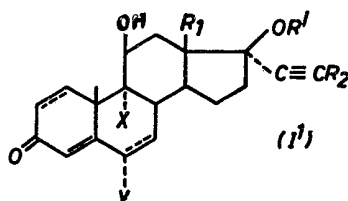


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(54) **17 α -Acetylene Derivatives of Androst-4-ene**

(57) New acetylene derivatives of androst-4-ene, of the general formula:



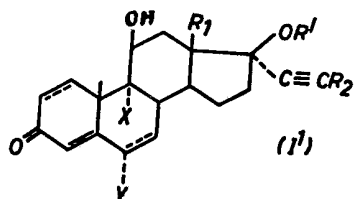
(wherein R₁ represents an alkyl radical, R' represents an acyl radical, R₂ represents a saturated or unsaturated aliphatic hydrocarbyl radical, a trifluoromethyl radical, an aryl radical or an aralkyl radical, Y

represents a hydrogen atom, a fluorine atom or a methyl radical, X represents a hydrogen atom or a chlorine, fluorine or bromine atom and the dotted lines in rings A and B represent optional second carbon-carbon bonds at the 1(2) and 6(7) positions, *with the proviso* that when R₁ represents a methyl radical and the B ring is saturated, X does not represent a chlorine, fluorine or bromine atom if Y represents a hydrogen atom and X does not represent a hydrogen atom if Y represents a fluorine atom) have anti-inflammatory activity especially when administered topically. They are prepared, for example, by esterifying the corresponding 17 β -hydroxy compounds.

SPECIFICATION
Acetylene Derivatives of Androst-4-ene

This invention relates to new acetylene derivatives of androst-4-ene, a process for preparing them and pharmaceutical compositions containing them.

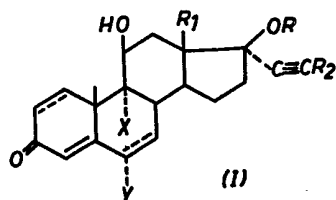
In one aspect this invention provides the compounds of the general formula:



wherein R_1 represents an alkyl radical containing from 1 to 3 carbon atoms, R' represents an acyl radical derived from an organic carboxylic acid containing from 1 to 18 carbon atoms or an acyl radical derived from an organic carbonic acid containing from 2 to 18 carbon atoms, R_2 represents a saturated or unsaturated, aliphatic hydrocarbyl radical containing from 1 to 12 carbon atoms, a trifluoromethyl radical, an aryl radical containing from 6 to 12 carbon atoms or an aralkyl radical containing from 7 to 12 carbon atoms, Y represents a hydrogen atom, a fluorine atom or a methyl radical, X represents a hydrogen atom or a chlorine, fluorine or bromine atom and the dotted lines in rings A and B represent optional second carbon-carbon bonds at the 1(2) and 6(7) positions, with the proviso that when R_1 represents a methyl radical and the B ring is saturated, X does not represent a chlorine, fluorine or bromine atom if Y represents a hydrogen atom and X does not represent a hydrogen atom if Y represents a fluorine atom.

Where general formulae are referred to herein by Roman numerals these formulae are as first defined unless otherwise stated. Equally substituents in general formulae are as first defined unless otherwise stated.

Among the compounds of the invention is the class of compounds of the general formula:



wherein R represents an acyl radical derived from an organic carboxylic acid containing from 1 to 18 carbon atoms.

R preferably represents the acyl residue of a saturated or unsaturated, aliphatic or cycloaliphatic carboxylic acid, and in particular R may be the acyl residue of an alkanolic acid such as acetic, propionic, butyric or isobutyric, valeric

or undecylic acid: of a hydroxy-alkanoic acid such as hydroxyacetic acid; of a cycloalkylcarboxylic or (cycloalkyl)-alkanoic acid such as cyclopropyl-, cyclo-pentyl- or cyclohexylcarboxylic acid, cyclopentyl- or cyclohexylacetic acid or cyclopentyl- or cyclohexylpropionic acid; of a benzoic acid; of a phenylalkanoic acid such as phenylacetic or phenylpropionic acid; of an amino acid such as diethylaminoacetic or aspartic acid; or of formic acid.

R' in addition to the residues set out above as being preferred for substituent R may also represent the acyl residue derived from an organic carbonic acid and by this it is meant that R' may represent a hydrocarbyloxycarbonyl radical. For example, R' may represent an optionally-substituted alkoxy carbonyl or alkenyloxycarbonyl residue or a cycloalkoxy carbonyl residue, such as a methoxycarbonyl, ethoxycarbonyl, cyclohexylmethoxycarbonyl, dicyclohexylmethoxycarbonyl, vinyloxycarbonyl or isopropenyloxycarbonyl residue.

R_1 preferably represent a methyl or ethyl radical, and a particularly preferred group of compounds are those of general formula I' wherein R_1 represents a methyl radical.

When R_2 represents a saturated aliphatic hydrocarbyl radical this may be, for example, a methyl, ethyl, *n*-propyl, *isopropyl*, *n*-butyl, *isobutyl*, *n*-pentyl, *n*-hexyl, 2-methylpentyl, 2,3-dimethylbutyl or 2,2-dimethylhexyl radical.

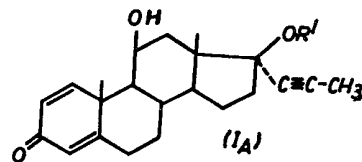
When R_2 represents an unsaturated aliphatic hydrocarbyl radical this may be, for example, a vinyl, *isopropenyl*, *isobutenyl*, allyl or 2-methylallyl radical.

When R_2 represents an aryl or aralkyl radical it is preferably a phenyl or benzyl radical.

A particularly preferred group of compounds are those compounds of general formula I' wherein R_2 represents a saturated or unsaturated aliphatic hydrocarbyl radical containing from 1 to 4 carbon atoms, and especially the methyl radical.

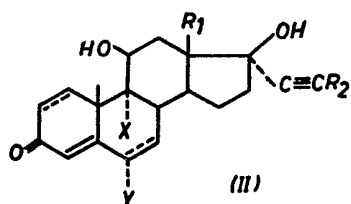
Among the compound of general formula I further groups of compounds which are particularly preferred are those compounds wherein the A ring is ethylenically unsaturated at the 1(2) position; those wherein the B ring is saturated; those wherein Y represents a hydrogen atom; and those wherein X represents a hydrogen atom.

The compounds of the general formula:



are especially preferred. The Examples set out hereinafter provide instances of specific compounds of the invention of significant interest.

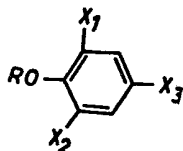
The invention also provides a process for preparing the compound of general formula I'; in which a compound of the general formula:



is reacted with an esterification agent capable of introducing the acyl radical R' only at the 17-position to obtain the corresponding compound of general formula I'.

5

The esterification agent is preferably a compound of the general formula:

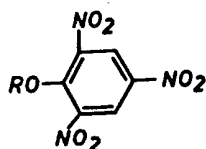


wherein X₁, X₂ and X₃, which may be the same or different, each represent a hydrogen atom or a nitro group with the proviso that at least one of X₁, X₂ and X₃ represents a nitro group.

10

In a preferred embodiment of the process the esterification agent is a compound of the general formula:

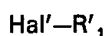
15



which may be formed *in situ* by the action of picric acid on a compound of general formula RHal wherein Hal represents a halogen atom and most preferably a chlorine atom.

20

The esterification agent used may alternatively be a compound of the general formula:



wherein Hal' represents a chlorine or bromine atom and R'₁ represents an acyl radical derived from an organic carbonic acid containing from 2 to 18 carbon atoms.

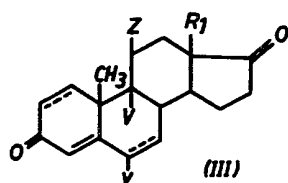
25

The esterification of the compound II is preferably carried out in the presence of a basic agent, and especially in the presence of an alkali-metal hydride or pyridine.

30

The starting materials of general formula II, used in the process of the invention, may be prepared by reacting a compound of the general formula:

35



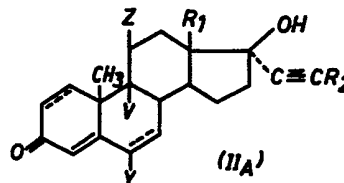
(wherein either Z and V form a 9β,11β-epoxy bridge or Z represents an 11β-OH radical and V

represents a 9α-hydrogen atom) with a compound of the general formula:

40



in the presence of a tertiary alcoholate to obtain a compound of the general formula:

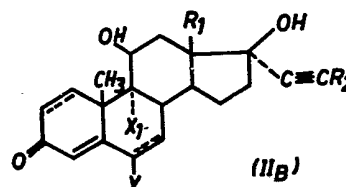


45 which, in the case where Z and V together form an epoxy bridge, is reacted with a compound of the general formula:



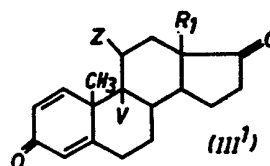
(wherein X₁ represents a chlorine, fluorine or bromine atom) to obtain the corresponding compound of the general formula:

50



The compound III used in this preparation is a compound of the general formula:

55



when it is desired to prepare a compound of general formula II, and hence a compound of general formula I' having 1(2)-ethylenic unsaturation in the A ring and a saturated B-ring.

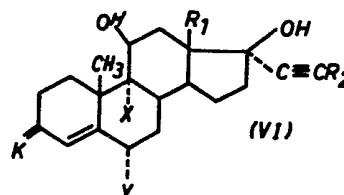
60

In the preparation of the compounds of general formula II the tertiary alcoholate is preferably an alkali metal *t*-butylate or *t*-amylate, such as sodium, potassium or lithium *t*-butylate or *t*-amylate.

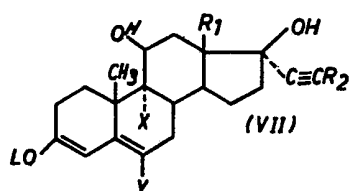
65

The products of general formula II can also be prepared by a modification of the preparation described above, in which a compound of the general formula:

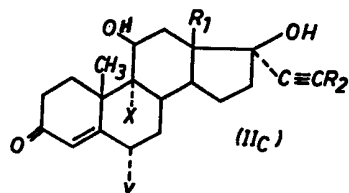
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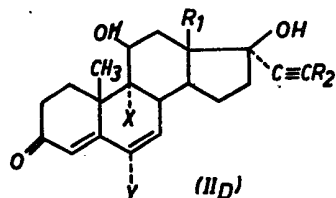
70 (wherein K represents a blocked ketone function in the form of a ketal or oxime) or a compound of the general formula:



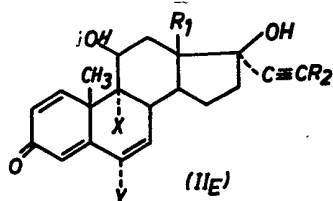
(wherein L represents an alkyl radical having from 1 to 4 carbon atoms) is reacted:
 either with an acid hydrolysis agent to obtain the
 5 corresponding compound of the general formula:



or with an agent capable of releasing the ketone
 function and of creating a $\Delta_{4,6}$ system of double
 bonds to obtain the corresponding compound of
 10 the general formula:



or with an agent capable of releasing the ketone
 function and of creating a $\Delta_{1,4,6}$ system of
 double bonds, to obtain the corresponding
 15 compound of the general formula:



When K represents a ketal group it is
 preferably a cyclic alkyl ketal group having from 2
 20 to 4 carbon atoms such as ethyleneketal or
 propyleneketal, or a dialkylketal such as dimethyl-
 or diethylketal.

When K represents an oxime this is preferably
 a $-\text{NOH}$ or $-\text{NOalk}_1$ group, wherein alk_1
 25 represents an alkyl radical containing from 1 to 4
 carbon atoms.

L preferably represents a methyl, ethyl or *n*-
 propyl radical.

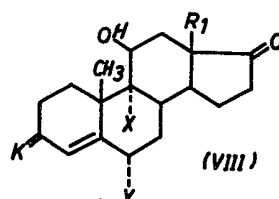
The acid hydrolysis agent used to prepare the
 compounds II_c is preferably hydrochloric,
 30 sulphuric, acetic, citric or *p*-toluenesulphonic acid.

The agent capable of releasing the ketone
 function and of creating a $\Delta_{4,6}$ system of double
 bonds is preferably a derivative of *p*-
 benzoquinone such as 2,3-dichloro-5,6-
 35 dicyanobenzoquinone or chloranil, with the
 reaction being effected in an aqueous solution of
 acetone. However, it is also possible to create

the $\Delta_{4,6}$ bond system biochemically, for example,
 by means of the bacterium "Arthrobacter
 40 Simplex"

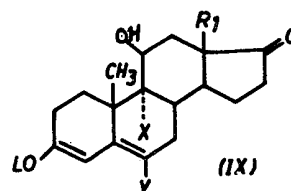
In order to release the ketone function and to
 create the $\Delta_{1,4,6}$ system of double bonds a
 derivative of *p*-benzoquinone such as chloranil or
 45 2,3-dichloro-5,6-dicyanobenzoquinone is
 preferably used, the reaction taking place in
 benzene.

The starting material of general formula VI or
 VII may itself be prepared by reacting a
 compound of the general formula:



50

or a compound of the general formula:



respectively, with a compound of the general
 formula:

55



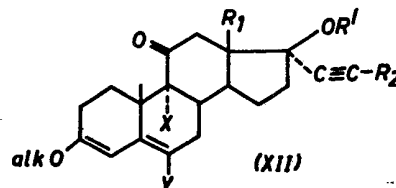
wherein T represents a lithium or potassium atom
 or a radical $-\text{MgHal}$.

The compound of general formula VIII or IX is
 of course chosen having regard to the desired
 60 final product. Thus, to prepare those compounds
 of general formula VI or VII wherein X represents
 a hydrogen atom, and thus ultimately compounds
 of general formula II wherein X represents a
 hydrogen atom, a compound of general formula
 65 VIII or IX is employed wherein X represents a
 hydrogen atom.

When T represents a radical $-\text{MgHal}$, the
 substituent Hal is preferably a bromine atom.

Some of the compounds of general formula II
 are described in published French Patent
 70 Specification No. 2,380,781. The compounds of
 general formulae III, VIII and IX are in general
 known products. They can be prepared, for
 example, according to the processes described in
 75 French Patents Nos. 1,359,611 and 1,222,424 or
 in U.S. Patents Nos. 3,010,957 and 3,072,684.

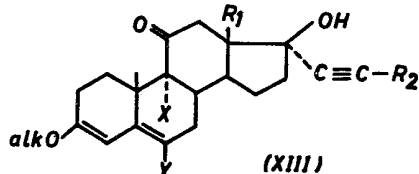
The invention also provides an alternative
 process for preparing the compounds of general
 formula I', in which an appropriate compound of
 80 the general formula:



(wherein alk represents an alkyl radical having from 1 to 12 carbon atoms) is reacted with a reducing agent to obtain the corresponding 11 β -OH compound and this formed product is then subjected *either* to the action of an acid hydrolysis agent *or* to the action of an agent capable of releasing the ketone function and of creating a Δ 4,6 system of double bonds *or* to the action of an agent capable of releasing the ketone function and of creating a Δ 1,4,6 system of double bonds so as in each case to obtain the corresponding compound of general formula I'.

The reducing agent used in the first step of this process is preferably an alkali-metal borohydride. The preferred agents employed to convert the 11 β -OH product obtained in the first step to the compound of general formula I' are those agents described as being preferred in the preparation of compounds II_C, II_D and II_E.

The starting materials of general formula XII may in turn be prepared by reacting a compound of the general formula:



with an esterification agent.

The esterification agent may be one of those agents described hereinbefore in relation to the conversion of compounds II into compounds I'. Alternatively the esterification agent may be an organic carboxylic acid or a functional derivative thereof.

The compounds of general formula XIII can be prepared, as described hereinafter in the Examples, by a similar process to that described herein for the preparation of the compounds of general formula VI or VII, but starting with the corresponding 17-oxo compounds which are themselves described in U.S. Patent No. 3,055,917.

The compounds of general formula I' have shown interesting pharmacological properties, and especially remarkable anti-inflammatory activity mainly when administered topically.

The compounds of general formula I' can be useful in the treatment of inflammatory reactions; they are of especial interest for the treatment of local inflammatory reactions such as oedema, dermatoses, pruritus, various forms of eczema and solar erythema.

The invention extends, therefore, to the compounds of general formula I' for use as medicaments in human or veterinary medicine, especially intended for topical application.

The compounds of Examples 2 and 3 set out hereinafter are particularly preferred for use as medicaments.

Before using the compounds of the invention in medicine, however, it is preferred to form the derivatives of the invention into pharmaceutical

compositions, by association with suitable pharmaceutical vehicles.

Accordingly, in a further aspect, this invention provides pharmaceutical compositions containing as active ingredient one or more compounds of general formula I', in association with a pharmaceutical vehicle.

The compositions of the invention preferably contain those derivatives mentioned hereinbefore as being preferred.

The term "pharmaceutical" is used herein to exclude any possibility that the nature of the vehicle, considered of course in relation to the route by which the composition is to be administered, could be harmful to the patient to be treated. The choice of a suitable vehicle is believed to be within the competence of those accustomed to the preparation of pharmaceutical formulations.

The compositions can be administered by a buccal, rectal or parenteral route, or preferably locally by topical application to the skin and mucous membranes. In respect of these routes the pharmaceutical vehicle may preferably be:

a) the ingestible excipient of a tablet or pill, such as a plain or coated compressed tablet; the ingestible container of a capsule or cachet; the ingestible pulverulent solid carrier of a powder or granules; or the ingestible liquid medium of a syrup, solution, suspension or emulsion;

b) the solid or liquid medium of a paste, cream, ointment or gel; or the liquified propellant gas of an aerosol;

c) a sterile injectable liquid solution or suspension medium; or

d) a base material of a suppository.

Whilst these pharmaceutical forms represent those most likely to be employed, they do not necessarily exhaust all possibilities.

The vehicles employed will generally include those excipients commonly employed in the formulation of pharmaceutical compositions. Such excipients may be solid or liquid as appropriate to the pharmaceutical form chosen, and may include a wide range of organic and inorganic solids, and aqueous and non-aqueous liquids; examples include talc, gum arabic, starch, lactose, magnesium stearate or fatty substances of animal or vegetable origin such as cocoa butter, paraffin derivatives or glycols. These excipients may be compounded with one or more wetting, dispersing or emulsifying agents and/or one or more preservatives.

The dosage of the active ingredient to be administered will of course vary with the compound concerned, the complaint and the patient being treated and the route of administration chosen. By way of illustration, the product of Example 2 may be administered in from 1 to 4 applications a day as an ointment containing from 0.1% to 5% of active material.

3-Ethoxy-11 β -hydroxy-6-methyl-androsta-3,5-dien-17-one, used as an intermediate in the process described herein, is a new compound,

and this invention extends to the compound *per se*.

The following Examples, Preparations, Formulations and Test Results are now given, though only by way of illustration, to show in more detail certain aspects of this invention.

Example 1

11 β -Hydroxy-17 α -(prop-1-ynyl)-17 β -valeroyloxy-androsta-1,4-dien-3-one.

0.79ml of valeroyl chloride and 0.6 cm³ of pyridine were added to a solution containing 1.68 g of picric acid in 20 cm³ of methylene chloride. The solution obtained was agitated for 10 minutes at ambient temperature and 2 g of 11 β , 17 β -dihydroxy-17 α -(prop-1-ynyl)-androsta-1,4-dien-3-one were added.

The reaction mixture was agitated for 68 hours at ambient temperature, then poured into a saturated aqueous solution of sodium

bicarbonate, extracted with methylene chloride and washed with a saturated aqueous solution of sodium bicarbonate. The product obtained was dried and evaporated to dryness to obtain 2.9 g of a product which was chromatographed on silica, eluting with 1:1 benzene/ethyl acetate. 1.7 g of a product were isolated and purified by recrystallisation from methanol. 941 mg of the desired product, melting at 194°C, were obtained.

Example 2

17 β -Acetoxy-11 β -hydroxy-17 α -(prop-1-ynyl)-androsta-1,4-dien-3-one.

Operating as in Example 1, but starting with 1.68 g of picric acid, 0.47 cm³ of acetyl chloride and 2 g of 11 β , 17 β -dihydroxy-17 α -(prop-1-ynyl)-androsta-1,4-dien-3-one and maintaining the agitation for 5 days, 1.57 g of a product were obtained. This product was recrystallised from *isopropyl* ether to obtain 1.033 g of the desired product, melting at 239°C.

Example 3

11 β -Hydroxy-17 β -propionyloxy-17 α -(prop-1-ynyl)-androsta-1,4-dien-3-one.

Operating as in Example 1 but starting with 2 g of 11 β , 17 β -dihydroxy-17 α -(prop-1-ynyl)-androsta-1,4-dien-3-one, 1.68 g of picric acid and 0.58 cm³ of propionyl chloride and maintaining the agitation for 92 hours, 1.35 g of a product were obtained. This product was recrystallised from methanol to obtain 997 mg of the desired product, melting at 214°C.

Example 4

17 β -Butyryloxy-11 β -hydroxy-17 α -(prop-1-ynyl)-androsta-1,4-dien-3-one.

Operating as in Example 1, but starting with 1.68 g of picric acid, 0.686 cm³ of butyryl chloride and 2 g of 11 β , 17 β -dihydroxy-17 α -(prop-1-ynyl)-androsta-1,4-dien-3-one and maintaining the agitation for four days, 1.205 g of a product were obtained. This product was

recrystallised from a mixture of methylene chloride and *isopropyl* ether to obtain 1.12 g of the desired product, melting at 205°C.

Example 5

65 11 β -Hydroxy-17 β -(3-methyl-1-oxo-butyloxy)-17 α -(prop-1-ynyl)-androsta-1,4-dien-3-one.

Operating as in Example 1, but starting with 1.68 g of picric acid, 0.819 cm³ of *isovaleryl* chloride and 2 g of 11 β , 17 β -dihydro-17 α -(prop-1-ynyl)-androsta-1,4-dien-3-one and maintaining the agitation for four days, 1.44 g of a product were obtained. This product was recrystallised from a mixture of methylene chloride and *isopropyl* ether to obtain 1.240 g of the desired product, melting at 214°C.

Example 6

11 β -Hydroxy-17 β -(ethoxycarbonyloxy)-17 α -(prop-1-ynyl)-androsta-1,4,6-trien-3-one.

Stage A: Esterification.

Under inert gas, 1.84 g of 3-ethoxy-11-oxo-17 β -hydroxy-21-methyl-pregna-3,5-dien-20-yne were added to a suspension of 240 mg of sodium hydride (at a concentration of 55% in mineral oil) in 10 cm³ of tetrahydrofuran. The reaction mixture was refluxed for 30 minutes and then cooled to 0°C. 1 cm³ of ethyl chloroformate was added and the reaction mixture was maintained at 0°C for 30 minutes, then poured into an aqueous solution of sodium bicarbonate, extracted with diethyl ether, dried and evaporated to dryness. The formed product was used without further treatment in the following stage.

Stage B: Reduction

2 g of potassium borohydride and 2 g of phenol were added to a solution of 2.5 g of the product from Stage A in 40 cm³ of dimethylformamide containing 10% of water. After agitation for 22 hours. 1 g of potassium borohydride and 1 g of phenol were added and the agitation was maintained for 24 hours.

The reaction mixture was poured on to 500 cm³ of a water/ice mixture, agitated for 2 hours, vacuum-filtered, washed with water, then with an aqueous solution of sodium bicarbonate and finally again with water and then dried to obtain the desired product.

Stage C: Formation of the Trienone.

A solution of the product of Stage B in 30 cm³ of benzene was added to a solution of 5 g of 2,3-dichloro-5,6-dicyanobenzo-quinone in 70 cm³ of benzene. The formed mixture was agitated at 20°C for 30 minutes, then poured into an aqueous solution of sodium bicarbonate, extracted with diethyl ether, washed with a 0.5N solution of sodium thiosulphate, then washed with a solution of sodium bicarbonate, dried and evaporated to dryness. The residue was chromatographed on silica, eluting with a 7:3 mixture of benzene and ethyl acetate to obtain the crude product expected which was recrystallised

from *isopropyl* ether to obtain 260 mg of pure product. M.Pt.=140°C.

Analysis: $C_{25}H_{30}O_5=410.49$
 Calculated: C% 73.14 H% 7.37
 Found: C% 72.9 H% 7.5

$[\alpha]_D^{20}=-80^{\circ}\pm 2.5^{\circ}$ (c=0.7% $CHCl_3$)

By direct esterification of the 11 β , 17 β -dihydroxy-17 α -(prop-1-ynyl)-androsta-1,4,6-trien-3-one with ethyl chloroformate in the presence of sodium hydride, the desired product was obtained, and was found to be identical to that obtained above.

Preliminary Preparation 1

11 β , 17 β -Dihydroxy-21-methyl-pregna-4,6-dien-20-yn-3-one.

Stage A: 3-Ethoxy-11 β , 17 β -dihydroxy-21-methyl-pregna-3,5-dien-20-yne.

70 cm³ of a 0.75 M solution of ethyl magnesium bromide in tetrahydrofuran were cooled to 0°C, and propyne was bubbled for two hours through the solution which was allowed to heat up to ambient temperature. 3.45 g of 3-ethoxy-11 β -hydroxy-androsta-3,5-dien-17-one and 14 cm³ of dry tetrahydrofuran were added, and the reaction solution was maintained at 20°C—25°C for 45 minutes. It was then poured into a cold solution of ammonium chloride and extracted with diethyl ether. The ethereal phase was washed with a saturated solution of sodium bicarbonate and dried on sodium sulphate. The solvent was evaporated under reduced pressure to obtain the desired product, which was used directly in the following Stage.

Stage B: 11 β , 17 β -Dihydroxy-21-methyl-pregna-4,6-dien-20-yn-3-one.

4 g of 3-ethoxy-11 β , 17 β -dihydroxy-21-methyl-pregna-3,5-dien-20-yne was dissolved in 100 cm³ of acetone. 5 cm³ of distilled water were added to the solution, followed by 4.8 g of 2,3-dichloro-5,6-dicyano-benzoquinone. The reaction mixture was agitated at ambient temperature for one hour, then poured into a saturated solution of sodium bicarbonate and extracted with methylene chloride. The organic phase was washed with a 0.5M solution of sodium thiosulphate, dried on sodium sulphate and concentrated to dryness to obtain 3.8 g of a product which was chromatographed on silica (eluant: benzene/ethyl acetate 50:50). The product having Rf=0.25 was isolated and purified by recrystallisation from *isopropyl* ether to obtain the desired product, melting at 200°C.

Analysis: $C_{22}H_{28}O_3=340.466$
 Calculated: C% 77.6 H% 8.29
 Found: C% 77.8 H% 8.3

Preliminary Preparation 2

11 β , 17 β -Dihydroxy-21-methyl-pregna-1,4,6-trien-20-yn-3-one.

Under agitation and under a current of nitrogen, a solution containing 3.7 g of 3-ethoxy 11 β ,17 β -dihydroxy-21-methyl-pregna-3,5-dien-

20-yne and 50 cm³ of benzene was poured into a solution containing 6.8 g of 2,3-dichloro-5,6-dicyanobenzoquinone. The agitation was continued for 25 minutes, then the reaction mixture was washed with an aqueous saturated solution of sodium bicarbonate, then with a 0.5M solution of sodium thiosulphate, and the organic phase was dried over sodium sulphate. The solvent was evaporated off under reduced pressure to obtain 2.75 g of a crude product which was chromatographed on silica (eluant: benzene/ethyl acetate 50:50). 1.2 g of the product having Rf=0.20 was isolated and recrystallised from the *isopropyl* ether/acetone/methylene chloride mixture to obtain 819 mg of the desired product, melting at 216°C.

Analysis: $C_{22}H_{26}O_3=338.45$
 Calculated: C% 78.07 H% 7.74
 Found: C% 77.9 H% 7.7

Preliminary Preparation 3

11 β , 17 β -Dihydroxy-21-phenyl-pregna-1,4-dien-20-yn-3-one.

Under agitation and at ambient temperature, 2.91 g of potassium *t*-butylate and 2.75 cm³ of phenyl acetylene were introduced into 100 cm³ of dioxan. The agitation was maintained for one hour and 3 g of 11 β -hydroxy-androsta-1,4-dien-3,17-dione (prepared according to the process indicated in U.S. Patent No. 3,010,957) and 30 cm³ of dioxan were then added. After the formed suspension had been agitated for 2 hours, an aqueous solution of acetic acid was added, and the reaction mixture was diluted with water and extracted with methylene chloride. The organic phase was washed with a saturated solution of sodium bicarbonate, and dried over sodium sulphate to obtain 4.25 g of a crude product which was chromatographed on silica, eluting with 6:4 benzene/ethyl acetate. 1.265 g of a product having Rf=0.20 were isolated and recrystallised from a mixture of methylene chloride and *isopropyl* ether to obtain the desired product, melting at 262°C.

$[\alpha]_D^{20}=-21^{\circ}\pm 2^{\circ}$ (C=0.7%, $CHCl_3$)

Preliminary Preparation 4

11 β , 17 β -Dihydroxy-21-trifluoromethyl-pregna-1,4-diene-20-yne-3-one.

At -70°C under an atmosphere of nitrogen, a solution containing 2.1 g of 11 β -hydroxy-androsta-1,4-diene-3,17-dione, 35 cm³ of anhydrous tetrahydrofuran and 3.5 cm³ of hexamethylphosphotriamide was agitated. A current of trifluoromethylacetylene was bubbled in, and drop by drop, a solution containing 3.4 g of 96% potassium *t*-butylate, 70 cm³ of tetrahydrofuran and 3.5 cm³ of hexamethylphosphotriamide was added. The product obtained was poured into an aqueous solution of ammonium chloride and extracted with diethyl ether. The organic phase was dried and the solvent was evaporated off. The product obtained was chromatographed on silica eluting

with 6:4 benzene/ethyl acetate and 2.7 g of a product was isolated. After recrystallisation from a mixture of *isopropyl ether* and methylene chloride, 2.248 g of the desired product, melting at 254—255°C, were obtained.
 $[\alpha]_D^{20} = -6.5^\circ \pm 1.5^\circ$ (C=0.75%, CHCl₃)

Preliminary Preparation 5

11β, 17β-Dihydroxy-6α,21-dimethyl-pregna-1,4-dien-20-yne-3-one.

10 Propyne was bubbled for 1 hour 30 minutes into a solution containing 200 cm³ of tetrahydrofuran and 10.3 g of 96% potassium *t*-butylate. After passage of propyne had been completed the agitation was continued for a few
 15 hours and 20 cm³ of hexamethylphosphotriamide were added. The reaction mixture was brought to -15°C and at that temperature, a solution containing 5.75 g of 11β-hydroxy-6α-methyl-androsta-1,4-dien-3,17-dione in 60 cm³ of
 20 tetrahydrofuran prepared according to the process described in French Patent No. 1,359,611, was introduced. The reaction mixture was agitated at -15°C for 4 hours, and then
 25 poured into an aqueous solution of hydrochloric acid, extracted with diethyl ether, washed with water and dried to obtain 6.05 g of a product which was purified by chromatography on silica eluting with 8:2 methylene chloride/acetone.
 30 Following a second purification by chromatography on silica eluting with 6:4 benzene/ethyl acetate and recrystallisation from *isopropyl ether*, 1.105 g of the desired product were obtained.
 M.Pt.=196°C. $[\alpha]_D^{20} = -14^\circ \pm 2^\circ$ (C=0.5%, CHCl₃)

35 Preliminary Preparation 6

11β, 17β-Dihydroxy-6,21-dimethyl-pregna-4,6-dien-20-yn-3-one.

At 0°C, under agitation and under a current of nitrogen, a current of propyne was bubbled into a
 40 1.15M solution of ethyl magnesium bromide in tetrahydrofuran. The reaction mixture was allowed to return to ambient temperature and agitated for a further one hour thirty minutes. 6.3 g of 3-ethoxy-11β-hydroxy-6-methyl-androsta-
 45 3,5-dien-17-one (for which a preparation is given below in Preliminary Preparation 10) were added, and the reaction mixture was again maintained under agitation for one hour thirty minutes, then
 50 poured into an aqueous solution of ammonium chloride, chilled and extracted with diethyl ether. The organic phase was washed with an aqueous solution of sodium bicarbonate and dried. The solvent was evaporated off under reduced
 55 pressure to isolate 4.7 g of a product which was dissolved in a solution containing 100 cm³ of acetone and 5 cm³ of water. 2.5 g of 2,3-dichloro-5,6-dicyanobenzoquinone were added, and the formed reaction mixture was poured into
 60 an aqueous solution of sodium bicarbonate and extracted with methylene chloride. The organic phase was washed with sodium

thiosulphate and dried on sodium sulphate, and the solvent was evaporated off under reduced pressure. The product obtained was
 65 chromatographed on silica, eluting with 1:1 benzene/ethyl acetate, to obtain 2.95 g of the desired product.

N.M.R. Spectrum : (CDCl₃) 60 MHz

CH₃ at 81.5 Hz, 71.5 Hz, 110 Hz

70 H at 270 Hz

Ethylenic H at 352 Hz.

Analysis: C₂₃H₃₀O₃=354.47

Calculated: C% 76.76 H% 8.57

Found: C% 76.6 H% 8.7

75 Preliminary Preparation 7

11β, 17β-Dihydroxy-21-phenyl-pregn-4-en-20-yne-3-one.

Drop by drop, at 0°C, 7.2 cm³ of phenylacetylene were added to a solution
 80 containing 40 cm³ of a 1.3M solution of *n*-butyl lithium in hexane and 40 cm³ of anhydrous tetrahydrofuran. 3 g of 3-ethoxy-11β-hydroxy-androsta-3,5-dien-17-one were then added. The reaction mixture was agitated at ambient
 85 temperature for 17 hours, then poured into an aqueous solution of ammonium chloride and extracted with ether. The product obtained was chromatographed on silica eluting with benzene/ethyl acetate, containing 0.2% of
 90 triethylamine. The product having R_f=0.35 was isolated and treated for 30 minutes with a solution containing 125 cm³ of methyl alcohol and 25 cm³ of a normal solution of hydrochloric acid. The resultant mixture was poured into water,
 95 extracted with methylene chloride and dried on sodium sulphate. The solvents were evaporated off and the product obtained was purified by chromatography to obtain 1.1 g of the desired product.
 100 $[\alpha]_D^{20} = -4^\circ \pm 2^\circ$ (C=0.7% CHCl₃)

Preliminary Preparation 8

11β, 17β-Dihydroxy-9α-fluoro-21-methyl-pregna-1,4-dien-20-yn-3-one.

105 **Stage A: 17β-Hydroxy-9β,11β-epoxy-21-methyl-pregna-1,4-dien-20-yn-3-one.**
 15.6 g of 0.6% potassium *t*-butylate were introduced into 600 cm³ of tetrahydrofuran
 Propyne was bubbled into the formed solution for one hour thirty minutes, then a solution
 110 containing 4 g of 9,11β-epoxy-androsta-1,4-dien-3,17-dione (prepared by the process of French Patent No. 1,222,424) in 40 cm³ of tetrahydrofuran was added. The reaction mixture was maintained under agitation for three days,
 115 then 30 cm³ of a 6N solution of hydrochloric acid were added and agitation continued for 30 minutes. The reaction mixture was poured into water, extracted with diethyl ether, washed with water, dried over sodium sulphate and then taken
 120 to dryness under reduced pressure. 4.5 g of product were obtained, and this was used in the following Stage.

Stage B: 11 β , 17 β -dihydroxy-9 α -fluoro-21-methyl-pregna-1,4-dien-20-yn-3-one.

A complex of 45 cm³ of hydrofluoric acid and dimethyl-formamide was poured at -40°C onto the product obtained in Stage A, in solution in 45 cm³ of dimethylformamide. The mixture was allowed to return to ambient temperature and maintained under agitation for 48 hours. It was then poured into a solution containing water, ice and ammonia, vacuum-filtered and rinsed until neutral. 3.5 g of product were obtained, and the mother liquors were extracted with diethyl ether to obtain a further 1.1 g of product. The two batches thus obtained were combined and purified by chromatography on silica, eluting with 6:4 benzene/ethyl acetate, then with 8:2 methylene chloride/acetone, and by recrystallisation from a mixture of methylene chloride and *isopropyl* ether, to obtain 1.115 g of the desired product, melting at 220°C:
 $[\alpha]_D^{20} = -2.5^\circ \pm 2^\circ (c=0.5\% \text{ CHCl}_3)$
 Analysis: C₂₂H₂₇O₃F=358.45
 Calculated: C% 73.71 H% 7.59 F% 5.29
 Found: C% 73.5 H% 7.7 F% 5.0

25 Preliminary Preparation 9

3-Ethoxy-11 α -hydroxy-androsta-3,5-dien-17-one.

43 g of 11 β -hydroxy-androst-4-ene-3,17-dione (prepared according to the process described in U.S. Patent No. 3,072,684), 215 cm³ of ethanol and 43 cm³ of a 0.26M solution of ethyl orthoformate were heated to 50°C, then 5.2 cm³ of a solution of 0.48 g of *p*-toluenesulphonic acid in 50 cm³ of ethanol were added. The solution obtained was maintained for 5 minutes at 50°C and 8.6 cm³ of triethylamine were added. The reaction mixture was then cooled to 20°C and 258 cm³ of water were added. The reaction mixture was cooled for one hour to from 0°C to +5°C, then filtered and washed with a 50:50:0.5 ethanol/water/pyridine mixture and to obtain 40.1 g of the desired product, which could be used as prepared.

Preliminary Preparation 10

45 3-Ethoxy-11 β -hydroxy-6-methyl-androsta-3,5-dien-17-one.

1.80 g of 11 β -hydroxy-6 α -methyl-androst-4-ene-3,17-dione were suspended in a solution containing 10 cm³ of ethanol and 2 cm³ of triethoxymethane. The suspension was agitated at 50°C under a current of nitrogen, then 0.25 cm³ of a solution containing 480 mg of *p*-toluenesulphonic acid in 50 cm³ of ethanol were added, followed after 5 minutes by 0.4 cm³ of triethylamine. The reaction mixture was then cooled with an ice bath and water was added drop by drop. The precipitate obtained was vacuum filtered, washed using a 7:3 methanol/water mixture, and dried to obtain 1.66 g of a product having R_f=0.55 (benzene/ethyl acetate, 1:1).

Preliminary Preparation 11

3-Ethoxy-11-oxo-17 β -hydroxy-21-methyl-pregna-3,5-dien-20-yne.

65 Dry propyne was bubbled for 2 hours into 132 cm³ of a 1.15M solution of ethyl magnesium bromide in tetrahydrofuran at 0°C. The solution was allowed to return to 20°C during the bubbling-in, then, over 40 minutes a solution of 70 20 g of 3-ethoxy-11,17-dioxo-androsta-3,5-diene (described in U.S. Patent No. 3,055,917) in 80 cm³ of dry tetrahydrofuran was introduced. The reaction mixture was agitated for 1 hour, poured on to a chilled solution of ammonium chloride, 75 extracted with diethyl ether, washed with water, dried and concentrated to dryness. The formed crystals were washed with *isopropyl* ether containing a few drops of pyridine to obtain 17.7 g of the desired product.
 80 M.Pt.=172°C.

Formulation: Ointment

An ointment for topical application was prepared from the following:

	Product of Example 2	1 g
85	Excipient q.s.v.	100 g
	Detail of the excipient	lanolin and Vaseline.

Test Results

Study of the Dermal Activity

The dermal activity of the products of 90 Examples 2 and 3, called hereinafter product A and product B was investigated by a test based on the oedema caused by croton.

Test Method

95 The technique employed was inspired by that of TONELLI *et al.* (Endocrinology 1965 77, p.625). Oedema was initiated in the mouse by application of croton oil to an ear.

To a mouse of a first batch a solution of croton oil was applied to the right ear.

100 To a mouse of a second batch a solution in croton oil of the product under test was applied to the right ear.

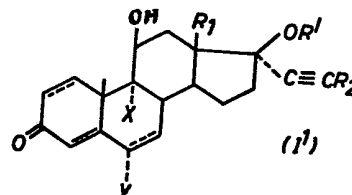
Nothing was applied to the left ears of the mice in either batch.

105 At the end of six hours the ears were cut off and weighed. The difference in weight between the right ear and the left ear gave the degree of inflammation.

110 It was established that at a dose of 0.2 mg/kg products A and B showed clear anti-inflammatory activity.

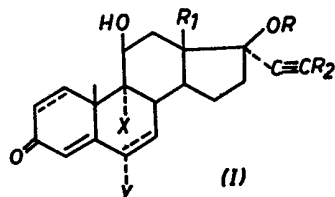
Claims

1. A compound of the general formula:

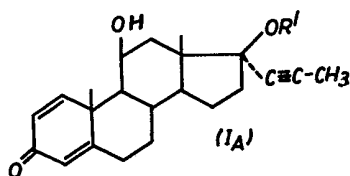


- wherein R_1 represents an alkyl radical containing from 1 to 3 carbon atoms, R' represents an acyl radical derived from an organic carboxylic acid containing from 1 to 18 carbon atoms or an acyl radical derived from an organic carbonic acid containing from 2 to 18 carbon atoms, R_2 represents a saturated or unsaturated, aliphatic hydrocarbyl radical containing from 1 to 12 carbon atoms, a trifluoromethyl radical, an aryl radical containing from 6 to 12 carbon atoms or an aralkyl radical containing from 7 to 12 carbon atoms, Y represents a hydrogen atom, a fluorine atom or a methyl radical, X represents a hydrogen atom, or a chlorine, fluorine or bromine atom and the dotted lines in rings A and B represent optional second carbon-carbon bonds at the 1(2) and 6(7) positions, *with the proviso* that when R_1 represents a methyl radical and the B ring is saturated, X does not represent a chlorine, fluorine or bromine atom if Y represents a hydrogen atom and X does not represent a hydrogen atom if Y represents a fluorine atom.

2. A compound of the general formula:



- 25 wherein R represents an acyl radical derived from an organic carboxylic acid containing from 1 to 18 carbon atoms.
3. A compound as claimed in claim 1 or claim 2, wherein R_1 represents a methyl radical.
- 30 4. A compound as claimed in any of claims 1 to 3, wherein R_2 represents a saturated or unsaturated aliphatic hydrocarbyl radical containing from 1 to 4 carbon atoms.
5. A compound as claimed in claim 4, wherein R_2 represents the methyl radical.
- 35 6. A compound as claimed in any of the preceding claims, wherein the A ring is ethylenically unsaturated at the 1(2) position.
7. A compound as claimed in any of the preceding claims, wherein the B ring is saturated.
- 40 8. A compound as claimed in any of the preceding claims, wherein Y represents a hydrogen atom.
9. A compound as claimed in any of the preceding claims, wherein X represents a hydrogen atom.
- 45 10. A compound of the general formula:



11. 11 β -Hydroxy-17 α -(prop-1-ynyl)-17 β -valeroyloxy-androsta-1,4-dien-3-one.
- 50 12. 17 β -Acetoxy-11 β -hydroxy-17 α -(prop-1-

ynyl)-androsta-1,4-dien-3-one.

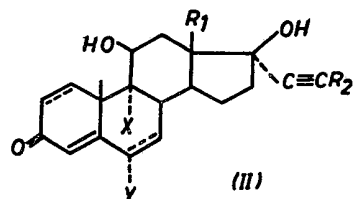
13. 11 β -Hydroxy-17 β -propionyloxy-17 α -(prop-1-ynyl)-androsta-1,4-dien-3-one.

55 14. 17 β -Butyryloxy-11 β -hydroxy-17 α -(prop-1-ynyl)-androsta-1,4-dien-3-one.

15. 11 β -Hydroxy-17 β -(3-methyl-1-oxobutyloxy)-17 α -(prop-1-ynyl)-androsta-1,4-dien-3-one.

60 16. 11 β -Hydroxy-17 β -(ethoxycarbonyloxy)-17 α -(prop-1-ynyl)-androsta-1,4,6-trien-3-one.

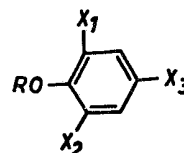
17. A process for preparing the compounds of general formula I', in which a compound of the general formula:



65

is reacted with an esterification agent capable of introducing the acyl radical R' only at the 17-position to obtain the corresponding compound of general formula I'.

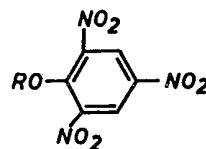
70 18. A process as claimed in claim 17, in which the esterification agent is a compound of the general formula:



75 wherein X_1 , X_2 , and X_3 , which may be the same or different, each represent a hydrogen atom or a nitro group *with the proviso* that at least one of X_1 , X_2 and X_3 represents a nitro group.

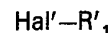
19. A process as claimed in claim 18 in which the esterification agent is a compound of the

80 general formula:



20. A process as claimed in claim 17, in which the esterification agent is a compound of the general formula:

85

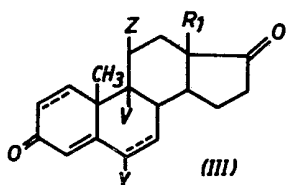


wherein Hal' represents a chlorine or bromine atom and R'_1 represents an acyl radical derived from an organic carbonic acid containing from 2 to 18 carbon atoms.

90 21. A process as claimed in any of claims 17 to 20, in which the esterification of the compound II is carried out in the presence of a basic agent.

22. A process as claimed in any of claims 17 to 21, in which the starting material of general formula II is prepared by reacting a compound of the general formula:

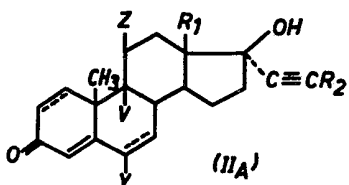
95



(wherein either Z and V form a $9\beta,11\beta$ -epoxy bridge or Z represents an 11β -OH radical and V represents a 9α -hydrogen atom) with a compound of the general formula:



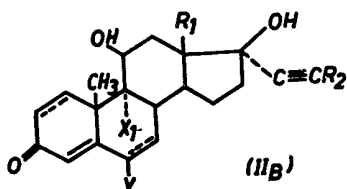
in the presence of a tertiary alcoholate to obtain a compound of the general formula:



10 which, in the case where Z and V together form an epoxy bridge, is reacted with a compound of the general formula:

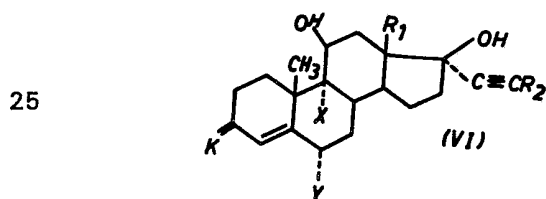


15 (wherein X_1 represents a chlorine, fluorine or bromine atom) to obtain the corresponding compound of the general formula:

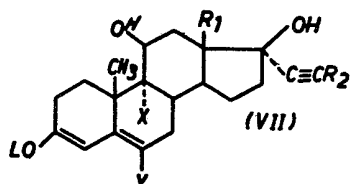


20 23. A process as claimed in claim 22, in which the tertiary alcoholate is an alkali metal *t*-butylate or *t*-amylate.

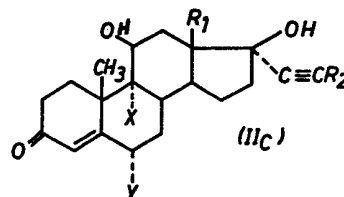
24. A process as claimed in any of claims 17 to 21, in which the starting material of general formula II is prepared by reacting a compound of the general formula:



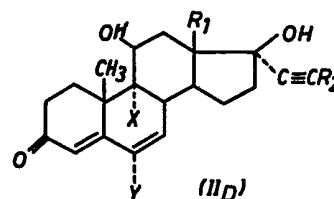
(wherein K represents a blocked ketone function in the form of a ketal or oxime) or a compound of the general formula:



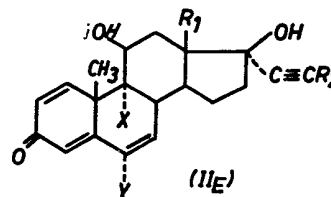
30 (wherein L represents an alkyl radical having from 1 to 4 carbon atoms):
either with an acid hydrolysis agent to obtain the corresponding compound of the general formula:



35 or with an agent capable of releasing the ketone function and of creating a $\Delta 4,6$ system of double bonds to obtain the corresponding compound of the general formula:



40 or with an agent capable of releasing the ketone function and of creating a $\Delta 1,4,6$ system of double bonds, to obtain the corresponding compound of the general formula:

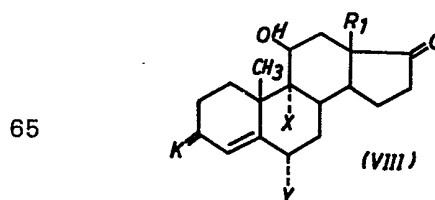


45 25. A process as claimed in claim 24, in which the acid hydrolysis agent used to prepare the compound II_c is hydrochloric, sulphuric, acetic, citric or *p*-toluenesulphonic acid.

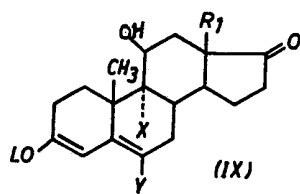
50 26. A process as claimed in claim 24, in which the agent capable of releasing the ketone function and of creating a $\Delta 4,6$ system of double bonds is 2,3-dichloro-5,6-dicyanobenzoquinone or chloranil, the reaction being effected in an aqueous solution of acetone.

55 27. A process as claimed in claim 24, in which the agent capable of releasing the ketone function and creating a $\Delta 1,4,6$ system of double bonds is chloranil or 2,3-dichloro-5,6-dicyanobenzoquinone, the reaction taking place in benzene.

60 28. A process as claimed in any of claims 24 to 27 in which the starting material of general formula VI or VII is prepared by reacting a compound of the general formula:



or a compound of the general formula:



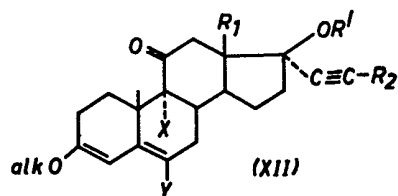
respectively, with a compound of the general formula:



5 wherein T represents a lithium or potassium atom or a radical-MgHal.

29. A process for preparing the compounds of general formula I', in which a compound of the general formula:

10



(wherein alk represents an alkyl radical having from 1 to 12 carbon atoms) is reacted with a reducing agent to obtain the corresponding 11 β -OH compound and this formed product is then subjected *either* to the action of an acid hydrolysis agent *or* to the action of an agent capable of releasing the ketone function and of creating a Δ 4,6 system of double bonds *or* to the action of an agent capable of releasing the ketone function and of creating a Δ 1,4,6 system of double bonds, so as in each case to obtain the corresponding compound of general formula I'.

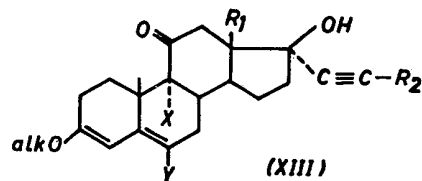
15 30. A process as claimed in claim 29, in which the reducing agent used in the first step of the process is an alkali-metal borohydride.

25 31. A process as claimed in claim 29 or claim 30, in which the agent employed to convert the

11 β -OH product obtained in the first step to the compound of general formula I' is an agent as defined in any of claims 25 to 27.

30 32. A process as claimed in any of claims 29 to 31, in which the starting material of general formula XII is prepared by reacting a compound of the general formula:

35



with an esterification agent.

33. A process as claimed in claim 32, in which the esterification agent is as defined in any of claims 18, 19 and 20.

40 34. A process as claimed in claim 32, in which the esterification agent is an organic carboxylic acid or a functional derivative thereof.

45 35. A process for preparing compounds of general formula I' substantially as described herein with reference to any one of the Examples.

36. The compounds of general formula I' as claimed in claim 1, for use as medicaments in human or veterinary medicine.

50 37. A pharmaceutical composition containing as active ingredient one or more compounds of general formula I', in association with a pharmaceutical vehicle.

55 38. A composition as claimed in claim 37, in which the active ingredient is or includes one or more compounds as claimed in any of claims 2 to 16.

39. A pharmaceutical composition substantially as described herein with reference to the formulation.

60 40. 3-Ethoxy-11 β -hydroxy-6-methyl-androsta-3,5-dien-17-one.