

PATENT SPECIFICATION

NO DRAWINGS

1.103.983



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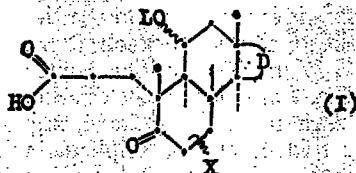
COMPLETE SPECIFICATION

Novel 3,5-Seco-A-Nor-Steroid Derivatives

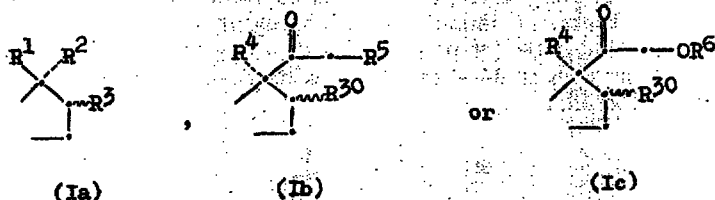
We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following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

The present invention is concerned with 3,5 - seco - A - nor - steroid derivatives.

The novel 3,5 - seco - A - nor - steroid derivatives provided by the present invention are compounds of the general formula



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

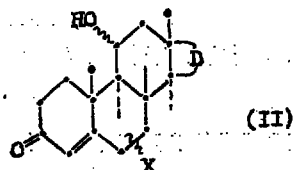


in which R¹ represents a hydroxy or esterified hydroxy group, R² represents a hydrogen atom or a lower-alkyl group or R¹ and R² together represent an oxo, lower - alkylene-dioxy or 17β - hydroxy - 17α - (lower alkanolic acid) lactone group, R³ represents a hydrogen atom or a lower - alkyl, hydroxy or esterified hydroxy group, R⁴ represents a hydrogen or halogen atom or a lower - alkyl, hydroxy or esterified hydroxy group, R⁵ represents a hydrogen or halogen atom, OR⁶ represents a hydroxy or esterified hydroxy group and R³⁰ 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, 16α,17α-ketals and acetals of those compounds containing grouping Ib or Ic in which R⁴ and R³⁰ each represent a hydroxy group, 17α,20;20,21 - bis(methylene-dioxy) derivatives of those compounds containing grouping Ic in which R⁴ and OR⁶ each represent a hydroxy group, 17α,21-ketals and acetals of those compounds con-

taining grouping Ic in which R⁴ and OR⁶ each represent a hydroxy group and compounds in which any 20-keto group is reduced to a 20-hydroxy group or in which said 20-hydroxy group is esterified, and salts of same.

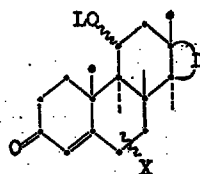
The novel 3,5 - seco - A - nor - steroid derivatives aforesaid are valuable intermediates for the manufacture of 9 β ,10 α - steroids of the androstane and pregnane series; for example, via the desA-steroids which form part of the subject matter of our copending Application for Letters Patent no: 36705/67 (now serial no: 1,103,987).

The novel 3,5 - seco - A - nor - steroid derivatives aforesaid can be prepared by esterifying an 11 - hydroxy - androst (or pregn) - 4 - en - 3 - one of the general formula



(wherein X and D have the significance given earlier) so as to form an esterified hydroxy group in the 11-position, oxidising the resulting ester by ozonolysis and, if desired, converting the resulting acid into a salt.

Thus, in the first stage of the preparation of the novel 3,5 - seco - A - nor-steroid derivatives aforesaid, an 11 - hydroxy - androst (pregn) - 4 - en - 3 - one is reacted with an acid or a reactive derivative thereof to form an esterified hydroxy group in the 11-position. By reactive derivative is meant, for example, a halide (e.g. a chloride) or an anhydride. Though either 11 β or 11 α - hydroxy - androst (or pregn) - 4 - en - 3 - ones of formula II can be used, it is preferable to use the 11 α - hydroxy - androst (or pregn) - 4 - en - 3 - ones. Prior to the esterification, it is preferable to protect hydroxy groups present in the C-16, C-17 or C-21 position. Suitable acids for the esterification of the 11 - hydroxy group (i.e. formation of an esterified hydroxy group in the 11-position) are inorganic acids such as phosphoric acid, organic carboxylic acids such as anthraquinone β - carboxylic acid or organic sulphonic acids. Examples of the latter are toluene - sulphonic acids (especially *p* - toluene - sulphonic acid), lower alkyl-sulphonic acids (such as methane - sulphonic acid) and nitrophenyl - sulphonic acids (especially *p* - nitro - phenyl - sulphonic acid). A lower alkyl - sulphonyloxy group such as the mesyloxy group is especially preferred as the esterified hydroxy group in the 11-position. However, when it is desired to react an 11-hydroxy - androst (or pregn) - 4 - en - 3 - one of formula II with an agent forming a sulphonyloxy group, an 11 α - hydroxy - androst (or pregn) - 4 - en - 3 - one should be used. The foregoing esterification yields an 11 - (esterified hydroxy) - androst (or pregn) - 4 - en - 3 - one of the general formula

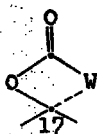


wherein X, D and LO have the significance given earlier.

In the next stage, the so-formed 11 - (esterified hydroxy) - androst (or pregn) - 4 - en - 3 - one of formula III is subjected to oxidative ring-opening of the A-ring to yield the corresponding 11 - (esterified hydroxy) - 5 - oxo - 3,5 - seco - A - norandrost - 3 - oic acid or 11 - (esterified hydroxy) - 5 - oxo - 3,5 - seco - A - norpregn - 3 - oic acid of formula I. The oxidative ring-opening of the A-ring of an 11-(esterified hydroxy) - androst (or pregn) - 4 - en - 3 - one of formula III 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 -70°C and 25°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. It should be noted that the oxidative ring-opening by ozonolysis does not require protection of any of the substituents at C-16 or C-17. Certain of these substituents may, however, be protected if desired.

It will be appreciated that the term 'lower alkyl' is used in this description and in the accompanying claims to mean both straight-chain and branched-chain alkyl groups containing not more than six carbon atoms (e.g. methyl, ethyl, propyl and *iso*-propyl). The term 'lower alkanoyl' means an alkanoyl group containing not more than six carbon atoms (e.g. acetyl). The term 'halogen' means iodine, bromine, chlorine and fluorine. The expression '17 β - hydroxy - 17 α - (lower alkanoyl)lactone' refers to a configuration at the C-17 carbon atom as illustrated as follows:



wherein W is a lower-alkylene group such as ethylene or propylene. The term 'lower alkylene' denotes an alkylene group containing not more than six carbon atoms. With regard to X, the preferred derivatives 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.

As mentioned earlier, certain of the substituents in the compounds of formula I and in the 11 - hydroxy - androst (or pregn) - 4 - en - 3 - ones of formula II can be present in protected form.

Thus, a 16 α - hydroxy, 17 α - hydroxy, 17 β - hydroxy or 21 - hydroxy group can be protected by esterification or etherification. Any available acid which will form an ester that can subsequently be hydrolysed to regenerate the hydroxy group is suitable. Examples of acids which are useful for this purpose are alkanoyl acids containing not more than six carbon atoms (e.g. acetic acid), caproic acid, benzoic acid, phosphoric acid and alkane dicarboxylic acids containing not more than six carbon atoms (e.g. succinic acid). Also, protection for the 16 α - hydroxy, 17 α - hydroxy or 21 - hydroxy groups can be effected by forming the lower-alkyl orthoethers thereof; that is to say, 16 α ,17 α - or 17 α ,21 - (lower alkyl) orthoethers. A suitable ether protecting group is, for example, the tetrahydropyranyl ether group. In compounds which contain the dihydroxy - acetone side-chain at the 17-carbon atom (for example, compounds containing grouping Ic' hereinbefore in which R⁴ and OR⁶ 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 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 16 α - hydroxy and 17 α -hydroxy group are present, these groups can be protected by the formation of a 16 α ,17 α -acetal or ketal. The various protecting groups mentioned earlier can be removed by methods known *per se*; for example, by mild acid hydrolysis.

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

The 16 α ,17 α - or 17 α ,21-acetals and ketals referred to earlier can be formed by reacting 16 α ,17 α - bis(hydroxy) or 17 α ,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 six carbon atoms) with the groups sought to be protected. Suitable aldehydes and ketones include lower-alkanals (that is to say, alkanals containing from two to six 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), *cyclo*alkanones (such as *cyclobutanone*, *cyclopentanone* and *cyclohexanone*), *cyclo*alkyl - (lower alkanals) (such as *cyclopentyl* carboxaldehyde and *cyclohexyl* carboxaldehyde), *cyclo*alkyl (lower alkyl) ketones (such as *cyclopentyl* propyl ketone, *cyclohexylmethyl* ethyl ketone), *dicyclo*alkyl ketones (such as *dicyclopentyl* ketones, *dicyclohexyl* ketone and *cyclopentyl cyclohexyl* ketone), *cyclo*alkyl monocyclic aromatic



4

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5

butanal

10

benzaldehydes

15

20

25

30



35



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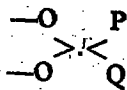
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ketones (such as cyclohexyl *p* - chloro - phenyl ketone, cyclopentyl *o* - methoxy - phenyl ketone, cyclopentyl *o,p* - dihydroxy - phenyl ketone and cyclohexyl - *m* - tolyl ketone), cycloalkyl (lower alkyl) monocyclic aromatic ketones (such as cyclopentylmethyl phenyl ketone), cycloalkyl monocyclic aromatic - (lower alkyl) ketones (such as cyclopentyl benzyl ketone and cyclohexyl phenethyl 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) - benzaldehyde (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 phenylacetaldehyde, α - phenyl - propionaldehyde, β - 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, α,α,α - trifluoro - acetophenone, propiophenone, butyrophenone, valerophenone, halo-phenone), (lower alkoxy) - phenyl lower - alkyl ketones (such as *p* - chloro - propiophenone), di(lower alkoxy) - phenyl lower - alkyl ketones (such as *p* - anisyl methyl ketone), (lower alkyl) - phenyl lower - alkyl ketones, hydroxy - phenyl lower-alkyl ketones, di(lower alkyl) - phenyl lower - alkyl ketones (such as methyl *p* - tolyl 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. Especially suitable are those aldehydes or ketones which, with the 16 α ,17 α - or 17 α ,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. The terms 'lower alkoxy' and 'lower alkanones' are used herein to mean alkoxy groups and alkanones respectively which contain not more than six carbon atoms.

The following Examples illustrate the manner in which the novel 3,5 - seco - A - nor - steroid derivatives provided by the invention can be obtained.

EXAMPLE 1.

6 ml of methanesulphonyl chloride were added to a solution of 20 g of 11 α -hydroxy-progesterone in 150 ml of pyridine maintained at 0°C, and the reaction mixture was allowed to stand overnight at 0°C. It was then diluted with a large excess of water and extracted with chloroform. The organic extracts were washed with 2 - N hydrochloric acid and water, then dried over anhydrous sodium sulphate and evaporated *in vacuo*. The solid residue was recrystallized from methanol to give 11 α - methanesulphonyloxy - progesterone of melting point 159.5°—160°C; $[\alpha]_D^{25} = +145.6^\circ$ ($c=1$ in chloroform).

A solution of 12 g of 11 α - methanesulphonyloxy - progesterone in 300 ml of (methylene chloride)/(ethyl acetate) (2:1) was treated with ozone at -70°C until the solution became blue in colour. The excess of ozone was removed by bubbling oxygen through the reaction mixture for five minutes. Methylene chloride was then removed under reduced pressure, and the solution diluted to 200 ml with ethyl acetate. After addition of 12 ml of 30 per cent aqueous hydrogen peroxide, the reaction mixture was allowed to stand overnight at 2°C (i.e. in the refrigerator), then evaporated to a volume of 75 ml and diluted with 125 ml of benzene. The aqueous carbonate followed by combining the aqueous extracts was acidified to pH 2 with cold concentrated hydrochloric acid and extracted with methylene chloride. This extract was dried over anhydrous sodium sulphate and evaporated to dryness *in vacuo*. The residue crystallized on trituration with ether/acetone mixture, yielding crude 11 α - meth-



anesulphonyloxy - 5,20 - dioxo - 3, 5 - seco - A - norpregnan - 3 - oic acid. After recrystallization from acetone/(petroleum ether) it had a melting point of 152°—153°C; $[\alpha]_D^{25} = +47.9^\circ$ ($c=1$ in chloroform).

A solution of 6 g of 11 α - methanesulphonyloxy - 5,20 - dioxo - 3,5 - seco - A - norpregnan - 3 - oic acid in 150 ml of methanol was mixed with a solution of 1.5 g of sodium carbonate in 55 ml of water. The mixture was then transferred into a 1 litre sublimation flask and evaporated to dryness to yield the sodium salt of 11 α - methanesulphonyloxy - 5,20 - dioxo - 3,5 - seco - A - norpregnan - 3 - oic acid.

EXAMPLE 2

A medium consisting of 20 g of EDAMINE enzymatic digest of lactalbumin, 3 g of corn steep liquor and 60 g of technical dextrose diluted to 1 litre with tap water and adjusted to a pH of 4.3—4.5 was prepared. 12 litres of this sterilised medium were inoculated with *Rhizopus nigricans* minus strain (A.T.C.C 6227b) and incubated for 24 hours at 28°C using a rate of aeration and stirring such that the oxygen uptake was 6.3—7 millimoles per hour per litre of Na₂SO₃ according to the method of COOPER *et al*, Ind. Eng. Chem., 1944, 36, 504. 6 g of 17 α - acetoxy - progesterone in 150 ml of acetone were added to this medium containing a 24 hour growth of *Rhizopus nigricans* minus strain. The resulting suspension of the steroid in the culture was incubated under the same conditions of temperature and aeration for an additional 24 hour period, after which the beer and mycelium were extracted. The mycelium was then filtered, washed twice, each time with a volume of acetone approximately equal in volume to the mycelium, and extracted twice, each time with a volume of methylene chloride approximately equal to the volume of the mycelium. The acetone and methylene chloride extracts including solvent were then added to the beer filtrate. The mixed extracts and beer filtrate were then extracted successively with 2 portions of methylene chloride, each portion being half the volume of the mixed extracts and beer filtrate, and then with 2 portions of methylene chloride, each portion being one quarter of the volume of the mixed extracts and beer filtrate. The combined methylene chloride extracts were then washed with 2 portions of a 2 per cent aqueous solution of sodium bicarbonate, each portion being one tenth of the the volume of the combined methylene chloride extracts. The methylene chloride extracts were then dried with ca 3—5 g of anhydrous sodium sulphate per litre of solvent and then filtered. The solvent was removed from the filtrate by distillation and the residue dissolved in a minimum of methylene chloride, filtered and the solvent evaporated from the filtrate. The resulting crystals were dried and washed five times, each time with a 5 ml portion of ether per gram of crystals. The crystals were recrystallized from ether, giving 17 α - acetoxy - 11 α - hydroxy - progesterone. 17 α - acetoxy - 11 α - methanesulphonyloxy - progesterone was prepared by treatment of 17 α - acetoxy - 11 α - hydroxy - progesterone with methanesulphonyl chloride according to the procedure of the first paragraph of Example 1.

17 α - Acetoxy - 5,20 - dioxo - 11 α - methanesulphonyloxy - 3,5 - seco - A - norpregnan - 3 - oic acid was prepared by ozonolysis of 17 α - acetoxy - 11 α - methanesulphonyloxy - progesterone according to the procedure of the second paragraph of Example 1.

17 α - Acetoxy - 5,20 - dioxo - 11 α - methanesulphonyloxy - 3,5 - seco - A - norpregnan - 3 - oic acid was converted into its sodium salt according to the procedure of the final paragraph of Example 1.

EXAMPLE 3

21 - Acetoxy - 11 α - hydroxy - 20,20 - ethylenedioxy - pregn - 4 - en - 3 - one was prepared by microbiological treatment of 21 - acetoxy - 20,20 - ethylenedioxy - pregn - 4 - en - 3 - one according to the procedure of the first paragraph of Example 2. 21 - Acetoxy - 11 α - methanesulphonyloxy - 20,20 - ethylenedioxy - pregn - 4 - en - 3 - one was prepared by treatment of 21 - acetoxy - 11 α - hydroxy - 20,20 - ethylenedioxy - pregn - 4 - en - 3 - one with methanesulphonyl chloride according to the procedure of the first paragraph of Example 1.

21 - Acetoxy - 11 α - methanesulphonyloxy - 20,20 - ethylenedioxy - 5 - oxo - 3,5 - seco - A - norpregnan - 3 - oic acid was prepared by ozonolysis of 21 - acetoxy - 11 α - methanesulphonyloxy - 20,20 - ethylenedioxy - pregn - 4 - en - 3 - one according to the procedure of the second paragraph of Example 1.

21 - Acetoxy - 11 α - methanesulphonyloxy - 20,20 - ethylenedioxy - 5 - oxo - 3,5 - seco - A - norpregnan - 3 - oic acid was converted into its sodium salt according to the procedure of the final paragraph of Example 1.

EXAMPLE 4

11 α - Methanesulphonyloxy - 16 α ,17 α - isopropylidenedioxy - progesterone was prepared by treatment of 11 α - hydroxy - 16 α ,17 α - isopropylidenedioxy - progesterone with methanesulphonyl chloride according to the procedure of the first paragraph of Example 1.

5,20 - Dioxo - 11 α - methanesulphonyloxy - 16 α ,17 α - isopropylidenedioxy - 3,5-seco - A - norpregnan - 3 - oic acid was prepared by ozonolysis of 11 α - methanesulphonyloxy - 16 α ,17 α - isopropylidenedioxy - progesterone according to the procedure of the second paragraph of Example 1.

5,20 - Dioxo - 11 α - methanesulphonyloxy - 16 α ,17 α - isopropylidenedioxy - 3,5-seco - A - norpregnan - 3 - oic acid was converted into its sodium salt according to the procedure of the final paragraph of Example 1.

EXAMPLE 5

11 α - Methanesulphonyloxy - 17 α - methyl - progesterone was prepared from 11 α - hydroxy - 17 α - methyl progesterone by treatment of the latter with methanesulphonyl chloride according to the procedure of the first paragraph of Example 1.

11 α - Methanesulphonyloxy - 17 α - methyl - 5,20 - dioxo - 3,5 - seco - A - norpregnan - 3 - oic acid was prepared from 11 α - methanesulphonyloxy - 17 α - methyl - progesterone by ozonolysis of the latter according to the procedure of the second paragraph of Example 1.

11 α - Methanesulphonyloxy - 17 α - methyl - 5,20 - dioxo - 3,5 - seco - A - norpregnan - 3 - oic acid was converted into its sodium salt according to the procedure of the final paragraph of Example 1.

EXAMPLE 6

A solution of 6 g of 11 α ,20 β - diacetoxy - pregn - 4 - en - 3 - one in 100 ml of methylene chloride and 50 ml of ethyl acetate was ozonized at -70°C. After methylene chloride had been removed by distillation *in vacuo*, the residual solution was diluted to 100 ml with ethyl acetate. 5 ml of 30 per cent hydrogen peroxide was added to this and the mixture was left overnight at room temperature. The reaction mixture was concentrated to dryness *in vacuo*, the residue taken up in 1 litre of ether, and the resulting solution extracted 10 times with 50 ml portions of 2 - N - aqueous sodium carbonate. The carbonate extract was then acidified with ice-cold concentrated hydrochloric acid. The precipitated product was separated by filtration and crystallized to give 11 α ,20 β - diacetoxy - 5 - oxo - 3,5 - seco - A - norpregnan - 3 - oic acid.

A methanolic solution of 5 g of 11 α ,20 β - diacetoxy - 5 - oxo - 3,5 - seco - A - norpregnan - 3 - oic acid was treated with 0.5 mol equivalents of sodium carbonate and evaporated to dryness *in vacuo* to yield the sodium salt of 11 α ,20 β - diacetoxy - 5 - oxo - 3,5 - seco - A - norpregnan - 3 - oic acid.

EXAMPLE 7

17 α ,20;20,21 - bis(methylenedioxy) - 11 α - methanesulphonyloxy - pregn - 4 - en - 3 - one was prepared by treatment of 17 α ,20;20,21 - bis(methylenedioxy) - 11 α - hydroxy - pregn - 4 - en - 3 - one with methanesulphonyl chloride according to the procedure of the first paragraph of Example 1.

17 α ,20;20,21 - bis(methylenedioxy) - 11 α - methanesulphonyloxy - 5 - oxo - 3,5-seco - A - norpregnan - 3 - oic acid was prepared by ozonolysis of 17 α ,20;20,21 - bis(methylenedioxy) - 11 α - methanesulphonyloxy - pregn - 4 - en - 3 - one according to the procedure of the second paragraph of Example 1.

17 α ,20;20,21 - Bis(methylenedioxy) - 11 α - methanesulphonyloxy - 5 - oxo - 3,5-seco - A - norpregnan - 3 - oic acid was converted into its sodium salt according to the procedure of the final paragraph of Example 1.

EXAMPLE 8

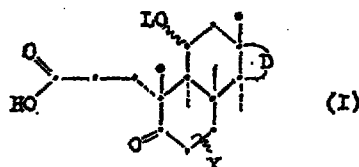
11 β - Formyloxy - 5,17 - dioxo - 3,5 - seco - A - norandrostan - 3 - oic acid was prepared from 11 β - formyloxy - androst - 4 - ene - 3,17 - dione by ozonolysis according to the procedure of the first paragraph of Example 1. The product thus obtained melted at 220°-221°C; $[\alpha]_D^{25} = +107^\circ$ (in dioxan). 11 β - Formyloxy - 5,17 - dioxo - 3,5 - seco - A - norandrostan - 3 - oic acid was converted into its sodium salt.

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

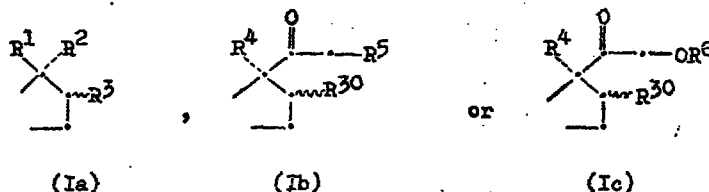
It will be appreciated that in the formulae given in this description and accompanying claims the dots denote carbon atoms or CH, CH₂ or CH₃ groups, the residual valencies being satisfied by hydrogen atoms; such valencies only being shown to indicate hydrogen atoms when configuration is of significance, and then as untermi-

WHAT WE CLAIM IS:—

1) Compounds of the general formula



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



in which R¹ represents a hydroxy or esterified hydroxy group, R² represents a hydrogen atom or a lower - alkyl group or R¹ and R² together represent an oxo, lower - alkylenedioxy or 17 β - hydroxy - 17 α - (lower alkanolic acid)lactone group, R³ represents a hydrogen atom or a lower - alkyl, hydroxy or esterified hydroxy group, R⁴ represents a hydrogen or halogen atom or a lower - alkyl, hydroxy or esterified hydroxy group, R⁵ represents a hydrogen or halogen atom, OR⁶ represents a hydroxy or esterified hydroxy group and R³⁰ 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 α ,17 α - ketals and acetals of those compounds containing grouping Ib or Ic in which R⁴ and R³⁰ each represent a hydroxy group, 17 α ,20;20,21 - bis(methylenedioxy) derivatives of those compounds containing grouping Ic in which R⁴ and OR⁶ each represent a hydroxy group, 17 α ,21 - ketals and acetals of those compounds containing grouping Ic in which R⁴ and OR⁶ each represent a hydroxy group and compounds in which any 20-keto group is reduced to a 20 - hydroxy group or in which said 20 - hydroxy group is esterified, and salts of same.

2) Compounds as formulated in claim 1, wherein the esterified hydroxy group LO has the α -configuration.

3) 5,20 - Dioxo - 11 α - hydroxy - A - nor - 3,5 - seco - pregnan - 3 - oic acid which is esterified with a sulphonic acid.

4) 5,20 - Dioxo - 11 α - mesyloxy - A - nor - 3,5 - seco - pregnan - 3 - oic acid.

5) 5,17 - Dioxo - 11 β - formyloxy - 3,5 - seco - A - norandrostan - 3 - oic acid.

W. D. WHITAKER,

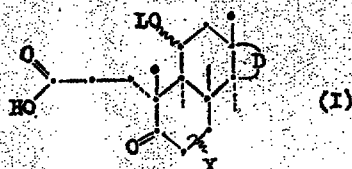
Patent Agent,

for F. Hoffmann-La Roche & Co.,
Aktiengesellschaft.

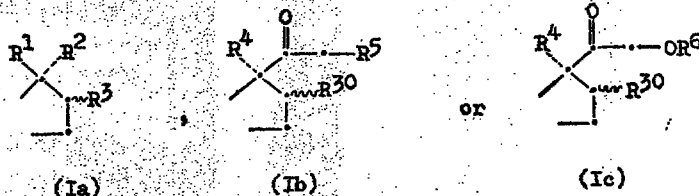
It will be appreciated that in the formulae given in this description and accompanying claims the dots denote carbon atoms or CH , CH_2 or CH_3 groups, the residual valencies being satisfied by hydrogen atoms; such valencies only being shown to indicate hydrogen atoms when configuration is of significance, and then as untruncated solid or broken lines. Valencies shown as solid lines denote β - configuration and those shown as broken lines denote α - 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 or halogen atom or a lower-alkyl, lower - alkylthio or lower - alkanoylthio group in the 6- or 7-position, LO represents an esterified hydroxy group and D represents a grouping of the formula



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 and R^2 together represent an oxo, lower - alkylenedioxy or 17 β - hydroxy - 17 α - (lower alkanoyl acid)lactone group, R^3 represents a hydrogen atom or a lower - alkyl, hydroxy or esterified hydroxy group, R^4 represents a hydrogen or halogen atom or a lower - alkyl, hydroxy or esterified hydroxy group, R^5 represents a hydrogen or halogen atom, OR^6 represents a hydroxy or esterified hydroxy group as well as 20 - ketals of those compounds containing grouping Ib, 16 α , 17 α - ketals and acetals of those compounds containing grouping Ib or Ic in which R^4 and R^{30} each represent a hydroxy group, 17 α , 20; 20, 21 - bis(methylenedioxy) derivatives of those compounds containing grouping Ic in which R^4 and OR^6 each represent a hydroxy group, 17 α , 21 - ketals and acetals of those compounds containing grouping Ic in which R^4 and OR^6 each represent a hydroxy group and compounds in which any 20-keto group is reduced to a 20 - hydroxy group or in which said 20 - hydroxy group is esterified, and salts of same.

- 2) Compounds as formulated in claim 1, wherein the esterified hydroxy group LO has the α -configuration.

3) 5,20 - Dioxo - 11 α - hydroxy - A - nor - 3,5 - seco - pregnan - 3 - oic acid which is esterified with a sulphonc acid.

- 4) 5,20 - Dioxo - 11 α - mesyloxy - A - nor - 3,5 - seco - pregnan - 3 - oic acid.
5) 5,17 - Dioxo - 11 β - formyloxy - 3,5 - seco - A - norandrostan - 3 - oic acid.

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