

## PATENT SPECIFICATION

NO DRAWINGS

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Int. Cl.:—C 07 c 169/00

## COMPLETE SPECIFICATION

A process for the manufacture of 9 $\beta$ ,10 $\alpha$ -Methyl-Steroids

5 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:—

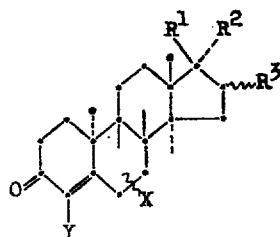
10 The present invention relates to the manufacture of 9 $\beta$ ,10 $\alpha$ -methyl-steroids. More particularly, the invention is concerned with a process for the manufacture of 9 $\beta$ ,10 $\alpha$ -methyl-steroids of the androstane and pregnane series.

15 Natural steroids possess a 9 $\alpha$ ,10 $\beta$ -stereochemical configuration. Steroid compounds possessing the unnatural 9 $\beta$ ,10 $\alpha$ -configuration represent a pharmaceutically valuable class of compounds which, even though numerous members are known, cannot be obtained by 20 totally classical chemical means. In fact, the only known methods for obtaining steroids possessing the unnatural 9 $\beta$ ,10 $\alpha$ -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.

25 It is an object of the present invention to provide a process which enables the preparation of 9 $\beta$ ,10 $\alpha$ -steroids without the necessity of proceeding through a photochemical reaction.

30 According to one of its aspects, the invention provides a means for obtaining, *inter alia*, the following 9 $\beta$ ,10 $\alpha$ -steroids:

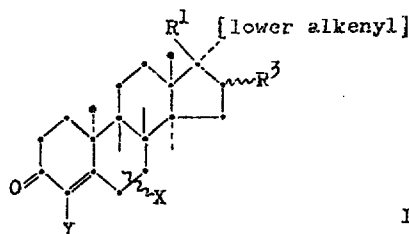
35 a) 9 $\beta$ ,10 $\alpha$ -steroids of the androstane series having the formula



I

wherein R<sup>1</sup> represents a hydroxy or lower-alkanoyloxy group, R<sup>2</sup> represents a hydrogen atom or a lower-alkyl group or R<sup>1</sup> together with R<sup>2</sup> represent an oxo or 17 $\beta$ -hydroxy-17 $\alpha$ -(lower alkanoyl acid) lactone group, R<sup>3</sup> represents a hydrogen atom or a lower-alkyl, hydroxy or lower-alkanoyloxy group, Y represents a hydrogen atom or a lower-alkyl group and X represents a hydrogen atom or a halogen atom or lower-alkyl, lower-alkylthio or lower-alkanylthio group in the 6-7-position. These steroids are useful as anabolic agents.

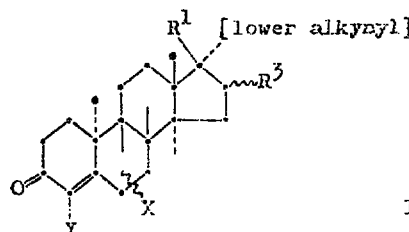
b) 9 $\beta$ ,10 $\alpha$ -androstanes of the formula



II

wherein R, R<sup>3</sup>, X and Y have the significance given earlier. These steroids are useful as anti-androgenic agents.

c) 9 $\beta$ ,10 $\alpha$ -androstanes of the formula



III

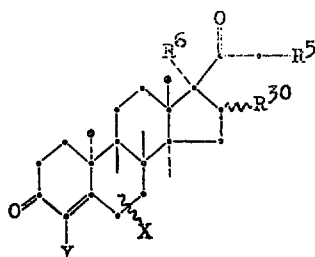
wherein R<sup>1</sup>, R<sup>3</sup>, X and Y have the significance given earlier. These steroids are useful as progestational agents.

d) 9 $\beta$ ,10 $\alpha$ -steroids of the 17 $\beta$ -pregnane series having the formula

and R<sup>6</sup> represents a hydrogen or halogen atom

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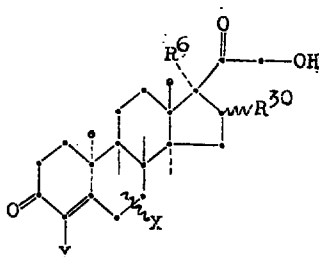
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IV

wherein X and Y have the significance given earlier, R<sup>30</sup> represents a hydrogen or fluorine atom or a lower-alkyl, hydroxy or lower-alkanoyloxy group, R<sup>5</sup> represents a hydrogen or halogen atom or a lower-alkyl or hydroxy group. These steroids are useful as progestational agents.

e) 9β,10α-steroids of the 17β-pregnane series having the formula



V

wherein R<sup>30</sup>, R<sup>6</sup>, X and Y have the significance given earlier. These steroids are useful as salt-retaining agents; for example, in the treatment of Addison's disease.

According to one aspect of the invention there is provided a process for the manufacture of 3-keto-4-dehydro and 3-keto-1,4-bis-dehydro-9β,10α-steroids of the androstane and pregnane series, which process comprises condensing a 9β,10β-desA-androstan-5-one or a 9β,10β-desA-pregnan-5-one with a lower-alkyl vinyl ketone or a lower-alkyl ethynyl ketone respectively.

It will be appreciated that the present process does not involve any modification of the substituents present in the 16 and/or 17-position of the desA-steroid starting materials. However, it may be necessary or desirable to protect certain of the 16 and/or 17-substituents in certain cases. It will further be appreciated that the desA-steroids may contain substituents which are present in protected form. The protecting groups can be inserted and split off by methods known *per se*. The various substituents which are susceptible to being protected are exemplified by the 16-hydroxy group in a compound of any one of formulae I to V, the 17β-hydroxy group in a compound of any one of formulae I to III, the 17α-hydroxy or 20-oxo group in a compound of any of formulae IV and V, the 21-hydroxy group of

a compound of formula V or the 17-oxo group of a compound of formula I.

The 17-oxo or 20-oxo group is suitably protected by ketalisation (e.g. by reaction with an alkanediol containing not more than 6 carbon atoms) to yield a 17-(lower alkylenedioxy) or 20-(lower alkylenedioxy) compound (i.e. a 17-ketal or a 20-ketal).

The 16-hydroxy, 17α-hydroxy, 17β-hydroxy or 21-hydroxy groups can be protected by esterification and/or etherification. Any available acid which will form an ester that can subsequently be hydrolysed to regenerate the hydroxyl group is suitable. Examples of acids which are useful for this purpose are alkanic acids containing not more than 6 carbon atoms (e.g. acetic acid), caproic acid, benzoic acid, phosphoric acid and alkane dicarboxylic acids containing not more than 6 carbon atoms (e.g. succinic acid). Also, protection for the 16α-hydroxy, 17α-hydroxy or 21-hydroxy groups can be effected by forming the lower-alkyl orthoesters thereof; that is, 16α,17α- or 17α,21-(lower alkyl) orthoesters. A suitable ether protecting group is, for example, the tetrahydropyranyl ether group.

In compounds containing the dihydroxy-acetone side chain at the 17-carbon atom (for example, compounds of formula V in which R<sup>6</sup> is a hydroxy group), this side chain can be protected by forming the 17,20; 20,21-bis-(methylenedioxy) group or by forming a 17,21-acetal or ketal group or by forming a 17,21-diester. The 17,21-acetal or ketal and 17,21-diester hinder the 20-ketone group and minimise the possibility of its participating in unwanted side-reactions. On the other hand, the 17,20;20,21 - bis (methylenedioxy) derivatives actually convert the ketone to a non-reactive derivative. When both a 16α-hydroxy and 17α-hydroxy group are present, these groups can be protected by the formation of a 16α,17α-acetal or ketal. The various protecting groups mentioned earlier can be removed by methods known *per se*; for example, by mild acid hydrolysis.

In compounds which contain a 20-oxo group but no 17α-hydroxy or 21-hydroxy group, the 20-oxo group can be protected by reduction to the hydroxy group (i.e. reduction to the corresponding carbinol). Thus, for example, the 17-acetal side chain can be protected by conversion to a 17-(α-hydroxy-ethyl) side chain. Regeneration of the 17-acetyl side chain can be simply effected by conventional oxidation means; for example, by oxidation with chromium trioxide in an organic solvent such as glacial acetic acid. Similarly, in compounds containing a 17-oxo group, this group can be protected by reduction to the hydroxy group (i.e. reduction to the corresponding carbinol). Thus, the 17-oxo group can be reduced to a 17β-hydroxy, 17α-hydrogen moiety, from which, when desired, the 17-oxo moiety can be regenerated by oxidation as described

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50

55 b2 hydroxy

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17α- 85

acetyl 95

100

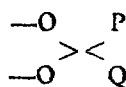
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earlier. Furthermore, a 20-hydroxy or 17 $\beta$ -hydroxy group can itself be protected by esterification; for example, with an alkanolic acid containing not more than 6 carbon atom (such as acetic acid) or caproic acid.

The 16 $\alpha$ ,17 $\alpha$  or 17 $\alpha$ ,21-acetals and ketals discussed hereinbefore can be formed by reacting 16 $\alpha$ ,17 $\alpha$ -bis(hydroxy) or 17 $\alpha$ ,21-bis(hydroxy) compounds with an aldehyde or a ketone. This is preferably effected by reacting a simple acetal or ketal (e.g. an alkylene glycol acetal or ketal of a suitable aldehyde or ketone containing not more than 6 carbon atoms) with the groups sought to be protected.

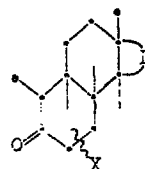
Suitable aldehydes and ketones include lower-alkanals (i.e. alkanals containing from 2 to 6 carbon atoms) (such as paraldehyde, propanal and hexanal), di(lower alkyl) ketones (such as acetone, diethyl ketone, dibutyl ketone, methyl ethyl ketone and methyl isobutyl ketone), cycloalkanones (such as cyclobutanone, cyclopentanone and cyclohexanone), cycloalkyl-(lower alkanals) (such as cyclopentyl carboxaldehyde and cyclohexyl carboxaldehyde), cycloalkyl (lower alkyl) ketones (such as cyclopentyl propyl ketone, cyclohexylmethyl ethyl ketone), dicycloalkyl ketones (such as dicyclopentyl ketone, dicyclohexyl ketone and cyclopentyl cyclohexyl ketone), cycloalkyl monocyclic aromatic ketones (such as cyclohexyl *p*-chloro-phenyl ketone, cyclopentyl *o*-methoxy-phenyl ketone, cyclopentyl, *o,p*-dihydroxy-phenyl ketone and cyclohexyl *m*-tolyl ketone), cycloalkyl (lower alkyl) monocyclic aromatic ketones (such as cyclopentylmethyl phenyl ketone), cycloalkyl monocyclic aromatic-(lower alkyl)ketones (such as cyclopentyl benzyl ketone and cyclohexyl phenethyl ketones), cycloalkyl-lower alkyl) monocyclic aromatic-(lower alkyl) ketones (such as cyclopentylmethyl benzyl ketone), halo-(lower alkanals) (such as chloral hydrate, trifluoro-acetaldehyde hemiacetal and heptafluoro-butanal ethyl hemiacetal), halo-(lower alkanones) (such as 1,1,1-trifluoro-acetone), monocyclic carbocyclic aromatic aldehydes (such as benzaldehyde, halo-benzaldehydes, for example, *p*-chloro-benzaldehyde, *p*-fluorobenzaldehyde), lower alkoxy - benzaldehydes (such as *o* - anisaldehyde), di-(lower alkoxy)-benzaldehydes (such as veratraldehyde), hydroxy-benzaldehydes (such as salicylaldehyde), lower alkyl-benzaldehydes (such as *m*-tolualdehyde and *p*-ethyl-benzaldehyde), di(lower alkyl)-benzaldehydes (such as *o,p*-dimethyl-benzaldehyde), monocyclic carboxylic aromatic lower alkanals (such as phenyl-acetaldehyde,  $\alpha$ -phenyl-propionaldehyde,  $\beta$ -phenyl-propionaldehyde, 4-phenyl-butyraldehyde) and aromatically-substituted halo-, lower alkoxy-, hydroxy-, lower alkyl- and cyano-derivatives thereof, monocyclic carbocyclic aromatic ketones (such as acetophenone,  $\alpha,\alpha,\alpha$ -trifluoro-acetophenone, propiophenone, butyrophenone, valerophenone), halo-phenyl

lower-alkyl ketones (e.g. *p*-chloro-acetophenone and *p*-chloro-propiophenone, (lower alkoxy)-phenyl lower-alkyl ketones (such as *p*-anisyl methyl ketone), di(lower alkoxy)-phenyl lower-alkyl ketones, hydroxy-phenyl lower-alkyl ketones, (lower alkyl)-phenyl lower-alkyl ketones (such as methyl *p*-tolyl ketone), di-(lower alkyl)-phenyl lower-alkyl ketones (such as *o,p*-xylyl methyl ketone), benzophenone and mono- or bis-substituted halo, lower-alkoxy, hydroxy and lower-alkyl derivatives thereof and monocyclic carbocyclic aromatic lower-alkanones (such as 1-phenyl-butanone-(3) and 1-phenyl-pentanone-(4) and aromatically substituted derivatives thereof. The terms 'lower alkoxy' and 'lower alkanone' are used herein to mean alkoxy groups and alkanones respectively which contain not more than 6 carbon atoms. Especially suitable are those aldehydes or ketones which, with the 16 $\alpha$ ,17 $\alpha$ - or 17 $\alpha$ ,21-bis(hydroxy) grouping form an acetal or ketal grouping of the formula

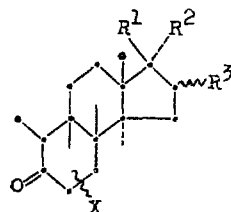


wherein P represents a hydrogen atom or a lower-alkyl group, Q represents a lower-alkyl or aryl group or P and Q together represent a lower-alkylene group such as tetramethylene or pentamethylene.

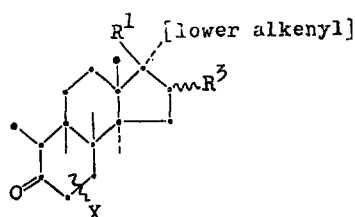
Thus, in one embodiment of the aforementioned condensation, 9 $\beta$ ,10 $\alpha$ -steroids of formulae I to V are manufactured by condensing a 9 $\beta$ ,10 $\beta$ -desA-androstan-5-one or a 9 $\beta$ ,10 $\beta$ -desA-pregnan-5-one of the formula



wherein X has the significance given earlier and D represents the grouping necessary to complete the steroid D-ring, with a lower-alkyl vinyl ketone. More particularly, the 9 $\beta$ ,10 $\alpha$ -androstanes of formula I are manufactured from 9 $\beta$ ,10 $\beta$ -desA-androstan-5-ones of the formula

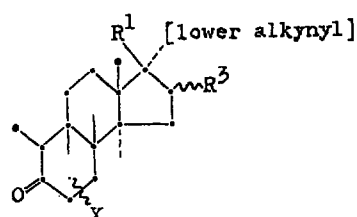


9 $\beta$ ,10 $\alpha$ -androstanes of formula II are manufactured from 9 $\beta$ ,10 $\beta$ -desA-androstan-5-ones of the formula



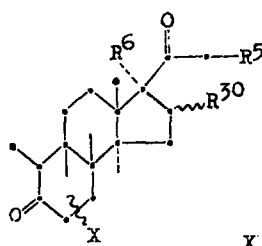
VIII

9 $\beta$ ,10 $\alpha$ -androstanes of formula III are manufactured from 9 $\beta$ ,10 $\beta$ -desA-androstan-5-ones of the formula



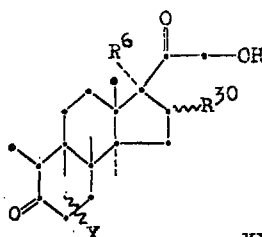
IX

9 $\beta$ ,10 $\alpha$ -17 $\beta$ -pregnanes of formula IV are manufactured from 9 $\beta$ ,10 $\beta$ -desA-pregnan-5-ones of the formula



X

10 and 9 $\beta$ ,10 $\alpha$ -17 $\beta$ -pregnanes of formula V are manufactured from 9 $\beta$ ,10 $\beta$ -desA-pregnan-5-ones of the formula



XI

in which formulae R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>30</sup>, R<sup>5</sup>, R<sup>6</sup> and X have the significance given earlier.

Methyl vinyl ketone is the preferred reactant. Prior to the condensation, it is desirable to protect the 20-keto group present in compounds of formulae X and XI, when it is not necessary to protect 16 $\alpha$ , 17 $\alpha$  or 21-hydroxy groups which are present, but groups protecting these moieties can be retained throughout the condensation reaction.

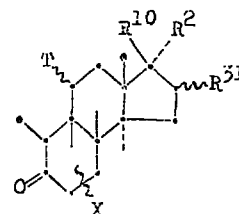
When a lower-alkyl vinyl ketone is used in the condensation, ring closure to ring A (containing a 3-oxo moiety) of the desired 9 $\beta$ ,10 $\alpha$ -steroid of formulae I—V occurs simultaneously with the condensation. As will be apparent, when a condensation partner based on butane (i.e. having a four carbon atom skeleton) is used a compound of one of formulae I to V wherein Y is a hydrogen atom is obtained. Similarly, when a condensation partner based on pentane is used a compound of one of formulae I to V wherein Y is the methyl group is obtained.

In addition to the manufacture of compounds of formulae I to V from compounds of formulae VI to XI using the aforementioned ketones, it is also possible according to this invention to manufacture compounds of formulae I to VI which, in the A-ring, are unsaturated in the 1,2-position as well as in the 4,5-position. Such 1,4-diene products corresponding to the compounds of formulae I to V can be manufactured from compounds of formulae VI to XI by condensation of the latter with a lower-alkyl ethynyl ketone such as ethynyl methyl ketone or ethynyl ethyl ketone. This condensation to give these 1,4-diene products is effected under the same conditions as that described earlier in connection with the substituted vinyl ketones. The so-obtained 1,4-dienes are useful in the same manner as the correspondingly substituted 4-ene-compounds of formulae I to V.

The condensation is suitably effected at below or above room temperature; for example, at the reflux temperature of the condensation medium or at ice-temperature (0°C) or below. Moreover, the condensation is suitably effected in an organic medium. Preferably, the solvent is an alkanol containing not more than six carbon atoms (e.g. 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 (e.g. acetic acid). It is suitable to catalyse the condensation, and this can be effected using a catalyst such as an alkali-metal alkoxide containing not more than six carbon atoms (e.g. sodium ethoxide), an alkali-metal hydroxide, a quaternary ammonium hydroxide (e.g. benzyl-trimethyl-ammonium hydroxide) or *paratoluene*-sulphonic acid.

Especially useful 9 $\beta$ ,10 $\beta$ -steroids for use in the foregoing condensation are:

a) 9 $\beta$ ,10 $\beta$ -desA-steroids of the androsterane series having the formula



VIIa

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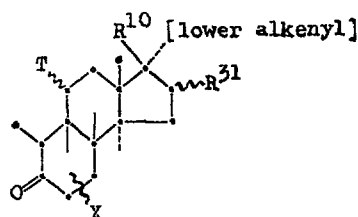
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85

hydrocarbon

wherein  $R^{10}$  represents a hydrogen atom or an esterified hydroxy group,  $R^2$  has the significance given earlier or  $R^{10}$  together with  $R^2$  represent an oxo, lower-alkylenedioxy or  $17\beta$ -hydroxy -  $17\alpha$  - (lower alkanolic acid) lactone group,  $R^{31}$  represents a hydrogen atom or a lower-alkyl, hydroxy or esterified hydroxy group, T represents a hydrogen atom or a hydroxy or esterified hydroxy group and X has the significance given earlier.

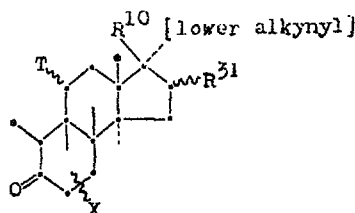
b)  $9\beta,10\beta$ -desA-androstanes of the formula



VIIIa

wherein  $R^{10}$ ,  $R^{31}$ , T and X have the significance given earlier.

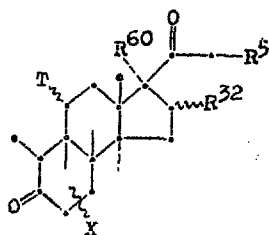
c)  $9\beta,10\beta$ -desA-androstanes of the formula



IXa

wherein  $R^{10}$ ,  $R^{31}$ , R and X have the significance given earlier.

d)  $9\beta,10\beta$ -desA-pregnanes of the formula

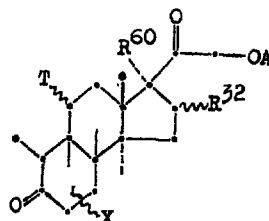


Xa

wherein  $R^3$ , T and X have the significance given earlier,  $R^{32}$  represents a hydrogen or fluorine atom or a lower-alkyl, hydroxy or esterified hydroxy group and  $R^{60}$  represents a hydrogen or halogen atom or a lower-alkyl, hydroxy or esterified hydroxy group, as well as 20-ketal derivatives thereof,  $16\alpha,17\alpha$ -ketal and acetal derivatives of such desA-steroids in which  $R^{32}$  and  $R^{60}$  each represent a hydroxy group, derivatives of such desA-steroids in which the 20-oxo group is reduced to a 20-hydroxy group and the corresponding desA-

steroids in which said 20-hydroxy group is esterified.

e)  $9\beta,10\beta$ -desA-pregnanes of the formula



XIa

wherein  $R^{32}$ ,  $R^{60}$ , T and X have the significance given earlier and OA represents a hydroxy or esterified hydroxy group,  $17\alpha,20$ ;- $20,21$ -bis(methylenedioxy) derivatives of said desA-steroids in which OA and  $R^{60}$  each represent a hydroxy group,  $17\alpha,21$ -ketals and acetals of said desA-steroids in which OA and  $R^{60}$  each represent a hydroxy group,  $16\alpha,17\alpha$ -ketals and acetals of said desA-steroids in which OA and  $R^{32}$  each represent a hydroxy group, derivatives of said desA-steroids in which the 20-keto group is reduced to a 20-hydroxy group and the corresponding desA-steroids in which said 20-hydroxy group is esterified.

The compounds of formulae I to V hereinbefore which are obtainable according to this invention are useful not only from a pharmaceutical point of view as described earlier, but also as intermediates for the manufacture of other  $9\beta,10\alpha$ -steroids. For example, compounds in which X represents a hydrogen atom or a lower-alkyl group can be modified so as to introduce unsaturation between C-6 and C-7. This can be effected by dehydrogenation; for example, by halogenation followed by dehydrohalogenation or by means of 2,3-dichloro-5,6-dicyano-benzoquinone according to known methods. Thus, for example, a  $9\beta,10\alpha$ -progesterone of formula IV in which X represents a hydrogen atom or a lower-alkyl group can be converted into a  $9\beta,10\alpha$ -pregna-4,6-dien-3,20-dione.

A further embodiment of this invention comprises the preparation of  $9\beta,10\alpha$ -steroids of formulae I to V containing an 11-hydroxy or 11-(esterified hydroxy) substituent. This can be effected by using an 11-hydroxy or 11-(esterified hydroxy) derivative of a desA-steroid of formulae VI to XI hereinbefore.

Condensation of the desA-steroids containing an 11-hydroxy or 11-(esterified hydroxy) group with a lower-alkyl vinyl ketone or a lower-alkyl ethynyl ketone as described earlier then yields the desired  $9\beta,10\alpha$ -steroids of formulae I to V containing an 11-hydroxy or 11-(esterified hydroxy) group. Such condensation can be effected as described earlier for the preparation of a compound of formulae I to



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45 hydroxy

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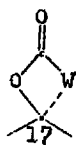
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V from a respective compound of formulae VI to XI. The so-obtained 9 $\beta$ ,10 $\alpha$ -steroids containing an 11-(esterified hydroxy) group can be hydrolysed to the corresponding compounds containing an 11-hydroxy group. The latter compounds are themselves useful as intermediates; for example, the 11-hydroxy group can be oxidised by methods known *per se* to yield the corresponding 11-oxo steroids corresponding to compounds of formulae I to V.

The pharmaceutically useful compounds prepared by the methods of this invention can be administered internally (for example, orally or parenterally) with dosage adjusted to individual requirements. They can be administered in conventional pharmaceutical forms (e.g. capsules, tablets, suspensions, solutions or the like).

As used in this specification the term 'lower alkyl' comprehends both straight- and branched-chain alkyl groups containing not more than 6 carbon atoms such as methyl, ethyl, propyl and isopropyl. Similarly, the term 'lower alkanoyl' means alkanoyl groups containing not more than 6 carbon atoms such as acetyl and the term 'lower alkanoyloxy' means alkanoyloxy groups containing not more than 6 carbon atoms such as acetoxy. Again, the term 'lower alkenyl' means alkenyl groups containing not more than 6 carbon atoms such as vinyl and the term 'lower alkynyl' means alkynyl groups containing not more than 6 carbon atoms such as ethynyl. The term 'halogen' means iodine, bromine, chlorine and fluorine.

The expression '17 $\beta$ -hydroxy-17-(lower alkanoyl) lactone' refers to a configuration at the C-17 carbon atoms illustrated as follows



wherein W is an alkylene group containing not more than 6 carbon atoms such as ethylene or propylene. With regard to X, the preferred compounds are those in which it represents a hydrogen atom or a lower-alkyl group in the 6- or 7-position or a halogen atom in the 7-position.

The 9 $\beta$ ,10 $\beta$ -desA-androstan (or pregnan)-5-ones required as starting materials for the present process can be prepared in accordance with the process described and claimed in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988) where some of said 9 $\beta$ ,10 $\beta$ -desA-androstan (or pregnan)-5-ones are claimed *per se*. Thus, said 9 $\beta$ ,10 $\beta$ -desA-androstan (or pregnan)-5-ones can be prepared by catalytically hydrogenating a desA-androst (or pregn)-9-en-5-one which, in turn, can be obtained in

accordance with the process described and claimed in the specification of our copending Application for Letters Patent no: 36705/67 (now serial no: 1,103,987) where some of them are claimed *per se*. In addition, certain intermediates useful in the production of said desA-androst (or pregn)-9-en-5-ones are claimed *per se* in the specifications of our copending Applications for Letters Patent nos: 36700/67, 36701/67, 36702/67, 36703/67 and 36704/67 (now serial nos: 1,103,982, 1,103,983, 1,103,984, 1,103,985 and 1,103,986, respectively).

The following Examples illustrate the invention:

#### EXAMPLE 1.

0.15 ml of freshly distilled methyl vinyl ketone were added to a solution of 132 mg of 17 $\alpha$ -ethyl-17 $\beta$ -hydroxy-desA-9 $\beta$ ,10 $\beta$ -androstan-5-one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] in 12.5 ml of absolute ethanol containing 34 mg of sodium ethoxide. The reaction mixture was then heated at reflux for 2 hours in a nitrogen atmosphere. After cooling the reaction mixture, 0.1 ml of glacial acetic acid were added thereto and the resulting mixture was then poured into 1 litre of ether. The resulting ether solution was washed with water, dried over anhydrous sodium sulphate and evaporated *in vacuo*. The residue was chromatographed on fluorescent silica-gel plates, with (60 per cent ethyl acetate)/(40 per cent heptane) as the solvent system. The fluorescent part of the layers was extracted with ethyl acetate. The residue obtained after evaporation of ethyl acetate was firstly crystallized from ether/(petroleum ether) and then a second time from pure ether, yielding 17 $\alpha$ -ethyl-9 $\beta$ ,10 $\alpha$ -testosterone of melting point 131°—135°C.

#### EXAMPLE 2.

20 $\beta$ -Hydroxy-9 $\beta$ ,10 $\alpha$ -pregn-4-en-3-one was prepared by condensation of 20 $\beta$ -hydroxy-9 $\beta$ ,10 $\beta$ -desA-pregnan-5-one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] with methyl vinyl ketone according to the procedure of Example 1. The product melts at 176.5°—178.5°C;  $[\alpha]_D^{25} = -143^\circ$  (in chloroform).

#### EXAMPLE 3.

17 $\alpha$ -Acetoxy-20 $\beta$ -hydroxy-9 $\beta$ ,10 $\alpha$ -pregn-4-en-3-one was prepared by condensing methyl vinyl ketone with 17 $\alpha$ -acetoxy-20 $\beta$ -hydroxy-9 $\beta$ ,10 $\beta$ -desA-pregnan-5-one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] according to the procedure of Example 1 except that the condensation is conducted in acetic acid and is catalyzed with *p*-toluene-sulphonic acid instead of conducting the con-



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densation in absolute ethanol and catalyzing it with sodium ethoxide.

#### EXAMPLE 4.

20 $\beta$  - Hydroxy - 4 - methyl - 9 $\beta$ ,10 $\alpha$ -pregn-4-en-3-one was prepared by condensing 20 $\beta$  - hydroxy - 9 $\beta$ ,10 $\beta$  - desA - pregnan-5-one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] and ethyl vinyl ketone according to the procedure of Example 1.

#### EXAMPLE 5.

17 $\alpha$  - [propyn - (1) - yl - (1)] - 17 $\beta$ -hydroxy - 9 $\beta$ ,10 $\alpha$  - androstan - 4 - en - 3-one was prepared by condensing methyl vinyl ketone with 17 $\alpha$  - [propyn - (1) - yl - (1)] - 17 $\beta$  - hydroxy - 9 $\beta$ ,10 $\beta$  - desA - androstan-5-one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] according to the procedure of Example 1. The product melted at 164°—165°C.

#### EXAMPLE 6.

17 $\alpha$  - [2 - methyl - propen - (2) - yl - (1)] - 17 $\beta$  - hydroxy - 9 $\beta$ ,10 $\alpha$  - androst - 4 - en - 3-one was prepared from 17 $\alpha$ -[2-methyl-propen - (2) - yl - (1)] - 17 $\beta$  - hydroxy-9 $\beta$ ,10 $\beta$  - desA - androstan - 5 - one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] by condensation of the latter with methyl vinyl ketone according to the procedure of Example 1. The product melted at 106°—108°C.

#### EXAMPLE 7.

16 $\alpha$  - Hydroxy - 20,20 - ethylenedioxy-9 $\beta$ ,10 $\alpha$  - pregn - 4 - en - 3 - one was prepared by condensing 16 $\alpha$ -acetoxy-20,20-ethylenedioxy - desA - 9 $\beta$ ,10 $\beta$  - pregnan - 5 - one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] with methyl vinyl ketone according to the procedure of Example 1.

#### EXAMPLE 8.

16 $\alpha$  - Methyl - 20,20 - ethylenedioxy-9 $\beta$ ,10 $\alpha$  - pregn - 4 - en - 3 - one was prepared by condensing 16 $\alpha$ -methyl-20,20-ethylene-dioxy - 9 $\beta$ ,10 $\beta$  - desA - pregnan - 5 - one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] with methyl vinyl ketone according to the procedure of Example 1.

#### EXAMPLE 9.

21 - Hydroxy - 20,20 - ethylenedioxy-9 $\beta$ ,10 $\alpha$  - pregn - 4 - en - 3 - one was prepared from 21-acetoxy-20,20-ethylenedioxy-9 $\beta$ ,10 $\beta$  - desA - pregnan - 5-one [prepared as

described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] by condensing the latter with methyl vinyl ketone according to the procedure of Example 3.

#### EXAMPLE 10.

20 $\beta$  - Hydroxy - 16 $\alpha$ ,17 $\alpha$  - isopropylidenedioxy - 9 $\beta$ ,10 $\alpha$  - pregn - 4 - en - 3 - one was prepared by condensing methyl vinyl ketone with 20 $\beta$  - hydroxy - 16 $\alpha$ ,17 $\alpha$  - isopropylidenedioxy - desA - 9 $\beta$ ,10 $\beta$  - pregnan - 5 - one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] according to the procedure of Example 1.

#### EXAMPLE 11.

7 $\alpha$ ,17 $\alpha$  - Dimethyl - 9 $\beta$ ,10 $\alpha$  - testosterone was prepared from 7 $\alpha$ ,17 $\alpha$  - dimethyl - 17 $\beta$ -hydroxy - desA - 9 $\beta$ ,10 $\beta$  - androstan - 5 - one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] by condensing the latter with methyl vinyl ketone according to the procedure of Example 1.

#### EXAMPLE 12.

20 $\beta$  - Hydroxy - 17 $\alpha$  - methyl - 9 $\beta$ ,10 $\alpha$ -pregn - 4 - en - 3 - one was prepared by condensing 17 $\alpha$  - methyl - 20 $\beta$  - hydroxy-9 $\beta$ ,10 $\beta$  - desA - pregnan - 5 - one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] with methyl vinyl ketone according to the procedure of Example 1.

#### EXAMPLE 13.

17 $\alpha$  - Methyl - 9 $\beta$ ,10 $\alpha$  - testosterone was prepared from 17 $\alpha$  - methyl - 17 $\beta$  - hydroxy-desA - 9 $\beta$ ,10 $\beta$  - androstan - 5 - one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] by condensation of the latter with methyl vinyl ketone according to the procedure of Example 1. The product melted at 128°—129°C.

#### EXAMPLE 14.

Condensation of 11 $\alpha$ ,20 $\beta$  - dihydroxy - 9 $\beta$ ,10 $\beta$  - desA - pregnan - 5 - one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] with methyl vinyl ketone according to the procedure of Example 1 gave 11 $\alpha$ ,20 $\beta$ -dihydroxy-9 $\beta$ ,10 $\alpha$ -pregn-4-en-3-one.

#### EXAMPLE 15.

3 - (17 $\beta$  - hydroxy - 3 - oxo - 9 $\beta$ ,10 $\alpha$ -andro - 4 - en - 17 $\alpha$  - yl) - propionic acid lactone was prepared by condensing 3-(17 $\beta$ -hydroxy - 5 - oxo - 9 $\beta$ ,10 $\beta$  - desA - androstan-17 $\alpha$  - yl) - propionic acid lactone [prepared as described in the specification of our copend-

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ing Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] with methyl vinyl ketone according to the procedure of Example 1.

5 EXAMPLE 16.

17 $\alpha$ ,20;20,21 - bis(methylenedioxy)-9 $\beta$ ,10 $\alpha$ -pregn-4-en-3-one was prepared by condensing methyl vinyl ketone with 17 $\alpha$ ,20;20,21-bis-(methylenedioxy) - 9 $\beta$ ,10 $\beta$  - desA - pregnan-5-one [prepared as described in the specifica-  
10 tion of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] according to the procedure of Example 1.

15 EXAMPLE 17.

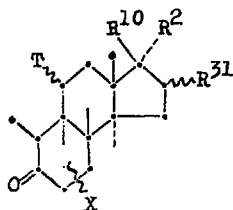
20 $\beta$  - hydroxy - 9 $\beta$ ,10 $\alpha$  - pregna - 1,4-dien-3-one was prepared by condensation of 20 $\beta$  - hydroxy - 9 $\beta$ ,10 $\beta$  - desA - pregnan - 5-one [prepared as described in the specification of our copending Application for Letters  
20 Patent no: 36706/67 (now serial no: 1,103,988)] with one equivalent of methyl ethynyl ketone in boiling benzene solution, catalyzed by sodium hydride.

25 It will be appreciated that when compounds of the pregnane series are referred to in this specification these compounds are of the 17 $\beta$ -pregnane series unless specifically indicated to the contrary.

30 WHAT WE CLAIM IS:—

1) A process for the manufacture of 3-keto-4-dehydro and 3-keto-1,4-bisdehydro-9 $\beta$ ,10 $\alpha$ -steroids of the androstane and pregnane series, which process comprises condensing a 9 $\beta$ ,10 $\beta$ -desA - androstan - 5 - one or 9 $\beta$ ,10 $\beta$  - desA - pregnan-5-one with a lower-alkyl vinyl ketone or a lower-alkyl ethynyl ketone respectively.

2) A process as set forth in claim 1, wherein a compound of the formula



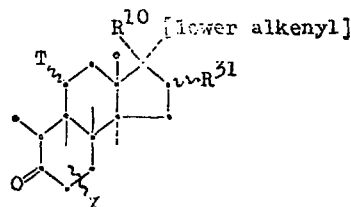
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wherein R<sup>10</sup> represents a hydroxy or esterified hydroxy group, R<sup>2</sup> represents a hydrogen atom or a lower-alkyl group or R<sup>10</sup> together with R<sup>2</sup> represents an oxo, lower-alkylenedioxy or 17 $\beta$  - hydroxy - 17 $\alpha$  - (lower alkanolic acid) lactone group, R<sup>31</sup> represents a hydrogen atom or a lower-alkyl, hydroxy or esterified hydroxy group, X represents a hydrogen or halogen atom or a lower-alkyl, lower alkylthio or lower-alkanoylthio group in the 6- of 7-position and T represents a hydrogen atom or a hydroxy or esterified hydroxy group, is used as the desA-steroid starting material.

3) A process as set forth in claim 2, wherein a 17 $\beta$  - hydroxy - 17 $\alpha$  - (lower alkyl)-9 $\beta$ ,10 $\beta$ -desA-androstan-5-one is used.

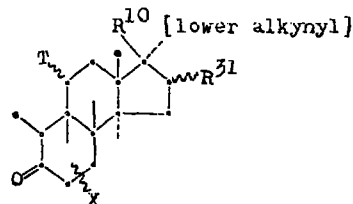
4) A process as set forth in claim 3, wherein a 17 $\beta$  - hydroxy - 17 $\alpha$  - ethyl - 9 $\beta$ ,10 $\beta$ -desA-androstan-5-one is used.

5) A process as set forth in claim 1, wherein a compound of the formula



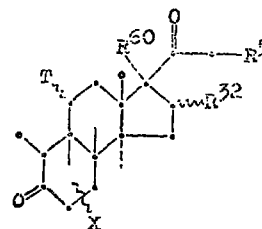
wherein R<sup>10</sup>, R<sup>31</sup>, T and X have the significance given in claim 2, is used as the desA-steroid starting material.

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



wherein R<sup>10</sup>, R<sup>31</sup>, T and X have the significance given in claim 1, is used as the desA-steroid starting material.

7) A process as set forth in claim 1, wherein a compound of the formula



wherein R<sup>32</sup> represents a hydrogen or fluorine atom or a lower-alkyl, hydroxy or esterified hydroxy group, R<sup>5</sup> represents a hydrogen or halogen atom, R<sup>60</sup> represents a hydrogen or halogen atom or a lower-alkyl, hydroxy or esterified hydroxy group and T and X have the significance given in claim 2, or a 20-ketal derivative thereof, a 16 $\alpha$ ,17 $\alpha$ -ketal or acetal derivative of such a compound in which R<sup>32</sup> and R<sup>60</sup> each represent a hydroxy group, a derivative of such a compound in which the 20-oxo group is reduced to a 20-hydroxy group or a corresponding compound in which said 20-hydroxy group is esterified, is used as the desA-steroid starting material.

8) A process as set forth in claim 7, wherein 20 - hydroxy - 17 $\beta$ ,17 $\alpha$ ,10 $\beta$  - desA - pregnan-5-one is used.

9) A process as set forth in claim 1, wherein a compound of the formula

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ing Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] with methyl vinyl ketone according to the procedure of Example 1.

5 **EXAMPLE 16.**

17 $\alpha$ ,20;20,21 - bis(methylenedioxy)-9 $\beta$ ,10 $\alpha$ -pregn-4-en-3-one was prepared by condensing methyl vinyl ketone with 17 $\alpha$ ,20;20,21-bis(methylenedioxy) - 9 $\beta$ ,10 $\beta$  - desA - pregnan-5-one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] according to the procedure of Example 1.

15 **EXAMPLE 17.**

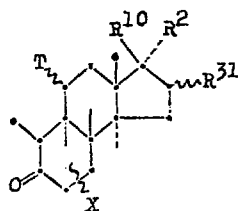
20 $\beta$  - hydroxy - 9 $\beta$ ,10 $\alpha$  - pregna - 1,4-dien-3-one was prepared by condensation of 20 $\beta$  - hydroxy - 9 $\beta$ ,10 $\beta$  - desA - pregnan - 5-one [prepared as described in the specification of our copending Application for Letters Patent no: 36706/67 (now serial no: 1,103,988)] with one equivalent of methyl ethynyl ketone in boiling benzene solution, catalyzed by sodium hydride.

25 It will be appreciated that when compounds of the pregnane series are referred to in this specification these compounds are of the 17 $\beta$ -pregnane series unless specifically indicated to the contrary.

30 **WHAT WE CLAIM IS:—**

1) A process for the manufacture of 3-keto-4-dehydro and 3-keto-1,4-bisdehydro-9 $\beta$ ,10 $\alpha$ -steroids of the androstane and pregnane series, which process comprises condensing a 9 $\beta$ ,10 $\beta$ -desA - androstan - 5 - one or 9 $\beta$ ,10 $\beta$  - desA - pregnan-5-one with a lower-alkyl vinyl ketone or a lower-alkyl ethynyl ketone respectively.

2) A process as set forth in claim 1, wherein a compound of the formula

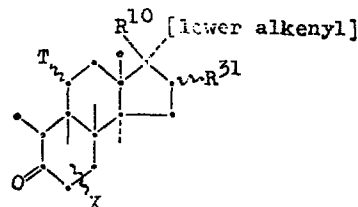


wherein R<sup>10</sup> represents a hydroxy or esterified hydroxy group, R<sup>2</sup> represents a hydrogen atom or a lower-alkyl group or R<sup>10</sup> together with R<sup>2</sup> represents an oxo, lower-alkylenedioxy or 17 $\beta$  - hydroxy - 17 $\alpha$  - (lower alkanolic acid) lactone group, R<sup>31</sup> represents a hydrogen atom or a lower-alkyl, hydroxy or esterified hydroxy group, X represents a hydrogen or halogen atom or a lower-alkyl, lower alkylthio or lower-alkanoylthio group in the 6- or 7-position and T represents a hydrogen atom or a hydroxy or esterified hydroxy group, is used as the desA-steroid starting material.

3) A process as set forth in claim 2, wherein a 17 $\beta$  - hydroxy - 17 $\alpha$  - (lower alkyl)-9 $\beta$ ,10 $\beta$ -desA-androstan-5-one is used.

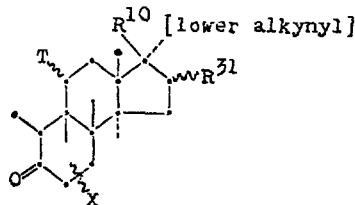
4) A process as set forth in claim 3, wherein a 17 $\beta$  - hydroxy - 17 $\alpha$  - ethyl - 9 $\beta$ ,10 $\beta$ -desA-androstan-5-one is used.

5) A process as set forth in claim 1, wherein a compound of the formula



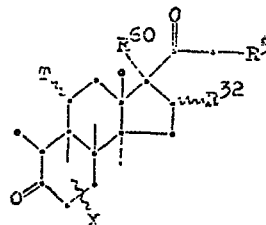
wherein R<sup>10</sup>, R<sup>31</sup>, T and X have the significance given in claim 2, is used as the desA-steroid starting material.

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



wherein R<sup>10</sup>, R<sup>31</sup>, T and X have the significance given in claim 1, is used as the desA-steroid starting material.

7) A process as set forth in claim 1, wherein a compound of the formula

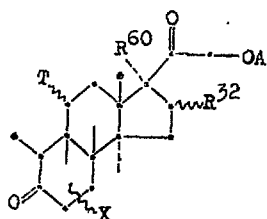


wherein R<sup>32</sup> represents a hydrogen or fluorine atom or a lower-alkyl, hydroxy or esterified hydroxy group, R<sup>5</sup> represents a hydrogen or halogen atom, R<sup>60</sup> represents a hydrogen or halogen atom or a lower-alkyl, hydroxy or esterified hydroxy group and T and X have the significance given in claim 2, or a 20-ketal derivative thereof, a 16 $\alpha$ ,17 $\alpha$ -ketal or acetal derivative of such a compound in which R<sup>32</sup> and R<sup>60</sup> each represent a hydroxy group, a derivative of such a compound in which the 20-oxo group is reduced to a 20-hydroxy group or a corresponding compound in which said 20-hydroxy group is esterified, is used as the desA-steroid starting material.

8) A process as set forth in claim 7, wherein 20 - hydroxy - 17 $\beta$ ,17 $\alpha$ ,10 $\beta$  - desA - pregnan-5-one is used.

9) A process as set forth in claim 1, wherein a compound of the formula





- wherein T and X have the significance given in claim 2,  $R^{32}$  and  $R^{60}$  have the significance given in claim 7 and OA represents a hydroxy or esterified hydroxy group, or a  $17\alpha,20;20,21$ -bis(methylenedioxy) derivatives of such a compound in which OA and  $R^{60}$  each represent a hydroxy group, a  $17\alpha,21$ -ketal or acetal derivative of such a compound in which OA and  $R^{60}$  each represent a hydroxy group, a  $16\alpha,17\alpha$ -ketal or acetal derivative of such a compound in which  $R^{32}$  and  $R^{60}$  each represent a hydroxy

group, a derivative of such a compound in which the 20-keto group is reduced to a 20-hydroxy group or a corresponding compound in which said 20-hydroxy group is esterified, is used as the desA-steroid starting material. 15

10) A process as set forth in any one of claims 1 to 9 inclusive wherein said desA-steroid is condensed with methyl vinyl ketone. 20

11) A process for the manufacture of  $9\beta,10\alpha$ -steroids of the androstane and pregnane series, substantially as described with reference to the Examples.

12)  $9\beta,10\alpha$ -steroids of the androstane and pregnane series, when manufactured by the process claimed in any one of claims 1 to 11 inclusive. 25

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