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(19)

(54) 11α-AMINO-3α-HYDROXY-STEROIDS

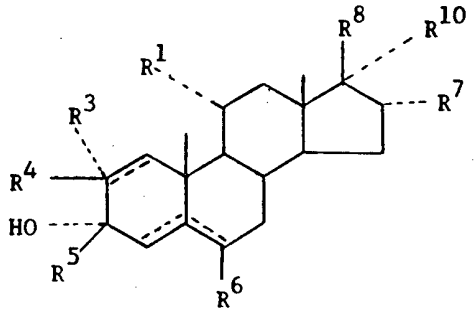
(71) We, GLAXO OPERATIONS UK LIMITED, formerly known as GLAXO LABORATORIES LIMITED, a British Company of Greenford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 11α-amino-3α-hydroxy steroids.

Many steroids possessing anaesthetic activity are now known, these mostly being 3α-hydroxy 5α- or Δ^4 compounds in the 17α-unsubstituted 20-oxo-pregnane and androstane series, the best compounds often having an 11-oxo group. These compounds are mostly insufficiently soluble in water, and it has been necessary to formulate them for administration in aqueous solutions of parenterally acceptable non-ionic surface active agents as for example described in British Patent Specification 1,317,184 with regard to the important anaesthetic 3α-hydroxy-5α-pregnane-11,20-dione. Anaesthetic steroids are also known which possess water-solubilising groups at various positions on the steroid nucleus, for example at the 2β- or 3α-position or the 21-position in a pregnane or the 17β-position in an androstane, but the introduction of the water-solubilising group has frequently resulted in a fall in activity or stability.

As described in our copending Application 13707/76 (Serial No. 1,581,234), from which the present application has been divided, we have found very interesting anaesthetic activity in a group of 3β-hydroxy 5α-,5β- or Δ^4 or Δ^5 pregnanes and androstanes and their D-homo analogues possessing an amino group, di-substituted by aliphatic or araliphatic groups, or a heterocyclic amino group at the 11α-position, particularly in the water soluble salts of these compounds with acids.

Our Application 13707/76 (Serial No. 1,581,234), thus describes steroids of the formula:



(I)

wherein

R^1 is a group $—NR^aR^b$, in which R^a and R^b (which may be the same or different) are $C_{1—6}$ alkyl, C_{3-6} alkenyl, or cycloalkyl groups (provided that R^a and R^b together contain 2—7 carbon atoms and that, when R^a and/or R^b is an alkenyl group, it may have one or two double bonds and the carbon atom or atoms adjacent to the nitrogen atom in the group $—NR^aR^b$ is or are saturated) or in which one of R^a and R^b is a benzyl or phenethyl group, the other group

being a methyl group, or in which R^a and R^b (together with the nitrogen atom) represent an azetidino, pyrrolidino, piperidino, hexamethylenimino or morpholino group, which groups may optionally be substituted by one or two methyl groups;

R^3 is a hydrogen atom or a C_{1-3} alkyl group;

R^4 is a hydrogen atom or a C_{1-5} alkyl, C_{1-5} alkoxy (which may be optionally substituted by a halogen atom, e.g. chlorine), benzyloxy, C_{2-5} alkanoyloxy, or thiocyanato group or a halogen atom;

R^5 is a hydrogen atom or a methyl group;

R^6 is a hydrogen atom or a methyl group;

R^7 represents a hydrogen atom or (except when R^8 is a group (c) as defined below) a chlorine atom; and

R^8 is (a) a cyano group; (b) a group —COR^9 where R^9 is a methyl group or such a group substituted by a fluorine atom, or by a C_{1-4} alkoxy, hydroxy, C_{1-4} alkyl, methoxymethyl, ethoxymethyl, C_{2-5} alkanoyloxy, benzoyloxy, or C_{2-5} alkoxycarbonyloxy group; or where R^9 is a C_{1-5} alkoxy or cyclopropyl group; or where R^9 is the group —NR^xR^y where R^x and R^y (which may be the same or different) are methyl or ethyl groups; or (c) a vinyl group or together with R^{10} a methylene group substituted in the Z configuration by a methyl or cyano group;

R^{10} is a hydrogen atom (except when R^8 and R^{10} together represent a substituted methylene group);

the broken lines indicate the optional presence of double bonds at the positions shown;

provided that at least one of R^3 and R^4 is a hydrogen atom; and R^3 and R^4 together represent a hydrogen atom when a 1,2-double bond is present; and that a 1,2-double bond is not present when a 4,5-double bond is present;

and that R^3 is a hydrogen atom, R^4 is a hydrogen atom or a methyl group and R^5 is a hydrogen atom or optionally (when R^4 is a hydrogen atom) a methyl group when a 5β-hydrogen atom is present;

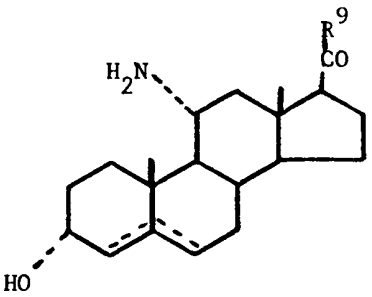
and the D-homo analogues thereof carrying R^8 at the 17aβ-position, R^{10} at the 17aα-position and R^7 at the 17-position;

and the acid addition salts thereof.

Application 13707/76 (Serial No. 1,581,234), also describes a number of processes for the preparation of the steroids of formula (I), and many of the intermediates required in these processes are themselves new compounds. An important process described is the alkylation of a corresponding 11α-amine, and a particularly important group of compounds described as intermediates are those having an unsubstituted or mono-substituted 11α-amino group, including the 20-ketals of those compounds which possess a 20-keto group. These compounds are the subject of the present invention.

Although we are unaware of any prior disclosure of any specific compound of this type, there have been disclosures (for example in British Patent Specifications 887,815 and 878,069) of general classes of steroids whose definitions embrace some of such amines.

The compounds of this invention are thus compounds of formula (I) as defined above (except in that R^1 is the group —NHR^a in which R^a is a hydrogen atom or a C_{1-6} alkyl, C_{3-6} cycloalkyl, benzyl or phenethyl group or a C_{3-6} alkenyl group having one or two double bonds in which the carbon atom adjacent to the nitrogen atom in the —NHR^a group is saturated) and the 20-ketals of compounds having a 20-keto group, but excluding compounds of the formula



(Ia)

(wherein R^9 is a methyl group or a methyl group substituted by a hydroxy or C_{2-5} alkanoyloxy group) and the 20-ketals thereof.

As indicated above, the R^a group may be a C_{1-6} alkyl group, which may be straight or branched, such as methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, pentyl, *iso*-pentyl or 1,3-dimethylbutyl groups; or a C_{3-6} alkenyl group such as allyl. When R^a is a cycloalkyl group, it may be for example a cyclopentyl or cyclohexyl group.

When R^a is a C_{3-6} alkenyl group there is preferably only one double bond present, e.g. as in an allyl group.

When a $2\alpha(R^3)$ substituent is present, it is preferably a methyl group.

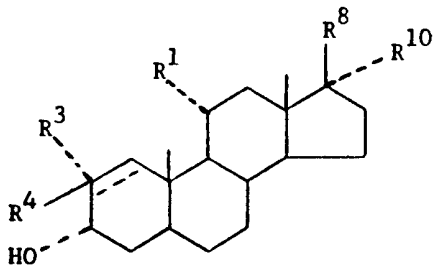
Where R^6 is a methyl group the 6-position is preferably saturated.

Compounds having having a $2\beta(R^4)$-substituent are particularly important in the 5α-series, examples of such substituents being a methyl, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, acetoxy or thiocyanato group or a chlorine, bromine or fluorine atom.

Compounds in the 5α- and 5β-hydrogen series are generally preferred, as are compounds in which the tetracyclic steroid system is saturated and in which R^6 and R^7 are both hydrogen atoms; R^5 is also preferably a hydrogen atom. When the steroid rings are unsaturated, Δ^1-compounds are preferred.

One group of compounds of the invention is of compounds in which R^a is other than benzyl or phenethyl; R^8 is other than the group —COR^9 where R^9 is a methyl group substituted by a C_{2-4} alkyl, benzoyloxy or alkoxycarbonyloxy group; and in which R^3, R^4 and R^5 are all hydrogen atoms when a 5β-hydrogen atom is present.

A preferred group of compounds are those of formula (II) (except for those falling within formula Ia above):



(II)

wherein:

R^1 is a group —NHR^a, in which R^a is a methyl, ethyl, propyl, *iso*-propyl, butyl or allyl group or hydrogen atom;

R^3 is a hydrogen atom or a methyl group;

R^4 is a hydrogen atom or a methyl, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, acetoxy or thiocyanato group or a fluorine, chlorine or bromine atom;

R^8 is (a) a cyano group; (b) a group —COR^9 where R^9 is a methyl group or such a group substituted by a methyl, hydroxy or acetoxy group, or R^9 is a cyclopropyl group; or (c) a vinyl group or, together with R^{10}, a Z-ethylidene group; and

R^{10} is a hydrogen atom (except when R^8 and R^{10} together represent an ethylidene group); the broken lines indicate the optional presence of a double bond at the 1,2-position;

provided that at least one of R^3 and R^4 is a hydrogen atom; that R^3 and R^4 together represent a hydrogen atom when a 1,2-double bond is present; and that R^3 is a hydrogen atom and R^4 is a hydrogen atom or a methyl group when a 5β- hydrogen atom is present;

and the D-homo analogues carrying R^8 at the $17a\beta$-position and R^{10} at the $17a\alpha$-position;

and the 20- ketals of compounds having a 20- keto group;

and the acid addition salts thereof.

R^8 is preferably a cyano group or a group —COR^9 where R^9 is a methyl group (optionally substituted by a hydroxy, methyl or acetoxy group) or a cyclopropyl group. The 1,2-position is preferably saturated.

In the compounds of formulae (II), and generally, R^8 is preferably an acetyl or cyano group; R^4 is preferably a hydrogen atom when a 5β-hydrogen atom is present, or is a hydrogen atom or an alkoxy group, advantageously an ethoxy group, when a 5α-hydrogen atom is present; and R^3 is preferably a hydrogen atom. It is especially preferred for R^8 to be an acetyl group, and ring D to have 5 members. 5α-Compounds are most preferred.

The bases of the invention form water soluble acid addition salts and these salts may be of use in isolating the product of a synthetic reaction.

Examples of suitable salts are hydrochlorides, hydrobromides, phosphates, sulphates, *p*-toluenesulphonates, methanesulphonates, citrates, tartrates, acetates, ascorbates, lactates, maleates, succinates, tricarballylates, glutarates, aconitates, citraconates, mesaconates, salicylates and glutaconates.

COMPOUND PREPARATION

The compounds of the invention may be prepared by a number of different methods, using generally known techniques. Suitable methods are described below.

1. Conversion of an unsubstituted 11α-amine into a mono-substituted 11α-amine.

This reaction may be performed by reacting a corresponding compound in which R^a is hydrogen with a compound of the formula R^aX where X is a readily displaceable group such as halide (e.g. iodide), a hydrocarbylsulphonyloxy group (e.g. toluene-p-sulphonyloxy), a hydrocarbyloxysulphonyloxy group (e.g. methoxysulphonyloxy) or a dialkoxyphosphonyloxy group (e.g. dimethoxyphosphonyloxy). The reaction is preferably carried out in the presence of a base (e.g. potassium carbonate or silver oxide) in solution at any suitable temperature from ambient to reflux, conveniently at ambient temperature. An excess of the compound R^aX, e.g. methyl iodide, may be used as the reaction solvent, but there are many other alternative solvents such as halogenated hydrocarbon solvents (e.g. methylene chloride), alkanols (e.g. ethanol or methanol) or acetonitrile.

When a 20-oxo group is present in the starting material, this may be protected as described below as a 20-ketal group. Such protection is not necessary in the N-substitution reaction, but a 20-ketal group is often present as a result of the earlier stages in the preparative sequence. Isolation of the product of the N-substitution reaction frequently involves acidic conditions which also serve to regenerate the desired 20-oxo group.

2. Reduction of the corresponding 11-oxime.

Compounds in which R^a is a hydrogen atom may be prepared by stereo-selectively reducing the corresponding 11-oxime. This reduction may be effected with an alkali or alkaline earth metal reducing agent in an alcohol and/or an amine and/or ammonia, e.g. sodium in n-propanol, if desired in the presence of a suitable solvent, e.g. tetrahydrofuran, at any suitable temperature up to and preferably at reflux.

The 11-oximes may themselves be prepared from the corresponding 11-oxo compounds in which the 20-oxo group (if present) is protected as a ketal group. The 11-oxo compound may for example be reacted with hydroxylamine under strongly alkaline conditions in aqueous alcohol (e.g. ethanol), preferably at reflux. When other oxo groups are absent, the reaction may be carried out under acidic conditions (*ca.* pH 4), e.g. in buffered pyridine.

The severe conditions used in the reduction of the 11-oxime make it necessary or desirable that certain of the optional substituents should be introduced after the formation of the 11α-amino group, examples of such groups being 17β-cyano and -alkoxycarbonyl, 21-alkanoyloxy and -halo, 2β-halo, -alkanoyloxy and -thiocyanato, and 16α-chloro.

3. A corresponding 11α-acylamino steroid (i.e. in which R^a is an acyl group) may be reduced, for example with lithium aluminium hydride in an ether solvent (e.g. tetrahydrofuran or dimethoxyethane) at any suitable temperature up to reflux. The starting material may possess a 20-ketal group, which should subsequently be converted into a 20-oxo group, or a 3α-esterified hydroxy group, which will be converted into a 3α-hydroxy group in the reaction.

The acylamino starting materials may be prepared by acylation of an appropriate 11α-unsubstituted amino compound (or a 20-ketal or 20-hydroxy derivative thereof), for example with the appropriate carboxylic acid (or a reactive derivative thereof, e.g. an acid halide ester or anhydride), if desired in the presence of an acid binding agent (e.g. pyridine). The 3α-hydroxy group and any other hydroxy group present will be acylated in this reaction and if desired may be regenerated by treatment with a base before the reduction; if a 20-hydroxy group is present, the acylamino intermediate may first be oxidised and ketalised to form the desired protected 20-oxo group. If the 11-acylamino compound possesses a 3-oxo group, this may then be reduced to form the desired 3α-hydroxy group.

4. Opening of a corresponding 2α,3α-epoxide.

This reaction may be used to prepare ring A-saturated 2β-substituted 5α-com-

pounds. The general method of preparing 2β-compounds by this route is described in our British Patent Specification 1,376,892. Thus in general the reaction comprises, treating the corresponding 2α,3α-epoxide with a compound HR^4 under acidic conditions (if necessary in the presence of an added acid catalyst, e.g. sulphuric acid, perchloric acid or boron trifluoride) or a compound which produces the anion $(R^4)^-$ (where R^4 is as defined above, other than hydrogen), and then (when the initial product possesses a deprotonated 3α-hydroxy group) treating the product with a source of protons (e.g. aqueous ammonium chloride) to form the 3α-hydroxy group. Examples of HR^4 reagents are alcohols, carboxylic acids, thiocyanic acid and hydrogen halides (HF may be used in the form of the HF-urea complex, conveniently in the absence of a solvent); examples of reagents which produce $(R^4)^-$ anions are metal alkyls such as lithium dimethyl cuprate, alkali metal or ammonium salts of HR^4 acids and alkali metal alkoxides. The reaction is preferably carried out under anhydrous conditions in a suitable solvent (e.g. a hydrocarbon or an ether) at any suitable temperature up to reflux. 2β-Halo and thiocyanato compounds may also be prepared in aqueous media.

The starting materials required for this reaction may for example be prepared by first introducing the desired 11α-amino group (e.g. by the methods of reactions 1 or 2 above) using a Δ^2-starting material, then forming a salt (e.g. with toluene-*p*-sulphonic acid) and then epoxidising the Δ^2-compound with a peracid, finally regenerating the free base. Δ^2-Compounds may be prepared by formation of the 3-methanesulphonate and subsequent elimination of methanesulphonic acid.

5. A corresponding 11α-amino compound (or a 20-ketal thereof) can be reductively alkylated with an appropriate monocarbonyl compound in the presence of a reducing agent. The reducing agents which may be used are those generally known for the reduction of imines, examples being formic acid (e.g. at any suitable temperature up to 100—120°C, for example from room temperature up to 100°, and using the carbonyl compound as the reaction solvent, in the presence or absence of water), an alkali metal borohydride or cyanoborohydride (e.g. sodium borohydride or cyanoborohydride, using an alcohol such as ethanol as solvent, suitably at room temperature), iron pentacarbonyl or an alkali metal hydrogen iron carbonylate (e.g. $Fe(CO)_5$ or $MHFe(CO)_4$ where M is sodium or potassium, at any suitable temperature up to reflux using an ether such as tetrahydrofuran or an alcohol or aqueous alcohol as solvent), hydrogen in the presence of a metal catalyst (using an alcohol, e.g. ethanol, an ether, e.g. dioxan or an ester, e.g. ethyl acetate, as reaction solvent, conveniently at room temperature), or aluminium amalgam in the presence of water (conveniently at room temperature, and in the presence of an ether solvent such as tetrahydrofuran).

The metal catalyst may, for example, be a noble metal catalyst such as platinum, platinum oxide, palladium or rhodium. The catalyst may be supported, e.g. on charcoal or kieselguhr. A homogeneous catalyst such as tristriphenylphosphine rhodium chloride may also be used. If desired the intermediate imino compound may be isolated. Thus, for example, the use of formaldehyde, acetaldehyde, or acetone can provide the 11α-N-methyl-, N-ethyl or N-*iso*-propyl amines respectively.

6. Ring A-saturated 2β-unsubstituted 5α-steroids of the invention may be prepared from appropriate 3-oxo compounds by stereospecific reduction, e.g. by the method of *Browne and Kirk* (J. Chem. Soc. C, 1969, 1653) or by the method of our British Patent Specification 1,409,239. The latter method preferably uses a pre-formed iridium catalyst reduction system. For example, a reduction system may be prepared from an iridium acid or salt (e.g. chloroiridic acid), a trivalent phosphorus compound such as a phosphorous acid ester (e.g. trimethyl phosphite) water and an organic reaction medium (e.g. an alcohol such as isopropanol). The reduction system is then neutralised (e.g. to a pH of 6 to 8.5) with an organic base such as a secondary or tertiary amine (e.g. triethylamine) and reacted with the steroid. When the catalyst system is preformed by heating at reflux, e.g. for 16 to 72 hours, the reduction can be accomplished for example in 2—3 hours at reflux; longer times may be necessary at room temperature.

7. Reduction of a corresponding 3-oxo-5β-compound.

3α-Hydroxy 5β-steroids may be prepared by hydride reduction of the corresponding 3-oxo compound (in which a 20-oxo group, if present, is optionally protected), for example with sodium borohydride using an alcohol (e.g. ethanol) or pyridine as solvent.

8. Reduction of the corresponding Δ^{16} compound.

Compounds in which R^8 is a group (a) or (b) as defined above may be prepared by hydrogenating the corresponding Δ^{16} compound in the presence of a hydrogenation catalyst (e.g. a palladium catalyst) in a suitable solvent (e.g. an alcohol, ether or ester). The reaction may be effected conveniently at or about room temperature and atmospheric pressure in the presence of a tertiary base, e.g. triethylamine, (except where an easily displaceable substituent (e.g. bromo) is at the 2β-position) and/or an acid, e.g. acetic acid.

9. Hydrochlorination of the corresponding Δ^{16} compound.

16α-Chloro compounds may be prepared by reacting the corresponding Δ^{16}-compound with hydrogen chloride in an anhydrous solvent (e.g. an ether) at a temperature of for example 15—40°C, as generally described in our British Patent Specification 1,380,248.

10. Dehydration of a corresponding 17β-carbamoyl compound or the oxime of a corresponding 17β-formyl compound.

17β-Cyano compounds may be prepared by dehydrating the appropriate oxime for example with acetic anhydride at reflux. The 3α-hydroxy group will generally be esterified in this reaction and has to be regenerated by de-esterification. The oxime starting material for this reaction may be prepared from the corresponding 17β-formyl compound (with $NH_2 . OH$), itself prepared by periodate cleavage of the corresponding 20,21-dihydroxy pregnane.

Alternatively, the corresponding 17β-(unsubstituted carbamoyl) compound can be dehydrated, e.g. using polyphosphate ethyl ester, as described in our British Patent Specification 1,380,246.

11. Esterification of a corresponding 17β-carboxylic acid.

17β-Alkoxycarbonyl compounds may be prepared by reacting the corresponding 17β-carboxylic acid or a reactive derivative thereof (e.g. an acid halide or anhydride or a salt) with the appropriate alcohol or alkyl halide. This reaction is preferably carried out at temperatures of -20°C to 110°C, as is described for example in our British Patent Specification 1,380,246.

The 17β-carboxylic acid can conveniently be formed by oxidising the corresponding 17β-acetyl compound, using for example NaOBr in an aqueous inert solvent (e.g. dioxan). The acids are conveniently obtained in the form of their triethylammonium salts by neutralisation and addition of triethylamine, followed by extraction into a suitable solvent (e.g. chloroform). These salts may be converted into their alkali metal salts by treatment with an alkali metal alkoxide (e.g. lithium methoxide).

12. Reaction of the corresponding 17β-carboxylic acid with an amine.

17β-(Substituted carbamoyl) compounds may be prepared by reacting the corresponding 17β-carboxylic acid or a reactive derivative thereof (e.g. an acid halide or ester) with an amine HNR^xR^y, where R^x and R^y are as defined above. The reaction is again preferably carried out in the presence of an acid binding agent, as is described generally in our British Patent Specification 1,380,246.

13. Acyloxylation of a corresponding 21-unsubstituted compound.

21-Alkanoyloxy and benzoyloxy compounds may be prepared by treating the corresponding 2-unsubstituted compound (in which the 3α-hydroxy group is optionally protected) with the appropriate lead tetraacylate, preferably in the presence of a Lewis acid (e.g. boron trifluoride) in a hydrocarbon/alcohol solvent. This reaction is generally described in our British Patent Specification 1,317,185.

14. Displacement of a 21-iodine atom by fluoride.

21-Fluorides may be prepared from the corresponding 21-iodo compounds by treatment with a source of fluoride ions (e.g. an alkali metal or silver fluoride), as described generally in our British Patent Specification 1,430,932.

15. Deacylation of a corresponding 21-acyloxy compound.

21-Hydroxy compounds may be prepared by hydrolysing a corresponding 21-acyloxy compound (e.g. a 21-acetoxy compound) under basic conditions, as generally described in our British Patent Specification 1,377,608.

16. Etherification of a corresponding 21-hydroxy or 21-halo compound.

21-Alkoxy compounds may be prepared by etherifying a corresponding compound having a 21-hydroxy group or a displaceable substituent at the 21-position (e.g. a 21-halo, such as a 21-bromo, compound) with for example an appropriate alkanol, diazoalkane or alkali metal alkoxide, these methods being again generally described in our British Patent Specification 1,377,608. The 3α-hydroxy group is desirably protected in these reactions.

17. Acyloxylation of a corresponding 21-substituted compound.

21-Alkanoyloxy and benzoyloxy compounds may be prepared by reacting a corresponding compound having a readily displaceable substituent at the 21-position (e.g. a bromine, chlorine or iodine atom or a hydrocarbyl sulphonyloxy group) with a salt of the appropriate carboxylic acid. This reaction is generally described in our British Patent Specification 1,317,185.

18. Acylation of the corresponding 21-alcohol.

21-Alkanoyloxy and benzoyloxy compounds may also be prepared by acylating the corresponding 21-alcohol, again as described generally in our British Patent Specification 1,317,185. 21-Carbonate esters may similarly be prepared by using for example the appropriate alkylchloroformate.

19. Dehydrohalogenation of a corresponding 2β-halo compound.

Δ^1-5α-Compounds may be prepared by dehydrohalogenating a corresponding 2β-halo compound (preferably a 2β-bromo compound) using for example a nitrogen- containing Lewis base, e.g. dimethylformamide or dimethylacetamide. The starting material may have a protected 3α-hydroxy group, and the reaction is advantageously carried out in the presence of an alkali metal or alkaline earth metal carbonate or halide (e.g. a mixture of calcium carbonate and lithium bromide) at a temperature of 80—170°C. This reaction is described generally in our British Patent Specification 1,380,248.

20. A 17β-vinyl group may for example be introduced by partial hydrogenation of an appropriate 17β-ethynyl compound.

The 17β-ethynyl compounds required in this preparation may themselves be prepared from a 17β-acetyl steroid by first forming the corresponding 20-hydrazone, iodinating the hydrazone (e.g. with iodine and triethylamine), and then dehydroiodinating the iodide (e.g. with ethanolic potassium hydroxide).

The 17β-ethynyl compounds may also be prepared by treating an appropriate 21-methanesulphonyloxy-20-oxo steroid with toluene-p-sulphonylhydrazide and then a base.

21. A 17β-vinyl group may also be introduced by treating an appropriate 20,21-epoxide with an alkali metal (e.g. potassium) selenocyanate, for example in an alcoholic solvent. The epoxides may be prepared as generally described in our British Patent Specification 1,377,608.

22. A Z-ethylidene or Z-cyanomethylene group may be introduced by a Wittig reaction, by reacting a 17-oxo steroid with for example a suitable organophosphorus reagent, such as (i) a substituted or unsubstituted methylenephosphorane (e.g. ethylidenetriphenyl phosphorane), which is conveniently prepared *in situ* using a base (e.g. sodium hydride) in a solvent (such as dimethylsulphoxide or tetrahydrofuran) and a substituted or unsubstituted methyl phosphonium salt (e.g. an ethyl triphenylphosphonium halide e.g. bromide or chloride), or (ii) a substituted methyl dialkylphosphonate (e.g. diethyl cyanomethylphosphonate).

23. Compounds in which R^9 is a methyl or cyclopropyl group or a methyl group substituted by a C_{1-4} alkyl group may be prepared by reacting the 17β-boxylic acid or more preferably a salt (e.g. a lithium or triethylamine salt) with the appropriate lithium alkyl (e.g. using 2—4 moles of the lithium alkyl per mole of the carboxylic acid or salt). Examples of suitable reaction solvents include ethers and hydrocarbons (e.g. diethyl ether and hexane); the reaction is conveniently effected at room temperature and is followed by protonation (e.g. by addition of water).

24. Deketalisation of a corresponding 20-ketal.

As indicated above, it is frequently necessary or desirable to protect a 20-oxo group during the preparation of the pregnanes of the invention, for example by ketalisation. The 20-oxo group may then be regenerated as the final step in the preparation. The ketal is preferably the corresponding 20,20-ethylenedioxy compound, and the 20-oxo group may be regenerated for example by hydrolysis in the presence of an acid (e.g. hydrochloric, sulphuric or acetic acid), or by exchange reaction with a ketone e.g. acetone in the presence of an acid catalyst, e.g. p-toluenesulphonic acid, at a temperature of 0—100°C.

25. Deprotection of a corresponding compound having a protected 3α-hydroxy group.

This method is sometimes a necessary last stage in the preparation of the compounds of the invention in that the 3α-hydroxy group is often either deliberately protected or is formed in the esterified state. The group present at the 3α-position in the starting materials in this reaction may thus be an ester group, e.g. an alkanoyloxy group, and such esters may be hydrolysed to give the desired 3α-hydroxy compounds under mild acidic or basic conditions. Weakly basic conditions are generally most convenient (using for example an alkali metal bicarbonate in aqueous methanol at any suitable temperature up to reflux). Dilute mineral acids (e.g. perchloric acid in aqueous methanol) may also be used. Strong bases (e.g. alkali metal hydroxides) may be used if the reaction is carried out briefly.

Alternatively, the starting material in this reaction may be a protected 3α-hydroxy compound such as a 3α-ether (e.g. 3α-tetrahydropyranyl ether) or a 3α-nitro-oxy compound. Such ether protecting groups may be removed by treatment with an aqueous acid, and such nitro-oxy group may be removed by reduction, for example using zinc and acetic acid.

26. Salt formation may be effected by reaction of the base with an acid.

The methods indicated above for preparing the compounds of the invention can be used as the last main step in a preparative sequence. The same general methods can be used for the introduction of the desired groups or unsaturation at an intermediate stage in the stepwise formation of the required compound, and it will be appreciated that these general methods can be combined in many different ways in such multi-stage processes, as will be apparent from the Examples below. Thus for example the desired 11α- amino group may be formed either before or after the reduction of a 3-oxo group or 16,17-double bond, and either before or after the introduction of an optional substituent at the 16,17β or 21-positions or the formation of a double bond at the 1,2-position. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product. In introducing certain of the substituents (by the methods described above, e.g. in acylation or esterification reactions) it can be desirable to protect the 11α-amino group. Conventional amine protection methods may be used, e.g. acylation (e.g. with trifluoroacetic or formic acid or a reactive derivative thereof) or silylation.

Other structural features which may be present in the compounds of the invention may be introduced by the following methods.

Methods generally suitable for introducing substituents at the 2α- and 3β-positions are described in our British Patent Specification 1,380,248.

Δ^4-Steroids may be obtained by the methods described in our British Patent Specification 1,372,175.

Compounds having an alkyl or substituted alkyl group at the 21-position or a cyclopropyl group at the 20-position may be prepared by the methods generally described in our British Patent Specification 1,436,324.

Compounds having a 6β-methyl group may be prepared by hydrogenating a corresponding 6-methyl-3-oxo-4,6-diene, followed by reduction of the 6β-methyl-3-oxo-compound formed e.g. using chloroiridic acid in the 5α-series as described above.

The D-homo, and Δ^5-compounds and $\Delta^{1,5}\beta$-compounds may be prepared by choice of starting materials containing these structural features.

The following Examples illustrate the invention. The synthesis of the intermediates required is described in the Preparations.

Temperatures are in °C.

Melting-points were determined on a Kofler block and are uncorrected. Optical

rotations were determined at room temperature on solutions in chloroform (ca. 1% w/v) unless otherwise stated.

Preparative TLC (thin layer chromatography) and CC (column chromatography) were carried out over silica.

Chloroiridic acid reagent was prepared by refluxing a mixture of chloroiridic acid (50 mg), isopropanol (94 ml), water (6 ml) and trimethyl phosphite (8 ml) for 24 hours and adjusting to pH 7 by the addition of triethylamine immediately prior to use.

Methylene chloride (dichloromethane) was redistilled and dried.

Solutions were dried either azeotropically or by use of magnesium or sodium sulphate.

In the Examples and Preparations which follow reagents and solvents which occur frequently have been abbreviated for simplicity. Thus, ethyl acetate = EA; petroleum ether (b.p. 60—80°C) = PE; acetonitrile = AN; chloroform = CH; dichloromethane = DM; diethylether = DE; dimethylsulphoxide = DSMO; pyridine = PY; THF = tetrahydrofuran;

water = W; benzene = B; toluene-4-sulphonic acid = PTSA; methyl acetate = MA; ethanol = ET; industrial methylated spirits = IMS; propan-1-ol = PR; 1,2-dichloroethane = DC; dioxan = D; petroleum ether (b.p. 40—60°C) = PT;

dimethylformamide = DMF; acetone = AC, methanol = ME; and room temperature = RT.

In the Preparations and Examples, 98—100% formic acid was used and formaldehyde was used as a 37—40% w/v aqueous solution.

In the Preparations the following known starting materials were used:

20,20-ethylenedioxy-3α-hydroxy-5α-pregnan-11-one (I)
3α-hydroxy-2β-methoxy-5α-pregnane-11,20-dione (II)
2β-butoxy-3α-hydroxy-5α-pregnane-11,20-dione (III)
20,20-ethylenedioxy-2α,3α-epoxy-5α-pregnan-11-one (IV)
2β-ethoxy-3α-hydroxy-5α-pregnane-11,20-dione (VII)
20,20-ethylenedioxy-3α-hydroxy-2α-methyl-5α-pregnan-11-one (VIII)
20,20-ethylenedioxy-3α-hydroxy-3β-methyl-5α-pregnan-11-one (IX)
6-methylpregna-4,6-diene-3,11,20-trione (X)
3α-hydroxy-21-methyl-5α-pregnane-11,20-dione (XI)
21,21-ethylene-3α-hydroxy-5α-pregnane-11,20-dione (XII)
3α-hydroxy-21-methoxy-5α-pregnane-11,20-dione (XIII)
2β-ethoxy-3α-hydroxy-5α-pregnane-11,20-dione (XIV)
3α-hydroxy-D-homo-5α-pregnane-11,20-dione (XV)
2β-ethoxy-3α-hydroxy-D-homo-5α-pregnane-11,20-dione (XVI)
20β,21-epoxy-3α-hydroxy-5α-pregnan-11-one (XVII)
5α-pregna-2,16-diene-11,20-dione (XVIII)
3α-hydroxy-5α-androstane-11,17-dione (XIX)
20,20-ethylenedioxy-3α-hydroxy-5β-pregnan-11-one (XXI)

Preparation 1

6β-Methyl-5α-pregnane-3,11,20-trione (XXIII)

X (1.7g) in EA (100ml) was hydrogenated at atmospheric pressure using 10% palladium on charcoal (Pd-C) (500mg) as catalyst. The catalyst was filtered off and the filtrate evaporated. Crystallisation of the residue from AC—PE gave the *title compound* (720mg), m.p. 174—176°, $[\alpha]_D$ +106°.

Preparation 2

3α-Hydroxy-6β-methyl-5α-pregnane-11,20-dione

XXIII (600mg) was heated under reflux with chloroiridic acid reagent (35ml) for a total of 8.5h. The reaction mixture was diluted with W and extracted with EA. Evaporation of the extract gave a foam which was purified by preparative TLC in EA—PE (1:1) to give the *title compound* (440mg) as a foam, $[\alpha]_D$ + 88°.

Preparation 3

2-N,N-Dimethylaminomethyl-2β-ethoxy-3α-hydroxy-5α-pregnane-11,20-dione. (XXIV)

XIV (10.0g) was dissolved in dry AN (50ml) and N,N-dimethyl(methylene)-ammonium chloride (5.0g) was added. The mixture was heated under reflux for 2h., cooled and partitioned between 2*N*-hydrochloric acid and EA and the acidic extract was basified with NaOH solution and extracted with CH (2 ×). The extract was dried (Na_2SO_4) and evaporated to give the *title compound* (10.7g) as a foam.

Preparation 4

2β-Ethoxy-3α-hydroxy-21-methylene-5α-pregnane-11,20-dione. (XXV)

XXIV (10.5g) was dissolved in ME (105ml) and iodomethane (10.5ml) was added. The mixture was maintained at 20° for 20h. and was then evaporated under reduced pressure. The residue was dissolved in DM (200ml) and stirred vigorously with 5% $NaHCO_3$ solution (100ml) for 1.5h. The layers were separated and the organic phase was dried (Na_2SO_4) and evaporated to give a foam. CC using EA—PE (1:1) gave the *title compound* (3.48g), m.p. 181—184°, $[\alpha]_D + 112°$.

Preparation 5

2β-Ethoxy-3α-hydroxy-21-methyl-5α-pregnane-11,20-dione

XXV (3.37g) was hydrogenated at atmospheric pressure and 23° in EA (150ml) over 5% Pd—C. The catalyst was removed by filtration and the filtrate was evaporated to give the *title compound* as a foam (3.27g), m.p. 147—149°, $[\alpha]_D + 92°$.

Preparation 6

3α-Hydroxy-5α-pregn-20-en-11-one

XVII (330mg) in W—ME (1:10; 11ml) was treated with potassium selenocyanate and the solution heated at 60°C for 20 hours. The solution was filtered through kieselguhr and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in DM and purified by CC eluting with EA—PE (1:1) to give a foam which was crystallised from DE—PE to give the *title compound* as a pale yellow solid (80mg), m.p. 137.5—139.5°.

Preparation 7

(Z)-3α-Hydroxy-5α-pregn-17(20)-en-11-one

Sodium hydride (80% dispersion in oil; 1.0g) was washed with PE and heated with dry DMSO at 70—80° until a green solution was obtained. The solution was cooled to RT and then treated with ethyl triphenylphosphonium iodide (13.3g) in DMSO (50ml). XIX (2.0g) in distilled DMSO (40ml) was added in one go and the mixture was heated to 40—60°. After six hours the reaction mixture was poured into W and extracted into DE. Evaporation of the washed and dried extract afforded an oil which was purified by CC using EA—PE (1:1) and crystallisation from EA—PE to give *title compound* (824mg), $[\alpha]_D + 29.0°$.

Preparation 8

20-Oximino-5α-pregna-2,16-dien-11-one. (XXVI)

A mixture of XVIII (60g), hydroxylammonium chloride (21g) and anhydrous PY (240ml) was left to stand at RT overnight before diluting with ice and W. The precipitate obtained was collected by filtration, washed with W and dried in vacuo at 80°, (62g). Crystallisation from EA afforded the *title compound*, m.p. 168—182°. $[\alpha]_D + 137°$.

Preparation 9

5α-Androst-2-ene-11,17-dione (XXVII)

A solution of XXVI (60g) in anhydrous PY (250ml) was treated with 225ml of a solution prepared from phosphorus oxychloride (55ml) in anhydrous PY (250ml) whilst maintaining the reaction temperature at $<5°$ during addition of the reagent. The reaction mixture was then added to a solution of concentrated HCl (350ml) in W (3l). This mixture was stirred for 60 hours before collecting the precipitate by filtration. The precipitate was washed with W, dissolved in hot IMS and treated with 2N HCl (50ml) at RT. After one hour, the reaction mixture was diluted with W and the precipitate obtained was collected by filtration, washed with W and dried. (38.4g). Crystallisation from ME afforded the *title compound*, m.p. 188—192°, $[\alpha]_D + 207°$.

Preparation 10

20,20-Ethylenedioxy-3α-hydroxy-2β-methyl-5α-pregnan-11-one

A stirred suspension of dried cuprous iodide (19.6g) in dry xylene (350ml) under nitrogen was cooled to $-10°$ and 1.9 M methyl lithium in DE (108ml) was added until the initial yellow precipitate redissolved to give an almost clear colourless solution. A solution of IV (12.9g) in xylene (430ml) was added dropwise at $-10°$ to $-5°$. After the addition, the mixture was stirred overnight at RT, and then poured into 25% NH_4Cl solution (1200ml). The mixture was extracted with DE and the extract was washed with 25% NH_4Cl solution and W. Evaporation of the DE left an oily solid

which from TLC was a 2:1 mixture of the starting material and the title compound. This solid was recycled using the same quantities of reagents, temperatures and times. The resulting solid was crystallised from EA—PE to give the *title compound* (7.22g), m.p. 167—168°, $[\alpha]_D + 68.1°$.

Preparation 11

20,20-Ethylenedioxy-2β-ethoxy-3α-hydroxy-5α-pregnan-11-one (XXXII)

A solution of VII (8.2g) in B (300ml) and ethylene glycol (40ml) was treated with PTSA (200mg) at reflux under a Dean & Stark water trap using vigorous stirring. After 6 hours solid $NaHCO_3$ (500mg) was added to the cooled mixture. Aqueous saturated $NaHCO_3$ solution (100ml) and W (50ml) were added and the organic phase was washed with W ($\times 3$), dried (Na_2SO_4) and evaporated to a foam which was purified by CC eluting with EA—PE (1:2) to give 6g of product, 500mg of which was crystallised from MA—PE to give the *title compound* (210mg), m.p. 124—127°C, $[\alpha]_D + 53°$.

Preparations 12—20

Table 1 summaries the preparation of 20-ketals by the following method.

A solution of the appropriate 20-ketone in B and ethylene glycol was refluxed under a Dean and Stark water trap in the presence of PTSA for the time indicated.

The cooled mixture was then worked-up by one of the following methods:

A. The mixture was treated with solid $NaHCO_3$ and diluted with (i) DE—W or (ii) W. The organic phase was separated, washed, dried and evaporated.

B. The mixture was diluted with aqueous $NaHCO_3$ solution and extracted with (i) EA or (ii) DM. The extract was washed, dried and evaporated.

C. The mixture was poured into aqueous $NaHCO_3$ solution, the layers separated and the aqueous layer extracted with B. The combined organic extracts were washed, dried and evaporated.

The material obtained by one of these procedures was purified by chromatography (CC or TLC) and/or crystallisation.

TABLE 1

Prep.	Starting material: Compd. or Prep. No.	Starting material: (g)	Vol. B (ml)	Ethylene glycol (ml)	PTSA (mg)	Reaction Time (hrs)	Chromatography: Type	Chromatography: system	Crystallisation solvent	Yield (g)	M.P. (°C)	$[\alpha]_D$	Method of work-up
12	II	6	150	40	300	24	–	–	DE	5.1	150–153	+52°	A (i)
13	III	7	180	20	200	18	CC	EA–PE	PE–DE	3	126–130	+42°	A (ii)
14	2	5.4	50	2.5	70	72	CC	EA–PE	DE–PT	2.64	112–113	+30.8°	B (i)
15	5	3.18	30	1.5	30	18	–	–	–	3.58		+48°	B (il
16	XII	3.8	110	5	36	120	CC	EA–PE	ME	.607	180–181	+51.3°	B (ii)
17	XI	3.19	110	5	36	5	CC	EA–PE	ME	1.28	126–127	+47.9°	B (ii)
18	XIII	1.5	55	2.5	15	3	–	–	ME–PY	1.04	188–189	+56°	B (ii)
19	XV	6.21	275	27.5	275	72	CC	EA–PE	EA–PE	2.22	156–157	+3.6°	C
20	XVI	1.95	100	10	100	17	TLC	EA–PE	DE–PE	1.62	140–141	+8.4°	C

Preparation 21

20,20-Ethylenedioxy-2β-ethoxy-3α-hydroxy-5α-pregnan-11-one 11-oxime (XXXIV)

A solution of XXXII (5g) in ET (200ml) was treated with a mixture of hydroxylamine hydrochloride (15g) and 40% NaOH solution (60ml) at reflux for 18 hours at *ca.* pH 11. The mixture was diluted with W to 2l. and the precipitate was filtered off, washed with W and dried *in vacuo* to give 4.5g. of product, a sample of which (500mg) was crystallised from MA—PE to give the *title compound* (150mg.), m.p. softens >170°C, $[\alpha]_D$ +83.3°.

Preparations 22—37

Table 2 summarises the Preparation of 11-oximes by the following method.

A solution of the corresponding 11-ketone in ET was refluxed with a mixture of hydroxylamine hydrochloride and aqueous NaOH at ⩾pH 11 for the time indicated. The cooled mixture was diluted with W, and the precipitate was filtered off, washed

and dried. The material obtained was purified by chromatography (CC or TLC) and/or crystallisation.

TABLE 2

Prep.	Starting Material: Compound or Prep. No.	Starting Material: Wt (g)	Vol. ET (ml)	Hydroxylamine HCl (g)	Reaction time (hrs)	Chromatography system	Crystallisation solvent	Yield (g)	M.P. (°C)	$[\alpha]_D$
22	12	5	150	10	24	–	ET–W	3	238–241	+90°
23	13	5.5	100	10	48	–	–	6	–	–
24	10	4	150	8	18	–	ET–W	3	224–229	+117°
25	VIII	6.1	100	12	96	–	EA–PE	3.95	218–219	+108°
26	IX	5.3	200	10.6	72	–	EA–PE	4.10	215–218	+94°
27	14	.88	15	1.75	48	–	–	.67	196–198	+54.9°
28	16	1.5	30	3	18	CC, EA–PE	EA–PE	.64	240–242	+90.2°
29	17	1.2	30	2.4	18	–	EA–PE	.88	230–232	+95.8°
30	18	1	30	2	18	–	EA–PE	.72	191–193	+91°
31	15	3.26	45	5.25	72	–	ME–PY (1%)–W	3.26	191–192	+90.7°
32	19 ③	2.22	70	8.8	67	–	DE–PE	1.88	189.5–190.5	+46.7°
33	20	4.51	180	13.5	48	TLC, EA–PE	DE–PE	2.97		+34.4°
34	6	1.6	50	2.4	18	–	ET–W	1.0	233.5–235.5	–
35	7	10.26	320 ①	3.25	47	–	ET–W	10.42	233–235	+48.1°
36 ②	39	.71	21	1.43	24	TLC, ME–CH	EA–PE	.22	176–193	+35.9°
37	I	9.5	250	10.5	24	–	ET–W	6	224–229	+93°

① IMS used as solvent; further hydroxylamine hydrochlorode (15.35g) and aqueous NaOH added after 41 hours.

② Work-up by partitioning between EA–W, The crude product was retreated with the same quantities of reagent for the same time

③ The crude product was retreated with a solution of NaOH (2.79g) in W (9ml) and then hydroxylamine hydrochloride (1.25g) at reflux for 89 hours.

Preparation 38

20,20-Ethylenedioxy-3α-hydroxy-5β-pregnan-11-one 11-oxime (XXXV)

A solution of XXI (11g.) in ET (150ml.) was treated with a mixture of hydroxylamine hydrochloride (15g.) and 50% NaOH (50ml.). The mixture was refluxed for 24 hours at pH 11, then diluted to 2l. with W. The precipitate (11g.) was filtered off, washed with water and dried. A portion (500mg.) was purified by preparative TLC and crystallised from DE—PE to give the *title compound* (100mg.), m.p. 224—228°C, $[\alpha]_D + 100$.

Preparation 39

2α,3α-Epoxy-5α-androstane-11,17-dione (XLVIII)

A mixture of XXVII (37.2g), *m*-chloroperbenzoic acid (30g) and CH (600ml) was allowed to stand for 0.5 hour at RT before partitioning between CH and saturated aqueous $NaHCO_3$ solution. The organic phase was isolated and washed with W, dried and evaporated to a low volume. Addition of PE followed by refrigeration overnight afforded crystalline material (27.5g). Recrystallisation from EA—PE afforded the *title compound* m.p. 166—167° $[\alpha]_D + 126°$.

Preparation 40

2β-Ethoxy-3α-hydroxy-5α-androstane-11,17-dione (XLIX)

A solution of XLVIII (5.0g) in absolute ET (250ml) was treated with eight drops of fuming H_2SO_4 at RT. After 45 minutes the reaction mixture was treated with aqueous $NaHCO_3$ and evaporated to low volume. W was added to the mixture which was then refrigerated overnight. The precipitate was collected by filtration, washed with W and dried. Recrystallisation from W—ET afforded the *title compound* (2.1g), m.p. 164—167°, $[\alpha]_D + 114°$.

Preparation 41

(Z)-2β-Ethoxy-3α-hydroxy-5α-pregn-17(20)-en-11-one

A mixture of XLIX (1.742g), ethyl triphenylphosphonium iodide (6.27g), sodium hydride (360mg) and Na— dried tetrahydrofuran (100ml) was stirred and refluxed under nitrogen. After 4.5 hours the reaction mixture was partitioned between EA and W. The organic phase was isolated, washed with W, dried (Na_2SO_4) and evaporated to give an oil (4.0g). CC (EA—PE 1:2) followed by preparative TLC (EA—PE 1:1 × 2) and crystallisation from EA—PE afforded the *title compound* (110mg), m.p. 172—178°, $[\alpha]_D + 25°$.

Preparation 42

11α-Amino-20,20-ethylenedioxy-5β-pregnan-3α-ol (XXXIX)

A solution of XXXV (2g.) in PR (250ml) at reflux was treated with Na (20g.) over 1 hour. When all the Na had dissolved, ME was added. The PR was removed by distillation during the cautious addition of W. The residue was extracted with DE and the extract was washed with W, dried (Na_2SO_4) and evaporated to leave a solid which was purified by CC, eluted with Me and crystallised from MA to give the *title compound* (220mg.) m.p. 153—155°C, $[\alpha]_D + 5°$ (*c* 0.65).

Preparation 43

11α-amino-20,20-ethylenedioxy-5α-pregnan-3α-ol (XL)

Sodium (100g) was added to a refluxing solution of 20,20-ethylenedioxy-3α-hydroxy-5α-pregnan-11-one 11-oxime (Preparation 37; 10g) in propan-1-ol (1.2l.) over 1.5 hours. Methanol (20ml) was added to destroy any excess of sodium and the mixture was distilled during the careful addition of water (800ml) until the propan-1-ol was removed. The residue was extracted into ethyl acetate (× 2) and the extract washed with water (× 2), dried over anhydrous sodium sulphate and evaporated. Crystallisation of the residue from ether gave the product (6g.). A further crystallisation of 200mg gave the *title compound* (110mg.) m.p. 175—177°C $[\alpha]_D + 5°$ ($CHCl_3$ C = 1%).

Example 1.

(Z)-11α-Amino-5α-pregn-17(20)-en-3α-ol (XLI)

A solution of (Z)-3α-hydroxy-5α-pregn-17(20)-en-11-one oxime (9.638g) in PR (200ml) was refluxed under N_2 whilst Na (9.6g.) was added portionwise. When all of the Na had reacted, about 90ml PR was distilled and then the residue was poured into W, ice was added and the crystalline solid (9.19g) was collected by filtration. A portion

(6.17g) was crystallized from ET—W to afford *title compound* (3.6g), m.p. 118—125°, $[\alpha]_D + 5.4°$.

Example 2.

11α-Amino-2β-ethoxy-3α-hydroxy-21-methyl-5α-pregnan-20-one. (LXII)

2β-Ethoxy-20,20-ethylenedioxy-3α-hydroxy-21-methyl-5α-pregnan-11-one oxime (2.8g) was dissolved in PR (150ml) and heated to reflux. Na (12.6g) was added and refluxing continued until all the Na had dissolved. The PR was removed by distillation with simultaneous addition of W. The resulting mixture was extracted with EA (2 ×) and the washed organic layer was re-extracted with 2N—HCl. The acidic extract was basified to pH 11 with 40% NaOH solution, extracted with EA (2 ×) dried (Na_2SO_4) and evaporated to give the *title compound* as a foam (1.94g).

Example 3.

11αAmino-2β-ethoxy-3α-hydroxy-D-homo-5α-pregnan-20-one. (LXIV)

Na (8g) was added portionwise to a refluxing solution of 2β-ethoxy-20,20-ethylenedioxy-3α-hydroxy-D-homo-5α-pregnan-11-one 11-oxime (4.0g) in PR (200ml). Refluxing was continued for 4hr. then ME (10ml) was added. The alcohol solvents were removed by distillation whilst adding W. The cooled aqueous suspension was extracted with EA (3 ×) and the combined extracts washed with saturated brine solution (2 ×), dried and evaporated to a foam. This was dissolved in EA and extracted with 2N—HCl (3 ×). The combined aqueous extracts were basified with 0.88 ammonia solution and extracted with EA. The combined EA extracts were washed with saturated brine solution, dried and evaporated to give the *title compound* as a foam (2.43g), $[\alpha]_D + 40°$.

Example 4.

11α-Amino-20,20-ethylenedioxy-2β-ethoxy-5α-pregnan-3α-ol. (XXXVIII)

A solution of XXXIV (4g) in PR (500ml) was treated at reflux with Na (40g) over 1 hour. When all the Na had dissolved, ME (20ml) was added. The mixture was then distilled with the constant addition of W until all the PR had been removed. The product was extracted into DE (× 2) and the extract was washed with W (× 2) dried (Na_2SO_4) and evaporated to leave a foam (3.7g), which was purified by CC, eluting with ME, to give the *title compound* as a foam (2.5g), $[\alpha]_D + 13.7°$.

Examples 5—14.

Table 3 summarises the preparation of 11α-amines by the following method:

A solution of the corresponding 11-oxime in PR was treated at reflux with sodium. When all the sodium had reacted the PR was distilled and simultaneously replaced with W.

The residual mixture was worked-up by one of the following methods:

A. The mixture was extracted with (i) DE or (ii) EA and the extract washed, dried and evaporated.

B. The precipitate formed was filtered off, washed and dried.

The material obtained was purified by crystallisation.

TABLE 3

Example	Starting Material		Vol PR (ml)	Wt Sodium (g)	Crystallisation Solvent	Yield (g)	M.P. (°C)	$[\alpha]_D$	Method of Work-up
	Prep. No.	Wt (g)							
5	24	2.8	500	30	DE	2.1	143–145	+37°	B
6	23	6	800	60	(1)	2	–	+8.5°	A (i)
7	22	3.6	500	40	MA–PE	2.5	156–158	+20°	A (i)
8	34	0.9	130	8	DE–PE	0.4	100–102	–	A (ii)
9	28	1	120	10	EA–PE	.412	156–157	+7°	A (ii)
10	29	1.16	100	10	EA–PE	.750	144–146	+9.8°	A (ii)
11	30	.945	100	9.45	ME	.389	188–189	+13.4°	B
12	27	1.85	110	9.3	EA–PE	1.08	143–144	-9.7°	A (ii)
13	26	3.5	420	34	EA–PE	2.6	155–157	+6.9°	A (ii)
14	25	3.87	450	16.53	DE–PE	2.31	116–118	+4.7°	A (ii)

(1) Purified by CC eluting with ME.

Example 15.

(Z)-11α-Amino-2β-ethoxy-5α-pregn-17(20)-en-3α-ol (LXV)

A refluxing solution (under nitrogen) of (Z)-2β-ethoxy-3α-hydroxy-5α-pregn-17(20)-en-11-one 11-oxime (450mg) in PR (15ml) was treated with pieces of Na (450mg). When there was no trace of Na left the mixture was added to chilled W to give a fine precipitate which was collected by filtration.

The solid was dissolved in EA, dried (Na_2SO_4) and evaporated to a froth which was partitioned between 2N HCl and DE. The insoluble material which separated was collected by filtration and partitioned between EA and 2N NaOH solution. The organic

phase was isolated, washed with W dried (Na_2SO_4) and evaporated to give a froth which was crystallised from PE to afford the *title compound* (110mg), m.p. 65—70°. $[\alpha]_D + 10°$.

Example 16.

11α-Amino-3α-hydroxy-D-homo-5α-pregnan-20-one (LXIII)

20,20 - Ethylenedioxy - 3α - hydroxy - D - homo - 5α - pregnan - 11 - one 11-oxime (1.87g) in PR (200ml) was treated with Na (10g) and worked-up as described in Example 3. Crystallisation from EA—PE gave the *title compound* (128mg), M.P. 154—157°, $[\alpha]_D + 36.1$.

Example 17.

11α-N-Allylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one

A solution of XXXVIII (750mg) in ET (10ml) was treated with allylbromide (2ml) and K_2CO_3 (1g) at 80° for 3 hours. The reaction mixture, after filtration, was evaporated to dryness and the residue partitioned between EA and brine (adjusted to ca. pH9 by addition of 2N—Na_2CO_3). The aqueous layer was extracted with further EA and the combined extracts washed with brine, dried (Na_2SO_4) and evaporated. Preparative TLC yielded the *title compound* as a gum (107mg).

Example 18.

11α-N-Cyclohexylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one

XXXVIII (0.5g) was mixed with cyclohexanone (2ml) in ET (20ml) at RT and $NaBH_3CN$ (250mg) and acetic acid (0.1ml) added. After 20 hours the mixture was acidified, basified, extracted with EA and the product purified by TLC to yield *title compound* (268mg) as a foam, $[\alpha]_D + 26.6°$.

Example 19.

11α-N-Benzylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one

XXXVIII (0.5g) was mixed with benzaldehyde (1ml) in ET (10ml) at RT and $NaBH_3CN$ (250mg) and acetic acid (0.1ml) added. After 1 hour the mixture was worked-up as in Example 18 and purified by CC and TLC to yield *title compound* (205mg) as a foam, $[\alpha]_D + 34.1°$.

Example 20.

(Z)-11α-N-Ethylamino-5α-pregn-17(20)-en-3α-ol

$NaBH_3CN$ (398mg) was added to a solution of XLI (1.027g) in ET (30ml) and when dissolution was complete acetaldehyde (9ml) was added. After 35 minutes the solution was diluted with 2N—HCl and W and washed with EA, basified with 2N—NaOH and the precipitated material extracted into EA. The washed organic extract was evaporated *in vacuo* to yield an oil. Purification by preparative TLC (ME—EA 1:1) gave an oil which crystallized on trituration with a little AN. Recrystallization from W—AN afforded *title compound* (287mg), m.p. 106—109°, $[\alpha]_D - 19.9°$.

Example 21.

(Z)-11α-N-Isopropylamino-5α-pregn-17(20)-en-3α-ol

A solution of XLI (422mg) in IMS (6ml) containing AC (1ml) was treated with $NaBH_3CN$ and the resulting mixture worked-up as described in Example 20. Purification by TLC (ET—CH 1:1) gave *title compound* (180mg) as a froth.

Example 22.

2β-Ethoxy-20,20-ethylenedioxy-11α-(4-methylpent-2-ylamino)-5α-pregnan-3α-ol Isomers A (L) & B (LI)

XXXVIII (1.06g) was refluxed with 4-methylpentan-2-one (2ml) in PR (40ml) under nitrogen for 20 hours. Reflux under nitrogen was maintained and Na (4g) was added over 3 hours. W (*ca* 50ml) was added and the PR was evaporated at reduced pressure. The aqueous residue was extracted with EA. The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated to a gum. This was purified by preparative TLC developed in ME—EA (1:9) to separate isomers of *title compound* giving isomer A (333mg) (gum) and isomer B (322mg) (gum).

Example 23.

11α-Amino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one (LIX)

XXXVIII (10g) was suspended in W (38ml) and treated with concentrated HCl

(12ml). The insoluble material was removed by filtration and washed with a small portion of W. This material was resuspended in W (50ml) and treated with 2N—NaOH to pH 9. The mixture was stirrred at 0° for 10 minutes and then the solid was collected by filtration and washed with W to give the *title compound*, m.p. 160—164°, $[\alpha]_D + 79.2°$.

Example 24.

2β-Ethoxy-3α-hydroxy-11α-(4-methylpent-2-ylamino)-5α-pregnan-20-one isomer A

L (330mg) was dissolved in ME (20ml) and 2N HCl (0.5ml) added. After 15 minutes at 21°, the mixture was neutralised with 2N—Na_2CO_3 solution and evaporated to small volume. The residue was partitioned between EA and brine. The aqueous layer was extracted with further EA and the combined organic solutions were washed with brine (2X), dried (Na_2SO_4) and evaporated to dryness (310 mg). This was purified by preparative TLC developed in 5% ME in EA and EA to give *title compound* as a white foam, $[\alpha]_D - 1°$.

Example 25.

2β-Ethoxy-3α-hydroxy-11α-(4-methylpent-2-ylamino)-5α-pregnan-20-one isomer B

LI (322mg) was treated as described in Example 24 to give the *title compound* (170mg) as a white foam, $[\alpha]_D + 2.1°$ (*c* 0.36).

Example 26.

11α-N-Ethylamino-3α-hydroxy-5β-pregnan-20-one

XXXIX (1g) was dissolved in ET (30ml), and K_2CO_3 (1g) and ethyl iodide (3ml) were added. The reaction mixture was stirred under reflux for 2.5 hours and then evaporated to dryness. The residue was redissolved in ET (10ml) and 2N—HCl (10ml) at RT and after 15 minutes it was basified with aqueous KOH. The steroid was extracted with EA and purified by preparative thick layer chromatography using EA—ME (3:1) as eluant to give the *title compound* (201mg) as a froth, $[\alpha]_D + 43°$.

Example 27.

11α-N-Butylamino-3α-hydroxy-5α-pregnan-20-one (LXVII)

A solution of 11α-amino-20,20-ethylenedioxy-5α-pregnan-3α-ol (XL) (1.5g) in 1-iodobutane (20ml) was treated at 80°C with K_2CO_3 (3g) and stirred for 3 hours. The mixture was partitioned between DE and W and the organic layer was extracted with 2N—HCl. The extract was basified with 4N NaOH solution and the oily deposit was extracted into DE. The extract was washed with W, dried (Na_2SO_4) evaporated to leave a foam (1.5g). A portion (500mg) was purified by preparative TLC in AC to give the *title compound* (350mg) as an oil $[\alpha]_D + 60°$.

Example 28.

3α-Hydroxy-11α-N-propylamino-5α-pregnan-20-one (LXVI)

A solution of XL (1g) in 1-iodopropane (10ml) was stirred at reflux with K_2CO_3 (3g) for 40 minutes and the mixture was worked-up as in Example 27. CC using Me and removal of solvent from later fractions left a residue which was crystallised from PE to give the *title compound* (450mg), m.p. 138—141°, $[\alpha]_D + 32°$.

Example 29.

11α-N-Ethylamino-3α-hydroxy-5α-pregnan-20-one (LXVIII)

A solution of XL (4g) in ethyliodide was stirred with Ag_2O (12g) at RT for 2 hours. Ag_2O was removed by filtration and the filtrate worked-up as in Example 27. CC and TLC yielded the *title compound* (400mg).

Example 30.

3α-Hydroxy-11α-N-isopropylamino-5β-pregnan-20-one

XXXIX (920mg) was dissolved in ET (40ml) and added to $NaBH_3CN$ (450mg). AC (4ml) was added followed by acetic acid (0.2ml) and the reaction mixture was kept at RT for 17 hours. The reaction mixture was divided into two parts for extraction.

(a) The solution was partitioned between EA and Na_2CO_3 solution and the organic layer was washed well with W, dried ($MgSO_4$) and evaporated to dryness. The residue was dissolved in ME (10ml) and 2N—HCl (10ml)

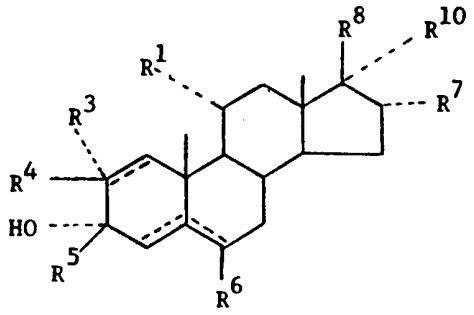
was added. The mixture was allowed to stand at RT for 30 minutes and then basified with Na_2CO_3 solution and the steroid extracted with EA.

(b) The second part of the reaction mixture was partitioned between EA and Na_2CO_3 solution as in (a) above and the organic layer was then shaken with 2N—HCl and left for 30 minutes. The reaction mixture was then basified with $NaHCO_3$ and extracted with EA. The combined EA extracts were washed with water, dried ($MgSO_4$) and evaporated.

(a) and (b) were combined and subjected to thick plate chromatography using EA as solvent and the steroid was eluted with EA—ME to yield *title compound* (590mg), $[\alpha]_D + 38°$.

WHAT WE CLAIM IS:—

1. Steroids of the formula:



wherein:

R^1 is a group —NHR^a, in which R^a is a hydrogen atom or a C_{1-6} alkyl, C_{3-6} cycloalkyl, benzyl or phenethyl group, or a C_{3-6} alkenyl group having one or two double bonds in which the carbon atom adjacent to the nitrogen atom of the —NHR^a group is saturated;

R^3 is a hydrogen atom or a C_{1-3} alkyl group;

R^4 is a hydrogen atom or a C_{1-3} alkyl, C_{1-5} alkoxy (which may be optionally substituted by a halogen atom), benzyloxy, C_{2-5} alkanoyloxy or thiocyanato group or a halogen atom;

R^5 is a hydrogen atom or a methyl group;

R^6 is a hydrogen atom or a methyl group;

R^7 is a hydrogen atom or (except when R^8 is a group (c) as defined below) a chlorine atom; and

R^8 is (a) a cyano group; (b) a group —COR^9 where R^9 is a methyl group or such a group substituted by a fluorine atom, or by a C_{1-4} alkoxy, hydroxy, C_{1-4} alkyl, methoxymethyl, ethoxymethyl, C_{2-5} alkanoyloxy, benzoyloxy, or C_{2-5} alkoxycarbonyloxy group; or where R^9 is a C_{1-5} alkoxy or cyclopropyl group; or where R^9 is the group —NR^xR^y where R^x and R^y (which may be the same or different) are methyl or ethyl groups; or (c) a vinyl group or together with R^{10} a methylene group substituted by a methyl or cyano group in the Z-configuration.

R^{10} is a hydrogen atom except when R^8 and R^{10} together represent a substituted methylene group;

the broken lines indicate the optional presence of double bonds at the positions shown;

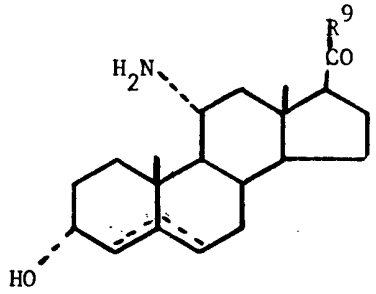
provided that at least one of R^3 and R^4 is a hydrogen atom; and R^3 and R^4 together represent a hydrogen atom when a 1,2-double bond is present; and that a 1,2-double bond is not present when a 4,5-double bond is present; and that R^3 is a hydrogen atom, R^4 is a hydrogen atom or a methyl group and R^5 is a hydrogen atom or optionally (when R^4 is a hydrogen atom) a methyl group when a 5β-hydrogen atom is present;

and the D-homo analogues thereof carrying R^8 at the 17aβ-position, R^{10} at the 17aα-position, and R^7 at the 17-position;

and the 20-ketals of compounds having a 20-keto group;

and the acid addition salts thereof;

but excluding compounds of the formula



(wherein R^9 is a methyl group or a methyl group substituted by a hydroxy or C_{2-5} alkanoyloxy group) and the 20-ketals thereof.

2. Compounds as claimed in claim 1, wherein R^8 is other than a benzyl or phenethyl group; R^8 is other than the group —COR^9 where R^9 is a methyl group substituted by a C_{2-4} alkyl, benzoyloxy or alkoxycarbonyloxy group; and wherein R^3, R^4 and R^5 are all hydrogen atoms when a 5β-hydrogen atom is present.

3. Compounds as claimed in claim 2 which possess a 5α- or 5β-hydrogen atom.

4. Compounds as claimed in claim 2 or claim 3 wherein the tetracyclic steroid system is saturated and R^5, R^6 and R^7 are all hydrogen atoms.

5. Compounds as claimed in any one of claims 2 to 4 wherein R^3 is a hydrogen atom or a methyl group.

6. Compounds as claimed in any one of claims 2 to 5 wherein ring D is a 5-membered ring.

7. Compounds as claimed in any one of claims 2 to 6 which possess a 5α-hydrogen atom.

8. Compounds as claimed in any one of claims 2 to 7 wherein R^8 is (a) a cyano group or (b) a group —COR^9 where R^9 is a methyl group or such a group substituted by a hydroxy, methyl or acetoxy group, or where R^9 is a cyclopropyl group.

9. Compounds as claimed in claim 8 wherein R^8 is an acetyl group.

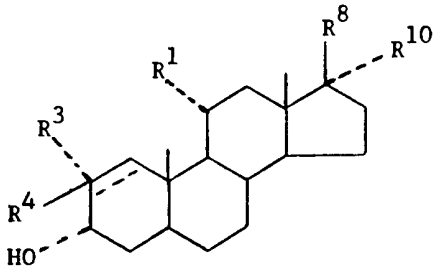
10. Compounds as claimed in claim 8 wherein R^8 is a cyano group.

11. 5α-compounds as claimed in any one of claims 2 to 10 wherein R^4 is a hydrogen atom or a methyl, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, acetoxy or thiocyanato group or a chlorine, bromine or fluorine atom.

12. Compounds as claimed in claim 11 wherein R^4 is a hydrogen atom or an ethoxy group.

13. Compounds as claimed in any one of claims 2 to 12 wherein R^a is a methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, pentyl, *iso*-pentyl, 1,3-dimethylbutyl, allyl, cyclopentyl or cyclohexyl group, or a hydrogen atom.

14. Compounds as claimed in claim 1 of the formula:



(II)

wherein:

R^1 is a group —NHR^a, in which R^a is a hydrogen or a methyl, ethyl, propyl, *iso*-propyl, butyl or allyl group;

R^3 is a hydrogen atom or a methyl group;

R^4 is a hydrogen atom or a methyl, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, acetoxy or thiocyanato group or a fluorine, chlorine or bromine atom;

R^8 is (a) a cyano group; (b) a group —COR^9 where R^9 is a methyl group or such a group substituted by a methyl, hydroxy or acetoxy group, or R^9 is a cyclopropyl group; or (c) a vinyl group or, together with R^{10}, a Z-ethylidene group; and

R^{10} is a hydrogen atom (except when R^8 and R^{10} together represent an ethylidene group);
the broken line indicates the optional presence of a double bond at the 1,2-position;
provided that at least one of R^3 and R^4 is a hydrogen atom; that R^3 and R^4 together represent a hydrogen atom when a 1,2-double bond is present; and that R^3 is a hydrogen atom and R^4 is a hydrogen atom or a methyl group when a 5β-hydrogen atom is present;
and the D-homo analogues carrying R^8 at the 17aβ-position and R^{10} at the 17aα-position;
and the 20-ketals of compounds having a 20-keto group;
and the acid addition salts thereof.

15. (Z)-11α-Amino-5α-pregn-17(20)-en-3α-ol.
16. 11α-Amino-2β-ethoxy-3α-hydroxy-21-methyl-5α-pregnan-20-one.
17. 11α-Amino-2β-ethoxy-3α-hydroxy-D-homo-5α-pregnan-20-one.
18. 11α-Amino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one.
19. (Z)-11α-Amino-2β-ethoxy-5α-pregn-17(20)-en-3α-ol.
20. 11α-Amino-3α-hydroxy-D-homo-5α-pregnan-20-one.
21. 11α-N-Allylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one.
22. 11α-N-Cyclohexylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one.
23. 11α-N-Benzylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one.
24. (Z)-11α-N-Ethylamino-5α-pregn-17(20)-en-3α-ol.
25. (Z)-11α-N-Isopropylamino-5α-pregn-17(20)-en-3α-ol.
26. 2β-Ethoxy-3α-hydroxy-11α-(4-methylpent-2-ylamino)-5α-pregnan-20-one.
27. 11α-Amino-5α-pregn-20-en-3α-ol.
28. 11α-N-Ethylamino-3α-hydroxy-5β-pregnan-20-one.
29. 11α-N-Butylamino-3α-hydroxy-5α-pregnan-20-one.
30. 3α-Hydroxy-11α-N-propylamino-5α-pregnan-20-one.
31. 11α-N-Ethylamino-3α-hydroxy-5α-pregnan-20-one.
32. 3α-Hydroxy-11α-N-isopropylamino-5β-pregnan-20-one.

33. A process for the preparation of a compound as claimed in claim 1 in which R^a is other than a hydrogen atom, which process comprises reacting a corresponding steroid in which R^a is a hydrogen atom with a compound of the formula R^aX where X is a readily displaceable substituent.

34. A process for the preparation of a compound as claimed in claim 1 in which R^a is other than a hydrogen atom, which comprises reducing a corresponding 11α-acylamino steroid.

35. A process for the preparation of a ring A-saturated 2β-substituted 5α-steroid as claimed in claim 1, which comprises opening the epoxide ring of a corresponding 2α,3α-epoxide by treatment with a compound HR^4 under acidic conditions or with a compound which produces the anion $(R^4)^-$ (where R^4 is as defined in claim 1, other than hydrogen), and then (when the initial product possesses a deprotonated 3α-hydroxy group) treating the product with a source of protons.

36. A process for the preparation of a compound as claimed in claim 1 in which R^a is other than a hydrogen atom, which comprises reductive alkylation of a corresponding 11α-amino steroid.

37. A process for the preparation of a 5β-steroid or ring A-saturated 2β-unsubstituted 5α-steroid as claimed in claim 1, which comprises reducing the corresponding 3-oxo steroid.

38. A process for the preparation of a compound as claimed in claim 1 in which R^a is a hydrogen atom, which comprises reducing the corresponding 11-oxime.

39. A process for the preparation of a compound as claimed in claim 1 in which R^b is a group (a) or (b) as defined in claim 1, which comprises reducing the corresponding Δ^{16} compound.

40. A process for the preparation of a 16α-chloro compound as claimed in claim 1, which comprises hydrochlorinating the corresponding Δ^{16} compound.

41. A process for the preparation of a 17β-cyano compound as claimed in claim 1, which comprises, dehydrating the corresponding 17β-carbamoyl compound or the oxime of the corresponding 17β-formyl compound.

42. A process for the preparation of a 17β-alkoxycarbonyl compound as claimed in claim 1, which comprises esterifying the corresponding 17β-carboxylic acid.

43. A process for the preparation of a 17β-(substituted carbamoyl) compound as claimed in claim 1, which comprises reacting the corresponding 17β-carboxylic acid or a reactive derivative thereof with an amine.

44. A process for the preparation of a 21-alkanoyloxy or 21-benzoyloxy compound

as claimed in claim 1, which comprises acyloxylation of the corresponding 21-unsubstituted compound.

45. A process for the preparation of a 21-fluoro compound as claimed in claim 1, which comprises, displacement of the iodine atom of the corresponding 21-iodo compound by fluoride.

46. A process for the preparation of a 21-hydroxy compound as claimed in claim 1 which comprises deacylating a corresponding 21-acyloxy compound.

47. A process for the preparation of a 21-alkoxy compound as claimed in claim 1, which comprises etherifying a corresponding compound having a 21-hydroxy group or a displaceable 21-substituent.

48. A process for the preparation of a 21-alkanoyloxy or 21-benzoyloxy compound as claimed in claim 1, which comprises acyloxylation of a corresponding compound having a readily displaceable 21-substituent.

49. A process for the preparation of a 21-alkanoyloxy or 21-benzoyloxy compound as claimed in claim 1, which comprises acylating the corresponding 21-alcohol.

50. A process for the preparation of a Δ^1-5α-compound as claimed in claim 1, which comprises dehydrohalogenating a corresponding 2β-halo compound.

51. A process for the preparation of a 20-oxo compound as claimed in claim 1, which comprises deketalising a corresponding 20-ketal.

52. A process for the preparation of a compound as claimed in Claim 1, which comprises deprotecting a corresponding compound having a protected 3α-hydroxy group.

53. A process for the preparation of a salt of a compound as claimed in claim 1, which comprises treating the appropriate free base with an acid.

54. A process for the preparation of a 17β-vinyl compound as claimed in claim 1, which comprises partially hydrogenating the corresponding 17β-ethynyl compound.

55. A process for the preparation of a 17β-vinyl compound as claimed in claim 1, which comprises treating the corresponding 20,21-epoxide with an alkali metal selenocyanate.

56. A process for the preparation of a 17-(Z)-ethylidene- or 17-(Z)-cyanomethylene compound as claimed in claim 1, which comprises reacting the corresponding 17-oxo steroid with an organophosphorus reagent.

57. A process for the preparation of a compound as claimed in claim 1 in which R^9 is a methyl or cyclopropyl group or a methyl group substituted by a C_{1-4} alkyl group, which comprises reacting a 17β-carboxylic acid or salt thereof with the appropriate lithium alkyl.

58. A process as claimed in any one of claims 33 to 56 in which the compound produced is a compound as claimed in claim 2.

59. A compound as claimed in claim 1 when prepared by a process as claimed in any one of claims 33 to 58.

60. Compounds as claimed in claim 1, said compounds being the products of any one of Examples 4—7, 9—14 and 22.

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