

1103,986



# PATENT SPECIFICATION

NO. DRAWINGS

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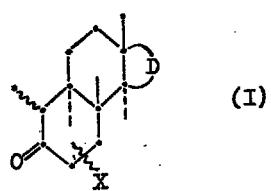
Int. Cl.:—C 07 c 49/38, C 07 c 173/00

## COMPLETE SPECIFICATION Novel Des-A-Steroids

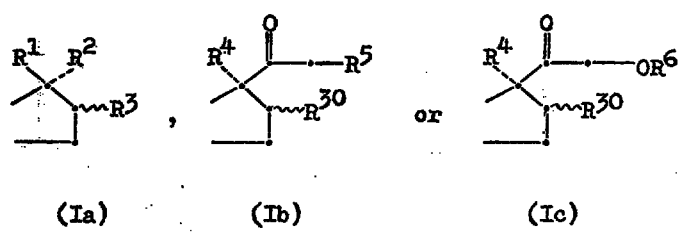
5 We, F. HOFFMANN-LA ROCHE & Co.,  
 AKTIENGESELLSCHAFT, a Swiss Company of  
 124—184 Grenzacherstrasse, Basle, Switzer-  
 land, do hereby declare the invention, for  
 which we pray that a patent may be granted  
 to us, and the method by which it is to be  
 performed, to be particularly described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

10 The present invention is concerned with  
 novel des-A-steroids.

The novel des-A-steroids provided by the  
 present invention are compounds of the  
 general formula



wherein X represents a hydrogen atom or a  
 lower-alkyl, lower-alkylthio or lower-alkanoyl-  
 thio group in the 6- or 7-position or a halo-  
 gen atom in the 7-position and D represents  
 a grouping of the formula



25 in which R<sup>1</sup> represents a hydroxy or esterified  
 hydroxy 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>  
 represents an oxo, lower-alkylenedioxy or  
 17β-hydroxy-17α-(lower alkanolic acid) lac-  
 30 tone group, R<sup>3</sup> represents a hydrogen atom  
 or a lower-alkyl, hydroxy or esterified hydroxy  
 group, R<sup>4</sup> represents a hydrogen or halogen  
 atom or a lower-alkyl, hydroxy or esterified  
 hydroxy group, R<sup>5</sup> represents a hydrogen or  
 halogen atom, OR<sup>6</sup> represents a hydroxy or  
 esterified hydroxy group and R<sup>30</sup> represents  
 a hydrogen or fluorine atom or a lower-alkyl,  
 hydroxy or esterified hydroxy group as well

as 20-ketals of those compounds containing  
 grouping Ib, 16-17-ketals and acetals of  
 those compounds containing grouping Ib or  
 Ic in which R<sup>4</sup> and R<sup>30</sup> each represent a  
 hydroxy group, 17-20; 20,21-bis(methylene-  
 dioxy) derivatives of those compounds con-  
 taining grouping Ic in which R<sup>4</sup> and OR<sup>6</sup>  
 each represent a hydroxy group, 17α,21-ketals  
 and acetals of those compounds containing  
 grouping Ic in which R<sup>4</sup> and OR<sup>6</sup> each repre-  
 sent a hydroxy group and compounds in which  
 any 20-ketal group is reduced to a 20-  
 hydroxy group and compounds in which said  
 20-hydroxy group is esterified.

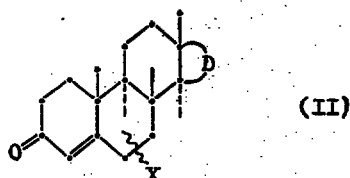
[Price 4s. 6d.]

35  
 16a, 17a-  
 17a, 20;  
 40  
 45

The novel des-A-steroids provided by the invention are valuable intermediates for the manufacture of  $9\beta,10\alpha$ -steroids of the androstane and pregnane series; for example via the des-A- $\Delta^9$ -steroids which form part of the subject matter of our copending application for Letters Patent no: 36705/67 (now serial no: 1103987).

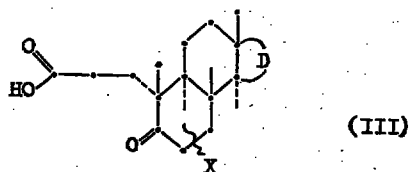
The novel des-A-steroids provided by the invention can be prepared by a number of methods.

Thus, according to one method, they can be prepared from steroids of 3-oxo-androst-4-ene or 3-oxo-17 $\beta$ -pregn-4-ene series by a reaction sequence which involves as a first step an oxidative ring-opening of ring-A of the natural steroid. For this oxidative ring-opening there can be used as starting materials, natural steroids of the 3-oxo-androst-4-ene or 3-oxo-17 $\beta$ -pregn-4-ene series of the general formula



wherein X and D have the significance given earlier.

The oxidative ring-opening of a natural steroid of formula II yields a 5-oxo-3,5-seco-A-norandrost-3-oic acid or a 5-oxo-3,5-seco-A-norpregn-3-oic acid of the general formula

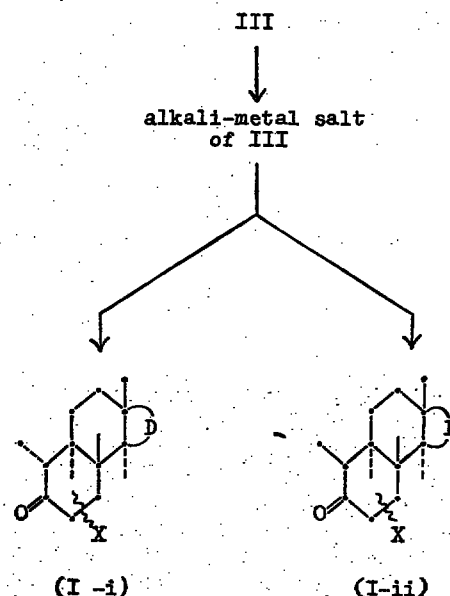


wherein X and D have the significance given earlier. The oxidative ring-opening of the compound of formula II can be performed by a variety of methods. In a preferred embodiment, it is effected by ozonolysis. The ozonolysis is suitably carried out in an organic solvent; for example, acetic acid, ethyl acetate, methanol, chloroform or methylene chloride or a mixture of two or more of such solvents such as (ethyl acetate)/(acetic acid) or (ethyl acetate)/(methylene chloride). Moreover, the ozonolysis is advantageously conducted at below room temperature. Thus, it is preferably conducted at a temperature between about  $-17^\circ\text{C}$  and  $25^\circ\text{C}$ . The resulting ozonides can be decomposed by conventional means; for example, by treatment with water, hydrogen peroxide in water, acetic acid or ethyl acetate. The oxidative ring-opening of

a compound of a formula II to give a compound of formula III can also be effected by other oxidation methods; for example, by treatment with hydrogen peroxide. It should be noted that an oxidative ring-opening either by ozonolysis or by treatment with hydrogen peroxide does not require protection of any of the substituents at C-16 or C-17. However, these substituents may be protected if desired. On the other hand, the oxidative ring-opening can also be effected by oxidation with chromium trioxide or by treatment with sodium periodate and potassium permanganate in potassium carbonate solution, but, if these oxidation agents are used, it is necessary to protect any secondary hydroxy groups which might be present (such as a 16,17 $\beta$ - or 21-hydroxy group). For the purpose of these oxidations, protection with non-aromatic protecting groups is preferred.

Some of the acids of formula III are claimed *per se* in the specification of our copending Application for Letters Patent no: 36702/67 (now serial no: 1103984).

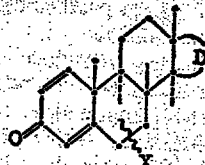
Following the oxidative ring-opening of the A-ring, the so-obtained 5-oxo-3,5-seco-A-norandrost-3-oic acid or 5-oxo-3,5-seco-A-norpregn-3-oic acid of formula III is converted into a mixture of a  $10\alpha$ -desA-androst-5-one and a  $10\beta$ -desA-androst-5-one or a mixture of a  $10\alpha$ -desA-pregn-5-one and a  $10\beta$ -desA-pregn-5-one as illustrated by the following scheme:



wherein X and D have the significance given earlier. Depending on the significance of D, the compounds of formula I-i are  $10\alpha$ -desA-androst-5-ones or  $10\alpha$ -desA-pregn-5-ones and the compounds of formula I-ii are  $10\beta$ -desA-androst-5-ones or  $10\beta$ -desA-pregn-5-ones. The conversion of a compound of a

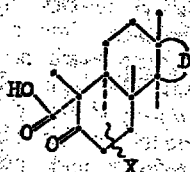
formula III into the compounds of formulae I—i and I—ii is effected by pyrolysis. In carrying out the pyrolysis, it is desirable to convert the 3-oic acid of formula III into a corresponding metal salt; for example, an alkali-metal salt such as the sodium salt. This conversion into a metal salt can be effected prior to pyrolysis (e.g. by treating the acid with sodium hydroxide) or *in situ* during the course of the pyrolysis (e.g. by fusing the 3-oic acid with a mixture of sodium acetate and potassium acetate). The pyrolysis can be carried out at atmospheric pressure or in a vacuum, but is preferably carried out in a vacuum, at a temperature of from about 200° C to 350°C in the presence of a proton acceptor; for example, an alkali-metal or alkaline-earth-metal salt of a weak organic acid such as, for example, potassium acetate, sodium acetate, sodium phenyl-acetate or sodium bicarbonate. Especially preferred is a vacuum of from about 0.001 to 0.5 mm of mercury. It is advantageous to conduct the pyrolysis under alkaline conditions; that is to say, at a pH greater than 7.

According to another method, compounds of formula I—i can be prepared from compounds of the general formula



(IV)

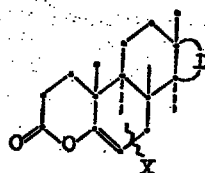
wherein X and D have the significance given earlier, by oxidative ring-opening of the A-ring thereof followed by elimination of the residue of the A-ring. The oxidative ring-opening of the compound of formula IV can be effected by ozonolysis as described earlier. Such ozonolysis of a compound of formula IV yields a compound of the general formula



(V)

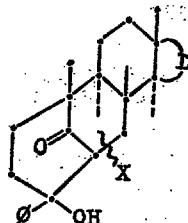
wherein X and D have the significance given earlier. The removal of the residue of the A-ring from the compound of formula V (i.e. decarboxylation) can be effected by heating the compound in an acidic or basic medium. It is preferred to heat to the reflux temperature of the medium, which is preferably an inert organic solvent such as an alkanol containing not more than 6 carbon atoms (e.g. ethanol), dioxan or ether. The decarboxylation mainly yields a compound of formula I—i, but a minor amount of the corresponding 10β-isomer or formula I—ii is also obtained.

According to yet another method, compounds of formula I—i can also be prepared from a compound of formula V by forming an enol-lactone thereof; that is to say, by forming a 4-oxa-androst-5-en-3-one or a 4-oxa-pregn-5-en-3-one of the general formula



(VI)

wherein X and D have the significance given earlier, which can then be reacted with a GRIGNARD reagent (such as phenyl-magnesium bromide or phenyl-lithium) to form an aldol of, for example, the formula



(VII)

wherein X and D have the significance given earlier and φ represents phenyl.

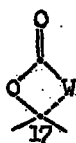
Upon treatment with an alkali-metal hydroxide such as potassium hydroxide at an elevated temperature (e.g. from about 200°C to 240°C) the aldol is converted into the corresponding 10α-desA-androstan-5-one or 10α-desA-pregnan-5-one of the formula I—i.

Although both the 10β-compounds of formula I—ii and the 10α-compounds of formula I—i are of value in the manufacture of 9β,10α-steroids of the androstane and pregnane series, it is sometimes preferable to convert the 10β-compounds of formula I—ii into the corresponding 10α-compounds of formula I—i. This conversion can be effected by treating a 10β-desA-androstan-5-one or 10β-desA-pregn-5-one of formula I—ii with any base capable of producing a carbanion; for example, it is suitable to use an alkali-metal alkoxide containing not more than 6 carbon atoms in an organic solvent such as an alkanol containing not more than 6 carbon atoms (for example, sodium ethoxide in an ethanol solution or sodium methoxide in a methanol solution).

The conversion of compounds of formula V into compounds of formula I—i and I—ii via the alkali-metal salt and pyrolysis thereof can be effected without protection of any of the substituents which might be present at C-16 or C-17. However, if desired, the conversion can be effected with protecting groups present on substituents in the C-16 or C-17 position.



It will be appreciated that the term 'lower alkyl' is used in this description and in the claims appended hereto to mean both straight-chain and branched-chain alkyl groups containing not more than 6 carbon atoms (e.g. methyl, ethyl, propyl and isopropyl). The term 'lower alkanoyl' is similarly used to mean alkanoyl groups containing not more than 6 carbon atoms (e.g. acetyl). The term 'halogen' means iodine, bromine, chlorine and fluorine. The expression '17 $\beta$ -hydroxy-17 $\alpha$ -(lower alkanoyl) lactone' refers to a configuration at the C-17 carbon atom as illustrated as follows:



wherein W is a low-alkylene group such as ethylene or propylene. The term 'lower alkylene' is used to mean an alkylene group containing not more than 6 carbon atoms. With regard to X, the preferred des-A-steroids provided by the invention 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 esterified hydroxy groups referred to earlier can be derived from any available acid that can subsequently be hydrolysed to regenerate the hydroxy group. Examples of acids which are useful for this purpose are alkanoyl 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).

The 20-ketals referred to earlier are suitably derived from alkanediols containing not more than 6 carbon atoms.

The 16 $\alpha$ ,17 $\alpha$ - and 17 $\alpha$ ,21-acetals referred to earlier can be derived 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 alkeneglycol 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 low-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 aromatic-(lower alkyl) ketones (such as cyclopentyl benzyl ketone and cyclohexyl phenethyl ketone), 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-butanol 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 and *p*-fluoro-benzaldehyde), 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*-dimethylbenzaldehyde), monocyclic carbocyclic 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 low-alkyl ketones (e.g. *p*-chloro-acetophenone and *p*-chloro-propiofenone), (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

lower-alkylene

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65

70

75

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95

100

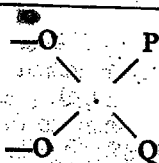
105

110

115

hemiacetal

Especially



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.

As mentioned earlier, it may be necessary to protect hydroxy groups present in the C-16, C-17 or C-21 position. The 16-hydroxy, 17 $\alpha$ -hydroxy, 17 $\beta$ -hydroxy or 21-hydroxy groups can be protected by esterification as described earlier or by etherification. A suitable ether protecting group is, for example, the tetrahydro-pyranyl ether group. Also, protection for the 16 $\alpha$ -hydroxy, 17 $\alpha$ -hydroxy or 21-hydroxy groups can be effected by forming the lower-alkyl orthoesters thereof; that is, 16 $\alpha$ ,17 $\alpha$ - or 17 $\alpha$ ,21- (lower alkyl) orthoesters. In compounds containing the dihydroxy-acetone side-chain at the 17-carbon atom (for example, compounds containing grouping Ic in which R<sup>4</sup> and OR<sup>5</sup> each represent 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 17,21-diester. The 17,21-acetal or ketal and 17,21-diester hinder the 20-ketone group and minimize 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 16 $\alpha$ -hydroxy and 17 $\alpha$ -hydroxy group are present, these groups can be protected by the formation of a 16 $\alpha$ ,17 $\alpha$ -acetal or ketal. The various protecting groups mentioned earlier can be removed by methods known *per se*; for example, by mild acid hydrolysis.

The following examples illustrate the manner in which the novel des-A-steroids provided by the invention can be obtained:

#### EXAMPLE 1

A solution of 3.2 g of 17 $\alpha$ -ethyl-testosterone in 50 ml of methylene chloride and 25 ml of ethyl acetate was ozonized at -70°C [acetone/(dry ice) bath] until the solution was blue in colour. After oxygen had been passed through, the solution was evaporated *in vacuo* at room temperature. The syrupy residue was then dissolved in 100 ml of glacial acetic acid and, after addition of 5 ml of 30 per cent hydrogen peroxide, left for 24 hours at 0°-5°C. Following this time, it was evaporated to dryness, dissolved in 1500 ml of ether, and extracted with 2-N sodium carbonate solution. The alkaline extract was poured in ice-cold hydrochloric acid. The resulting crystalline 17 $\alpha$ -ethyl-17 $\beta$ -

hydroxy - 5 - oxo - 3,5 - seco - A - norandrostan-3-oic acid was filtered, washed with water and dried. After recrystallization from acetone, it melted at 196-197°C.

A solution of 1.5 g of 17 $\alpha$ -ethyl-17 $\beta$ -hydroxy - 5 - oxo - 3,5 - seco - A - norandrost-3-oic acid in 100 ml of methanol was titrated with 2-N sodium methoxide to the reddish colour of phenolphthalein, and then evaporated to dryness *in vacuo*, giving the sodium salt of 17 $\alpha$ -ethyl-17 $\beta$ -hydroxy-5-oxo - 3,5 - seco - A - norandrost-3 - oic acid as the residue. 5 g of sodium phenylacetate were added to the residue and the mixture was pyrolysed *in vacuo* (pressure less than 0.1 mm) at 285°-295°C for 2.5 hours. The sublimate was dissolved in acetone, filtered and the filtrate concentrated *in vacuo*. The resulting syrupy residue was chromatographed on a column of 60 g of activated magnesium silicate adsorbent. The fractions eluted with benzene and 0.5 per cent ethyl acetate in benzene were combined and gave 17 $\alpha$  - ethyl - 17 $\beta$  - hydroxy - 10 $\alpha$  - desA - androstan-5-one, which had a melting point of 94°-95°C after recrystallization from petroleum ether. The fractions eluted with 2 per cent and 5 per cent ethyl acetate in benzene were combined and gave 17 $\alpha$ -ethyl-17 $\beta$ -hydroxy - 10 $\beta$  - desA - androstan - 5 - one, which had a melting point of 185°-185.5°C after two recrystallizations from petroleum ether.

One equivalent of sodium ethoxide dissolved in 5 ml of absolute ethanol was added to a solution of 100 mg of 17 $\alpha$ -ethyl-17 $\beta$ -hydroxy - 10 $\beta$  - desA - androstan - 5 - one in 10 ml of absolute ethanol. The reaction mixture was maintained at room temperature overnight, then acidified with glacial acetic acid, poured in water and extracted with methylene chloride. The extract was washed with water, dried over anhydrous sodium sulphate and concentrated *in vacuo*. Thin layer chromatography showed the product to be 17 $\alpha$  - ethyl - 17 $\beta$  - hydroxy - 10 $\alpha$  - desA - androstan-5-one. It was obtained in a crystalline state from (petroleum/ether)/ether, and melted at 89°-95°C.

17 $\alpha$  - Ethyl - 17 $\beta$  - hydroxy - 10 $\alpha$  - desA - androstan-5-one was also prepared as follows:

A solution of 3 g of 17 $\alpha$ -ethyl-17 $\beta$ -hydroxy-androsta-1,4-dien-3-one in 75 ml of methylene chloride and 25 ml of ethyl acetate was ozonized at -70°C until it became blue. After evaporation to dryness, the residue was dissolved in 100 ml of glacial acetic acid containing 5 ml of 30 per cent hydrogen peroxide and the solution allowed to stand at room temperature for 2 days. The reaction mixture was concentrated to dryness and the residue dissolved in 1 litre of ether. The ether solution was then extruded ten times with 25 ml portions of aqueous 2-N sodium carbonate solution and the carbonate extracts



were acidified with ice-cold concentrated hydrochloric acid. The non-crystalline precipitate containing 17 $\alpha$ -ethyl-17 $\beta$ -hydroxy-10 $\alpha$ -carboxy-desA-androstan-5-one was separated by filtration, dried, dissolved in 135 ml of absolute ethanol and, after addition of 9 ml of aqueous 2-N sodium hydroxide, boiled for 1 hour. The reaction mixture was concentrated to a small volume *in vacuo* and diluted with 1750 ml of ether. The ether solution was washed with water, dried over anhydrous sodium sulphate and concentrated to dryness *in vacuo*. The residue was crystallized from ether/(petroleum ether) to give 17 $\alpha$ -ethyl-17 $\beta$ -hydroxy-10 $\alpha$ -desA-androstan-5-one of melting point 89°-90°C.

## EXAMPLE 2

17 $\beta$ -Hydroxy-5-oxo-3,5-seco-A-norandrostane-3-oic was prepared by ozonolysis of testosterone according to the procedure of the first paragraph of Example 1.

17 $\beta$ -Hydroxy-10 $\alpha$ -desA-androstan-5-one and 17 $\beta$ -hydroxy-10 $\beta$ -desA-androstan-5-one were prepared from 17 $\beta$ -hydroxy-5-oxo-3,5-seco-A-norandrostane-3-oic acid according to the procedure of the second and third paragraphs of Example 1.

## EXAMPLE 3

16 $\alpha$ -Acetoxy-20,20-ethylenedioxy-pregn-4-en-3-one was prepared by acetylation of 16 $\alpha$ -hydroxy-20,20-ethylenedioxy-pregn-4-en-3-one with one equivalent of acetic anhydride in pyridine solution at room temperature for 2 hours, followed by concentration to dryness *in vacuo*. 16 $\alpha$ -acetoxy-20,20-ethylenedioxy-5-oxo-3,5-seco-A-norpregnan-3-oic acid was prepared by ozonolysis of 16 $\alpha$ -acetoxy-20,20-ethylenedioxy-pregn-4-en-3-one according to the procedure of the first paragraph of Example 1.

16 $\alpha$ -Acetoxy-20,20-ethylenedioxy-10 $\alpha$ -desA-pregnan-5-one and 16 $\alpha$ -acetoxy-20,20-ethylenedioxy-10 $\beta$ -desA-pregnan-5-one were prepared from 16 $\alpha$ -acetoxy-20,20-ethylenedioxy-5-oxo-3,5-seco-A-norpregnan-3-oic acid by conversion of the latter to its sodium salt followed by pyrolysis (according to the second and third paragraphs of Example 1) and reacetylation with acetic anhydride and pyridine.

## EXAMPLE 4

3 $\beta$ -Hydroxy-16 $\alpha$ -methyl-20,20-ethylenedioxy-pregn-5-ene was prepared by ketalisation of 3 $\beta$ -hydroxy-16 $\alpha$ -methyl-pregn-5-en-20-one in benzene solution with ethylene glycol using *paratoluene*-sulphonic acid as catalyst. Pyridine/chromic acid oxidation of the so-obtained 3 $\beta$ -hydroxy-16 $\alpha$ -methyl-20,20-ethylenedioxy-pregn-5-ene yielded 16 $\alpha$ -methyl-20,20-ethylenedioxy-pregn-4-en-3-one. 16 $\alpha$ -methyl-20,20-ethy-

lenedioxy-5-oxo-3,5-seco-A-norpregnan-3-oic was prepared by ozonolysis of 16 $\alpha$ -methyl-20,20-ethylenedioxy-pregn-4-en-3-one according to the procedure of the first paragraph of Example 1.

16 $\alpha$ -Methyl-20,20-ethylenedioxy-10 $\alpha$ -desA-pregnan-5-one and 16 $\alpha$ -methyl-20,20-ethylenedioxy-10 $\beta$ -desA-pregnan-5-one were prepared from 16 $\alpha$ -methyl-20,20-ethylenedioxy-5-oxo-3,5-seco-A-norpregnan-3-oic acid by conversion of the latter to its sodium salt followed by pyrolysis according to the procedure of the second and third paragraphs of Example 1.

## EXAMPLE 5

7 $\alpha$ ,17 $\alpha$ -Dimethyl-17 $\beta$ -hydroxy-5-oxo-3,5-seco-A-norandrostane-3-oic acid was prepared from 7 $\alpha$ ,17 $\alpha$ -dimethyl-testosterone by ozonolysis of the latter according to the procedure of the first paragraph of Example 1.

7 $\alpha$ ,17 $\alpha$ -Dimethyl-17 $\beta$ -hydroxy-10 $\alpha$ -desA-androstan-5-one and 7 $\alpha$ ,17 $\alpha$ -dimethyl-17 $\beta$ -hydroxy-10 $\beta$ -desA-androstan-5-one were prepared from 7 $\alpha$ ,17 $\alpha$ -dimethyl-17 $\beta$ -hydroxy-5-oxo-3,5-seco-A-norandrostane-3-oic acid by conversion of the latter to its sodium salt followed by pyrolysis according to the procedure of the second and third paragraphs of Example 1.

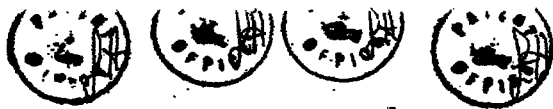
## EXAMPLE 6

17 $\alpha$ -Methyl-17 $\beta$ -hydroxy-5-oxo-3,5-seco-A-norandrostane-3-oic acid was prepared from 17 $\alpha$ -methyl-testosterone by ozonolysis according to the procedure of the first paragraph of Example 1. The so-obtained product melted at 191°-194°C;  $[\alpha]_D^{25} = +9.8^\circ$  ( $c=1$  in chloroform).

17 $\alpha$ -methyl-17 $\beta$ -hydroxy-10 $\alpha$ -desA-androstan-5-one and 17 $\alpha$ -methyl-17 $\beta$ -hydroxy-10 $\beta$ -desA-androstan-5-one were prepared from 17 $\alpha$ -methyl-17 $\beta$ -hydroxy-5-oxo-3,5-seco-A-norandrostane-3-oic acid by conversion of the latter to its sodium salt followed by pyrolysis according to the procedure of the second and third paragraphs of Example 1. The so-obtained 17 $\alpha$ -methyl-17 $\beta$ -hydroxy-10 $\alpha$ -desA-androstan-5-one melted at 96°-97°C;  $[\alpha]_D^{25} = -28.2^\circ$  ( $c=0.5$  in chloroform) and the 10 $\beta$ -isomer melted at 165°-167°C;  $[\alpha]_D^{25} = -19.8^\circ$  ( $c=0.5$  in chloroform).

## EXAMPLE 7

3-(17 $\beta$ -hydroxy-5-oxo-3,5-seco-A-norandrostane-17 $\alpha$ -yl-3-oic acid)-propionic acid lactone was prepared by ozonolysis of 3-(3-oxo-17 $\beta$ -hydroxy-androst-4-en-17 $\alpha$ -yl)-propionic acid lactone, according to the procedure of the first paragraph of Example 1.



acid 5 3 - (17 $\beta$  - hydroxy - 5 - oxo - 10 $\alpha$  - desA - androstan - 17 $\alpha$  - yl) - propionic acid lactone and 3 - (17 $\beta$  - hydroxy - 5 - oxo - 10 $\beta$  - desA - androstan - 17 $\alpha$  - yl) - propionic acid lactone were prepared from 3-(17 $\beta$  - hydroxy - 5 - oxo - 3,5 - seco - A - nor - androstan - 17 $\alpha$  - yl - 3 - oic acid) - propionic acid lactone by conversion of the latter to its sodium salt followed by pyrolysis according to the procedure of the second and third paragraphs of Example 1.

## EXAMPLE 8

20 $\beta$  - Acetoxy - 5 - oxo - 3,5 - seco - A - norpregnan-3-oic acid was prepared by ozonolysis of 20 $\beta$ -acetoxy-pregn-4-en-3-one according to the procedure of the first paragraph of Example 1.

5 - 20 $\beta$  - hydroxy - 10 $\alpha$  - desA - pregnan - 5 $\alpha$  - one and 20 $\beta$  - hydroxy - 10 $\beta$  - desA - pregnan were prepared from 20 $\beta$ -hydroxy-5-oxo - 3,5 - seco - A - norpregnan - 3 - oic acid by conversion of the latter to its sodium salt followed by pyrolysis according to the procedure of the second and third paragraphs of Example 1.

## EXAMPLE 9

5,20 - Dioxo - 3,5 - seco - A - norpregnan-3-oic acid was prepared by ozonolysis of progesterone according to the first paragraph of Example 1.

10 $\alpha$  - desA - pregna - 5,20 - dione and 10 $\beta$  - desA - pregnan - 5,20 - dione were prepared from 5,20-dioxo-3,5-seco-A-norpregnan-3-oic acid by conversion of the latter to its sodium salt followed by pyrolysis according to the procedure of the second and third paragraphs of Example 1.

The activated magnesium silicate adsorbent

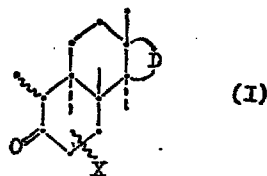
used in the foregoing Examples is a synthetic magnesia-silicagel marketed by the Floridin Company, Tallahassee, Florida. 100-200 mesh material was used.

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.

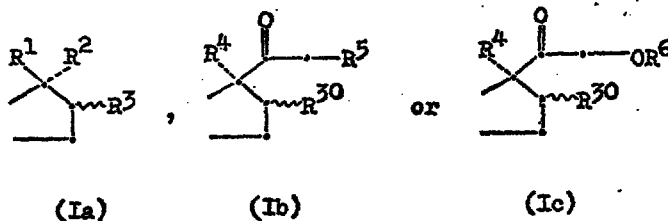
It will be appreciated that in the formulae given in this description and accompanying claims the dots denote carbon atoms or CH, CH<sub>2</sub> or CH<sub>3</sub> groups, the residual valencies being satisfied by hydrogen atoms; such valencies only being shown to indicate hydrogen atoms when configuration is of significance, and then as untruncated solid or broken lines. Valencies shown as solid lines denote  $\beta$ -configuration and those shown as broken lines denote  $\alpha$ -configuration. The dots representing angular methyl groups are enlarged solely for reasons of clarity.

## WHAT WE CLAIM IS:—

1) Compounds of the general formula:



wherein X represents a hydrogen atom or a lower-alkyl, lower-alkylthio or lower-alkanoylthio group in the 6- or 7-position or a halogen atom in the 7-position and D represents a grouping of the formula



70 in which R<sup>1</sup> represents a hydroxy or esterified hydroxy 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> represents an oxo, lower-alkylenedioxy 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 esterified hydroxy group, R<sup>4</sup> represents a hydrogen or esterified atom or a lower-alkyl, hydroxy or esterified hydroxy group, R<sup>5</sup> represents a hydrogen or halogen atom, OR<sup>6</sup> represents a hydroxy or esterified hydroxy group and R<sup>30</sup> represents

a hydrogen or fluorine atom or a lower-alkyl, hydroxy or esterified hydroxy group as well as 20-ketals of those compounds containing grouping Ib, 16 $\alpha$ ,17 $\alpha$ -ketals and acetals of those compounds containing grouping Ib or Ic in which R<sup>4</sup> and R<sup>30</sup> each represent a hydroxy group, 17 $\alpha$ ,20;20,21-bis(methylenedioxy) derivatives of those compounds containing grouping Ic in which R<sup>4</sup> and OR<sup>6</sup> each represent a hydroxy group, 17 $\alpha$ ,21-ketals and acetals of those compounds containing grouping Ic in which R<sup>4</sup> and OR<sup>6</sup> each repre-



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Tallahassee

acid 5 3 - (17 $\beta$  - hydroxy - 5 - oxo - 10 $\alpha$  - desA - androstan - 17 $\alpha$  - yl) - propionic acid lactone and 3 - (17 $\beta$  - hydroxy - 5 - oxo - 10 $\beta$  - desA - androstan - 17 $\alpha$  - yl) - propionic acid lactone were prepared from 3 - (17 $\beta$  - hydroxy - 5 - oxo - 3,5 - seco - A - nor - androstan - 17 $\alpha$  - yl - 3 - oic acid) - propionic acid lactone by conversion of the latter to its sodium salt followed by pyrolysis according to the procedure of the second and third paragraphs of Example 1.

#### EXAMPLE 8

20 $\beta$  - Acetoxy - 5 - oxo - 3,5 - seco - A - norpregnan-3-oic acid was prepared by ozonolysis of 20 $\beta$ -acetoxy-pregn-4-en-3-one according to the procedure of the first paragraph of Example 1.

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The activated magnesium silicate adsorbent

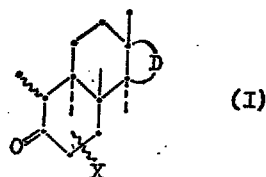
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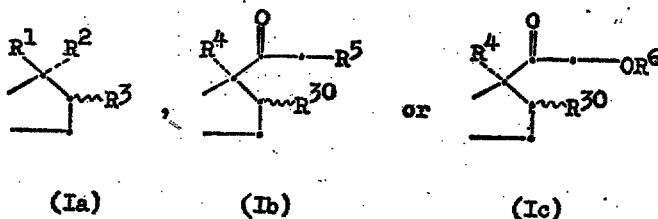
It will be appreciated that in the formulae given in this description and accompanying claims the dots denote carbon atoms or CH, CH<sub>2</sub> or CH<sub>3</sub> groups, the residual valencies being satisfied by hydrogen atoms; such valencies only being shown to indicate hydrogen atoms when configuration is of significance, and then as unternminated solid or broken lines. Valencies shown as solid lines denote  $\beta$ -configuration and those shown as broken lines denote  $\alpha$ -configuration. The dots representing angular methyl groups are enlarged solely for reasons of clarity.

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a hydrogen or fluorine atom or a lower-alkyl, hydroxy or esterified hydroxy group as well as 20-ketals of those compounds containing grouping Ib, 16 $\alpha$ ,17 $\alpha$ -ketals and acetals of those compounds containing grouping Ib or Ic in which R<sup>4</sup> and R<sup>30</sup> each represent a hydroxy group, 17 $\alpha$ ,20;20,21-bis(methylenedioxy) derivatives of those compounds containing grouping Ic in which R<sup>4</sup> and OR<sup>6</sup> each represent a hydroxy group, 17 $\alpha$ ,21-ketals and acetals of those compounds containing grouping Ic in which R<sup>4</sup> and OR<sup>6</sup> each repre-

lower-alkanoylthio



sent a hydroxy group and compounds in which any 20-keto group is reduced to a 20-hydroxy group and compounds in which said 20-hydroxy group is esterified.

- 5 2)  $17\alpha$  - (Lower alkyl) -  $17\beta$  - hydroxy -  $10\alpha$ -desA-androstan-5-ones.  
3)  $17\alpha$  - Ethyl -  $17\beta$  - hydroxy -  $10\alpha$  - desA-androstan-5-one.

4)  $17\alpha$  - (Lower alkyl) -  $17\beta$  - hydroxy -  $10\beta$ -desA-androstan-5-ones.

5)  $17\alpha$  - Ethyl -  $17\beta$  - hydroxy -  $10\beta$  - desA-androstan-5-one.

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Aktiengesellschaft.

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