



PATENT SPECIFICATION

NO DRAWINGS

L 103,985

Date of Application and filing Complete Specification: 29 March, 1965.

No. 36703/67.

Application made in United States of America (No. 400,206) on 29 Sept., 1964.

(Divided out of No. 1,103,574.)

Complete Specification Published: 21 Feb., 1968.

© Crown Copyright 1968.

Index at acceptance:—C2 C(3A12A3, 3A12B6, 3A12C4, 3C4)

Int. Cl.:—C 07 c 49/38, C 07 c 143/68

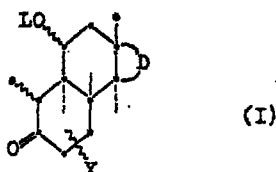
COMPLETE SPECIFICATION

Novel Des-A-Steroids

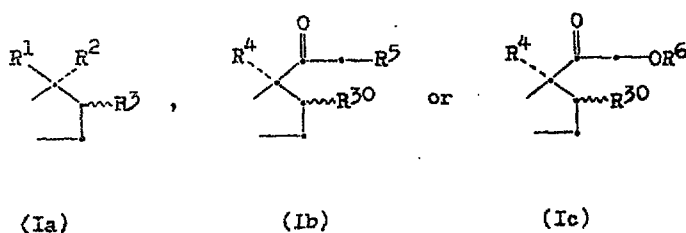
We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following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

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

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



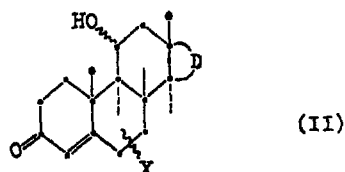
wherein X represents a hydrogen or halogen atom or a lower-alkyl, lower-alkylthio or lower-alkanoylthio group in the 6- or 7-position, LO represents a hydroxy or esterified hydroxy group and D represents a grouping of the formula



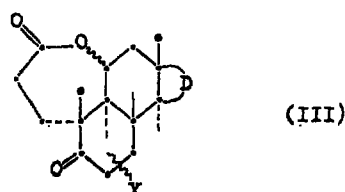
in which R¹ represents a hydroxy or esterified hydroxy group, R² represents a hydrogen atom or a lower-alkyl group or R¹ together with R² represents an oxo, lower-alkylenedioxy or 17β-hydroxy-17α-(lower alkanolic acid) lactone group, R³ represents a hydrogen atom or a lower-alkyl, hydroxy or esterified 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.

The novel des-A-steroids provided by the invention are valuable intermediates for the manufacture of 9β,10α-steroids of the androstane and pregnane series; for example, via the des-A-Δ⁹-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 oxidising an 11-hydroxy-androst(or pregn)-4-en-3-one of the general formula



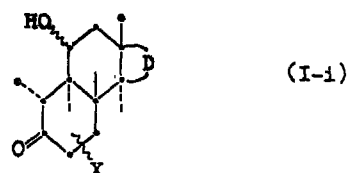
wherein X and D have the significance given earlier, by ozonolysis or by treatment with hydrogen peroxide, converting the resulting 5-oxo-11-hydroxy-3, 5-seco-A-norandrost(an or pregnan)-3-oic acid 3,11-lactone of the general formula



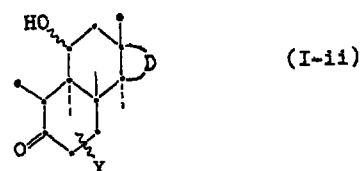
into an alkali-metal salt of the corresponding free acid, pyrolysing said alkali-metal salt and, if desired, esterifying the resulting 11-hydroxy-desA-androst(an or pregnan)-5-one so as to form an esterified hydroxy group in the 11-position.

The oxidation of an 11-hydroxy-androst(or pregn)-4-en-3-one of formula II and conversion of the resulting 5-oxo-11-hydroxy-3,5-seco-A-norandrost(an or pregnan)-3-oic acid 3,11-lactone into an alkali-metal salt of the corresponding keto-acid can be carried out by the methods described in the specification of our copending Application for Letters Patent no: 36700/67 (now serial no: 1103574) where said lactones and salts are claimed *per se*.

The pyrolysis, which can be carried out without isolation of the salt from the mixture in which it is obtained, yields a mixture of an 11-hydroxy-10 α -desA-androst(an-5-one and an 11-hydroxy-10 β -desA-androst(an-5-one or a mixture of an 11-hydroxy-10 α -desA-pregnan-5-one and an 11-hydroxy-10 β -desA-pregnan-5-one. The 10 α -pyrolysis products can be represented by the formula



(wherein X and D have the significance given earlier) and the 10 β pyrolysis products can be represented by the formula

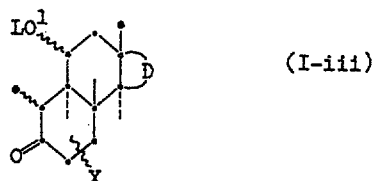


(wherein X and D have the significance given earlier).

The pyrolysis can be carried out at atmospheric pressure or in a vacuum, but it is preferably carried out in a vacuum, at a temperature 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, at a pH of greater than 7.

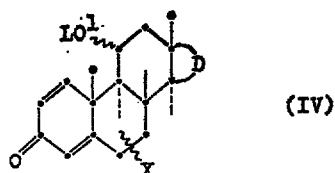
The 10α pyrolysis products of formula I—i hereinbefore can be converted into the more desirable 10β pyrolysis products of formula I—ii hereinbefore. This conversion can be effected by treating the 10α pyrolysis product with any base capable of producing a carbanion; for example, it is suitable to use 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 11-hydroxy-desA-androstan(or pregnan)-5-ones resulting from the foregoing pyrolysis can be subjected to esterification so as to convert the 11-hydroxy group to an esterified hydroxy group in the 11-position. This esterification can be effected by reaction with an acid or a reactive derivative thereof. By reactive derivative is meant, for example, a halide (e.g. a chloride) or an anhydride. 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 and 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-alkylsulphonyloxy group such as the mesyloxy group is especially preferred as the esterified hydroxy group in the 11-position. When it is desired to react a 11-hydroxy-desA-androstan(or pregnan)-5-one pyrolysis product with an agent forming a sulphonyloxy group, an 11 α -hydroxy pyrolysis product should be used. By the foregoing esterification there is thus obtained a compound of the formula

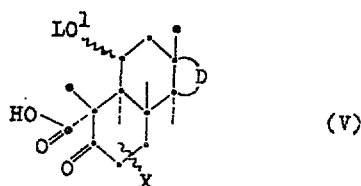


wherein X and D have the significance given earlier and LO^1 represents an esterified hydroxy group.

The compounds of formula I—iii can also be produced from compounds of the formula



wherein X, D and LO^1 have the significance given earlier. The compounds of formula IV can be produced from the corresponding 11-hydroxy compounds by esterification as described earlier in connection with the preparation of compounds of formula I—iii from the pyrolysis products of formula I—i and I—ii. The compounds of formula I—iii can be produced from the compounds of formula IV by oxidative ring-opening of the A-ring of a compound of formula IV followed by elimination of the residue of the A-ring. The oxidative ring-opening can be carried out by ozonolysis as described in the specification of our copending Application for Letters Patent no: 36700/67 (now serial no: 1103574) for the ozonolysis of an 11-hydroxy-androst(or pregn)-4-en-3-one of formula II to a 3,11-lactone of formula III. However, the ozonolysis of a compound of formula IV yields a compound of the formula





5
10
15

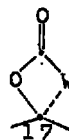
5

10

15

wherein X, D and LO¹ have the significance given earlier. A compound of formula V can then be converted into a compound of formula I—iii by removal of the residue of the A-ring (i.e. decarboxylation). This can be effected by heating the compound of formula V 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 an 10 α compound of formula I—iii, but a minor amount of the corresponding 10 β -isomer is also obtained.

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). Similarly, the term 'lower alkanoyl' is used to mean alkanoyl groups containing not more than 6 carbon atoms (e.g. acetyl). The term 'halogen' means chlorine, bromine, iodine and fluorine. The expression '17 β -hydroxy-17 α -(lower alkanoyl) lactone' refers to a configuration at the C-17 carbon atom illustrated as follows:—



wherein W is a lower-alkylene group such as ethylene or propylene. The term 'lower alkylene' means an alkylene group containing not more than 6 carbon atoms. With regard to X, the preferred desA-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 following Examples illustrate the manner in which the novel des-A-steroids provided by the invention can be prepared:—

EXAMPLE 1

A solution of 6.4 g of 11 α -hydroxy-progesterone in 100 ml of ethyl acetate and 50 ml of methylene chloride was treated with ozone at -70°C until the solution became blue in colour. Oxygen was then passed through and the solution evaporated *in vacuo* at room temperature. The so-obtained syrupy residue was dissolved in 100 ml of glacial acetic acid and, after the addition of 5 ml of 30 per cent hydrogen peroxide, left for 24 hours at 2°C (in an ice-box). The solution was then evaporated *in vacuo* and the residue triturated with ether, yielding crystals. Recrystallization from acetone yielded 11 α -hydroxy-3,5-seco-A-norpregnane-5,20-dione-3-oic acid, 3,11-lactone of melting point $253^{\circ}\text{—}256^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{25} = +193.3^{\circ}$ ($c=1$ in chloroform).

A methanolic solution of 7.5 g of 11 α -hydroxy-3,5-seco-A-norpregnane-5,20-dione-3-oic acid 3,11-lactone was treated with one equivalent of 10-N sodium hydroxide solution and then evaporated to dryness. 26 g of sodium phenylacetate were added to the so-obtained sodium salt and the mixture was pyrolysed at 295°C *in vacuo* for 2 hours. The crude sublimate was chromatographed on a silica-gel column and eluted with 10 per cent ethyl acetate in benzene. The amorphous solid 11 α -hydroxy-10 α -desA-pregnane-5,20-dione was first eluted from the column; Infrared spectrum in chloroform: 3620 and 3600 cm^{-1} ($-\text{OH}$), 1706 cm^{-1} (carbonyl group). Nuclear magnetic resonance spectrum in deuteriochloroform: a doublet for 10 α -CH₃ at 73.5 and 80.5 cycles per second downfield from tetramethyl-silane at 60 megacycles per second. Further elution of the column with 10 per cent ethyl acetate in benzene yielded crystalline 11 α -hydroxy-10 β -desA-pregnane-5,20-dione which was recrystallised from (methylene chloride)/(petroleum ether) and had a melting point of $150^{\circ}\text{—}152^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} = +84.0^{\circ}$ ($c=0.5$ in absolute ethanol).

100 mg of 11 α -hydroxy-10 β -desA-pregnane-5,20-dione were added to a solution of 100 mg of methanesulphonyl chloride in 0.7 ml of pyridine. The mixture was allowed to stand overnight at 2°C in a refrigerator, then diluted with 100 ml of



cm^{-1}

35

40

45

50

55

5

10

15

20

25

30

35

40

45

50

55

water and extracted with three 150 ml portions of chloroform and 100 ml of methylene chloride. The combined organic extracts were washed with water, 1-N hydrochloric acid and again with water, then dried over anhydrous sodium sulphate and evaporated *in vacuo*. The crystalline residue was recrystallized from ether, giving 11 α -hydroxy-10 β -desA-pregnane-5,20-dione methanesulphonate of melting point 139°C—140°C; $[\alpha]_D^{25} = +46^\circ$ ($c=0.5$ in absolute ethanol).

EXAMPLE 2

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*. 5 g of potassium acetate were added to the residue which was then pyrolysed at 295°C and 0.02 mm. The sublimate was chromatographed on a silica gel column to give 11 α ,20 β -diacetoxy-10 β -desA-pregnan-5-one.

EXAMPLE 3

11 β -Formyloxy-androsta-1,4-diene-3,17-dione was prepared by dissolving 11 β -hydroxy-androsta-1,4-diene-3,17-dione in an excess of formic acid and, after 1 hour at room temperature, pouring the reaction mixture on ice, then extracting in ether, drying the ether extract and evaporating. The product was then obtained by crystallization.

A solution of 11 β -formyloxy-androsta-1,4-diene-3,17-dione in methylene chloride and ethyl acetate was ozonized at -70° until it became blue. After evaporation to dryness the residue was dissolved in glacial acetic acid containing 5 per cent by volume 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 ether. The ether solution was then extracted with aqueous 2-N sodium carbonate solution and the carbonate extracts were acidified with ice-cold concentrated hydrochloric acid. The precipitate containing 11 β -formyloxy-10 ζ -carboxy-desA-androstane-5,17-dione was separated by filtration, dried, dissolved in ether and, after addition of aqueous 2-N sodium hydroxide, boiled for 1 hour. The reaction mixture was concentrated to a small volume *in vacuo* and diluted with 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 11 β -formyloxy-10 ζ -desA-androstane-5,17-dione. The product thus obtained melted at 117°—117.5°C; $[\alpha]_D^{25} = +93^\circ$ (in dioxan).

By hydrolysis of 11 β -formyloxy-10 ζ -desA-androstane-5,17-dione in 2% methanolic potassium hydroxide there was obtained 11 β -hydroxy-10 ζ -desA-androstane-5,17-dione which melted at 154°C; $[\alpha]_D^{26} = +96^\circ$ (in dioxan).

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 untermiated 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.

methanolic

Carbonate

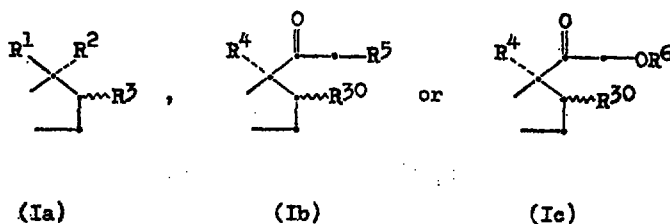
 -70°C

WHAT WE CLAIM IS:—

1. Compounds of the general formula



- 5 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 a hydroxy or esterified hydroxy group and D represents a grouping of the formula 5



10 in which R¹ represents a hydroxy or esterified hydroxy group, R² represents a hydrogen atom or a lower-alkyl group or R¹ together with R² represents an oxo, lower-alkylenedioxy or 17β-hydroxy-17α-(lower alkanic 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 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. 15

2. Compounds as set forth in claim 1, wherein the methyl group in the 10-position has the β-configuration.

3. 11α-Hydroxy-10β-desA-pregnan-5,20-dione.

4. 11α-Hydroxy-10β-desA-pregnan-5,20-dione which is esterified with a sulphonic acid. 20

5. 11α-Hydroxy-10β-desA-pregnan-5,20-dione methanesulphonate. 20

W. D. WHITAKER,
Patent Agent.
for F. Hoffman-La Roche & Co.,
Aktiengesellschaft.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1968.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which
copies may be obtained.

