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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

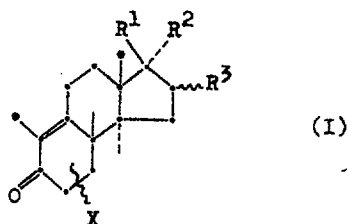
The preparation of Des-A-Steroids

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:—

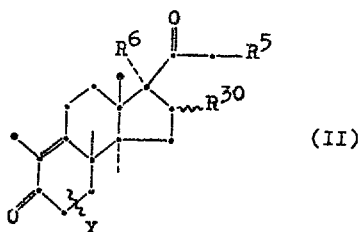
5 The present invention relates to a process for the preparation of des-A-steroids. More particularly, the invention is concerned with a process for the preparation of desA-androst(or pregn)-9-en-5-ones and with certain novel desA-androst(or pregn)-9-en-5-ones. 5

10 The desA-androst(or pregn)-9-en-5-one products of the present process are valuable intermediates for the manufacture of $9\beta,10\alpha$ -steroids of the androstane or pregnane series; for example, they can be catalytically hydrogenated as described and claimed in the specification of our copending Application for Letters Patent No. 36706/67 (now serial No: 1,103,988) to yield $9\beta,10\beta$ -desA-androstan(or pregnan)-5-ones which can be condensed with a lower-alkyl vinyl ketone or a lower-alkyl ethynyl ketone as described and claimed in the specification of our copending Application for Letters Patent No. 13173/65 (now serial No: 1,103,574) to yield $9\beta,10\alpha$ -steroids. 15

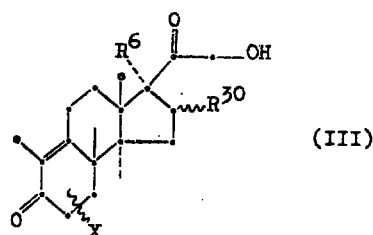
Especially useful des-A-steroids obtained by carrying out the present process are desA-androst-9-en-5-ones of the formula



20 and desA-pregnan-5-ones of the formula



and



in which formulae R^1 represents a hydroxy or lower-alkanoyloxy group, R^2 represents a hydrogen atom or a lower-alkyl group or R^1 together with R^2 represents an oxo or 17β -hydroxy- 17α -(lower alkanoyl) lactone group, R^3 represents a hydrogen atom or a lower-alkyl, hydroxy or lower-alkanoyloxy group, R^{30} represents a hydrogen or fluorine atom or a lower-alkyl, hydroxy or lower-alkanoyloxy group, R^5 represents a hydrogen or halogen atom, R^6 represents a hydrogen or halogen atom or a lower-alkyl or hydroxy group and X represents a hydrogen or halogen atom or a lower-alkyl, lower-alkylthio or lower-alkanoylthio group in the 6- or 7-position.

According to the process of the present invention, desA-androst(or pregn)-9-en-5-ones are prepared *either* by subjecting a 3-oxo-androst(or pregn)-4-ene to ozonolysis, pyrolysing an alkali-metal salt of the resulting 5-oxo-3,5-seco-A-norandrost(an or norpregnan)-3-oic acid and introducing a 9,10-double bond into the resulting desA-androst(an or pregnan)-5-one by means of a two-step sequence of halogenation and dehydrohalogenation *or* by esterifying an 11-hydroxy-androst(or pregn)-4-en-3-one so as to form an esterified hydroxy group in the 11-position, oxidising the resulting ester by ozonolysis or by treatment with hydrogen peroxide to form an 11-(esterified hydroxy)-5-oxo-3,5-seco-A-norandrost(an or norpregnan)-3-oic acid, converting said acid into an alkali-metal salt and pyrolysing said alkali-metal salt *or* by oxidising an 11-hydroxy-androst(or pregn)-4-en-3-one by ozonolysis or by treatment with hydrogen peroxide, converting the resulting 5-oxo-11-hydroxy-3,5-seco-A-norandrost(an or norpregnan)-3-oic acid 3,11-lactone into an alkali-metal salt of the corresponding keto-acid, pyrolysing said alkali-metal salt, esterifying the resulting 11-hydroxy-desA-androst(an or pregnan)-5-one so as to form an esterified hydroxy group in the 11-position and treating the resulting 11-(esterified hydroxy)-desA-androst(an or pregnan)-5-one with a basic agent to remove the acid corresponding to the esterified hydroxy group with concomitant formation of a 9,10-double bond.

It will be appreciated that the process of the present invention does not involve any modification of the substituents present in the 16- and/or 17-position of the natural steroid starting materials. However, having regard to the use of the desA-androst(or pregn)-9-en-5-one product for the manufacture of $9\beta,10\alpha$ -steroids of the androstane or pregnane series as mentioned earlier, it is necessary or desirable to protect certain of the 16 and/or 17-substituents against one or more of the reaction steps involved. It is also convenient to initially protect such a substituent in the natural steroid starting material and maintain the substituent in its protected form throughout the entire reaction sequence, regenerating the desired substituent only when the $9\beta,10\alpha$ -steroid has been obtained. On the other hand, it is sometimes convenient to insert a protecting group before a certain reaction step or sequence of reaction steps. Said protecting group can then be maintained until a final reaction step or can be split off at some intermediate stage. The protecting groups can be inserted and split off by methods known *per se*. The desirability of having protecting groups present will be further discussed hereinafter where the specific process steps will be discussed in detail. The various substituents which are susceptible to being protected are exemplified by the 16-hydroxy, 17β -hydroxy, 17α -hydroxy, 21-hydroxy, 17-oxo and 20-oxo groups.

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 hydroxy group is suitable. 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). Also, protection for the 16α -hydroxy, 17α -hydroxy or 21-hydroxy

groups can be effected by forming the lower-alkyl *ortho*esters thereof; that is, 16 α ,17 α - or 17 α ,21-(lower alkyl) *ortho*esters. A suitable ether protecting group is, for example, the tetrahydro-pyranyl ether group.

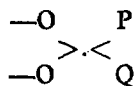
5 In compounds containing the dihydroxy-acetone side chain at the 17-carbon atom (for example, compounds of formula III in which R⁶ is a hydroxy group), this side chain can be protected by forming the 17,20;20,21-bis(methylenedioxy) group or by forming a 17,21-acetal or ketal group or by forming a 17,21-diester. 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 10 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.

15 In compounds which contain a 20-oxo group but no 17 α -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-acetyl 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 20 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 17 β -hydroxy, 17 α -hydrogen moiety, from which, when desired, the 17-oxo moiety can be regenerated by oxidation as described earlier. Furthermore, a 20-hydroxy or 17 β -hydroxy group can itself be 25 protected by esterification; for example, with an alkanolic acid containing not more than 6 carbon atoms (such as acetic acid) or caproic acid.

The 16 α ,17 α or 17 α ,21-acetals and ketals discussed hereinbefore 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 6 carbon atoms) with the groups sought to be protected.

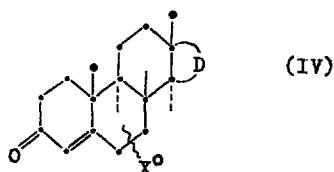
Suitable aldehydes and ketones include lower-alkanals (i.e. alkanals containing from 2 to 6 carbon atoms) (such as paraldehyde, propanal and hexanal), di(lower alkyl) ketones (such as acetone, diethyl ketone, dibutyl ketone, methyl ethyl ketone and methyl isobutyl ketone), *cyclo*alkanones (such as *cyclobutanone*, *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* ketone, *dicyclohexyl* ketone and *cyclopentyl cyclohexyl* ketone), *cyclo*alkyl 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), *cyclo*alkyl (lower alkyl) monocyclic aromatic ketones (such as *cyclopentylmethyl* phenyl ketone), *cyclo*alkyl monocyclic aromatic-(lower alkyl) ketones (such as *cyclopentyl benzyl* ketone and *cyclohexyl phenethyl* ketone), *cyclo*alkyl-(lower alkyl) monocyclic aromatic-(lower alkyl) ketones (such as *cyclopentylmethyl benzyl* ketone), halo-(lower alkanals) (such as chloral hydrate, trifluoro-acetaldehyde hemiacetal and hepta-fluoro-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 and *p*-fluoro-benzaldehyde), lower alkoxy-benzaldehydes (such as *o*-anisaldehyde), di(lower alkoxy)-benzaldehydes (such as veratraldehyde), hydroxy - benzaldehyde (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 carbocyclic 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-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), benzo-phenone 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 α ,17 α - or 17 α ,21-bis(hydroxy) grouping form an acetal or ketal grouping of the formula

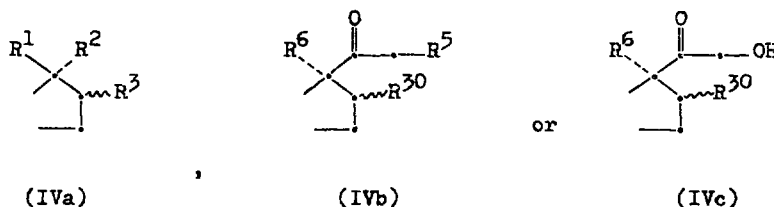


wherein P represents a hydrogen atom or a lower-alkyl group, Q represents a lower-alkyl or aryl group or P and Q together represent a lower-alkylene group such as tetramethylene or pentamethylene.

As will be evident from the foregoing, the desA-androst(or pregn)-9-en-5-ones aforesaid are prepared by three main methods. Thus, according to one method, they can be prepared from steroids of the 3-oxo-androst-4-ene or 3-oxo-17 β -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 β -pregn-4-ene series of the formula

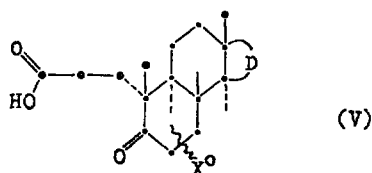


wherein X^o represents a hydrogen atom or a lower-alkyl, lower-alkylthio or lower-alkanoylthio group in the 6-position or a halogen atom or lower-alkyl, lower-alkylthio or lower-alkanoylthio group in the 7-position and D represents a grouping of the formula



in which R¹, R², R³, R³⁰, R⁵ and R⁶ have the significance given earlier.

The oxidative ring-opening of a natural steroid of formula IV 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 formula

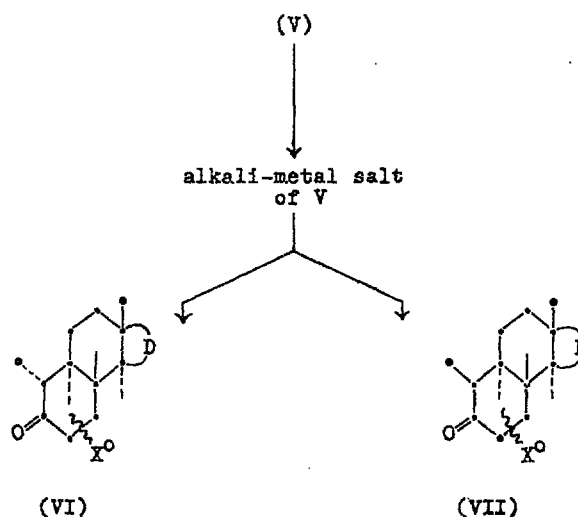


wherein X^o and D have the significance given earlier. The oxidative ring-opening of the compound of formula IV can be performed by a variety of methods. In a preferred embodiment, it is effected by ozonolysis. The ozonolysis is suitably carried out in an organic solvent; for example, acetic acid, ethyl 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 con-

ducted 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. The oxidative ring-opening of a compound of formula IV to give a compound of formula V can also be effected by other oxidation methods; for example, by treatment with hydrogen peroxide. It should be noted that an oxidative ring-opening by either ozonolysis or by treatment with hydrogen peroxide does not require protection of any of the substituents at C-16 or C-17. However, as stated earlier, it may be desirable to protect these substituents against some subsequent reaction in the total reaction sequence being carried out. 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 β - or 21-hydroxy group). For the purpose of these oxidations, protection with non-aromatic protecting groups is preferred.

Some of the 5-oxo-3,5-seco-A-norandrostan-3-oic acids of formula V hereinbefore are claimed *per se* in the specification of our copending Application for Letters Patent no: 36702/67 (now serial no: 1,103,984).

Following the oxidative ring-opening of the A-ring, the so-obtained 5-oxo-3,5-seco-A-norandrostan-3-oic acid or 5-oxo-3,5-seco-A-norpregnan-3-oic acid of formula V is converted into a mixture of the 10 α -desA-androstan-5-one and a 10 β -desA-androstan-5-one or a mixture of a 10 α -desA-pregnan-5-one and a 10 β -desA-pregnan-5-one as illustrated by the following scheme

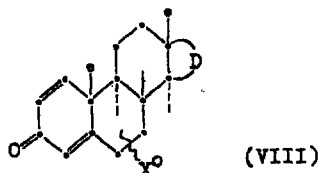


wherein X^o and D have the significance given earlier. Depending on the significance of D, the compounds of formula VI are 10 α -desA-androstan-5-ones or 10 α -desA-pregnan-5-ones and the compounds of formula VII are 10 β -desA-androstan-5-ones or 10 β -desA-pregnan-5-ones. The conversion of a compound of formula V into the compounds of formula VI and VII is effected by pyrolysis. In carrying out the pyrolysis, it is desirable to convert the 3-oic acid of formula V 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 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. Accordingly, it is advantageous to conduct the pyrolysis under alkaline conditions; that is, at a pH of greater than 7.

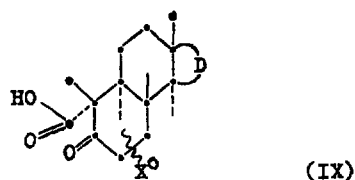
Many of the compounds of formulae VI and VII hereinbefore are claimed *per se*

in the specification of our copending Application for Letters Patent no: 36704/67 (now serial no: 1,103,986).

The compounds of formula VI can also be prepared from compounds of the formula

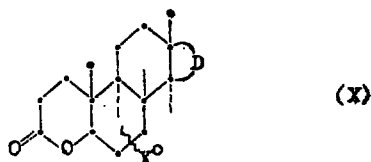


, wherein X° and D have the significance given earlier, by oxidative ring-opening of the A-ring thereof followed by elimination of the residue of the A-ring. The oxidative ring-opening of the compound of formula VIII can be effected by ozonolysis as described earlier. Such ozonolysis of a compound of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

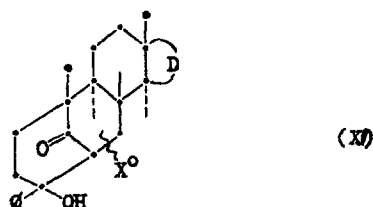


wherein X° and D have the significance given earlier. The removal of the residue of the A-ring from the compound of formula IX (i.e. decarboxylation) can be effected by heating the compound in an acidic or basic medium. It is preferred to heat to the reflux temperature of the medium, which is preferably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

Compounds of formula VI can also be obtained 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 formula



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

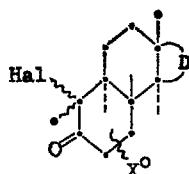


wherein X° and D have the significance given earlier and $\emptyset$ stands for the phenyl group. Upon treatment with an alkali-metal hydroxide such as potassium hydroxide at an elevated temperature (e.g. from about 200°C to 240°C) the aldol is converted into the corresponding 10 α -desA-androstan-5-one or 10 α -desA-pregnan-5-one of formula VI.

It should be noted that though the pyrolysis of a compound of formula V yields both the 10β -compounds of formula VII and the 10α -compounds of formula VI and though either of these isomers can be used in the halogenation and dehydrohalogenation steps of this reaction sequence to be described hereinafter, it is sometimes preferable to convert the 10β -compound of formula VII into the corresponding 10α -compound of formula VI. This conversion can be effected by treating a 10β -desA-androstan-5-one or 10β -desA-pregn-5-one of formula VII 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 formulae VI and VII 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.

As stated earlier, the 10α -desA-androstan-5-ones or 10α -desA-pregnan-5-ones of formula VI or the 10β -desA-androstan-5-ones or 10β -desA-pregnan-5-ones of formula VII can be converted by means of a two-step sequence of halogenation and dehydrohalogenation into the desA-androst-9-en-5-one or desA-pregn-9-en-5-one of formulae I, II and III hereinbefore. In a preferred embodiment, a 10α -desA-androstan-5-one or 10α -desA-pregnan-5-one of formula VI is subjected to the sequence of halogenation and dehydrohalogenation. Halogenation of a compound of formula VI or a compound of formula VII yields a mixture of corresponding halogenated compounds including one of the formula



(XII)

wherein X^o and D have the significance given earlier and Hal stands for a halogen atom (preferably the bromine or chlorine atom). Dehydrohalogenation of a compound of formula XII then yields a desired 9-en-compound of formula I, II or III. Keto groups other than the 5-keto group may require protection prior to the halogenation. In the case of compounds of formulae VI and VII containing the C—17 dihydroxyacetone side chain, shown in formula III wherein R^o is a hydroxy group, this protection can be effected by formation of the $17\alpha,20;20,21$ -bis(methylenedioxy) derivative. In other cases wherein a C—17 oxo or C—20 oxo group is present, protection can be effected by reduction to the corresponding carbinol either directly prior to the halogenation or prior to some other step in the sequence leading to the compounds of formulae VI and VII.

The halogenation can be effected with halogenating agents such as bromine or sulphuryl chloride. Bromination is especially preferred. The bromination is suitably effected by treatment with bromine at room temperature or below, preferably at ice temperature or below. Suitably it is conducted in an organic medium; for example, an organic acid such as acetic acid, an ether such as anhydrous ether, dioxan or tetrahydro-furan or a chlorinated organic solvent such as methylene chloride, chloroform or carbon tetrachloride, with the addition of hydrogen bromide as a catalyst.

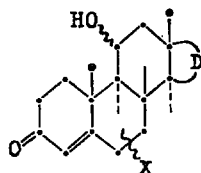
The subsequent dehydrohalogenation of a compound of formula XII is preferably carried out under mild dehydrohalogenating conditions; for example, using an alkali-metal carbonate (e.g. lithium carbonate) or an alkali-metal halide (e.g. a lithium halide) in an organic solvent such as N,N-di(lower alkyl)-formamide, or with an organic base such as collidine or pyridine. The dehydrohalogenation is advantageously carried out at slightly elevated temperatures; for example, from about 50°C to 150°C , preferably from about 80°C to 120°C .

Separation of the desired desA-androst-9-en-5-one or desA-pregn-9-en-5-one of formulae I, II and III can be effected by conventional means. As indicated earlier, the halogenation may result in halogenated byproducts in addition to the desired compound of formula XII. Accordingly, the separation is preferably effected after first subjecting the reaction mixture to dehalogenation. This serves to dehalogenate the

halogenated byproducts formed by the halogenation but not dehalogenated by the dehydrohalogenation. Following such dehalogenation, the mixture can then readily be separated by conventional means (for example, by column chromatography) to yield the desired compound of formulae I, II and III. Treatment with zinc and sodium acetate in an acetic acid solution at an elevated temperature (for example, about 80°C) is but one example of a suitable means for bringing about the dehalogenation.

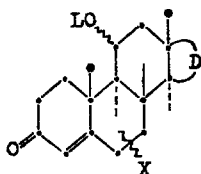
In the case of compounds of formula VI or VII which contain a halogen atom on a carbon atom directly adjacent to a keto group, it is preferable to protect such a halogen atom against dehalogenation prior to subjecting the compound of formula VI or VII to the two-step sequence of halogenation and dehydrohalogenation. Such grouping containing a halogen atom on a carbon atom directly adjacent to a keto group is seen in a compound of formula II or III wherein R^3 or R^4 represents a halogen atom. Thus, if a 10 α - or 10 β -desA-pregnan-5-one of formula VI or VII containing a 17 α - or 21-halo substituent is to be subjected to the halogenation/dehydrohalogenation it is desirable to first protect the 17 α - or 21-halo substituent. This protection can be effected, for example by ketalization of the 20-oxo group.

According to another method, the desA-androst(or pregn)-9-en-5-ones aforesaid can be prepared from steroids of the 3-oxo-androst-4-ene or 3-oxo-17 β -pregn-4-ene series which contain an 11-hydroxy substituent. In one embodiment, an 11-hydroxy steroid of the formula



(XIII)

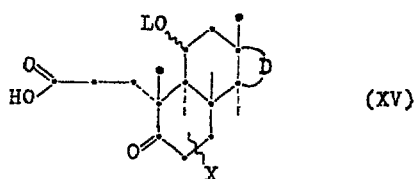
, wherein X and D have the significance given earlier, is reacted with an acid or a reactive derivative thereof to form an esterified hydroxy group in the 11-position. By reactive derivative is meant, for example, a halide (e.g. a chloride) or an anhydride. Though either 11 β - or 11 α -hydroxy steroids of formula XIII can be used, it is preferable to use the latter. 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-alkylsulphonyloxy 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 a compound of formula XIII with an agent forming a sulphonyloxy group, a 11 α -hydroxy compound should be used. The foregoing esterification of 11-hydroxy steroids of formula XIII yields compounds of the formula



(XIV)

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

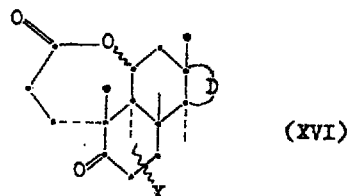
In the next step of this particular reaction sequence, the so-formed 11-(esterified hydroxy)-compound of formula XIV is subjected to an oxidative ring-opening of the A-ring to yield the corresponding 11-(esterified hydroxy)-5-oxo-3,5-seco-A-nor-androstan-3-oic acid or 11-(esterified hydroxy)-5-oxo-3,5-seco-A-norpregnan-3-oic acid of the formula



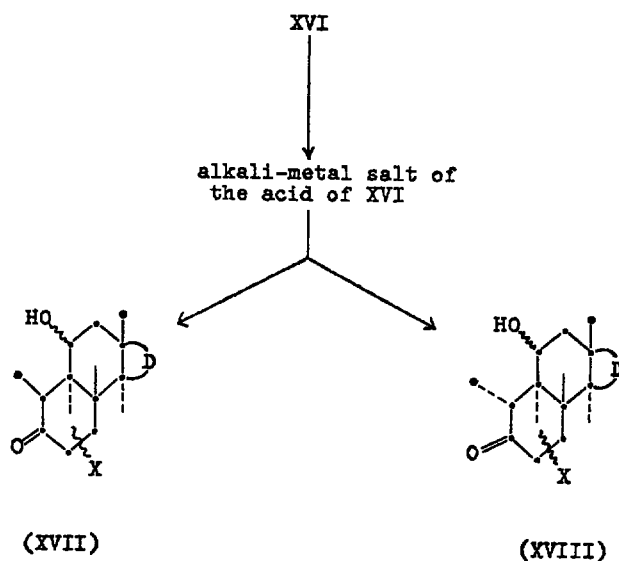
wherein X, D and LO have the significance given earlier. The oxidative ring-opening of the A-ring of a compound of formula XIV to give a compound of formula XV can be effected by ozonolysis as described hereinbefore in connection with compounds of formula IV. Pyrolysis of the so-formed compound of formula XV under the conditions described earlier in connection with compounds of formula V directly yields the desired desA-androst-9-en-5-one or desA-pregn-9-en-5-one of formulae I, II and III. Thus, pyrolysis of a compound of formula XV directly results in elimination of the esterified hydroxy group in the 11-position as well as a splitting off of the residue of ring A attached to the 10-position. This procedure of starting from an 11-hydroxy- (preferably 11 α -hydroxy)-steroid of formula XIII and proceeding through intermediates of formulae XIV and XV to compounds of formulae I, II and III represents a particularly elegant procedure for preparing the latter compounds.

The compounds of formula XV hereinbefore are claimed *per se* in the specification of our copending Application for Letters Patent no: 36701/67 (now serial no: 1,103,983).

According to yet another method, 11-hydroxy-steroids of formula XIII can be directly subjected to an oxidative ring-opening of the A-ring by ozonolysis or treatment with hydrogen peroxide as described earlier in connection with compounds of formula IV. This oxidative ring-opening of the A-ring of a compound of formula XIII yields an 11-hydroxy-5-oxo-3,5-seco-A-norandrost-3-oic acid, 3,11-lactone or an 11-hydroxy-5-oxo-3,5-seco-A-norpregn-3-oic acid 3,11-lactone of the formula



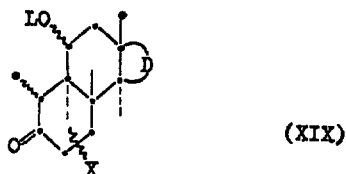
wherein X and D have the significance given earlier. Treatment of the 3,11-lactone of formula XVI with an alkali-metal hydroxide such as sodium hydroxide gives the salt of the corresponding keto-acid. Without isolation, this salt can then be subjected to pyrolysis yielding a mixture of an 11-hydroxy-10 α -desA-androst-5-one and an 11-hydroxy-10 β -desA-androst-5-one or a mixture of an 11-hydroxy-10 α -desA-pregn-5-one and an 11-hydroxy-10 β -desA-pregn-5-one as illustrated by the following scheme



Certain of the 3,11-lactones of formula XVI hereinbefore and salts of the corresponding keto-acids are claimed *per se* in the specification of our copending Application for Letters Patent No. 36700/67 (now serial no: 1,103,982).

The pyrolysis of an alkali-metal salt of a compound of formula XVI can be effected under the same conditions as described earlier for the pyrolysis of compounds of formula V to compounds of formula VI and VII. Though either the 10 β -compound of formula XVII or the 10 α -compound of formula XVIII can be subjected to the subsequent steps of this particular reaction sequence, it is suitable to use the 10 β -compound of formula XVII. Conversion of the 10 α -compound of formula XVIII into the 10 β -compound of formula XVII can be effected under the same conditions as described earlier for the conversion of a compound of formula VII to a compound of formula VI.

In the next step of this reaction sequence, the 11-hydroxy compound of formula XVII or of formula XVIII 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 with the same acids or acid derivatives and in the same manner as described earlier for the esterification of a compound of formula XIII to a compound of formula XIV. As in that instance, it is also preferred to form a mesyloxy group in the 11-position though, of course, other of the esterified hydroxy groups described earlier are also useful. There is thus obtained a compound of the formula



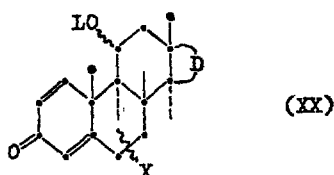
wherein X, D and LO have the significance given earlier.

Certain of the compounds of formulae XVII, XVIII and XIX hereinbefore are claimed *per se* in the specification of our copending Application for Letters Patent no: 36703/67 (now serial no: 1,103,985).

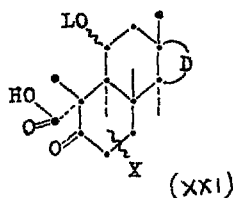
The esterified hydroxy group can then be eliminated from the 11-position of a compound of formula XIX and this results in a direct formation of a desA-androst-9-en-5-one or a desA-pregn-9-en-5-one of formulae I, II and III. This elimination is effected by treatment with a basic agent, suitably by subjecting the said compound to alkaline conditions in an anhydrous organic solvent. Preferably, it is effected by heating; that is to say, at a temperature between about room temperature and the reflux temperature of the reaction mixture. Thus, treatment of a compound of formula XIX with either an inorganic or organic base results in the formation of the

desired compound of formulae I,II or III. A weak base is preferably used; for example, a salt of a carboxylic acid (e.g. an alcanoic acid containing not more than 6 carbon atoms) with an alkali metal or an alkaline-earth-metal (for example, sodium acetate or potassium acetate). As indicated, the elimination is suitably conducted in an anhydrous organic solvent. Suitable solvents are N,N-di(lower alkyl)-formamides (e.g. N,N-dimethyl-formamide) and alcanoic acids containing not more than 6 carbon atoms (e.g. acetic acid). When a proton accepting solvent (such as N,N-dimethyl-formamide) is used, it itself can serve as the base for the elimination reaction. Thus, if the solvent is basic then the elimination can be carried out without the addition of a separate basic material.

Compounds of formula XIX can also be produced from compounds of the formula

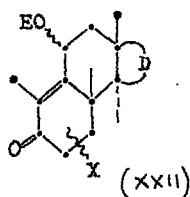


wherein X,D and LO have the significance given earlier. The compounds of formula XX can be produced from the corresponding 11-hydroxy compounds by esterification as described earlier in connection with the preparation of compounds of formula XIV from compounds of formula XIII. The compounds of formula XIX can be produced from the compounds of formula XX by oxidative ring-opening of the A-ring of a compound of formula XX followed by elimination of the residue of the A-ring. The oxidative ring-opening can be carried out by ozonolysis as described earlier for the conversion of a compound of formula XIV into a compound of formula XV. This ozonolysis of a compound of formula XX yields a compound of the formula



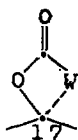
wherein X, D and LO have the significance given earlier. A compound of formula XXI can then be converted into a compound of formula XIX by removal of the residue of the A-ring (i.e. decarboxylation). This can be effected as described earlier for the conversion of a compound of formula IX into a compound of formula VI.

The 11-hydroxy-10 α -desA-androstan-5-ones or 11-hydroxy-10 α -desA-pregnan-5-ones of formula XVIII or the 11-hydroxy-10 β -desA-androstan-5-ones or, preferably, the 11-hydroxy-10 β -desA-pregnan-5-ones of formula XVII can also be esterified, preferably with a carboxylic acid such as an alcanoic acid containing not more than 6 carbon atoms (e.g. acetic acid) or benzoic acid. Conversion of the resulting 11-(esterified hydroxy) compound then yields an 11-(esterified hydroxy)-desA-androst-9-en-5-one [that is, a compound of formula I containing an 11-(esterified hydroxy) group] or an 11-(esterified hydroxy)-desA-pregn-9-en-5-one [that is, a compound of formula II or III containing an 11-(esterified hydroxy) group]. This conversion can be effected by halogenation followed by dehalogenation as described earlier for the conversion of a compound of formula VI or VII to a compound of formulae I,II or III. These 11-(esterified hydroxy)-9-ene compounds can be formulated thus:



wherein X and D have the significance given earlier and EO is an esterified hydroxy group.

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' means alkanoyl groups containing not more than 6 carbon atoms (e.g. acetyl). The term 'lower alkanoyloxy' means alkanoyloxy groups containing not more than 6 carbon atoms (e.g. acetoxy). The term 'halogen' means iodine, chlorine, bromine or 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 alkylene groups containing not more than 6 carbon atoms. 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 following Examples, some of which include the preparation of the starting material, illustrate the invention:

EXAMPLE 1

A solution of 3.2 g of 17 α -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 α -ethyl-17 β -hydroxy-5-oxo-3,5-seco-A-norandrostane-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 α -ethyl-17 β -hydroxy-5-oxo-3,5-seco-A-norandrostane-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 α -ethyl-17 β -hydroxy-5-oxo-3,5-seco-A-norandrostane-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 α -ethyl-17 β -hydroxy-10 α -desA-androstane-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 give 17 α -ethyl-17 β -hydroxy-10 β -desA-androstane-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 α -ethyl-17 β -hydroxy-10 β -desA-androstane-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 α -ethyl-17 β -hydroxy-10 α -desA-androstane-5-one. It was obtained in a crystalline state from (petroleum ether)/ether, and melted at 89° — 95°C .

17 α -Ethyl-17 β -hydroxy-10 α -desA-androstane-5-one was also obtained as follows: A solution of 3 g of 17 α -ethyl-17 β -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 extracted 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 α -ethyl-17 β -hydroxy-10 α -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 α -ethyl-17 β -hydroxy-10 α -desA-androstan-5-one of melting point 89°–90°C.
- 1.13 g of 17 α -ethyl-17 β -hydroxy-10 α -desA-androstan-5-one were dissolved in 120 ml of anhydrous ether (or 1.13 g of the 10 β -isomer were dissolved in 300 ml of anhydrous ether), and, after cooling in a salt-ice bath, several drops of 30 per cent hydrobromic acid in acetic acid were added. This was followed by the dropwise addition during five minutes of 0.684 g of bromine dissolved in 2 ml of acetic acid. This addition was synchronized with the decolouration rate of the reaction mixture. Immediately after this, 5 ml of a saturated solution of sodium bisulphite and 5 ml of 2-N sodium carbonate solution were added. The mixture was then transferred into a separatory funnel, 500 ml of ether were added and the mixture was shaken and separated. The ether part was washed with water, dried and evaporated. The resulting bromides were dissolved in 100 ml of N,N-dimethyl-formamide and, after addition of 3 g of lithium carbonate, the solution was heated at 100°C for 45 minutes. After cooling, it was poured into 1 litre of ether, washed with water, 1-N hydrochloric acid, 2-N sodium carbonate and water, dried and evaporated. The residue was dissolved in 40 ml of glacial acetic acid, 1.2 g of sodium acetate and 1.2 g of zinc powder were added, and the so-formed mixture was heated for 10 minutes at 80°C. It was then poured into 1 litre of ethyl acetate and the resulting solution was washed with saturated sodium bicarbonate and then with water, dried and evaporated. The residue was chromatographed on a column of activated magnesium silicate adsorbent. The fraction with benzene and 0.5 per cent ethyl acetate in benzene gave regenerated starting material. Fractions with 1 and 2 per cent ethyl acetate in benzene gave 17 α -ethyl-17 β -hydroxy-desA-androst-9-en-5-one, which after sublimation (140°C and 0.1 mm Hg vacuum), was obtained as a glass. $[\alpha]_D^{25} = -36.6^\circ$ ($c = 1$ in chloroform).

EXAMPLE 2

- 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 solution which was obtained by extraction with 8 portions of 75 ml of 2-N sodium 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 -methanesulphonyloxy-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 150ml 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. 20 g of sodium phenylacetate were added to the so-formed sodium salt, and after closing the top part of the apparatus this mixture was

pyrolysed at 290°C and 0.02 mm for 4 hours. The product, which collected on the cold finger, was dissolved in ether and filtered. The filtrate was evaporated to dryness. Purification of the residue by chromatography on a 40 g silica gel column (benzene eluant) gave crystalline desA-pregn-9-ene-5,20-dione which had a melting point of 111°—113°C after recrystallization from ether. $[\alpha]_D^{25} = +56.8^\circ$ ($c = 0.25$ per cent in methanol).

DesA-pregn-9-ene-5,20-dione was also obtained from 11 α -methanesulphonyloxy-5,20-dioxo-3,5-seco-A-norpregnan-3-oic acid as follows:

A mixture of 10g of 11 α -methanesulphonyloxy-5,20-dioxo-3,5-seco-A-norpregnan-3-oic acid and 100 g of a 1:1 (by weight) mixture of fused sodium acetate and fused potassium acetate was charged to a 250 ml stirred flask, which was equipped with a gas inlet tube and an air condenser, protected with a salt bath at 275°—300°C for 3 hours while a gentle stream of nitrogen was passed over the surface of the melt. The stirred mixture was cooled to 90°C, 100 ml of water and 35 ml of methylene chloride were added and stirring was maintained until all of the salt had dissolved. The aqueous layer was extracted with two 100 ml portions of methylene chloride and the combined organic extract, after being washed with two 75 ml portions of 2-N sodium carbonate and two 100 ml portions of water, was dried with sodium sulphate and evaporated. The neutral residual oil weighed 4.85 g. From ultra violet ($\lambda_{\text{max}}^{\text{EtOH}} = 247\text{—}248\text{m}\mu$; $\epsilon = 9650$) and thin layer chromatography analysis acid)/methanol (1:1) V/V and 10 per cent (phosphomolybdic acid)/methanol sprays] this crude product was shown to contain ca. 2.9 g of desA-pregn-9-ene-5,20-dione.

DesA-pregn-9-ene-5,20-dione was converted to 20 β -hydroxy-desA-pregn-9-en-5-one as follows:

A cooled solution of 1.2 g of sodium borohydride in 22 ml of methanol was slowly added to a solution of 1.2 g of desA-pregn-9-ene-5,20-dione in 20 ml of methanol maintained at 0°C and the resulting mixture was left for 72 hours at 0°C. It was then diluted with 100 ml of water and extracted with four 100 ml portions of chloroform. The extract was dried over anhydrous sodium sulphate and evaporated *in vacuo*, yielding a colourless oily product. This product was dissolved in 250 ml of chloroform and 6 g of manganese dioxide were added to the solution, which was then stirred for 72 hours at room temperature, filtered and the filtrate evaporated to dryness *in vacuo*. The residue was chromatographed on a silica gel column and the eluates with 5 per cent ethyl acetate in benzene gave, after concentration, crystalline 20 β -hydroxy-desA-pregn-9-en-5-one which, when recrystallized from (methylene chloride)/(petroleum ether) formed colourless needles of melting point 122°—123°C; $[\alpha]_D^{25} = -33^\circ$ ($c = 0.5$ in absolute ethanol).

EXAMPLE 3

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°—256°C. $[\alpha]_D^{25} = +193.3^\circ$ ($c = 1$ 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 percent 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} (—OH), 1706 cm^{-1} (carbonyl group). Nuclear magnetic resonance spectrum in deuterochloroform: 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 β -dione which was recrystallized from (methylene chloride)/(petroleum ether) and had a melting point of 150°—152°C; $[\alpha]_D^{25} = +84.0^\circ$ ($c=0.5$ 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 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°—140°C. $[\alpha]_D^{25} = +46^\circ$ ($c=0.5$ in absolute ethanol).

A solution of 200 mg of 11 α -hydroxy-10 β -desA-pregnane-5,20-dione methanesulphonate in 50 ml of N,N-dimethyl-formamide was heated at reflux for 8 hours and then evaporated to dryness. The residue was chromatographed on a column of activated magnesium silicate adsorbent. Elution with 2 per cent (ethyl acetate)/benzene and evaporation of the eluant yielded desA-pregn-9-ene-5,20-dione in the form of colourless needles, melting point 111°—113°C. This product was shown by mixed melting point to be identical with a sample of the same compound prepared as described in the third paragraph of Example 2.

EXAMPLE 4

A) The preparation of the starting material:

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 Na₂SO₄ 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 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.

B) The process:

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 2.

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 2.

17 α -Acetoxy-desA-pregn-9-ene-5,20-dione was prepared from 17 α -acetoxy-5,20-dioxo-11 α -methanesulphonyloxy-3,5-seco-A-norpregnan-3-oic acid by the conversion of the latter to its sodium salt followed by pyrolysis according to the procedure of the third paragraph of Example 2.

17 α -Acetoxy-20 β -hydroxy-desA-pregn-9-en-5-one was prepared from 17 α -acetoxy-desA-pregn-9-ene-5,20-dione by reduction and reoxidation according to the procedure of the final paragraph of Example 2.

EXAMPLE 5

17 β -Hydroxy-5-oxo-3,5-seco-A-norandrost-3-oic acid was prepared by ozonolysis of testosterone according to the procedure of the first paragraph of Example 1.

17 β -Hydroxy-10 α -desA-androst-5-one- and 17 β -hydroxy-10 β -desA-androst-5-one were prepared from 17 β -hydroxy-5-oxo-3,5-seco-A-norandrost-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.

17 β -Hydroxy-desA-androst-9-en-5-one was prepared from 17 β -hydroxy-10 α -desA-androst-5-one by bromination followed by dehydrobromination according to the procedure of the final paragraph of Example 1.

DesA-androst-9-ene-5,17-dione was prepared from 17 β -hydroxy-desA-androst-9-en-5-one by oxidation of the latter with a 2 per cent chromic acid solution in 90 per cent acetic acid. The so-obtained desA-androst-9-ene-5,17-dione was recrystallized from cyclohexane and melted at 123°—123.5°C; $[\alpha]_{D^{25}} = +83^\circ$ (c=0.1021 in dioxan).

EXAMPLE 6

16 α -Acetoxy-20,20-ethylenedioxy-pregn-4-en-3-one was prepared by acetylation of 16 α -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 α -Acetoxy-20,20-ethylenedioxy-5-oxo-3,5-seco-A-norpregnan-3-oic acid was prepared by ozonolysis of 16 α -acetoxy-20,20-ethylenedioxy-pregn-4-en-3-one according to the procedure of the first paragraph of Example 1.

16 α -Acetoxy-20,20-ethylenedioxy-10 α -desA-pregnan-5-one and 16 α -acetoxy-20,20-ethylenedioxy-10 β -desA-pregnan-5-one were prepared from 16 α -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 procedure of the second and third paragraphs of Example 1) and reacetylation with acetic anhydride and pyridine.

16 α -Acetoxy-20,20-ethylenedioxy-desA-pregn-9-en-5-one was prepared from 16 α -acetoxy-20,20-ethylenedioxy-10 α -desA-pregnan-5-one by bromination followed by dehydrobromination according to the procedure of the final paragraph of Example 1.

EXAMPLE 7

A) *The preparation of the starting material:*

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

B) *The process:*

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

16 α -Methyl-20,20-ethylenedioxy-10 α -desA-pregnan-5-one and 16 α -methyl-20,20-ethylenedioxy-10 β -desA-pregnan-5-one were prepared from 16 α -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.

16 α -Methyl-20,20-ethylenedioxy-desA-pregn-9-en-5-one was prepared from 16 α -methyl-20,20-ethylenedioxy-10 α -desA-pregnan-5-one by bromination followed by dehydrobromination according to the procedure of the final paragraph of Example 1.

EXAMPLE 8

A) *The preparation of the starting material:*

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 Example 4A.

B) *The Process:*

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 2.

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 2.

21-Acetoxy-20,20-ethylenedioxy-desA-pregn-9-en-5-one was prepared from 21-acetoxy - 20,20 - ethylenedioxy - 11 α - methanesulphonyloxy - 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 third paragraph of Example 2, except that the crude product was reacylated by treatment with (acetic/anhydride)/pyridine prior to working up.

EXAMPLE 9

11 α -Methanesulphonyl-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 2.

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 2.

16 α ,17 α -isopropylidenedioxy-desA-pregn-9-en-5,20-dione was prepared from 5,20 - dioxo - 11 α - methanesulphonyloxy - 16 α ,17 α - isopropylidenedioxy - 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 third paragraph of Example 2.

20 β - Hydroxy - 16 α ,17 α - isopropylidenedioxy - desA - pregn - 9 - en - 5 - one was prepared from 16 α ,17 α -isopropylidenedioxy - desA - pregn - 9 - ene - 5,20-dione by reduction and reoxidation according to the procedure of the final paragraph of Example 2.

EXAMPLE 10

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

7 α ,17 α - Dimethyl - 17 β - hydroxy - 10 α - desA androstan - 5 - one and 7 β ,17 α - dimethyl - 17 β - hydroxy - 10 β - desA - androstan 5 - one were prepared from 7 β ,17 α -dimethyl-17 β -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.

7 α ,17 α - Dimethyl - 17 β - hydroxy - desA - androst - 9 - en - 5 - one was prepared from 7 α ,17 α -dimethyl-17 β -hydroxy-10 α -desA-androstan-5-one by bromination followed by dehydrobromination according to the procedure of the final paragraph of Example 1.

EXAMPLE 11

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 2.

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 2.

17 α -Methyl-desA-pregn-9-ene-5,20-dione was prepared from 11 α -methanesulphonyloxy-17 α -methyl-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 third paragraph of Example 2.

20 β -Hydroxy-17 α -methyl-desA-pregn-9-en-5-one was prepared from 17 α -methyl-desA-pregn-9-ene-5,20-dione according to the procedure of the final paragraph of Example 2.

EXAMPLE 12

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

17 α -Methyl-17 β -hydroxy-desA-androst-9-en-5-one was prepared from 17 α -methyl-17 β -hydroxy-10 α -desA-androstan-5-one by bromination followed by dehydrobromination according to the procedure of the final paragraph of Example 1.

EXAMPLE 13

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.

Bromination and subsequent dehydrobromination of 11 α ,20 β -diacetoxy-10 β -desA-pregnan-5-one according to the procedure of the final paragraph of Example 1 gave 11 α ,20 β -diacetoxy-desA-pregn-9-en-5-one.

EXAMPLE 14

3 - (17 β - Hydroxy - 5 - oxo - 3,5 - seco - A - norandrost-17 α - yl - 3 - oic acid)-propionic acid lactone was prepared by ozonolysis of 3-(3-oxo-17 β -hydroxy-androst - 4 - en - 17 α - yl) - propionic acid lactone, according to the procedure of the first paragraph of Example 1.

3 - (17 β - hydroxy - 5 - oxo - 10 α - desA - androstan - 17 α - yl) - propionic acid lactone and 3-(17 β -hydroxy-5-oxo-10 β -desA-androstan-17 α -yl)-propionic acid lactone were prepared from 3-(17 β -hydroxy-5-oxo-3,5-seco-A-norandrost-17 α -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.

3 - (17 β - hydroxy - 5 - oxo - desA - androst - 9 - en - 17 α - yl) - propionic acid lactone was prepared from 3-(17 β -hydroxy-5-oxo-10 α -desA-androstan-17 α -yl)-propionic acid lactone by bromination followed by dehydrobromination according to the procedure of the final paragraph of Example 1.

EXAMPLE 15

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 2.

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 2.

17 α ,20;20,21 - bis(methylenedioxy) - desA - pregn - 9 - en - 5 - one was prepared from 17 α ,20;20,21-bis(methylenedioxy)-11 α -methanesulphonyloxy-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 third paragraph of Example 2.

EXAMPLE 16

5 11 β -Formyloxy-androstane-5,17-dione was obtained 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. 5

10 11 β - Formyloxy - 10 ξ - desA - androstane - 5,17 - dione was prepared from 11 β -formyloxy-androsta-1,4-diene-3,17-dione by ozonolysis followed by decarboxylation according to the procedure of the penultimate paragraph of Example 1. The product thus obtained melted at 117°—117.5°C; $[\alpha]_D^{25} = +93^\circ$ (in dioxan). 10

By hydrolysis of 11 β -formyloxy-10 ξ -desA-androstane-5,17-dione in 2% methanolic potassium hydroxide there was obtained 11 β -hydroxy-10 ξ -desA-androstan-5,17-dione which melted at 154°C; $[\alpha]_D^{25} = +96^\circ$ (in dioxan).

15 250 mg of 11 β -hydroxy-10 ξ -desA-androstane-5,17-dione and 250 mg of *para*-toluene-sulphonic acid monohydrate in 20 ml of benzene were heated at reflux in a nitrogen atmosphere for 6 hours. The reaction mixture was then washed with an aqueous solution of sodium bicarbonate and then with water, dried over sodium sulphate, filtered and evaporated to dryness. The residue was chromatographed in methylene chloride over 5 g of silica gel. Triturating the residue obtained from the first 250 ml of eluate yielded crystals of desA-androst-9-en-5,17-dione which melted at 123°—123.5°C after recrystallization from *cyclohexane*. 15

EXAMPLE 17

25 11 β -Formyloxy-5,17-dioxo-3,5-seco-A-norandrostane-3-oic acid was prepared from 11 β -formyloxy-4-ene-3,17-dione by ozonolysis according to the procedure of the second paragraph of Example 2. The product thus obtained melted at 220°—221°C; $[\alpha]_D^{25} = +107^\circ$ (in dioxan). 25

30 3.7 g of the sodium salt of 11 β -formyloxy-5,17-dioxo-3,5-seco-A-norandrostane-3-oic acid and 12 g of sodium phenylacetate were fused together *in vacuo* (0.1 Torr). When the bath temperature reached 220°C the molten mass began to decompose. The bath was heated further (within 0.5 hour) to a temperature of 290°C. Once this temperature had been reached the mixture was left for another 10 minutes at the initial pressure of 0.1 Torr. The distilled material was then chromatographed over 30 g of aluminium oxide (activity grade 3). Elution with a total of 200 ml of (petroleum ether)/benzene (2:1), followed by evaporation of the solvent and trituration of the residue in the presence of petroleum ether, yielded desA-androst-9-ene-5,17-dione which melted at 123°—123.5°C after recrystallization from *cyclohexane*; $[\alpha]_D^{25} = +83^\circ$ ($c = 0.1021$ in dioxan). 30

EXAMPLE 18

40 20 β -Acetoxy-5-oxo-3,5-seco-A-norpregnan-3-oic acid was prepared by ozonolysis of 20 β -acetoxy-pregn-4-en-3-one according to the procedure of Example 1. 40

45 20 β - hydroxy - 10 α - desA - pregnan - 5 - one and 20 β - hydroxy - 10 β - desA - pregnan - 5-one were prepared from 20 β -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. 45

50 20 β - hydroxy - desA - pregn - 9 - en - 5 - one was prepared from 20 β -hydroxy-10 α -desA-pregnan-5-one by bromination followed by dehydrobromination according to the procedure of the final paragraph of Example 1. The product thus obtained melted at 122°—123°C after recrystallization from (methylene chloride)/(petroleum ether). 50

EXAMPLE 19

55 5,20-Dioxo-3,5-seco-A-norpregnan-3-oic acid was prepared by ozonolysis of progesterone according to the procedure of the first paragraph of Example 1. 55

10 α - desA - pregnan - 5,20 - dione and 10 β - 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.

DesA-pregn-9-ene-5,20-dione was prepared from 10 α -desA-pregnan-5,20-dione by bromination followed by dehydrobromination according to the procedure of the

final paragraph of Example 1. The product thus obtained melted at 111°—113°C after recrystallization from ether.

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 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 of 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-

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:—

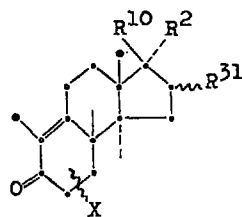
1. A process for the preparation of desA-androst (or pregn)-9-en-5-ones, which process comprises *either* subjecting a 3-oxo-androst (or pregn)-4-ene to ozonolysis, pyrolysing an alkali-metal salt of the resulting 5-oxo-3,5-seco-A-norandrost (or norpregnan)-3-oic acid and introducing a 9,10-double bond into the resulting desA-androst (or pregn)-5-one by means of a 2-step sequence of halogenation and dehydrohalogenation *or* esterifying an 11-hydroxy-androst (or pregn)-4-en-3-one so as to form an esterified hydroxy group in the 11-position, oxidising the resulting ester by ozonolysis *or* by treatment with hydrogen peroxide to form an 11-(esterified hydroxy)-5-oxo-3,5-seco-A-norandrost (or norpregnan)-3-oic acid, converting said acid into an alkali-metal salt and pyrolysing said alkali-metal salt *or* oxidising an 11-hydroxy-androst (or pregn)-4-en-3-one by ozonolysis *or* by treatment with hydrogen peroxide, converting the resulting 5-oxo-11-hydroxy-3,5-seco-A-norandrost (or norpregnan)-3-oic acid 3,11-lactone into an alkali-metal salt of the corresponding keto-acid, pyrolysing said alkali-metal salt, esterifying the resulting 11-hydroxy-desA-androst (or pregn)-5-one so as to form an esterified hydroxy group in the 11-position and treating the resulting 11-(esterified hydroxy)-desA-androst (or pregn)-5-one with a basic agent to remove the acid corresponding to the esterified hydroxy group with concomitant formation of a 9,10-double bond.

2. A process as set forth in claim 1, wherein the pyrolysis is carried out under alkaline conditions.

3. A process for the preparation of desA-androst (or pregn)-9-en-5-ones, substantially as described with reference to the Examples.

4. DesA-androst (or pregn)-9-en-5-ones, when prepared by the process claimed in claim 1, claim 2 or claim 3.

5. Compounds of the formula



wherein R¹⁰ represents a hydroxy or esterified hydroxy group, R² represents a hydrogen atom or a lower-alkyl group or R¹⁰ together with R² represents a 17 β -hydroxy-17 α -(lower alkanolic acid) lactone group, R³¹ represents a hydrogen atom or a lower-alkyl, hydroxy or esterified hydroxy group and X represents a hydrogen or halogen atom or a lower-alkyl, lower-alkylthio or lower-alkanoylthio group in the 6- or 7-position.

6. A 17 α -(lower alkyl)-17 β -hydroxy-desA-androst-9-en-5-one.

7. 17 α -(Methyl or ethyl)-17 β -hydroxy-desA-androst-9-en-5-one.

final paragraph of Example 1. The product thus obtained melted at 111°—113°C after recrystallization from ether.

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 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 of 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- nated 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:—

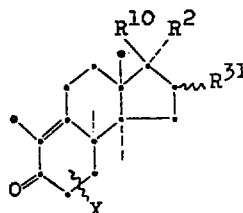
1. A process for the preparation of desA-androst (or pregn)-9-en-5-ones, which process comprises *either* subjecting a 3-oxo-androst (or pregn)-4-ene to ozonolysis, pyrolysing an alkali-metal salt of the resulting 5-oxo-3,5-seco-A-norandrostan (or norpregnan)-3-oic acid and introducing a 9,10-double bond into the resulting desA-androstan (or pregnan)-5-one by means of a 2-step sequence of halogenation and dehydrohalogenation *or* esterifying an 11-hydroxy-androst (or pregn)-4-en-3-one so as to form an esterified hydroxy group in the 11-position, oxidising the resulting ester by ozonolysis or by treatment with hydrogen peroxide to form an 11-(esterified hydroxy)-5-oxo-3,5-seco-A-norandrostan (or norpregnan)-3-oic acid, converting said acid into an alkali-metal salt and pyrolysing said alkali-metal salt *or* oxidising an 11-hydroxy-androst (or pregn)-4-en-3-one by ozonolysis or by treatment with hydrogen peroxide, converting the resulting 5-oxo-11-hydroxy-3,5-seco-A-norandrostan (or norpregnan)-3-oic acid 3,11-lactone into an alkali-metal salt of the corresponding keto-acid, pyrolysing said alkali-metal salt, esterifying the resulting 11-hydroxy-desA-androstan (or pregnan)-5-one so as to form an esterified hydroxy group in the 11-position and treating the resulting 11-(esterified hydroxy)-desA-androstan (or pregnan)-5-one with a basic agent to remove the acid corresponding to the esterified hydroxy group with concomitant formation of a 9,10-double bond.

2. A process as set forth in claim 1, wherein the pyrolysis is carried out under alkaline conditions.

3. A process for the preparation of desA-androst (or pregn)-9-en-5-ones, substantially as described with reference to the Examples.

4. DesA-androst (or pregn)-9-en-5-ones, when prepared by the process claimed in claim 1, claim 2 or claim 3.

5. Compounds of the formula



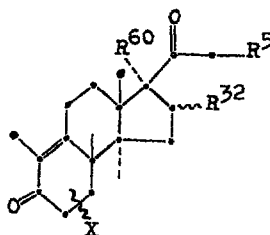
wherein R¹⁰ represents a hydroxy or esterified hydroxy group, R² represents a hydrogen atom or a lower-alkyl group or R¹⁰ together with R² represents a 17 β -hydroxy-17 α -(lower alkanolic acid) lactone group, R³¹ represents a hydrogen atom or a lower-alkyl, hydroxy or esterified hydroxy group and X represents a hydrogen or halogen atom or a lower-alkyl, lower-alkylthio or lower-alkanoylthio group in the 6- or 7-position.

6. A 17 α -(lower alkyl)-17 β -hydroxy-desA-androst-9-en-5-one.

7. 17 α -(Methyl or ethyl)-17 β -hydroxy-desA-androst-9-en-5-one.

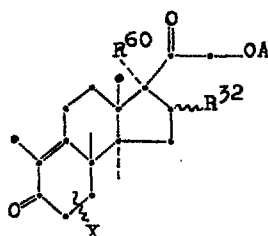


8. Compounds of the formula



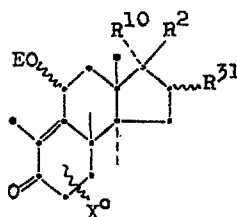
wherein X has the significance given in claim 5, R³² represents a hydrogen or fluorine atom or a lower-alkyl, hydroxy or esterified hydroxy group, R⁵ represents a hydrogen or halogen atom, and R⁶⁰ represents a hydrogen or halogen atom or a lower-alkyl, hydroxy or esterified hydroxy group, 20-ketals thereof, 16 α ,17 α -ketals and acetals of those compounds in which R³² and R⁶⁰ each represent a hydroxy group, derivatives thereof in which the 20-oxo group is reduced to a 20-hydroxy group and the corresponding derivatives in which said 20-hydroxy group is esterified.

9. DesA-pregn-9-ene-5,20-dione. 5
10. A 20-(lower alkylenedioxy)-desA-pregn-9-en-5-one. 10
11. 20-Ethylenedioxy-desA-pregn-9-en-5-one.
12. A 20-Hydroxy-desA-pregn-9-en-5-one.
13. 20 β -hydroxy-desA-pregn-9-en-5-one.
14. A 17 α -(lower alkanoyloxy)-desA-pregn-9-ene-5,20-dione. 15
15. A 17 α -(lower alkanoyloxy)-20-hydroxy-desA-pregn-9-en-5-one.
16. A 16 α -(lower alkanoyloxy)-20-(lower alkylenedioxy)-desA-pregn-9-en-5-one.
17. A 16 α -(lower alkanoyloxy)-20-(lower alkanoyloxy)-desA-pregn-9-en-5-one.
18. A 16 α -methyl-20-(lower alkylenedioxy)-desA-pregn-9-en-5-one.
19. A 16 α ,17 α -ketal or acetal of 16 α ,17 α ,20-trihydroxy-desA-pregn-9-en-5-one. 20
20. A 17 α -(lower alkyl)-desA-pregn-9-en-5,20-dione.
21. Compounds of the formula



wherein X has the significance given in claim 5, R³² and R⁶⁰ have the significance in claim 8 and OA represents a hydroxy or esterified hydroxy group, 17 α ,20;20,21-bis-(methylenedioxy) derivatives of those compounds in which OA and R⁶⁰ each represent a hydroxy group, 16 α ,17 α -ketals and acetals of those compounds in which R³² and R⁶⁰ each represent a hydroxy group, 17 α ,21-ketals and acetals of those compounds in which OA and R⁶⁰ each represent a hydroxy group, derivatives thereof in which the 20-keto group is reduced to a 20-hydroxy group and the corresponding derivatives in which said 20-hydroxy group is esterified.

22. 17 α ,21-Dihydroxy-desA-pregn-9-en-5,20-dione. 25
23. 17 α ,20;20,21-Bis(methylenedioxy)-desA-pregn-9-en-5-one.
24. A 21-(lower alkanoyloxy)-20-(lower alkylenedioxy)-desA-pregn-9-en-5-one. 30
25. Compounds of the formula 35

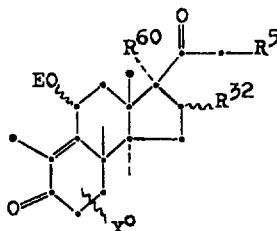


wherein R¹⁰, R² and R³¹ have the significance given in claim 5 or R¹⁰ together with



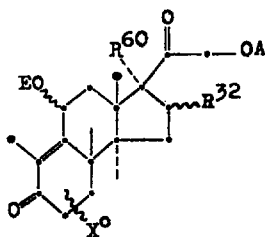
R^2 represents an oxo, lower-alkylenedioxy or 17 β -hydroxy-17 α -(lower alkanolic acid) lactone group, X^o represents a hydrogen atom or a lower-alkyl, lower-alkylthio or lower-alkanoylthio group in the 6- or 7-position or a halogen atom in the 7-position and EO represents an esterified hydroxy group.

26. Compounds of the formula



wherein R^1 , R^{60} and R^{32} have the significance given in claim 8 and X^o and EO have the significance given in claim 25, 20-ketals thereof, 16 α ,17 α -ketals and acetals of those compounds in which R^{32} and R^{60} each represent a hydroxy group, derivatives thereof in which the 20-oxo group is reduced to a 20-hydroxy group and the corresponding derivatives in which said 20-hydroxy group is esterified.

27. Compounds of the formula



wherein R^{32} and R^{60} have the significance given in claim 8, OA has the significance given in claim 21 and EO and X^o have the significance given in claim 25, 17 α ,20;20,21-bis(methylenedioxy) derivatives of those compounds in which OA and R^{60} each represent a hydroxy group, 16 α ,17 α -ketals and acetals of those compounds in which R^{32} and R^{60} each represent a hydroxy group, 17 α ,21-ketals and acetals of those compounds in which OA and R^{60} each represent a hydroxy group, derivatives thereof in which the 20-keto group is reduced to a 20-hydroxy group and the corresponding derivatives in which said 20-hydroxy group is esterified.

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