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(54) 11α-AMINO-3α-HYDROXY-STEROIDS

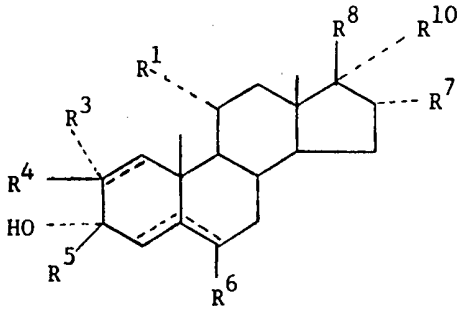
(71) We, GLAXO OPERATIONS UK LIMITED, formerly known as Glaxo Laboratories Limited, a British Company of Greenford, Middlesex do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the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

This invention relates to anaesthetic 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 1317184 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.

We have now found very interesting anaesthetic activity in a group of 3α-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.

This invention thus provides 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} alkeny (containing one or two double bowls), 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, 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 substituted methylene group in which the substituent is in the Z-configuration and is 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.

In the tests we have carried out, the compounds of the invention have been shown generally to be good anaesthetics, usually giving rapid induction of anaesthesia when administered intravenously. The water soluble salts are particularly important in that they can be formulated in aqueous solution and in general comparison to known water soluble anaesthetic steroids they are superior as regards their potency and/or quality of anaesthesia and/or freedom from side effects such as thrombophlebitis. The aqueous solutions of the water soluble salts have also in general been found to be very stable. The compounds of the invention are of use for inducing anaesthesia which is to be maintained for example by an inhalation anaesthetic, such as ether, halothane, nitrous oxide or trichloroethylene. The compounds may also be capable of maintaining anaesthesia to a sufficient degree to enable surgical operations to be conducted without the aid of an inhalation anaesthetic, the anaesthesia being maintained if necessary by repeated or continuous administration. The compounds may have other useful central nervous system depressant activities, for example they may be of use as sedatives.

As indicated above, the R^a and R^b groups may be C_{1-6} alkyl groups, 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 C_{3-6} alkenyl groups such as allyl groups. When R^a or R^b is a cycloalkyl group, it may be for example a cyclopentyl or cyclohexyl group.

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

When —NR^aR^b represents a heterocyclic group, it is preferably a pyrrolidino group.

Preferably one of R^a and R^b is a methyl group, the other group being a methyl, ethyl, propyl, *iso*-propyl or butyl group. Compounds wherein both R^a and R^b are methyl groups are especially preferred.

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

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

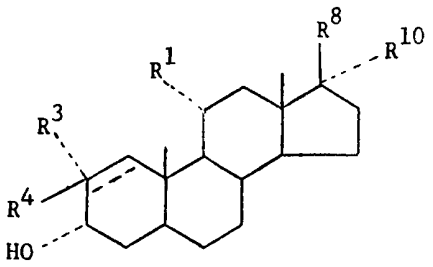
Compounds having a 2β(R^4)-substituent are particularly important in the 5α-series, examples of such substituents being a methyl, methoxy, ethoxy, propoxy,

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 steriod 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'-compounds are preferred.

One group of compounds of the invention is compounds in which R^a and R^b are other than benzyl or phenethyl groups; R^8 is other than the group $—COR^9$ where R^9 is a methyl group substituted by a C_{2-4} alkyl 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):



(I)

wherein:

R^1 is a group $—NR^aR^b$, in which one of R^a and R^b is a methyl group, the other group being a methyl, ethyl, propyl, *iso*-propyl, butyl or allyl group, or in which both R^a and R^b are ethyl groups, or in which R^a and R^b (together with the nitrogen atom) represent a pyrrolidino 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 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 17aβ-position and R^{10} at the 17aα-position;

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 (I) and (II) 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, ring D to have 5 members and for $—NR^aR^b$ to be a dimethylamino group. 5α-Compounds are most preferred.

As indicated above, the ability of the bases of the invention to form water soluble acid addition salts is particularly important. Thus, the compounds of the invention in the form of their bases can be formulated simply in aqueous acidic solution.

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. The citrate and hydrochloride salts are particularly preferred for use as anaesthetics.

When these salts are used as anaesthetics they should be physiologically acceptable at the dosage at which they are administered. Other salts may, however, be of use in for example isolation of the product from a synthetic reaction.

Preferred compounds are:

1. 11α-N,N-dimethylamino-3α-hydroxy-5α-pregnan-20-one;
2. 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-0ne;
3. 11α-N,N-dimethylamino-3α-hydroxy-2β-methyl-5α-pregnan-20-one;
4. 1α-N,N-dimethylamino-3α-hydroxy-2α-methyl-5α-pregnan-20-one;
5. 11α-N,N-dimethylamino-3α-hydroxy-5β-pregnan-20-one;
6. 11α-N,N-dimethylamino-3α-hydroxy-5α-androstane-17β-carbonitrile;
7. 11α-N-butyl-N-methylamino-3α-hydroxy-5α-pregnan-20-one;.
8. 2β-chloro-11α-N,N-dimethylamino-3α-hydroxy-5α-pregnan-20-one;
9. 11α-N,N-dimethylamino-2β-fluoro-3α-hydroxy-5α-pregnan-20-one;
10. 11α-N,N-dimethylamino-3α-hydroxy-2β-methoxy-5α-pregnan-20-one;
11. 2β-ethoxy-11α-N-ethyl-N-methylamino-3α-hydroxy-5α-pregnan-20-one;
12. 11α-N-ethyl-N-methylamino-3α-hydroxy-5α-pregnan-20-one;
13. 3α-hydroxy-11α-N-methyl-N-propylamino-5α-pregnan-20-one;
14. 11α-N-ethyl-N-methylamino-3α-hydroxy-2β-methoxy-5α-pregnan-20-one;
15. 3α-hydroxy-11α-N-*iso*-propyl-N-methylamino-2β-methoxy-5α-pregnan-20-one;
16. 11α-N-allyl-N-methylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one;
17. 2β-ethoxy-3α-hydroxy-11α-pyrrolidino-5α-pregnan-20-one;
18. 11α-N,N-dimethylamino-3α-hydroxy-2β-propoxy-5α-pregnan-20-one;
19. 11α-N,N-dimethylamino-3α-hydroxy-2β-*iso*-propoxy-5α-pregnan-20-one;
20. 2β-acetoxy-11α-N,N-dimethylamino-3α-hydroxy-5α-pregnan-20-one;
21. 2β-acetoxy-11α-N-ethyl-N-methylamino-3α-hydroxy-5α-pregnan-20-one;
22. 2β-acetoxy-3α-hydroxy-11α-N-*iso*-propyl-N-methylamino-5α-pregnan-20-one;
23. 11α-N-ethyl-N-methylamino-2β-fluoro-3α-hydroxy-5α-pregnan-20-one;
24. 2β-fluoro-3α-hydroxy-11α-N-*iso*-propyl-N-methylamino-5α-pregnan-20-one;
25. 2β-chloro-11α-N-ethyl-N-methylamino-3α-hydroxy-5α-pregnan-20-one;
26. 2β-chloro-3α-hydroxy-11α-N-*iso*-propyl-N-methylamino-5α-pregnan-20-one;
27. 2β-bromo-11α-N,N-dimethylamino-3α-hydroxy-5α-pregnan-20-one;
28. 11α-N,N-dimethylamino-3α-hydroxy-2β-thiocyanato-5α-pregnan-20-one;
29. 11α-N,N-dimethylamino-3α-hydroxy-5α-pregn-1-en-20-one;
30. 11α-N,N-dimethylamino-3α-hydroxy-D-homo-5α-pregnan-20-one;
31. 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-D-homo-5α-pregnan-20-one;
32. 11α-N,N-dimethylamino-2₁,21-ethylene-3α-hydroxy-5α-pregnan-20-one;
33. 11α-N,N-dimethylamino-3α-hydroxy-21-methyl-5α-pregnan-20-one;
34. 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-21-methyl-5α-pregnan-20-one;
35. 21-acetoxy-11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one;
36. 11α-N,N-diethylamino-3α-hydroxy-5β-pregnan-20-one;
37. 3α-hydroxy-11α-N-*iso*-propyl-N-methylamino-5β-pregnan-20-one;
38. 11α-N-ethyl-N-methylamino-3α-hydroxy-5β-pregnan-20-one;
39. 3α,21-dihydroxy-11α-N,N-dimethylamino-5β-pregnan-20-one;
40. 21-acetoxy-11α-N,N-dimethylamino-3α-hydroxy-5β-pregnan-20-one;
41. 11α-N,N-dimethylamino-3α-hydroxy-5β-androstane-17β-carbonitrile;
42. 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-androstane-17β-carbonitrile;
43. (Z)-11α-N,N-dimethylamino-3α-hydroxy-5α-pregn-17(20)-ene;
44. methyl 11α - N,N - dimethylamino - 2β - ethoxy - 3α - hydroxy - 5α - androstane - 17β - carboxylate;
45. 11α-N,N-dimethylamino-3α-hydroxy-5α-pregn-20(21)-ene;
46. 2β-butoxy-11α-N,N-dimethylamino-3α-hydroxy-5α-pregnan-20-one;
47. 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-21-propyl-5α-pregnan-20-one;

and the physiologically acceptable water soluble salts of these compounds.

All of the above compounds have shown good activity in our tests in the form of their citrate salts in aqueous solutions (sometimes in the presence of sodium and chloride ions). Good activity has similarly been shown in our tests for the tricarballylate, hydrochloride, phosphate and methanesulphonate of compound No. 1; the acetate, methanesulphonate, hydrochloride, succinate, citraconate, aconitate and mesaconate of compound No. 2; the acetate hydrochloride, tartrate, lactate, tricarballylate, phosphate, methanesulphonate and succinate of compound No. 5; and the acetate salt of compound No. 10.

Of the above-mentioned compounds, compound Nos. 1, 2, 5, 6, 8, 9, 31, 36-38, 41 and 42 and their salts are particularly preferred.

Compound No. 5 and its physiologically acceptable water soluble salts (particularly the hydrochloride and citrate) are especially preferred. Compound No. 2 and its physiologically acceptable water soluble salts (particularly the hydrochloride and citrate) are most preferred.

PHARMACEUTICAL FORMULATIONS

The compounds of the invention may be formulated as convenient, following generally known pharmaceutical practices, (including both human and veterinary medical practices), with the aid of one or more pharmaceutical carriers or excipients. For anaesthetic purposes, the steroids will be given by injection and thus one aspect of this invention comprises a composition for parenteral administration comprising one or more compounds in accordance with the invention in a parenterally acceptable vehicle.

When the compounds (e.g. the salts) are sufficiently soluable in water they may be presented in aqueous injection vehicles. The preparation of suitable solutions by bringing the free bases into solution in aqueous acid is described below. For induction anaesthesia, these solutions will usually contain 0.1—4% (conveniently 0.2—2%) w/v of the active compound, but stronger solutions may be prepared with the more soluble salts. If desired, the free base and the acid required for salt formation may be packed separately in two-pack form for formulation as and when needed. Alternatively the steroid salt and the aqueous injection vehicle may be packed separately in two-pack form.

Although the compounds of the invention are preferably formulated as simple aqueous solutions of their salts, the free bases or salts may also be formulated in an aqueous solution of a parenterally acceptable non-ionic surface active agent in the same way (and using the same proportions of materials) as described in our British Patent Specification 1317184 for 3α-hydroxy-5α-pregnane-11,20-dione. The simple aqueous solutions have the advantage for example of avoiding anaphylactoid responses in surfactant-sensitive subjects.

The aqueous solutions may be adjusted in tonicity, for example with sodium chloride.

The anaesthetic solutions according to the invention are generally administered by intravenous injection although in certain cases (e.g. with children or animals) intramuscular injection might be preferred.

The simple aqueous solutions of the salts may also be administered subcutaneously. For intramuscular injection hydrochloride salts may be particularly suitable.

As is usual in the case of anaesthetics, the quantity of steroid used to induce anaesthesia depends upon the weight of the individual to be anaesthetised. For intravenous administration in the average man a dose of from 0.1 to 8.0 mg/kg will in general be found to be satisfactory to induce anaesthesia, the preferred dose being within the range of from 0.2 to 4.0 mg/kg. The dose will naturally vary to some extent, dependent upon the physical condition of the patient and the degree and period of anaesthesia required.

If it is desired to maintain prolonged anaesthesia, repeated doses of the above solutions may be used, such repeated doses being generally either of the same order or lower than the original dose. Alternatively continuous administration may be undertaken using solutions containing 0.01—0.4% (preferably 0.02—0.2) w/v of the active compound at for example a rate of 0.0125—0.2 (e.g. 0.025—0.1) mg/kg/min. Continuous administration may also be used to produce sedation for prolonged periods.

Where the anaesthetic solutions are administered intramuscularly or subcutaneously, higher doses are generally necessary.

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 or mono-substituted 11α-amine into a di-substituted amine. (The amine starting materials for this reaction form the subject matter of our divisional Application No. 41590/79 (Serial No. 1581235)).

This reaction may be performed by reacting a corresponding compound of formula (I) in which either or both of R^a and R^b 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), hydrocarbyloxysulphonyloxy (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 hydro-

carbon solvents (e.g. methylene chloride), alkanols (e.g. ethanol or methanol) or acetronitrile.

When a N-mono-substituted starting material is used, the reaction can produce N,N-di-substituted compounds of the invention in which R^a and R^b are either the same or different groups.

The N-mono-substituted starting materials may be prepared in similar manner by reacting a compound of formula I in which both R^a and R^b are hydrogen atoms with a compound of formula R^aX as described above.

Compounds where $—NR^aR^b$ is a heterocyclic amino group may also be prepared by this method, by use of a reagent $X—R^a—R^b—X$ where X is as defined above (e.g. a 2,2'-dihaloethyl ether or a dihaloalkane, such as 1,4-diodobutane).

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.

The 11α-amino starting materials required for this reaction may for example 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. In introducing certain of these substituents (by the methods described below, 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.

2. A corresponding 11α-acylamino steroid (i.e. in which one of R^a and R^b is as defined above and the other 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-mono-substituted 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.

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

This reaction may be used to prepare ring A-saturated 2β-substituted 5α-compounds, and it is the preferred way of making the 2β-halo, alkoxy, alkanoyloxy and thiocyanato compounds. The general method of preparing 2β-compounds by this route is described in our British Patent Specification 1376892. 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-substituted amino group (e.g. by the method of reaction 1 above) using a Δ^2 — starting material, then forming a salt (e.g. with toluene-*p*-sulphonic acid) and the exposidising the Δ^2 — compound with a peracid, finally regenrating the free base. Δ^2 — Compounds may be prepared by formation of the 3-methanesulphonate and subsequent elimination of methanesulphonic acid.

4. A corresponding 11α-amino or 11α-mono-substituted amino compound (or a 20-ketal thereof) can be reductively alkylated with an appropriate mono- or di-carbonyl compound in the presence of a reducing agent. For example, with 11α-amino compounds the use of mono-carbonyl compounds, such as formaldehyde or acetaldehyde, can provide the 11α-dimethyl or -diethyl amines, whereas a dicarbonyl compound can provide compound in which $—NR^aR^b$ is a heterocyclic amino group (e.g. glutardialdehyde may be used to form a piperidino group). When an 11α-N-mono-substituted starting material is used, a mono-carbonyl compound should be used. 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 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.

11α-N-Mono-substituted amino starting materials can be prepared in similar manner by reacting the corresponding 11α-amino compound with an appropriate aldehyde or ketone in the presence of a reducing agent as described above. Thus, for example, the use of formaldehyde, acetaldehyde or acetone can provide the 11α-N-methyl-,N-ethyl or N-*iso*-propyl amines respectively. Whether an 11α-N-mono- or N,N-disubstituted compound is obtained is dependent partly on the proportion of ketone or aldehyde used.

5. 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 1409239. 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), atrivalent 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 performed 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.

6. 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.

7. Inversion of derivatives of the corresponding 3β-hydroxy compounds.

This preparative method is suitable for the preparation of compounds which are unsubstituted at the 3β-position and do not possess a 5,6-double bond. The starting material may be a corresponding compound possessing a readily displaceable 3β-group such as a hydrocarbylsulphonyloxy (e.g. p-toluenesulphonyloxy or mesyloxy) group, and the 3β-group may be displaced by hydrolysis (e.g. in acid conditions) to give the desired 3α-hydroxy compounds. Methods for preparing Δ^4 compounds by this route are described in our British Patent Specification 1372175.

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 1380248.

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 1380246.

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 1380246.

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 1380246.

13. Acyloxylation of a corresponding 21-unsubstituted compound.

21-Alkanoyloxy and benzoyloxy compounds may be prepared by treating the corresponding 21-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 1317185.

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

21-Flourides 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 1430932.

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 1377608.

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 1377608. 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 1317185.

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 1317185. 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 1380248.

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 1377608.

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-carboxylic 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 by inversion from a 3β-hydroxy compound (for example by treating the 3β-alcohol with diethyl azodicarboxylate in the presence of an acid such as formic or benzoic acid and a phosphine such as triphenylphosphine). 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 groups may be removed by reduction, for example using zinc and acetic acid.

26. Salt formation.

Compounds of the invention are desirably used in the form of a salt, and thus salt formation by reaction of the base with an acid is particularly important.

A generally convenient method of forming the salts is to mix appropriate quantities of the free base and the acid in a mixture of water and a solvent for the base (e.g. an alcohol such as ethanol), removing the solvent (e.g. by evaporation) and then if desired dissolving the residue in water.

In some cases solid salts can be formed by treating the free base with acid (e.g. citric acid, HCl) in an anhydrous solvent, such as diethyl ether. In most cases it is possible to form an aqueous solution of the salt by simply mixing the free base with an aqueous acid. If desired one or more steroid bases and/or one or more acids may be used.

In these preparations, the base and the acid are not necessarily used in equivalent quantities. When the acid is a weak acid, an excess of the acid is sometimes desirable. In the preparation of aqueous solutions, in some cases for example it is found that an excess of the base may be used, implying that the free base is dissolved to some extent in the solution of the salt.

If desired the pH of the salt solution may subsequently be adjusted by addition of a base, e.g. sodium hydroxide and/or disodium hydrogen citrate.

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-substituted 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.

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 1380248.

Δ^4-Steroids may be obtained by the methods described in our British Patent Specification 1372175.

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 1436324.

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 Δ^1,5β-compounds may be prepared by choice of starting materials containing these structural features.

The following examples illustrate the invention.

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 = DMSO; 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)
3β-hydroxy-20,20-ethylenedioxy-5α-pregnan-11-one oxime (V)
20,20-ethylenedioxy-5α-pregn-2-en-11-one (VI)
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)
3α,20β,21-trihydroxy-5α-pregnan-11-one (XX)
20,20-ethylenedioxy-3α-hydroxy-5β-pregnan-11-one (XXI)
3α,20β,21-trihydroxy-5β-pregnan-11-one (XXII)

Many compounds which were subjected to further reactions have been allocated numbers in order to avoid repetition of their full names. So that the compounds which correspond to these numbers can be readily identified the following index is given:

Compound No:	Prep. No:	Compound No:	Prep. No;
XXIII	2	LV	97
XXIV	4	LVI	98
XXV	5	LVII	86
XXVI	9	LVIII	103
XXVII	10	LIX	93
XXVIII	12	LX	94
XXIX	183*	LXI	85
XXX	14	LXII	11
XXXI	15	LXIII	66
XXXII	17	LXIV	47
XXXIII	27	LXV	64
XXXIV	28	LXVI	70
XXXV	29	LXVII	69
XXXVI	48	LXVIII	71
XXXVII	49	LXIX	87
XXXVIII	50	LXX	101
XXXIX	51	LXXI	102
XL	63 69	LXXII	100
XLI	1	LXXIII	29*
XLII	73	LXXIV	74*
XLIII	76	LXXV	13
XLIV	67	LXXVI	104
XLV	83	LXXVII	105
XLVI	81	LXXVIII	106
XLVII	82	LXXIX	107
XLVIII	90	LXXX	109
XLIX	91	LXXI	110
L	80	LXXXII	111
I	80	LXXXIII	112
LII	84	LXXXIV	114
LIII	65	LXXXV	115
LIV	99	* Example No:	

It should be noted that compound XXX (Preparation 14) is a compound of formula I in accordance with the invention, although it is used below as an intermediate.

Preparation 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 (9.638 g) in PR (200 ml) was refluxed under N_2 whilst Na (9.6 g.) was added portionwise. When all of the Na had reacted, about 90 ml PR was distilled and then the residue was poured into W, ice was added and the crystalline solid (9.19 g) was collected by filtration. A portion (6.17 g) was crystallized from ET-W to afford *title compound* (3.6 g), m.p. 118—125°, $[\alpha]_D$ + 5.4°.

Preparation 2

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

X (1.7g) in EA (100 ml) was hydrogenated at atmospheric pressure using 10% palladium on charcoal (Pd-C) (500 mg) 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. 175—176°C, $[\alpha]_D$ = 106°.

Preparation 3

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

XXIII (600 mg) was heated under reflux with chloroiridic acid reagent (35 ml) 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* (440 mg) as a foam, $[\alpha]_D$ + 88°.

Preparation 4

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

XIV (10.0 g) was dissolved in dry AN (50 ml) and N,N-dimethyl(methylene)ammonium chloride (5.0 g) 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* (10.7 g) as a foam.

Preparation 5

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

XXIV (10.5 g) was dissolved in ME (105 ml) and iodomethane (10.5 ml) was added. The mixture was maintained at 20° for 20h. and was then evaporated under reduced pressure. The residue was dissolved in DM (200 ml) and stirred vigorously with 5% $NaHCO_3$ solution (100 ml) 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* (3.48 g), m.p. 181—184°, $[\alpha]_D$ + 112°.

Preparation 6

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

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

Preparation 7

3α-Hydroxy-5α-pregn-20-en-11-one

XVII (330 mg) in W-ME (1:10; 11 ml) 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 (80 mg), m.p. 137.5—139.5°.

Preparation 8

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

Sodium hydride (80% dispersion in oil; 1.0 g) 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 (13.3 g) in DMSO (50 ml). XIX (2.0 g) in distilled DMSO (40 ml) 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* (824 mg), $[\alpha]_D$ + 29.0°.

Preparation 9

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

A mixture of XVIII (60 g), hydroxylammonium chloride (21 g) and anhydrous PY (240 ml) 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°, (62 g). Crystallisation from EA afforded the *title compound,* m.p. 168—182°. $[\alpha]_D$. + 137°.

Preparation 10

5α-Androst-2-ene-11,17-dione (XXVII)

A solution of XXVI (60 g) in anhydrous PY (250 ml) was treated with 225 ml of a solution prepared from phosphorus oxychloride (55 ml) in anhydrous PY (250 ml) 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 (3 1). 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 (50 ml) 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. (38.4 g). Crystallisation from ME afforded the *title compound*, m.p. 188—192°, $[\alpha]_D$ 207°.

Preparation 11

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 (2.8 g) was dissolved in PR (150 ml) and heated to reflux. Na (12.6 g) 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 (1.94 g).

Preparation 12

21-Bromo-11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one (XXVIII)

A solution of 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one hydrochloride (450 mg) in dry ME (50 ml) was treated dropwise with a solution of bromine (0.1 ml) in ME (5 ml) at 0°C with stirring. Each subsequent drop of reagent solution was added when the colour from prior additions was discharged. When the addition was complete 10% K_2CO_3 solution (150 ml) was added and the mixture stirred for 15 minutes. The precipitate was filtered off and washed with W and dried. Purification by preparative TLC in EA-PE (1:1) gave *title compound* (230 mg).

Preparation 13

11α-N,N-Dimethylamino-2β-ethoxy-3α-hydroxy-5α-androstane 17β-carboxylic acid lithium salt (LXXV)

Bromine (4.3 ml) was added to a stirred solution of NaOH (12.1 g) in W (90 ml) at −5 to 0°. D (42 ml) was added and this mixture was added to a stirred solution of 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one (10.0 g) in D (316 ml) and W (90 ml) at 8°. The mixture was stirred at 5 to 10° for 3.5 h. A solution of sodium sulphite heptahydrate (4.66 g) in W (20 ml) was added and the mixture was boiled for 15 min. The solution was filtered hot and the cooled filtrate was extracted with CH. The CH extract was washed with W and the combined aqueous fractions was acidified with concentrated HCl to pH 3. Triethylamine (50 ml) was added and the solution was extracted with CH. The extract was dried ($MgSO_4$) and evaporated to dryness to give the crude triethylammonium salt, which was dissolved in ME (20 ml) and treated with a solution of lithium methoxide (20.4 mmoles) in ME (35.7 ml). The resulting solution was evaporated to dryness and the residue was crystallised from a mixture of ME (36 ml), PT (36 ml), and DE (354 ml) to give the *title compound* (7.03 g), m.p. >300°, $[\alpha]_D$ + 9.1.

Preparation 14

3α,21-Dihydroxy-11α-N,N-dimethylamino-2β-ethoxy-5α-pregnan-20-one (XXX)

A solution of XXIX (2.8 g) in ME (100 ml) was treated at RT with 10% K_2CO_3 solution (15 ml) for 15 minutes. The mixture was diluted with W to 700 ml and the oily precipitate extracted into DE (3×). The extracts were washed with W, dried (Na_2SO_4) and evaporated to a foam (2.5 g). A sample (300 mg) was purified by preparative TLC in EA-PE (1:1) to give *title compound* (160 mg), as a foam, $[\alpha]_D$ + 65°.

Preparation 15

11α-N,N-Dimethylamino-2β-ethoxy-5α-pregnane-3α,20β,21-triol (XXXI)

A solution of XXX (2.2 g) in ME (50 ml) was treated with sodium borohydride (230 mg). After 10 minuted the mixture was diluted with 10% K_2CO_3 solution (80 ml) and W to 300 ml. The mixture was extracted with DE (×3) and the extracts were washed with W, dried (Na_2SO_4) and evaporated to a foam which was purified by CC eluting with DM-AC (1:1) to give *title compound* (700 mg) as a foam, $[\alpha]_D$ − 5°.

Preparation 16

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

A stirred suspension of dried cuprous iodide (19.6 g) in dry xylene (350 ml) under nitrogen was cooled to −10° and 1.9 M methyl lithium in DE (108 ml) was added until the initial yellow precipitate redissolved to give an almost clear colourless solution. A solution of IV (12.9 g) in Xylene (430 ml) 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 (1200 ml). 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* (7.22 g), m.p. 167—168°, $[\alpha]_D$ + 68.1°.

Preparation 17

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

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

Preparations 18—26

Table 1 summarises 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 & 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
18	II	6	150	40	300	24	–	–	DE	5.1	150–153	+52°	A (i)
19	III	7	180	20	200	18	CC	EA–PE	PE–DE	3	126–130	+42°	A (ii)
20	3	5.4	50	2.5	70	72	CC	EA–PE	DE–PT	2.64	112–113	+30.8°	B (i)
21	6	3.18	30	1.5	30	18	–	–	–	3.58		+48°	B (i)
22	XII	3.8	110	5	36	120	CC	EA–PE	ME	.607	180–181	+51.3°	B (ii)
23	XI	3.19	110	5	36	5	CC	EA–PE	ME	1.28	126–127	+47.9°	B (ii)
24	XIII	1.5	55	2.5	15	3	–	–	ME–PY	1.04	188–189	+56°	B (ii)
25	XV	6.21	275	27.5	275	72	CC	EA–PE	EA–PE	2.22	156–157	+3.6°	C
26	XVI	1.95	100	10	100	17	TLC	EA–PE	DE–PE	1.62	140–141	+8.4°	C

Preparation 27

20,20-Ethylenedioxy-5α-pregn-2-en-11-one 11-oxime (XXXIII)

A solution of VI (5 g) in ET (150 ml) was treated with a mixture of hydroxylamine hydrochloride (10 g) and 50% NaOH solution (40 ml) at pH 11. The mixture was refluxed for 3 days, diluted with W and the precipitate was filtered off, washed with W and dried. The residue (5.5 g) was crystallised from MA-PE (×2) to give the product (2.2 g). A portion (200 mg) was further crystallised to give the *title compound* (150 mg), m.p. 174—179°C, $[\alpha]_D$ + 144°.

Preparation 28

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

A solution of XXXII (5 g) in ET (200 ml) was treated with a mixture of hydroxylamine hydrochloride (15 g) and 40% NaOH solution (60 ml) at reflux for 18 hours at *ca.* pH 11. The mixture was diluted with W to 2 l. and the precipitate was

filtered off, washed with W and dried *in vacuo* to give 4.5 g of product, a sample of which (500 mg) was crystallised from MA-PE to give the *title compound* (150 mg), m.p. softens >170°C, $[\alpha]_D$ + 83.3°.

Preparation 29

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

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

Preparations 30—46

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 $\geqslant$ 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)	$[\alpha]_D$
30	I	9.5	250	10.5	24	–	ET–W	6	224–229	+93°
31	18	5	150	10	24	–	ET–W	3	238–241	+90°
32	19	5.5	100	10	48	–	–	6	–	–
33	16	4	150	8	18	–	ET–W	3	224–229	+117°
34	VIII	6.1	100	12	96	–	EA–PE	3.95	218–219	+108°
35	IX	5.3	200	10.6	72	–	EA–PE	4.10	215–218	+94°
36	20	.88	15	1.75	48	–	–	.67	196–198	+54.9°
37	22	1.5	30	3	18	CC, EA–PE	EA–PE	.64	240–242	+90.2°
38	23	1.2	30	2.4	18	–	EA–PE	.88	230–232	+95.8°
39	24	1	30	2	18	–	EA–PE	.72	191–193	+91°
40	21	3.26	45	5.25	72	–	ME–PY (1%)–W	3.26	191–192	+90.7°
41	25 ③	2.22	70	8.8	67	–	DE–PE	1.88	189.5–190.5	+46.7
42	26	4.51	180	13.5	48	TLC, EA–PE	DE–PE	2.97		+34.4°
43	7	1.6	50	2.4	18	–	ET–W	1.0	233.5–235.5	–
44	8	10.26	320 ①	3.25	47	–	ET–W	10.42	233–235	+48.1°
45 ②	92	.71	21	1.43	24	TLC, ME–CH	EA–PE	.22	176–193	+35.9°
46	XX	3.5	150	9	48	–	ET–W	3	148–151	+80°

① IMS used as solvent; further hydroxylamine hydrochloride (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 47

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

Na (8 g) was added portion wise to a refluxing solution of 2β-ethoxy-20,20-ethylenedioxy-3α-hydroxy-D-homo-5α-pregnan-11-one 11-oxime (4.0 g) in PR (200 ml). Refluxing was continued for 4 hr then ME (10 ml) 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 (2.43 g), $[\alpha]_D$ + 40°.

Preparation 48

3α,20β,21-Trihydroxy-5β-pregnan-11-one 11-oxime (XXXVI)

50% KOH solution (32 ml) was added to a solution of hydroxylamine hydrochloride (16 g) in W (32 ml) with cooling and the resulting mixture added to a solution of XXII (8 g) in ET (256 ml). The reaction mixture was refluxed for 4 days, some ET was distilled off and the mixture poured into iced 2N-HCl. The steroid was extracted with EA and crystallised from EA to give *title compound* (6.7 g) m.p. 226—229°, $[\alpha]_D$ + 82° (*c* 0.7 D).

Preparation 49

20,20-Ethylenedioxy-5α-pregn-2-en-11α-amine (XXXVII)

A solution of XXXIII (1.85 g) in PR (250 ml) was treated at reflux with Na (20 g) added over 1.5 hours. When the Na had been consumed ME (20 ml) was added and the mixture was diluted to 2 l with W. The mixture was extracted with DE and the extract was washed with W, dried (Na_2SO_4) and evaporated to leave *title compound* as an oil (2 g).

Preparation 50

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

A solution of XXXIV (4 g) in PR (500 ml) was treated at reflux with Na (40 g) over 1 hour. When all the Na had dissolved, ME (20 ml) 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 (3.7 g), which was purified by CC, eluting with ME, to give the *title compound* as a foam (2.5 g), $[\alpha]_D$ + 13.7°.

Preparation 51

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

Solution of XXXV (2 g) in PR (250 ml) at reflux was treated with Na (20 g) 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* (220 mg), 153—155°C, $[\alpha]_D$ + 5° (*c* 0.65).

Preparations 52—63

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

Prep.	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)							
52	33	2.8	500	30	DE	2.1	143–145	+37°	B
53	32	6	800	60	(1)	2	–	+8.5°	A (i)
54	31	3.6	500	40	MA–PE	2.5	156–158	+20°	A (i)
55 (2)	46	3.2	500	35	–	.950	–	–	A (ii)
56	43	0.9	130	8	DE–PE	0.4	100–102	–	A (ii)
57	37	1	120	10	EA–PE	.412	156–157	+7°	A (ii)
58	38	1.16	100	10	EA–PE	.750	144–146	+9.8°	A (ii)
59	39	.945	100	9.45	ME	.389	188–189	+13.4°	B
60	36	1.85	110	9.3	EA–PE	1.08	143–144	-9.7°	A (ii)
61	35	3.5	420	34	EA–PE	2.6	155–157	+6.9°	A (ii)
62	34	3.87	450	26.53	DE–PE	2.31	116–118	+4.7°	A (ii)
63 (2)	30	10	1200	100	DE	6	175–177	+5°	A (ii)

(1) Purified by CC eluting with ME.
(2) ME added prior to addition of W.

Preparation 64

(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 (450 mg) in PR (15 ml) was treated with pieces of Na (450 mg). 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* (110 mg), m.p. 65—70°. $[\alpha]_D$ + 10°.

Preparation 65

11α-Dimethylamino-5β-pregnane-3α,20β,21-triol (LIII)

XXXVI (5.75 g) was dissolved in PR (500 ml) and Na (6 g) was added portionwise under nitrogen. The excess PR was removed *in vacuo* and EA (1L) was added to the cooled reaction mixture. The solution was washed with W (×4), dried ($MgSO_4$) and evaporated. The crude amine was dissolved in HCHO (60 ml) and HCOOH (1.2 ml). The solution was heated to 100° for 6 minutes and poured onto ice, basified with 50% NaOH solution and the steroid extracted with EA. The resulting gum was redissolved in ME (80 ml) and 25% aqueous NaOH (20 ml) was added. The solution was allowed to stand at RT for 45 minutes, and then acidified with HCl. The solution was washed with EA and basified with 50% NaOH solution. Extraction with EA afforded material which was triturated with pentane, and crystallised from MA-pentane to give *title compound* (1.8 g), 124—128°.

Preparation 66

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

20,20-Ethylenedioxy-3α-hydroxy-D-homo-5α-pregnan-11-one 11-oxime (1.87 g) in PR (200 ml) was treated with Na (10 g) and worked-up as described in Preparation 47. Crystallization from EA-PE gave the *title compound* (128 mg), M.P. 154—157°, $[\alpha]_D$ + 36.1°.

Preparation 67

11α-Amino-3β-hydroxy-5α-pregnan-20-one (XLIV)

To a solution (under nitrogen) of V (7.0 g) in refluxing PR (700 ml) was added small pieces of Na metal (14 g). When all the Na metal had been consumed, the reaction mixture was evaporated to *ca.*200 ml and cold W was added. Overnight refrigeration afforded a precipitate which was collected by filtration and then partitioned between 2N-HCl and DE. The aqueous phase was basified with 2N-NaOH solution and extracted with DE. The organic extract was washed with W and evaporated to low volume. The crystalline material which separated was collected by filtration and crystallised from DE to give the *title compound*, m.p. 150—152°, $[\alpha]_D$ + 58.3°.

Preparation 68

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

XXXIX (1 g) was dissolved in ET (30 ml), and K_2CO_3 (1 g) and ethyl iodide (3 ml) were added. The reaction mixture was stirred under reflux for 2.5 hours and then evaporated to dryness. The residue was redissolved in ET (10 ml) and 2N-HCl (10 ml) 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-MA (3:1) as eluant to give *title compound* (201 mg) as a froth, $[\alpha]_D$ + 43°.

Preparation 69

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

A solution of 11α-amino-20,20-ethylenedioxy-5α-pregnan-3α-ol (XL) (1.5 g) in 1-iodobutane (20 ml) was treated at 80°C with K_2CO_3 (3 g) 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) and evaporated to leave a foam (1.5 g). A portion (500 mg) was purified by preparative TLC in AC to give the *title compound* (350 mg) as an oil, $[\alpha]_D$ + 60°.

Preparation 70

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

A solution of XL (1 g) in 1-iodopropane (10 ml) was stirred at reflux with K_2CO_3 (3 g) for 40 minutes and the mixture was worked-up as in Preparation 69. CC using Me and removal of solvent from later fractions left a residue which was crystallised from PE to give the *title compound* (450 mg), m.p. 138—141°, $[\alpha]_D$ + 32°.

Preparation 71

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

A solution of XL (4 g) in ethyliodide was stirred with Ag_2O (12 g) at RT for 2 hours. Ag_2O was removed by filtration and the filtrate worked-up as in Preparation 69. CC and TCL yielded the *title compound* (400 mg).

Preparation 72

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

A solution of XXXVIII (750 mg) in ET (10 ml) was treated with allylbromide (2 ml) and K_2CO_3 (1 g) 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 (107 mg).

Preparation 73

11α-Ethylamino-5α-pregn-2-en-20-one (XLII)

XXXVII (1 g) was mixed with acetaldehyde (0.4 ml) in ET (20 ml) at 21° and sodium cyanoborohydride (400 mg) was added. After 15 mins. the clear solution was made alkaline with $NaHCO_3$ solution. Brine was added and the mixture was extracted with EA (3×). The combined organic solutions were washed with brine (3×) and then were shaken with 2N—HCl. Excess 40% aqueous NaOH solution was added and the layers separated. The organic solution was washed with brine (2×) and evaporated to dryness. The resulting oil was chromatographed in EA—PE to give the *title compound* as a crystalline solid (77 mg). A sample was recrystallised from ET—W and showed m.p. 105—108°, $[\alpha]_D$ + 89.6°.

Preparation 74

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

XXXVIII (0.5 g) was mixed with cyclohexanone (2 ml) in ET (20 ml) at RT and $NaBH_3CN$ (250 mg) and acetic acid (0.1 ml) added. After 20 hours the mixture was worked-up as in Preparation 73 and purified by TLC to yield *title compound* (268 mg) as a foam, $[\alpha]_D$ + 26.6°.

Preparation 75

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

XXXVIII (0.5 g) was mixed with benzaldehyde (1 ml) in ET (10 ml) at RT and $NaBH_3CN$ (250 mg) and acetic acid (0.1 ml) added. After 1 hour the mixture was worked-up as in Preparation 73 and purified by CC and TLC to yield *title compound* (205 mg) as a foam, $[\alpha]_D$ + 34.1°.

Preparation 76

11α-Isopropylamino-5α-pregn-2-en-20-one (XLIII)

XXXVII (200 mg) was mixed with AC (0.2 ml) in ET (5 ml) containing $NaBH_3$.CN (200 mg). After 3½ hours the mixture was worked-up as in Preparation 73 and purified by CC in EA—PE followed by recrystallisation from ET—W to give *title compound* (55 mg). m.p. 99—101°. $[\alpha]_D$ + 80.6° (*c* 0.52).

Preparation 77

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

XXXIX (920 mg) was dissolved in ET (40 ml) and added to $NaBH_3CN$ (450 mg). AC (4 ml) was added, followed by acetic acid (0.2 ml) 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 (10 ml) and 2N—HCl (10 ml) 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* (590 mg), $[\alpha]_D$ + 38°.

Preparation 78

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

$NaBH_3CN$ (398 mg) was added to a solution of XLI (1.027 g) in ET (30 ml) and when dissolution was complete acetaldehyde (9 ml) 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* (278 mg), m.p. 106—109° $[\alpha]_D$ + −19.9°.

Preparation 79

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

A solution of XLI (422 mg) in IMS (6 ml) containing AC (1 ml) was treated with $NaBH_3CN$ and the resulting mixture worked-up as described in Preparation 78. Purification by TLC (ET—CH 1:1) gave *title compound* (180 mg) as a froth.

Preparation 80

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

XXXVIII (1.06 g) was refluxed with 4-methylpentan-2-one (2 ml) in PR (40 ml) under nitrogen for 20 hours. Reflux under nitrogen was maintained and Na (4 g) was added over 3 hours. W (*ca* 50 ml) 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 (333 mg) (gum) and isomer B (322 mg) (gum).

Preparation 81

11α-N-Ethyl-N-methylamino-5α-pregn-2-en-20-one (XLVI)

XLII (658 mg) was heated at 100° for 5 mins. with formic acid (0.32 ml) in aqueous HCHO solution (37% solution, 2.5 ml). The mixture was cooled to 21° and excess aqueous Na_2CO_3 solution added. The mixture was extracted with EA and the combined organic layers were washed with saturated brine, dried and evaporated to dryness. The residual gum was filtered through silica gel in EA—PE (1:9). Evaporation of the elute gave the *title compound* (477mg), $[\alpha]_D$ + 111°.

Preparation 82

11α-N-Isopropyl-N-methylamino-5α-pregn-2-en-20-one (XLVII)

Reaction of XLIII (838 mg) with 37% aqueous HCHO (3.3 ml) containing formic acid (0.43 ml) in a similar manner to that described in Preparation 81 and recrystallisation from ET—W gave *title compound* (643 mg), m.p. 88—99°, $[\alpha]_D$ + 113.5°.

Preparation 83

11α-N,N-Dimethylamino-5α-pregn-2-en-20-one (XLV)

XXXVII (8.2 g) was heated at 95° to 110° in HCHO (37% aqueous solution, 32 ml) and formic acid (4 ml) for 6 minutes. The mixture was cooled rapidly and partitioned between EA and 2N—NA_2CO_3 solution. The aqueous layer was extracted with EA and the combined organic solutions were washed with brine before evaporation to leave a solid, which was dissolved in EA and filtered through silica gel. The eluate was evaporated and the residue was recrystallised from ME to give the *title compound* (4.0 g), m.p. 123—126°, $[\alpha]_D$ + 110°.

Preparation 84

11α-N,N-Dimethylamino-5α-pregnane-3α,20β,21-triol (LII)

11α-Amino-5α-pregnane-3α-,21-triol (950 mg) was dissolved in ME (20 ml) and methyl iodide (10 ml) and stirred at RT with K_2CO_3 (3 g) for 4 hours. Work-up as in Preparation 69 and purification by TLC in AC and crystallisation from DE gave *title compound* (160 mg), m.p. 121—125° $[\alpha]_D$ + 16.7°.

Preparation 85

11α - N,N - Dimethylamino - 2β - ethoxy - 20,20 - ethylenedioxy - 5α - pregnan - 3α - ol (LXI)

XXXVIII (5.0 g) was dissolved in a mixture of 40% aqueous HCHO (60 ml) and 98—100% formic acid (2.1 ml) and the resulting solution was heated on a steam bath for 15 minutes. The solution was cooled, diluted with W (190 ml) and saturated aqueous $NaHCO_3$ (25 ml) and pH brought to 11 by the addition of NaOH (0.3 g) dissolved in W (30 ml). The resultant precipitate was collected by filtration, washed with W and dried to give the *title compound* (5.41 g), $[\alpha]_D$ + 57.5° m.p. 70°.

Preparation 86

11α-Dimethylamino-3β-hydroxy-5α-pregnan-20-one (LVII)

A mixture of XLIV (0.5 g), 37% HCHO solution (3 ml) and 98% formic acid (0.3 ml) was kept at 100° for 3 minutes before pouring into aqueous $NaHCO_3$ solution. The precipitate obtained was collected by filtration and partitioned between EA and 2N—HCl. The acidic phase was basified with 2N NaOH solution, extracted with EA, washed with W and evaporated to a froth. CC (EA—PE 1:2) and crystallisation from EA—PE afforded the *title compound* (300 mg), m.p. 119—121°, $[\alpha]_D$ + 68.0°.

Preparation 87

11α - N,N - Dimethylamino - 2α,3α - epoxy - 5α - pregnan - 20 - one (LXIX)

XLV (1.9 g) and PTSA (1.0 g) were dissolved in DC (150 ml) and *m*-chloroperbenzoic acid (1.25 g) was added. After stirring the mixture at 20° for 15 hours, the organic solution was washed successively with dilute aqueous Na_2S_2O5 solution, $NaHCO_3$ solution and W. Each time the organic layer was back extracted with DC. The combined organic solutions were dried ($MgSO_4$) and evaporated. The residue was filtered through silica gel in 1:3 EA—PE and the eluate evaporated to give crystals which on recrystallisation from PE gave the *title compound* (0.51 g), m.p. 154—157°, $[\alpha]_D$ + 80.0°.

Preparation 88

2α-3α-Epoxy-11α-N-ethyl-N-methylamino-5α-pregnan-20-one

XLVI (6.0 g) and PTSA (3.21 g) were dissolved in DC (300ml) and *m*-chloroperbenzoic acid (4.4 g) was added. After 1 hour the mixture was worked up as in Preparation 87 (except that DM was used in place of DC). Purification by CC using EA—PE yielded *title compound* (4.49 g) $[\alpha]_D$ + >9.5°.

Preparation 89

2α,3α-Epoxy-11α-N-isopropyl-N-methylamino-5α-pregnan-20-one

XLVII (300 mg) and PTSA (154 mg) were dissolved in DC (30 ml) and *m*-chloroperbenzoic acid (210 mg) was added. After 30 mins. further oxidant (60 mg) was added. After a further 30 minutes the mixture was worked up as in preparation 87. Purification by preparative TLC (EA—PE) and recrystallisation from W—ET yielded *title compound* (114 mg), m.p. 114—116°, $[\alpha]_D$ + 84.5°.

Preparation 90

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

A mixture of XXVII (37.2 g), *m*-chloroperbenzoic acid (30 g) and CH (600 ml) 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 (27.5 g). Recrystallisation from EA—PE afforded the *title compound* m.p. 166—167° $[\alpha]_D$ + 126°.

Preparation 91

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

A solution of XLVIII (5.0 g) in absolute ET (250 ml) 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* (2.1 g), m.p. 164—167°, $[\alpha]_D$ + 114°.

Preparation 92

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

A mixture of XLIX (1.742 g), ethyl triphenylphosphonium iodide (6.27 g), sodium hydride (360 mg) and Na- dried tetrahydrofuran (100 ml) 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 (4.0 g). CC (EA—PE 1:2) followed by preparative TLC (EA—PE 1:1 × 2) and crystallisation from EA—PE afforded the *title compound* (110 mg), m.p. 172—178°, $[\alpha]_D$ + 25°.

Preparation 93

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

XXXVIII (10 g) was suspended in W (38 ml) and treated with concentrated HCl (12 ml). The insoluble material was removed by filtration and washed with a small portion of W. This material was resuspended in W (50 ml) and treated with 2N-NaOH to pH 9. The mixture was stirred 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°.

Preparation 94

11α-Amino-3α-hydroxy-5β-pregnan-20-one (LX)

XXXIX (2 g) was dissolved in ME (20 ml) and 2N-HCl (20 ml) was added. The reaction mixture was kept at RT for 15 minutes, basified with iced NaOH solution and the white solid collected by filtration. Crystallisation from ME—W gave *title compound* (1.13 g), m.p. 128—130°.

Preparation 95

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

L (330 mg) was dissolved in ME (20 ml) and 2N HCl (0.5 ml) 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°.

Preparation 96

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

LI (322 mg) was treated as described in preparation 95 to give the *title compound* (170 mg) as a white foam, $[\alpha]_D$ + 2.1° (*c* 0.36).

Preparation 97

11α - N,N - Dimethylamino - 3α - hydroxy - 5α - androstane - 17β - carbaldehyde oxime (LV)

A solution of LII (250 mg) in D (15 ml) and W (3 ml) was treated with periodic acid (1 g) for 30 minutes. Aqueous NaOH solution (2N; 10 ml) and W (200 ml) were added and the oily precipitate was extracted into DE. The extract was washed with W, dried (Na_2SO_4) and evaporated to leave 11α-N,N-dimethylamino-3α-hydroxy-5α-androstane-17β-carbaldehyde as a foam (185 mg).

The aldehyde was dissolved in ET (50 ml) and a mixture of $NH_2OH.HCl$ (300 mg) and NaOH solution (2N; 5 ml) to pH 11 was added. After 15 minutes the mixture was diluted with W and the precipitate was extracted into DE. The extract was washed with W, dried (Na_2SO_4) and evaporated to leave a foam which was crystallised from PE—DE to give the *title compound* (130 mg) m.p. 107.5—110°C, $[\alpha]_D$ + 4°.

Preparation 98

11α - N,N - Dimethylamino - 2β - ethoxy- 3α - hydroxy - 5α - androstane - 17β - carbaldehyde oxime (LVI)

XXXI (650 mg) was treated as described in Preparation 97 and crystallised from hexane — DE to give *title compound* (380 mg), m.p. 99—102°, $[\alpha]_D$ + 12°.

Preparation 99

11α - Dimethylamino - 3α - hydroxy - 5β - androstane - 17β - carbaldehyde (LIV)

LIII (1.3 g) was dissolved in D (65 ml) and periodic acid (1.3 g) in W (6.5 ml) was added. The reaction mixture was kept at RT for 15 minutes, poured into aqueous $NaHCO_3$ and the steroid was extracted with EA. A portion of the steroid (300 mg) was subjected to preparative thick plate chromatography using EA—PT 1:3. Elution with ME gave *title compound* as a foam (150 mg), $[\alpha]_D$ + 24° (*c* 0.5).

Preparation 100

3α - Acetoxy - 11α - dimethylamino - 5β - androstane - 17β - carbonitrile (LXXII)

50% Aqueous KOH (4 ml) was added to a solution of $NH_2OH.HCl$ (2 g) in W (4 ml) with cooling. This solution was then added to LIV (860 mg) in ET (32 ml) and the mixture was kept at RT for 10 minutes. Dilution with W and extraction with EA gave the 17β-oxime (890 mg).

This material was dissolved in acetic anhydride (20 ml) and refluxed for 15 minutes. After dilution with iced aqueous $NaHCO_3$ solution the mixture was stirred for a further 30 minutes. The steroid was extracted with EA and subjected to preparative TLC using EA—PT 1:3 as solvent. Elution with ME and crystallization from EA—ME gave *title compound* (560 mg) m.p. 148—152°.

Preparation 101

3α - Acetoxy - 11α - N,N - dimethylamino - 5α - androstane - 17β - carbonitrile (LXX)

A solution of LV (1.30 g) in acetic anhydride (20 ml) was refluxed for 1 hour. The mixture was poured into iced saturated $NaHCO_3$ solution (300 ml) and the precipitate was extracted into DE. The extract was washed with W, dried (Na_2SO_4) and evaporated to leave a foam which was purified by preparative TLC in EA—PE (1:15) and crystallised from DE to give the *title compound* (300 mg), m.p. 167—171°C, $[\alpha]_D$ + 53°.

Preparation 102

3α - Acetoxy - 11α - N, N - dimethylamino - 2β - ethoxy - 5α - androstane -17β - carbonitrile (LXXI)

LVI (500 mg) was treated as described in preparation 101 and purified by preparative TLC in AC—PE to give *title compound* (380 mg), $[\alpha]_D$ + 57°.

Preparation 103

11α-N,N-Dimethylamino-5α-pregnane-3,20-dione (LVIII)

A cold solution of LVII (181 mg) in AC (10 ml) was treated dropwise with Jones' reagent (0.25 ml) (Prepared from CrO_3 (66.7 g) in W and Conc H_2SO_4 (53.3 ml) diluted to 250 ml with W). The reaction mixture was partitioned between EA and aqueous $NaHCO_3$ solution, the organic phase was isolated, washed with W, dried (Na_2SO_4) and evaporated to a solid (170 mg). Crystallisation from DE—PE afforded the *title compound* (158 mg) m.p. 146—152°, $[\alpha]_D$ + 62.5°.

Preparation 104

17,17 - Ethylenedioxy - 2β - ethoxy - 3α - hydroxy - 5α - androstan - 11 - one LXXVI)

A mixture of XLIX (8.0 g), PTSA (160 mg), ethylene glycol (13 mls), triethyl orthoformate (8.3 ml) and CH (80 ml) was kept at RT overnight before partitioning between CH and saturated $NaHCO_3$ solution. The organic phase was isolated, washed with W and dried (Na_2SO_4). Evaporation of this solution afforded a froth which was purified by preparative TLC (AC—PE) and crystallisation from EA—PE to give the *title compound* (60 mg), mp. 142—145°, $[\alpha]_D$ + 18.2°.

Preparation 105

17,17 - Ethylenedioxy - 2β - ethoxy - 3α - hydroxy - 5α - androstan - 11 - one 11 - oxime (LXXVII)

A mixture of LXXVI (8.2 g), $NH_2OH.HCl$ (15 g), 44% aqueous NaOH (90 ml) and ET (500 ml) was stirred and refluxed for 24 hours before being evaporated to about ½ volume. Addition of W followed by refrigeration overnight afforded a precipitate which was collected by filtration, washed with water and dried (6.4 g). Crystallisation from EA—PE afforded the *title compound* mp. 136—140°, $[\alpha]_D$ + 41.1°.

Preparation 106

11α - Amino - 2β - ethoxy - 3α - hydroxy - 5α - androstan - 17 - one (LXXVIII)

LXXVII (5.7 g) in refluxing PR (400 ml) was treated with small pieces of Na metal (7.5 g) under N_2. The reaction mixture was evaporated to low volume and partitioned between EA and W. The organic phase was washed with W. dried (Na_2SO_4) and evaporated to a froth. This froth was partitioned between 2N—HCl and PE. The acidic layer was basified with 2N—NaOH and extracted with EA. The EA phase was washed with W, dried (Na_2SO_4) and evaporated to a froth. Crystallisation with DE afforded the *title compound* (2.43 g), mp. 144—148°. $[\alpha]_D$ + 61.5°.

Preparation 107

11α - Dimethylamino - 2β - ethoxy - 3α - hydroxy - 5α - androstan - 17 - one (LXXIX)

A solution of LXXVIII (2.2 g), HCO_2H (1.2 ml) and HCHO (12 ml) was kept at *ca* 100° for 3 minutes before pouring saturated $NaHCO_3$ solution. Vigorous stirring afforded a precipitate which was collected by filtration, washed with W and dried. CC(EA—PE) followed by PTLC (EA—PE) and crystallisation from ET—W afforded the *title compound*, mp. 65—68°, $[\alpha]_D$ + 41.7°.

Preparation 108

11α-Aminotigogenin

11-Oxotigogenin 11-oxime (2.0 g) in PR (140 ml) was heated to reflux and Na (10 g) was added. When the Na had reacted the PR was distilled off and the volume was maintained by addition of W. The aqueous liquors were extracted with EA and the extract was washed with W, dried (Na_2SO_4), and evaporated. The solid residue was crystallised from EA-PE to give the *title compound* (450 mg), m.p. 180—182°, $[\alpha]_D$– 72.5°.

Preparation 109

3α,26-Diacetoxy-11α-N,N-dimethylamino-5α-furost-20(22)-ene (LXXX)

11α-Dimethylaminotigogenin (2.0 g) in acetic anhydride (6 ml) and PY (3 ml) was heated on a steam bath for 30 minutes. The mixture was evaporated to give a solid. This was dissolved in octanoic acid (10 ml) and acetic anhydride (1 ml), and the mixture was distilled under N_2 until the internal temperature reached 240°. This temperature was maintained for 2 hours when the mixture was allowed to cool and was extracted into EA. The extracts were washed with dilute $NaHCO_3$ solution and W and evaporated to give a gum. This was dissolved in ME (20 ml), treated with KOH (2.0 g) and heated on a steam bath for 2 hours. The product was precipitated by the addition of warm W and isolated by filtration. This was dissolved in acetic anhydride (6 ml) and PY (3 ml) and heated on a steam bath for 30 minutes. The crude product was isolated by evaporation and was then purified by CC and crystallised from DE to give the *title compound* (500 mg), m.p. 131—134°, $[\alpha]_D$ + 4.2°.

Preparation 110

3β-Acetoxy-11α-N,N-dimethylamino-5α-pregn-16-en-20-one (LXXXI)

LXXX (2.0 g) in acetic acid (21 ml) was cooled to 10° in a W bath and treated with CrO_3 (800 mg) in W (7 ml). The reaction mixture was stirred for 30 minutes, and poured into B and W. The B liquors were separated and the aqueous liquors extracted with B. The combined B extracts were washed with dilute $NaHCO_3$ solution and W, filtered and evaporated to give crude 3β-acetoxy-11α-N,N-dimethylamino-16β(4-acetoxy-pentanoyloxy)-5α-pregnan-20-one (1.9 g) as a foam.

The foam (1.9 g) in acetic acid (5 ml) containing a trace of PY was heated at reflux for 30 minutes. The mixture was allowed to cool and evaporated to give an oil. This was dissolved in EA, washed with 5% $NaHCO_3$ solution and W. The EA liquors were dried (NA_2SO_4) and evaporated to give a foam. This was purified by preparative T.L.C. to give the *title compound* (250 mg), $[\alpha]_D$ + 9.3°.

Preparation 111

11α-N,N-Dimethylamino-3β-hydroxy-5α-pregn-16-en-20-one (LXXXII)

LXXXI (6.0 g) in D (100 ml) was treated with KOH (2.0 g) in W (20 ml) and stirred at RT for 72 hours. The solution was concentrated by evaporation, diluted with W and extracted with EA. The extracts were washed with W, dried (Na_2SO_4) and evaporated to give a foam. This was purified by CC and crystallization from EA to give the *title compound* (466 mg), m.p. 135—140°, $[\alpha]_D$ + 12.9°.

Preparation 112

11α-N,N-Dimethylamino-3α-hydroxy-5α-pregn-16-en-20-one (LXXXIII)

LXXXII (900 mg) in THF (35 ml) was treated with HCO_2H (0.27 ml) and triphenylphosphine (1.96 g) and stirred at RT for 15 minutes. Diethylazodicarboxylate (865 mg) in THF (8 ml) was added slowly to the reaction mixture and the solution was stirred at RT for six hours. The reaction mixture was concentrated by evaporation and the residue was dissolved in EA and washed with $NaHCO_3$ solution and W. The EA liquors were dried (Na_2SO_4) and evaporated to give a solid. This was purified by CC to give the crude 3α-formate. This was dissolved in ME (10 ml), treated with 60% $HClO_4$ (12 drops) and stirred at RT for 3 hours. The reaction mixture was concentrated by evaporation, diluted with 5% $NaHCO_3$ solution (10 ml) and W (20 ml) and extracted with EA. The EA extracts were washed with W, dried (Na_2SO_4) and evaporated to give a foam. This was purified by preparative t.l.c. to give the *title compound* as a foam (300 mg), $[\alpha]_D$ + 16°.

Preparation 113

11α-N,N-Dimethylaminotigogenin

11α-Aminotigogenin (1.1 g) in HCHO (25 ml) and HCO_2H (0.25 ml) was heated to *ca* 100° for 15 minutes. The solution was allowed to cool, diluted with saturated $NaHCO_3$ (50 ml) and W (150 ml). The precipitated product was isolated by filtration and crystallised from ME-W to give the *title compound*, (256 mg), m.p. 103—105°, $[\alpha]_D$ −78.1°.

Preparation 114

11α-Aminopregn-4-ene-3,20-dione (LXXXIV)

40%-Aqueous NaOH (60 ml), and then NH_2OH-HCl (15 g) were added to a suspension of 3,3; 20,20-bisethylene-dioxypregn-5-en-11-one (5.0 g) in ET (200 ml). The mixture was refluxed for a total of 107 hours, then cooled and diluted with W (2 l) with stirring. The precipitate (5.01 g) was collected, washed with W (2 l) and dried *in vacuo* at 60° over P_2O_5. The PMR spectrum ($CDCl_3$) showed the material to contain 3,3; 20,20-bisethylene-dioxypregn-5-en-11-one 11-oxime.

Na (4.5 g) was added in portions over 30 minutes to a stirred refluxing solution of the oxime (4.50 g) in PR (225 ml). The mixture was refluxed for 2 hours, when ME (10 ml) was added cautiously. The alcohol solvents were then removed by distillation whilst adding W (225 ml) to maintain the volume. The resulting aqueous suspension was cooled and extracted with EA and the extract was washed with saturated brine solution, dried and evaporated to a solid. This was partitioned between 2N-HCl and EA. The aqueous portion was washed with EA, then covered with EA, basified with 0.88 ammonia solution and the layers separated. The aqueous layer was extracted with additional EA then the combined extracts were washed with saturated brine solution, dried and evaporated to a solid. This was crystallised from EA-PE to give the *title compound* (1.12 g), m.p. 146—148°, $[\alpha]_D$ + 180°.

Preparation 115

11α-Dimethylaminopregn-4-ene-3,20-dione (LXXXV)

HCO_2H (0.29 ml) was added to a suspension of LXXXIV (1.00 g) in HCHO (8 ml) and the mixture was heated to *ca* 100° for 15 minutes then cooled and partitioned between 5% aqueous $NaHCO_3$ and EA. The organic extract was washed with saturated brine solution, dried and evaporated. The residue was crystallised from AN to afford the *title compound* (0.67 g), m.p. 159—162°, $[\alpha]_D$ + 174°.

Example 1

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

A solution of XXXVIII (500 mg) in methyl iodide (5 ml) was stirred with K_2CO_3 (1.5 g) for 2 hours. The mixture was partitioned between DE and W and the organic phase was extracted with 2N-HCl. The combined extracts were washed with DE and basified with 6N-NaOH. The oily precipitate was extracted into DE and the extract was washed with W dried (Na_2SO_4) and evaporated to leave a foam which was purified by preparative TLC in AC-PE (1:3) and crystallisation from PE-DE to give the *title compound* (180 mg), m.p. 139—143°C, $[\alpha]_D$ + 84°.

Example 2

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

XXXVIII (10 g) was stirred in a mixture of HCHO solution (120 ml) and formic acid (4.3 ml) at RT for 6½ hours.

DM (40 ml) was added to the mixture which was then adjusted to pH 11 with NaOH solution. The organic phase was separated, washed with W and extracted first with a solution of concentrated H_2SO_4 (4.0 ml) in W (70 ml) and then with W. The acidic extracts were combined and adjusted to pH 11 with NaOH solution and re-extracted with DM. The organic extracts were washed with W and evaporated under reduced pressure to a solid which was purified by filtration through silica gel in DM-MA (9:1) and crystallisation from AC-W to give the *title compound* (6.43 g), $[\alpha]_D$ + 84.1°, m.p. 123—131°.

Example 3.

11α-Dimethylamino-3α-hydroxy-5β-pregnan-20-one

XXXIX (500 mg) was partially dissolved in HCHO (10 ml) and formic acid (0.2 ml) and the reaction mixture was heated to *ca* 100° under nitrogen for 5 minutes. The reaction mixture was poured into $NaHCO_3$ solution and the steroid was extracted into EA and the extract washed with W. The organic layer was extracted with 2N-HCl and the extract was basified with NaOH solutions and extracted with EA. Removal of solvent from the extract left a foam which was dissolved in a small amount of CH and added to a column of silica in PT. Elution with EA-PT (1:1) and removal of solvent from the eluate gave the *title compound* as a white froth (370 mg), $[\alpha]_D$ + 83° (C, 1.5).

Example 4.

11α-Dimethylamino-3α-hydroxy-5β-pregnan-20-one

XXXIX (2.8 g) was dissolved in methyl iodide (30 ml) and K_2CO_3 (3 g) was added. The reaction mixture was stirred for 17 hours, the methyl iodide was evaporated and the solid residue was partitioned between EA and W. The organic layer was washed with W, dried ($MgSO_4$) and evaporated. The residue was dissolved in a small volume of CH and added to a column of basic alumina (60 g) in PT. The column was washed with EA and the eluate evaporated to give a froth.

The froth was dissolved in ME (20 ml), 2N-HCl (5 ml) was added and the solution was allowed to stand at RT for 15 minutes, and was poured into iced $NaHCO_3$ solution. The solid was filtered off and purified by preparative TLC using AC-PT (1:3) as solvent. Elution with EA gave the *title compound* (800 mg), $[\alpha]_D$ + 85°.

Example 5

11α-Dimethylamino-3α-hydroxy-5α-pregnan-20-one

XXXIX (200 mg) was stirred at RT with HCHO (4 ml) and formic acid (0.08 ml) for 23 hours. The solution was poured into 2N-HCl (20 ml) and kept at RT for a further 15 minutes. Dilution with aqueous $NaHCO_3$ solution and extraction with EA gave *title compound* similar by TLC and gas phase chromatography to the product of Example 3.

Examples 6-23

Table 4 summarises the preparation of the following compounds from the corresponding 11α-amino-20-ketal:

6. 11α-N,N-Dimethylamino-3α-hydroxy-5α-pregnan-20-one
7. 11α-N,N-Dimethylamino-3α-hydroxy-6β-methyl-5α-pregnan-20-one
8. 11α-N,N-Dimethylamino-21,21-ethylene-3α-hydroxy-5α-pregnan-20-one
9. 11α-N,N-Dimethylamino-3α-hydroxy-21-methyl-5α-pregnan-20-one
10. 11α-N,N-Dimethylamino-3α-hydroxy-21-methoxy-5α-pregnan-20-one
11. 11α-N,N-Dimethylamino-3α-hydroxy-2α-methyl-5α-pregnan-20-one
12. 11α-N,N-Dimethylamino-3α-hydroxy-3β-methyl-5α-pregnan-20-one
13. 3α-Hydroxy-11α-morpholino-5β-pregnan-20-one
14. 11α-N,N-Dimethylamino-3α-hydroxy-2β-methoxy-5α-pregnan-20-one
15. 11α-N,N-Dipropylamino-3α-hydroxy-5α-pregnan-20-one
16. 3α-Hydroxy-11α-morpholino-5α-pregnan-20-one
17. 11α-N,N-Dimethylamino-3α-hydroxy-2β-methyl-5α-pregnan-20-one
18. 2β-Butoxy-11α-N,N-dimethylamino-3α-hydroxy-5α-pregnan-20-one
19. 2β-Ethoxy-3α-hydroxy-11α-morpholino-5αn-20-one
20. 2β-Ethoxy-3α-hydroxy-11α-pyrrolidino-5α-pregnan-20-one

21. 11α-Azetidino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one
22. 11α-N,N-Diallylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one
23. 11α-N,N-Diethylamino-3α-hydroxy-5α-pregnan-20-one.

The following methods of preparation were used:

A. The 11α-amine was heated to *ca* 100° with formic acid inaqueous HCHO, the mixture cooled and partitioned between EA and 5% aqueous $NaHCO_3$ solution. The EA extract was extracted with 2N-HCl and the aqueous extract basified with 40% NaHO solution, re-extracted with EA, washed with W, dried and evaporated.

B. The 11α-amine was stirred at R.T. (unless otherwise stated) with an alkylhalide and K_2CO_3. The reaction mixture was then worked up by one of the following methods:

(i) K_2CO_3 was filtered off and the alkyl halide removed under reduced pressure. The mixture was partitioned between EA and W and the organic phase extracted with 2N-HCl. The aqueous layer was basified with aqueous NaOH solution and extracted with EA. The EA layer was washed, dried and evaporated.

(ii) The mixture was partitioned between (a) DE or (b) CH and W and the organic phase extracted with 2N-HCl. The acidic phase was basified with aqueous NaOH solution and re-extracted with DE. The extracts were washed, dried and evaporated.

(iii) As described in Preparation 72.

(iv) The mixture was diluted with DE and W and the organic layer washed with W, dried and evaporated.

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

TABLE 4

Ex.	Starting Material		Alkylating Agent		Reaction Time	Yield (g)	Chromatography	Crystallisation solvent	m.p. (°C)	$[\alpha]_D$	Method
	Prep. No.	Wt (g)		Amount							
6	63	2	HCHO/ HCO_2H	40ml/ 0.8ml	10 mins	1.51	CC EA	EA–PE	123–124	+79°	A
7	60	0.6	HCHO/ HCO_2H	12ml/ 0.24ml	10 mins	0.33	CC EA	EA–PE	122–123	+57.4	A
8	57	0.54	HCHO/ HCO_2H	11ml/ 0.21ml	10 mins	0.38	CC EA	–	–	+125.5°	A
9	58	0.6	HCHO/ HCO_2H	12ml/ 0.24ml	10 mins	0.33	CC EA TLC EA–PE	–	–	+68.9°	A
10	59	0.7	HCHO/ HCO_2H	14ml/ 0.28ml	10 mins	0.3	CC EA	–	–	+80.5°	A
11	62	1.7	MeI/ K_2CO_3	10ml/ 4.5g	7 hrs.	0.83	CC ME	DE–PE	133–136	+87.9°	B (i)
12	61	2.1	MeI/ K_2CO_3	38ml/ 6.3g	4 hrs	0.63	CC ME	EA–PE	161–171	+82.5°	B (i)
13	51	1.5	$(ClC_2H_4)_2O$/ K_2CO_3	9ml/ 0.9g	Reflux 4 hrs	0.23	CC EA–PT EA	AC–W	191–194	+53°	B (i)
14	54	1.5	MeI/ K_2CO_3	20ml/ 3g	3 hrs	0.8	CC EA	DE–PE	154–157	+87.3°	B (ii) (a)
15	63	1	$CH_3CH_2CH_2I$/ K_2CO_3	10ml/ 3g	Reflux 40 mins	0.25	CC ME TLC AC–PE	ME–W	80–85	+62.5°	B (ii) (a)
16	63	1	$(ClC_2H_4)_2O$/ K_2CO_3	4ml/ 0.6g	140° 2 hrs	0.45	TLC	–	–	+60°	B (ii) (b)

TABLE 4 (cont.)

Ex.	Starting Material		Alkylating Agent		Reaction Time	Yield (%)	Chromatography	Crystallisation solvent	m.p.(°C)	$[\alpha]_D$	Method
	Prep. No.	Wt (g)		Amount							
17	52	1.5	MeI/ K_2CO_3	80ml/ 4g	5 hrs	0.6	CC AC–DM TLC AC–PE	DE–PE	121–123	+100°	B (ii) (a)
18	53	3	MeI/ K_2CO_3	20ml/ 5g	5 hrs	0.61	CC CH TLC AC–PE	–	–	+58°	B (ii) (a)
19	50	0.5	$(ClC_2H_4)_2O$/ K_2CO_3	3ml/ 0.3g	140° 2 hrs	0.31	TLC EA	–	–	+29.8°	B (iii)
20 (2)	50	0.5	$I(CH_2)_4I$/ K_2CO_3	4ml/ 1g	Reflux 18 hrs	0.13	CC EA–PE TLC EA–PE	–	–	(3)	B (iii)
21 (2)	50	0.5	$Br(CH_2)_3Br$/ K_2CO_3/NaI	4ml/ 1g/ 0.2g	Reflux 17½ hrs	0.17	TLC EA–PE	–	–	+32° (*c* 0.6)	B (iii)
22 (2)	50	0.75	CH_2=$CHCH_2Br$/ K_2CO_3	2ml/ 1g	80° 3 hrs	0.25	TLC EA–PE	–	–	+30°	B (iii)
23[1]	63	0.7	EtI/ K_2CO_3	4ml/ 0.7 g	3 days at RT 6 hrs at reflux	0.4	TLC EA–PE	–	–	+47°	B (iv)

(1) DM (30ml) used as solvent
(2) ET (10ml) used as solvent
(3) *τ* values ($CDCl_3$) include 6.14 (s, 3β-H), 6.2–6.4 (M, 2β-H and $-OCH_2CH_3$), 7.0 (triplets of doublets, J H, and 3 H_Z, 11β-H), 7.2–7.7 (M, $-CH_2-N-CH_2-$), 7.90 (S, 21–CH_3), 8.85 (t, J 7H_Z, $-OCH_2CH_3$), 8.99 (S, 10–CH_3) and 9.37 (S, 13–CH_3).

Example 24

11α-Diethylamino-3α-hydroxy-5β-pregnan-20-one

XXXIX (0.5 g) was dissolved in ET (25 ml) and acetaldehyde (5 ml) and $NaBH_3CN$ (250 mg) was added. The reaction was kept at RT for 15 minutes and was then acidified with 2N-NCl. After a further 15 minutes the solution was basified with KOH and extracted with EA. Crystallisation from ME-W gave the *title compound* (354 mg), m.p. 123—125°, $[\alpha]_D$ + 36°.

Example 25

11α-Diethylamino-3α-hydroxy-5β-pregnan-20-one

XXXIX (50 mg) was dissolved in ET (2.5 ml) and acetaldehyde (0.25 ml) and $NaBH_4$ (25 mg) were added. The reaction was kept at RT for 30 minutes and then worked up as in Example 24 to give *title compound*, which by gas chromatography was identical to the product from Example 24.

Example 26

2β-Ethoxy-3α-hydroxy-11α-piperidino-5α-pregnan-20-one

XXXVIII (0.5 g) was mixed with 25% aq. glutaric dialdehyde solution (2 ml) in ET (10 ml) at RT and $NaBH_3CN$ (250 mg) and acetic acid (0.1 ml) added. After 6 hours the mixture was worked-up as in Preparation 73 and purified by CC and TLC to yield *title compound* (211 mg) as a foam, $[\alpha]_D$ + 35.2°.

Example 27

3α-Hydroxy-11α-piperidino-5β-pregnan-20-one

XXXIX (1 g) was mixed with $NaBH_3$ CN (500 mg) and 25% aqueous solution of glutaric dialdehyde (5 ml) in ET (10 ml) at RT and acetic acid (0.2 ml) added. After 3 hours, the mixture was partitioned between EA and $NaHCO_3$ solution. The organic solution was washed with 2N-HCl and the combined acidic extract was washed with EA, basified using 50% NaOH solution, extracted with EA, washed with W, dried ($MgSO_4$) and evaporated to give a foam.

This material was purified by preparative TLC eluting with ME containing *ca* 1% W and the solution evaporated.

The product was then dissolved in DE filtered and evaporated giving *title compound* (318 mg), $[\alpha]_D$ + 58.5°.

Example 28

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

(a) LIX (200 mg) heated to *ca* 100° with HCHO (4 ml) and formic acid (0.08 ml) for 10 minutes. The reaction mixture was then poured into $NaHCO_3$ solution and the steroid extracted with EA. Preparative TLC using AC-PT (3:7) and crystallisation from DE-PT gave *title compound* (50 mg), m.p. 140—143°.

(b) LIX (250 mg) was dissolved in EA (25 ml) and 37% aqueous HCHO (0.5 ml). 10% Palladium on charcoal (250 mg) was added and the solution hydrogenated for 17 hours. The catalyst was removed by filtration through kieselguhr, and the solution was washed with W, dried ($MgSO_4$) and evaporated to dryness. Preparative TLC using CH-MA-ME (49:49:2) followed by crystallisation from AC-W gave the *title compound* (100 mg), m.p. 129—134°.

(c) LIX (100 mg) was dissolved in EA (10 ml) and HCHO (0.2 ml). Tris(triphenylphosphine)chloro rhodium (50 mg) was added and the solution was hydrogenated for 17 hours. It was then washed with W and the organic layer was dried ($MgSO_4$) and evaporated to dryness. Chromatography on thick plates using MA-PT-ME (33:65:2) as solvent gave the *title compound* (30 mg) identical by TLC and gas phase chromatography to the product of part (a).

Example 29

11α-N,N-Dimethylamino-3α-hydroxy-5β-pregnan-20-one (LXXIII)

(a) LX (50 mg) was stirred at RT with HCHO (1 ml) and formic acid (0.02 ml) for 23 hours to give the *title compound* similar to product of Example 3 by TLC.

(b) LX (50 mg) was dissolved in EA (10 ml) and paraformaldehyde (100 mg), and 10% platinum on carbon (50 mg) added. The reaction mixture was stirred for 17 hours under hydrogen to give the *title compound* identical with the product of Example 3 by TLC.

(c) LX (00 mg) was dissolved in EA (10 ml) and HCHO (1 ml) and 10% Pd/C (100 mg) was added. The reaction mixture was hydrogenated for 17 hours and the catalyst removed by filtration through kieselguhr. The solution was washed with W,

dried ($MgSO_4$) and evaporated to dryness to give the *title compound* (100 mg), which resembled the product of Example 3 by TLC and p.m.r. spectroscopy.

(d) A solution of HCHO in EA (20 ml; prepared by heating paraformaldehyde at 200° and bubbling the HCHO gas into the EA for 5 minutes) was added to LX (100 mg) and 10% Pd/C (100 mg) in EA (5 ml). The reaction mixture was stirred with hydrogen for 30 minutes to give the *title compound* identical by TLC to the product of Example 3.

Example 30

11α-N,N-Dimethylamino-2β-ethoxy-3α-hydroxy-21-methyl-5α-pregnan-20-one

LXII (1.00 g) was heated for 10 mins at *ca* 100° in a mixture of HCHO solution (20 ml) and formic acid (0.4 ml). The cooled reaction mixture was diluted with 5% $NaHCO_3$ solution (50 ml) and extracted with EA. The organic extracts were extracted with 2N—HCl, basified to pH 11 with 40% NaOH solution and re-extracted with DM. The extract was dried (Na_2SO_4) and evaporated to give a foam which was purified by CC using EA as eluent to give the *title compound* as a foam (828 mg), $[\alpha]_D$ + 72°.

Example 31

11α-Dimethylamino-3α-hydroxy-D-homo-5α-pregnan-20-one

A suspension of LXIII (656 mg) in HCHO (5 ml) was treated with formic acid (0.21 mg) and the mixture heated to *ca* 100° for 5 mins. The cooled solution was partitioned between EA and 2N-Na_2CO_3. The organic portion was washed with saturated brine solution, dried and evaporated to give a foam (704 mg). This was purified by preparative TLC (ME) and crystallization from ME to afford the *title compound* m.p. 116—118°, $[\alpha]_D$ + 41.5°.

Example 32

11α-Dimethylamino-2β-ethoxy-3α-hydroxy-D-homo-5α-pregnan-20-one

Formic acid (0.29 ml) was added to a suspension of LXIV (1 g) in HCHO. The mixture was heated on a steam bath for 20 mins, cooled and partitioned between EA and 5% aqueous $NaHCO_3$. The organic extract was washed with saturated brine solution, dried and evaporated to a foam. This was purified by preparative TLC (ME), and crystallization from AN to afford the *title compound* (469 mg), m.p. 132.5—133.5°, $[\alpha]_D$ + 46.8°.

Example 33

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

A mixture of LXV (1.8 g), HCHO (12 ml) and formic acid (1.2 ml) was kept at *ca* 100° for 5 minutes before pouring into aqueous $NaHCO_3$ solution. The precipitated solid was collected by filtration, washed with W and dissolved in EA. Evaporation afforded a froth which was filtered through a plug of silica in EA—PE 1:1. Recrystallisation from ME—W then afforded the *title compound*, m.p. 63—78°, $[\alpha]_D$ − 2°.

Example 34

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

A suspension of XLI (550 mg) in HCHO (4 ml) was treated with formic acid (0.3 ml) and the mixture was agitated until the steroid had dissolved. The solution was heated to *ca* 100° for 10 minutes, cooled and diluted with excess NaOH solution. The precipitated material was extracted into EA, the extract was washed with W and then 2NHCl. The acid extract was washed with EA, basified with NaOH and re-extracted with EA. Evaporation of the washed organic extract afforded crystalline material which was purified by preparative TLC (5% ME—CH) and crystallization from ME—W to afford *title compound* (309 mg), m.p. 59—61°, $[\alpha]_D$ − 8.1°.

Example 35

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

A solution of XLI (608 mg) in ET (20 ml) was treated with acetic acid (0.1 ml) and $NaBH_3CN$ (231 mg). The mixture was kept at RT for 27 minutes and then acetaldehyde (3 ml) was added. After a further 15 minutes the mixture was worked-up as in Example 24 and purified by preparative TLC (EA) and crystallization from AN—W to yield *title compound* (333 mg), m.p. 89—90°, $[\alpha]_D$ − 38.1.

Example 36

(Z)-11α-Piperidino-5α-pregn-17(20)-en-3α-0l

A solution of XLI (795 mg) in IMS (10 ml) was treated with $NaBH_3CN$ (395 mg), 25% aqueous glutaric dialdehyde (2 ml) and acetic acid (0.1 ml). The mixture was kept at RT for 1 hour and then worked up as in Example 24. Purification by preparative TLC using 10% ME—EA yielded the *title compound* as a froth (410 mg), $[\alpha]_D$ – 15.3'.

Example 37

11α-Dimethylamino-5α-pregn-20-en-3α-ol

11α-Amino-5α-pregn-20-en-3α-ol (650 mg) in methyl iodide (15 ml) was stirred with K_2CO_3 for six hours. The reaction mixture was evaporated to dryness under reduced pressure and the residue was partitioned between EA and W. The organic layer was washed with W and then extracted with dilute HCl. The acidic extract was washed with EA, basified with concentrated ammonia solution and extracted with EA. The organic extract was washed with W, dried ($MgSO_4$) and evaporated to give a foam. This was purified by preparative TLC (EA—PE 1:1) to give the *title compound* as a crystalline sold (279 mg), m.p. 131—133°.

Example 38—46

Table 5 summarises the preparation of 11α-N,N-disubstituted amines from the appropriate 11α-N-mono-substituted amines by the following method:—

The amine was dissolved in HCHO solution containing formic acid and the mixture heated to *ca* 100°.

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

A. The mixture was partitioned between EA and aqueous $NaHCO_3$ and the EA extract washed with brine, dried and evaporated.

B. The mixture was diluted with W and extracted in EA. The aqueous layer was basified with NaOH, extracted with EA, and evaporated. The original EA washings were washed with NaOH and W and evaporated. The residues were combined.

C. The mixture was neutralised with NaOH and extracted with EA. The washed extract was evaporated.

D. The mixture was diluted with saturated $NaHCO_3$ solution and the precipitate collected.

The material from one of these procedure was purified by CC or preparative TLC and/or crystallisation.

The following compounds were prepared:

38. 11α-N-Cyclohexyl-N-methylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one
39. 2β-Ethoxy-3α-hydroxy-11α-(N-methyl-N-4-methylpent-2-ylamino)-5α-pregnan-20-one, isomer A
40. 2β-Ethoxy-3α-hydroxy-11α-(N-methyl-N-4-methylpent-2-ylamino)-5α-pregnan-20-one, isomer B
41. 11α-N-Benzyl-N-methylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one
42. 11α-N-Allyl-N-methylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one
43. (Z)-11α-N-Ethyl-N-methylamino-5α-pregn-17(20)-en-3α-ol
44. (Z)-11α-N-Isopropyl-N-methylamino-5α-pregn-17(20)-en-3α-ol
45. 11α-N-Ethyl-N-methylamino-3α-hydroxy-5β-pregnan-20-one
46. 3α-Hydroxy-11α-N-*iso*-propyl-N-methylamino-5β-pregnan-20-one

TABLE 5

Ex.	Starting Material		HCHO (ml)	HCO_2H (ml)	Reaction Time (mins)	Yield (mg)	Chromatography	Crystallisation solvent	m.p. (°C)	$[\alpha]_D$	Method
	Prep. No.	Wt (g)									
38	74	1	3.8	0.49	5	819	CC EA–PE	ET–W	63–70	+34.4°	A
39	95	0.67	2.5	0.32	5	624	CC EA–PE	–	–	+51.5°	A
40	96	0.27	1	0.13	5	187	CC EA–PE	–	–	+84.0° (c, 0.44)	A
41	75	0.47	1.9	0.25	5	100	TLC EA–PE	DE	–	+57.5° (*c* 0.33)	A
42	72	0.26	1	0.12	5	170	TLC EA–PE	–	–	+60.0°	A
43	78	0.22	4	0.3	12	137	TLC ME–E[A]	AN–W	104–107	-2°	B
44	79	0.42	4	0.3	10	313	–	ET–W AN–W	128–130	±0°	C
45	68	0.60	15	0.15	10	328	TLC EA–PT	–	–	+81°	D
46	77	0.4	10	0.1	5	270	TLC EA–ME	–	–	+79°	D

Example 47

3α-Hydroxy-11α-N-methyl-N-propylamino-5α-pregnan-20-one

A solution of LXVI (380 mg) in methyl iodide (10 ml) was stirred with K_2CO_3 (1 g) for 4 hours. The mixture was diluted with DE and W and the organic phase was extracted into 2N—HCl. The extract was basified with 6N—NaOH and the oily precipitate extracted into DE. The extracts were washed with W, dried (Na_2SO_4) and evaporated to leave a foam which was purified by preparative TLC and crystallisation from PE to give the *title compound* (210 mg), m.p. 149—152°C, $[\alpha]_D$ + 90°.

Example 48

11α-N-Butyl-N-methylamino-3α-hydroxy-5α-pregnan-20-one

A solution of LXVII (1 g) in methyl iodide (40 ml) was stirred with K_2CO_3 (3 g) for 3 hours. Work-up as in Example 47 and purification by preparative TLC in AC—PE (1:3) gave *title compound* (680 mg), $[\alpha]_D$ + 83°.

Example 49

11α-N-Ethyl-N-methylamino-3α-phydroxy-5α-pregnan-20-0ne

A solution of LXVIII (370 mg) in methyl iodide (2 ml) and DM (40 ml) was stirred with K_2CO_3 (1 g) for 3 hours. DE and W were added and the organic phase was washed with W. dried (Na_2CO_4) and evaporated to leave a foam which was purified by preparative TLC in AC—PE (1:3) to give the *title compound* (350 mg) as a foam, $[\alpha]_D$ + 83.7°.

Example 50

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

LXIX (560 mg) was stirred with boron trifluoride etherate (0.5 ml) in Et (25 ml) at 20° for 4 days. The mixture was concentrated by evaporation and partitioned between EA and 2N—Na_2CO_3 solution. The aqueous layer was extracted with further EA and the combined organic solutions were washed with saturated brine, dried ($MgSO_4$) and evaporated to leave an oil. This oil was purified by preparative TLC and recrystallisation from PE to give the *title compound* (46 mg), m.p. 131—137.5°, $[\alpha]_D$ + 83.3°.

Example 51

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

60% Aqueous perchloric acid (2 ml) was added to a stirred solution of LXIX (1 g) in ET (100 ml) at 20°.

After 2 hours Na_2CO_3 solution was added to raise the mixture to pH 9 and most of the ET was evaporated. The residue was partitioned between EA and W. The aqueous layer was extracted with further EA and the combined organic solutions were washed with saturated brine, dried (Na_2SO_4) and evaporated to a gum. This gum was purified by preparative TLC and recrystallisation from ET—W to give the *title compound* (504 mg), m.p. 119—123°, $[\alpha]_D$ + 83°.

Examples 52—70

Table 6 summarises the preparation of 2β-substituted-11α-di-substituted amines from the corresponding 2α,3α-epoxide by the following method:—

The 2α, 3α-epoxide was treated with the appropriate alcohol or acid in the presence of a catalyst (where necessary) at RT (or 100°C in the case of 2β-acetoxy compounds) for the time indicated. The mixture was diluted with aqueous Na_2CO_3 solution (or aqueous NaOH in the case of 2β-fluoro compounds) and worked-up by one of the following methods:—

A. The mixture was extracted with EA and the extract washed with brine, dried and evaporated.

B. The solid which precipitated was collected by filtration, washed and dried.

C. The alcohol was evaporated and the aqueous residue extracted as in A above.

The material from one of these procedures was further purified by CC and/or preparative TLC and/or crystallation.

The following 2β-substituted derivatives of 3α-hydroxy-11α-N,N-dimethylamino-5α-pregnan-20-one were prepared:—

(Example Nos. are given in brackets)

2β-fluoro (66), -chloro (61), -bromo (65), -thiocyanato (64), -acetoxy (69), -propoxy (54) -benzyloxy (59, -chloroethoxy (60), and -*iso*-propoxy (52);

and of 11α-N-ethyl-N-methylamino-3α-hydroxy-5α-pregnan-20-one:—

2β-fluoro (68),-chloro (62), -methoxy (55), -ethoxy (53) and -acetoxy (70);

and of 3α-hydroxy-11α-N-*iso*-propyl-N-methyl-5α-pregnan-20-one:—

2β-fluoro (67), -chloro (63), -methoxy (56), -ethoxy (57) and -acetoxy (58).

$HC10_4$ was used as a 60% aqueous solution.

TABLE 6

Ex	Starting Material		Acid or Alcohol		Catalyst		Reaction Time	Yield (mg)	Chromato-graphy	Crystalli-sation solvent	m.p. °C	$[\alpha]_D$	Method of workup
	Prep. No.	Wt. (mg)		Vol (ml)		Vol (ml)							
52	87	750	Propan-2-ol	15	H_2SO_4	0.12	4 hrs	143	CC EA-PE TLC	–	–	+82° (*c*0.6)	A
53	88	500	ET	50	$HClO_4$	1	3¼ hrs	236	TLC EA-PE	–	–	+82°	A
54	87	750	PR	100	$HClO_4$	1.5	1 hr	452	TLC EA-PE	–	–	+73.8°	C
55	88	500	ME	50	$HClO_4$	1	37 mins	349	TLC EA-PE	–	–	+80.5°	C
56	89	300	ME	30	$HClO_4$	0.66	25 mins	233	TLC EA-PE	–	–	+79°	C
57	89	400	ET	30	$HClO_4$	0.5	1 hr	178	TLC EA-PE	–	–	+75°	C
58	89	300	Acetic acid	3	–	–	3 hrs	173	TLC EA-PE	–	–	+78.5°	A
59	87	424	Benzyl alcohol	5	$HClO_4$	0.8	45 mins	141	TLC EA	–	–	+67°	A ①
60	87	388	2-chloro-ethanol	10	$HClO_4$	0.8	40 mins	202	TLC EA	–	–	+63°	A
61	87	300	conc. HCl	2.4	–	–	15 min	101	–	PE	135–149	+86.8°	B
62	88	500	conc HCl	4	–	–	37 mins	362	TLC EA-PE	–	–	+61.2°	B
63	89	300	conc HCl	2.5	–	–	30 mins	127	TLC EA-PE	Pentane	127–129	+73.5° (*c*0.56)	B
64	87 ②	500	HSCN in DE ③	–	–	–	45 mins	279	CC EA	PE	183–185	+88.5°	A

TABLE 6 cont.

Ex	Starting Material		Acid or Alcohol		Catalyst		Reaction Time	Yield (mg)	Chromatography	Crystallisation solvent	m.p. °C	$[\alpha]_D$	Method of workup
	Prep. No.	Wt. (mg)		Vol (ml)		Vol (ml)							
65	87	1500	47% aq HBr	10	–	–	15	267	CC EA-PE	EA-PE	139–142	+90.5°	A
66	87	500	HF④	6.2	–	–	19 hrs	276	CC, TLC EA-PE	–	–	+69.5°	B
67	89	500	HF④	6.2	–	–	19 hrs	182	TLC EA-PE	–	–	+72.1°	B
68	88	500	HF④	6.2	–	–	5 hrs	148	TLC EA-PE	–	–	+79° (*c*0.43)	A
69	87	500	Acetic acid	10	–	–	1½ hrs	263	CC EA-PE	EA-PE	156–158.5	+81° (*c*1.6)	B
70	88	500	Acetic acid	5	–	–	2¾ hrs	333	TLC EA-PE	–	–	+82°	B

① After preparative TLC further purified by dissolving in EA and extracting into HCl. The extract was basified with NaOH and re-extracted with EA, washed, dried and evaporated.

② Dissolved in DC (10 ml)

③ Prepared by extraction of a mixture prepared from KSCN (3.0g) and phosphoric acid (4.6g).

④ Preformed complex of urea (5g) and HF.

Example 71

11α-N,N-Dimethylamino-3α-hydroxy-5α-androstane-17β-carbonitrile

A solution of LXX (500 mg) in ME (150 ml) was treated with saturated $NaHCO_3$ solution (20 ml) at reflux for 24 hours. The mixture was diluted with W to 1 l. and the precipitate was filtered off, washed with W and dried. The solid (340 mg) was purified by preparative TLC in EA—PE (1:2) and crystallisation from DE—PE to give the title compound (170 mg) m.p. 183—186°C, $[\alpha]_D$ +47.5°.

Example 72

11α-N,N-Dimethylamino-2β-ethoxy-3α-hydroxy-5α-androstane-17β-carbonitrile

A solution of LXXI (320 mg) in ME (80 ml) was treated at reflux with standard $NaHCO_3$ solution (8 ml). After 5 hours the mixture was diluted to 600 ml with W and the precipitate was extracted into DE. The extracts were washed with W, dried (Na_2SO_4) and evaporated to a foam (300 mg) which was purified by preparative TLC in AC—PE (1:3) to give *title compound* (250 mg) as a foam, $[\alpha]_D$ +46°.

Example 73

11α-Dimethylamino-3α-hydroxy-5β-androstane-17β-carbonitrile

$KHCO_3$ (1 g) in W (20 ml) was added to a solution of LXXII (500 mg) in ME (50 ml) and the mixture was refluxed under nitrogen for 2 hours. Dilution with W and extraction with EA gave crude product which was crystallised from DE—PE and ME—W to afford *title compound* (170 mg), m.p. 137—139°, $[\alpha]_D$ +67°.

Example 74

21-Acetoxy-11α-N,N-dimethylamino-3α-hydroxy-5β-pregnan-20-one (LXXIV)

Lead tetra-acetate (1.0 g) was added to a solution of LXXIII (0.5 g) in benzene (18 ml) and ME (1.15 ml). The solution was cooled to 10° and boron trifluoride etherate (2.85 ml) was added; the reaction mixture was stirred at 10° for 5 hours and then was poured into aqueous $NaHCO_3$ solution. The steroid was extracted into DE and subjected to preparative TLC in 2:1 EA—PT. Elution with EA followed by crystallisation from DE gave the *title compound* (100 mg), m.p. 150—152°.

Example 75

3α,21-Dihydroxy-11α-dimethylamino-5β-pregnan-20-one

LXXIV (500 mg) was dissolved in ME (20 ml) and aqueous $KHCO_3$ (5 ml, 20%) was added. The solution was refluxed under nitrogen for 2 hours, and was then poured into W and the steroid extracted with EA. Preparative TLC using AC—PT 1:2 as solvent and elution with AC gave *title compound* as a white froth (310 mg), $[\alpha]_D$ +47°.

Example 76

11α-Dimethylamino-3α-hydroxy-5α-pregnan-20-one

LVIII (110 mg) was treated with a refluxing solution of chloroiridic acid reagent (3 ml) for one hour before partitioning between EA and aqueous $NaHCO_3$ solution. The organic phase was isolated, washed with W and evaporated to a froth. Crystallisation from PE afforded the *title compound* (78 mg), m.p. 119—122°, $[\alpha]_D$ +76.0°.

Example 77

11α-Dimethylamino-3α-hydroxy-5α-pregnan-20-one

To a mixture of LVII (362 mg), formic acid (0.11 ml), triphenylphosphine (787 mg) and tetrahydrofuran (15 ml) was added a solution of diethylazodicarboxylate (348 mg) in tetrahydrofuran (3 ml). The reaction mixture was left to stand at RT overnight before partitioning between EA and aqueous $NaHCO_3$ solution. The organic phase was isolated, washed with W, dried (Na_2SO_4) and evaporated to give a froth. CC (eluting with DM) afforded a froth which was dissolved in ME (10 ml) and treated with 10 drops of perchloric acid. After 0.5 hour, the reaction mixture was worked up as in Example 76. Crystallisation from PE afforded the *title compound* (106 mg), m.p. 119—123°, $[\alpha]_D$ +76.7°.

Example 78

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

XLV (100 mg) was stirred with PTSA (61 mg) in DC (10 ml) and ET (5 ml) for 5 minutes. *m*-Chloroperbenzoic acid (75 mg) was added and after 24 hours at 20° TLC showed formation of the *title compound.*

Example 79

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

LXI (3.0 g) was dissolved in DM (20 ml) and the solution was extracted with a solution of conc H_2SO_4 (1.8 ml) in W (25 ml) and then with W (15 ml). The combined aqueous extracts were kept at RT for 10 minutes and then brought to pH 11 by the addition of NaOH solution. The precipitate was extracted into DM and

the extracts were washed with W. The dried ($MgSO_4$) solution was subjected to CC eluting with DM—MA (9:1). The eluate was evaporated to give a foam which was crystallised from AC—W (4:1) to give the *title compound* (1.66 g), $[\alpha]_D$ +74°, m.p. 135—143°.

Example 80

Methyl 11α - N,N - dimethylamino - 2β - ethoxy - 3α - hydroxy - 5α - androstane-17β - carboxylate

Iodomethane (8.4 ml) was added to a solution of LXXV (3.5 g) in dimethylformamide (30 ml) and triethylamine (25 ml). After stirring for 20 h, the mixture was poured into 5% $NaHCO_3$ solution (50 ml) and was extracted with CH. The combined extracts are dried ($MgSO_4$) and evaporated. The residue was purified by CC using 1:4 EA—PE as eluent to give the *title compound* as a foam (965 mg), $[\alpha]_D$ +35°.

Example 81

11α-N,N-Dimethylamino-2β-ethoxy-3α-hydroxy-21-propyl-5α-pregnan-20-one

Butyl lithium in hexane (8.6 ml, 1.7 M) was added to a suspension of LXXV (2.0 g) in DE (12 ml) under nitrogen with cooling in ice-W. The mixture was stirred vigorously at 20° for 31 h, and was then diluted with W (25 ml). The mixture was extracted with EA and the combined extracts were washed with 0.1 N—NaOH. The dried ($MgSO_4$) extract was evaporated to give a foam which was purified by preparative TLC on alumina using 1:2 EA—PE as eluent to give the *title compound* (146 mg) as a foam, $[\alpha]_D$ +75°.

Example 82

11α-Dimethylamino-3α-hydroxy-5α-pregn-1-en-20-one

2β-Bromo-11α-N,N-dimethylamino-3α-hydroxy-5α-pregnan-20-one (2.76 g) was stirred with dihydropyran (7 ml) and PTSA (1.30 g) in B (150 ml) at 21°. After one hour, the clear solution was washed with excess 2N—Na_2CO_3 solution, brine and dried (Na_2SO_4). The B was evaporated to an oil which was then dissolved in DMF (75 ml) and heated at 105° to 115° with $CaCO_3$ (7.5 g) and LiBr (10 g) for 19 hours. The mixture was diluted with ME and insoluble solids were separated by filtration. The residue was washed with further ME and the combined solutions were diluted to *ca* 300 ml.

This solution was adjusted to pH 1 with 2N—HCl and after 1 hour at 21°, 2N—Na_2CO_3 solution was added to raise the mixture to pH 9.0 and the ME was evaporated at reduced pressure. The residue was extracted twice with EA and the combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to an oil. Residual DMF was evaporated using an oil pump leaving a gum. This was dissolved in 1:1 EA—PE and filtered through silica gel (30 g) to give the crude product. This was purified by preparative TLC (EA—PE) to give *title compound* (611 mg), $[\alpha]_D$ +1.5°.

Example 83—157

Preparation of salts

Table 7 summarises the properties and preparation of aqueous solutions of salts of the invention by one of the following methods:—

A. The 11α-amine was added to a solution of the acid in W and the mixture stirred or shaken until a clear solution was obtained. The solution was made up with W to the weight indicated, filtered through a membrane and the pH determined.

B. As A above except that prior to making up with W the solution was filtered and treated dropwise with 0.1 M NaOH solution until the precipitate initially formed did not quite redissolve on stirring.

C. A solution of the 11α-amine in ET was treated with a solution of the acid in W. The mixture was evaporated *in vacuo* and dried to constant weight. The residue was dissolved in a little W and any material which then remained undissolved collected in a weighed funnel and the weight of the dissolved free base calculated. The solution was made up with W to the weight indicated and its pH measured.

D. The 11α-amine was added to a solution of the acid in W and the mixture stirred or shaken. As free base remained undissolved, further acid was added and the mixture agitated again. The solution was made up with W and any material which then remained undissolved was collected in a weighed funnel and the

weight of dissolved free base calculated and the pH of the solution measured.

E. The 11α-amine was added to a solution of the acid in W and the mixture stirred or shaken. The solution was made up with W to the weight indicated. The material remaining undissolved was collected in a weighed funnel and the weight of dissolved free base calculated and the pH of the solution measured. The solid citric acid used was its monohydrate.

TABLE 7

Ex.	Free Base Ex. No.	Salt	Method	Dissolved 11α-amine (mg)	Molarity of acid solution	Acid	Wt of solution (g)	pH
83	6	citrate	B	120.5	0.1	3.4ml	24	6.5
84	6	,,	C	120	0.1	3.34ml	12	3.6
85	6	hydro-chloride	B	120	0.1	3.4ml	12	4.85
86	6	phosphate	B	120	0.1	3.4ml	10	5.7
87	6	mesylate	B	120	0.1	3.4ml	10	3.3
88	6	tricar-ballylate	B	120	0.1	2.3ml	12	6.05
89	7	citrate	B	100	–	54mg	10	5.0
90	8	,,	A	102	–	55mg	10	3.7
91	9	,,	A	101	–	56mg	10	3.8
92	10	,,	A	103	–	55mg	10	3.7
93	11	,,	A	101	–	57mg	10	3.7
94	12	,,	A	102	–	57mg	10.06	3.7
95	12	acetate	E	84	0.5	1.59ml	10	4.4
96	14	citrate	B	100	0.1	2.6ml	10	4.8
97	14	acetate	B	100	0.5	1.5ml	10	3.9
98	15	citrate	B	100	0.1	2.5ml	10	3.5
99	16	,,	C	100	0.1	4.5ml	16.5	3.0
100	17	,,	B	350	0.1	9.0ml	35	5.1
101	18	,,	B	100	0.1	2.5ml	10	4.0
102	19	,,	D	16	–	48mg	5	2.45
103	20	,,	E	32	–	24.5mg	5	3.26
104	21	,,	E	45	–	25.5mg	5	3.58
105	23	,,	B	130	0.1	3.3ml	13	3.3
106	24	,,	B	100	–	54mg	10	4.5
107	26	,,	E	41	–	23.5mg	5	3.4
108	27	,,	D	100	–	104.2mg	12	3.0
109	30	,,	A	100	–	50mg	10	3.7

TABLE 7 cont.

Ex.	Free Base Ex. No.	Salt	Method	Dissolved 11α-amine (mg)	Molarity of acid solution	Acid	Wt of solution (g)	pH
110	31	citrate	E	94	–	60mg	10	3.8
111	32	,,	A	100	–	50mg	10	3.7
112	37	,,	D*	96	–	121.6mg	20	3.1
113	34	,,	A	100	–	62mg	10	3.65
114	35	,,	D	103	–	74mg	10.29	3.45
115	36	,,	D	102	–	114mg	10.21	3.0
116	33	,,	A	78	–	63mg	7.8	3.16
117	38	,,	E	17	–	22mg	5	2.85
118	39	,,	D	25	–	44mg	5	2.65
119	40	,,	D	41	–	44mg	5	2.8
120	42	,,	D	43	–	48mg	5	2.9
121	43	,,	A	87	–	51mg	8.7	3.75
122	44	,,	D	99	–	105mg	10.28	3.1
123	45	,,	A	100	–	55.9mg	10	3.75
124	46	,,	A	100	–	54mg	10	3.75
125	47	,,	B	100	0.1	2.6ml	10	4.9
126	48	,,	B	101	0.1	2.5 ml	10.1	3.6
127	49	,,	B	125	0.1	3.2ml	12.5	6.0
128	52	,,	E	48	–	25mg	5	3.65
129	53	,,	A	50	–	25mg	5	3.6
130	54	,,	D	48	–	50mg	5	3.0
131	55	,,	A	50	–	26mg	5	3.75
132	56	,,	E	43	–	26mg	5	3.5
133	57	,,	E	48	–	24mg	5	3.45
134	58	,,	E	41	–	24mg	5	3.5
135	61	,,	E	47	–	53mg	5	2.97
136	62	,,	E	50	–	38.5mg	5	3.18
137	63	,,	D	33	–	50mg	5	2.8

TABLE 7 cont.

Ex.	Free Base Ex. No.	Salt	Method	Dissolved 11α-amine (mg)	Molarity of acid solution	Acid	Wt of solution (g)	pH
138	64	citrate	D	43	–	50mg	5	2.82
139	65	,,	D	21	–	48mg	5	2.55
140	66	,,	E	49	–	27mg	5	3.58
141	67	,,	D	45	–	52mg	5	2.95
142	68	,,	A	50	–	27mg	5	3.6
143	69	,,	E	49	–	25.5mg	5	3.52
144	70	,,	E	49	–	24mg	5	3.6
145	71	,,	B	100	–	61mg	10	5.4
146	72	,,	B	100	–	54mg	10	5.05
147	73	,,	A	100	–	61mg	10	3.6
148	74	,,	A	100	–	51mg	10	3.7
149	75	,,	A	100	–	56mg	10	3.7
150	80	,,	B	100	–	50mg	10	4.5
151	81	,,	B	60	–	56mg	6	3.7
152	82	,,	D	24	–	58mg	5	2.6
153	59	,,	E	47	–	23mg	5	3.6
154	60	,,	E	46	–	24mg	5	3.5
155	183	,,	A	25	–	26mg	5	3.0
156	186	,,	A	80	–	42mg	8	3.60
157	188	,,	E	86	–	52mg	8.9	3.5

* As material remained undissolved after second addition of acid, ET was added dropwise until complete solution was attained and the resulting solution was evaporated to dryness under reduced pressure. The residue was dried and dissolved in W.

Example 158—171

Preparation of salts of 11α-N,N-Dimethylamino-2β-ethoxy-5α-pregnan-20-one (Table 8)

The amine was added to a solution of the acid in W and the mixture stirred or shaken until a clear solution was obtained. The solution was then either:

(A) treated dropwise with 0.1 M—NaOH until the precipitate initially formed just redissolved, made up to the weight indicated with W, filtered through a membrane and the pH determined; or

(B) made up with W to the weight indicated, filtered through a membrane and the pH determined.

TABLE 8

Ex.	Salt	Method	Dissolved 11α-amine (mg)	Molarity of acid solution	Acid	Wt of solution (g)	pH
158	citrate	A	500	0.1	12.4ml	50	4.4
159	acetate	B	50	0.5	0.75ml	5	4.0
160	lactate	A	101	0.5	1.5ml	10	4.2
161	mesylate	A	100	0.1	2.5ml	10	4.05
162	phosphate	A	100	0.525	0.5ml	10	3.6
163	(+)-tartrate	A	101	–	37.5mg	10	4.5
164	tricarballylate	A	101	–	46mg	10	4.9
165	hydrochloride	A	101	0.1	2.5ml	10	3.55
166	sulphate	B	100	0.05	2.5ml	10	3.3
167	citraconate	A	100	–	36mg	10	3.8
168	mesaconate	B	81	–	52mg	8.1	3.02
169	aconitate	B	81	–	35mg	8.1	3.38
170	succinate	B	100	–	58mg	10	3.7
171	salicylate	B	81	–	27.6mg	8.1	4.48

Examples 172—180

Preparation of salts of 11α-N,N-dimethylamino-3α-hydroxy-5β-pregnan-20-one (Table 9)

The amine was added to a solution of the acid in W and the mixture stirred or shaken until a clear solution was obtained. The solution was made up with W to the right indicated, filtered through a membrane and the pH determined.

TABLE 9

Ex.	Salt	Dissolved 11α-amine (mg)	Molarity of acid solution	Acid	Wt of solution (g)	pH
172	citrate	120	0.1	4.0ml	12	3.2
173	hydrochloride	50	0.1	1.4ml	5.06	2.9
174	acetate	50	0.5	0.55ml	5	4.5
175	succinate	50	–	16.3mg	5	4.5
176	mesylate	50	0.1	1.4ml	5	3.85
177	phosphate	50	0.52	0.4ml	5	2.5
178	tricarballylate	50	–	24.4mg	5	4.15
179	lactate	50	0.5	0.14ml	5	4.1
180	(+)-tartrate	50	–	20.7mg	5	3.65

Example 181

11α - N,N - Dimethylamino - 2β - ethoxy - 3α - hydroxy - 5α - pregnan - 20 - one hydrochloride salt

A solution of 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one (10.5 g) in dry DE (80 ml) was stirred while a stream of HCl was passed through. The precipitated solid was collected by filtration under pressure of a nitrogen atmosphere and washed well with dry DE and dried to give *title compound* (11.5 g) m.p. dec. 200°C, $[\alpha]_D$ +35° (ME).

Example 182

11α - N,N - Dimethylamino - 2β - ethoxy - 3α - hydroxy - 5α - pregnan - 20 - one citrate salt

A solution of 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one (1 g) in DE (20 ml) was added to a stirred solution of citric acid monohydrate (1.05 g) in DE (60 ml). An immediate precipitate was formed which was collected by filtration under nitrogen pressure to give *title compound* containing 1 mole of citric acid in excess.

The filtrate was evaporated to half volume and the precipitate collected by filtration to give further *title compound* containing 1 mole of citric acid in excess τ values (D_2O) include 9.35 (s, 18—H), 8.87 (s, 19—H), 8.84 (t, J 7Hz, —OCH_2CH_3), 7.78 (s, 21—H), 7.67 (triplet of doublet, J 12 and 5 Hz, 11β—H), 7.02 and 7.24 (ABq, J 16 Hz, —CH_2— of citric acid), 6.97 and 7.09 (2 singlets, 11α-$^+NH(CH_3)_2$), 6.2—6.6 (m, —OCH_2CH_3, 2α—H and 1β—H) and 6.05 (m, 3β—H).

Example 183

21 - Acetoxy - 11α - N,N - dimethylamino - 2β - ethoxy - 3α - hydroxy - 5α-pregnan - 20 - one (XXIX)

A solution of XXVIII (200 mg) in AC (10 ml) was stirred at RT with anhydrous potassium acetate (200 mg) for 4 hours. The mixture was diluted with W to 100 ml and the precipitate extracted into DE. The extract was washed with W, dried (Na_2SO_4) and evaporated to a foam (180 mg) which was purified by preparative TLC in EA—PE (1:1) to give *title compound* (114 mg) as a foam, $[\alpha]_D$ +90.5°.

Example 184

11α-Dimethylamino-3α-hydroxy-5β-pregnan-20-one

11α-Amino-5β-pregnane-3α,20β-diol (44 mg) in 37% aqueous HCHO (1 ml) and HCO_2H (0.01 ml) was heated on a steam bath for 5 minutes. The cooled

solution was diluted with $NaHCO_3$ solution and extracted with EA. Evaporation of the washed and dried ($MgSO_4$) organic extract afforded a gum which was purified by preparative TLC in AC—PE (2:3) to give 11α-dimethylamino-5β-pregnane-3α, 20β-diol.

This latter compound (40 mg) in AC (4 ml) was treated at 0° with Jones reagent (0.24 ml). After 15 minutes the mixture was poured into iced $NaHCO_3$ solution and extracted with EA. The washed and dried ($MgSO_4$) extract was evaporated to give a solid which was purified by filtration through silica gel in AC—PE (1:10) and crystallization from ME—W to yield 11α-dimethylamino-5β-pregnane-3,20-dione (10 mg).

A solution of the latter compound (250 mg) in ET (17 ml) was stirred at RT for 15 minutes with $NaBH_4$ (125 mg). Excess $NaBH_4$ was decomposed by the addition of a little acetic acid and the mixture was then diluted with $NaHCO_3$ solution and extracted with EA. Evaporation of the washed and dried ($MgSO_4$) extract gave a foam which was purified by preparative TLC using AC—PE (1:5) to afford the *title compound*, $[\alpha]_D$ +66.2°.

Example 185

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

The triethylammonium salt of the free acid compound LXXV (500 mg) was dissolved in dry THF (5 ml). Methyl lithium (7.2 ml), 1.7M solution in DE) was added and the mixture was stirred at 20° under nitrogen for 28h. W (25 ml) was added and the mixture was extracted with EA (3X). The combined extract was dried ($MgSO_4$) and evaporated to give *title compound* (372 mg) similar to the product of Example 1 by the chromatography.

Example 186

(Z)-17-Caynomethylene-11α-dimethylamino-2β-ethoxy-5α- and rostan-3α-ol

To a mixture of NaH (500 mg), diethyl cyanomethyl phosphonate (4 ml) and dry THF (16 ml) was added a solution of LXXIX (1.2 g) in dry THF (12 ml). The reaction mixture was stirred at RT overnight before being partitioned between EA and W. The organic phase was washed with W, dried (Na_2SO_4) and evaporated to an oil. Purification by CC (EA—PE) and crystallisation from ME—W afforded *the title compound.* (833 mg). m.p. 128—146° $[\alpha]_D$ – 10.8° shown by n.m.r. to contain the corresponding E-isomer.

Example 187

11α-Dimethylamino-3α-hydroxy-5α-pregnan-20-one

LXXXIII (100 mg) in EA (10 ml) containing a few drops of acetic acid was hydrogenated at atmospheric pressure using 5% Pd-C as the catalyst. After 24 hours, the catalyst was removed by filtration through kieselguhr and the filtrate evaporated to give the *title compound* (70 mg) similar to the product of Example 6 by P.M.R. G.L.C. and T.L.C.

Example 188

11α-Dimethylamino-3α-hydroxypregn-4-en-20-one

A solution of $NaBH_4$ (117 mg) in W (5 ml) was added to a stirred solution of LXXXV (500 mg) in THF (20 ml). The solution was stirred for 5¼ hr at *ca* + 21° and then glacial acetic acid was added dropwise until effervescence ceased. The solution was partitioned between W and EA and the organic extract was washed with saturated brine solution and dried. Evaporation gave 11α-dimethylamino-pregn-4-ene-3β,20ξ-diol (510 mg).

A solution of diethyl azodicarboxylate (348 mg) indry THF (2 ml) was added dropwise over *ca* 5 min to a stirred solution of the above diol (361 mg) in dry THF (12 ml) containing triphenylphosphine (787 mg) and chloroacetic acid (283 mg). The solution was stirred at *ca* + 21° for 1 hr. and then partitioned between 5%-aqueous $NaHCO_3$ and EA. The organic extract was washed with saturated brine solution, dried and evaporated to give a solid (1.58 g). This was purified by preparative TLC (EA—PE) to give 3α-chloroacetoxy-11α-dimethylamino-pregn-4-en-20ξ-ol.

A solution of the above compound (438 mg) in AC (10 ml) was cooled to 0 to 5° with stirring and Jones reagent (0.3 ml) was added dropwise over *ca* 3 min. After a further 20 min at 0 to 5° the mixture was partitioned between 2½%-aqueous $NaHCO_3$ and EA. The organic extract was washed with saturated brine solution, dried and evaporated to give a foam. This was purified by preparative TLC

(EA—PE) to give 3α-chloroacetoxy-11α-dimethylaminopregn-4-en-20-one.

A solution of this compound (469 mg) in ME (15 ml) was brought to reflux and a solution of $HaHCO_3$ (181 mg) in W (2.5 ml) was added. The mixture was refluxed for 30 min., then cooled and partitioned between W and EA. The organic extract was washed with saturated brine solution (100 ml), dried and evaporated to give liquid. This was purified by preparative TLC (EA—PE) to give a liquid (123 mg). The PMR spectrum showed the material to contain the *title compound* and 11α-dimethylamino-3β-hydroxypregn-4-en-20-one.

The above epimeric mixture (121 mg) was mixed with similarly derived material (158 mg) and resubjected to TLC purification (EA—PE). The more polar band was eluted with AC and evaporated to give the *title compound* as a foam (123 mg), $[\alpha]_D$ + 170°.

Example 189

11α-Dimethylamino-2β-ethoxy-21-fluoro-3α-hydroxy-5α-pregnan-20-one and its citrate salt.

A mixture containing XXVIII (4.9g) (NaI) (5g) and AC (300 ml) was refluxed for 30 minutes before evaporating to low volume and partitioning between DE and W. The organic phase was washed with W, dried (Na_2SO_4) and evaporated to a froth. This froth was dissolved in AN (350 ml) and treated with a solution of AgF (3 g) in W (15 ml) at 45° for 24 hours. The reaction mixture was partitioned between DE and K_2CO_3 solution. The organic phase was washed with W, dried (Na_2SO_4) and evaporated to a froth. Purification by preparative TLC (EA—PE 1:1) afforded *the title compound* as a froth (240 mg) $[\alpha]_D$ + 69.8°.

The above free base (85 mg) was stirred with a solution of citric acid (82 mg) in W (8 ml). The solution was made up to 8.5 g with W and an insoluble residue (15 mg) removed by filtration to give a solution of concentration 8.2 mg/ml and pH 2.9.

The above compound and its salts is also one of the preferred compounds according to the invention. An additional preferred group of compounds are those of formulae (I) or (II) in which R^9 is a methyl group substituted by a flurorine atom.

Examples A—F

Formulations of 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one

A. Single dose injection, 5 mg/ml

	% w/v
steroid	0.50
citric acid	0.26
sodium chloride	0.80
sodium hydroxide	to pH 4.5
water for Injections to	100.00

Citric acid was dissolved in most of the water and the steroid added with stirring under a nitrogen blanket. Once the steroid was in solution, the sodium chloride was added and dissolved. Then the pH was adjusted with sodium hydroxide solution and the product made up to volume. The solution was clarified by membrane filtration and filled under nitrogen into clean glass ampoules. The sealed containers were sterilised by moist heat.

Single dose injection, 5 mg/ml

	% w/v
steroid	0.50
hydrochloric acid (pure)	0.11
sodium chloride	0.62
disodium hydrogen citrate	0.32
sodium hydroxide	to pH 4.5
Water for Injections to	100.00

The steroid was added to a dilute solution of the hydrochloric acid and dissolved by stirring under a nitrogen blanket. Disodium hydrogen citrate and sodium chloride were added and dissolved, the pH adjusted with sodium hydroxide solution and the product made up to volume. The solution was clarified by

membrane filtration and filled under nitrogen into glass ampoules. The sealed containers were sterilised by moist heat.

C. Solution for intravenous infusion

	% w/v
steroid	0.050
citric acid	0.026
sodium chloride	0.89
sodium hydroxide	to pH 4.5
Water for Injections to	100.00

Dissolve the citric acid in most of the water and add the steroid with stirring under a nitrogen blanket. Once the steroid is in solution, add the sodium chloride and dissolve. Adjust the pH with sodium hydroxide solution and make the product up to volume. Clarify the solution by membrane filtration and fill into clean glass bottles under nitrogen. Close the bottles with rubber plugs holding them in position by aluminium sealing rings and sterilise by moist heat.

D. Solution for intravenous infusion

	% w/v
steroid	0.050
hydrochloric acid (pure)	0.011
disodium hydrogen citrate	0.032
sodium chloride	0.87
sodium hydroxide	to pH 4.5
Water for Injections to	100.00

Add the steroid to a dilute solution of hydrochloric acid and dissolve by stirring under a nitrogen blanket. Add and dissolve disodium hydrogen citrate and sodium chloride, adjust the pH with sodium hydroxide solution and make the product up to volume. Clarify the solution by membrane filtration and fill into clean glass bottles under nitrogen. close the bottles with rubber plugs, holding them in position by aluminium sealing rings and sterilise by moist heat.

E. Multidose injection

	% w/v
steroid	1.00
citric acid	0.52
sodium chloride	0.50
benzyl alcohol	1.00v/v
sodium hydroxide	to pH 4.5
Water for Injections to	100.00

Dissolve benzyl alcohol in most of the water and add and dissolve citric acid. Add and dissolve the steroid by stirring under a nitrogen blanket. Then dissolve sodium chloride and adjust the pH with sodium hydroxide solution. Make up the product to volume and sterilise by membrane filtration. Then fill the solution aseptically under nitrogen into sterile glass vials and close them with sterile rubber plugs or seals, holding them in position by aluminium sealing rings.

F. Multidose injection

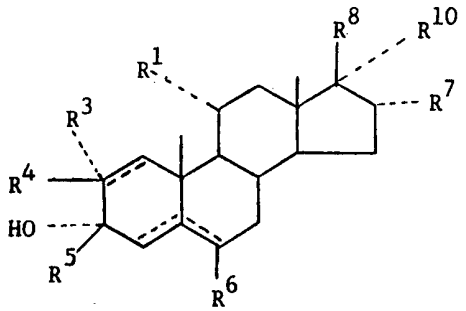
	% w/v
steroid	1.00
hydrochloric acid (pure)	0.22
disodium hydrogen citrate	0.65
sodium chloride	0.15
benzyl alcohol	1.00v/v
sodium hydroxide	to pH 4.5
Water for Injections to	100.00

Dissolve benzyl alcohol in a dilute solution of hydrochloric acid and then dissolve the steroid with stirring under a nitrogen blanket. Add and dissolve disodium hydrogen citrate and sodium chloride. Adjust the pH with sodium hydroxide solution, make the product up to volume and sterilise by membrane filtration. Fill the solution aseptically under nitrogen into sterile glass vials and close the vials with sterile rubber plugs or seals, holding them in position with aluminium sealing rings.

Similar formulations wherein 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one is replaced by 11α-N,N-dimethylamino-3α-hydroxy-5β-pregnan-20-one may also be prepared.

WHAT WE CLAIM IS:—

1. 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} alkeny (containing one or two double bonds), 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, 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^4 is a hydrogen atom or a C_{1-5} 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 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 substituted methylene group in which the substituent is in the Z-configuration and is 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^6 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.

2. Compounds as claimed in claim 1, wherein R^a and R^b are other than benzyl or phenethyl groups; R^8 is other than the group —COR^9 where R^9 is a methyl group substituted by a C_{2-4} alkyl 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 thio-cyanato group or a chlorine, bromine or fluorine atom.

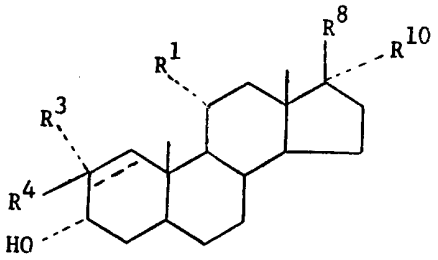
12. Compounds as claimed in claim 11 wherein R^4 is a hydrogen atom or an ethoxy group.

13. Compounds as claimed in any one of claims 2 to 12 wherein R^a and R^b are methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, pentyl, *iso*-pentyl, 1,3-dimethylbutyl, allyl, cyclopentyl or cyclohexyl groups, or wherein –NR^aR^b represents a pyrrolidino group.

14. Compounds as claimed in claim 13 wherein one of R^a and R^b is a methyl group and the other is a methyl, ethyl, propyl, *iso*-propyl, butyl or allyl group.

15. Compounds asclaimed in claim 13 wherein both R^a and R^b are methyl groups.

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



(II)

wherein:

R^1 is a group –NR^aR^b, in which one of R^a and R^b is a methyl group, the other group being a methyl, ethyl, propyl, *iso*-propyl, butyl or allyl group, or in which both R^a and R^b are ethyl groups, or in which R^a and R^b (together with the nitrogen atom) represent a pyrrolidino 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 acid addition salts thereof.

17. Compounds as claimed in claim 16 wherein R^1 is a dimethylamino group, R^3 is a hydrogen atom, R^4 is a hydrogen atom or an alkoxy group, R^8 is an acetyl or cyano group and ring D has 5 members.

18. Compounds as claimed in claim 2 in the form of their hydrochloride, hydrobromide, phosphate, sulphate, *p*-toluenesulphonate, methanesulphonate, citrate, tartrate, acetate, ascorbate, lactate, maleate, succinate, tricarballylate, glutarate or glutaconate salts.

19. Compounds as claimed in any one of claims 1 to 17 in the form of their aconitate, citraconate, mesaconate or salicylate salts.

20. Compounds as claimed in claim 2 in the form of their citrate or hydrochloride salts.

21. Compounds as claimed in claim 2, said compounds being 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one and the physiologically acceptable acid addition salts thereof.

22. Compounds as claimed in claim 2, said compounds being:

11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one and its citrate, acetate, methanesulphonate, lactate, phosphate, tartrate, tricarballylate, hydrochloride, and succinate salts.

23. Compounds as claimed in claim 2, said compounds being:

the citraconate, aconitate and mesaconate salts of 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one.

24. 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one citrate.

25. Compounds as claimed in claim 2, said compounds being 11α-N-dimethylamino-3α-hydroxy-5β-pregnan-20-one and the physiologically acceptable acid addition salts thereof.

26. Compounds as claimed in claim 1, said compounds being:

11α-N,N-dimethylamino-3α-hydroxy-5β-pregnan-20-one and its citrate, acetate, hydrochloride, tartrate, lactate, tricarballylate, phosphate, methanesulphonate and succinate salts.

27. Compounds as claimed in claim 2, said compounds being:

11α-N,N-dimethylamino-3α-hydroxy-5α-pregnan-20-one;

11α-N,N-dimethylamino-3α-hydroxy-5α-androstane-17β-carbonitrile;

2β-chloro-11α-N,N-dimethylamino-3α-hydroxy-5α-pregnan-20-one;

11α-N,N-dimethylamino-2β-fluoro-3β-hydroxy-5α-pregnan-20-one; and

11α-N,N-diethylamino-3α-hydroxy-5β-pregnan-20-one; and the physiologically acceptable acid addition salts thereof.

28. Compounds as claimed in claim 1, said compounds being:

11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-D-homo-5α-pregnan-20-one;

3α-hydroxy-11α-N-*iso*-propyl-N-methylamino-5β-pregnan-20-one;

11α-N,N-ethyl-N-methylamino-3α-hydroxy-5β-pregnan-20-one;

11α-N,N-dimethylamino-3α-hydroxy-5β-androstane-17β-carbonitrile;

11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-androstane-17β-carbonitrile;

and the physiologically acceptable acid addition thereof.

29. Compounds as claimed in claim 2, said compounds being:

11α-N,N-dimethlamino-3α-hydroxy-2β-methyl-5α-pregnan-20-one;

11α-N,N-dimethylamino-3α-hydroxy-2α-methyl-5α-pregnan-20-one;

11α-N-butyl-N-methylamino-3α-hydroxy-5α-pregnan-20-one;

11α-dimethylamino-3α-hydroxy-2β-methoxy-5α-pregnan-20-one;

2β-ethoxy-11α-N-ethyl-N-methylamino-3α-hydroxy-5α-pregnan-20-one;

11α-N-ethyl-N-methylamino-3α-hydroxy-5β-pregnan-20-one;

3α-hydroxy-11α-N-methyl-N-propylamino-5α-pregnan-20-one;

11α-N,N-dimethylamino-3α-hydroxy-2β-propoxy-5α-pregnan-20-one;

11α-N,N-dimethylamino-3α-hydroxy-2β-iso-*propoxy*-5α-pregnan-20-one;

2β-acetoxy-11α-N,N-dimethylamino-3α-hydroxy-5α-pregnan-20-one;

2β-bromo-11α-N,N-dimethylamino-3α-hydroxy-5α-pregnan-20-one;

11α-N,N-dimethylamino-3α-hydroxy-2β-thiocyanato-5α-pregnan-20-one;

21-acetoxy-11α-N,N-dimethylamino-3α-hydroxy-5β-pregnan-20-one;

11α-N,N-dimethylamino-3α-hydroxy-5α-pregn-20(21)-ene;

and the physiologically acceptable acid addition salts thereof.

30. Compounds as claimed in claim 1, said compounds being:
11α-N-ethyl-N-methylamino-3α-hydroxy-2β-methoxy-5α-pregnan-20-one;
3α-hydroxy-11α-N-*iso*-propyl-M-methylamino-2β-methoxy-5α-pregnan-20-one;
11-α-N-ally-N-methylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one;
2β-ethoxy-3α-hydroxy-11α-pyrrolidino-5α-pregnan-20-one;
2β-acetoxy-11α-N-ethyl-N-methylamino-3α-hydroxy-5α-pregnan-20-one;
2β-acetoxy-3α-hydroxy-11α-N-*iso*-propyl-N-methylamino-5α-pregnan-20-one;
11α-N-ethyl-N-methylamino-2β-fluoro-3α-hydroxy-5α-pregnan-20-one;
2β-fluoro-3α-hydroxy-11α-N-*iso*-propyl-N-methylamino-5α-pregnan-20-one;
2β-chloro-11α-N-ethyl-N-methylamino-3α-hydroxy-5α-pregnan-20-one;
2β-chloro-3α-hydroxy-11α-N-*iso*-propyl-N-methylamino-5α-pregnan-20-one;
11α-N,N-dimethylamino-3α-hydroxy-5α-pregn-1-en-20-one;
11α-N,N-dimethylamino-3α-hydroxy-D-homo-5α-pregnan-20-one;
11α-N,N-dimethylamino-21,21-ethylene-3α-hydroxy-5α-pregnan-20-one;
11α-N,N-dimethylamino-3α-hydroxy-21-methyl-5α-pregnan-20-one;
11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-21-methyl-5α-pregnan-20-one;
21-acetoxy-11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one;
3α,21-dihydroxy-11α-N,N-dimethylamino-5β-pregnan-20-one;
(Z)-11α-N,N-dimethylamino-3α-hydroxy-5α-pregn-17(20)-ene;
methyl 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-androstane-17β-carboxylate;
2β-butoxy-11α-N,N-dimethylamino-3α-hydroxy-5α-pregnan-20-one;
11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-21-propyl-5α-pregnan-20-one;
and the physiologically acceptable acid addition salts thereof.

31. Compounds as claimed in claim 27 or claim 29 wherein said salts are citrates.

32. Compounds as claimed in claim 28 or claim 30 wherein said salts are citrates.

33. A pharmaceutical composition comprising one or more compounds as claimed in any one of the preceding claims, together with one or more pharmaceutical carriers or excipients.

34. A composition as claimed in claim 33 in the form of a solution of said compound or compounds in a parenterally acceptable vehicle.

35. A composition as claimed in claim 24 in the form of a simple aqueous acidic solution of said compound or compounds.

36. A composition as claimed in any one of claims 33 to 35 wherein the said compound is a compound as claimed in claim 2.

37. A composition as claimed in claim 35 wherein said compound is a compound in any one of claims 21, 22, 25 or 26.

38. A composition as claimed in claim 35 wherein said compound is the compound claimed in claim 24.

39. A process for the preparation of a compound as claimed in claim 1, which process comprises reacting a corresponding steroid in which either or both of R^a and R^b is a hydrogen atom with a compound of the formula R^aX or (in the preparation of a compound in which R^1 is a heterocyclic amino group) a compound of the formula $X\text{-}R^a\text{-}R^b\text{-}X$ (where X is a readily displaceable substituent).

40. A process for the preparation of a compound as claimed in claim 1 which comprises reducing a corresponding 11α-acylamino steroid.

41. A process for the preparation of a ring A-saturated 2β- substituted 5α-steroids as claimed in claim 1 which comprises treating corresponding 2α,3α-epoxide 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 possess a deprotonated 3α-hydroxy group, treating the product with a source of protons.

42. A process for the preparation of a compound as claimed in claim 1 which comprises reductive alkylation of a corresponding 11α-amino or 11α-mono-substituted amino steroid.

43. A process for the preparation of 5β-steroids or ring A-saturated 2β-unsubstituted 5α-steroids as claimed in claim 1 which comprises reducing the corresponding 3-oxo steriod.

44. A process for the preparation of 3β-unsubstituted compounds as claimed in

claim 1 which do not possess a 5,6-double bond, which comprises inversion of the 3-hydroxy group of a derivative of a corresponding 3β-hydroxy compound.

45. A process for the preparation of compounds in which R^8 is a group (a) or (b) as defined in claim 1 which comprises reducing the corresponding Δ^{16} compound.

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

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

48. A process for the preparation of 17β-alkoxy-carbonyl compounds as claimed in claim 1 which comprises esterifying the corresponding 17β-carboxylic acid.

49. A process for the preparation of 17β-(substituted carbamoyl) compounds as claimed in claim 1 which comprises reacting the corresponding 17β-carboxylic acid with an amine.

50. A process for the preparation of 21-alkanoyloxy or 21-benzoyloxy compounds as claimed in claim 1 which comprises acyloxyation of the corresponding 21-unsubstituted compound.

51. A process for the preparation of 21-fluoro compounds as claimed in claim 1 which comprises displacement of the iodine atom of the corresponding 21-iode compound by fluoride.

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

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

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

55. A process for the preparation of 21-alkanoyloxy or 21-benzoyloxy compounds as claimed in claim 1 which comprises acylating the corresponding 21-alcohol.

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

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

58. 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.

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

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

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

62. A process for the preparation of 17-(Z)-ethylidene or 17-(Z)-cyano-methylene compounds as claimed in claim 1 which comprises reacting the corresponding 17-oxo steroid with an organophosphorus reagent.

63. A process for the preparation of compounds as claimed in claim 1 in which R^9 is a methyl or cylopropyl 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.

64. A process as claimed in any one of claims 39 to 62 wherein the compound prepared is a compound as claimed in claim 2.

65. A process for the preparation of 11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one or an acid addition salt thereof, which comprises reductive alkylation of the corresponding 11α-amino-20-ketal, followed, where a salt is required, by treatment with an acid.

66. A pharmaceutical composition substantially as described therein in any one of Examples A to F.

67. A compound as claimed in claim 1, said compound being the product of

any one Examples 7, 12, 15, 16, 23 and 48, or a physiologically acceptable salt thereof.

68. A compound as claimed in claim 1, said compound being the product of any one of Examples, 10, 13, 19, 21, 22, 26, 27, 33, 35, 36, 38—41, 43—46, 57, 59, 60, 186 and 188, or a physiologically acceptable salt thereof.

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