta,10\alpha$ -fractions can be effected by conventional means; for example, by crystallization and/or by chromatography (e.g. on alumina or silica gel).

A double bond can be introduced into the 4,5-position of the hydrogenation products of formula IV by dehydration. This yields a $9\alpha,10\alpha$ - or $9\beta,10\alpha$ -steroid of the formula



VI

wherein X, Y and D have the significance given earlier.

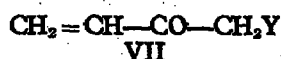
The dehydration of the steroids of formula IV can be effected either under basic or under acidic catalytic dehydration conditions. Thus, it can be effected in either basic solution or acidic solution. An example of a suitable base in an organic solvent is, for example, an alkali-metal or alkaline-earth-metal hydroxide or lower-alkoxide in a lower-alkanol (for example potassium hydroxide in methanol or sodium ethoxide in ethanol). Especially preferred is an alkali-metal or alkaline-earth-metal lower-alkoxide in a lower-alkanol. As an acidic solution there can be used, for example, *paratoluene*-sulphonic acid in toluene or a carboxylic acid (e.g. a lower-alkanoic acid such as acetic acid). When the dehydration is conducted under alkaline conditions, steroids of formula IV containing a 7-halo substituent (e.g. chlorine) are converted into the corresponding $\Delta^{4,6}$ unsaturated steroids. Thus, for example $9\beta,10\alpha$ -pregna-4,6-diene-3,20-dione is obtained from a 5-hydroxy-7-chloro- $9\beta,10\alpha$ -pregnane-3,20-dione.

A double bond can be introduced into the 4,5-position of the hydrogenation products of formula V by selective dehydrogenation in the 4,5-position. This selective 4,5-dehydrogenation can be effected by procedures which are known for the conversion of *cyclohexanone* derivatives into the corresponding *cyclohexenone* and *cyclohexadienone* derivatives; for example by treatment of the hydrogenation products of formula V with 2,3-dichloro-5,6-dicyano-benzoquinone in inert organic solvents (such as dioxan or benzene) at elevated temperature or at room temperature with a catalytic amount of hydrochloric acid. Selenium dioxide in a lower-alkanol (preferably in boiling tertiary butanol) or benzene or benzene in admixture with acetic acid or pyridine or with a little water may also be used.

Another route to the desired Δ^4 -steroids involves a two-step sequence of halogenation and dehydrohalogenation. The halogenation of steroids of formula III can be effected using halogenating agents such as bromine or sulphuryl chloride. Bromination is especially preferred. The bromination is suitably effected by treatment with bromine at room temperature or below, preferably at ice-temperature or below. Suitably it is conducted in an organic medium; for example, an organic acid (such as acetic acid), an ether (such as an anhydrous ether, dioxan or tetrahydro-furan) or a chlorinated organic solvent (such as methylene chloride, chloroform, carbon tetrachloride) with the addition of hydrogen bromide as a catalyst.

The subsequent dehydrohalogenation is preferably conducted under mild dehydrohalogenating conditions; for example, using an alkali-metal carbonate (e.g. lithium carbonate) or an alkali-metal halide (e.g. a lithium halide) in an organic solvent such as a di(lower alkyl)-formamide, or with an organic base such as collidine or pyridine.

The starting materials of the general formula I can be prepared by condensing a desA-androst-9-en-5-one or a desA-pregn-9-en-5-one with a lower-alkyl vinyl ketone of the general formula



wherein Y has the significance given earlier.

The condensation is suitably effected at below or above room temperature; for example, at the reflux temperature of the reaction medium or at ice-temperature (0°C) or below. Moreover, the condensation is suitably effected in an organic medium. Preferably the medium is a lower-alkanol (such as methanol or ethanol) or another non-ketonic organic solvent such as an ether (e.g. dioxan), an aromatic hydrocarbon (e.g. benzene, toluene, xylene), or an organic acid (such as acetic acid). It is suitable to catalyze the condensation, and this can be effected by using a catalyst such as an alkali-metal lower-alkoxide (for example, sodium ethoxide), an alkali-metal hydroxide, a quaternary ammonium hydroxide (such as benzyl trimethyl ammonium hydroxide) or *paratoluene-sulphonic acid*.

The following compounds can be used in place of the lower-alkyl vinyl ketone of formula VII for carrying out the condensation: 1,3-dichloro-but-2-ene, 1,3-dichloro-pent-2-ene, 1-bromo-butan-3-one, 1-bromo-butan-3-one lower-alkylene ketal, 1-bromo-butan-3-ol, esterified 1-bromo-butan-3-ol, etherified 1-bromo-butan-3-ol, 1-bromo-pentan-3-one, 1-bromo-pentan-3-one lower-alkylene ketal, 1-bromo-pentan-3-ol, esterified 1-bromo-pentan-3-ol, etherified 1-bromo-pentan-3-ol, 1-dialkylamino-3-butanone, 1-dialkylamino-3-pentanone and quaternary ammonium salts of the last two compounds.

When a lower-alkyl vinyl ketone, 1-bromo-butan-3-one or 1-bromo-pentan-3-one is used in the condensation, ring closure to ring A (containing a 3-oxo substituent) of the desired 10 α -steroid of formula I occurs simultaneously with the condensation. However, when 1,3-dichloro-but-2-ene, 1,3-dichloro-pent-2-ene, 1-bromo-butan-3-one lower-alkylene ketal, 1-bromo-butan-3-ol, 1-bromo-butan-3-ol ether, esterified 1-bromo-butan-3-ol, 1-bromo-pentan-3-one lower-alkylene ketal, 1-bromo-pentan-3-ol, 1-bromo-pentan-3-ol ether or esterified 1-bromo-pentan-3-ol is used in the condensation, a subsequent step to generate the 3-oxo substituent is required. When 1-bromo-butan-3-ol or 1-bromo-pentan-3-ol is used in the condensation, the oxo substituent can be generated by oxidation and, for this purpose, it is suitable to use oxidation methods which are known *per se*; for example, oxidation by means of chromic acid or chromium trioxide in acetic acid. When esterified or etherified 1-bromo-butan-3-ol or esterified or etherified 1-bromo-pentan-3-ol is used as the reaction partner hydrolysis of the esterified or etherified hydroxy group should be effected prior to oxidation. Suitable ester-forming residues are, for example, those of carboxylic acids (e.g. a lower-alkanoic acid such as acetic acid, or benzoic acid) and hydrolysis of the condensation products obtained by using such 1-bromo-pentan-3-ol esters is suitably carried out by alkaline hydrolysis (e.g. using an aqueous alkali-metal hydroxide such as aqueous sodium hydroxide). Suitable ethers are, for example, lower-alkyl ethers (i.e. 3-methyl, 3-ethyl or like ethers) and these are suitably hydrolyzed by acid hydrolysis (e.g. by using an aqueous mineral acid such as hydrochloric acid, sulphuric acid or the like). When a 1-bromo-butan-3-one lower-alkylene ketal or a 1-bromo-pentan-3-one lower-alkylene ketal is used in the condensation, mild acid hydrolysis of the ketal moiety results in generation of the 3-oxo substituent. Finally, when 1,3-dichloro-but-2-ene or 1,3-dichloro-pent-2-ene is used in the condensation the 3-oxo substituent can be generated by treatment with a concentrated mineral acid, preferably with a strong acid such as hydrochloric acid or sulphuric acid. It will be appreciated that when a condensation component based on butane (i.e. having a four carbon atom skeleton) is used, a starting material of formula I wherein Y is hydrogen is obtained. Similarly, when a condensation component based on pentane is used, a starting material of formula I wherein Y is methyl is obtained.

Starting materials of formula II can be obtained from the starting materials of formula I by dehydration. This dehydration can be effected in the same manner as described earlier for the dehydration of a hydrogenation product of formula IV to a steroid of formula VI.

Starting materials of formula III can be obtained from starting materials of formula II by selective reduction. This selective reduction is suitably effected using an (alkali-metal)/ammonia reduction technique. Thus, reduction of the 10 α -androst-4,9(11)-dien-3-ones or 10 α -pregna-4,9(11)-dien-3-ones of formula II with an (alkali metal)/ammonia reducing agent such as lithium/ammonia results in selective reduction of the double bond linking the carbon atoms in the 4- and 5-positions and yields a mixture of 9(11)-en-3-one-5 α ,10 α -steroids and 9(11)-en-3-one-5 β ,10 α -steroids of formula III. Said mixture can be separated by conventional means and the so-obtained starting materials of formula III can then be subjected to the catalytic hydrogenation of the process of the invention.

The desA-androst(or pregn)-9-en-5-ones mentioned earlier can be prepared, for example, from steroids of the androstane or 17 β -pregnane series by ozonolysis and

pyrolysis of the 3-keto-androst-4-ene or 3-keto-pregn-4-ene and introducing into the resulting desA-androstan-5-one or desA-pregnan-5-one a 9-double bond; for example by a two-step sequence of bromination and dehydrobromination.

The catalytic hydrogenation of the process provided by the invention may also result in reduction of reducible substituents present on the steroidal structure of the starting materials. For example, reduction of keto groups in the 3-, 17- and/or 20-positions may occur. If reduction of reducible groups is undesirable, said groups can be protected prior to the hydrogenation; for example, if reduction of keto groups to hydroxy groups is undesirable, then the keto groups can be protected by ketalization as described earlier. Thus, 3,3;17,17-bis(ethylenedioxy)-10 α -androsta-4,9(11)-diene can be subjected to hydrogenation in place of 10 α -androsta-4,9(11)-diene-3,17-dione. Alternatively, when the keto groups are not protected and they are converted into hydroxy groups during the hydrogenation, said hydroxy groups can be reconverted into keto groups by a conventional oxidation technique; for example, by oxidation with chromium trioxide in an organic solvent such as glacial acetic acid, N,N-dimethylformamide or acetone or by an OPPENAUER oxidation.

The products produced by carrying out the process of this invention can be used, for example, as anabolic, progestational or salt-retaining agents or as intermediates for the manufacture of pharmaceutically valuable compounds.

As used in this specification the term "lower" denotes that the groups prefixed by this term contain up to 7 carbon atoms. The term "lower alkyl" comprehends both straight and branched chain alkyl groups. The acetyl group may be mentioned as an example of a lower-alkanoyl group. The term "esterified hydroxy" includes lower-alkanoyloxy groups such as acetoxy. Halogen comprehends iodine, bromine, chlorine and fluorine.

The hydrogenation products of formula IV are novel and it will be appreciated that they also form part of this invention. The preferred hydrogenation products of formula IV are 17 α -(lower alkyl)-5,17 β -dihydroxy-9 α ,10 α -androstan-3-ones (especially 17 α -ethyl-5 α ,17 β -dihydroxy-9 α ,10 α -androstan-3-one), 5,17 β -dihydroxy-9 α ,10 α -androstan-3-ones (especially 5 α ,17 β -dihydroxy-9 α ,10 α -androstan-3-one) and 5-hydroxy-9 α ,10 α -pregnane-3,20-diones (especially 5 α -hydroxy-9 α ,10 α -pregnane-3,20-dione).

The starting materials of formulae I, II and III are novel and it will be appreciated that both they and the process for their preparation form part of this invention. The preferred starting materials of formula I are 5-hydroxy-10 α -androst-9(11)-ene-3,17-diones (especially 5 α -hydroxy-10 α -androst-9(11)-ene-3,17-dione), 5,17 β -dihydroxy-10 α -androst-9(11)-en-3-ones (especially 5 α ,17 β -dihydroxy-10 α -androst-9(11)-en-3-one), 17 α -(lower alkyl)-5,17 β -dihydroxy-10 α -androst-9(11)-en-3-ones (especially 17 α -ethyl-5 α ,17 β -dihydroxy-10 α -androst-9(11)-en-3-one) and 5-hydroxy-10 α -pregnadihydroxy-10 α -androst-9(11)-en-3-ones (especially 5 α -hydroxy-10 α -pregnadihydroxy-10 α -androst-9(11)-en-3-one) and 5-hydroxy-10 α -pregn-9(11)-ene-3,20-diones (especially 5 α -hydroxy-10 α -pregn-9(11)-ene-3,20-dione). The preferred starting materials of formula II are 10 α -androsta-4,9(11)-diene-3,17-dione, 17 α -(lower alkyl)-17 β -hydroxy-10 α -androsta-4,9(11)-dien-3-ones (especially 17 α -ethyl-17 β -hydroxy-10 α -androsta-4,9(11)-dien-3-one) and 10 α -pregna-4,9(11)-diene-3,20-dione. The preferred starting materials of formula III are 5 α ,10 α -androst-9(11)-ene-3,17-dione, 5 β ,10 α -androst-9(11)-ene-3,17-dione, 10 α -androst-9(11)-en-17 β -ol-3-one, 5 β ,10 α -androst-9(11)-en-17 β -ol-3-one, 5 α ,10 α -pregn-9(11)-ene-3,20-dione and 5 β ,10 α -pregn-9(11)-ene-3,20-dione.

In order that the process provided by the invention may be more easily understood and readily carried into effect, the following Examples are given by way of illustration:

EXAMPLE 1.

A) The preparation of the starting material:

To a solution of 4.5 g of desA-pregn-9-ene-5,20-dione in 150 ml of absolute ethanol cooled in an ice-salt bath was first added a solution of 1.15 g of sodium ethoxide in 70 ml of absolute ethanol, and then 4.5 ml of freshly distilled methyl vinyl ketone were added dropwise. The reaction mixture was left overnight in a refrigerator (at +2°), then acidified with glacial acetic acid and diluted with a large volume of ether (2 litres). The ether solution was washed with 2N sodium carbonate solution, water, dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residue was chromatographed on a silica gel column. The fractions eluted with 3 per cent ethyl acetate in benzene were combined and evaporated. The

residue was crystallized from ether, yielding 10 α -pregna-4,9(11)-diene-3,20-dione of melting point 162°—167°C [α]_D²⁵ = -60° (c=0.10 in dioxan).

The eluates with 10 per cent ethyl acetate in benzene gave crystalline 5 α -hydroxy-10 α -pregn-9(11)-ene-3,20-dione of melting point 197°—198.5°C [after recrystallization from (ethyl acetate)/(petroleum ether)]; [α]_D²⁵ = +88° (c=1, chloroform).

B) The process:

A suspension of 1.5 g of platinum dioxide in a solution of 330 mg of 5 α -hydroxy-10 α -pregn-9(11)-ene-3,20-dione in 60 ml of glacial acetic acid was hydrogenated at room temperature and 50 pounds per square inch pressure for 6 hours. The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The crystalline residue was dissolved in 200 ml of methylene chloride and, after addition of 9 ml 2 per cent chromium trioxide in 90 per cent acetic acid was stirred at room temperature overnight. It was then diluted with 300 ml of methylene chloride and washed with 10 per cent aqueous sodium hydrogen sulphite and water, dried over anhydrous sodium sulphate and concentrated *in vacuo* to dryness. Crystallization of the residue from acetone gives 5 α -hydroxy-9 α ,10 α -pregnane-3,20-dione of melting point 217°—220°C; [α]_D²⁵ +86° (C=1, methanol).

EXAMPLE 2.

A solution of 195 mg of 5 α -hydroxy-9 α ,10 α -pregnane-3,20-dione and one mol equivalent of sodium ethoxide in 30 ml of absolute ethanol was heated under reflux for 48 hours. It was acidified with glacial acetic acid and diluted with 1 litre of ether. The cloudy solution was washed with six 50 ml portions of 2-N sodium carbonate solution, then with water, dried over anhydrous sodium sulphate and concentrated *in vacuo* to dryness. The crystalline residue was chromatographed on a silica gel column with 3 per cent ethyl acetate in benzene to give 10 α -progesterone of melting point 193.5°—195°C (from ether); [α]_D²⁵ -125.6° (c=0.5 in chloroform).

EXAMPLE 3.

285 mg of 10 α -androst-4,9(11)-diene-3,17-dione were dissolved in 20 ml of glacial acetic acid, mixed with a suspension of 100 mg of finely divided platinum in 10 ml of glacial acetic acid and finally hydrogenated at 25°C at normal pressure in a hydrogenation apparatus equipped with a magnetic stirrer. The hydrogenation was interrupted when 105.8 ml of hydrogen had been absorbed. The hydrogenation solution was filtered, the filtrate concentrated *in vacuo* to 5 ml, mixed with a solution of 250 mg of chromium trioxide in 2.5 ml of 90 per cent glacial acetic acid (in order to effect reoxidation of the hydroxy group now present in both the 3- and 17-positions to the keto group) and the reaction mixture maintained for 2.5 hours at 55°C. Then 5 ml of ethanol were added to the mixture which was warmed for a further 10 minutes at 55°C, poured into water and extracted three times, each time with 50 ml of benzene. The combined benzenic extracts were then washed five times, each time with 50 ml of water, dried over sodium sulphate, filtered, concentrated and evaporated *in vacuo* at 50°C to dryness. The resulting oily residue was dissolved in 30 ml of (petroleum ether)/benzene (9:1) and chromatographed on a column of 28 g of aluminium oxide (neutral, activity III). The (petroleum ether)/benzene (1:2) and (1:4) eluates contained, as established by thin layer chromatographic analysis, the 9 α ,10 α -isomer, namely 5 α ,9 α ,10 α -androstane-3,17-dione. The residue obtained upon evaporation of this eluate, yielded crystals of said product which, upon recrystallization from petroleum ether, melted at 133°—133.5°C [α]_D²⁵ +88° (c=0.103 in dioxan).

The (petroleum ether)/benzene (1:9) and the benzene eluates contained, as established by thin layer chromatographic analysis, the 9 β ,10 α -isomer, namely 5 β ,9 β ,10 α -androstane-3,17-dione. The residue obtained upon evaporation of this eluate yielded, upon recrystallization from acetone/(petroleum ether), said product in purified form. This melted at 130°—131°C [α]_D²⁵ +48° (c=0.107 in dioxan).

EXAMPLE 4.

According to the method described earlier, a mixture of 100 mg of 10 α -androst-4,9(11)-diene-3,17-dione in 30 ml of glacial acetic acid was hydrogenated with platinum catalyst prepared by hydrogenation of 500 mg of platinum oxide. The hydrogenation was interrupted after 37.2 ml of hydrogen had been absorbed. The hydrogenated solution was then filtered and the filtrate concentrated to 2 ml. After the addition of 50 mg of chromium trioxide in 0.5 ml of 90 per cent acetic acid, the mixture was permitted to stand at room temperature for 2.5 days. The work-up yielded the crude product in the form of an oil which soon crystallized. By chromatographic

purification on 15 g of aluminium oxide and crystallization, there was obtained 5 β ,9 β ,10 α -androstane-3,17-dione (melting point 131°—132°C) and also 5 α ,9 α ,10 α -androstane-3,17-dione (melting point 133°—134°C).

EXAMPLE 5.

A) *The preparation of the starting material:*

The starting material was prepared as described in Example 1 A.

B) *The process:*

135 mg of 10 α -pregna-4,9(11)-diene-3,20-dione were dissolved in 9 ml of pure ethanol and added to a prehydrogenated suspension of 200 mg of palladium/carbon (5 per cent) in 5 ml of ethanol. The mixture was hydrogenated until saturation at room temperature and normal pressure. The absorption of 2 mol equivalents of hydrogen (27 ml of hydrogen) occurred very quickly in the course of the first 0.5 hour. At the end of 1 hour, the hydrogenation was interrupted and the hydrogenated solution separated from the catalyst and evaporated. Chromatographic separation of the crystalline residue on a column of 11 g of aluminium oxide (neutral, activity III) yielded in the (petroleum ether)/benzene (1:4) and (1:2) fractions, 5 α ,9 α ,10 α -pregnane-3,20-dione which, after a two-fold recrystallization, melted at 164°—165°C. The (petroleum ether)/benzene (1:1) and the benzene eluates contained 5 β ,9 β ,10 α -pregnane-3,20-dione melting at 125°—126°C.

EXAMPLE 6.

A) *The preparation of the starting material:*

7.454 g of 17 α -ethyl-17 β -hydroxy-desA-androst-9-en-5-one were added to a solution of sodium ethoxide (prepared from 654 mg of sodium and 630 ml of absolute ethanol) and, after cooling in an ice-salt bath, 7.5 ml of freshly distilled methyl vinyl ketone were introduced dropwise into the mixture. The mixture was then kept for 90 hours at -5°C. After addition of 2 ml of glacial acetic acid, the solution was concentrated to a small volume and diluted with 2 litres of ether. The ether solution was washed with 2-N sodium carbonate solution, water, dried over anhydrous sodium sulphate and concentrated to dryness *in vacuo*. The oily residue was chromatographed on a silica gel column. The fractions eluted with 5 and 10 per cent ethyl acetate in benzene were combined and gave starting conjugated ketone. The eluates eluted using 20 per cent ethyl acetate in benzene gave crystalline 17 α -ethyl-5 α ,17 β -dihydroxy-10 α -androst-9(11)-en-3-one of melting point 200°—202°C after recrystallization from acetone; $[\alpha]_D^{25} = -4.40$ ($c = 0.5$ in methanol).

A solution of 3.2 g of 17 α -ethyl-5 α ,17 β -dihydroxy-10 α -androst-9(11)-en-3-one in 25 ml of absolute ethanol was combined with a solution of sodium ethoxide prepared from 0.23 g of sodium and 25 ml of absolute ethanol. The reaction mixture was then left for 4 hours at room temperature. Then, after addition of 1 ml of glacial acetic acid, it was diluted with 1 litre of ether. The ether solution was washed with 2-N sodium carbonate solution and with water, then dried over anhydrous sodium sulphate and concentrated to dryness *in vacuo*. The residue was chromatographed on a silica gel column with 7.5 per cent ethyl acetate in benzene. The crystalline fractions were combined and, after recrystallization from ether, gave 17 α -ethyl-17 β -hydroxy-10 α -androst-4,9(11)-dien-3-one of melting point 184.5°—185.5°C $[\alpha]_D^{25} = -134.3^\circ$ ($c = 0.28$ in methanol).

B) *The process:*

314 mg of 17 α -ethyl-10 α - $\Delta^9(11)$ -testosterone were dissolved in 31 ml of glacial acetic acid and hydrogenated using 300 mg of platinum catalyst. The crude hydrogenation product was then treated with chromium trioxide. Chromatography of the reaction product on alumina gave 17 α -ethyl-5 β ,9 β ,10 α -androst-17 β -ol-3-one of melting point 123°—124°C, $[\alpha]_D^{25} = -47^\circ$ (in dioxan), 17 α -ethyl-5 α ,9 α ,10 α -androst-17 β -ol-3-one of melting point 204°—205°C, $[\alpha]_D^{25} = -19^\circ$ (in dioxan) and a small amount of 17 α -ethyl-5 α ,9 β ,10 α -androst-17 β -ol-3-one of melting point 124°—125°C, $[\alpha]_D^{25} = +5^\circ$ (in dioxan).

EXAMPLE 7.

A) *The preparation of the starting material:*

285 mg of 10 α -androst-4,9(11)-diene-3,17-dione in 30 ml of ethanol were hydrogenated using 100 mg of platinum at room temperature and normal pressure. The hydrogenation was interrupted after the absorption of 69.3 ml of hydrogen. The hydrogenated solution was filtered, the filtrate concentrated to dryness *in vacuo*,

dissolved in 5 ml of glacial acetic acid and, after the addition of 135 mg of chromium trioxide, dissolved in 1.35 ml of 90 per cent acetic acid, and then permitted to stand at room temperature for 22 hours. The work-up yielded a crude product melting at 160°—170°C which, upon crystallization from acetone/hexane, yielded purified 5 α ,10 α -androst-9(11)-ene-3,17-dione melting at 174°—176°C.

B) *The process:*

100 mg of 5 α ,10 α -androst-9(11)-ene-3,17-dione were hydrogenated with platinum in glacial acetic acid and reoxidized with chromium trioxide in 90 per cent acetic acid. The chromatographic purification and crystallization yielded purified 5 α ,9 α ,10 α -androstane-3,17-dione and 5 α ,9 β ,10 α -androstane-3,17-dione.

EXAMPLE 8.

A) *The preparation of the starting material:*

A solution of 500 mg of 10 α -androst-4,9(11)-diene-3,17-dione in 50 ml of tetrahydrofuran was added under reflux [acetone/(dry ice) condenser] in the course of 3 minutes with stirring to a solution of 100 mg of lithium in 100 ml of liquid ammonia. Thereafter, the resulting reaction mixture was cautiously treated with 5 g of ammonium chloride, added to 100 ml of ether and then immediately evaporated at 25°C. The residual solution was washed with water, dried over sodium sulphate, filtered and evaporated to dryness *in vacuo*, whereby a crude amorphous reaction product was obtained. This was chromatographed on 20 g of aluminium oxide (neutral, activity III). The (petroleum ether)/benzene (1:1) and (1:2) eluates yielded 5 β ,10 α -androst-9(11)-ene-3,17-dione which, upon crystallization from hexane, melted at 132°—134°C.

B) *The process:*

89 mg of 5 β ,10 α -androst-9(11)-ene-3,17-dione were hydrogenated with platinum in glacial acetic acid and reoxidized. Chromatography of the resulting crude product yielded, besides 5 β ,9 α ,10 α -androstane-3,17-dione, 5 β ,9 β ,10 α -androstane-3,17-dione which, after crystallization from diisopropyl ether, melted at 131°—132°C.

EXAMPLE 9.

A) *The preparation of the starting material:*

The starting material was obtained from benzene and benzene/ether (9:1) eluates of the reaction product obtained in Example 8A. These benzene and benzene-ether (9:1) eluates yielded 5 β ,10 α -androst-9(11)-en-17 β -ol-3-one melting at 170°—173°C after crystallization from benzene/(isopropyl ether).

B) *The process:*

100 mg of 5 β ,10 α -androst-9(11)-ene-17 β -ol-3-one were hydrogenated with platinum in glacial acetic acid and reoxidized with chromium trioxide. The chromatographic purification yielded 5 β ,9 β ,10 α -androstane-3,17-dione melting at 131°—132°C after crystallization from acetone/hexane.

EXAMPLE 10.

A) *The preparation of the starting material:*

313 mg of 10 α -pregna-4,9(11)-diene-3,20-dione dissolved in 20 ml of ethanol were hydrogenated at room temperature and normal pressure using 100 mg of platinum. The hydrogenation was terminated after the absorption of 27 ml of hydrogen. The hydrogenated solution was filtered and evaporated *in vacuo* to dryness. The crystalline residue melting at 151°—156°C was established as a single substance by thin-layer chromatography. After several recrystallizations from acetone/hexane, there was obtained 5 α ,10 α -pregn-9(11)-ene-3,20-dione melting at 167°—168°C.

B) *The process:*

230 mg of 5 α ,10 α -pregn-9(11)-ene-3,20-dione dissolved in 20 ml of glacial acetic acid were mixed with a suspension of platinum catalyst obtained by hydrogenation of 100 mg of platinum oxide in 5 ml of glacial acetic acid, and the mixture then hydrogenated until saturation. The foam obtained after removal of the catalyst by filtration and evaporation of the filtrate was dissolved in 10 ml of acetone and then, with stirring at 0°C, 0.3 ml of JONES reagent (J. Chem. Soc. 1946: 39) added thereto. After the reaction time of 4 minutes, the mixture was poured into an ice/(sodium bicarbonate) mixture and extracted with ether/(methylene chloride) (3:1) and the organic phase washed until neutral with water. It was then evaporated and the residue chromatographically separated yielding a crystalline residue which, upon a two-fold

recrystallization from acetone/hexane, gave purified 5 α ,9 α ,10 α -pregnane-3,20-dione melting at 164°—165°C. From subsequent fractions, 5 α ,9 β ,10 α -pregnane-3,20-dione melting at 105°—106°C was obtained.

EXAMPLE 11.

A) *The preparation of the starting material:*

A solution of 200 mg of 10 α -pregna-4,9(11)-diene-3,20-dione in 28 ml of ether/dioxan (1:1) was added under reflux [acetone/(dry-ice) condenser] in the course of 3 minutes with stirring to a solution of 150 mg of lithium in 100 ml of liquid ammonia. After 0.5 hour, the blue-coloured reaction mixture was cautiously treated with 5 g of ammonium chloride, added to 150 ml of ether and then immediately evaporated at 25°C. The residual solution was washed with water, dried over sodium sulphate, filtered and evaporated to dryness *in vacuo*. The resulting oily crude product was oxidized with 0.17 ml of JONES reagent in 4 ml of acetone at 0°C and, after the usual work-up, the resulting crystals were chromatographed on 9 g of aluminium oxide (neutral, activity III). The hexane/benzene (4:1) eluate yielded at first, 5 α ,10 α -pregn-9(11)-ene-3,20-dione. The more polar eluates yielded 5 β ,10 α -pregn-9(11)-ene-3,20-dione which, after crystallization from acetone/hexane, melted at 176°—178°C.

B) *The process:*

50 mg of 5 β ,10 α -pregn-9(11)-ene-3,20-dione were hydrogenated with platinum in glacial acetic acid and reoxidized. Chromatography of the so-obtained crude product yielded 5 β ,9 β ,10 α -pregnane-3,20-dione which, upon crystallization from (methylene chloride)/(isopropyl ether), melted at 125°C. 5 β ,9 α ,10 α -Pregnane-3,20-dione was also obtained.

EXAMPLE 12.

A solution of 1.056 g of bromine in 10 ml of acetic acid was added within 5 minutes to a well stirred solution of 1.9 g of 5 β ,9 β ,10 α -pregnane-3,20-dione in 20 ml of acetic acid, which contained 0.5 ml of 33 per cent hydrogen bromide in acetic acid. The reaction mixture was stirred for another 10 minutes and then diluted with 50 ml of ice-water. The crystalline precipitate was filtered off, washed with water and dried *in vacuo* at room temperature. After recrystallization from ethyl acetate, the 2 β -bromo-5 β ,9 β ,10 α -pregnane-3,20-dione melted at 160°—161°C.

1.5 g of this substance were dissolved in 40 ml of N,N-dimethyl-formamide. After the addition of 1.5 g of lithium chloride and 1.5 g of lithium carbonate, the mixture was heated to reflux under nitrogen for 2 hours. Water was then added and the organic material extracted with ether. The extract was washed with water, dried with sodium sulphate and evaporated to dryness. The residue was chromatographed on silica gel. With benzene/acetone (99:1), 800 mg of 5 β ,9 β ,10 α -pregn-1-ene-3,20-dione of melting point 91°—93°C were eluted. Further elution with benzene/acetone (98:2) afforded 250 mg of 9 β ,10 α -pregn-4-ene-3,20-dione of melting point 155°—157°C (from ethanol).

EXAMPLE 13.

A solution of 0.96 g of bromine in 10 ml of acetic acid was dropped within 5 minutes into a stirred solution of 1.9 g of 5 α ,9 β ,10 α -pregnane-3,20-dione in 20 ml of acetic acid, which contained 10 drops of 33 per cent hydrogen bromide in acetic acid. The solution was stirred for another 10 minutes, then diluted with ice-water and extracted with ether. The ether solution was washed with cold sodium bicarbonate solution and water, dried with sodium sulphate and evaporated to dryness. The residue was chromatographed on silica gel. The benzene/acetone (99:1) fractions afforded 890 mg of 4 β -bromo-5 α ,9 β ,10 α -pregnane-3,20-dione of melting point 178°—179°C.

A solution of 200 mg of this substance, 200 mg of lithium chloride and 200 mg of lithium carbonate in 5 ml of N,N-dimethyl-formamide was heated under reflux for 2 hours. After dilution with water, the mixture was extracted with ether. The ether extract afforded a crystalline residue which gave 9 β ,10 α -pregn-4-ene-3,20-dione of melting point 154°—156°C after crystallization from ethanol.

EXAMPLE 14.

636 mg of 17 α -ethyl-17 β -hydroxy-5 β ,9 β ,10 α -androstan-3-one were dissolved in 8 ml of acetic acid. One drop of 33 per cent hydrogen bromide in acetic acid was added to the well-stirred solution and immediately afterwards a solution of 352 mg of bromine and 190 mg of sodium acetate in 10 ml of acetic acid was added within 0.25 hour. The reaction mixture was stirred for another 0.25 hour and then diluted with water. The crystalline precipitate was filtered off and dried *in vacuo*.

This crude 2 β -bromo-17 α -ethyl-17 β -hydroxy-5 β ,9 β ,10 α -androst-3-one was dissolved in 10 ml of N,N-dimethyl-formamide. After addition of 600 mg of lithium chloride and 600 mg of lithium carbonate, the solution was heated to reflux for 2 hours. The mixture was then diluted with water and extracted with ether. The crude product isolated from the ether extract was chromatographed on aluminium oxide of activity II. The benzene/(petroleum ether) (1:1) eluates contained the 17 α -ethyl-17 β -hydroxy-5 β ,9 β ,10 α -androst-1-en-3-one, whereas the benzene/(petroleum ether) (2:1) fractions yielded the 17 α -ethyl-17 β -hydroxy-9 β ,10 α -androst-4-en-3-one of melting point 131°—133°C.

EXAMPLE 15.

One drop of 33 per cent hydrogen bromide in acetic acid was added to a stirred solution of 200 mg of 5 α ,9 α ,10 α -pregnane-3,20-dione in 5 ml of acetic acid. A solution of 108 mg of bromine in 5 ml of acetic acid was added within 10 minutes. The mixture was stirred for another 0.25 hour, then diluted with ice-water and extracted with ether. The extract was washed with sodium bicarbonate solution and water, dried over sodium sulphate and concentrated. There was obtained 257 mg of a yellow oil. This material was dissolved in 10 ml of N,N-dimethyl-formamide. After addition of 260 mg of lithium chloride and 260 mg of lithium carbonate, the mixture was heated to reflux for 2 hours. After the work-up the residue (205 mg) was chromatographed on silica gel. The first fractions yielded 5 α ,9 α ,10 α -pregn-1-ene-3,20-dione of melting point 180°—183°C (from acetone/hexane). The later fractions afforded 10 α -pregn-4-ene-3,20-dione.

EXAMPLE 16.

0.2 ml of 11 per cent hydrobromic acid in acetic acid and a solution of 2 mmol of bromine in 1 ml of acetic acid were added within 3 minutes at 5°C while stirring to a solution of 305 mg of 5 α ,9 α ,10 α -pregnane-3,20-dione in 6 ml of acetic acid. The solution was kept at room temperature for 40 minutes, then poured on ice and extracted with methylene chloride. The organic phase was washed three times with water, dried over sodium sulphate and evaporated. This crude bromination product was heated under reflux for 2 hours in 10 ml of acetone and 500 mg of sodium iodide, then poured on ice and extracted with methylene chloride. The methylene chloride layer was washed once with an aqueous sodium thiosulphate solution and three times with water, dried over sodium sulphate and evaporated. 150 mg of an oily residue were obtained and this was heated under reflux for 1.5 hours with 5 ml of N,N-dimethyl-formamide, 200 mg of lithium carbonate and 200 mg of lithium bromide. Chromatography on silica gel of the crude dehydrobromination product yielded 9 α ,10 α -progesterone of melting point 193.5°—195°C (from acetone/hexane).

EXAMPLE 17.

200 mg of 17 α -ethyl-17 β -acetoxy-5 α ,9 β ,10 α -androst-3-one and 150 mg of 2,3-dichloro-5,6-dicyano-benzoquinone dissolved in a mixture of 10 ml of benzene and 10 ml of dioxan containing 29 mg of hydrogen chloride was stirred at room temperature for 40 minutes. The reaction mixture was then neutralized with 90 mg of calcium carbonate and heated under reflux for 0.25 hour. The mixture was poured on ice, extracted with ether/(methylene chloride) (3:1), the organic phase was washed once with 2-N sodium hydroxide solution, then with water until neutral and dried over sodium sulphate. The residue obtained after evaporation of the solvent was chromatographed on silica gel with isopropyl ether. After elution of 107 mg of starting material, 17 α -ethyl-17 β -acetoxy-9 β ,10 α -androst-4-en-3-one was isolated which melted at 182°—184°C after recrystallization from acetone/hexane.

An ethereal solution of 17 α -ethyl-17 β -acetoxy-9 β ,10 α -androst-4-en-3-one was stirred with an equal amount of lithium aluminium hydride at room temperature for 1.5 hours. The unreacted hydride was decomposed with a few drops of water and the precipitation removed by filtration. The filtrate was evaporated to dryness, the residue obtained redissolved in chloroform and treated at room temperature for 1 hour with a large excess of manganese dioxide in order to re-oxidise the 3,17 β -diol formed to the 3-keto-17 β -hydroxy compound. The reaction mixture was diluted with ether and the organic phase washed with water, dried over sodium sulphate and evaporated. The partially crystalline 17 α -ethyl-17 β -hydroxy-9 β ,10 α -androst-4-en-3-one melted at 131°—133°C after several recrystallisations from acetone/ether.

EXAMPLE 18.

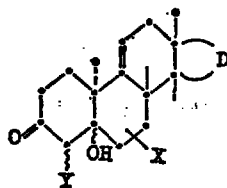
A solution of 200 mg of 17 α -ethyl-17 β -hydroxy-5 β ,9 β ,10 α -androstan-3-one and 100 mg of N-bromo-succinimide in 15 ml of carbon tetrachloride was heated under reflux and irradiated with a high pressure mercury lamp for 25 minutes. The reaction mixture was diluted with ether, washed once with 2-N sodium hydroxide solution, then with water until neutral, dried over sodium sulphate and evaporated to dryness. The residue (280 mg) was redissolved in 20 ml of N,N-dimethyl-formamide and heated under reflux under nitrogen for 2 hours with 180 mg of lithium carbonate and 180 mg of lithium bromide. Water was then added and the organic material extracted with ether, the ethereal solution dried over sodium sulphate and evaporated to dryness. Chromatography of the residue on silica gel with cyclohexane/(ethyl acetate) (1:1) yielded, after elution of starting material and 17 α -ethyl-17 β -hydroxy-5 β ,9 β ,10 α -androstan-1-en-3-one, 17 α -ethyl-17 β -hydroxy-9 β ,10 α -androstan-4-en-3-one of melting point 131°—133°C.

EXAMPLE 19.

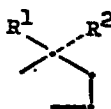
17 α -ethyl-17 β -hydroxy-5 α ,10 α -androstan-3-one was brominated and dehydrobrominated as described earlier. From the crude reaction product 17 α -ethyl-17 β -hydroxy-5 α ,9 α ,10 α -androstan-1-en-3-one and 17 α -ethyl-17 β -hydroxy-9 α ,10 α -androstan-4-en-3-one (melting point = 213°—214°C) were isolated by chromatography on silica gel with isopropyl ether.

WHAT WE CLAIM IS:—

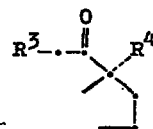
- 1) A process for the manufacture of 9 α ,10 α - and 9 β ,10 α -steroids of the androstane and pregnane series, which process comprises catalytically hydrogenating a 10 α - Δ 9(11)-steroid of the androstane or pregnane series and, if desired, introducing a double bond into the 4,5-position of the hydrogenation product.
- 2) A process as set forth in claim 1, wherein a 5-hydroxy-10 α -androstan(or pregn)-9(11)-en-3-one is used as the starting material.
- 3) A process as set forth in claim 2, wherein a steroid of the formula



wherein X represents a hydrogen or halogen atom or a lower-alkyl group in the 6- or 7-position, Y is a hydrogen atom or a lower-alkyl group and D represents a moiety of the formula



or



in which R¹ represents a hydroxy or esterified hydroxy group, R² represents a hydrogen atom or a lower-alkyl group or R¹ together with R² represents an oxo group, R³ represents a hydrogen or halogen atom or a hydroxy or esterified hydroxy group and R⁴ represents a hydrogen or halogen atom or a lower-alkyl, hydroxy or esterified hydroxy group, is used as the starting material.

- 4) A process as set forth in claim 1, wherein a 10 α -androstan(or pregn)-4,9(11)-dien-3-one is used as the starting material.

EXAMPLE 18.

A solution of 200 mg of 17 α -ethyl-17 β -hydroxy-5 β ,9 β ,10 α -androst-3-one and 100 mg of N-bromo-succinimide in 15 ml of carbon tetrachloride was heated under reflux and irradiated with a high pressure mercury lamp for 25 minutes. The reaction mixture was diluted with ether, washed once with 2-N sodium hydroxide solution, then with water until neutral, dried over sodium sulphate and evaporated to dryness. The residue (280 mg) was redissolved in 20 ml of N,N-dimethyl-formamide and heated under reflux under nitrogen for 2 hours with 180 mg of lithium carbonate and 180 mg of lithium bromide. Water was then added and the organic material extracted with ether, the ethereal solution dried over sodium sulphate and evaporated to dryness. Chromatography of the residue on silica gel with cyclohexane/(ethyl acetate) (1:1) yielded, after elution of starting material and 17 α -ethyl-17 β -hydroxy-5 β ,9 β ,10 α -androst-1-en-3-one, 17 α -ethyl-17 β -hydroxy-9 β ,10 α -androst-4-en-3-one of melting point 131°—133°C.

EXAMPLE 19.

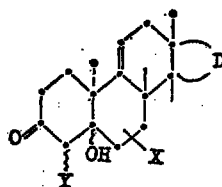
17 α -ethyl-17 β -hydroxy-5 α ,10 α -androst-3-one was brominated and dehydrobrominated as described earlier. From the crude reaction product 17 α -ethyl-17 β -hydroxy-5 α ,9 α ,10 α -androst-1-en-3-one and 17 α -ethyl-17 β -hydroxy-9 α ,10 α -androst-4-en-3-one (melting point = 213°—214°C) were isolated by chromatography on silica gel with isopropyl ether.

WHAT WE CLAIM IS:—

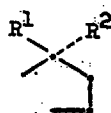
1) A process for the manufacture of 9 α ,10 α - and 9 β ,10 α -steroids of the androstane and pregnane series, which process comprises catalytically hydrogenating a 10 α - Δ 9(11)-steroid of the androstane or pregnane series and, if desired, introducing a double bond into the 4,5-position of the hydrogenation product.

2) A process as set forth in claim 1, wherein a 5-hydroxy-10 α -androst(or pregn)-9(11)-en-3-one is used as the starting material.

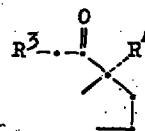
3) A process as set forth in claim 2, wherein a steroid of the formula



wherein X represents a hydrogen or halogen atom or a lower-alkyl group in the 6- or 7-position, Y is a hydrogen atom or a lower-alkyl group and D represents a moiety of the formula



OR

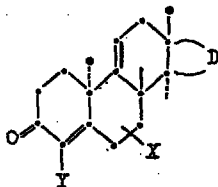


in which R¹ represents a hydroxy or esterified hydroxy group, R² represents a hydrogen atom or a lower-alkyl group or R¹ together with R² represents an oxo group, R³ represents a hydrogen or halogen atom or a hydroxy or esterified hydroxy group and R⁴ represents a hydrogen or halogen atom or a lower-alkyl, hydroxy or esterified hydroxy group, is used as the starting material.

4) A process as set forth in claim 1, wherein a 10 α -androst(or pregna)-4,9(11)-dien-3-one is used as the starting material.

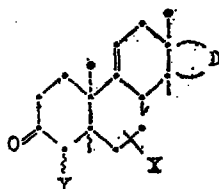


5) A process as set forth in claim 4, wherein a steroid of the formula



wherein X, Y and D have the significance given in claim 3, is used as the starting material.

6) A process as set forth in claim 1, wherein a steroid of the formula



wherein X, Y and D have the significance given in claim 3, is used as the starting material.

7) A process as set forth in any one of claims 3, 5 and 6, wherein in the steroid starting material X is a hydrogen atom or a lower-alkyl group.

8) A process as set forth in any one of claims 3, 5 and 6, wherein in the steroid starting material X is a halogen atom in the 7-position.

9) A process as set forth in claim 2 or claim 3, wherein a double bond is introduced into the 4,5-position of the hydrogenation product by dehydration.

10) A process as set forth in any of claims 4 to 6 inclusive, wherein a double bond is introduced into the 4,5-position of the hydrogenation product by selective dehydrogenation.

11) A process as set forth in claim 2 which includes the initial step of preparing the starting materials set forth therein by condensing a desA-androst(or pregn)-9-en-5-one with a lower-alkyl vinyl ketone.

12) A process as set forth in claim 11, wherein the lower-alkyl vinyl ketone used has the formula



wherein Y has the significance given in claim 3.

13) A process as set forth in claim 4, which includes the initial step of preparing the starting material set forth therein by dehydrating a 5-hydroxy-9 α ,10 α -androst(or pregn)-9(11)-en-3-one.

14) A process as set forth in claim 13, wherein a steroid of the formula given in claim 3 is dehydrated.

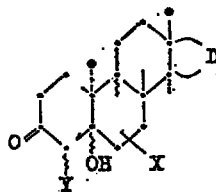
15) A process as set forth in claim 6, which includes the initial step of preparing the starting materials set forth therein by selectively reducing a steroid as set forth in claim 5.

16) A process for the manufacture of 9 α ,10 α - and 9 β ,10 α -steroids, substantially as described with reference to the Examples.

17) 9 α ,10 α - and 9 β ,10 α -steroids, when manufactured by the process claimed in any one of the preceding claims.



18) Steroids of the formula



wherein X, Y and D have the significance given in claim 3.

- | | | |
|----|--|----|
| 5 | 19) 17 α -(lower alkyl)-5,17 β -dihydroxy-9 α ,10 α -androstan-3-ones. | 5 |
| | 20) 17 α -Ethyl-5 α ,17 β -dihydroxy-9 α ,10 α -androstan-3-one. | |
| | 21) 5,17 β -Dihydroxy-9 α ,10 α -androstan-3-ones. | |
| | 22) 5 α ,17 β -Dihydroxy-9 α ,10 α -androstan-3-one. | |
| | 23) 5-Hydroxy-9 α ,10 α -pregnane-3,20-diones. | |
| 10 | 24) 5 α -Hydroxy-9 α ,10 α -pregnane-3,20-dione. | 10 |
| | 25) Steroids as formulated in claim 3. | |
| | 26) 5-Hydroxy-10 α -androst-9(11)-ene-3,17-diones. | |
| | 27) 5 α -Hydroxy-10 α -androst-9(11)-ene-3,17-dione. | |
| | 28) 5,17 β -Dihydroxy-10 α -androst-9(11)-en-3-ones. | |
| 15 | 29) 5 α ,17 β -dihydroxy-10 α -androst-9(11)-en-3-one. | 15 |
| | 30) 17 α -(Lower alkyl)-5,17 β -dihydroxy-10 α -androst-9(11)-en-3-ones. | |
| | 31) 17 α -Ethyl-5 α ,17 β -dihydroxy-10 α -androst-9(11)-en-3-one. | |
| | 32) 5-Hydroxy-10 α -pregn-9(11)-ene-3,20-diones. | |
| | 33) 5 α -Hydroxy-10 α -pregn-9(11)-ene-3,20-dione. | |
| 20 | 34) Steroids as formulated in claim 5. | 20 |
| | 35) 10 α -Androsta-4,9(11)-diene-3,17-dione. | |
| | 36) 17 α -(Lower alkyl)-17 β -hydroxy-10 α -androsta-4,9(11)-dien-3-one. | |
| | 37) 17 α -Ethyl-17 β -hydroxy-10 α -androsta-4,9(11)-dien-3-one. | |
| | 38) 10 α -Pregna-4,9(11)-diene-3,20-dione. | |
| 25 | 39) Steroids as formulated in claim 6. | 25 |
| | 40) 5 α ,10 α -Androst-9(11)-ene-3,17-dione. | |
| | 41) 5 β ,10 α -Androst-9(11)-ene-3,17-dione. | |
| | 42) 10 α -Androst-9(11)-en-17 β -ol-3-one. | |
| | 43) 5 β ,10 α -Androst-9(11)-en-17 β -ol-3-one. | |
| 30 | 44) 5 α ,10 α -Pregn-9(11)-ene-3,20-dione. | 30 |
| | 45) 5 β ,10 α -Pregn-9(11)-ene-3,20-dione. | |

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Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to Patents Nos. 929,272 and 929,271.

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